Cancer and Benign Tumors

PART XX

Chapter 540

Epidemiology of Childhood and Adolescent Cancer

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Cancer in patients younger than 20 years is uncommon, with an age-adjusted annual incidence of 19.6 per 100,000 children age 0-19 years, representing only approximately 1% of all new cancer cases in a year in the United States, or an estimated 16,000 new cases in 2021. This translates to nearly a 1 in 300 chance of developing cancer by age 20 years. Although the relative 5-year survival rates have improved from 61% in 1975–1977 to 85.1% in 2011–2017 in all age-groups 0-19 years (Fig. 540.1), **malignant neoplasms** remain the leading cause of disease-related (noninjury) mortality (9%) among persons 1-19 years of age, with 1,800-1,900 cancer-related deaths annually in the United States among children and adolescents 0-19 years of age. The relative contribution of cancer to the overall mortality in infants 0-1 year old and adolescents 15-19 years old is lower than for children age 1-14 years. The impressive improvements in survival over the last four decades are attributed primarily to advances in treatment, supportive care, and enrollment in clinical trials for the majority of patients. Ongoing multi-institutional cooperative clinical trials are investigating novel therapies and ways to improve survival rates further while decreasing treatment-related long-term complications. Because increasingly more patients survive their disease, clinical investigations also are focusing on the quality of life among survivors and the late outcomes of therapy for pediatric and adult survivors of childhood cancer. The **National Cancer Institute** (NCI; https://www.cancer.gov/types/childhood-cancers/) estimated that as of January 1, 2018, there were approximately 483,000 persons alive (in all age-groups) who had survived childhood cancer (diagnosed at ages 0-19 years). Given the overall improvement in survival rates coupled with the increased incidence of childhood cancer observed in recent decades, the number of survivors will continue to increase.

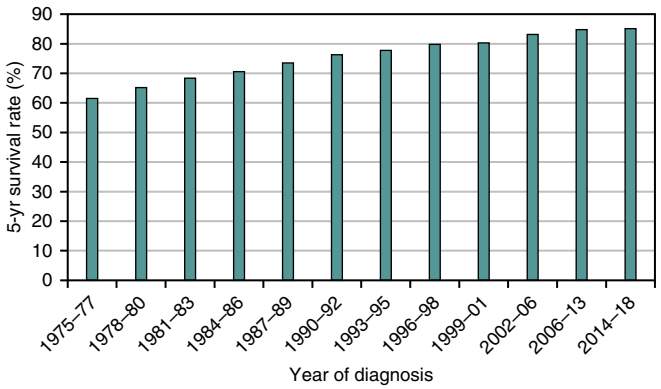

Fig. 540.1 The 5-year relative survival rates (%) by year of diagnosis of all cancers in children ≤19 years old. The difference between the periods 1975–1977 and 2014–2018 is statistically significant ($p < .05$). Rates based on follow-up of patients into 2018 from Surveillance, Epidemiology, and End Results (SEER) database. *(Data compiled from Howlader N, Noone AM, Krapcho M, et al., eds. SEER Cancer Statistics Review, 1975-2018. Bethesda, MD: National Cancer Institute. https://seer.cancer.gov/csr/1975_2018/. Based on November 2020 SEER data submission, posted to the SEER website, April 2021.)*

Pediatric malignancies differ greatly from adult malignancies in both prognosis and distribution by histology and tumor site. **Lymphohematopoietic cancers** (i.e., acute lymphoblastic leukemia, myeloid leukemia, Hodgkin and non-Hodgkin lymphomas) account for approximately 40%, **central nervous system cancers** for approximately 30%, and **embryonal tumors** and **sarcomas** for approximately 10% among the broad categories of childhood cancers (Table 540.1). In contrast, the **epithelial tumors** (or **adenocarcinomas**) of organs such as lung, colon, breast, and prostate often seen among adults, are rare malignancies in children. Incidence patterns in the pediatric age-group show two peaks, in early childhood and in adolescence (Fig. 540.2). During the first year of life, *embryonal tumors* such as neuroblastoma, nephroblastoma (Wilms tumor), retinoblastoma, rhabdomyosarcoma, hepatoblastoma, and medulloblastoma are most common (Figs. 540.3 and 540.4). These tumors are much less common in older children and adults after cell differentiation processes have slowed considerably. Embryonal tumors, acute leukemias, non-Hodgkin lymphomas, and gliomas peak in incidence from 2-5 years of age. As children age, bone malignancies, Hodgkin disease, gonadal germ cell malignancies (testicular and ovarian carcinomas), and other carcinomas increase in incidence. Adolescence is a transitional period between the common early childhood malignancies and characteristic carcinomas of adulthood (see Fig. 540.4).

Incidence rates also vary by *gender* (generally higher in males vs females), *ethnicity* (leukemia more common in Hispanic children than White or Black children; brain tumors more common in White children), and between countries (data assembled by the International Agency for Research in Cancer in Lyon, France, http://www.iarc.who.int/). These variations are not fully understood but likely reflect differences in genetic susceptibility and environmental exposures related to both known and unknown causes and risk factors for cancer (Table 540.2). Over the past four decades, 1975–2018, the U.S. Surveillance, Epidemiology, and End Results Program (SEER) data show some increases in the incidence of children and adolescents diagnosed with cancer (annual percent change about 1%), particularly in occurrence of leukemia, brain, and lymphoma and among adolescents. Interestingly, a similar increased incidence of malignancies diagnosed in childhood was observed between 1980 and 2010 in an international population-based registry study involving 62 countries. Reasons postulated to explain these increases include, but are not limited to, improved diagnosis, better record keeping, and development of data registries. Further analysis of trends among subpopulations, geographic variations, and incidence rates in high-income vs low-income countries are needed to clarify the role of *genetic ancestry, environmental factors,* and *technology* as explanations of these time trends in cancer in children.

Table 540.1 Age-Adjusted Incidence and Survival Rates of Malignant Neoplasms by Tumor Type in U.S. Children

	ANNUAL INCIDENCE RATES PER 1 MILLION CHILDREN, 2014–2018					5-YR SURVIVAL (%), AGE ≤19 YR AT DIAGNOSIS, 2011–2017
	AGE <1 YR	AGE 1-4 YR	AGE 5-9 YR	AGE 10-14 YR	AGE 15-19 YR	
All malignancies combined	265	227	137	164	252	85.1
All Leukemias (ALL/AML)	51 (18/20)	93 (78/11)	4.5 (37/4)	36 (24/8)	37 (19.5/10)	85 (89/68)
Lymphoma (Hodgkin)	— (—)	9 (1)	17 (3.5)	28 (13)	54 (33)	94 (98)
CNS tumors	46	54	50	52	64	74
Neuroblastoma	56	21	4	1	1	82
Nephroblastoma/Wilms (renal cell carcinoma)	16 (—)	19 (—)	6 (—)	1 (1)	— (1.5)	93
Bone	—	2	7	16	15	71
Soft tissue sarcomas	14	11	9	13	17	74
Retinoblastoma	31.5	8	—	—	—	96
Hepatoblastoma (hepatic carcinoma)	14 (—)	6 (—)	0.8 (—)	0.4 (0.7)	— (1.5)	82
Germ cell tumors	20	4	3	9	29	92
Malignant epithelial cancer	2.5	2	6	24	68.5	94
Thyroid / melanoma	–*/–†	–*/1†	2*/2†	11*/3†	35*/9†	(99*/94†)

*Thyroid carcinoma.
†Malignant melanoma.
—, Indicates that the rate could not be calculated with <16 cases for the time interval.
ALL, Acute lymphoid leukemia; AML, acute myeloid leukemia; CNS, central nervous system.
Data compiled from Howlader N, Noone AM, Krapcho M, et al., eds. SEER cancer statistics review, 1975-2018. Bethesda, MD: National Cancer Institute, 2020. Based on November 2020 SEER data submission, posted to SEER website, April 2021.
Based on the International Classification of Childhood Cancer (ICCC). Rates are per 1 million children and are age-adjusted to the 2000 U.S. standard population.

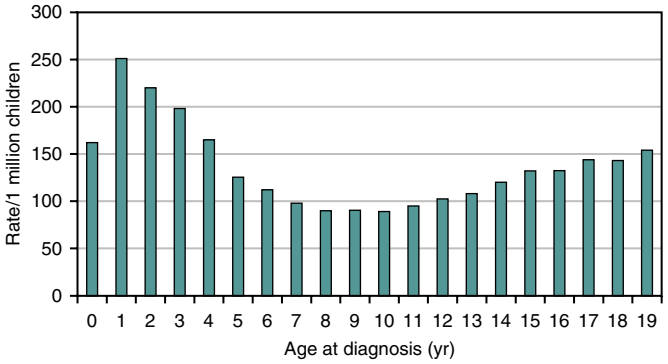

Fig. 540.2 Age-specific cancer incidence rates per 1 million children within the United States. *(Rates based on data from 2000–2017 from Surveillance, Epidemiology, and End Results [SEER] database http://seer.cancer.gov/csr/1975_2018/ and data compiled from Marcotte EL, Domingues AM, Sample JM, et al. Racial and ethnic disparities in pediatric cancer incidence among children and young adults in the United States by single year of age. Cancer 2021;127[19]:3651–3663. http://seer.cancer.gov/csr/1975_2018/.)*

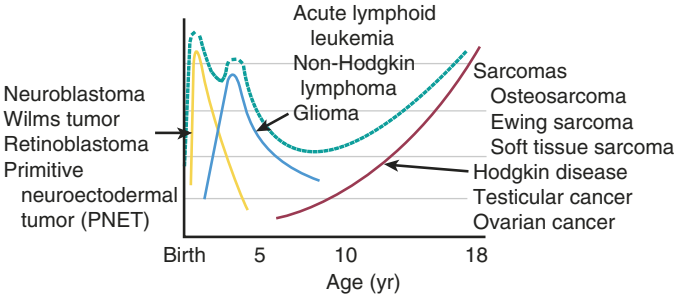

Fig. 540.3 Generalized incidence of the most common types of cancer in children by age. The cumulative incidence of all cancers is shown as a *dashed green line. (Courtesy Archie Bleyer, MD.)*

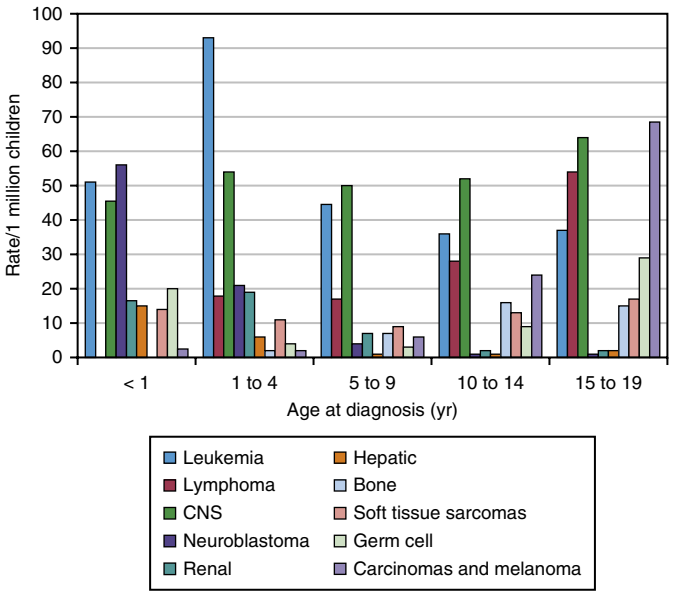

Fig. 540.4 Surveillance, Epidemiology, and End Results (SEER) cancer incidence rates per 1 million children by International Classification of Childhood Cancer (ICCC) and age <20 years. CNS, Central nervous system. *(Data compiled from Howlader N, Noone AM, Krapcho M, et al., eds. SEER cancer statistics review, 1975-2018. Bethesda, MD: National Cancer Institute, 2020. http://seer.cancer.gov/csr/1975_2018/. Based on November 2020 SEER data submission, posted to the SEER website, April 2021.)*

Table 540.2 Known Risk Factors for Selected Childhood Cancers

CANCER TYPE	RISK FACTOR	COMMENTS
Acute lymphoid leukemia	Ionizing radiation	Therapeutic irradiation for cancer treatment
	Ethnicity	Hispanic children have higher incidence compared with White or Black children White children have a higher rate than Black children
	Immunodeficiency	SCID, Wiskott-Aldrich syndrome
	Genetic factors*	Down syndrome is associated with an estimated 10-20–fold increased risk NF1 Li-Fraumeni syndrome (*TP53* pathogenic variants) Noonan syndrome Chromosome breakage syndromes Bloom syndrome Ataxia-telangiectasia
Acute myeloid leukemias/ myelodysplastic syndrome	Chemotherapeutic agents	Alkylating agents and epipodophyllotoxins associated with risk of secondary leukemia
	Genetic factors*	Down syndrome (particularly acute megakaryocytic leukemia) NF1 Fanconi anemia and other inherited marrow failure syndromes Li-Fraumeni syndrome GATA2 deficiency Noonan syndrome Familial monosomy 7 and other chromosomal pathogenic variants
Brain cancers	Therapeutic ionizing radiation to the head	Radiation therapy as part of cancer treatment
	Genetic factors*	NF1 is strongly associated with optic gliomas, and, to a lesser extent, with other central nervous system tumors Li-Fraumeni syndrome Tuberous sclerosis Noonan syndrome Von Hippel-Landau syndrome FAP syndrome
Hodgkin disease	Family history	Monozygotic twins and siblings of cases are at increased risk
	Infections	EBV is associated with increased risk
Non-Hodgkin lymphoma	Immunodeficiency	Congenital immunodeficiency disorders (e.g., SCID and Wiskott-Aldrich syndrome) Immunosuppressive therapy for other conditions associated with increased risk
	Infections	EBV is associated with Burkitt lymphoma PTLD-EBV plays role in development of B-cell lymphoproliferative disease seen in immunocompromised hosts, especially those on immunosuppression following organ transplantation
Osteosarcoma	Ionizing radiation	Cancer radiation therapy
	Chemotherapy	Alkylating agents increase risk
	Genetic factors*	Li-Fraumeni syndrome Second malignancy in hereditary retinoblastoma with *RB1* pathogenic variant
Ewing sarcoma	Ethnicity	White children have about a ninefold higher incidence rate than Black children in the United States
Neuroblastoma		Beckwith-Wiedemann syndrome Li-Fraumeni
Retinoblastoma	Genetic factors*	Familial; pathogenic variant of *RB1* without other syndromic features—also with high risk of second malignancies
Wilms tumor	Genetic factors*	WAGR syndrome *WT1* germline pathogenic variant Beckwith-Wiedemann syndrome Li-Fraumeni syndrome
	Ethnicity	Asian children reportedly have about half the rates of White and Black children
Rhabdomyosarcoma	Genetic factors*	Li-Fraumeni syndrome NF1 Beckwith-Wiedemann syndrome DICER1 syndrome Gorlin syndrome

Continued

Table 540.2 Known Risk Factors for Selected Childhood Cancers—cont'd

CANCER TYPE	RISK FACTOR	COMMENTS
Hepatoblastoma	Genetic factors*	Beckwith-Wiedemann syndrome Gardner syndrome; FAP
Malignant germ cell tumors	Cryptorchidism	Cryptorchidism is a risk factor for testicular germ cell tumors

*See Chapter 541 for additional information.
SCID, Severe combined immunodeficiency syndrome; NF1, neurofibromatosis type1; FAP, familial adenomatous polyposis; EBV, Epstein-Barr virus; PTLD, posttransplant lymphoproliferative disorder; WAGR, Wilms, aniridia, genitourinary anomalies, and retardation syndrome.
From Ripperger T, Bielack SS, Borkhardt A, et al. Childhood cancer predisposition syndromes – a concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology. *Am J Med Genet.* 2017;173:1017–1037, with data compiled from Porter CC, Druley TE, Erez A, et al. Recommendations for surveillance for children with leukemia-predisposing conditions. *Clin Cancer Res.* 2017;23(11):e14–e22.

Childhood cancer includes a diverse array of malignant tumors, termed "cancers," and nonmalignant tumors arising from disorders of genetic processes involved in control of cellular growth and development. Although many genetic conditions are associated with increased risks for childhood cancer, such conditions are believed to account for 8–10% of all occurrences (see Chapter 541). The most notable germline genetic conditions that impart susceptibility to childhood cancer are Li-Fraumeni *(P53)* syndrome, neurofibromatosis types 1 and 2, Down syndrome, Beckwith-Wiedemann syndrome, tuberous sclerosis, von Hippel-Landau disease, Noonan syndrome, ataxia-telangiectasia, and familial adenomatous polyposis syndrome and associated conditions (see Table 540.2). Consensus guidelines for surveillance screening in pediatric cancer predisposition syndromes were developed during a workshop of the Pediatric Cancer Working Group of the **American Association for Cancer Research** (AACR) and are available online through the AACR Open Access journal website (http://clincancerres.aacrjournals.org/content/23/11).

Compared with adult epithelial tumors, an extremely small fraction of pediatric cancers appears to be explained by known **environmental exposures** (see Table 540.2). Ionizing radiation exposure and several chemotherapeutic agents explain only a small number of pediatric cases (see Chapter 758). The association between fetal exposures and pediatric cancer is largely not established, with the exception of maternal diethylstilbestrol intake during pregnancy and subsequent vaginal adenocarcinoma in adolescent daughters. Environmental exposures that have been studied without convincing evidence for a causal role include nonionizing power frequency electromagnetic fields, pesticides, parental occupational chemical exposures, dietary factors, in vitro fertilization, and tobacco smoke exposure. Viruses associated with certain pediatric cancers include **polyomaviruses** (BK, JC, SV40) associated with brain cancer and **Epstein-Barr virus** (EBV) associated with certain subtypes of non-Hodgkin lymphoma.

The etiology of cancer in children still is poorly understood, and epidemiology studies demonstrate that the likely mechanisms are multifactorial, possibly resulting from potential interactions between genetic susceptibility traits and environmental exposures. Ongoing studies are investigating the role of **polymorphisms** of genes encoding enzymes, which function in the activation or metabolism of xenobiotics, protection of cells against oxidative stress, DNA repair, and/or immune modulation.

Curative therapy with chemotherapy, radiation, and/or surgery can adversely affect a child's development and result in serious long-term medical and psychosocial effects in childhood and adulthood. Potential adverse late effects include subsequent second malignancy, early mortality, infertility, reduced stature, cardiomyopathy, pulmonary fibrosis, osteoporosis, neurocognitive impairment, affective disorders, and altered social functioning (see Chapter 542). Much has been learned about the incidence of late effects from large, multisite cohort studies such as the **Childhood Cancer Survivor Study**, an ongoing study of medical and psychosocial outcomes in survivors, which has provided data for the development of clinical care guidelines for survivors (http://www.survivorshipguidelines.org).

Given the relative rarity of specific types of childhood cancer and the sophisticated technology and expertise required for diagnosis, treatment, and monitoring of late effects, all children with cancer should be treated with standardized clinical protocols in pediatric clinical research settings whenever possible. Promoting such treatment, the **Children's Oncology Group** is an international multi-institutional research consortium that facilitates cooperative clinical, biologic, and epidemiologic research in more than 200 affiliated institutions in the United States, Canada, and other countries (http://childrensoncologygroup.org/). Coordinated participation in such research trials has been a major factor in the increased survival for many children with cancer.

INFLUENCING THE INCIDENCE OF CANCER

There are only a few recognized environmental causes of childhood cancer that can be avoided or counteracted. One example is immunization against **hepatitis B**, which decreases the risk of hepatocellular carcinoma in adolescence and adulthood, and **human papillomavirus** vaccination, which prevents cervical cancer and HPV-positive oropharyngeal cancers and anal cancers. Associations between cumulative radiation exposure from common diagnostic radiologic tests such as CT scans and an increased risk of malignancy later in life are of great concern for pediatricians. Guidelines to ensure the safe clinical use of diagnostic imaging are being evaluated (http://www.imagegently.org/). An objective of pediatric medicine is *to teach children how to adopt healthy lifestyles to reduce their risk of cancer during adulthood,* such as avoiding tobacco, alcohol, high-fat diets, and obesity.

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Chapter 541

Molecular and Cellular Biology of Cancer

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Cancer is a complex of diseases arising from alterations that can occur in a wide variety of genes. Multiple pathogenic gene variants and other genetic aberrations, some germline but most acquired (somatic), are required for cells to become fully malignant. These genetic changes lead to alterations in normal cellular processes that control cell proliferation and survival, including signal transduction, cell-cycle control, DNA repair, cellular growth and differentiation, translational regulation, senescence, and apoptosis (programmed cell death).

GENES INVOLVED IN ONCOGENESIS

Two major classes of genes are implicated in the development of cancer: oncogenes and tumor-suppressor genes. **Protooncogenes** are cellular genes that are important for normal cellular function and code for various proteins, including transcription factors, growth factors, and growth factor receptors. These proteins are vital components in the networks of signal transduction that regulate cell growth, division, and differentiation. Protooncogenes can be altered to form **oncogenes**—genes that, when translated, can contribute to malignant transformation of a cell.

Oncogenes can be divided into five different classes based on their mechanisms of action. Changes in any of these normal cellular components can result in unchecked cell growth. Some oncogenes code for **growth factors** that bind to a receptor and stimulate the production of a protein. Other oncogenes code for **growth factor receptors**, which are proteins on the cell surface. When growth factors bind to a growth factor receptor, they can turn the receptor on or off. Pathogenic genetic variants or posttranslational modifications of the receptor can result in it being permanently turned on, with consequent unregulated growth. **Signal transducers** or effectors make up another class. Signal transducers are responsible for taking the signal from the cell surface receptor to the cell nucleus. **Transcription factors** are molecules that bind to specific areas of the DNA and control transcription. **MYC** and **MYCN** are examples of transcription factors that when activated by pathogenic variants or amplification cause overstimulation of cell division. The final class of oncogenes **interferes with apoptosis**, or programmed cell death. Cells that no longer respond to the signal to die can lead to uncontrolled cell proliferation.

The three main mechanisms by which protooncogenes are activated are **amplification**, **pathogenic variants**, and **translocation** or **interstitial deletion** (Table 541.1). *MYC* or *MYCN,* which code for proteins that regulate transcription, are examples of protooncogenes that are activated by amplification. Patients with neuroblastoma in which the *MYCN* gene is amplified 10-300–fold have a poorer clinical outcome. Point pathogenic genetic variants can also activate protooncogenes. The *NOTCH1* protooncogene codes for a membrane-bound receptor integral to cell fate and differentiation pathways during normal development that undergoes proteolytic cleavage on ligand-induced activation, so that the protein can enter the nucleus and activate target gene transcription. *NOTCH1* has pathogenic variants in approximately 75% of **T-cell acute lymphoblastic leukemias** (ALLs), resulting in a *constitutively activated* protein important in leukemogenesis.

The third mechanism by which protooncogenes become activated is chromosomal translocation or interstitial deletion. In some leukemias and lymphomas, transcription factor–controlling sequences are relocated adjacent to transcriptionally active T-cell receptors or immunoglobulin genes, resulting in dysregulated transcription of these genes and leukemogenesis. A prominent example are translocations that bring *c-MYC* under control of the immunoglobulin heavy-chain gene *(IGH)* or kappa *(IGκ)* or lambda *(IGλ)* light-chain genes in **Burkitt lymphoma**. Chromosomal translocations that join genes from two different chromosomes or interstitial deletions or inversions within a chromosome can also result in **fusion genes**; transcription of the fusion gene results in production of a chimeric protein with new and potentially oncogenic activity. Examples of cancers associated with fusion genes include the childhood solid tumors **Ewing sarcoma [t(11;22)]** and **alveolar rhabdomyosarcoma [t(2;13)** or **t(1;13)]**. These translocations result in novel messenger RNA transcripts that are useful as diagnostic markers. The best-described translocation in leukemia is the **Philadelphia chromosome t(9;22)**, which produces the BCR-ABL1 protein found in **chronic myelogenous leukemia** and specific subtypes of **ALL**. BCR-ABL1 is a constitutively active tyrosine kinase. In addition, the protein is localized to the cytoplasm instead of the nucleus, exposing the kinase to a new spectrum of substrates.

Alteration in the regulation of **tumor-suppressor genes** is another mechanism involved in oncogenesis. Tumor-suppressor genes are important regulators of cellular growth and apoptosis. They have been called *recessive* oncogenes because the inactivation of both alleles of a tumor-suppressor gene is typically required for expression of a malignant phenotype.

Knudson's "2-hit" model of cancer development was based on the eye tumor **retinoblastoma** developing at a significantly younger age in children with the familial versus the sporadic form of the disease, and that tumors were often multifocal in familial cases but were almost always unifocal in sporadic cases. Knudson postulated that sporadic cases of retinoblastoma required somatic pathogenic variants to inactivate both copies of a gene, whereas in familial cases, children must inherit an inactivated allele from one parent and consequently only require the somatic inactivation of the remaining normal allele. This hypothesis was confirmed 15 years later following the discovery of the ***RB*** tumor-suppressor gene.

Another major tumor-suppressor protein is **TP53**, which is known as the "guardian of the genome" because it detects the presence of chromosomal damage and prevents the cell from dividing until repairs have been made. In the presence of damage beyond repair, TP53 initiates apoptosis and the cell dies. More than 50% of all tumors have abnormal TP53 proteins. Pathogenic variants in the *TP53* gene are important in many cancers, including breast, colorectal, lung, esophageal, stomach, ovarian, and prostatic carcinomas, as well as gliomas, sarcomas, and some leukemias.

SYNDROMES PREDISPOSING TO CANCER

Several syndromes are associated with an increased risk of developing malignancies, which can be characterized by different mechanisms (Table 541.2). One mechanism involves the *inactivation of tumor-suppressor genes* such as *RB* in **familial retinoblastoma**. Interestingly, patients with retinoblastoma in which one of the alleles is inactivated throughout the patient's body are also at a very high risk for developing osteosarcoma. A familial syndrome, **Li-Fraumeni syndrome**, in which one *TP53* pathogenic variant allele is inherited, also has been described in patients who develop sarcomas, leukemias, adrenocortical carcinoma, and cancers of the breast, bone, lung, and brain. **Neurofibromatosis** (NF) is a condition characterized by the proliferation of cells of neural crest origin. NF patients are at a higher risk of developing nervous system tumors, breast cancer, leukemia, pheochromocytomas, and other tumors. NF is inherited in an autosomal dominant manner, although 50% of cases present without a family history and occur secondary to the high rate of spontaneous pathogenic variants of the *NF1* gene.

A second mechanism responsible for an inherited predisposition to develop cancer involves *defects in DNA repair.* Syndromes associated with an excessive number of broken chromosomes caused by repair defects include **Bloom syndrome** (short stature, photosensitive telangiectatic erythema), **ataxia-telangiectasia** (childhood ataxia with progressive neuromotor degeneration, ocular telangiectasias), and **Fanconi anemia** (short stature, skeletal and renal anomalies, pancytopenia). As a result of the decreased ability to repair chromosomal defects, cells accumulate

Table 541.1 Oncogene Activators of Pediatric Tumors

MECHANISM	CHROMOSOME	GENES	PROTEIN FUNCTION	TUMOR
Chromosomal translocation	t(9;22)	*BCR::ABL1*	Chimeric tyrosine kinase	CML, ALL
	t(1;19)	*TCF3 (E2A)::PBX1*	Chimeric transcription factor	ALL
	t(8;14)	*MYC::IGH*	Transcription factor	Burkitt lymphoma
	t(15;17)	*PML::RARA*	Chimeric transcription factor	APML
	11q23 and others (over 50 fusions partners)	*KMT2A (MLL)*	Regulation of gene expression	Infant leukemia, ALL, AML, treatment-related leukemias
	t(12;21)	*ETV6::RUNX1*	Chimeric protein	ALL
	t(2;13) or t(1;13)	*PAX3* or *PAX7::FOXO1*	Transcription factor	Rhabdomyosarcoma
	t(11;22)	*EWS::FLI1*	Transcription factor	Ewing sarcoma
Gene amplification	2p	*MYCN*	Transcription factor	Neuroblastoma
	7p	*EGFR*	Growth factor receptor, tyrosine kinase	Glioblastoma, lung cancer
Point pathogenic gene variant	1p or 12p	*NRAS* or *KRAS*	Guanosine triphosphatase	AML, ALL, JMML, rhabdomyosarcoma, neuroblastoma
	10q	*RET*	Tyrosine kinase	MEN2
	2p	*ALK*	Tyrosine kinase	Neuroblastoma
	9q	*NOTCH1*	Transmembrane receptor	ALL

ALL, Acute lymphoblastic leukemia; AML, acute myeloid leukemia; APML, acute promyelocytic leukemia; CML, chronic myelogenous leukemia; JMML, juvenile myelomonocytic leukemia; MEN2, multiple endocrine neoplasia, type 2.

Table 541.2 Familial or Genetic Susceptibility to Malignancy

DISORDER	TUMOR/CANCER	COMMENT
CHROMOSOMAL DELETION/ANEUPLOIDY SYNDROMES		
Chromosome 11p13 deletion syndrome	Wilms tumor	Also known as WAGR syndrome (Wilms tumor, aniridia, genitourinary abnormalities, mental retardation); deletion typically includes *WT1* gene
Chromosome 13q14 deletion syndrome	Retinoblastoma, sarcoma	Associated with intellectual disability, characteristic craniofacial abnormalities; deletion typically includes *RB1* gene
Trisomy 21	ALL, AML, AMKL, TMD	Risk of ALL is increased 20-fold, risk of AMKL is increased 500-fold; high cure rates; more prone to chemotherapy toxicity; AMKL associated with *GATA1* pathogenic variants
Klinefelter syndrome (47,XXY)	Breast cancer, extragonadal germ cell tumors	
Trisomy 8	Myeloid neoplasms	Most commonly mosaic trisomy 8
Monosomy 5 or 7	AML, MDS	
CHROMOSOMAL INSTABILITY SYNDROMES		
Xeroderma pigmentosum	Basal cell and squamous cell carcinomas, melanoma	Autosomal recessive; failure to repair UV-damaged DNA; *XP/POLH* pathogenic variants
Fanconi anemia	AML, MDS, rare head, neck, and skin tumors, GI and GU cancers	Autosomal recessive; chromosome fragility; positive diepoxybutane (DEB) test result; pathogenic variants in *FANCX* gene family (includes at least 21 members)
Bloom syndrome	AML, MDS, ALL, lymphoma, and solid tumors	Associated with growth deficiency, malar rash; autosomal recessive; increase sister chromatid exchange (SCE); pathogenic variants in *BLM* gene; member of the RecQ helicase gene (unwinds DNA)
Ataxia-telangiectasia	Lymphoma, leukemia, less often central nervous system and other solid tumors	Associated with progressive ataxia, oculocutaneous telangiectasias; autosomal recessive; sensitive to radiation-induced DNA damage; increased risk of treatment-related morbidity; biallelic pathogenic variant in *ATM* tumor-suppressor gene
Nijmegen breakage syndrome	Leukemia, lymphoma	Associated with microcephaly, characteristic facies, immunodeficiency; biallelic pathogenic variants in *NBN* gene
Werner syndrome (progeria)	Soft tissue sarcomas, osteosarcoma, melanoma	Associated with accelerated aging; autosomal recessive; pathogenic variants in *WRN* gene

Table 541.2 Familial or Genetic Susceptibility to Malignancy—cont'd

DISORDER	TUMOR/CANCER	COMMENT
IMMUNODEFICIENCY SYNDROMES		
Wiskott-Aldrich syndrome	Lymphoma, leukemia	Associated with thrombocytopenia, eczema, and recurrent infections; X-linked recessive; *WASP* pathogenic variants
X-linked lymphoproliferative syndrome (XLP)	B-cell lymphoproliferative disease, lymphomas, HLH	Associated with fulminant and often fatal EBV infection; X-linked; pathogenic variants in the *SH2D1A* gene
X-linked agammaglobulinemia (XLA)	Lymphoproliferative disorders, colorectal cancer	Associated with absence of B cells; X-linked; pathogenic variants in *BTK* gene
Severe combined immunodeficiency (SCID)	Leukemia, lymphoma	X-linked or autosomal recessive; pathogenic variants in *IL2RG* and *ADA* genes
SYNDROMES ARISING FROM PATHOGENIC VARIANTS IN TUMOR SUPRESSORS OR ONCOGENES		
Neurofibromatosis 1	Neurofibroma, optic glioma, acoustic neuroma, astrocytoma, meningioma, pheochromocytoma, rhabdomyosarcoma, MPNST, neuroblastoma, leukemias	Associated with café-au-lait macules, axillary/inguinal freckling, Lisch nodules; autosomal dominant; pathogenic variants in tumor-suppressor gene *NF1*
Neurofibromatosis 2	Bilateral acoustic neuromas, meningiomas	Autosomal dominant; pathogenic variants in tumor-suppressor gene *NF2*
Tuberous sclerosis	Facial angiofibromas, renal cell carcinoma, renal angiomyolipomas, myocardial rhabdomyoma	Autosomal dominant; pathogenic variants in tumor-suppressor gene *TSC1* or *TSC2*
Noonan syndrome	JMML, ALL, neuroblastoma, brain tumors	Associated with distinct facial features, short stature, and heart defects; autosomal dominant; caused by RAS/MAPK pathway pathogenic variants (most frequently *PTPN11*)
Gorlin-Goltz syndrome (nevoid basal cell carcinoma syndrome)	Multiple basal cell carcinomas, medulloblastoma	Associated with odontogenic keratocysts, skeletal and skin anomalies; autosomal dominant; pathogenic variants in *PTCH1 or SUFU* gene
Li-Fraumeni syndrome	Osteosarcoma, soft tissue sarcoma, acute leukemias, breast and brain cancer, adrenal cortical tumors	Autosomal dominant; pathogenic variants in *TP53* tumor-suppressor gene
Beckwith-Wiedemann syndrome (BWS)	Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma	Associated with macrosomia, macroglossia, hemihypertrophy, omphalocele; epigenetic/genomic alterations of chromosome 11p15
Von Hippel-Landau syndrome	Hemangioblastomas of the brain and retina, pheochromocytoma, renal cell carcinoma	Autosomal dominant; pathogenic variants of tumor-suppressor *VHL* gene
Multiple endocrine neoplasia, type 1 (Wermer syndrome)	Parathyroid, pancreatic islet cell and pituitary tumors	Associated with hyperparathyroidism, ZES; autosomal dominant; pathogenic variants in *MEN1* tumor-suppressor gene
Multiple endocrine neoplasia syndrome, type 2A (Sipple syndrome)	Medullary thyroid carcinoma, parathyroid tumors, pheochromocytoma	Associated with hyperparathyroidism; autosomal dominant; pathogenic variants in *RET* gene
Multiple endocrine neoplasia type 2B (multiple mucosal neuroma syndrome)	Mucosal neuromas, pheochromocytoma, medullary thyroid carcinoma	Associated with Marfan habitus, neuropathy; autosomal dominant; pathogenic variants in *RET* gene
Familial adenomatous polyposis (FAP)	Colorectal, thyroid, stomach and small intestinal cancer, hepatoblastoma	Associated with multiple colon polyps; autosomal dominant; pathogenic variants in *APC* gene
Juvenile polyposis syndrome	Colorectal, stomach, small intestinal and rectal cancer	Autosomal dominant; pathogenic variants in *BMPR1A* and *SMAD4* gene
Hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome)	Colorectal cancer, endometrial and stomach cancer, many other cancers	Autosomal dominant; pathogenic variants in DNA mismatch repair genes *MSH2, MLH1, PMS1, PMS2,* and *MSH6*
Turcot syndrome	Colorectal cancer, brain tumors (glioblastoma, medulloblastoma)	Autosomal dominant; pathogenic variants in *APC* or *MLH1* gene
Gardner syndrome	Colorectal cancer, other tumors similar to FAP	Subtype of FAP; autosomal dominant; pathogenic variants in *APC* gene
Constitutional mismatch repair deficiency syndrome (CMMRD)	Many different types of hematologic malignancies and brain and CNS tumors, colorectal carcinomas, and several other rare tumors	Autosomal recessive; homozygous germline pathogenic variants in the *MLH1, MSH2, MSH6,* or *PMS2* genes; tumors with very high variant burden, pathogenic variants of only one allele of the same genes results in Lynch syndrome
Peutz-Jeghers syndrome	Breast cancer, colorectal cancer, pancreatic cancer	Associated with hamartomatous polyps of GI tract; freckling of mouth, lips, fingers, and toes; autosomal dominant; pathogenic variants in *STK11* gene

Continued

Table 541.2 Familial or Genetic Susceptibility to Malignancy—cont'd

DISORDER	TUMOR/CANCER	COMMENT
Hereditary hemochromatosis	Hepatocellular carcinoma	Autosomal dominant; pathogenic variants in the *HFE* gene; malignancy associated with cirrhotic liver
Glycogen storage disease type 1 (von Gierke disease)	Hepatocellular carcinoma, liver adenomas	Autosomal recessive; pathogenic variants in *G6PC* or *SLC37A4* gene
Diamond-Blackfan anemia (DBA)	Colorectal and other GI cancers, AML, MDS, osteogenic sarcoma	Autosomal dominant; pathogenic variants in the small or large subunit-associated ribosomal protein genes (most often *RPS19*)
Shwachman-Diamond syndrome	AML, MDS	Associated with neutropenia, diarrhea, and failure to thrive; autosomal recessive; pathogenic variants in *SBDS* gene
DICER1 syndrome	Pleuropulmonary blastoma (PPB), cystic nephromas, ovarian Sertoli-Leydig tumors, multinodular goiter	Autosomal dominant; associated with pathogenic variants in *DICER1* gene
Familial neuroblastoma	Neuroblastoma	Autosomal dominant; pathogenic variants in *ALK* or *PHOX2B* gene
Hereditary paraganglioma-pheochromocytoma syndrome (PGL/PCC)	PGL, PCCs	Autosomal dominant; pathogenic variants in the mitochondrial enzyme succinate dehydrogenase protein family (*SDHA, B, C,* or *D*)
Severe congenital or cyclic neutropenia	AML, MDS	Associated with increased bacterial infections; typically autosomal dominant; pathogenic variants in *ELANE* or *HAX1* (Kostmann syndrome) gene
Rhabdoid predisposition syndrome 1 and 2	Atypical teratoid rhabdoid tumors, rhabdoid tumor of kidney, medulloblastoma, choroid plexus tumor	*SMARCB1/SMARCA4* tumor suppression genes
Predisposition to medulloblastoma	Medulloblastoma	*SUFU,* tumor suppression gene
Rothmund-Thomson syndrome	Skin, bone	*ANAPC1/RECQL4* stability gene
Multiple exostosis	Chondrosarcoma	*EXT1/EXT2,* tumor suppression gene
PTEN Hamartoma tumor syndromes: Cowden, Bannayan-Riley-Ruvalcaba, proteus, proteus-like syndromes	Breast, thyroid, renal, colon, melanoma	*PTEN, AKT1, PIK3CA, AKT3, PIK3R2, WWP1* germline or somatic pathogenic variants
BRCA1/2	Brain, solid tumors in children	Heterozygous pathogenic variants increase risk

ALL, Acute lymphoblastic leukemia; AML, acute myeloid leukemia; AMKL, acute megakaryocytic leukemia; CNS, central nervous system; EBV, Epstein-Barr virus; GI, gastrointestinal; GU, genitourinary; HLH, hemophagocytic lymphohistiocytosis; JMML, juvenile myelomonocytic leukemia; MAPK, mitogen-activated protein kinase; MDS, myelodysplastic syndrome; MPNST, malignant peripheral nerve sheath tumor; PTEN, phosphatase and tensin homolog; TMD, transient myeloproliferative disorder; UV, ultraviolet; ZES, Zollinger-Ellison syndrome.

abnormal DNA that results in significantly increased rates of cancer, especially leukemia. **Xeroderma pigmentosum** likewise increases the risk of skin cancer because of defects in repair to DNA damaged by ultraviolet light. **Constitutional mismatch repair deficiency syndrome** (CMMRD) is a disorder that results from the loss of both alleles of genes integral in repairing errors that occur during DNA replication, leading to the accumulation of multiple potentially pathogenic genetic alterations. These disorders display an autosomal recessive pattern.

The third category of inherited cancer predisposition is characterized by *defects in immune surveillance.* This group includes patients with **Wiskott-Aldrich syndrome**, severe combined immunodeficiency, common variable immunodeficiency, and the X-linked lymphoproliferative syndrome. The most common types of malignancy in these patients are lymphoma and leukemia. Cure rates for immunodeficient children with cancer are much poorer than for immunocompetent children with similar malignancies, suggesting a role for the immune system in cancer treatment as well as in cancer prevention.

Genome-wide association studies (GWAS) in a diverse array of childhood tumors, including ALL and neuroblastoma, have defined common **single nucleotide polymorphisms (SNPs)** in genes that are associated with cancer predisposition and collectively define regions of the genome that are critical in tumorigenesis. These alterations may occur in the coding or noncoding regions of the genome and typically lead to a relatively modest increase in cancer risk (2-10–fold over background) compared to the cancer susceptibility syndromes previously discussed, which may be associated with a lifetime risk of 50–100% of developing cancer. Furthermore, **whole genome sequencing** efforts across diverse pediatric cancers have identified that at least 8% of children who develop malignancy have a germline cancer-predisposing gene pathogenic variant. Many of these predisposing pathogenic variants occur in children without a family history of cancer or a known cancer predisposition syndrome.

OTHER FACTORS ASSOCIATED WITH ONCOGENESIS

Viruses

Several viruses have been implicated in the pathogenesis of malignancy. The association of the **Epstein-Barr virus (EBV)** with Burkitt lymphoma and nasopharyngeal carcinoma was identified more than 40 years ago, although EBV infection alone is not sufficient for malignant transformation. EBV is also associated with mixed cellularity and lymphocyte-depleted Hodgkin disease, as well as some T-cell lymphomas, which is particularly intriguing because EBV normally does not infect T lymphocytes. The most conclusive evidence for a role of EBV in lymphogenesis is the direct causal role of EBV for **B-cell lymphoproliferative disease** in immunocompromised persons, especially those with HIV infection or those receiving immunosuppression after organ

transplantation. **Human herpesvirus 8 (HHV-8)** is associated with the development of Kaposi sarcoma.

Children who are chronically infected with **hepatitis B virus** (hepatitis B surface antigen positive) have a 100-fold increased risk of developing **hepatocellular carcinoma**. In adults the latency period between viral infection and development of hepatocellular carcinoma approaches 20 years. However, in children who acquire the viral infection through perinatal transmission, the latency period can be as short as 6-7 years. The additional factors that are required for the malignant transformation of virally infected hepatocytes are not clear. **Hepatitis C virus** infection is another risk factor for hepatocellular carcinoma and is also associated with a subset of B-cell non-Hodgkin lymphomas such as splenic lymphoma.

Almost all cervical carcinomas are caused by **human papillomaviruses (HPVs)**. High-risk HPVs include types 16 and 18 but also types 31, 33, 34, 45, 52, and 58, which together cause >90% of cervical cancers. Vaccines against the major oncogenic subtypes are now available and are likely to save hundreds of millions of lives worldwide. The low-risk HPVs, including 6 and 11, which are commonly found in genital warts, are almost never associated with malignancies. Like other virus-associated cancers, the presence of HPV alone is not sufficient to cause malignant transformation. The mechanism by which the HPV-associated **oncoproteins HPV E6** and **E7** induce malignant transformation is thought to involve both the TP53 and the RB tumor-suppressor proteins, as well as other pathways that are critical in cell cycle progression, maintenance of telomerase and genomic stability, and apoptosis.

Radiation

Children who are exposed to ionizing radiation, either via environmental factors or from medical diagnostics or treatment, are also at an increased of developing cancer over their lifetime, especially leukemias, brain, breast, skin, or thyroid malignancies. This increased pediatric cancer risk is likely due both to the enhanced radiosensitivity of the developing organs of children and their longer postexposure life expectancy. Diagnostic imaging (e.g., CT scans) and therapeutic radiation for children with cancer are a major source of childhood radiation exposure. However, CT scan dose-reduction strategies, the increased use of MRI in pediatric medical centers, and the shift in therapeutic practice in oncology to proton radiotherapy all have been integral in lowering the exposure of children to ionizing radiation.

Genomic Imprinting

The development of cancer has also been linked to *genomic imprinting*, which is the selective inactivation of one of two alleles of certain genes depending on parental origin. **Beckwith-Wiedemann syndrome (BWS)** (see Chapter 113), the most commonly identified imprinting disorder, is an overgrowth syndrome characterized by macrosomia, macroglossia, hemihypertrophy, omphalocele, and renal anomalies that is also associated with an increased risk of Wilms tumor, hepatoblastoma, rhabdomyosarcoma, neuroblastoma, and adrenocortical carcinoma. This increased risk in developing cancer is directly associated with changes in the promoter methylation patterns (or loss of heterozygosity) of imprinted genes on chromosome 11p15.5. Normally, the maternally derived *IGF2* (insulin-like growth factor receptor 2) allele at this genomic locus is inactivated, thus suppressing *IGF2* expression. However, children with BWS show a gain of methylation in this promoter region, which allows for expression from both maternal and paternal *IGF2* alleles, leading to growth factor overexpression. Concurrently, the neighboring maternal *H19* gene (which encodes ncRNA and miRNA critical in growth suppression) is silenced by this hypermethylation, ultimately resulting in a progrowth phenotype and predisposition to tumor development.

Telomerase

Telomeres are a series of tens to thousands of TTAGGG DNA sequence repeats at the ends of chromosomes that are important for stabilizing the chromosomal ends and limiting breakage, translocation, and loss of DNA material. With DNA replication there is a progressive shortening of telomere length, which is a hallmark of cellular aging and acts as a replicative senescence signal. In a majority of cancers, **telomerase** (encoded by the *TERT* gene), an enzyme that adds telomeres to the ends of chromosomes, becomes activated, usually through pathologic variants in the *TERT* promoter. The telomerase-driven maintenance of telomere length in tumors enables unrestrained cellular proliferation by relieving a main checkpoint to cellular life span.

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Chapter 542

Principles of Cancer Diagnosis

Julia C. Meade, Erika D. Friehling, and A. Kim Ritchey

Childhood cancer is uncommon and can manifest with symptoms seen with nonmalignant illnesses. The challenge for the pediatrician is to be alert to the clues suggesting a diagnosis of cancer. In addition to the classic manifestations, any persistent, unexplained symptom or sign should be evaluated as potentially emanating from a cancerous or precancerous condition.

SIGNS AND SYMPTOMS

The symptoms and signs of cancer are variable and nonspecific in pediatric patients. The types of cancer that occur during the first 20 years of life vary dramatically as a function of age—more so than at any other comparable age range (see Chapter 540). Unlike cancers in adults, childhood cancers usually originate from the deeper, visceral structures and from the parenchyma of organs rather than from the epithelial layers that line the ducts and glands of organs and compose the skin. In children, dissemination of disease at diagnosis is common, and presenting symptoms or signs are often caused by systemic involvement. **Pain was one of the initial presenting symptoms in >50% of children with cancer in one study.** Infants and young children cannot express or localize their symptoms well.

Solid tumors may produce **mass effects** that are nonspecific, such as compression of the thoracic airways or superior vena cava (lymphoma), the optic chiasm and hypothalamic-pituitary region (craniopharyngioma), and the fourth ventricle (cerebellar astrocytoma). Another factor is the variability in the physiology and biology of the host related to growth and development during infancy, childhood, and adolescence.

The signs of cancer in children are often attributed to other causes before the malignancy is recognized. Delays in diagnosis are particularly problematic during late adolescence and are the result of a variety of factors prominent in this age-group, including historic lack and complexity of health insurance coverage.

Although there is no clearly established set of warning signs of cancer in young people, the most common cancers in children suggest some guidelines that may be helpful in early recognition of signs and symptoms of cancer (Table 542.1). Most of the symptoms and signs are not specific and might represent other possibilities in a differential diagnosis. Nonetheless, these clues encompass the common cancers of childhood and have been very useful in early detection.

PHYSICAL EXAMINATION

Physical examination findings in a child with malignancy are dependent on whether the cancer is systemic or localized. The cancers most common in children involve the lymphoid and hematopoietic system. When the bone marrow is compromised by malignancy (e.g., leukemia, disseminated neuroblastoma), typical findings include pallor from anemia; bleeding, petechiae, or purpura from thrombocytopenia or coagulopathy; cellulitis or other localized infection from leukopenia; and skin nodules (especially in infants) and hepatosplenomegaly

Table 542.1 Common Manifestations of Childhood Malignancies

	SIGNS AND SYMPTOMS	POTENTIAL ETIOLOGY AND POSSIBLE DIAGNOSIS
Constitutional/ systemic	Fever, persistent or recurrent infection, neutropenia	Bone marrow infiltration from leukemia, neuroblastoma
	Fever of unknown origin, weight loss, night sweats	Hodgkin and non-Hodgkin lymphoma
	Painless, persistent lymphadenopathy	Leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma, thyroid carcinoma
	Hypertension	Renal or adrenal tumor such as neuroblastoma, pheochromocytoma, or Wilms tumor
	Soft tissue mass	Ewing sarcoma, osteosarcoma, neuroblastoma, thyroid carcinoma, rhabdomyosarcoma, Langerhans cell histiocytosis
	Pain	Bone marrow involvement (ALL) or metastatic disease (neuroblastoma), primary bone tumors, Langerhans cell histiocytosis
Neurologic/ ophthalmologic	Headache with emesis, visual disturbances, ataxia, papilledema, cranial nerve palsies	Increased intracranial pressure from primary brain tumor or metastasis
	Leukocoria (white pupil)	Retinoblastoma
	Periorbital ecchymosis	Neuroblastoma
	Miosis, ptosis, heterochromia	Horner syndrome: compression of cervical sympathetic nerves from neuroblastoma
	Opsoclonus myoclonus, ataxia	Paraneoplastic syndrome from neuroblastoma
	Exophthalmos, proptosis	Mass effect from rhabdomyosarcoma, lymphoma, or Langerhans cell histiocytosis
Respiratory/ thoracic	Cough, stridor, pneumonia, tracheal-bronchial compression; superior vena cava syndrome	Anterior mediastinal mass due to germ cell tumor, non-Hodgkin lymphoma, or Hodgkin lymphoma
	Vertebral or nerve root compression; dysphagia	Posterior mediastinal mass from neuroblastoma or Ewing sarcoma
Gastrointestinal	Abdominal mass	Neuroblastoma, Wilms tumor, lymphoma
	Diarrhea	Vasoactive intestinal peptide secretion from neuroblastoma, ganglioneuroma
Hematologic	Pallor, anemia	Bone marrow infiltration from leukemia, neuroblastoma
	Petechiae, thrombocytopenia	Bone marrow infiltration from leukemia, neuroblastoma
Musculoskeletal	Bone pain, limp, arthralgia	Osteosarcoma, Ewing sarcoma, leukemia, metastatic neuroblastoma
Endocrine	Diabetes insipidus	Pituitary tumor, Langerhans cell histiocytosis
	Poor growth	Diencephalic syndrome from hypothalamic tumor
	Galactorrhea	Pituitary tumor/prolactinoma
	Precocious puberty	Germ cell tumor (cranial or extracranial), adrenocortical carcinoma, hepatoblastoma

ALL, Acute lymphoblastic leukemia
Adapted from Marcdante KJ, Kliegman RM, Jenson HB, et al., eds. *Nelson Essentials of Pediatrics*. 6th ed. Philadelphia: Saunders; 2011. p. 588.

from malignant leukocytosis. Abnormalities found in lymphatic malignancies include peripheral **adenopathy** (Fig. 542.1) and signs of superior vena cava syndrome from an anterior **mediastinal mass** (Fig. 542.2), including respiratory distress, and facial and neck plethora and edema. Enlargement of cervical lymph nodes is common in children, but when persistent, progressive, and painless, it often suggests **lymphoma**. Supraclavicular adenopathy suggests underlying malignancy.

Abnormalities of the central nervous system (CNS) that can indicate cancer include headaches, vomiting, cranial nerve palsies, ataxia, afebrile seizures, ptosis, decreased visual activity, neuroendocrine deficits, and increased intracranial pressure, which may be diagnosed by the presence of papilledema (Fig. 542.3). Any focal neurologic deficit in the motor or sensory system, especially a decrease in cranial nerve function, should prompt further investigation for malignancy.

Ophthalmologic presentation of malignancy includes a **white pupillary reflex** (Fig. 542.4) rather than the usual red reflection from incident light. A white pupillary reflex is essentially pathognomonic for retinoblastoma, although some benign conditions can mimic this finding. **Proptosis** can be produced by rhabdomyosarcoma, neuroblastoma, lymphoma, and Langerhans cell histiocytosis. In the few first years of life, Horner syndrome, periorbital ecchymosis, iris heterochromia, and opsoclonus-myoclonus all suggest a diagnosis of neuroblastoma.

Abdominal masses can be divided into upper and lower locations. Malignancies in the upper abdomen include Wilms tumor, neuroblastoma, and hepatoblastoma. Enlargement of the liver or spleen

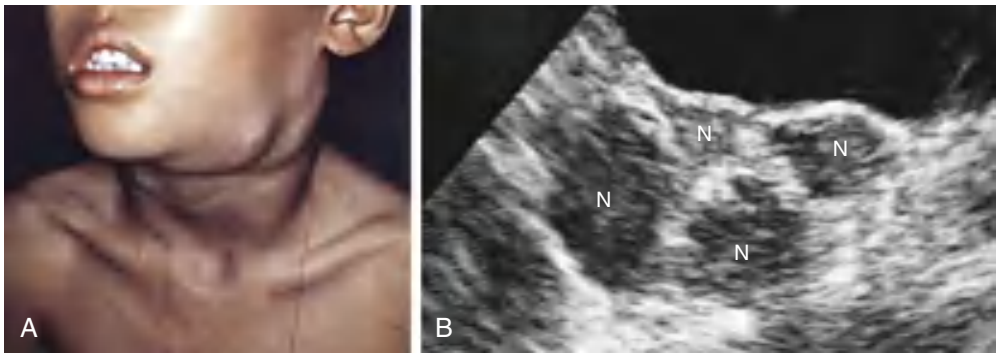

Fig. 542.1 Cervical lymphadenopathy. Manifestations on physical examination (**A**), and ultrasound examination (**B**). N, Abnormally enlarged lymph nodes. *(From Sinniah D, D'Angio GJ, Chatten J, et al. Atlas of Pediatric Oncology. London: Arnold; 1996.)*

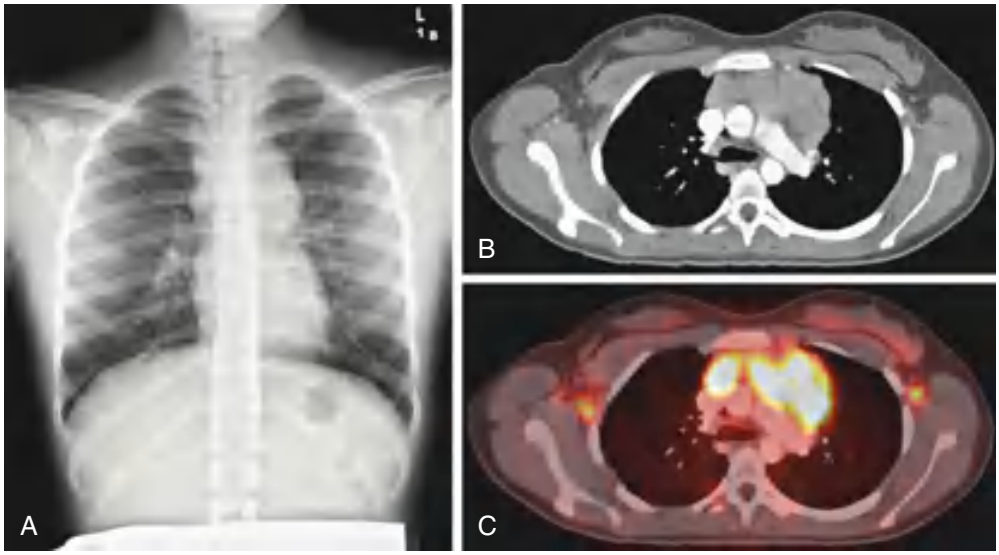

Fig. 542.2 Anterior upper mediastinal mass from non-Hodgkin lymphoma. **A,** Plain chest radiograph. **B,** CT scan. **C,** PET scan.

Fig. 542.3 Papilledema on fundoscopic examination. *(From Sinniah D, D'Angio GJ, Chatten J, et al. Atlas of Pediatric Oncology. London: Arnold; 1996.)*

Fig 542.4 White pupillary reflex in the left eye. *(From Sinniah D, D'Angio GJ, Chatten J, et al. Atlas of Pediatric Oncology. London: Arnold; 1996.)*

from leukemia can be mistaken for an upper abdominal mass. Lower abdominal masses non-Hodgkin lymphoma, neuroblastoma, germ cell tumors (ovarian), and sarcomas.

Rhabdomyosarcoma can occur as an extremity mass, particularly in adolescents, but also as a mass in the head and neck region (e.g., orbit, nasopharynx, and others). These tumors can be deceptively benign in

appearance, but as with all unexplained masses, require immediate attention. Sacrococcygeal masses in neonates are usually **teratomas**, which are usually benign but can undergo malignant transformation if not removed promptly. **Neuroblastoma** can present as "blueberry muffin" spots on the skin of neonates or as periorbital ecchymosis in older children.

AGE-RELATED MANIFESTATIONS

Because various types of cancer in children occur at specific ages, the physician should tailor the history and physical examination based on the age of the child. The **embryonal tumors**, including neuroblastoma, retinoblastoma, and hepatoblastoma usually occur during the first 2 years of life (see Fig. 540.4). The peak age for presentation of **Wilms tumor** is 3-4 years. Two thirds of patients with **rhabdomyosarcoma** present before age 6 with another smaller peak in adolescence. From 1-4 years of age, **acute lymphoblastic leukemia** peaks in incidence. **Brain tumors** have a peak incidence in the first decade of life. **Non-Hodgkin lymphomas** are uncommon earlier than 5 years of age but steadily increase thereafter. During adolescence, bone tumors, Hodgkin lymphoma, and gonadal and soft tissue sarcomas predominate. Hence, for infants and toddlers, special attention should be paid to the possibility of embryonal and intraabdominal tumors. Preschool-age and early school-age children showing compatible signs and symptoms should be specifically evaluated for **leukemia**. School-age children might present with lymphoma or with brain tumors. Adolescents require assessment for bone and soft tissue sarcomas and gonadal malignancies, as well as for Hodgkin lymphoma.

EARLY DETECTION

The prognosis of malignancy in children depends primarily on tumor type, extent of disease at diagnosis, and rapidity of response to treatment. Early diagnosis helps to ensure that appropriate therapy is given in a timely manner and thus optimizes the chances of cure. Because most physicians in general practice rarely encounter children with undiagnosed cancer, they should remember to investigate the possibility of malignancy, especially when they encounter an atypical course of a common childhood condition, unusual manifestations that do not fit common conditions, and any persistent symptom that defies diagnosis. It is also good practice to obtain a three-generation family pedigree with specific attention to a family history of cancer. A strong family history of cancer would suggest a referral for a cancer predisposition evaluation.

Delays in diagnosis are particularly likely in certain clinical situations. The cardinal symptom of both **osteosarcoma** and **Ewing sarcoma** is localized and usually persistent pain. Because these tumors occur during the second decade of life, a time of increased physical activity, patients often assume the pain results from trauma. Prompt radiologic evaluation can help confirm the diagnosis. **Lymphoma**, especially during adolescence, often manifests as an anterior mediastinal mass. Symptoms such as chronic cough, unexplained shortness of breath, or "new-onset asthma" are typical with this presentation and are often overlooked. Tumors of the nasopharynx or middle ear can mimic infection. Prolonged, unexplained ear pain, nasal discharge, retropharyngeal swelling, and trismus should be investigated as possible signs of malignancy.

Early symptoms of **leukemia** may be limited to prolonged or unexplained low-grade fever. Bone and joint pain may present with refusal to walk. Blood counts with abnormalities in two or more cell lines might indicate the need for bone marrow examination, even when leukemic blast cells are not seen in the blood smear (see Table 542.1).

Mass screening for children with malignancy is not feasible. A screening program to detect early-stage neuroblastoma was successful in documenting more cases of the disease but had no impact on overall outcome. However, certain children are at increased risk for cancer and require an individualized plan to ensure early detection of malignancy. Select examples include children with certain chromosome abnormalities, such as Down syndrome, Klinefelter syndrome, and WAGR syndrome (Wilms tumor, *a*niridia, *g*enital abnormalities, mental *r*etardation); children with overgrowth syndromes, such as Beckwith-Wiedemann syndrome or hemihypertrophy; and children with certain inherited single-gene disorders, including hereditary retinoblastoma, Li-Fraumeni syndrome, familial adenomatous polyposis, and neurofibromatosis (see Table 541.2).

ENSURING THE DIAGNOSIS

When a malignant neoplasm is suspected, the immediate goal is to confirm the diagnosis. A tentative diagnosis can often be established based on the patient's age, symptoms, and location of masses. Selected imaging techniques and tumor markers can facilitate the diagnostic approach (Table 542.2 and Fig. 542.5). Especially when a solid tumor is present, the pediatric oncologist, surgeon, and pathologist should work as a team to determine the site of biopsy, amount of tissue required, and whether percutaneous image-guided biopsy, incisional biopsy, or excisional biopsy and tumor resection are indicated. For select situations, at the time of the initial diagnostic procedure, plans for bone marrow aspiration and biopsy and placement of central venous access may be appropriate.

Pathologic evaluation of pediatric malignancies requires appropriate handling of tissue so that multiple different techniques can be used to obtain a diagnosis. It is important that some fresh tissue not be placed in formalin. Along with routine light microscopy, pathologic evaluation may include immunochemistry, flow cytometry, cytogenetics, molecular genetic studies (e.g., fluorescence in situ hybridization, tumor whole exome sequencing, and evaluation of circulating tumor genes with cell-free DNA detection in blood). Additional technologies include DNA microarray analysis and cancer genome sequencing that can identify specific gene expression patterns and sequences in tumors, which can facilitate more accurate classification and treatment.

STAGING

Once a specific diagnosis is confirmed, studies to define the extent of the malignancy are necessary to determine prognosis and treatment. Table 542.2 outlines the minimum evaluation required for common pediatric malignancies. In addition, for many tumors (e.g., Wilms tumor, neuroblastoma, rhabdomyosarcoma), a surgical staging system is used. Surgical stage can be determined at the time of the initial diagnostic procedure or subsequently. For example, a patient who has abdominal surgery for possible Wilms tumor should have careful evaluation and biopsy of all adjacent lymph nodes. A child with rhabdomyosarcoma can require a subsequent biopsy of sentinel lymph nodes as determined by scintigraphy or dye injection adjacent to the primary tumor. The pathologist facilitates staging by examining margins of the specimen to determine residual tumor.

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Table 542.2 Workup of Common Pediatric Malignancies to Assess Primary Tumor and Potential Metastases

MALIGNANCY	BONE MARROW ASPIRATE OR BIOPSY	CHEST X-RAY FILM	CT SCAN	MRI	PET SCAN	BONE SCAN	CSF ANALYSIS	SPECIFIC MARKERS	OTHER TESTS
Leukemia	Yes (includes flow cytometry, cytogenetics, molecular studies)	Yes	—	—	—	—	Yes	—	—
Non-Hodgkin lymphoma	Yes (includes flow cytometry, cytogenetics, molecular studies)	Yes	Yes	—	Yes	Yes (selected cases)	Yes	—	—
Hodgkin lymphoma	Yes (in advanced stage)	Yes	Yes	—	Yes	—	—	—	—
CNS tumors	—	—	—	Yes	—	—	Yes (selected cases)	Yes (selected cases)	—
Neuroblastoma	Yes (includes cytogenetics, molecular studies)	—	Yes	Yes	—	—	—	Urine VMA, HVA	MIBG or PET scan; bone x-rays
Wilms tumor	—	Yes	Yes	—	—	—	—	—	—
Rhabdomyo-sarcoma	Yes	Yes	Yes	Yes (select sites)	—	Yes (selected cases)	Yes (for paramenin-geal tumors only)	—	—
Osteosarcoma	—	Yes	Yes (of chest)	Yes (for primary tumors)	—	Yes (selected cases)	—	—	—
Ewing sarcoma	Yes (selected cases)	Yes	Yes (of chest)	Yes (for primary tumors)	Yes	Yes (selected cases)	—	—	—
Germ cell tumors	—	Yes	Yes	Consider MRI of brain	—	—	—	AFP, HCG	—
Liver tumors	—	Yes	Yes	—	—	—	—	AFP, HCG	—
Retinoblastoma	Selected cases	—	Yes	Yes (includes brain)	—	Yes (selected cases)	Selected cases	—	—

AFP, α-Fetoprotein; CNS, central nervous system; CSF, cerebrospinal fluid; HCG, human chorionic gonadotropin; HVA, homovanillic acid; MIBG, metaiodobenzylguanidine; VMA, vanillylmandelic acid.

Modified from Marcdante KJ, Kliegman RM, Jenson HB, et al., eds. *Nelson Essentials of Pediatrics*. 6th ed. Philadelphia: Saunders; 2011. p. 589.

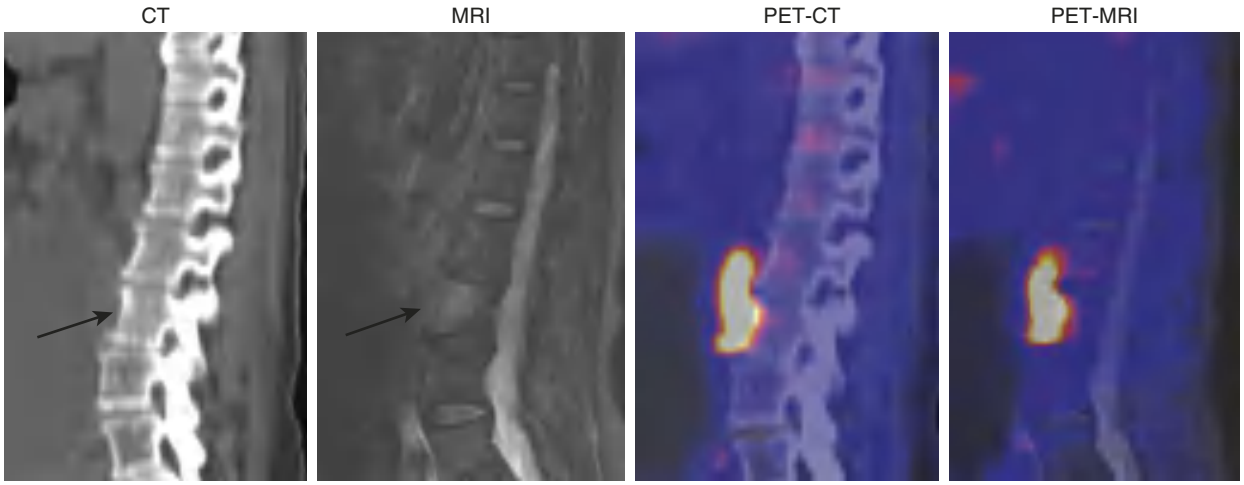

Fig. 542.5 Neuroblastoma PET/CT sagittal fused image demonstrated partial mis-registration of avid disease, occult on the low-dose noncontrast CT. PET/MRI sagittal fused image demonstrated correct image co-registration with corresponding T2-weighted hyperintensity in L3 vertebra, confirming L3 marrow involvement, delineated on the MR and not on the CT *(arrow). (From Sepehrizadeh T, Jong I, DeVeer M, Malhotra A. PET/MRI in paediatric disease. Eur J Radiol. 2021;144:109987. Fig. 2.)*

Chapter 543

Principles of Cancer Treatment

Erika D. Friehling, Julia C. Meade, Archie Bleyer, and A. Kim Ritchey

Treatment of children with cancer begins with an absolute requirement for the *correct diagnosis* (including subtype), proceeds through accurate and thorough *staging* of the extent of disease and determination of *prognostic subgroup*, provides appropriate multidisciplinary and usually multimodal therapy, and requires assiduous evaluation for possible recurrent disease and late effects of the disease and the therapies rendered. Throughout treatment, every child with cancer should have the benefit of the expertise of specialized teams of providers of pediatric cancer care, including pediatric oncologists, pathologists, radiologists, surgeons, radiation oncologists, nurses, and support staff, including nutritionists, social workers, psychologists, pharmacists, other medical specialists, and teachers trained to work with seriously ill children.

The best chance for cure of cancer is during the initial course of treatment; the cure rates for patients with recurrent disease are much lower than those for patients with primary disease. All patients with cancer should be referred to an appropriate specialized center as soon as possible when the diagnosis of cancer is suspected. All such centers in North America are identified on the **Children's Oncology Group** website (http://www.childrensoncologygroup.org) and on the **National Cancer Institute** (NCI) cancer trials website (http://www.clinicaltrials.gov). In the United States, the NCI's Clinical Trials Cooperative Groups Program is associated with a >80% reduction in the incidence of mortality from childhood cancer over 40 years despite an overall increase in cancer incidence during this interval (Fig. 543.1). After what appeared to be a plateau in the rate of decline in mortality in the early 2000s, there is evidence that the mortality rate continues to decline. Notably, a greater decline in mortality has been seen in the adolescent and young adult population when compared with children <15 years old, reversing prior trends (Fig. 543.2). The most current information on treatment of all types of childhood cancer is available in the PDQ (Physician Data Query) on the NCI website (http://www.cancer.gov/cancertopics/pdq/pediatrictreatment).

DIAGNOSIS AND STAGING

Accurate diagnosis and staging of the extent of disease are imperative because the nature of therapy depends strongly on the type of cancer. In addition, **prognostic subgroups** based on the stage of disease have been established for most cancers that occur in children. Accordingly, children with a better prognosis are treated with less intensive therapy, including lower doses of chemotherapy or radiation therapy, a shorter duration of treatment, or elimination of at least one treatment modality (radiation therapy, chemotherapy, surgery). Accurate staging thus reduces the risk of excessive acute toxicity and long-term effects of therapy in patients whose prognosis indicates that less therapy is required for cure. **Overtreatment** of patients with a more favorable prognosis is a definite risk if the patient is not referred to a cancer treatment center. Conversely, **undertreatment** also is a clear risk if the diagnosis and stage are not correct, resulting in a compromise of an otherwise high potential for cure.

Diagnostic imaging is a critical phase of evaluation in most children with solid tumors. MRI, CT, ultrasonography, scintigraphy (nuclear medicine scans), positron emission tomography (PET), and spectroscopy, as appropriate, all serve a clear purpose in the evaluation of children with cancer, not only before treatment to determine the extent of disease and the appropriate therapy but also during follow-up to determine whether the therapy was effective (see Chapter 542). In addition, response to treatment as determined by imaging techniques is being increasingly used to guide changes in the therapy.

Expertise in pathology and laboratory medicine provides critical diagnostic support and guides therapy in most children with cancer. Relatively noninvasive methods of obtaining tumor tissue such as percutaneous image-guided biopsy can be performed in pediatric centers with appropriate expertise in diagnostic imaging, interventional radiology, cytology, and anesthesia support. Sentinel node mapping is helpful in the staging of some children's cancers. Determining the adequacy of surgery by evaluating frozen sections of the surgical margins for tumor cells is essential in many tumor operations.

A MULTIMODAL, MULTIDISCIPLINARY APPROACH

Many pediatric subspecialists are involved in the evaluation, treatment, and management of children with cancer, including provision of primary therapy and supportive care services (Fig. 543.3). More than two of the primary modalities are often used together, with chemotherapy the most widely used, followed in order of use by surgery, radiation therapy, and biologic agent therapy (Fig. 543.4).

The **leukemias** that occur in childhood usually are managed with chemotherapy alone, with a small proportion of patients receiving cranial radiation therapy to prevent or treat overt central nervous system (CNS) leukemia. Children with **non-Hodgkin lymphoma** also are treated with chemotherapy alone, except for radiation therapy for CNS involvement. Localized therapy with surgery or irradiation, or both, is an important component of treatment of most solid tumors, including **Hodgkin lymphoma**, but systemic multiagent chemotherapy usually is necessary because tumor dissemination generally is present even if undetectable. Chemotherapy alone usually is not adequate to eradicate gross residual tumors. Therefore it is not unusual for children with malignant tumors to require treatment with all three modalities (see Fig. 543.4). Unfortunately, most treatments that are effective in children with cancer have a narrow therapeutic index (a low ratio of efficacy to toxicity). The acute and late effects of these treatments can be minimized but not entirely avoided.

Biologic agent therapy is an important modality in a few childhood cancers (see Fig. 543.4). This type of treatment generally refers to immunotherapy, biologic response modifiers, or endogenously occurring molecules that have therapeutic effects in supraphysiologic doses. Examples are retinoic acid therapy in acute promyelocytic leukemia, monoclonal antibody therapy for neuroblastoma and certain non-Hodgkin lymphomas, tyrosine kinase inhibitors such as imatinib mesylate for chronic myelogenous and Philadelphia chromosome–positive leukemias, and radioactive metaiodobenzylguanidine (MIBG) therapy for neuroblastoma. In addition, immune therapy directed at tumor cell antigens with modification of T-cell receptors (TCRs) or chimeric antigen receptors (CARs) have improved survival in patients with chemotherapy-resistant diseases (leukemia, lymphoma) and have shown promise in solid tumors and brain tumors.

Chemotherapy is used more widely in children than in adults because children better tolerate the acute adverse effects, and the malignant diseases that occur in childhood are more responsive to chemotherapy than are malignant diseases of adults. **Radiation therapy** is used sparingly in children because of its association with growth impairment and with the development of second malignant neoplasms.

Whenever possible, treatment is given on an outpatient basis. Children should remain living at home and in school as much as possible throughout treatment. Increasingly, pediatric cancer therapies are being administered to ambulatory patients, with the advent of such innovations as programmable infusion pumps, oral chemotherapeutic regimens, early discharge from hospital with intensive outpatient supportive care, and home healthcare services. Some patients miss a considerable amount of school in the first year after diagnosis because of the intensity of therapy or its adverse effects and the ensuing complications of the disease or therapy. Tutoring should be encouraged so that children do not fall behind in their schooling; counseling should be provided as appropriate. In-hospital school services should be provided for patients who must spend much of their time as inpatients receiving therapy for disease or for managing adverse effects. Upon completion of therapy, referral for pediatric neuropsychiatric testing in a specialized center is often recommended to ensure they are well supported in their education.

De novo or acquired resistance to chemotherapy and radiation therapy remains an obstacle to cure. Ongoing discoveries of molecular and cellular

mechanisms that explain the cancer process have led to increasingly specific antineoplastic therapies, generally referred to as **molecularly targeted therapies**. Their most prominent feature is a relative lack of normal tissue toxicity, such that the additional therapeutic benefit occurs with minimum additional toxicity. Many biologic agent therapies, such as imatinib and selumetinib, fall into this category (Table 543.1). **Complementary** and **alternative** therapies are increasingly being provided by parents to their children with cancer, with or without knowledge of the medical professionals entrusted with the child's care (see Chapter 7). Collaboration with the family and a pharmacist specializing in chemotherapy can minimize unwanted interactions from supplements.

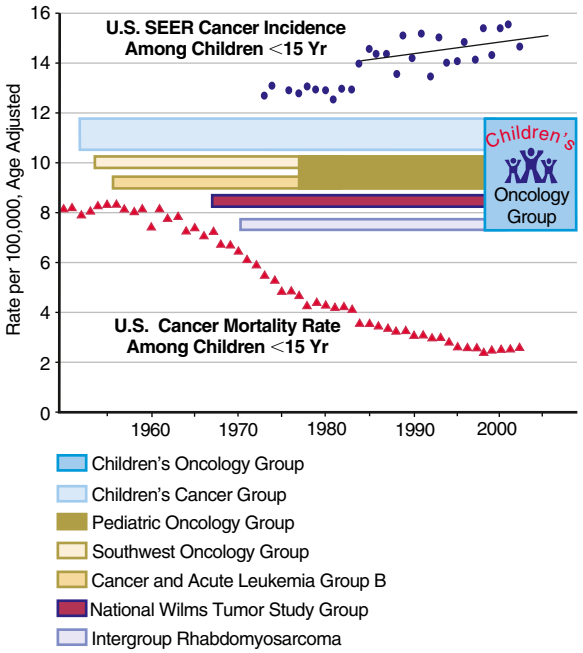

Fig. 543.1 Reduction in the national cancer mortality rate among children younger than 15 years of age *(triangles)* in the United States as a direct consequence of the National Cooperative Group Program sponsored by the National Cancer Institute and compared with the rising incidence of cancer before age 15 *(circles)*. The *horizontal bars* indicate the duration of the existence of the national pediatric cancer cooperative groups, beginning with the Children's Cancer Group in 1955. Other groups are the Pediatric Oncology Group, which was derived from the Pediatrics Divisions of the Southwest Oncology Group and the Cancer and Acute Leukemia Group B; the National Wilms Tumor Study Group; and the Intergroup Rhabdomyosarcoma Study Group. In 2000 the four pediatric cooperative groups merged into the Children's Oncology Group. *(Incidence and mortality rate data from Ries LAG, Eisner MP, Kosary CL, et al., eds. SEER Cancer Statistics Review, 1975–2002. Bethesda, MD: National Cancer Institute; http://seer.cancer.gov/csr/1975_2002/, based on November 2004 SEER [Surveillance, Epidemiology, and End Results] data submission. The mortality rate data are national rates, and the incidence data are derived from the SEER program, representing approximately 15% of the United States. The most current information on treatment of all types of childhood cancer is available in the PDQ [Physician Data Query] on the NCI website, http://www.cancer.gov/cancertopics/pdq/pediatrictreatment.)*

DISCUSSING THE TREATMENT PLAN WITH THE PATIENT AND FAMILY

The diagnostic and treatment plan must be carefully explained to parents and, if the child is old enough to understand, to the patient. Children should be given as much information as they can understand and would be useful to them. All questions should be answered openly and honestly. Effects of treatment, such as loss of hair during chemotherapy, the possible need to amputate a limb, and possible temporary or permanent functional impairment, must be anticipated and fully discussed. The possibility and probability of death from cancer should be covered in an age-appropriate manner. It usually is necessary to repeat explanations several times before

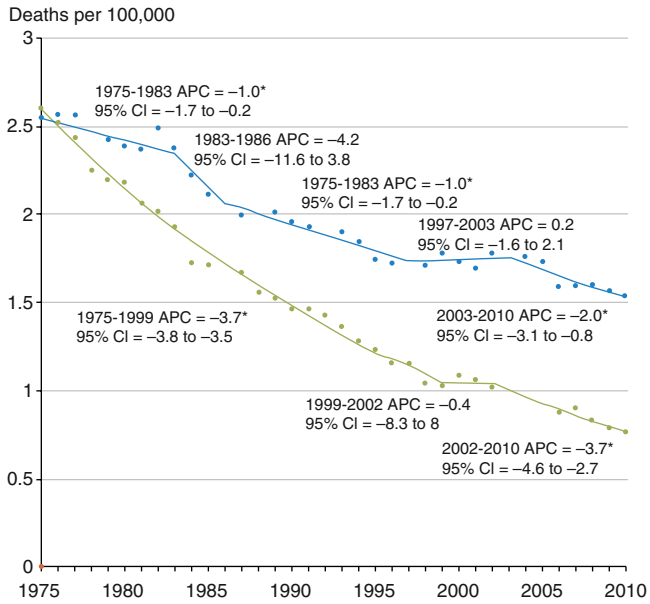

Fig. 543.2 Age-adjusted mortality trends for all malignant cancers among children <20 yr old in the United States from 1975 through 2010, along with annual percentage changes (APCs) for join point segments. *Asterisk* indicates that the slope of the join point segment is statistically different from zero ($p < .05$). The *green line* indicates leukemias and lymphomas, and the *blue line* indicates all other cancer sites; CI, confidence interval. *(From Smith MA, Altekruse SF, Adamson PC, et al. Declining childhood and adolescent cancer mortality. Cancer. 2014;120:2497–2506.)*

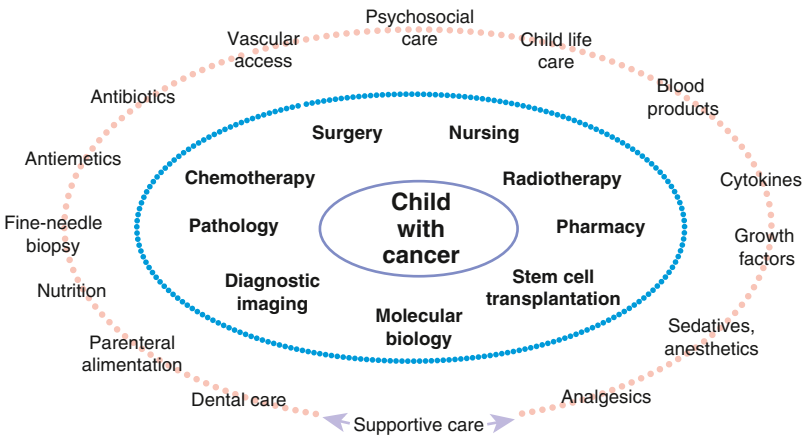

Fig. 543.3 Multidisciplinary care of children with cancer. The *inner circle* designates primary modalities, and the *outer ring* identifies supportive care elements to which all children with cancer have access.

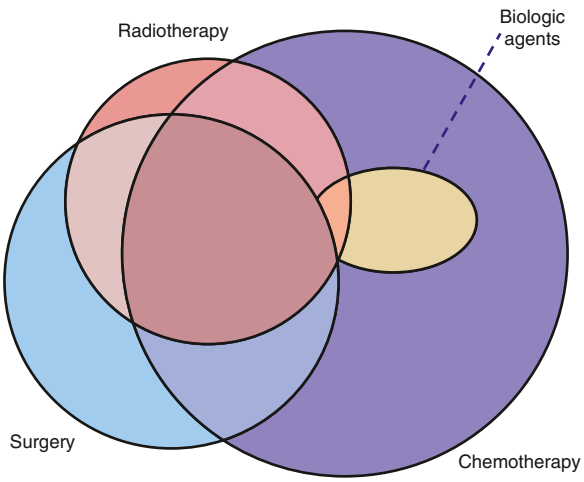

Fig. 543.4 The primary modalities of therapy used in the treatment of children with cancer. The relative sizes of the circles designate the approximate proportion of overall role in the management of pediatric cancers.

Table 543.1 Tyrosine Kinase Inhibitors and Monoclonal Antibodies for Pediatric Cancers

AGENT	TARGET	MALIGNANCY
Imatinib	BCR-ABL	CML Philadelphia chromosome–positive ALL
	PDGFRα cKIT	Hypereosinophilic syndrome Gastrointestinal stromal tumor
Dasatinib, nilotinib	BCR-ABL	CML Philadelphia chromosome–positive ALL
Brentuximab	CD30	Hodgkin lymphoma
Rituximab	CD20	Non-Hodgkin lymphoma
Selumetinib	MAPK/MEK	Plexiform neurofibroma Low-grade glioma
Bevacizumab	VEGFR-1, -2	Low-grade glioma
Crizotinib, lorlatinib	ALK/ROS	Neuroblastoma Anaplastic large cell lymphoma Inflammatory myofibroblastic tumor
Dinutuximab	GD2	Neuroblastoma
Blinatumomab	CD19	Leukemia Lymphoma

ALL, Acute lymphoblastic leukemia; CML, chronic myelogenous leukemia.

distraught family members fully understand. Throughout treatment, parents, patients, siblings, and medical staff will all need help in expressing feelings of anxiety, depression, guilt, and anger. The pediatrician, pediatric oncologist, and nurses should call on experienced professionals, including pediatric social workers, child psychologists and psychiatrists, child life specialists, and teachers with special expertise in managing students with cancer, to assist when needed.

TREATMENTS

Chemotherapy

The most widely used modality in pediatric cancer therapy is chemotherapy (see Fig. 543.4). Therapy usually involves a combination of drugs with different mechanisms of action and nonoverlapping toxicities. Sequential single-drug therapy rarely results in complete responses, and partial responses usually are infrequent, transient, and grow progressively shorter in duration with each drug used. Most of the cytotoxic drugs for childhood cancer are selected from several classes of agents, including alkylating agents, antimetabolites, antibiotics, hormones, plant alkaloids, and topoisomerase inhibitors (Table 543.2). The increased metabolic and cell cycle activity of malignant cells makes them more susceptible to the cytotoxic effects of these types of agents (Fig. 543.5).

Because most antineoplastic agents are cell cycle dependent, their adverse effects usually are related to the proliferation kinetics of individual cell populations. Most susceptible are tissues or organs with high rates of cell turnover: bone marrow, oral and intestinal mucosa, epidermis, liver, and spermatogonia. The most common acute adverse effects are **myelosuppression** (with neutropenia and thrombocytopenia the most problematic), immunosuppression, nausea and vomiting, hepatic dysfunction, upper and lower gastrointestinal mucositis, dermatitis, and alopecia. Fortunately, the tissues affected also recover relatively quickly, so that the acute adverse effects are usually reversible. Life-threatening effects of many chemotherapy agents include severe neutropenia with infection, fungemia, or fungal pneumonia as a result of immunosuppression, and septicemia, not infrequently linked to indwelling intravascular devices (Table 543.3; see Chapters 223 and 224). **Cardiomyopathy** caused by anthracyclines (e.g., doxorubicin, daunorubicin) and **renal failure** from platinum-containing agents also may be life-threatening or disabling. Assistance from a supportive care team can also provide safe and effective support for toxicities associated with chemotherapy, such as pain and nausea.

Least susceptible to chemotherapy and radiation therapy are cells that do not replicate or that replicate slowly, such as neurons, muscle cells, connective tissue, and bone. Children are not exempt from toxicities of these tissues, probably because they are still undergoing proliferation, although at a slower pace than other tissues, during growth and growth spurts.

Physically, children can endure the acute adverse effects of chemotherapy better than adults can in many ways. The maximum tolerated dosage in children, when expressed based on body surface area or body weight, typically is greater than that in adults. A comparison of anticancer drugs tested in phase I trials in both adult and pediatric patients showed that the maximum tolerated dosage in children was greater than that in adults for 70% of the agents, equal to that in adults for 15%, and less than the adult dose for only 15% of the agents. For all the drugs that were compared, the mean pediatric maximum tolerated dosage was greater than the adult mean.

Pharmacogenomics

Interindividual variability in the response to similar doses of a given medication is an inherent characteristic of both adult and pediatric populations. Variations in the germline genome can lead to differences in drug response at the level of individual patients. **Pharmacogenomics** represents the combination of pharmacology and genomics and is defined as the broader application of genetic testing strategies to identify factors predictive of drug efficacy and risk of adverse drug reactions.

Thiopurine *S*-methyltransferase **(TPMT)** is an enzyme that catalyzes the methylation of the chemotherapy 6-mercaptopurine (6MP) used in the treatment of acute lymphoblastic leukemia (ALL). To exert its cytotoxic effects, 6MP requires metabolism to thioguanine nucleotides, and this reaction is prevented by TPMT. Of the general population, 89% has normal TPMT activity, 11% has intermediate activity, and 0.3% has low activity. In patients with low or intermediate activity variants of TPMT, there is accumulation of cytotoxic thioguanine nucleotides (Fig. 543.6). These patients are at increased risk for **severe myelosuppression** if treated with routine doses of thiopurines and require a 10-15–fold reduction in dose to minimize this risk.

TPMT genotype is not the only determinant of intolerance to thiopurines; genetic variation in *NUDT15,* a nucleotide diphosphatase that reduces the incorporation of thioguanine into DNA, may also be involved. Reduction or loss of *NUDT15* activity results in increased cytotoxicity. Patients who have inherited reduced-function *NUDT15* alleles tolerate thiopurine doses that are much lower (10%) than normal. It is reasonable to expect that both *TPMT* and *NUDT15* genotypes will need to be considered for individualized thiopurine treatment, identifying patients who will benefit from specific dosing regimens and those who will be at risk for short-term and long-term toxicities.

Immunotherapy

Tumor-directed immune therapies employ and enhance the patient's immune system to kill malignant cells. Tumor antigen–specific monoclonal antibodies have been incorporated into the standard therapy of

Table 543.2 Common Chemotherapeutic Agents Used in Pediatric Cancer

DRUG	MECHANISM OF ACTION OR CLASSIFICATION	INDICATION(S)	ADVERSE REACTIONS (PARTIAL LIST)	COMMENTS
Methotrexate	Folic acid antagonist; inhibits dihydrofolate reductase	ALL, non-Hodgkin lymphoma, osteosarcoma, Hodgkin lymphoma, medulloblastoma	Myelosuppression, mucositis, stomatitis, dermatitis, hepatitis With long-term administration, osteopenia and bone fractures With high-dose administration, renal and CNS toxicity With intrathecal administration, arachnoiditis, leukoencephalopathy, and leukomyelopathy	Systemic administration may be PO, IM, or IV; also may be administered intrathecally Plasma methotrexate levels must be monitored with high-dose therapy and when low doses are administered to patients with renal dysfunction, and leucovorin rescue applied accordingly
6-Mercaptopurine (Purinethol)	Purine analog; inhibits purine synthesis	ALL	Myelosuppression, hepatic necrosis, mucositis; allopurinol increases toxicity	Allopurinol inhibits metabolism
Cytarabine (cytosine arabinoside; Ara-C)	Pyrimidine analog; inhibits DNA polymerase	ALL, AML, non-Hodgkin lymphoma, Hodgkin lymphoma	Nausea, vomiting, myelosuppression, conjunctivitis, mucositis, CNS dysfunction With intrathecal administration, arachnoiditis, leukoencephalopathy, and leukomyelopathy	Systemic administration may be PO, IM, or IV; may also be administered intrathecally
Cyclophosphamide (Cytoxan)	Alkylates guanine; inhibits DNA synthesis	ALL, non-Hodgkin lymphoma, Hodgkin lymphoma, soft tissue sarcoma, Ewing sarcoma, Wilms tumor, neuroblastoma	Nausea, vomiting, myelosuppression, hemorrhagic cystitis, pulmonary fibrosis, inappropriate ADH secretion, bladder cancer, anaphylaxis	Requires hepatic activation and thus is less effective in presence of liver dysfunction Mesna prevents hemorrhagic cystitis
Ifosfamide (IFEX)	Alkylates guanine; inhibits DNA synthesis	Non-Hodgkin lymphoma, Wilms tumor, soft tissue sarcoma	Nausea, vomiting, myelosuppression, hemorrhagic cystitis, pulmonary fibrosis, inappropriate ADH secretion, CNS dysfunction, cardiac toxicity, anaphylaxis	Mesna prevents hemorrhagic cystitis
Doxorubicin (Adriamycin), daunorubicin (Cerubidine), and idarubicin (Idamycin)	Binds to DNA, intercalation	ALL, AML, osteosarcoma, Ewing sarcoma, Hodgkin lymphoma, non-Hodgkin lymphoma, neuroblastoma	Nausea, vomiting, cardiomyopathy, red urine, tissue necrosis on extravasation, myelosuppression, conjunctivitis, radiation dermatitis, arrhythmia	Dexrazoxane reduces risk of cardiotoxicity
Dactinomycin	Binds to DNA, inhibits transcription	Wilms tumor, rhabdomyosarcoma, Ewing sarcoma	Nausea, vomiting tissue necrosis on extravasation, myelosuppression, radiation dermatitis, mucosal ulceration	
Bleomycin (Blenoxane)	Binds to DNA, cleaves DNA strands	Hodgkin disease, non-Hodgkin lymphoma, germ cell tumors	Nausea, vomiting, pneumonitis, stomatitis, Raynaud phenomenon, pulmonary fibrosis, dermatitis	
Vincristine (Oncovin)	Inhibits microtubule formation	ALL, non-Hodgkin lymphoma, Hodgkin disease, Wilms tumor, Ewing sarcoma, neuroblastoma, rhabdomyosarcoma	Local cellulitis, peripheral neuropathy, constipation, ileus, jaw pain, inappropriate ADH secretion, seizures, ptosis, minimal myelosuppression	IV administration only; must not be allowed to extravasate
Vinblastine (Velban)	Inhibits microtubule formation	Hodgkin lymphoma, non-Hodgkin lymphoma, Langerhans cell histiocytosis, CNS tumors	Local cellulitis, leukopenia	IV administration only; must not be allowed to extravasate
L-Asparaginase	Depletion of L-asparagine	ALL; AML, when used in combination with cytarabine	Allergic reaction pancreatitis, hyperglycemia, platelet dysfunction and coagulopathy, encephalopathy	Pegaspargase now preferred to L-asparaginase
Pegaspargase (Oncaspar) Calaspargase-pegol-mknl (Asparlas)	Polyethylene glycol conjugate of L-asparagine	ALL	Indicated for prolonged asparagine depletion and for patients with allergy to L-asparaginase	

Continued

Table 543.2 Common Chemotherapeutic Agents Used in Pediatric Cancer—cont'd

DRUG	MECHANISM OF ACTION OR CLASSIFICATION	INDICATION(S)	ADVERSE REACTIONS (PARTIAL LIST)	COMMENTS
Prednisone and dexamethasone (Decadron)	Lymphatic cell lysis	ALL; Hodgkin lymphoma, non-Hodgkin lymphoma	Cushing syndrome, cataracts, diabetes, hypertension, myopathy, osteoporosis, avascular necrosis, infection, peptic ulceration, psychosis	
Carmustine (BiCNU)	Carbamylation of DNA; inhibits DNA synthesis	CNS tumors, non-Hodgkin lymphoma, Hodgkin lymphoma	Nausea, vomiting, delayed myelosuppression (4-6 wk); pulmonary fibrosis, carcinogenic stomatitis	Phenobarbital increases metabolism, decreases activity
Carboplatin and cisplatin (Platinol)	Inhibits DNA synthesis	Osteosarcoma, neuroblastoma, CNS tumors, germ cell tumors	Nausea, vomiting, renal dysfunction, myelosuppression, ototoxicity, tetany, neurotoxicity, hemolytic-uremic syndrome, anaphylaxis	Aminoglycosides may increase nephrotoxicity
Etoposide (Vepesid)	Topoisomerase inhibitor	ALL, non-Hodgkin lymphoma, germ cell tumor, Ewing sarcoma	Nausea, vomiting, myelosuppression, secondary leukemia	
Tretinoin (all *trans*-retinoic acid) and isotretinoin (*cis*-retinoic acid; Accutane)	Enhances normal differentiation	Acute promyelocytic leukemia; neuroblastoma	Dry mouth, hair loss, pseudotumor cerebri, premature epiphyseal closure, birth defects	

ADH, Antidiuretic hormone; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CNS, central nervous system; IM, intramuscular; IV, intravenous; PO, oral.

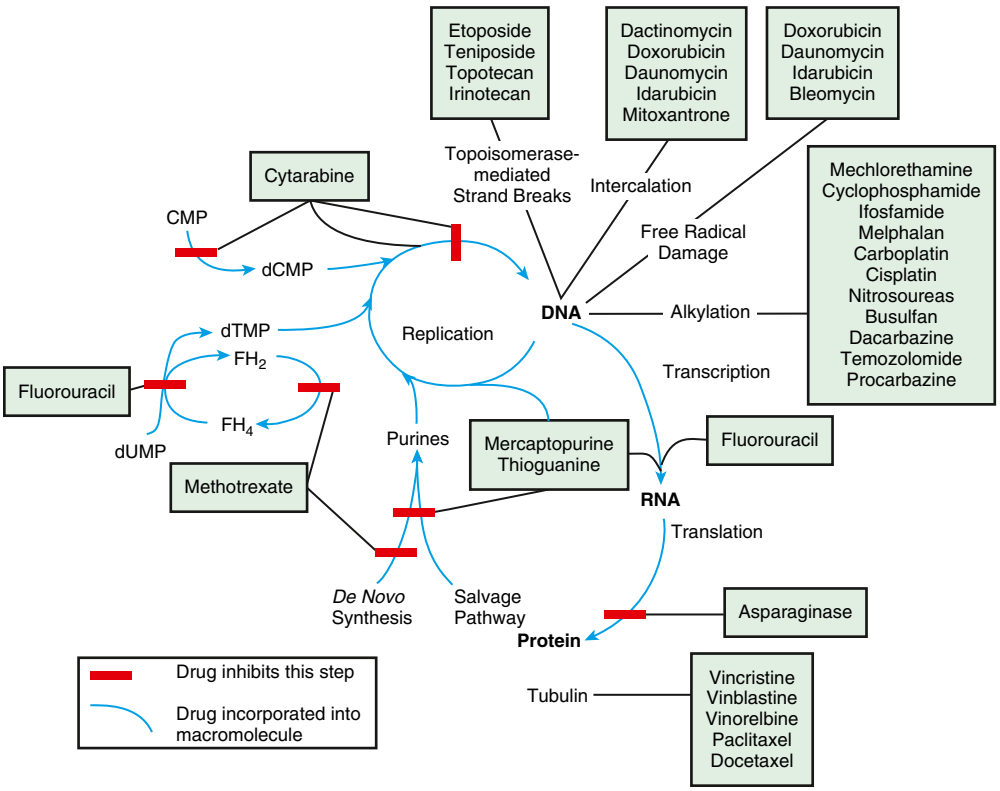

Fig. 543.5 Site of action of the commonly used anticancer drugs. CMP, Cytidine monophosphate; dCMP, deoxycytidine monophosphate; dTMP, deoxythymidine monophosphate; dUMP, deoxyuridine monophosphate; FH_2, dihydrofolate; FH_4, tetrahydrofolate. *(Redrawn from Adamson PC, Balis FM, Blaney SM. General principles of chemotherapy. In: Pizzo PA, Poplack DG, eds. Principles and Practice of Pediatric Oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2011: p. 283.)*

neuroblastoma (anti–ganglioside GD_2). The antiangiogenic agent bevacizumab (monoclonal antibody against vascular endothelial growth factor A) is used in the treatment of low-grade gliomas.

Chimeric antigen receptor T cells (CAR-T cells) are genetically engineered to make new TCRs that can recognize and attach to an antigen on the tumor cell. This results in T-cell proliferation, cytolysis, and cytokine release with subsequent tumor cell death (Fig. 543.7). The B-cell antigen CD19 is the antigen targeted in children with ALL and some adults with lymphoma. The response to therapy in children with chemotherapy-resistant ALL is dramatic. Other antigens may be targeted, including CD22, CD30 (lymphomas), CD171, GD2 (neuroblastoma), EGFR, and HER2 (glioblastoma).

Side effects of CAR-T therapy are common and potentially serious and are caused by the **cytokine release syndrome (CRS)**. Manifestations

Table 543.3 Infectious Complications of Malignancy

PREDISPOSING FACTOR	ETIOLOGY	SITE OF INFECTION	INFECTIOUS AGENTS
Neutropenia	Chemotherapy, bone marrow infiltration	Sepsis, shock, pneumonia, soft tissue, proctitis, mucositis	Viridans group streptococcus, *Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa, Candida, Aspergillus,* anaerobic oral and rectal bacteria
Immunosuppression, lymphopenia, lymphocyte-monocyte dysfunction	Chemotherapy, corticosteroid	Pneumonia, meningitis, disseminated viral infection	*Pneumocystis jiroveci, Cryptococcus neoformans, Mycobacterium, Nocardia, Listeria monocytogenes, Candida, Aspergillus, Strongyloides, Toxoplasma,* varicella-zoster virus, cytomegalovirus, herpes simplex
Indwelling central venous catheter	Nutrition, administration of chemotherapy	Line sepsis, tract of tunnel, exit site	*S. epidermidis, S. aureus, Candida albicans, P. aeruginosa, Aspergillus, Corynebacterium, Enterococcus faecalis, Mycobacterium fortuitum, Propionibacterium acnes*

Modified from Kliegman RM, Marcdante KJ, Jenson HB, et al., eds. *Nelson Essentials of Pediatrics*. 6th ed. Philadelphia: Saunders; 2011.

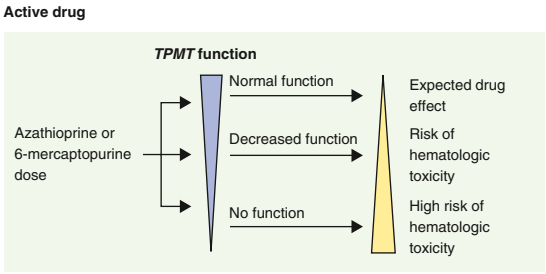

Fig. 543.6 The impact of variable pharmacokinetic gene function on the effect of bioactivation of prodrug versus inactivation of an active drug. *(From Roden DM, McLeod HL, Relling MV, et al. Pharmacogenomics. Lancet. 2019;394[10197]:521–532. Fig. 2)*

of CRS include hypotension, vascular leak, myalgias, cerebral edema, seizures, and confusion. Symptoms correlate with the extent of the tumor burden and require supportive care. Tocilizumab, an anti–interleukin-6 receptor monoclonal antibody, is the treatment of choice for CRS. B-cell aplasia may also develop and requires immune globulin replacement.

Immune checkpoint inhibitors are drugs (monoclonal antibodies) which enhance the ability of T-cells to attack cancer cells. Checkpoints on T-cells and cancer cells include PD-1/PD-L1 (programed death protein and programed death ligand-1), which normally dampen the T-cell response. CTLA-4 and LAG-3 are additional immune checkpoint molecules. Thus checkpoint inhibitors allow the T-cell to kill the cancer cells more effectively. Immune-related adverse events (irAEs) due to activated T cells include autoimmune-like disorders affecting many tissues including skin, liver, lung, CNS, and gastrointestinal and endocrine organs.

Surgery

Superb pediatric surgical and anesthesia services are indispensable for children with cancer. The pediatric surgeon's role varies depending on the type of tumor. For **solid tumors**, complete resection with documented evidence of negative margins often is required for cure or long-term control. Considerable prolongation of life usually depends on the tumor's resectability and the actual extent of resection.

Except for pontine gliomas and retinoblastoma, all solid tumors in children require a tissue diagnosis; therefore biopsy of the suspected neoplasm is paramount. Staging with sentinel node biopsies has become the standard of care for several pediatric malignancies. Surgical expertise is essential for implantation of vascular access devices and removal and replacement of such devices when infection or thrombosis supervenes (see Chapter 224).

Minimally invasive endoscopic surgical techniques are being used when indicated and, if the patient's condition permits, for biopsy and resection of tumor, direct ascertainment of residual disease and assessment of response, lysis of adhesions, and splenectomy.

Radiation Therapy

Radiation therapy is used sparingly in children, who are more susceptible than adults to the adverse delayed effects of ionizing radiation. A major advance in pediatric radiation therapy is the application of **conformal radiation** to children with cancer. This technique, most often applied as **intensity-modulated radiation therapy**, spares normal tissue by conforming the radiation volume to the shape of the tumor, thereby enabling delivery of higher doses to the tumor with lower exposure of normal tissue adjacent to the tumor or in the path of the radiation beam. Another example is **proton-beam radiotherapy**. With more focused beams and better sedation and immobilization techniques, radiation therapy is becoming more common in children. Acute adverse effects from radiation therapy depend on which part of the body is irradiated and the means of administration. **Dermatitis** is the most common general adverse effect because skin is always in the treatment field. Nausea and diarrhea are common subacute adverse effects with abdominal radiation therapy. **Mucositis** typically occurs to some extent whenever oral or intestinal mucosa is in the treatment volume. **Somnolence** is common with cranial irradiation. **Alopecia** occurs where hair is in the radiation field.

Most radiation therapy schedules require treatment 5 days per week for 4-7 weeks, depending on the dose needed to control the tumor and the amount and nature of normal tissue in the field. Most adverse effects are not noted until the second half of the course of irradiation. Late effects can occur months to years after radiation therapy and usually are dose-dependent manifestations. The type of delayed toxicity also depends on the site of irradiation. Examples are impaired growth resulting from cranial or vertebral irradiation, endocrine dysfunction from hypothalamic irradiation, pulmonary or cardiac insufficiency from chest irradiation, strictures and adhesions from abdominal irradiation, and infertility from pelvic irradiation. Second malignancy can also develop in the radiation field, such as breast cancer from chest irradiation and brain tumors from CNS irradiation.

ACUTE TOXIC EFFECTS AND SUPPORTIVE CARE

Adverse treatment effects that occur early in therapy can result in oncologic emergencies. These include metabolic disorders, bone marrow suppression, and compression by tumors on vital structures (Table 543.4). In **tumor lysis syndrome (TLS)**, uric acid, phosphate, and potassium are released in the circulation in large quantities from death of tumor cells. Hyperuricemia can lead to impairment of renal function, which further exacerbates the metabolic abnormalities. TLS can occur before therapy in patients with a large tumor burden (e.g., Burkitt lymphoma, lymphoblastic lymphoma, and leukemia presenting with a high white blood cell count), but it is usually seen within 12-48 hours of initiating chemotherapy. TLS is infrequently reported in other tumors (Hodgkin lymphoma, neuroblastoma, hepatoblastoma). Before therapy is initiated, the serum levels of uric acid, electrolytes, calcium, phosphorus, and creatinine should be measured, and adequate hydration ensured. Allopurinol (a xanthine oxidase inhibitor) should be started to prevent further accumulation of uric acid. In patients with established TLS with high uric acid levels or those at high risk for TLS, rasburicase (an enzyme that degrades uric acid) should be given. Symptomatic hyperkalemia and hyperphosphatemia with subsequent hypocalcemia can develop in the setting of inadequate renal function.

Virtually all chemotherapy regimens can produce **myelosuppression**, as can malignancies that invade and replace bone marrow. **Anemia** can

Fig. 543.7 Chimeric antigen receptor (CAR) T-cell therapy. CAR T-cell therapy is a type of treatment in which a patient's T cells are genetically engineered in the laboratory so they will bind to specific proteins (antigens) on cancer cells and kill them. *(1)* A patient's T cells are removed from their blood. Then *(2)* the gene for a special receptor called a chimeric antigen receptor is inserted into the T cells in the laboratory. The gene encodes the engineered CAR protein that is expressed on the surface of the patient's T cells, creating a CAR T cell. *(3)* Millions of CAR T cells are grown in the laboratory. *(4)* They are then given to the patient by intravenous infusion. *(5)* The CAR T cells bind to antigens on the cancer cells and kill them. *(Courtesy National Institutes of Health, National Cancer Institute, Bethesda, Maryland. https://www.cancer.gov/about-cancer/treatment/research/car-t-cell-therapy-infographic)*

Table 543.4 Oncologic Emergencies

CONDITION	MANIFESTATIONS	ETIOLOGY	MALIGNANCY	TREATMENT
METABOLIC				
Hyperuricemia	Uric acid nephropathy	Tumor lysis syndrome	Lymphoma, leukemia	Allopurinol, hydration, rasburicase
Hyperkalemia	Arrhythmias, cardiac arrest	Tumor lysis syndrome	Lymphoma, leukemia	Kayexalate, sodium bicarbonate, calcium gluconate, glucose, and insulin; check for pseudohyperkalemia from leukemic cell lysis in test tube
Hyperphosphatemia	Hypocalcemic tetany; metastatic calcification, photophobia, pruritus	Tumor lysis syndrome	Lymphoma, leukemia	Hydration, forced diuresis; stop alkalinization; oral aluminum hydroxide to bind phosphate
Hyponatremia	Seizure, lethargy (may also be asymptomatic)	SIADH; fluid, sodium losses in vomiting	Leukemia, CNS tumor	Restrict free water for SIADH; replace sodium if depleted
Hypercalcemia	Anorexia, nausea, polyuria, pancreatitis, gastric ulcers; prolonged PR, shortened QT interval	Bone resorption; ectopic parathormone, vitamin D, or prostaglandins	Metastasis to bone, rhabdomyosarcoma, leukemia	Hydration and furosemide diuresis; corticosteroids; calcitonin, bisphosphonates
HEMATOLOGIC				
Anemia	Pallor, weakness, heart failure	Bone marrow suppression or infiltration; blood loss	Any with chemotherapy	Packed red blood cell transfusion
Thrombocytopenia	Petechiae, hemorrhage	Bone marrow suppression or infiltration	Any with chemotherapy	Platelet transfusion
Disseminated intravascular coagulation	Shock, hemorrhage	Sepsis, hypotension, tumor factors	Promyelocytic leukemia, others	Fresh-frozen plasma; platelets, cryoprecipitate, treat underlying disorder
Neutropenia	Infection	Bone marrow suppression or infiltration	Any with chemotherapy	If febrile, administer broad-spectrum antibiotics, and filgrastim (G-CSF) if appropriate

Table 543.4 Oncologic Emergencies—cont'd

CONDITION	MANIFESTATIONS	ETIOLOGY	MALIGNANCY	TREATMENT
Hyperleukocytosis (>100,000/mm^3)	Hemorrhage, thrombosis; pulmonary infiltrates, hypoxia; tumor lysis syndrome	Leukostasis; vascular occlusion	Leukemia	Leukapheresis; chemotherapy; hydroxyurea
Graft versus host disease	Dermatitis, diarrhea, hepatitis	Immunosuppression and nonirradiated blood products; bone marrow transplantation	Any with immunosuppression	Corticosteroids; cyclosporine; tacrolimus; antithymocyte globulin
SPACE-OCCUPYING LESIONS				
Spinal cord compression	Back pain ± radicular *Cord above T10:* symmetric weakness, increased deep tendon reflex; sensory level present; toes up *Conus medullaris (T10-L2):* symmetric weakness, increased knee reflexes; decreased ankle reflexes; saddle sensory loss; toes up or down *Cauda equina (below L2):* asymmetric weakness; loss of deep tendon reflex and sensory deficit; toes down	Metastasis to vertebra and extramedullary space	Neuroblastoma, ewing, glioma	Corticosteroids, surgery, chemotherapy, radiotherapy
Increased intracranial pressure	Confusion, coma, emesis, headache, hypertension, bradycardia, seizures, papilledema, hydrocephalus; cranial nerve III and VI palsies	Primary or metastatic brain tumor	Medulloblastoma, glioma	Corticosteroids, ventriculostomy, radiotherapy, chemotherapy
Superior vena cava syndrome	Distended neck veins, plethora, edema of head and neck, cyanosis, Horner syndrome	Superior mediastinal mass	Lymphoma Germ cell tumor	Chemotherapy, radiotherapy
Tracheal compression	Respiratory distress	Mediastinal mass compressing trachea	Lymphoma Neuroblastoma	Radiation, corticosteroids

CNS, Central nervous system; G-CSF, granulocyte colony-stimulating factor; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
Adapted from Kliegman RM, Marcdante KJ, Jenson HB, et al., eds. *Nelson Essentials of Pediatrics*. 6th ed. Philadelphia: Saunders; 2011. p. 590.

be corrected by transfusions of packed erythrocytes, and **thrombocytopenia** can be corrected by platelet infusions. Patients receiving immunosuppressive therapy should receive irradiated blood products to prevent graft-versus-host disease and leukoreduced blood products to prevent transfusion-associated reactions and infections. **Neutropenia** (neutrophil counts <500/μL) poses a risk of life-threatening infection. Patients with febrile neutropenia should be hospitalized and treated with empirical broad-spectrum intravenous antimicrobial therapy pending the results of appropriate cultures of blood, urine, or any obvious sites of infection (see Chapter 223). Treatment is continued until fever resolves and the neutrophil count rises. If fever persists for more than 3-5 days while the patient is receiving broad-spectrum antibiotics, the possibility of fungal infection must be considered. Fungal infections caused by *Candida* and *Aspergillus* are common in immunosuppressed patients. Opportunistic organisms such as *Pneumocystis jiroveci* can produce fatal pneumonia. Prophylactic treatment with trimethoprim-sulfamethoxazole is given when severe or prolonged immunosuppression is anticipated.

Viruses of low pathogenicity can produce serious disease in the setting of immunosuppression caused by malignancy or its treatment. Patients should not be given live-virus vaccines. Children who are receiving chemotherapy and who are exposed to chickenpox should receive varicella-zoster immunoglobulin, or if varicella-zoster immunoglobulin is not available, oral acyclovir should be considered. If clinical disease develops, the child should be hospitalized and treated with intravenous acyclovir.

Depending on the type of cancer therapy, patients can lose >10% body weight. Patients sometimes reduce their food intake because of temporary, treatment-associated nausea, stomatitis, and vomiting. Appetite loss is not a cause for alarm. **Malnutrition** is a particular risk in patients receiving radiation therapy involving the abdomen or the head and neck, intensive chemotherapy, or total body irradiation and high-dose chemotherapy before marrow transplantation. If oral supplementation proves inadequate, such patients may require enteral tube feedings or parenteral hyperalimentation.

Adequate **pain management** is critical. The World Health Organization (WHO) guidelines are particularly useful in the management of pain associated with cancer and cancer therapy (see Chapter 93). Assistance from a **supportive care** team can provide safe and effective support for toxicities associated with chemotherapy, such as pain and nausea.

LATE EFFECTS

Late effects of therapy can cause substantial morbidity (Table 543.5). The type of late effects depends on the child's age at treatment, the location(s) of the cancer, and the therapy administered. These effects can be either from the tumor or its treatment. For example, a brain or spinal tumor can leave the child with a permanent paresis or autonomic dysfunction; anthracycline-induced cardiomyopathy usually produces refractory cardiac dysfunction; and the leukoencephalopathy caused by intrathecal methotrexate and CNS radiation therapy often is only partially reversible.

Successful surgical resection can result in loss of important functional structures. Irradiation can produce irreversible organ damage, with symptoms and functional limitations depending on the organ involved and the severity of the damage. Many problems related to radiation therapy do not become obvious until the patient is fully grown, such as asymmetry between irradiated and nonirradiated areas or extremities. Irradiation of fields that include endocrine organs can cause hypothyroidism, pituitary dysfunction, or infertility. In sufficient doses, cranial irradiation can produce neurologic dysfunction, and spinal irradiation can produce growth deficiency.

Chemotherapy also carries the risk of long-lasting organ damage. Of particular concern are **leukoencephalopathy** after high-dose

methotrexate therapy; **infertility** in patients treated with alkylating agents (e.g., cyclophosphamide); **myocardial damage** caused by anthracyclines; **pulmonary fibrosis** caused by bleomycin; **renal dysfunction** caused by ifosfamide, nitrosourea, or platinum agents; and **hearing loss** from cisplatin. Development of these sequelae may be dose related and usually is irreversible. Appropriate baseline and intermittent testing should be performed before these drugs are administered to ensure that there is no preexisting damage to the organs likely to be affected and to permit monitoring of the effects of treatment-induced changes.

Perhaps the most serious late effect is the occurrence of **second cancers** in patients successfully cured of a first malignancy. The risk

Table 543.5 Late Effects and High-Risk Features of Childhood Cancer and Its Treatment

LATE EFFECTS	EXPOSURE	SELECTED HIGH-RISK FACTORS	AT-RISK DIAGNOSTIC GROUPS
NEUROCOGNITIVE			
Neurocognitive deficits Functional deficits in: • Executive function • Sustained attention • Memory • Processing speed • Visual-motor integration Learning deficits Diminished IQ Behavioral change	Chemotherapy: • Methotrexate Radiation affecting brain: • Cranial • Ear/infratemporal • Total body irradiation (TBI)	Age <3 yr old at time of treatment Female Supratentorial tumor Premorbid or family history of learning or attention problems Radiation doses >24 Gy Whole-brain irradiation	Acute lymphoblastic leukemia Brain tumor Sarcoma (head and neck or osteosarcoma)
NEUROSENSORY			
Hearing loss, sensorineural	Chemotherapy: • Cisplatin • Carboplatin Radiation affecting hearing: • Cranial • Infratemporal • Nasopharyngeal	Higher cisplatin dose (360 mg/m^2) Higher radiation dose impacting ear (>30 Gy) Concurrent radiation and cisplatin	Brain tumor Germ cell tumor Sarcoma (head and neck) Neuroblastoma Hepatoblastoma
Hearing loss, conductive Tympanosclerosis Otosclerosis Eustachian tube dysfunction	Radiation affecting hearing: • Cranial • Infratemporal • Nasopharyngeal	Higher radiation dose affecting ear (>30 Gy)	Brain tumor Sarcoma (head and neck)
Visual impairment Cataracts Lacrimal duct atrophy Xerophthalmia Retinopathy Glaucoma	Chemotherapy: • Busulfan • Glucocorticoids Radiation affecting eye: • Cranial • Orbital/eye • TBI	Higher radiation dose impacting eye (≥15 Gy for cataracts; >45 Gy for retinopathy and visual impairment)	Brain tumor Acute lymphoblastic leukemia Retinoblastoma Rhabdomyosarcoma (orbital) Allogeneic HSCT
Peripheral neuropathy, sensory	Chemotherapy: • Vincristine • Vinblastine • Cisplatin • Carboplatin Brentuximab vedotin	Higher cisplatin dose (≥300 mg/m^2)	Acute lymphoblastic leukemia Brain tumor Hodgkin lymphoma Germ cell tumor Non-Hodgkin lymphoma Sarcoma Neuroblastoma Wilms tumor Carcinoma
NEUROMOTOR			
Peripheral neuropathy, motor	Chemotherapy: • Vincristine • Vinblastine Brentuximab vedotin		Acute lymphoblastic leukemia Hodgkin lymphoma Non-Hodgkin lymphoma Sarcoma Brain tumor Neuroblastoma Wilms tumor
ENDOCRINE			
GH deficiency Precocious puberty	Radiation affecting HPA: • Cranial • Orbital/eye	Female Radiation dose to HPA >18 Gy	Acute lymphoblastic leukemia Sarcoma (facial) Carcinoma (nasopharyngeal)
Obesity	Ear/infratemporal Nasopharyngeal	Female Younger age (<4 yr)	Acute lymphoblastic leukemia
Hypothyroidism, central Gonadotropin deficiency Adrenal insufficiency, central	TBI	Radiation dose to HPA >18 Gy	Brain tumor Sarcoma (facial) Carcinoma (nasopharyngeal)
Hypothyroidism, primary	Neck, mantle irradiation	Radiation dose to thyroid >20 Gy	Hodgkin lymphoma

Table 543.5 Late Effects and High-Risk Features of Childhood Cancer and Its Treatment—cont'd

LATE EFFECTS	EXPOSURE	SELECTED HIGH-RISK FACTORS	AT-RISK DIAGNOSTIC GROUPS
REPRODUCTIVE			
Gonadal dysfunction Delayed or arrested puberty Premature menopause Germ cell dysfunction or failure Infertility	Chemotherapy, alkylating: • Busulfan • Carmustine (BiCNU) • Chlorambucil • Cyclophosphamide • Ifosfamide • Lomustine (CCNU) • Mechlorethamine • Melphalan • Procarbazine Radiation affecting reproductive system: • Whole abdomen (females) • Pelvic • Lumbar/sacral spine (females) • Testicular (males) • TBI	Higher alkylating agent dose Alkylating agent conditioning for HSCT Radiation dose ≥15 Gy in prepubertal females Radiation dose ≥10 Gy in pubertal females For germ cell failure in males, any pelvic irradiation For androgen insufficiency, gonadal irradiation, ≥20-30 Gy in males	Acute lymphoblastic leukemia, high risk Brain tumor Hodgkin lymphoma, advanced or unfavorable Non-Hodgkin lymphoma, advanced or unfavorable Sarcoma Neuroblastoma Wilms tumor, advanced Autologous or allogeneic HSCT
CARDIAC			
Cardiomyopathy Arrhythmias	Chemotherapy: • Daunorubicin • Doxorubicin • Idarubicin	Female Age <5 yr old at time of treatment Higher doses of chemotherapy (≥300 mg/m^2) Higher doses of cardiac radiation (≥30 Gy) Combined-modality therapy with cardiotoxic chemotherapy and irradiation	Hodgkin lymphoma Leukemia Non-Hodgkin lymphoma Sarcoma Wilms tumor Neuroblastoma
Cardiomyopathy Arrhythmias Pericardial fibrosis Valvular disease Myocardial infarction Atherosclerotic heart disease	Radiation affecting heart: • Chest • Mantle • Mediastinum • Axilla • Spine • Upper abdomen		
PULMONARY			
Pulmonary fibrosis Interstitial pneumonitis Restrictive lung disease Obstructive lung disease	Chemotherapy: • Bleomycin • Busulfan • Carmustine (BiCNU) • Lomustine (CCNU) Radiation impacting lungs: • Mantle • Mediastinum • Whole lung • TBI	Higher doses of chemotherapy Combined modality therapy with pulmonary toxic chemotherapy and irradiation	Brain tumor Germ cell tumor Hodgkin lymphoma Sarcoma (chest wall or intrathoracic) Autologous or allogeneic HCST
GASTROINTESTINAL			
Chronic enterocolitis Strictures Bowel obstruction	Radiation affecting GI tract (≥30 Gy) Abdominal surgery	Higher radiation dose to bowel (≥45 Gy) Combined modality therapy with abdominal irradiation and radiomimetic chemotherapy (dactinomycin or anthracyclines) Combined modality therapy with abdominal surgery and irradiation	Sarcoma (retroperitoneal or pelvic primary)
HEPATIC			
Hepatic fibrosis Cirrhosis	Radiation affecting liver	Higher radiation dose or treatment volume (20-30 Gy to entire liver or ≥40 Gy to at least one third of liver)	Sarcoma Neuroblastoma
RENAL			
Renal insufficiency Hypertension Glomerular injury Tubular injury	Chemotherapy: • Ifosfamide • Cisplatin • Carboplatin Radiation affecting kidneys: • Whole abdomen • Upper abdominal fields • TBI	Higher ifosfamide dose (≥60 g/m^2) Higher cisplatin dose (≥200 mg/m^2) Renal radiation dose (≥15 Gy) Combined modality therapy with above agents	Brain tumor Germ cell tumor Sarcoma Wilms tumor Neuroblastoma Hepatoblastoma Carcinoma Autologous or allogeneic HSCT

GH, Growth hormone; HPA, hypothalamic-pituitary-adrenal axis; HSCT, hematopoietic stem cell transplantation; IQ, intelligence quotient.
From Kurt BA, Armstrong GT, Cash DK, et al. Primary care management of the childhood cancer survivor. *J Pediatr*. 2008;152:458–466.

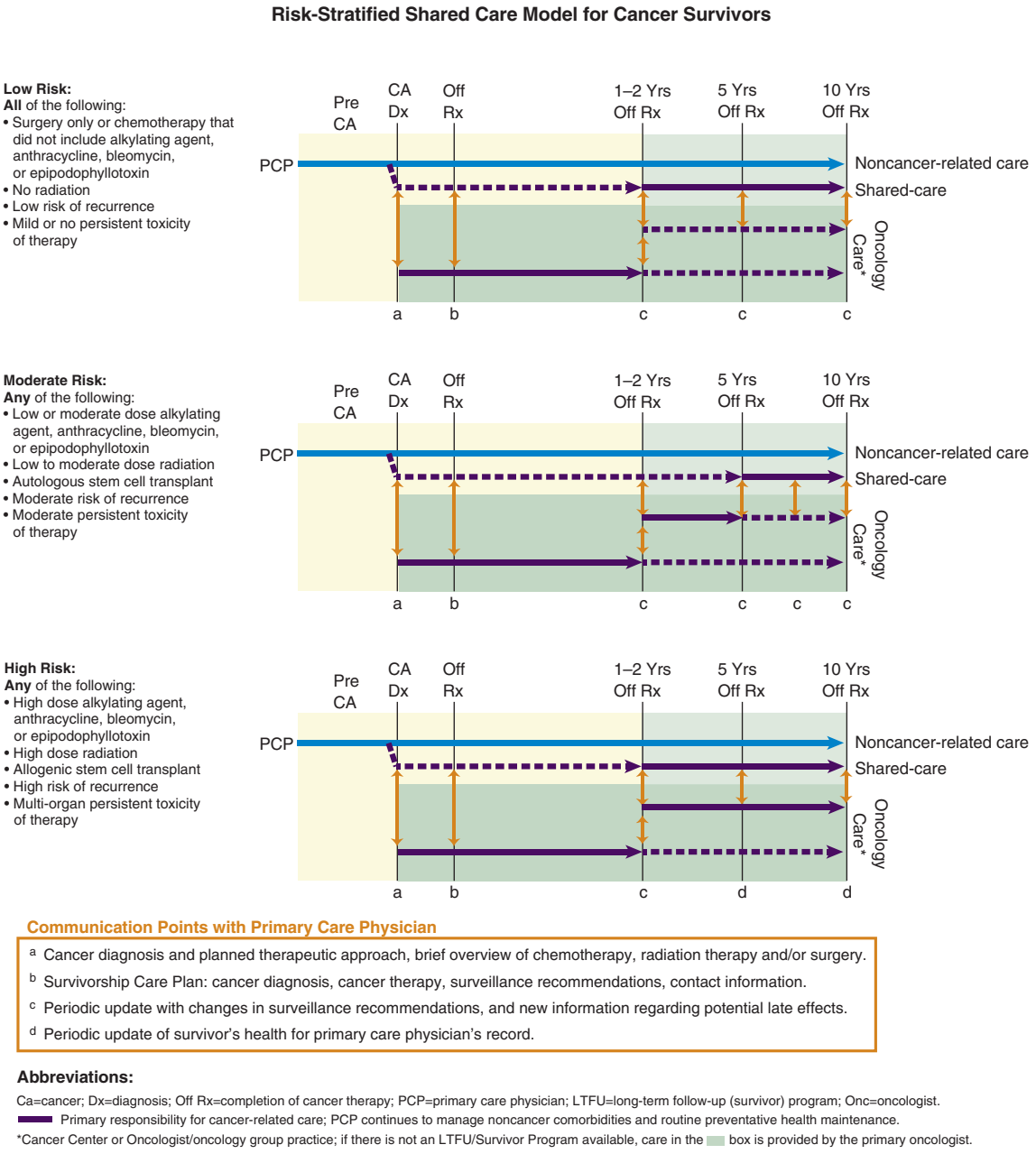

Fig. 543.8 Proposed risk-stratified shared care model for childhood cancer survivors. *Purple solid line* denotes primary responsibility cancer-related care; risk stratification is based on determination of the long-term follow-up staff. *(Adapted from McCabe MS, Partridge A, Grunfeld, E, Hudson MM. Risk-based health care, the cancer survivor, the oncologist, and the primary care physician. Semin Oncol. 2013;40:804–812; with data from Oeffinger KC, McCabe MS. Models for delivering survivorship care. J Clin Oncol. 2006;24:5117–5124.)*

appears to be cumulative, increasing by approximately 0.5% per year, resulting in approximately a 12% incidence at 25 years after treatment. Patients who have been treated for childhood cancer should be examined annually with particular attention to possible late effects of therapy, including second malignancies (Fig. 543.8).

Risk-stratified therapy over the past few decades has been shown to reduce late morbidity and mortality. A good resource for the pediatrician, patient, and family who must anticipate the possibilities is available at http://www.survivorshipguidelines.org.

PALLIATIVE CARE

At all stages of caring for children with cancer, principles of palliative care should be applied to relieve pain and suffering and to provide comfort (see Chapter 8). Early involvement of palliative or supportive care teams is beneficial. **Pain** is a serious cause of suffering among patients with cancer. It may be the result of organ obstruction or compression or bone metastasis, or it may be neuropathic. Pain should be managed in a stepwise manner, as recommended by the WHO, in accordance with the principles of selecting the appropriate analgesic, prescribing the appropriate dosage, administering the drug by the appropriate route, and choosing an appropriate dosing schedule to prevent persistent pain and to relieve breakthrough pain (see Chapter 93). In addition, the dosage should be titrated aggressively while attempts are made to prevent, anticipate, and manage side effects. Adjuvant drugs and sequential trials of analgesic drugs should be considered.

The goals in the care of dying patients are to avoid distress for the patient, family, and caregivers; to provide care consistent with the patient's and family's wishes; and to comply with and advocate for clinical, cultural, and ethical standards.

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Chapter 544

The Leukemias

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INTRODUCTION

The leukemias are the most common malignant neoplasms in childhood, accounting for approximately 31% of all malignancies that occur in children younger than 15 years old. Each year, leukemia is diagnosed in approximately 3,100 children and adolescents <20 years old in the United States, an annual incidence of 4.8 cases per 100,000 children. Acute lymphoblastic leukemia (ALL) accounts for approximately 77% of cases of childhood leukemia, acute myelogenous leukemia (AML) for approximately 11%, chronic myelogenous leukemia (CML) for 2–3%, and juvenile myelomonocytic leukemia (JMML) for 1–2%. The remaining cases consist of a variety of acute and chronic leukemias that do not fit classic definitions for ALL, AML, CML, or JMML.

The leukemias may be defined as a group of malignant diseases in which genetic abnormalities in a hematopoietic cell give rise to an unregulated clonal proliferation of cells. The progeny of these cells have a growth advantage over normal cellular elements because of their increased rate of proliferation and a decreased rate of spontaneous apoptosis. The result is a disruption of normal marrow function and, ultimately, marrow failure. The clinical features, laboratory findings, and responses to therapy vary depending on the type of leukemia.

544.1 Acute Lymphoblastic Leukemia

Erika D. Friehling, A. Kim Ritchey, Julia C. Meade, and Archie Bleyer

Leukemia (ALL) was the first disseminated cancer shown to be curable. It is a heterogeneous group of malignancies with distinctive genetic abnormalities that result in varying clinical behaviors and responses to therapy.

EPIDEMIOLOGY

Acute lymphoblastic leukemia is diagnosed in approximately 3,100 children and adolescents <20 years old in the United States each year. It has a striking peak incidence at 2-3 years of age and occurs more in males than in females at all ages. The disease is more common in children with certain chromosomal abnormalities, such as Down syndrome, Li-Fraumeni, Bloom syndrome, and ataxia-telangiectasia. Among identical twins, the risk to the second twin if one twin develops leukemia is greater than that in the general population. The risk is >70% if ALL is diagnosed in the first twin during the first year of life and the twins shared the same (monochorionic) placenta. If the first twin develops ALL by 5-7 years of age, the risk to the second twin is at least twice that of the general population, regardless of zygosity.

ETIOLOGY

In virtually all cases, the etiology of ALL is unknown, although several genetic and environmental factors are associated with childhood leukemia (Table 544.1). Most cases of ALL are thought to be caused by post-conception somatic pathogenic gene variants in lymphoid cells. However, the identification of the leukemia-specific fusion-gene sequences in archived neonatal blood spots of some children who develop ALL at a later date indicates the importance of in utero events in the initiation of the malignant process in some cases. The long lag period before the onset of the disease in some children, reported to be as long as 14 years, supports the concept that additional genetic modifications are required for disease expression. Moreover, those same pathogenic variants have been found in neonatal blood spots of children who *never* go on to develop leukemia.

Exposure to medical diagnostic radiation both in utero and in childhood is associated with an increased incidence of ALL (see Chapter 758). In addition, published descriptions and investigations of geographic clusters of cases have raised concern that environmental factors can increase the incidence of ALL. Thus far, no such factors other than radiation have been identified in the United States. In certain developing countries, there is an association between B-cell ALL (B-ALL) and Epstein-Barr virus (EBV) infections.

CELLULAR CLASSIFICATION

The classification of ALL depends on characterizing the malignant cells in the bone marrow to determine the morphology, phenotype as measured by cell membrane markers, and cytogenetic and molecular genetic features. **Morphology** is usually adequate alone to establish a diagnosis, but the other studies are essential for disease classification, which can have a major influence on the prognosis and the choice of appropriate therapy. The current system used is the World Health Organization (WHO) classification of leukemias. Phenotypically, surface markers show that approximately 85% of cases of ALL are classified as **B-lymphoblastic leukemia** (previously termed precursor B-ALL or pre–B-ALL), approximately 15% are **T-lymphoblastic leukemia**, and approximately 1% are derived from mature B cells. The rare leukemia of mature B cells is termed **Burkitt leukemia** and is one of the most rapidly growing cancers in humans, requiring a different therapeutic approach than other subtypes of ALL. A small percentage of children with leukemia have a disease characterized by surface markers of both lymphoid and myeloid derivation.

Chromosomal abnormalities are used to subclassify ALL into prognostic groups (Table 544.2). Many genetic alterations, including inactivation of tumor-suppressor genes and pathogenic gene variants that activate the *JAK-STAT* or *RAS* pathways, have been discovered (Fig. 544.1).

The polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH) techniques offer the ability to pinpoint molecular genetic abnormalities and can be used to detect small numbers of malignant cells at diagnosis as well as during follow-up (**minimal residual disease [MRD]**, see later) and are of proven clinical utility. DNA microarray and whole genome sequencing make it possible to analyze the expression of thousands of genes in the leukemic cell.

Table 544.1 Predisposing Factors of Acute Lymphoblastic Leukemia

GENETIC SUSCEPTIBILITY
Congenital syndromes: Down syndrome, Fanconi anemia, ataxia telangiectasia, Bloom syndrome, Nijmegen breakage syndrome
Inherited gene variants: *ARID5B, IKZF1, CEBPE, CDKN2A,* or *CDKN2B, PIP4K2A, ETV6*
Constitutional Robertsonian translocation between chromosomes 15 and 21, rob(15;21)(q10;q10)
Single nucleotide polymorphisms: rs12402181 in miR-3117 and rs62571442 in miR-3689d2
ENVIRONMENTAL FACTORS
Pesticide exposure
Ionizing radiation
Childhood infections

From Malard F, Mohty M. Acute lymphoblastic leukaemia. *Lancet.* 2020;395:1146–1158. Panel, p. 1147.

CLINICAL MANIFESTATIONS

The initial presentation of ALL usually is nonspecific and relatively brief. Anorexia, fatigue, malaise, irritability, and intermittent low-grade fever are often present. Bone or joint pain, particularly in the lower extremities, may be present. Less often, symptoms may be of several months' duration, may be localized predominantly to the bones or joints, and may include joint swelling. Bone pain is severe and can wake the patient at night. As the disease progresses, signs and symptoms of **bone marrow failure** become more obvious with the occurrence of pallor, fatigue, exercise intolerance, bruising, oral mucosal bleeding or epistaxis, and fever, which may be caused by infection or the leukemia. Organ infiltration can cause lymphadenopathy, hepatosplenomegaly, testicular enlargement, or central nervous system (CNS) involvement (cranial neuropathies, headache, seizures). Respiratory distress may be caused by severe anemia or mediastinal node compression of the airways.

On **physical examination,** findings of pallor, listlessness, purpuric and petechial skin lesions, or mucous membrane hemorrhage can reflect bone marrow failure (see Chapter 542). The proliferative nature of the disease may be manifested as lymphadenopathy, splenomegaly, or, less often, hepatomegaly. Patients with bone or joint pain may have exquisite tenderness over the bone or objective evidence of joint swelling and effusion. Nonetheless, with marrow involvement, deep bone pain may be present, but tenderness will not be elicited. Rarely, patients show signs of increased intracranial pressure that indicate leukemic involvement of the CNS. These include papilledema (see Fig. 542.3), retinal hemorrhages, and cranial nerve palsies. Respiratory distress usually is related to anemia but can occur in patients as the result of a large anterior mediastinal mass (e.g., in the thymus or nodes). This problem is most frequently seen in adolescent males with T-cell ALL (T-ALL). **T-ALL** also usually has a higher leukocyte count.

B-lymphoblastic leukemia is the most common immunophenotype, with onset at 1-10 years of age. The median leukocyte count at presentation is 33,000/μL, although 75% of patients have counts <20,000/μL; thrombocytopenia is seen in 75% of patients and hepatosplenomegaly in 30–40% of patients. In all types of leukemia, CNS symptoms are seen at presentation in 5% of patients. Leukemia cells can be seen in the cerebrospinal fluid (CSF) of 10–15% of patients, but only 3–5% are diagnosed with CNS leukemia, defined as >5 WBCs/μL with blasts present. Testicular involvement is rarely evident at diagnosis, but prior studies indicate occult involvement in 25% of males. There is no indication for testicular biopsy.

DIAGNOSIS

The diagnosis of ALL is strongly suggested by peripheral blood findings that indicate bone marrow failure. Anemia and thrombocytopenia are seen in most patients. Leukemic cells might not be reported in the peripheral blood in routine laboratory examinations. Many patients with ALL present with total leukocyte counts of <10,000/μL. In such cases, the leukemic cells often are reported initially to be "atypical lymphocytes," and it is only on further evaluation that the cells are

Table 544.2 Main Genetic Subtypes of B-Cell Acute Lymphoblastic Leukemia

	FREQUENCY	PATHOGENIC VARIANTS	PROGNOSIS
High hyperdiploid (gain of ≥5 chromosomes)	25% children; 3% AYAs and adults	RTK-RAS signaling pathway, histone modifiers	Favorable
Near-haploid (24-31 chromosomes)	2% children; <1% AYAs and adults	RAS-activating, *IKZF3*	Poor
Low-hypodiploid (32-39 chromosomes)	<1% children; 5% AYAs; >10% adults	*TP53, IKZF2, RB1*	Very poor
MLL (KMT2A) rearrangements	>80% infants; <1% children; 4% AYAs; 15% adults	*MLL (KMT2A)* rearrangement, few additional pathogenic variants (PI3K-RAS signaling pathway)	Very poor
ETV6-RUNX1 translocation, t(12;21)(q13;q22)	30% children; <5% AYAs and adults	*ETV6-RUNX1*	Favorable
TCF3-PBX1 translocation, t(1;19)(q23;p13)	5% children, AYAs and adults	*TCF3-PBX1*	Favorable
TCF3-HLF variant of t(1;19)(q23;p13)	<1% acute lymphoblastic leukemia	*TCF3-HLF*	Poor
BCR-ABL1 Philadelphia chromosome, t(9;22)(q34;q11)	2–5% children, 6% AYAs; >25% adults	*BCR-ABL1* fusion gene, common deletions of *IKZF1, CDKN2A, CDKN2B,* and *PAX5*	Poor (improved with tyrosine kinase inhibitors)
Philadelphia chromosome-like acute lymphoblastic leukemia	10% children; 25–30% AYAs; 20% adults	Rearrangements of *CRLF2* (about 50%), *ABL*-class tyrosine kinase genes (12%) and *JAK2* (10%); pathogenic variants of *EPOR* (3–10%); pathogenic variants activating JAK-STAT (10%) and RAS (2–8%) signaling pathways	Poor
DUX4 and *ERG*-deregulated acute lymphoblastic leukemia	5–10% acute lymphoblastic leukemia	*DUX4* rearrangement and overexpression, *ERG* deletions	Favorable, including if coexistence of *IKZF1* pathogenic variants (about 40% of patients)
MEF2D-rearranged acute lymphoblastic leukemia	4% children; 7% AYAs and adults	*MEF2D* is fused to *BCL9* (most frequent fusion event), *HNRNPUL1, SS18, FOXJ2, CSF1R,* or *DAZAP1*	Poor
ZNF384-rearranged acute lymphoblastic leukemia	5% children; 10% AYAs and adults	*ZNF384* rearranged with a transcriptional regulator or chromatin modifier (*EP300, CREBBP, TAF15, SYNRG,* EWSR1, *TCF3, ARID1B, BMP2K,* or *SMARCA2*)	Intermediate

AYAs, Adolescents and young adults.
From Malard F, Mohty M. Acute lymphoblastic leukaemia. *Lancet.* 2020;395:1146–1158. Table 1, p. 1148.

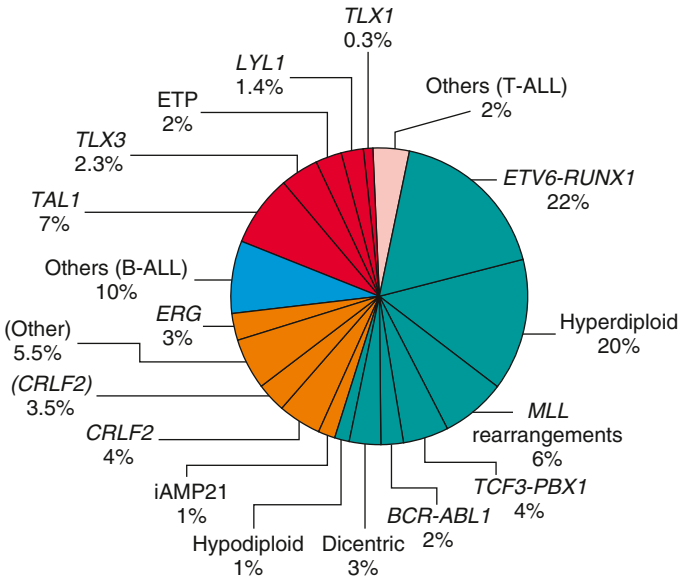
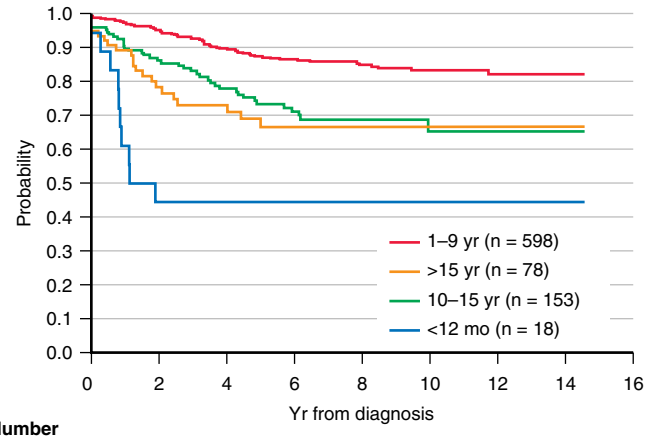


Fig. 544.1 Estimated frequency of specific genotypes in childhood acute lymphoblastic leukemia (ALL). *Teal wedges* refer to B-cell ALL (B-ALL), *orange* to recently identified subtypes of B-ALL, and *red wedges* to T-cell ALL (T-ALL). *(From Mullighan CG. Genomic characterization of childhood acute lymphoblastic leukemia. Semin Hematol. 2013;50:314–324.)*

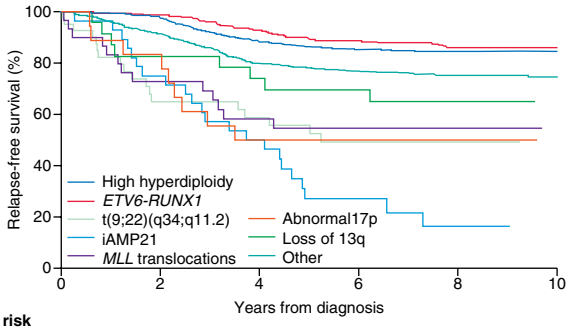


Number at risk									
<12 mo	18	11	8	8	6	1	1	0	0
1–9 yr	598	528	378	295	213	149	85	31	4
10–15 yr	153	130	100	77	50	26	11	6	1
>15 yr	78	60	40	29	20	7	1	0	0

Fig. 544.2 Kaplan-Meier estimates of event-free survival according to age at diagnosis of acute lymphoblastic leukemia. *(From Pui CH, Robinson LL, Look AT. Acute lymphoblastic leukaemia. Lancet. 2008;371:1030–1042.)*

found to be part of a malignant clone. When the results of an analysis of peripheral blood suggest the possibility of leukemia, flow cytometry can rapidly facilitate the diagnosis. The bone marrow should be examined promptly to confirm the diagnosis. It is important that all studies necessary to confirm a diagnosis and adequately classify the type of leukemia be performed, including bone marrow aspiration and biopsy, flow cytometry, cytogenetics, and molecular studies.

ALL is diagnosed by a bone marrow evaluation that demonstrates >25% of the bone marrow cells as a homogeneous population of lymphoblasts. Initial evaluation also includes CSF examination. If lymphoblasts are found and the CSF leukocyte count is elevated, overt CNS or



Number at risk						
High hyperdiploidy	551	529	470	434	249	98
ETV6-RUNX1	365	355	331	301	167	47
t(9;22)(q34;q11.2)	42	22	19	14	8	2
iAMP21	28	21	14	6	1	0
MLL translocations	30	20	16	14	9	1
Abnormal17p	18	15	9	8	7	2
Loss of 13q	24	19	17	15	9	4
Other	644	567	483	440	258	105

Fig. 544.3 Kaplan-Meier analysis of relapse-free survival according to biologic subtype of leukemia. *(From Moorman AV, Ensor HM, Richards SM, et al. Prognostic effect of chromosomal abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: Results from the UK Medical Research Council ALL97/99 randomised trial. Lancet Oncol. 2010;11:429–438.)*

meningeal leukemia is present. This finding reflects a poorer stage and indicates the need for additional CNS and systemic therapies. The staging lumbar puncture (LP) may be performed in conjunction with the first dose of intrathecal chemotherapy, if the diagnosis of leukemia was previously established from bone marrow evaluation. An experienced proceduralist should perform the initial LP, because a traumatic LP is associated with an increased risk of CNS relapse.

DIFFERENTIAL DIAGNOSIS

The diagnosis of leukemia is readily made in the patient with typical signs and symptoms, anemia, thrombocytopenia, and elevated WBC count with blasts present on smear. Elevation of the lactate dehydrogenase (LDH) is often a clue to the diagnosis of ALL. When pancytopenia is present without peripheral blasts, aplastic anemia (congenital or acquired), marrow infiltration from metastatic disease, and hemophagocytic lymphohistiocytosis should be considered. Failure of a single cell line, as seen in transient erythroblastopenia of childhood, immune thrombocytopenia, and congenital or acquired neutropenia, is rarely the presenting feature of ALL. A high index of suspicion is required to differentiate ALL from infectious mononucleosis in patients with acute onset of fever and lymphadenopathy and from juvenile idiopathic arthritis in patients with fever, bone pain but often no tenderness, and joint swelling. These presentations also can require bone marrow examination.

ALL must be differentiated from AML and other malignant diseases that invade the bone marrow and can have clinical and laboratory findings similar to ALL, including neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, and retinoblastoma.

TREATMENT

The single most important prognostic factor in ALL is the treatment: without effective therapy, the disease is fatal. Considerable progress has been made in overall survival for children with ALL through use of multiagent chemotherapeutic regimens, intensification of therapy, and selection of treatment based on relapse risk. Survival is also related to age (Fig. 544.2) and biologic subtype (Fig. 544.3).

Risk-stratified therapy is the standard of current ALL treatment and accounts for age at diagnosis, initial WBC count, immunophenotypic and cytogenetic characteristics of blast populations, rapidity of early treatment response (i.e., how quickly the leukemic cells can be cleared from the marrow or peripheral blood), and assessment of MRD at the end of induction therapy (Table 544.3). Different

Table 544.3 Prognostic Factors for Acute Lymphoblastic Leukemia

	FAVORABLE FACTOR	ADVERSE FACTOR
DEMOGRAPHIC AND CLINICAL FEATURES		
Age	1 year to <10 years	<1 year or ≥10 years
Sex	Female	Male
Ethnicity	White, Asian	Black, Hispanic
CLINICAL, BIOLOGIC, OR GENETIC FEATURES OF LEUKEMIA		
CNS involvement	No	Yes
Blood count at diagnosis	Low blood count; $<50 \times 10^9$ cells/L for B-cell acute lymphoblastic leukemia and $<100 \times 10^9$ cells/L for T-cell acute lymphoblastic leukemia	High blood count; $\geq 50 \times 10^9$/L for B-cell acute lymphoblastic leukemia and $\geq 100 \times 10^9$ cells/L for T-cell acute lymphoblastic leukemia
Immunophenotype	B-cell lineage	T-cell lineage
Cytogenetic features	Hyperdiploidy, *ETV6-RUNX*, *TCF3-PBX1*, and trisomy of chromosomes 4, 10, or 17	Hypodiploidy, *BCR-ABL1* Philadelphia chromosome-positive, *MLL* rearrangements, *TCF3-HLF*, and complex karyotype (≥5 chromosomal abnormalities)
Genomic features	*DUX4*-rearrangement (*ERG* deletion)	*IKZF1* deletions or pathogenic variants, Philadelphia chromosome-like, *MEF2D*-rearrangement
RESPONSE TO TREATMENT		
Minimal residual disease at specified time points	Low minimal residual disease $<10^{-3}$ nucleated cells or undetectable	Persistence of minimal residual disease $\geq 10^{-3}$ nucleated cells, the higher this value the worse the prognosis

From Malard F, Mohty M. Acute lymphoblastic leukaemia. *Lancet.* 2020;395:1146–1158. Table 2, p. 1150.

study groups use various factors to define risk, but age 1-10 years and a leukocyte count <50,000/μL are used by the National Cancer Institute (NCI) to define standard risk. Children who are younger than 1 year or older than 10 years or who have an initial leukocyte count of >50,000/μL are considered to be high risk. Additional characteristics that adversely affect outcome include T-cell immunophenotype or a slow response to initial therapy. Chromosomal abnormalities, including hypodiploidy, the Philadelphia chromosome, and *KMT2A (MLL)* gene rearrangements, portend a poorer outcome. Other genetic pathogenic variants, such as in the *IKZF1* gene, have been shown to be associated with a poor prognosis and may become important in treatment algorithms in the future. More favorable characteristics include a rapid response to therapy, hyperdiploidy, trisomy of specific chromosomes (4, 10, and 17), and rearrangements of the *ETV6-RUNX1* (formerly *TEL-AML1*) genes.

The outcome for patients at higher risk can be improved by administration of more intensive therapy despite the greater toxicity of such therapy. Infants with ALL, along with patients who present with specific chromosomal abnormalities, such as t(4;11), have an even higher risk of relapse despite intensive therapy. However, the poor outcome of Philadelphia chromosome–positive ALL with t(9;22) has been dramatically changed by the addition of imatinib to an intensive chemotherapy backbone. **Imatinib** is an agent specifically designed to inhibit the BCR-ABL kinase resulting from the translocation. With this approach, the event-free survival has improved from 30% to 70%. Clinical trials demonstrate that the prognosis for patients with a slower response to initial therapy may be improved by therapy that is more intensive than the therapy considered necessary for patients who respond more rapidly.

Most children with ALL are treated in clinical trials conducted by national or international cooperative groups. Standard treatment involves chemotherapy for 2-3 years, and most achieve remission at the end of the induction phase. Patients in clinical remission can have MRD that can only be detected with specific molecular probes to translocations and other DNA markers contained in leukemic cells or specialized flow cytometry. MRD can be quantitative and can provide an estimate of the burden of leukemic cells present in the marrow. Higher levels of MRD present at the end of induction suggest a poorer prognosis and higher risk of subsequent relapse. MRD of >0.01% on the marrow on day 29 of induction is a significant risk factor for shorter event-free survival for all risk categories, compared with patients with negative MRD. Therapy for ALL intensifies treatment in patients with evidence of MRD at the end of induction.

Initial therapy, termed **remission induction**, is designed to eradicate the leukemic cells from the bone marrow. During this phase, therapy is given for 4 weeks and consists of vincristine weekly, a corticosteroid such as dexamethasone or prednisone, and usually a single dose of a long-acting, pegylated asparaginase preparation. Patients at higher risk also receive daunorubicin at weekly intervals. With this approach, 98% of patients are in remission, as defined by <5% blasts in the marrow and a return of neutrophil and platelet counts to near-normal levels after 4-5 weeks of treatment. Intrathecal chemotherapy is always given at the start of treatment and at least once more during induction.

The second phase of treatment, **consolidation**, focuses on intensive CNS therapy in combination with continued intensive systemic therapy to prevent later CNS relapses. Intrathecal chemotherapy is given repeatedly by LP. The likelihood of later CNS relapse is thereby reduced to <5%, from historical incidence as high as 60%. A small percentage of patients with features that predict a high risk of CNS relapse may receive irradiation to the brain in later phases of therapy. This includes patients who at diagnosis have lymphoblasts in the CSF and either an elevated CSF leukocyte count or physical signs of CNS leukemia, such as cranial nerve palsy.

Subsequently, many regimens provide 14-28 weeks of therapy, with the drugs and schedules used varying depending on the risk group of the patient. This period of treatment is often termed **intensification** and includes phases of aggressive treatment **(delayed intensification)** as well as relatively less toxic phases of treatment **(interim maintenance)**. Multiagent chemotherapy, including such medications as cytarabine, methotrexate, asparaginase, and vincristine, is used during these phases to eradicate residual disease.

Finally, patients enter the **maintenance** phase of therapy, which lasts for 2-3 years, depending on the protocol used. Patients are given daily mercaptopurine and weekly oral methotrexate, usually with intermittent doses of vincristine and a corticosteroid.

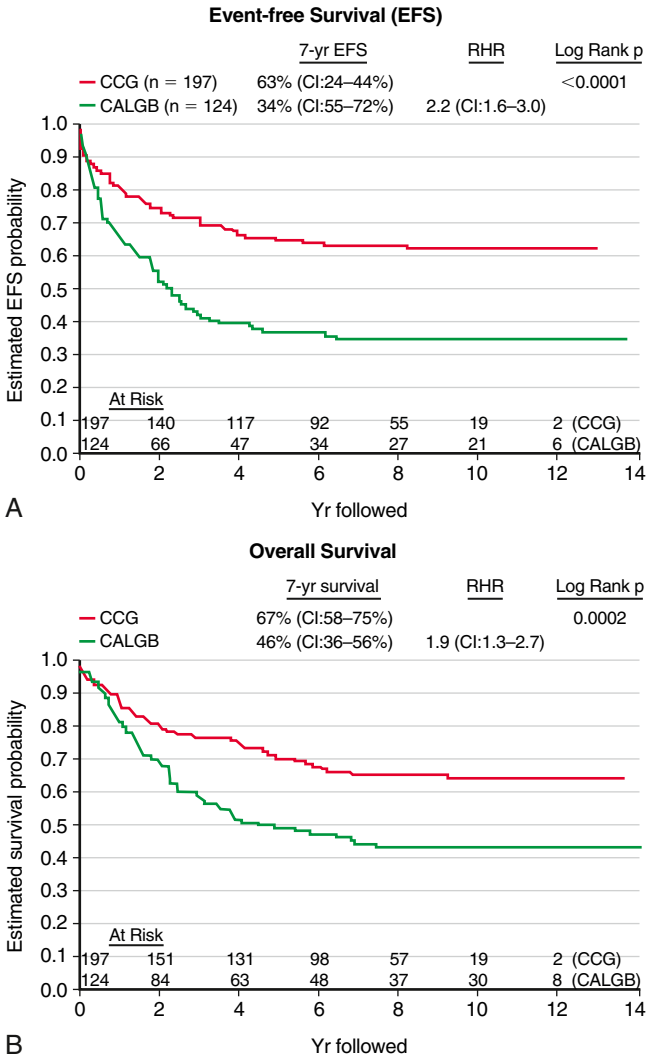


Fig. 544.4 Comparison of event-free survival (A) and overall survival (B) among Cancer and Leukemia Group B (CALGB) (adult protocol, *green line*) and Children's Cancer Group (CCG) (pediatric protocol, *red line*) patients. CI, Confidence interval; EFS, event-free survival; RHR, relative hazard rate. *(From Stock W, La M, Sanford B, et al. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. Blood. 2008;112:1646–1654.)*

A small number of patients with particularly poor prognostic features, such as those with induction failure or extreme hypodiploidy, may undergo bone marrow transplantation during the first remission.

Adolescents and **young adults** with ALL have a poor prognosis compared to children <15 years old. They often have adverse prognostic factors and require more intensive therapy. Patients in this age-group have a superior outcome when treated with pediatric rather than adult treatment protocols (Fig. 544.4). Although the explanation for these findings may be multifactorial, it is important that these patients be treated with pediatric treatment protocols, ideally in a pediatric cancer center.

Genetic polymorphisms of enzymes important in drug metabolism may impact both the efficacy and the toxicity of chemotherapeutic medications. **Pharmacogenetic testing** of the thiopurine *S*-methyltransferase *(TPMT)* gene, which encodes one of the metabolizing enzymes of mercaptopurine, can identify patients with varying levels of TPMT enzyme activity. Decreased TPMT enzyme activity results in accumulation of a toxic metabolite of mercaptopurine and severe myelosuppression, requiring dose reductions of the chemotherapy (see Chapter 543).

Treatment of Relapse

The major impediment to a successful outcome is **relapse** of the disease. Outcomes remain poor among those who relapse, with the most important prognostic indicators being time from diagnosis and site of relapsed disease. In addition, other factors, such as immunophenotype (T-ALL worse than B-ALL) and age at initial diagnosis, have prognostic significance.

Relapse occurs in the bone marrow in 15–20% of patients with ALL and has the most serious implications, especially if it occurs during or shortly after completion of therapy. Intensive chemotherapy with agents not previously used in the patient followed by allogeneic stem cell transplantation can result in long-term survival for some patients with bone marrow relapse (see Chapter 177). **Chimeric antigen receptor** (CAR) T-cell technology will have an increasing role in the treatment of patients who have experienced a relapse of ALL (see Chapter 543). In addition, therapy targeted to the possible underlying pathogenic pathways (tyrosine kinase inhibitors) or cell receptors (blinatumomab) have demonstrated promising results in patients with relapsed or refractory disease (Fig. 544.5)

The incidence of **CNS relapse** has decreased to <5% since introduction of preventive CNS therapy. CNS relapse may be discovered at a routine LP in the asymptomatic patient. Symptomatic patients with relapse in the CNS usually present with signs and symptoms of increased intracranial pressure and can present with isolated cranial nerve palsies. The diagnosis is confirmed by demonstrating the presence of leukemic cells in the CSF. The treatment includes intrathecal medication and cranial or craniospinal irradiation. Systemic chemotherapy also must be used, because these patients are at high risk for subsequent bone marrow relapse. Most patients with leukemic relapse confined to the CNS do well, especially those in whom the CNS relapse occurs longer than 18 months after initiation of chemotherapy.

Testicular relapse occurs in <2% of males with ALL, usually after completion of therapy. Such relapse occurs as painless swelling of one or both testes. The diagnosis is confirmed by biopsy of the affected testis. Treatment includes systemic chemotherapy and possibly local irradiation. A high proportion of males with a testicular relapse can be successfully retreated, and the survival rate of these patients is good.

The most current information on treatment of childhood ALL is available in the PDQ (Physician Data Query) on the NCI website (http://www.cancer.gov/cancertopics/pdq/treatment/childALL/healthprofessional/).

SUPPORTIVE CARE

Close attention to the medical supportive care needs of the patients is essential in successfully administering aggressive chemotherapeutic programs. Patients with high WBC counts are especially prone to **tumor lysis syndrome** as therapy is initiated. The kidney failure associated with very high levels of serum uric acid can be prevented or treated with allopurinol or urate oxidase. Chemotherapy often produces severe myelosuppression, which can require erythrocyte and platelet transfusion and always requires a high index of suspicion and aggressive empirical antimicrobial therapy for sepsis in febrile children with neutropenia. Patients must receive prophylactic treatment for *Pneumocystis jiroveci* pneumonia during chemotherapy and for several months after completing treatment.

The successful therapy of ALL is a direct result of intensive and often toxic treatment. However, such intensive therapy can incur substantial academic, developmental, and psychosocial costs for children with ALL and considerable financial costs and stress for their families. Both long-term and acute toxicity effects can occur. An array of cancer care professionals with training and experience in addressing the myriad of problems that can arise is essential to minimize the complications and achieve an optimal outcome.

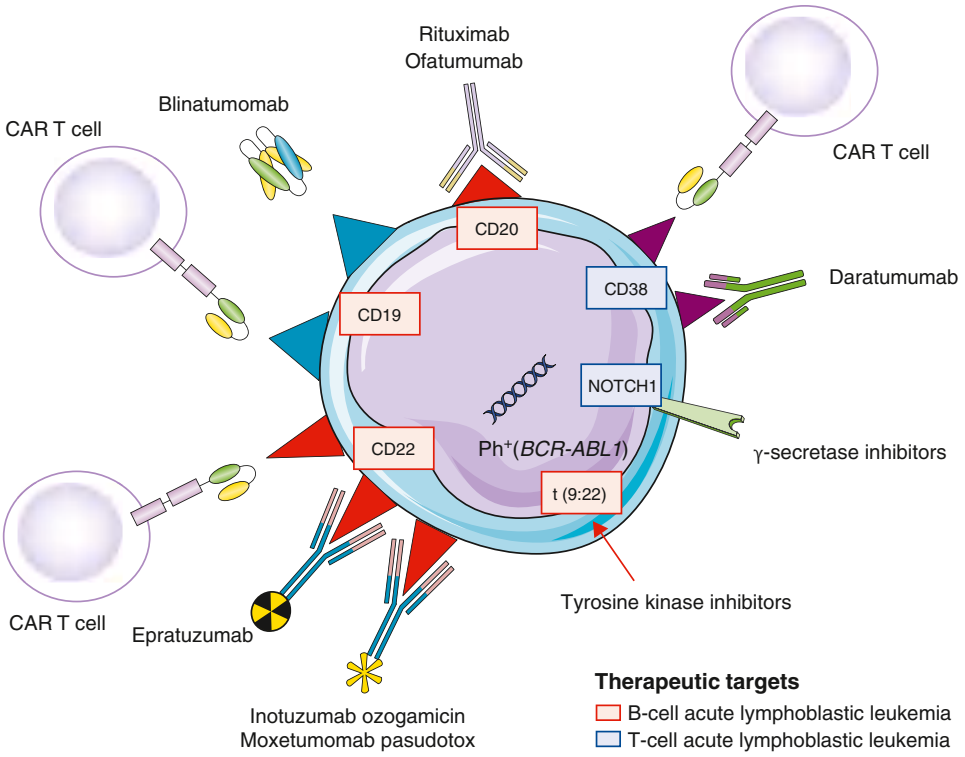


Fig. 544.5 New targeted therapy for acute lymphoblastic leukemia. CAR, Chimeric antigen receptor. *(From Malard F, Mohty M. Acute lymphoblastic leukaemia. Lancet. 2020;395:1146–1158. Fig. 2, p. 1153.)*

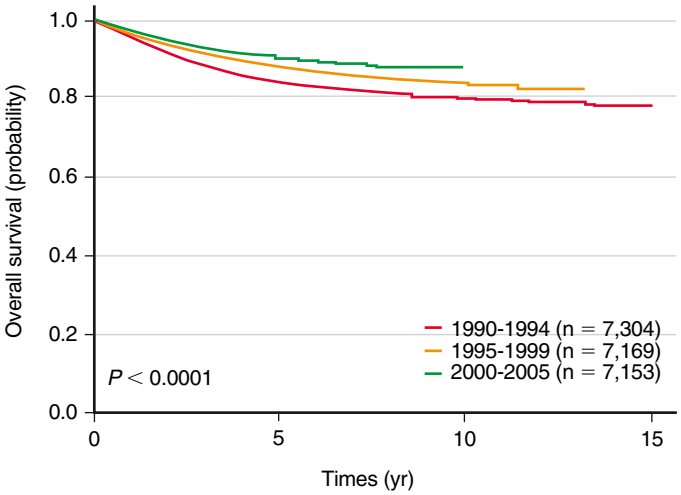


Fig. 544.6 Overall survival probabilities by treatment era for patients with acute lymphoblastic leukemia (ALL) in Children's Oncology Group trials in 1990–1994, 1995–1999, and 2000–2005. *(From Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the Children's Oncology Group. J Clin Oncol. 2012;30:1663–1669.)*

PROGNOSIS

Improvements in therapy and risk stratification have resulted in significant increases in survival rates, with current data showing overall 5-year survival of approximately 90% (Fig. 544.6). Although survivors are more likely to experience significant chronic medical conditions compared with siblings, including musculoskeletal, cardiac, and neurologic conditions, risk-adapted therapy has resulted in a decrease in late effects. Overall, long-term management following ALL should be conducted in a clinic where children and adolescents can be followed by a variety of specialists to address the challenges of these unique patients.

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544.2 Acute Myelogenous Leukemia

Julia C. Meade, Erika D. Friehling, A. Kim Ritchey, David G. Tubergen, and Archie Bleyer

EPIDEMIOLOGY

AML accounts for 11% of the cases of childhood leukemia in the United States; it is diagnosed in approximately 370 children annually. The relative frequency of AML increases in adolescence, representing 36% of cases of leukemia in 15-19 year olds. **Acute promyelocytic leukemia (APL)** is a subtype that is more common in certain regions of the world, but the incidence of the other types is generally uniform. Environmental risk factors have been identified, including ionizing radiation, chemotherapeutic agents (e.g., alkylating agents, epipodophyllotoxin), and organic solvents (benzene). Approximately 10% of children with AML are found to have a germline pathogenic variant predisposing them to leukemia. Certain syndromes are also known to increase the risk of leukemia: Down syndrome, Fanconi anemia, Bloom syndrome, Kostmann syndrome, Shwachman-Diamond syndrome, Diamond-Blackfan syndrome, Li-Fraumeni syndrome, and neurofibromatosis type 1 (see Table 544.1).

CELLULAR CLASSIFICATION

The characteristic feature of AML is that >20% of bone marrow cells on bone marrow aspiration or biopsy touch preparations constitute a fairly homogeneous population of blast cells, with features similar to those that characterize early differentiation states of the myeloid-monocyte-megakaryocyte series of blood cells. Current practice requires the use of flow cytometry to identify cell surface antigens and use of chromosomal and molecular genetic techniques for additional diagnostic precision and to aid the choice of therapy. The WHO has proposed a new classification system that incorporates morphology, chromosome abnormalities, and specific gene pathogenic variants. This system provides significant biologic and prognostic information (Table 544.4).

CLINICAL MANIFESTATIONS

The production of symptoms and signs of AML is a result of replacement of bone marrow by malignant cells and caused by secondary bone

marrow failure. Patients with AML can present with any or all of the findings associated with marrow failure in ALL. In addition, patients with AML may present with signs and symptoms that are uncommon in ALL, including **subcutaneous nodules** or "blueberry muffin" lesions (especially in infants), infiltration of the gingiva (especially in monocytic subtypes), signs and laboratory findings of **disseminated intravascular coagulation** (especially indicative of APL), and discrete masses, known as **chloromas** or **granulocytic sarcomas**. These masses can occur in the absence of apparent bone marrow involvement and typically are associated with a t(8;21) translocation. Chloromas also may be seen in the orbit and epidural space.

DIAGNOSIS

Analysis of bone marrow aspiration and biopsy specimens of patients with AML typically reveals the features of a hypercellular marrow consisting of a monotonous pattern of cells. Flow cytometry and special stains assist in identifying myeloperoxidase-containing cells, thus confirming both the myelogenous origin of the leukemia and the diagnosis. Some chromosomal abnormalities and molecular genetic markers are characteristic of specific subtypes of disease (Table 544.5).

Table 544.4 WHO Classification of Acute Myeloid Neoplasms

Acute myeloid leukemia with recurrent genetic abnormalities
- AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
- APL with *PML-RARA*
- AML with t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*
- AML with t(6;9)(p23;q34.1); *DEK-NUP214*
- AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
- AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); *RBM15-MKL1*
- *Provisional entity: AML with BCR-ABL1*
- AML with variant NPM1
- AML with biallelic pathogenic variants of CEBPA
- *Provisional entity: AML with variant RUNX1*

AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukemia, not otherwise specified
- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Pure erythroid leukemia
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis

Myeloid sarcoma
Myeloid proliferations related to Down syndrome
- Transient abnormal myelopoiesis
- Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

AML, Acute myelogenous leukemia; APL, acute promyelocytic leukemia.
Adapted from Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood.* 2016;127:2391–2405.

PROGNOSIS AND TREATMENT

Aggressive multiagent chemotherapy is successful in inducing remission in approximately 85–90% of patients. Survival has increased dramatically since the 1970s, when only 15% of newly diagnosed patients survived, compared with a current survival rate of 60–70% with modern therapy (Fig. 544.7). Various induction chemotherapy regimens exist, typically including an anthracycline in combination with high-dose cytarabine. Targeting therapy to genetic markers may be beneficial (see Table 544.5). Up to 5% of patients die of either infection or bleeding before a remission can be achieved. Post-remission therapy is chosen based on a combination of cytogenetic and molecular markers of the leukemia as well as the response to induction chemotherapy (MRD assessment). Selected patients with favorable prognostic features [t(8;21); t(15;17); inv(16); *NPM1* pathogenic variants] and robust response to induction chemotherapy have improved outcomes with chemotherapy alone, with stem cell transplantation only recommended after a relapse. However, patients with unfavorable prognostic features (e.g., monosomies 7 and 5, 5q−, and 11q23 abnormalities) who have inferior outcomes with chemotherapy might benefit from stem cell transplant in first remission. With improvements in supportive care, there is no longer a substantial difference in mortality when comparing matched-related stem cell transplants to matched-unrelated stem cell transplants for AML.

Acute promyelocytic leukemia, characterized by a gene rearrangement involving the retinoic acid receptor [t(15;17); PML-RARA], is very responsive to **all-*trans*-retinoic acid (ATRA, tretinoin)** combined with anthracyclines and cytarabine. The success of this therapy makes marrow transplantation in first remission unnecessary for patients with this disease. Arsenic trioxide is an effective noncytotoxic therapy for APL. Data from trials in adults and children show that the use of combined ATRA and arsenic without cytotoxic drugs for initial therapy for selected patients is feasible and highly effective.

Increased **supportive care** is needed in patients with AML because the intensive therapy they receive produces prolonged bone marrow suppression with a very high incidence of serious infections, especially viridans streptococcal sepsis and fungal infection. These patients require prolonged hospitalization and prophylactic antimicrobials.

The most current information on treatment of AML is available in the PDQ (Physician Data Query) on the NCI website (http://www.cancer.gov/cancertopics/pdq/treatment/childAML/healthprofessional/).

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Table 544.5 Prognostic Implications of Common Chromosomal Abnormalities in Pediatric Acute Myelogenous Leukemia

CHROMOSOMAL ABNORMALITY	GENETIC ALTERATION	USUAL MORPHOLOGY	PROGNOSIS
t(8;21)	*RUNX1-RUNX1T1*	Myeloblasts with differentiation	Favorable
inv(16)	*CBFB-MYHII*	Myeloblasts plus abnormal eosinophils with dysplastic basophilic granules	Favorable
t(15;17)	*PML-RARA*	Promyelocytic	Favorable
11q23 abnormalities	*KMT2A(MLL)* rearrangements	Monocytic	Unfavorable
FLT3 alterations	*FLT3*-ITD	Any	Unfavorable
del(7q), −7	Unknown	Myeloblasts without differentiation	Unfavorable

Adapted from Nathan DG, Orkin SH, Ginsburg D, et al., eds. *Nathan and Oski's Hematology of Infancy and Childhood.* 6th ed. Philadelphia: Saunders; 2003: p. 1177.

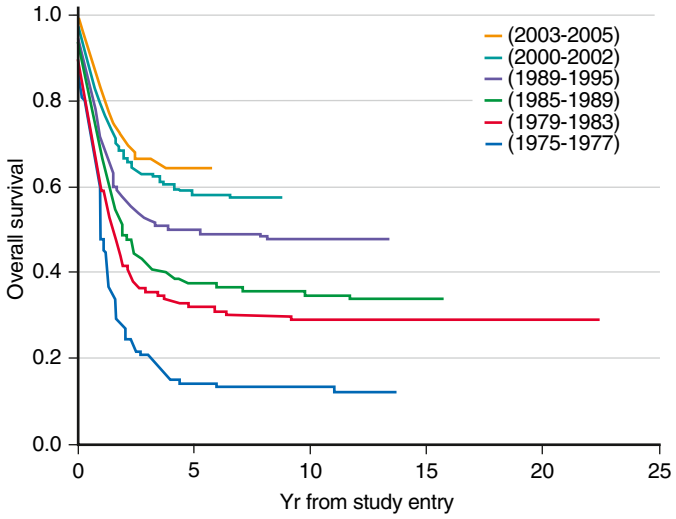

Fig. 544.7 Overall survival showing incremental improvements over the last 40 years in Children's Oncology Group and legacy trials in childhood acute myelogenous leukemia (AML). *(From Gamis AS, Alonzo TA, Perentesis JP, Meshinchi S. On behalf of the COG Acute Myeloid Leukemia Committee: Children's Oncology Group's 2013 blueprint for research: acute myeloid leukemia. Pediatr Blood Cancer. 2013;60:964–971.)*

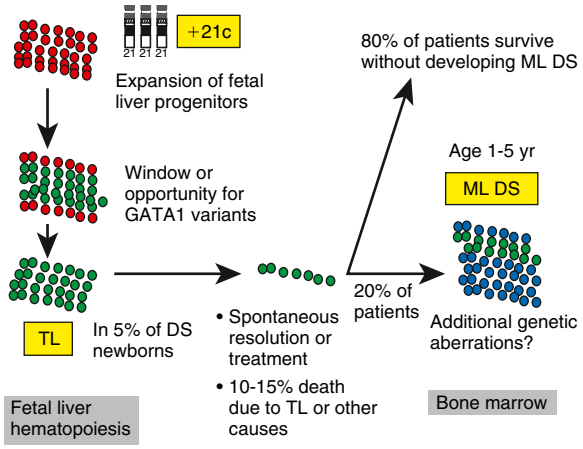

Fig. 544.8 Stepwise development of myeloid leukemia in Down syndrome (ML DS) following transient leukemia (TL). TL arises from expanded fetal liver progenitors as a result of constitutional trisomy 21, providing a window of opportunity for the occurrence of acquired mutations in the hematopoietic transcription factor GATA1. In most cases, TL spontaneously disappears, but some children need treatment because of severe TL-related symptoms. Approximately 20% of children with TL subsequently develop ML DS, which requires additional hits. *(From Zwaan MC, Reinhardt D, Hitzler J, Vyas P. Acute leukemias in children with Down syndrome. Pediatr Clin North Am. 2008;55:53–70.)*

544.3 Down Syndrome and Acute Leukemia and Transient Abnormal Myelopoiesis

A. Kim Ritchey, Julia C. Meade, Erika D. Friehling, David G. Tubergen, and Archie Bleyer

Acute leukemia occurs about 15-20 times more frequently in children with Down syndrome than in the general population (see Chapters 57 and 541). The ratio of ALL to AML in patients with Down syndrome is the same as that in the general population. The exception is during the first 3 years of life, when AML is more common. In children with Down syndrome who have ALL, the expected outcome of treatment has been slightly inferior to that for other children, a difference that can be partially explained by a lack of good prognostic characteristics, such as *ETV6-RUNX1* and trisomies, as well as the presence of genetic abnormalities associated with an inferior prognosis, such as *IKZF1*. However, studies of patients with Down syndrome and standard risk ALL show a 94% 10-year event-free survival. Patients with Down syndrome demonstrate a remarkable sensitivity to methotrexate and other antimetabolites, resulting in substantial toxicity if standard doses are administered. However, in the case of AML, patients with Down syndrome have much better outcomes than children without Down syndrome, with a >90% long-term survival rate. After induction therapy, these patients receive therapy that is less intensive to decrease toxicity while maintaining excellent cure rates.

Approximately 10% of neonates with Down syndrome develop a **transient abnormal myelopoiesis (TAM)**, a unique myeloproliferative disorder characterized by high leukocyte counts, blast cells in the peripheral blood, and associated anemia, thrombocytopenia, jaundice, and hepatosplenomegaly. Hydrops fetalis is an uncommon manifestation of TAM and is associated with pleural effusions, ascites, cardiac infiltration, hepatic dysfunction, and anemia. Mortality is rare from TAM but is associated with hyperleukocytosis, prematurity, ascites, coagulopathy, and renal or hepatic dysfunction. These features usually resolve within the first 3 months of life. Although these neonates can require temporary transfusion support, they usually do not require chemotherapy. Low-dose cytarabine has been used to decrease mortality in patients with high WBC counts and life-threatening complications. Patients who have Down syndrome and who develop TAM require close follow-up, because 20–30% will develop typical leukemia (often **acute megakaryocytic leukemia**) by 3 years of age (mean onset, 16 months). *GATA1* variants (a transcription factor that controls megakaryopoiesis) are present in blasts from patients with Down syndrome who have TAM and also in those with leukemia (Fig. 544.8). The presence of flow cytometry minimal residual disease at 3 months after a diagnosis of TAM is a risk factor for the development of myeloid leukemia.

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544.4 Chronic Myelogenous Leukemia

Erika D. Friehling, Julia C. Meade, A. Kim Ritchey, David G. Tubergen, and Archie Bleyer

Chronic myelogenous leukemia (**CML**) is a clonal disorder of the hematopoietic tissue that accounts for 2–3% of all cases of childhood leukemia. Approximately 99% of the cases are characterized by a specific translocation, t(9;22)(q34;q11), known as the **Philadelphia chromosome**, resulting in a *BCR-ABL* fusion protein.

The presenting symptoms of CML are nonspecific and can include fever, fatigue, weight loss, and anorexia. Splenomegaly also may be present, resulting in pain in the left upper quadrant of the

abdomen. The diagnosis is suggested by a high WBC count with myeloid cells at all stages of differentiation in the peripheral blood and bone marrow. It is confirmed by cytogenetic and molecular studies that demonstrate the presence of the characteristic Philadelphia chromosome and the *BCR-ABL* gene rearrangement. This translocation, although characteristic of CML, is also found in a small percentage of patients with ALL.

The disease is characterized by an initial **chronic phase** in which the malignant clone produces an elevated leukocyte count with a predominance of mature forms but with increased numbers of immature granulocytes. In addition to leukocytosis, blood counts can reveal mild anemia and thrombocytosis. Typically, the chronic phase terminates 3-4 years after onset, when the CML moves into the **accelerated** or "blast crisis" **phase**. At this point, the blood counts rise dramatically, and the clinical picture is indistinguishable from acute leukemia. Additional manifestations can occur, including neurologic symptoms from hyperleukocytosis, which causes increased blood viscosity with decreased CNS perfusion.

Imatinib (Gleevec), an agent designed specifically to inhibit the *BCR-ABL* tyrosine kinase, has been used in adults and children and has shown an ability to produce major cytogenetic responses in >70% of patients (see Table 542.1). Experience in children suggests it can be used safely with results comparable to those seen in adults. Second-generation tyrosine kinase inhibitors, such as **dasatinib and nilotinib**, have improved remission rates in adults and are now included in the first-line therapy in that population. Both agents have been studied in children and have been found to be effective and safe. While waiting for a response to the tyrosine kinase inhibitor, disabling or threatening signs and symptoms of CML can be controlled during the chronic phase with hydroxyurea, which gradually returns the leukocyte count to normal. **Treatment with a tyrosine kinase inhibitor is the current standard for pediatric CML.** Although not considered curative at this time, prolonged responses can be seen, and studies in adults have shown that, in select cases, treatment with the tyrosine kinase inhibitor can be stopped. The role of potentially curative human leukocyte antigen (HLA)-matched family donor stem cell transplant in management of pediatric CML is debated.

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544.5 Juvenile Myelomonocytic Leukemia

Julia C. Meade, Erika D. Friehling, A. Kim Ritchey, David G. Tubergen, and Archie Bleyer

JMML, formerly termed **juvenile chronic myelogenous leukemia,** is a clonal proliferation of hematopoietic stem cells that typically affects children <2 years old. JMML is rare, constituting <1% of all cases of childhood leukemia. Patients with this disease do not have the Philadelphia chromosome characteristic of CML. Patients with JMML present with rashes, lymphadenopathy, splenomegaly, and hemorrhagic manifestations. Analysis of the peripheral blood often shows an elevated leukocyte count with increased monocytes, thrombocytopenia, and anemia with the presence of erythroblasts. The bone marrow shows a myelodysplastic pattern, with blasts accounting for <20% of cells. Most patients with JMML have been found to have pathogenic variants that lead to activation of the ***RAS* oncogene pathway**. About 90% have molecular changes in *NRAS, KRAS, NF1, CBL,* and *PTPN11*. Patients with **neurofibromatosis type 1** and **Noonan syndrome** have a predilection for this type of leukemia because they have germline mutations involved in *RAS* signaling. JMML in the setting of Noonan syndrome and CBL syndrome is unique, with most patients having a spontaneous resolution. However, for other patients with JMML, stem cell transplantation offers the best opportunity for cure, although outcomes are still poor.

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544.6 Infant Leukemia

A. Kim Ritchey, Erika D. Friehling, Julia C. Meade, David G. Tubergen, and Archie Bleyer

The incidence of infant acute leukemia is about 40 cases per million, or about 160 cases per year in the United States. Approximately 2% of cases of childhood leukemia occur before age 1 year. In contrast to the situation in older children, the ratio of ALL in infants to AML is 2:1. Leukemic clones have been noted in cord blood at birth before symptoms appear, and in one case, the same clone was noted in maternal cells (maternal-to-fetal transmission). Chromosome translocations can also occur in utero during fetal hematopoiesis, leading to malignant clone formation.

Several unique biologic features and a particularly poor prognosis are characteristic of ALL during infancy. Almost all are B cell with infrequent T cell. Seventy to 80% of the cases demonstrate rearrangements of the *KMT2A (MLL)* gene, found at the site of the 11q23 band translocation, the majority of which are the t(4;11). This subset of patients largely accounts for the very high relapse rate. These patients often present with hyperleukocytosis and extensive tissue infiltration producing organomegaly, including CNS disease. Subcutaneous nodules, known as **leukemia cutis**, and tachypnea caused by diffuse pulmonary infiltration by leukemic cells are observed more often in infants than in older children. The leukemic cell morphology is usually that of large, irregular lymphoblasts, with a phenotype negative for the CD10 (common ALL antigen) marker (pro-B), unlike most older children with B-ALL, who are $CD10^+$.

Very intensive chemotherapy programs, including stem cell transplantation, are being explored in infants with *KMT2A (MLL)* gene rearrangements, but none has yet proved satisfactory. Infants defined as high risk (*KMT2A*, age <6 months and WBC ≥300,000) have survival of only 30%, whereas infants with the *KMT2A* without other high-risk features have survival of 58%. Infants with leukemia who lack the *KMT2A* rearrangement have a prognosis somewhat inferior to that of older children with ALL.

Infants with AML often present with CNS or skin involvement and have a subtype known as **acute myelomonocytic leukemia.** The treatment may be the same as that for older children with AML, with similar outcome. Meticulous supportive care is necessary because of the young age and aggressive therapy needed in these patients.

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Chapter 545

Lymphoma

Jessica Hochberg, Stanton C. Goldman, and Mitchell S. Cairo

INTRODUCTION

Lymphoma is the third most common cancer among U.S. children (≤14 years old), with an annual incidence of 15 cases per 1 million children. It is the most common cancer in adolescents, accounting for >25% of newly diagnosed cancers in those 15-19 years old. The two broad categories of lymphoma, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), have different clinical manifestations and treatments.*

545.1 Hodgkin Lymphoma

Stanton C. Goldman, Jessica Hochberg, and Mitchell S. Cairo

Hodgkin lymphoma (HL) is a malignant process involving the lymphoreticular system that accounts for 6% of childhood cancers. In the United States, HL accounts for approximately 5% of cancers in children ≤14 years old; it accounts for approximately 15% of cancers in adolescents (15-19 years), making HL the most common malignancy in this age-group.

EPIDEMIOLOGY

The worldwide incidence of HL is approximately 2-4 new cases per 100,000 population per year. There is a bimodal age distribution, with peaks at 15-35 years of age and again after 50 years. HL is the most common cancer seen in adolescents and young adults and the third most common in children <15 years old. In developing countries, the early peak tends to occur before adolescence. A male predominance is found among young children but lessens with age. Infectious agents may be involved, such as human herpesvirus 6, cytomegalovirus, and Epstein-Barr virus (EBV). The role of EBV is supported by prospective serologic studies. Infection with EBV confers a fourfold higher risk of developing HL and may precede the diagnosis by years. EBV antigens have been demonstrated in HL tissues, particularly type II latent membrane proteins 1 and 2. Some studies have suggested that elevated copies of EBV by polymerase chain reaction correspond to worse prognosis. The EBV antigens latent membrane protein 1 and 2 have been used as targets for cytotoxic T-lymphocyte therapy in patients with relapsed/refractory HL.

PATHOGENESIS

The **Reed-Sternberg (RS) cell,** a pathognomonic feature of HL, is a large cell (15-45 μm in diameter) with multiple or multilobulated nuclei. This cell type is considered the hallmark of HL, although similar cells are seen in infectious mononucleosis, NHL, and other conditions. The RS cell is clonal in origin and arises from the germinal center B cells but typically has lost most B-cell gene expression and function. There is no single simple genetic aberration that leads to malignant transformation of the RS cell; rather, a combination of somatic pathogenic variants, chromosomal instability, and complex chromosomal rearrangements has been reported with no particular pattern or frequency. This typically leads to cell regulation defects such as constitutive activation of the nuclear factor (NF)-κB pathway or abnormal regulation of the Bcl-2 family of proteins. HL is characterized by a variable number of RS cells surrounded by an inflammatory infiltrate of lymphocytes, macrophages, plasma cells, and eosinophils in different proportions, depending on the HL histologic subtype. The interaction between the RS cell and these background inflammatory cells with their associated cytokine release is important in the development and progression of HL. Reactive infiltration of eosinophils and $CD68^+$ macrophages and increased concentrations of cytokines, such as interleukin (IL)-1 and IL-6 and tumor necrosis factor, are all associated with an unfavorable prognosis. Other factors associated with a worse prognosis include advanced stage, the presence of systemic symptoms, decreased response to therapy, and slow response to therapy. In addition, evidence of $CD8^+$ T cells surrounding the RS cell offers evidence of an important role in T-cell promotion of malignant cell survival, perhaps through the CD30 and CD40 ligands found on RS cells as well as immune checkpoint inhibition pathways. Other features that distinguish the histologic subtypes include various degrees of fibrosis and the presence of collagen bands, necrosis, or malignant reticular cells (Fig. 545.1). The distribution of subtypes varies with age.

The **Revised World Health Organization Classification of Lymphoid Neoplasms** includes two modifications of the older Rye system. HL appears to arise in lymphoid tissue and spread to adjacent lymph node areas in a relatively orderly manner (Table 545.1). Hematogenous spread also occurs, leading to involvement of the liver, spleen, bone, bone marrow (BM), or brain, and is usually associated with systemic symptoms.

CLINICAL MANIFESTATIONS

Patients typically present with painless, nontender, firm, rubbery cervical or supraclavicular lymphadenopathy and usually some degree of mediastinal involvement. Clinically detectable hepatosplenomegaly may be encountered. Depending on the extent and location of nodal and extranodal disease, patients may present with symptoms and signs of airway obstruction (dyspnea, hypoxia, cough), pleural or pericardial effusion, hepatocellular dysfunction, or BM infiltration (anemia, neutropenia, or thrombocytopenia). Systemic symptoms, classified as **B symptoms**, that are considered important in staging are unexplained fever >38°C (100.4°F), weight loss >10% total body weight over 6 months, and drenching night sweats. Less common and not considered of prognostic significance are symptoms of pruritus, lethargy, anorexia, or pain. Patients also exhibit immune system deficiencies that often persist during and after therapy.

DIAGNOSIS

Any patient with persistent, unexplained lymphadenopathy unassociated with an obvious underlying inflammatory or infectious process should undergo chest radiography to identify the presence of a large mediastinal mass before undergoing lymph node biopsy (Fig. 545.2). Formal excisional biopsy is preferred over needle biopsy to ensure that adequate tissue is obtained, both for light microscopy and for appropriate immunohistochemical and molecular studies. Once the diagnosis of HL is established, extent of disease (stage) should be determined to allow selection of appropriate therapy (Table 545.2). Evaluation includes history, physical examination, and imaging studies, including chest radiograph; CT scans of the neck, chest, abdomen, and pelvis; and PET scan (Fig. 545.3). Laboratory studies should include a CBC to identify abnormalities that might suggest marrow involvement, ESR, and measurement of serum ferritin, which is of some prognostic significance and, if abnormal at diagnosis, serves as a baseline to evaluate the effects of treatment. A chest radiograph is particularly important for measuring the size of the mediastinal mass in relation to the maximal diameter of the thorax (see Fig. 545.2). This determines "bulk" disease and becomes prognostically significant. Chest CT more clearly defines the extent of a mediastinal mass if present and identifies hilar nodes and pulmonary parenchymal involvement, which may not be evident on chest radiographs (see Fig. 545.3). BM aspiration and biopsy should be performed to rule out advanced disease. Bone scans are performed in patients with bone pain and/or elevation of alkaline phosphatase. Fluorodeoxyglucose (FDG) PET imaging has advantages over traditional gallium scanning, with higher resolution, better dosimetry, less intestinal activity, and the potential to quantify disease (Table 545.3).

* The views expressed are the result of independent work and do not necessarily represent the views or findings of the U.S. Food and Drug Administration or the United States.

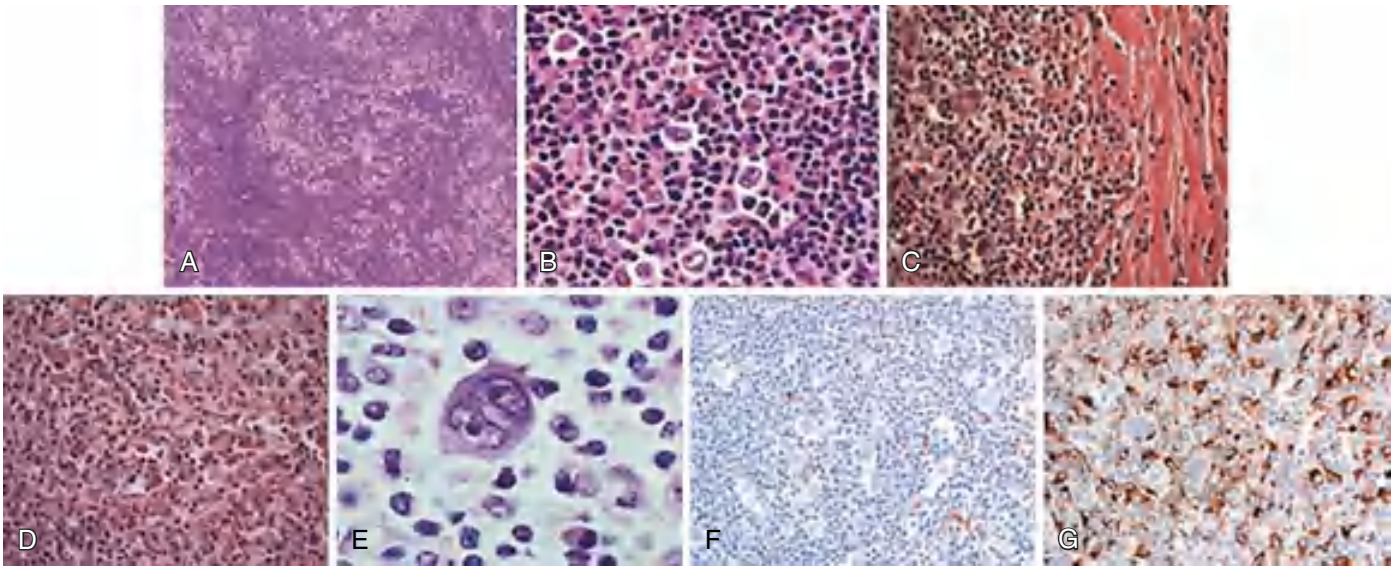

Fig. 545.1 Histologic subtypes of Hodgkin lymphoma. **A,** Hematoxylin and eosin (H&E) stains of nodular lymphocyte–predominant Hodgkin lymphoma (NLPHL) demonstrating a nodular proliferation with a moth-eaten appearance. **B,** High-power view demonstrating the neoplastic L and H cells found in NLPHL. **C,** Classic Hodgkin lymphoma, nodular sclerosis subtype. Large mononuclear and binucleate Reed-Sternberg cells are seen admixed in the inflammatory cell background. **D,** Classic Hodgkin lymphoma, mixed cellularity subtype, demonstrating increased numbers of Reed-Sternberg cells in a mixed inflammatory background without sclerotic changes. **E,** High-power view of a classic Reed-Sternberg cell showing binucleate cells with prominent eosinophilic nucleoli and relatively abundant cytoplasm. **F,** Few $CD68^+$ macrophages in a patient with successful treatment. **G,** Many $CD68^+$ macrophages in a treatment failure patient.

Table 545.1 New World Health Organization/Revised European–American Classification of Lymphoid Neoplasms for Hodgkin Lymphoma

Nodular lymphocyte predominance
Classical Hodgkin lymphoma
Lymphocyte rich
Mixed cellularity
Nodular sclerosis
Lymphocyte depletion

From Harris NL, Jaffe ES, Diebold J, et al. The World Health Organization classification of neoplastic diseases of the haematopoietic and lymphoid tissues: report of the Clinical Advisory Committee Meeting, Airlie House, Virginia, November 1997. *Histopathology*. 2000;36:69–87.

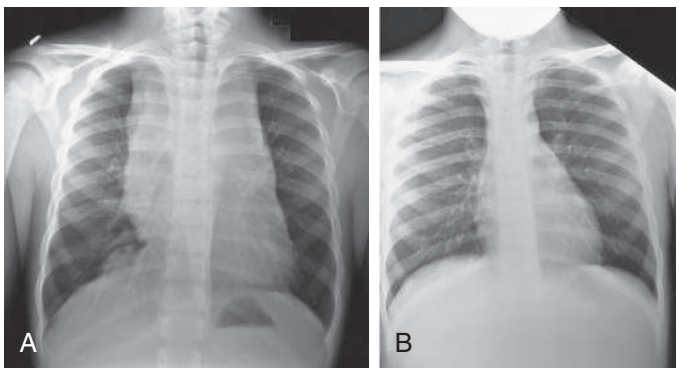

Fig. 545.2 **A,** Anterior mediastinal mass in a patient with Hodgkin disease before therapy. **B,** After 2 months of chemotherapy, the mediastinal mass has disappeared.

PET scans are essential as a prognostic tool in HL, enabling therapy to be reduced in those predicted to have a good outcome and identifying those at risk of relapse.

The staging classification currently used for HL was initially adopted at the **Ann Arbor Conference** in 1971 and was revised in 1989. The **Lugano classification** was developed in 2014 and incorporates standardized staging and response criteria for FDG-PET–avid lymphomas (see Table 545.2). HL can be subclassified into A or B categories: *A* is used to identify asymptomatic patients, and *B* is used for patients who exhibit any B symptoms. Extralymphatic disease resulting from direct extension of an involved lymph node region is designated by category *E*. A *complete response* in HL is defined as the complete resolution of disease on clinical examination and imaging studies, or at least 70–80% reduction of disease and a change from initial positivity to negativity on PET scanning, reflecting residual fibrosis, which is common.

Table 545.2 Lugano Classification for Hodgkin Lymphoma*

STAGE	INVOLVEMENT	EXTRANODAL STATUS
I	One node or group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky	II as above with "bulky" disease	Not applicable
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Lung, liver, bone marrow, bone marrow, bone

*The absence or presence of fever >38°C (100.4°F) for 3 (some suggest 7) consecutive days, drenching night sweats, or unexplained loss of >10% of body weight in the 6 months preceding admission are to be denoted in all cases by the suffix letter A or B, respectively.

From *Cheson* BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059–3067.

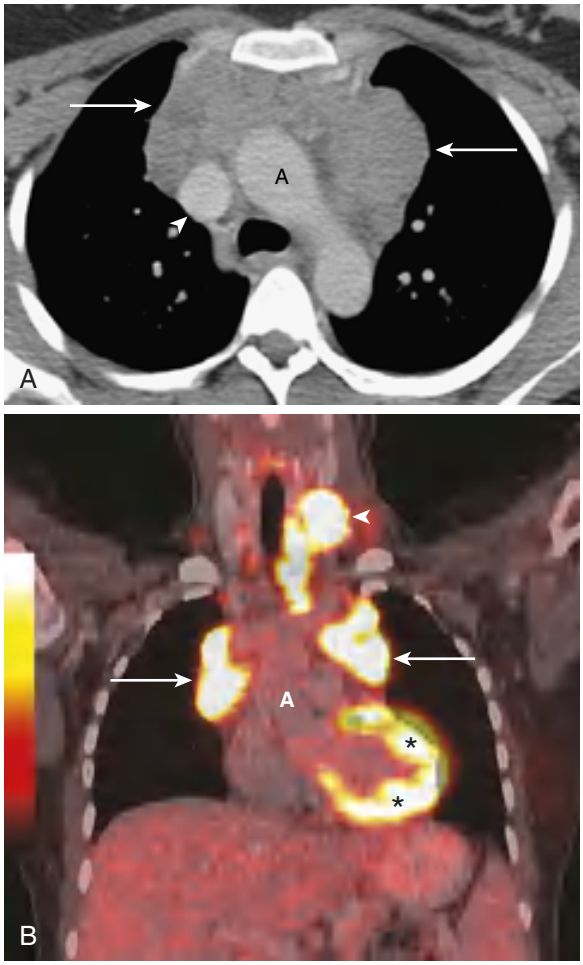

Fig. 545.3 Hodgkin lymphoma in a young individual. **A,** CT shows a homogeneous anterior mediastinal mass *(arrows)*. The *arrowhead* points to the superior vena cava. **B,** PET/CT in the coronal plane. The mass shows marked fluorodeoxyglucose (FDG) activity *(arrows)*. Note the associated left neck mass *(arrowhead)*. The left ventricle activity *(asterisks)* is normal. A, Ascending aorta. *(From Haaga JR, Boll DT, et al., eds. CT and MRI of the Whole Body [Vol, 1]. Philadelphia: Elsevier; 2017: Fig. 38-89, p. 1065.)*

Table 545.3	TEP Evaluation After Two Chemotherapy Cycles Using Deauville Criteria 5-Point Scale
	^{18}F-FDG UPTAKE
1	No uptake
2	Uptake lower than or equal to that of mediastinal blood pool
3	Uptake higher than that of mediastinum and lower than or equal to that of the liver
4	Uptake moderately higher than that of the liver at any site
5	Uptake markedly higher than that of the liver at any site or at new sites of disease, or both
X	New areas of uptake unlikely to be related to lymphoma

^{18}F-FDG, fluorodeoxyglucose F^{18}; TEP, technical expert panel.
From Brice P, de *Kerviler* E, Friedberg JW. Classical Hodgkin lymphoma. *Lancet.* 2021;398:1518–1526. Table 2.

TREATMENT

Multiple agents allow different mechanisms of action to have nonoverlapping toxicities so that full doses can be given to each patient. Chemotherapy and radiation therapy are both effective in the treatment of HL. Treatment of HL in pediatric patients is **risk adapted** and involves the use of combined chemotherapy with or without low-dose involved-field radiation therapy based on response. Treatment is determined largely by disease stage, presence or absence of B symptoms, and the presence of *bulky nodal disease*. The development of effective multiagent combination **chemotherapy** and **immunotherapy** is a major milestone in the treatment of HL, resulting in a complete response rate of 70–80% and cure rate of 40–50% in patients with advanced-stage disease. However, this regimen also led to significant acute and long-term toxicity. The desire to reduce side effects and morbidity has stimulated attempts to reduce the intensity of chemotherapy, as well as radiation dose and volume. Combinations of chemotherapy have reduced the risk of secondary cancers. Also, current radiation therapy uses lower amounts of overall radiation in addition to narrowing the radiation treatment field to either involved-field or even involved-node irradiation. The current **Children's Oncology Group** and other trials are investigating whether radiation therapy can be eliminated altogether in patients who have a very good rapid early response to induction chemotherapy.

Chemotherapy agents used to treat children and adolescents with HL include cyclophosphamide, procarbazine, vincristine or vinblastine, prednisone or dexamethasone, doxorubicin, bleomycin, dacarbazine, etoposide, methotrexate, and cytosine arabinoside. The combination chemotherapy regimens in current use are based on **COPP** (cyclophosphamide, vincristine [Oncovin], procarbazine, and prednisone) or **ABVD** (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine), with the addition of prednisone, cyclophosphamide, and etoposide (**ABVE-PC** and **BEACOPP**) or **BAVD** (brentuximab vedotin, doxorubicin [Adriamycin], vincristine, dacarbazine) in various combinations for intermediate- and high-risk groups (Table 545.4). *Risk-adapted protocols* are based on both staging criteria and rapidity of response to initial chemotherapy. The aim is to reduce total drug doses and treatment duration and to eliminate radiation therapy, if possible.

Agents such as those that disrupt the NF-κB pathway or monoclonal antibodies (mAbs) that target RS tumor cells, as well as the benign reactive cells that surround them, are being investigated. Ongoing clinical trials report encouraging results with anti-CD20 antibody **(rituximab)**, particularly in nodular lymphocyte-predominant HL, for which trials in relapsed disease have shown an overall response rate of 94%. In addition, anti-CD30 agents are being used that target the RS cells themselves, where CD30 is abundantly expressed. **Brentuximab vedotin** is an antibody–drug conjugate approved by the U.S. Food and Drug Administration to treat HL. It combines the chimeric anti-CD30 antibody brentuximab linked to the antimitotic agent monomethyl auristatin E. This agent shows impressive efficacy as single-agent therapy in refractory HL and is being tested as part of up-front therapy combined with chemotherapy in patients with newly diagnosed disease where pediatric trials incorporating brentuximab to replace vincristine in the OEPA/COPDac backbone have demonstrated overall safety, tolerability, and efficacy with 97% event-free survival (EFS) and the ability to limit radiation to involved node radiation sites only. Furthermore, the combination of both brentuximab and rituximab, together with **AVD** chemotherapy in newly diagnosed patients, has shown 100% efficacy while allowing for the elimination of toxic alkylator agents, topoisomerase inhibitors, bleomycin, and any radiation in the majority of patients. **EBV-specific cytotoxic T lymphocytes (CTLs)** can also be generated from allogeneic donors for patients with advanced HL. In clinical trials, these cells show promising results, with enhanced antiviral activity and stabilization of disease. EBV-CTLs have been developed and are currently being investigated. These enhanced EBV-CTLs are designed to be latent membrane protein 1 and 2 specific and can be generated from second-party (in the case of BM transplant recipients) or even third-party donors for patients with refractory disease. These approaches represent an exciting direction in adoptive cellular tumor

Table 545.4 Chemotherapy Regimens for Children, Adolescents, and Young Adults with Hodgkin Lymphoma

CHEMOTHERAPY REGIMEN	CORRESPONDING AGENTS
ABVD	Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine
ABVD-Rituxan	Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine, rituximab
ABvVD	Doxorubicin (Adriamycin), brentuximab, vinblastine, dacarbazine
ABvVD-R	Doxorubicin (Adriamycin), brentuximab, vinblastine, dacarbazine, rituximab
AEPA/CAPDac	Brentuximab, etoposide, prednisone, and doxorubicin/cyclophosphamide, brentuximab, prednisone, and dacarbazine
ABVE (DBVE)	Doxorubicin (Adriamycin), bleomycin, vincristine, etoposide
VAMP	Vincristine, doxorubicin (Adriamycin), methotrexate, prednisone
OPPA ± COPP (females)	Vincristine (Oncovin), prednisone, procarbazine, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
OEPA ± COPP (males)	Vincristine (Oncovin), etoposide, prednisone, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
COPP/ABV	Cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine, doxorubicin (Adriamycin), bleomycin, vinblastine
BEACOPP (advanced stage)	Bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
COPP	Cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine
CHOP	Cyclophosphamide, doxorubicin (Adriamycin), vincristine (Oncovin), prednisone
ABVE-PC (DBVE-PC)	Doxorubicin (Adriamycin), bleomycin, vincristine, etoposide, prednisone, cyclophosphamide
ICE ± (Brentuximab)	Ifosfamide, carboplatin, etoposide ± brentuximab
Ifos/Vino ± (Brentuximab)	Ifosfamide, vinorelbine ± brentuximab

immunology, and it remains to be determined whether CTLs will have improved cytotoxicity that can overcome inhibitory signals.

RELAPSE

Most relapses occur within the first 3 years after diagnosis, but relapses as late as 10 years have been reported. Relapse cannot be predicted accurately with this disease. Poor prognostic features include tumor bulk, stage at diagnosis, extralymphatic disease, and presence of B symptoms. Patients who achieve an initial chemosensitive response but relapse or progress before 12 months from diagnosis are candidates for myeloablative chemotherapy and autologous stem cell transplantation (SCT), with or without radiation therapy. Retrospective studies show a significant decrease in relapse in patients with HL following allogeneic vs autologous SCT. Reduced-intensity conditioning or nonmyeloablative regimens are successful at reducing regimen-related morbidity and mortality associated with myeloablative allogeneic SCT while still achieving a strong graft versus HL effect. For more difficult-to-treat refractory cases, radioimmunotherapy agents such as Zevalin and Bexxar are being trialed, often in combination with SCT strategies. Both are monoclonal anti-CD20 antibodies to which a radioactive isotope is directly linked. Clinical trials show each to be more effective than rituximab in NHL patients, and there is some interest in studying their use in the CD20 subpopulation of HL patients. Tumors can evade the host immune system by exploiting immune checkpoint pathways, such as the CTL-associated protein four (CTLA-4) and **programmed-death protein 1 (PD-1)** pathways. PD-1 is a negative co-stimulatory receptor with increased expression reported on T cells. PD-1 is critical for suppression of T-cell activation, with binding of **programmed-death ligand 1 (PD-L1)** resulting in "T-cell exhaustion." Blockade of this interaction renders previously anergic T cells responsive to antigen. Evidence has shown that antitumor immune responses can be improved by blocking immune checkpoint inhibitors in the tumor microenvironment. Phase I trials of the PD-1 blocking mAbs **nivolumab** and **pembrolizumab** have shown significant promise in refractory patients. Phase II clinical trials suggest that combining immunotherapy such as rituximab or brentuximab with PD-1 checkpoint blockade will be highly effective against relapsed lymphomas and well tolerated, without treatment-related adverse events. With the success seen in relapsed or refractory patients, PD-1 blockade likely will have a role in frontline therapy as well where studies have shown promise in combination with chemotherapy in adults, with pediatric trials currently under investigation.

PROGNOSIS

With the use of current therapeutic regimens, patients with favorable prognostic factors and early-stage disease have an EFS of 85–90% and an overall survival (OS) at 5 years of >95%. Patients with advanced-stage disease have slightly lower EFS (80–85%) and OS (90%), respectively, although OS has approached 100% with dose-intense chemotherapy (Table 545.5). Prognosis after relapse depends on the time from completion of treatment to recurrence, site of relapse (nodal vs extranodal), and presence of B symptoms at relapse. Patients whose disease relapses >12 months after chemotherapy alone or combined-modality therapy have the best prognosis, and their relapses usually respond to additional standard therapy, resulting in a long-term survival of 60–70%. A myeloablative autologous SCT in patients with refractory disease or relapse within 12 months of therapy results in a long-term survival rate of only 40–50%. Allogeneic SCT has shown promise in patients with poor-risk features at relapse/progression.

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545.2 Non-Hodgkin Lymphoma

Stanton C. Goldman, Jessica Hochberg, and Mitchell S. Cairo

Non-Hodgkin lymphoma (**NHL**) accounts for approximately 60% of lymphomas in children and is the second most common malignancy between ages 15 and 35 years. The annual incidence of pediatric NHL in the United States is 750-800 cases per year. In contrast to adult NHL, which is predominantly indolent, pediatric NHL is usually *high grade*. Although >70% of patients present with advanced disease, the prognosis has improved dramatically, with survival rates of 90–95% for localized disease and 80–95% for advanced disease.

EPIDEMIOLOGY

Although most children and adolescents with NHL present with de novo disease, a small number of patients have NHL secondary to specific etiologies, including inherited or acquired immunodeficiencies (e.g., severe combined immunodeficiency syndrome, Wiskott-Aldrich syndrome), virus-associated malignancy (e.g., HIV, EBV), and as part of genetic syndromes (e.g., ataxia-telangiectasia, Bloom syndrome).

Table 545.5 Treatment Regimens and Outcome by Disease Staging

		LOCALIZED/LOW STAGE	INTERMEDIATE	ADVANCED
Hodgkin lymphoma	**Treatment**	*POG study 9426/GPOH-HD 95:* ABVD-type therapy ± IFRT (risk adapted based on early response to chemotherapy)	*Stanford/DAL-HD-90:* COPP-based or dose-intense multiagent chemotherapy + low-dose RT *POG 9426/CCG 5942:* ABVD-type therapy ± IFRT (risk adapted) *ABvVD-R*	*POG 8725/DAL-HD-90:* Dose-intense multiagent chemotherapy + low-dose RT *HD9/HD12/CCG 59704:* Dose-intense BEACOPP ± IFRT *AEPA/CAPDac* *ABvVD-R*
	Prognosis	5-yr EFS: 85–90% 5-yr OS: 95%	*Stanford/DAL-HD-90:* 5-yr EFS: 89–92% *POG 9426/CCG 5942:* 5-yr EFS: 84% 5-yr OS: 91% *ABvVD-R:* 5-yr EFS/OS: 100%	*POG 8725:* 5-yr EFS: 72–89% (age-based) *DAL-HD-90:* 5-yr EFS: 86% 5-yr OS: 85–90% *HD9/HD12/CCG 59704:* 5-yr EFS/OS: 88-93/~100% *AEPA/CAPDac:* 3 yr EFS/OS: 97.4%/98.7% *ABvVD-R:* 5-yr EFS/OS: 100%
Burkitt lymphoma and diffuse large B-cell lymphoma	**Treatment**	*FAB/LMB 96 Group A therapy:* Complete surgical resection followed by two cycles of chemotherapy	*FAB/LMB 96 Group B therapy:* Reduced cyclophosphamide and no maintenance therapy *COG ANHL01P1*: FAB/LMB Group B therapy + rituximab	*FAB/LMB 96 standard-intensity Group C therapy*: Reduction, induction, intensification, and maintenance therapy *COG ANHL01P1*: FAB/LMB Group C therapy + rituximab
	Prognosis	4-yr EFS: 98% (CI_{95} 94-99.5%) 4-yr OS: 99% (CI_{95} 96-99.9%)	*FAB/LMB96:* 4-yr EFS: 92% (CI_{95} 90–94%) 4-yr OS: 95% (CI_{95} 93–96%) *PMB DLBCL has worse prognosis (EFS/OS: 66/73%) *COG ANHL01P1:* 3-yr EFS 93% (CI_{95} 79-98%) 3-yr OS 95% (CI_{95} 83–99%)	*FAB/LMB96:* 4-yr FS:BM−/CNS−: 91% ± 3%BMCNS+: 85% ± 6%BM+/CNS+: 66% ± 7% *COG ANHL01P1:* 3-yr EFS/OS:BM+ or CNS+: 90% (CI_{95} 75–96%) CNS+: 93% (CI_{95} 61–99%)
Lymphoblastic lymphoma	**Treatment**	*NHL-BFM86/90/95:* Two cycles of ALL-type therapy *COG A5971:* ALL-type therapy × 2 yr without prophylactic cranial RT	No intermediate group; disease classified as localized (stages I/II) or advanced (stages III/IV)	*NHL-BFM86/90/95:* ALL-type therapy × 2 yr ± px CRT *CCG 5941:* Intensive chemotherapy × 1 yr + cranial RT if CNS + at diagnosis
	Prognosis	*COG A5971:* 5-yr EFS: 90 (CI_{95} 78–96%) 5-yr OS: 96 (CI_{95} 84–99%)	No intermediate group; see above	*NHL-BFM95:* 5-yr EFS: 90% ± 3% (III), 95 ± 5% (IV) *CCG 5941:* 5-yr EFS/OS: 78% ± 5%/85% ± 4%
Anaplastic large cell lymphoma	**Treatment**	*EICHNL ALCL 99:* Short intensive chemotherapy + HD MTX Completely resected stage I disease may be treated with surgery alone	No intermediate group; disease classified as standard risk (no skin, visceral, or mediastinal involvement) or high risk (presence of skin, mediastinal, or visceral involvement)	*ALCL 99, CCG 5941:* Short intensive chemotherapy + HD MTX *COG ANHL0131*: APO (doxorubicin, prednisone, vincristine) ± vinblastine
	Prognosis	*EICHNL database:* 5-yr PFS: 89% (CI_{95} 82–96%) 5-yr OS: 94% (CI_{95} 89–99%)	No intermediate group; see above	*ALCL 99:* 2-yr EFS: 71% (CI_{95} 75–77%) 2-yr OS: 94% (CI_{95} 89-95%) *COG 5941:* 5-yr EFS 68% (CI_{95} 57–78%) 5-yr OS: 80% (CI_{95} 69–87%) *COG ANHL0131:* 2-yr EFS 79% (CI_{95} 71–88%) 2-yr OS 89% (CI_{95} 83–95%)

ABVD, Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine; ABvVD-R, doxorubicin (adriamycin), bleomycin, vinblastine, dacarbazine rituximab; AEPA/CAPDac, Adcetris (brentuximab vedotin), etoposide, prednisone, doxorubicin (adriamycin), cyclophosphamide, adcetris (brentuximab vedotin), prednisone, cacarbazine; ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; ANHL, Children's Oncology Group non-hodgkin lymphoma study; BEACOPP, bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine; BM, bone marrow (involvement); CCG, Children's Cancer Group; CI_{95}, 95% confidence interval; CNS, central nervous system (involvement); COG, Children's Oncology Group; COPP, cyclophosphamide, vincristine (Oncovin), prednisone, procarbazine; CRT, chemoradiotherapy; DAL-HD, German-Austrian Lymphoma Froup Hodgkin 90 Study; EFS, event-free survival; EICHNL, European Intergroup for Childhood Non-Hodgkin Lymphoma; FAB, French-American-British; HD MTX, high-dose methotrexate; IFRT, involved-field radiation therapy; LMB, Lymphome Malins de Burkitt; MTX, methotrexate; NHL-BFM, non-Hodgkin lymphoma Berlin-Frankfurt-Munster; OS, overall survival; PFS, progression-free survival; PMB DLBCL, primary mediastinal B-cell diffuse large B-cell lymphoma; POG, Pediatric Oncology Group; px, prophylactic; RT, radiation therapy.

However, most children in North America and Europe in whom NHL develops have no obvious genetic or environmental etiology.

PATHOGENESIS

Three most prevalent subtypes of childhood and adolescent NHL with different treatment approaches are **lymphoblastic lymphoma (LBL), mature B-cell lymphoma**, and **anaplastic large cell lymphoma** (**ALCL**; Figs. 545.4 and 545.5). LBL arises from precursor T lymphocytes and less often from precursor B lymphocytes, with biology and treatment approaches similar to acute lymphoblastic leukemia. Mature B-cell lymphomas comprise two main pathologies, **Burkitt lymphoma (BL)** and **diffuse large B-cell lymphoma (DLBCL)**. DLBCL is further divided into several subtypes: the *germinal center B-cell–like* subtype, which carries a favorable prognosis and accounts for most pediatric cases of DLBCL, and the subtypes with poorer prognosis, including *activated B-cell–like* and *primary mediastinal B-cell* subtypes. Primary mediastinal B-cell subtype of DLBCL shares molecular signature more akin to HL then germinal center–derived DLBCL. Most cases of ALCL are of mature T-cell origin, with a smaller percentage of null-cell and B-cell origin. Cellular surface markers can aid in differentiating NHL subtypes and present opportunities for specific antibody-targeted treatments. BL and DLBCL express the mature B-cell antigens CD20 (the target of rituximab) and CD22, whereas ALCL expresses the CD30 antigen (the target of the antibody conjugate brentuximab vedotin). Some pathologic subtypes have specific cytogenetic aberrations. Children with BL frequently have a driver genetic change involving the *MYC* gene juxtaposed to an immunoglobulin chain in the form of translocations: t(8;14) (90%) or, less often, a t(2;8) or t(8;22) translocation (10%). Children with BL who have additional chromosomal aberrations such as 13q deletion or complex karyotype have a poorer prognosis. Unlike adult DLBCL, a higher proportion of pediatric DLBCL may also have c-myc dysregulation with t(8;14) translocation (30%) and often have a complex (80%) and aneuploid (80%) karyotype. In recent years a Burkitt morphology lymphoma (Burkitt-like) that lacks a c-myc driver has been categorized by findings of 11q aberrations and several target genes such as chromatin remodeling complex pathogenic variants (INO80) that likely contribute to lymphomagenesis (Fig. 545.6). Patients with ALCL usually have a driver t(2;5) translocation (90%), which results in the formation of a fusion gene encoding the constitutively active nucleophosmin–anaplastic lymphoma kinase (ALK) tyrosine kinase and can be targeted by the oral agent, crizotinib. T-cell LBL harbors many of the same cytogenetic abnormalities as T-cell acute lymphoblastic leukemia (T-ALL), including rearrangements with breakpoints at 14q11.2 involving the T-cell receptor and multiple other rearranged genes. Loss of heterozygosity at chromosome 6q defines a poor-risk subgroup of T-LBL patients.

Genomic studies have offered insights into NHL pathogenesis as well as elucidated potential targets for novel therapies. Gene expression profiling of T-LBL and T-ALL has implicated the activation of oncogenic transcription factors as a result of aberrant T-cell receptor gene rearrangement. One of the most frequently activated signaling pathways is NOTCH1, which may be amenable to therapeutic targeting with γ-secretase inhibitors. In BL and DLBCL, extensive genomic work has identified unique gene expression signatures that

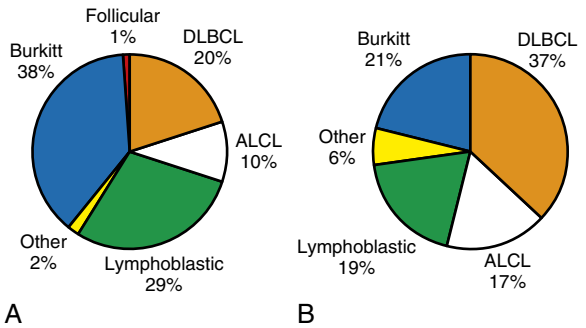

Fig. 545.4 Incidence of non-Hodgkin lymphoma subtypes. **A,** In 0- to 14-yr-old children. **B,** In 15- to 19-yr-old adolescents. ALCL, Anaplastic large cell lymphoma; DLBCL, diffuse large B-cell lymphoma. *(Adapted from Hochberg J, Waxman IM, Kelly KM, et al. Adolescent non-Hodgkin lymphoma and Hodgkin lymphoma: state of the science. Br J Haematol. 2008;144:24–40.)*

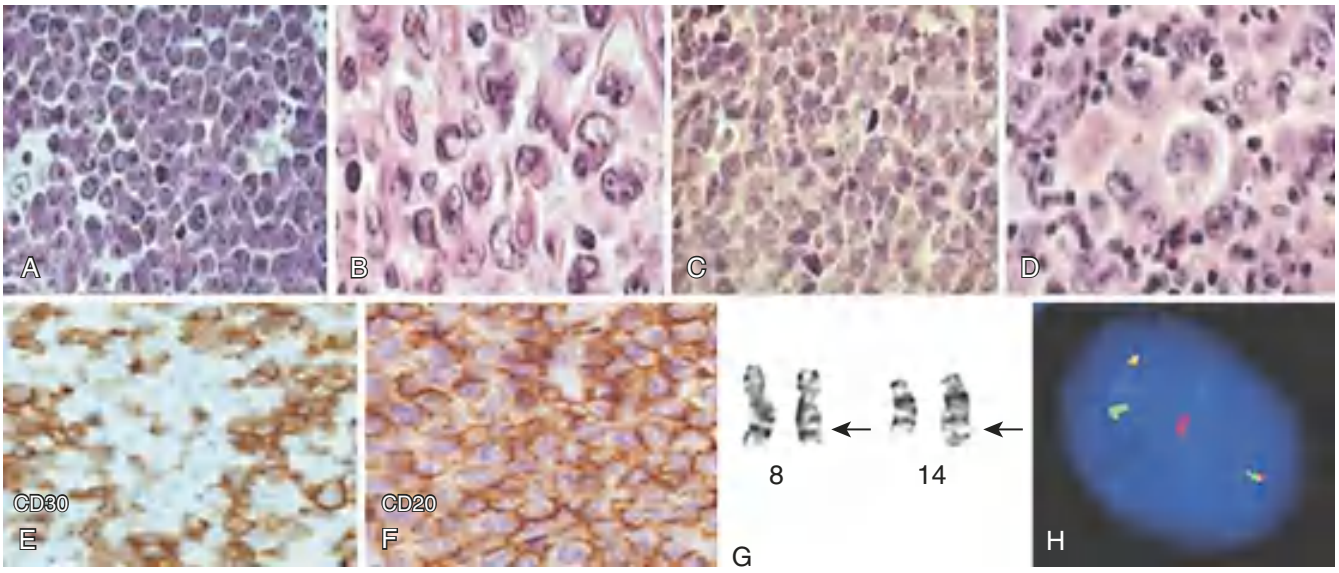

Fig. 545.5 Histologic subtypes of childhood and adolescent non-Hodgkin lymphoma. **A-D,** Hematoxylin and eosin (H&E) stains showing morphology of Burkitt lymphoma (**A,** high power), diffuse large B-cell lymphoma (**B,** high power), precursor T-lymphoblastic lymphoma (**C,** high power), and anaplastic large cell lymphoma (**D,** high power). **E** and **F,** Characteristic surface markers for anaplastic large cell lymphoma (ALCL) (CD30; **E**) and BL (CD20; **F**). **G** and **H,** Cytogenetic analysis of Burkitt lymphoma (BL) demonstrating t(8;14). **G,** Karyotype showing the conventional t(8;14)(q24;q32). **H,** Interphase fluorescence in situ hybridization showing a balanced translocation involving MYC and immunoglobulin (Ig) H loci. The chromosome eight centromere is labeled with spectrum aqua, MYC probe is labeled with spectrum orange, and IgH is labeled with spectrum green. Two fusion signals are seen, as well as one red and one green, representing the normal chromosomes. *(**A-D** from Cairo MS, Raetz E, Lim MS, et al. Childhood and adolescent non-Hodgkin lymphoma: new insights in biology and critical challenges for the future. Pediatr Blood Cancer. 2005;45:753–769; **E-H** from Giulino-Roth, Cesarman E. Molecular biology of Burkitt lymphoma. In Robertson ES, ed. Burkitt's Lymphoma. New York: Springer; 2012.)*

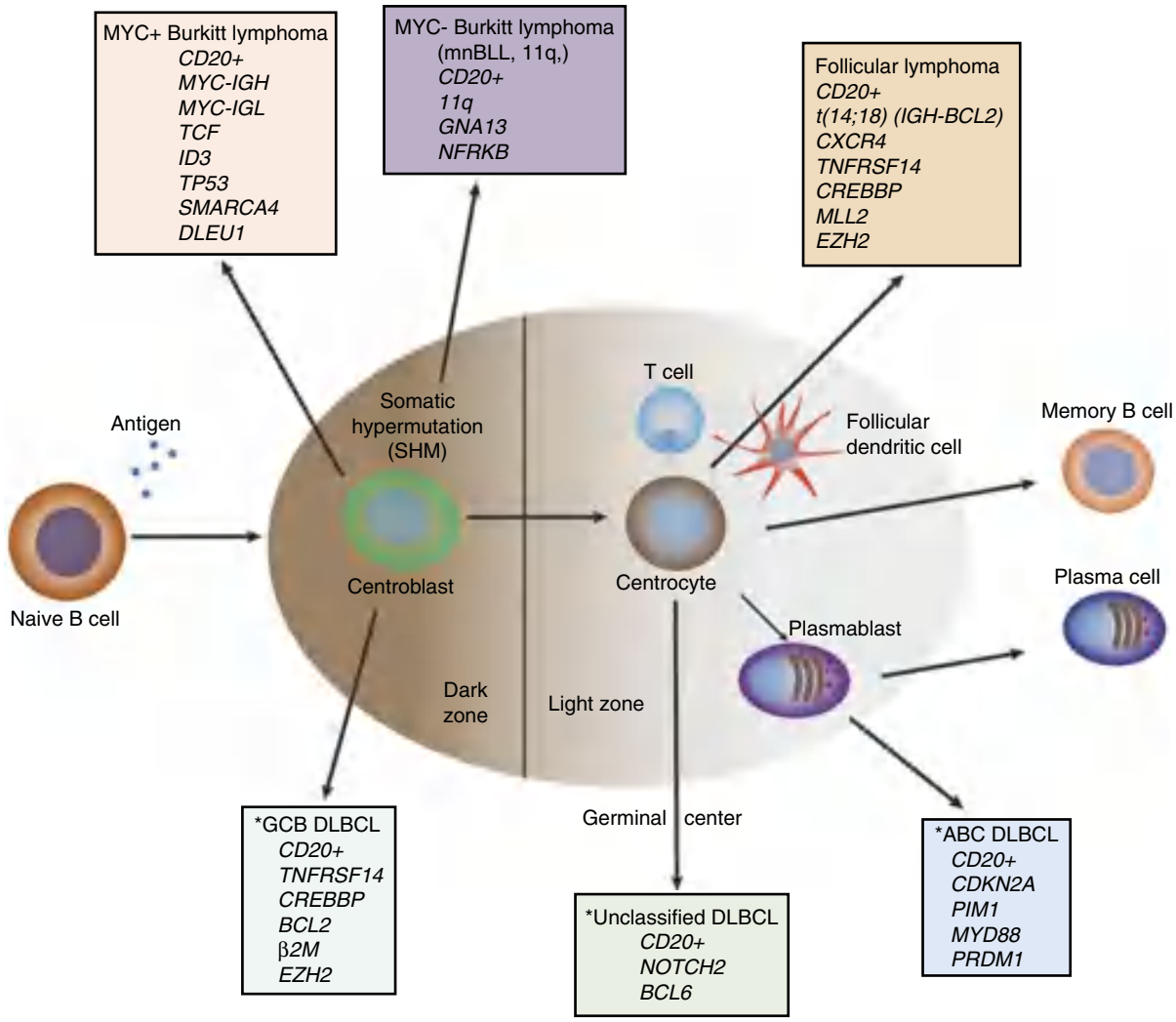

Fig. 545.6 Germinal center–derived B-cell lymphomagenesis. *Diffuse large B-cell lymphoma (DLBCL), recently subclassified as MCD, BNS, N1, and EZB subgroups. *(From Cairo, MS. A new Burkitt "look-alike" lymphoma. Blood. 2019;133[9]:889–891.)*

differentiate these two mature B-cell neoplasms. In addition, next-generation sequencing of BL has identified genetic lesions in *TCF3* and *ID3,* which lead to activation of the AKT/PI3 kinase pathway. Other genetic lesions that have been described in BL include loss of function of the chromatin remodeling genes *ARID1A* and *SMARCA4.* Importantly, many of these alterations are potentially targetable by agents that are in development.

CLINICAL MANIFESTATIONS

The clinical manifestations of childhood and adolescent NHL depend primarily on pathologic subtype and sites of involvement. The current revised staging system used for NHL is the **International Pediatric Non-Hodgkin Lymphoma Staging System (IPNHLSS),** which reflects our increasing ability to diagnose lower levels of organ involvement with disease. For instance, the older staging system (St. Jude/Murphy classification) did not account for molecular or flow cytometry involvement of BM, which is now reflected in the new system (Tables 545.6 and 545.7). Patients are further classified based on risk categories according to pediatric international cooperative group trials. Approximately 70% of patients with NHL present with advanced disease (stage III or IV), including extranodal disease with BM and CNS involvement. B symptoms of fever, weight loss, and night sweats can be seen, particularly in ALCL, but unlike HL, are not prognostic.

The primary site of tumor involvement and the pattern of metastasis vary by pathologic subtype. LBL typically manifests as a symptomatic mediastinal mass and also has a predilection for spreading to the BM, CNS, and testes in males. BL commonly manifests as a diffuse leukemia presentation or massive abdominal (*sporadic* type) or head and neck (*endemic* type) tumor and can metastasize to the BM or CNS. DLBCL usually manifests as either an abdominal or a mediastinal primary tumor and, rarely, disseminates to the BM or CNS. ALCL manifests either as a primary cutaneous manifestation (10%) or as systemic disease (90%) with dissemination to liver, spleen, lung, or mediastinum. BM or CNS disease is rare in ALCL. Site-specific manifestations of NHL include painless, rapid lymph node enlargement; cough or dyspnea with thoracic involvement; superior mediastinal syndrome; ascites, increased abdominal girth or intestinal obstruction with an abdominal mass; nasal congestion, earache, hearing loss, or tonsil enlargement with Waldeyer ring involvement; and localized bone pain.

NHL can present as a life-threatening **oncologic emergency**. These manifestations are important to recognize because these patients require intensive supportive care and, in some cases, alternative treatment. **Superior mediastinal syndrome** can occur as a consequence of a large mediastinal mass causing obstruction of blood flow or respiratory airways. Spinal cord tumors can cause cord compression and acute paraplegias requiring emergent radiation therapy. **Tumor lysis syndrome** (TLS) can occur from rapid cell turnover, which is especially common in BL. TLS can result in severe metabolic abnormalities, including hyperuricemia, hyperphosphatemia, hyperkalemia, and

Table 545.6 International Pediatric Non-Hodgkin Lymphoma Staging System (IPNHLSS)*

STAGE I
• A single tumor with the exclusion of the mediastinum and abdomen (N: nodal; EN: extranodal; bone (B) or skin (S): EN-B, EN-S)
STAGE II
• A single extranodal tumor with regional node involvement • Two or more nodal areas on the same side of the diaphragm • A primary gastrointestinal tract tumor (usually in the ileocecal area), with or without involvement of associated mesenteric nodes, that is completely resectable (if malignant ascites or extension of the tumor to adjacent organs, it should be regarded as stage III)
STAGE III
• Two or more extranodal tumor(s) (including bone or skin: EN-B, EN-S) above and/or below the diaphragm • Two or more nodal areas above and below the diaphragm • Any intrathoracic tumor (mediastinal, hilar, pulmonary, pleural, or thymic) • Intraabdominal and retroperitoneal disease, including liver, spleen, kidney, and/or ovary localizations, regardless of degree of resection (except a primary gastrointestinal tract tumor [usually in the ileocecal region], with or without involvement of associated mesenteric nodes, that is completely resectable) • Any paraspinal or epidural tumor, whether or not other sites are involved • Single bone lesion with concomitant involvement of extranodal and/or nonregional nodal sites
STAGE IV
• Any of the previous findings with initial involvement of the central nervous system (stage IV CNS), bone marrow (stage IV BM), or both (stage IV combined) based on conventional methods, see Table 545.7 • For each stage, type of examination and degree of BM and CNS involvement should be specified, using the abbreviations listed in Table 545.7 to identify involvement

*Based on the classification proposed by Murphy (Murphy SB. Classification, staging and end results of treatment of childhood non-Hodgkin's lymphomas: dissimilarities from lymphomas in adults. *Semin Oncol*. 7:332–339, 1980.)

From Rosolen A, Perkins SL, Pinkerton CR, et al. Revised International Pediatric Non-Hodgkin Lymphoma Staging System. *J Clin Oncol*. 2015;33(18):2112–2118.

Table 545.7 Additional IPNHLSS Information*

BONE MARROW (BM) INVOLVEMENT
Stage IV disease, caused by BM involvement, is currently defined by morphologic evidence of ≥5% blasts or lymphoma cells by bone marrow aspiration. This applies to any histologic subtype and will be maintained in the IPNHLSS.
However, for each stage, type and degree of BM involvement (by bone marrow aspiration) should be specified, using the abbreviations below to identify involvement: BMm = BM positive by morphology (specify % lymphoma cells). BMi = BM positive by immunophenotypic methods (immunohistochemical/flow cytometry analysis) (specify % lymphoma cells). BMc = BM positive by cytogenetic/FISH analysis (specify % lymphoma cells). BMmol = BM positive by molecular techniques (PCR based) (specify level of involvement).
Same approach should be used for peripheral blood (PB) involvement (i.e., PBm, PBi, PBc, PBmol).
Note: Definition of BM involvement should be obtained from analysis of bilateral BM aspirates and BM biopsy.
CENTRAL NERVOUS SYSTEM (CNS) INVOLVEMENT
CNS is considered involved in case of: 1. Any CNS tumor mass (identified by imaging techniques; i.e., CT, MRI). 2. In case of cranial nerve palsy that cannot be explained by extradural lesions. 3. In case of blasts morphologically identified in the cerebrospinal fluid (CSF).
Condition that defines CNS positivity should be specified: CNS positive/mass; CNS positive/palsy; CNS positive/blasts.
CSF status: CSF positivity is based on morphologic evidence of lymphoma cells.
CSF should be considered positive when any number of blasts is detected.
CSF unknown (e.g., not performed, technical difficulties).
Similar to BM, type of CSF involvement should be described whenever possible: CSFm = CSF positive by morphology (specify the number of blasts per microliter). CSFi = CSF positive by immunophenotype methods (immunohistochemical/flow cytometry analysis) (specify % lymphoma cells). CSFc = CSF positive by cytogenetic/FISH analysis (specify % lymphoma cells). CSFmol = CSF positive by molecular techniques (PCR based) (specify level of involvement).

*Until sufficient data are available, PET should be used with caution for staging, and PET results should be compared and discussed in light of other, more consolidated imaging approaches.

IPNHLSS, International Pediatric Non-Hodgkin Lymphoma Staging System Information; FISH, fluorescence in situ hybridization; PCR, polymerase chain reaction.

From Rosolen A, Perkins SL, Pinkerton CR, et al. Revised International Pediatric Non-Hodgkin Lymphoma Staging System. *J Clin Oncol*. 2015;33(18):2112–2118.

hypocalcemia. This can rapidly lead to renal insufficiency/failure, as well as cardiac abnormalities, if not aggressively treated.

LABORATORY FINDINGS

Recommended laboratory and radiologic testing includes CBC; measurements of electrolytes, lactate dehydrogenase, uric acid, calcium, phosphorus, BUN, creatinine, bilirubin, alanine aminotransferase, and aspartate aminotransferase; BM aspiration and biopsy; lumbar puncture with cerebrospinal fluid cytology, cell count, and protein; chest radiographs; and abdominal ultrasound for initial diagnosis. Staging relies on more detailed anatomic imaging, with CT for neck, chest, abdomen, and pelvic imaging and MRI the preferred modality for suspected CNS disease of brain and spine (Fig. 545.7). PET scan, usually with radioactive FDG for functional imaging, is more sensitive and has replaced gallium imaging. It is also an excellent modality for judging treatment response to therapy. Tumor tissue (i.e., biopsy, BM, cerebrospinal fluid, pleurocentesis/paracentesis fluid) should be tested by flow cytometry for immunophenotypic origin (T, B, or null) and cytogenetics (karyotype). Additional tests might include fluorescent in situ hybridization (FISH) or quantitative reverse-transcription polymerase chain reaction (RT-PCR) for specific genetic translocations, T- and B-cell gene rearrangement studies, and molecular profiling by oligonucleotide microarray or next-generation sequencing.

TREATMENT

The primary modality of treatment for childhood and adolescent NHL is *multiagent systemic chemotherapy and/or immunotherapy with intrathecal chemotherapy* (see Table 545.5). An international pediatric NHL response classification has been developed (IPNHLRC) (Tables 545.8 and 545.9). Surgery is used mainly for diagnosis. Radiation therapy is used only in special circumstances, such as CNS involvement in LBL or the presence of acute superior mediastinal syndrome or paraplegias. Newly diagnosed patients, especially those with BL or LBL, are at high risk for TLS. These patients require vigorous hydration, frequent electrolyte monitoring, and either a xanthine oxidase inhibitor (e.g., allopurinol, 10 mg/kg/day orally in three divided doses daily) or a recombinant urate oxidase (e.g., rasburicase, 0.2 mg/kg/day intravenously once daily for up to 5 days). Recombinant urate oxidase is preferred in patients with a high risk of tumor lysis but is *contraindicated* in patients with a history of G6PD deficiency.

Burkitt Lymphoma and Diffuse Large B-Cell Lymphoma

Pediatric BL and DLBCL (except mediastinal primary B cell) are treated with the same mature B-cell NHL chemoimmunotherapy regimens

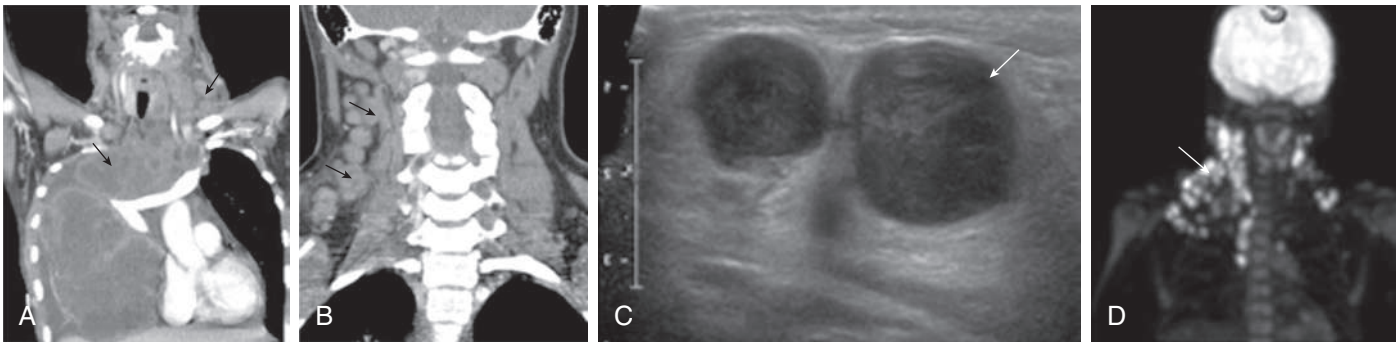

Fig. 545.7 Lymphoma. Coronal postcontrast CT images demonstrate extensive cervical (**A**) and mediastinal (**B**) lymphadenopathy *(arrows)*. **C,** Sonographic image demonstrates two enlarged lymph nodes with abnormal internal morphology *(arrow)*. **D,** PET scan demonstrates metabolically active conglomeration of right-sided cervical lymph nodes *(arrow)*. *(From Haaga JR, Boll DT, et al., eds. CT and MRI of the Whole Body (Vol. 1). Philadelphia: Elsevier; 2017: Fig. 26-15, p. 768.)*

Table 545.8 International Pediatric Non-Hodgkin Lymphoma Response Criteria (IPNHLRC)

Complete Response (CR): disappearance of all disease (three designations)

1. Complete (CR):
   a. CT or MRI reveals no residual disease or new lesions.
   b. Resected residual mass that is pathologically (morphologically) negative for disease (detection of disease with more sensitive techniques, as described in "supporting data," Table 545.9).
   c. Bone marrow (BM) and cerebrospinal fluid (CSF) morphologically free of disease (detection of disease with more sensitive techniques, as described in Table 545.9).
2. Complete Response, biopsy negative (CRb):
   a. Residual mass has no morphologic evidence of disease from limited or core biopsy (detection of disease with more sensitive techniques, as described in Table 545.9) with no new lesions by imaging examination.
   b. BM and CSF morphologically free of disease (detection of disease with more sensitive techniques, as described in Table 545.9).
   c. No new and/or progressive disease elsewhere.
3. Complete Response, unconfirmed (CRu):
   a. Residual mass is negative by FDG-PET; no new lesions by imaging examination.
   b. BM and CSF morphologically free of disease (detection of disease with more sensitive techniques, as described in Table 545.9).
   c. No new and/or progressive disease elsewhere.

Partial Response (PR): 50% decrease in the sum of the product of the greatest perpendicular diameters (SPD) on CT or MRI. FDG-PET may be positive (Deauville score of 4 or 5 with reduced lesional uptake compared with baseline). No new and/or PD. Morphologic evidence of disease may be present in the BM or CSF if present at diagnosis (detection of disease with more sensitive techniques, as described in Table 545.9); however, there should be a 50% reduction in the percentage of lymphoma cells.

Minor Response (MR): Decrease in SPD is >25% but <50% on CT or MRI. No new and/or PD. Morphologic evidence of disease may be present in the BM or CSF if present at diagnosis (detection of disease with more sensitive techniques, as described in Table 545.9); however, there should be a 25–50% reduction in the percentage of lymphoma cells.

No Response (NR): For those who do not meet CR, PR, MR, or PD criteria.

Progressive Disease (PD): For those with >25% increase in the SPD on CT or MRI, Deauville score 4 or 5 on FDG-PET with an increase in lesional uptake from baseline, or the development of new morphologic evidence of disease in the BM or CSF.

FDG-PET, Fluorodeoxyglucose positron emission tomography.
From Sandlund JT, Guillerman RP, Perkins SL, et al. International Pediatric Non-Hodgkin Lymphoma Response Criteria. *J Clin Oncol.* 2015;33(18):2106–2111.

Table 545.9 Supporting IPNHLRC Data

BONE MARROW (BM) INVOLVEMENT

BM involvement is currently defined by morphologic evidence of lymphoma cells. This applies to any histologic subtypes.

Type and degree of BM involvement should be specified, using the following abbreviations:
- BMm = BM positive by morphology (specify % lymphoma cells).
- BMi = BM positive by immunophenotypic methods (histochemical/flow cytometry analysis) (specify % lymphoma cells).
- BMc = BM positive by cytogenetic/FISH analysis (specify % lymphoma cells).
- BMmol= BM positive by molecular techniques.

Same approach should be used for peripheral blood (PB) involvement (i.e., PBm, PBi, PBc, PBmol).

CENTRAL NERVOUS SYSTEM (CNS) INVOLVEMENT

Cerebrospinal fluid (CSF) status: CSF positivity is based on morphologic evidence of lymphoma cells.

CSF should be considered positive when any number of blasts is detected.

CSF unknown (e.g., not performed, technical difficulties).

Similar to BM, type of CSF involvement should be described whenever possible:
- CSFm = CSF positive by morphology (specify the number of blasts/μL).
- CSFi = CSF positive by immunophenotypic methods (histochemical/flow cytometry analysis) (specify % lymphoma cells).
- CSFc = BM positive by cytogenetic/FISH analysis (specify % lymphoma cells).
- CSFmol = CSF positive by molecular techniques.

RESIDUAL MASS (RM)

RMm = Tumor detected by standard morphologic evaluation.
RMi = Tumor detected by immunophenotypic methods (immunohistochemical or flow cytometry analysis).
RMc = Tumor detected by cytogenetic/FISH analysis.
RMmol = Tumor detected by molecular techniques.

FISH, Fluorescence in situ hybridization.
From Sandlund JT, Guillerman RP, Perkins SL, et al. International Pediatric Non-Hodgkin Lymphoma Response Criteria. *J Clin Oncol.* 2015;33(18):2106–2111.

based on stage and risk stratification. For patients with localized disease, multiagent chemotherapy is given over 6 weeks, and the prognosis is excellent. In the international French-American-British Lymphoma, mature B cell [FAB/LMB 96] trial, patients with localized, completely resected disease received two cycles of COPAD (cyclophosphamide, vincristine, prednisone, and doxorubicin), resulting in a 4-year OS of 99%. Advanced disease is usually treated with a 4- to 6-month regimen of multiagent chemoimmunotherapy, such as FAB/LMB 96 protocol therapy or

NHL-Berlin-Frankfurt-Mulnster-95 (BFM 95) protocol therapy with the addition of rituximab, with an OS of 79–90%. A subset of patients who likely require a different treatment approach have **primary mediastinal B-cell lymphoma (PMBCL)**. PMBCL is a histologic subtype that represents 2% of mature B-NHLs. Pediatric patients with PMBCL had an inferior outcome when treated with standard mature B-NHL protocols (EFS of only 66%). Alternative treatment strategies, including prolonged infusional chemotherapy, rituximab, and chimeric antigen receptor T cells expressing anti-CD19 mAbs, may benefit this group (see Chapter 543).

Rituximab is a mAb directed at CD20 that, when combined with standard chemotherapy, improves outcomes in adult patients with aggressive B-NHL (usually DLBCL). A window study of rituximab given to pediatric patients with newly diagnosed BL and DLBCL demonstrated its activity as a single agent with a response rate of 41%. Additionally, a Children's Oncology Group study examined the safety and pharmacokinetics of rituximab when added to standard chemotherapy for intermediate-risk patients. Rituximab was found to be safe, and survival in this cohort was the best reported to date (3-year OS of 95%). In a similar cohort of CNS-positive patients, the addition of rituximab to the chemotherapy backbone resulted in a 93% EFS. Based on this pilot data, an international randomized study of rituximab added to standard multiagent chemotherapy in advanced-stage pediatric patients enrolled over 300 patients. The randomized trial demonstrated that the addition of rituximab markedly prolonged EFS and OS. The EFS at 3 years was 94% compared to 82% in patients who received chemotherapy alone. As expected with an antibody to a protein on the surface of normal mature B cells, there was a higher incidence of low immunoglobulin levels in rituximab-treated patients up to 1 year poststudy entry. Rituximab is standard-of-care therapy for pediatric mature B-NHL with advanced disease at presentation. These patients make up roughly ~30% of all mature B-NHL. A study of dose substitution of anthracycline (doxorubicin) intensity with rituximab in children and adolescents with good-risk mature B-cell lymphoma noted reduction of anthracycline dramatically reduced mucositis and febrile admissions during the intensive induction phases of therapy and was associated with 100% EFS and OS. With the success of rituximab in pediatric mature B-NHL and the poor outcome of recurrent or refractory disease, there is interest in improving immunotherapy in up-front patients. Polatuzumab vedotin is a CD79b-directed antibody conjugated to an antimitotic agent. The therapy has been approved in conjunction with rituximab and chemotherapy for adult refractory DLBCL. A study to determine the feasibility and safety of the addition of polatuzumab vedotin in combination with rituximab and FAB chemotherapy in patients with intermediate and high-risk mature B-NHL is in progress.

Lymphoblastic Lymphoma

Localized or advanced LBL requires 12-24 months of therapy, including chemotherapy, intrathecal therapy, and cranial radiation in CNS-positive lymphomas. The best results in advanced LBL have been obtained using therapeutic approaches mirroring those for childhood acute leukemia, including induction, consolidation, interim maintenance, and reinduction (advanced disease only) phases, as well as a year-long maintenance phase with 6-mercaptopurine and methotrexate. For patients with relapsed disease, the outcome is poor (OS of 10%), and novel treatments are needed. *Nelarabine,* a purine analog with significant T-lymphocyte toxicity, has completed testing in primary therapy for T-LBL in conjunction with a much larger cohort of T-ALL patients. Nelarabine was demonstrated in the trial to improve disease-free survival at 4 years and to reduce the risk of CNS relapses. The smaller subset of patients with advanced LBL did not have a benefit demonstrated to nelarabine, but this subset was underpowered, and most U.S. centers are now including nelarabine in the up-front treatment of all T-LBL patients.

Anaplastic Large Cell Lymphoma

For patients who present with localized disease, surgical resection alone is sufficient. The majority of patients, however, have advanced disease, which requires multiagent chemotherapy. Various chemotherapy regimens have been studied, with similar outcomes and survival of 70–79%. CNS prophylaxis consists of intrathecal chemotherapy, although this may be omitted with the substitution of high-dose methotrexate.

Two novel targeted agents have shown substantial promise in early-phase trials in ALCL. The CD30 antibody–drug conjugate **brentuximab vedotin** and the ALK inhibitor **crizotinib** both have impressive activity and minimal toxicity in patients with relapsed ALCL. A trial piloted the addition of brentuximab vedotin in newly diagnosed advanced ALCL patients with impressive 2-year EFS of 79% and OS of 97% among ~70 patients. There were no toxic deaths with combination brentuximab and chemotherapy and no severe neurotoxicity.

Relapsed Non-Hodgkin Lymphoma

Patients with NHL in whom progressive or relapsed disease develops require reinduction chemotherapy and may require either allogeneic or autologous SCT. A notable exception is ALCL, where low-dose approaches such as prolonged vinblastine have been efficacious for some patients. The specific reinduction regimen or transplantation type depends on the pathologic subtype, previous therapy, site of reoccurrence, and stem cell donor availability. Novel reinduction approaches are being investigated, including a type II CD20 antibody, *obinutuzumab,* alone and in combination with chemotherapy, *ibrutinib,* a BTK inhibitor alone and in combination with chemotherapy, and *idelalisib,* a PI3K delta inhibitor alone and in combination with chemotherapy. Although there are no randomized trials examining autologous versus allogeneic SCT for relapsed NHL, data from retrospective studies suggest that outcomes are similar, with the exception of LBL and ALCL, for which allogeneic SCT is superior, perhaps because of a graft versus lymphoma effect.

Native (autologous) patient T cells have been genetically manipulated to produce a T-cell vs leukemia or lymphoma response. Tisagenlecleucel (Kymriah) is a CD19-directed genetically modified autologous T-cell immunotherapy first approved for patients under 25 years with precursor B-ALL. The immunotherapy has been approved in adults with relapsed mature DLBCL after two prior lines of systemic therapy. An additional CD19-directed immunotherapy, axicabtagene ciloleucel, has been approved for recurrent adult mature B-NHL. The responses have been less impressive in adult DLBL to those seen in childhood adolescent and young adult ALL, but continued work with different target antigens and genetic manipulation of the constructs is ongoing. These T-cell–modified products, although autologous, can lead to a cytokine release syndrome and CNS toxicities that can be severe.

Because relapsed NHL can be difficult to treat, efforts have been made to identify patients at higher risk of relapse to tailor initial therapy. The measurement of **minimal residual disease** may serve as a prognostic marker and aid in risk stratification. Minimal residual disease is prognostic in ALCL and LBL. In ALCL, there is also evidence that a humoral response to the ALK kinase can be used to predict outcome, with a superior outcome in patients who mount an antibody titer to ALK.

COMPLICATIONS

Patients receiving multiagent chemotherapy for advanced disease are at acute risk for mucositis, infections, cytopenias that require red blood cell and platelet blood product transfusions, electrolyte imbalances, and poor nutrition. Long-term complications include the risk of growth retardation, cardiac toxicity, gonadal toxicity with infertility, and secondary malignancies.

PROGNOSIS

The prognosis is excellent for most forms of childhood and adolescent NHL (see Table 545.5). Patients with localized disease have a 90–100% survival rate, and those with advanced disease have an 80–95% survival rate. Because outcomes for pediatric patients with NHL have improved substantially, the focus has now shifted to minimizing the *long-term toxicity of therapy.* Novel targeted agents are desirable because they have the potential to improve outcomes and decrease the reliance on toxic conventional chemotherapy. An ongoing multi-institutional study is testing the reduction of anthracycline to decrease short-term (mucositis) and long-term (cardiac health) complications of therapy by incorporation of immunotherapy in mature B-NHL, with promising results to date.

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545.3 Late Effects in Children and Adolescents with Lymphoma

Jessica Hochberg, Stanton C. Goldman, and Mitchell S. Cairo

The majority of patients with newly diagnosed HL and NHL have OS rates >90%. There are approximately 270,000 survivors of childhood cancer in the United States, or about one of every 640 adults between ages 20 and 40. However, this survival has often been achieved at the expense of an increased relative risk of long-term complications, including solid tumors, leukemia, cardiac disease, pulmonary complications, thyroid disease, and infertility. An analysis of >1,000 long-term childhood NHL survivors found increased rates of death >20 years after treatment. A review of the National Cancer Institute Surveillance, Epidemiology, and End Results data over a 25-year follow-up demonstrates that the relative survival curves do not plateau after 10 years following diagnosis of HL, but rather accelerate. This finding highlights the importance of late morbidity and mortality among survivors of lymphoma. The incidence of Grade 3-5 adverse health conditions is >15% in adult survivors of childhood HL treated with chemoradiotherapy regimens. Radiation therapy has been shown to further compound the risk for late mortality, obesity, and organ dysfunction with worsening effects on cardiovascular, pulmonary, and thyroid function. The first **Childhood Cancer Survivor Study**, a retrospective cohort study of 10,397 cancer survivors, shows that 62.3% of survivors report at least one chronic condition, with 27.5% reporting severe or life-threatening conditions. The survivor's adjusted relative risk of a severe or life-threatening chronic condition, compared with that of a sibling, was 8.2 (95% confidence interval, 6.9-9.7). Studying disease-specific health outcomes, both HL and NHL were found to be associated with a cumulative incidence of chronic health conditions **approaching 70–80%, with severe conditions reported in ~50% of HL survivors** (Fig. 545.8).

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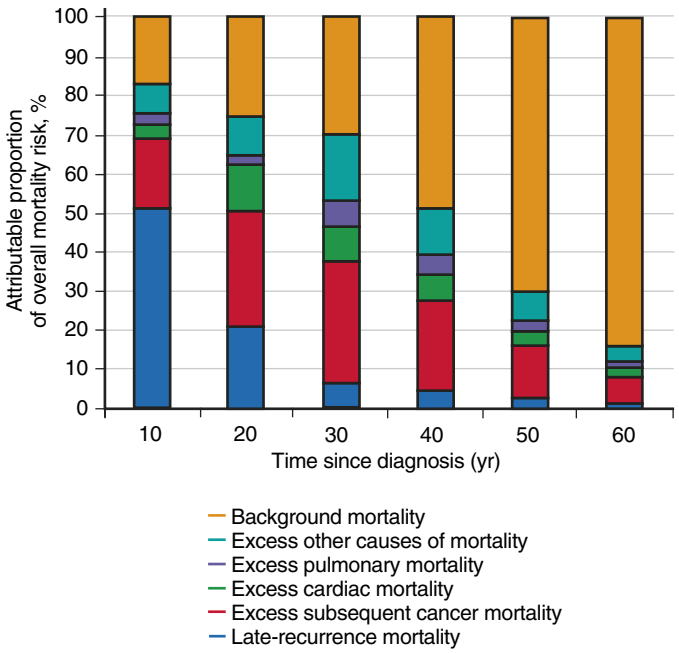

Fig. 545.8 Percentage of attributable proportions of overall mortality risk in survivors of childhood cancer. *(Adapted from Yeh JM, Nekhlyudov L, Goldie SJ, et al. A model-based estimate of cumulative excess mortality in survivors of childhood cancer. Ann Intern Med. 2010;152[7]:409– 417.)*

Chapter 546

Central Nervous System Tumors in Childhood

Wafik Zaky

Primary central nervous system (CNS) tumors are a heterogeneous group of diseases that are, collectively, the most common malignancy in childhood and adolescence. The overall mortality among this group approaches 30%. Patients with CNS tumors have the highest morbidity, primarily neurologic, of all children with malignancies. Outcomes have improved with innovations in neurosurgery, imaging, and radiation therapy as well as the introduction of chemotherapy and biologic agents as a therapeutic modality. The treatment approach for the majority of these tumors is multimodal. Surgery with complete resection, if feasible, is the foundation, with radiation therapy and chemotherapy utilized according to the diagnosis, patient age, and other factors.

ETIOLOGY

The etiology of pediatric CNS tumors is not well defined. An overall female predominance exists in the incidence of CNS tumors, but male predominance is noted in the incidence of high-grade tumors like glioblastoma multiforme, medulloblastoma, and ependymoma. Familial syndromes associated with an increased incidence of brain tumors account for approximately 5% of cases (Table 546.1). Cranial exposure to ionizing radiation also is associated with a higher incidence of CNS tumors. There are sporadic reports of CNS tumors within families without evidence of a heritable syndrome.

EPIDEMIOLOGY

Approximately 5,550 primary brain tumors are diagnosed each year in children and adolescents in the United States, with an average annual age adjusted incidence rate of 5.65 per 100,000 population. It is the most common cancer in patients 0-14 years of age and the leading cause of cancer-related death in this age-group.

PATHOGENESIS

More than 100 histologic categories and subtypes of primary brain tumors are described in the World Health Organization (WHO) classification of tumors of the CNS. In children 0-14 years of age, the most common tumors are pilocytic astrocytomas (PAs) and embryonal tumors (i.e., medulloblastoma/primitive neuroectodermal tumors [PNETs]). In adolescents (15-19 years), the most common tumors are pituitary/craniopharyngeal tumors and PAs (Fig. 546.1).

There is a slight predominance of infratentorial tumor location (43.2%), followed by the supratentorial region (40.9%), spinal cord (4.9%), and multiple sites (11%) (Fig. 546.2, Table 546.2). There are age-related differences in the primary location of tumor. During the first year of life, supratentorial tumors predominate and include, most commonly, choroid plexus complex tumors and germ cell tumors. In children 1-10 years of age, infratentorial tumors predominate, due to the high incidence of juvenile PA and medulloblastoma. After 10 years of age, supratentorial tumors predominate, with diffuse astrocytomas (DAs) most common. Tumors of the optic pathway and hypothalamus region, the brainstem, and the pineal–midbrain region are more common in children and adolescents than in adults. Additionally, some tumors are more common in males (astrocytic and germ cell tumors), whereas meningioma and craniopharyngiomas are more common in females. Malignant tumors are more common in White children (embryonal and astrocytic neoplasms), whereas low-grade tumors are more common in Black children (meningiomas and craniopharyngiomas).

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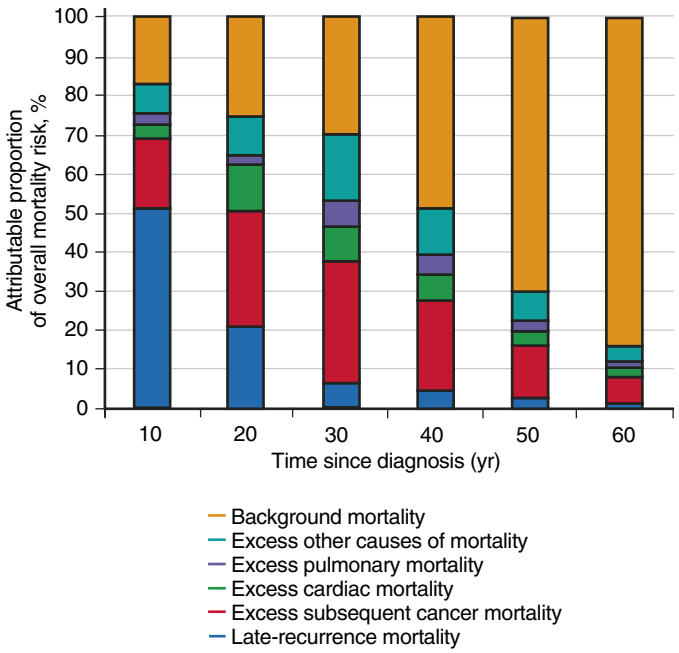

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Table 546.1 Familial Syndromes Associated with Pediatric Brain Tumors

SYNDROME	CENTRAL NERVOUS SYSTEM MANIFESTATIONS	CHROMOSOME	GENE
Neurofibromatosis type 1 (autosomal dominant)	Optic pathway gliomas, astrocytoma, malignant peripheral nerve sheath tumors, neurofibromas	17q11	*NF1*
Neurofibromatosis type 2 (autosomal dominant)	Vestibular schwannomas, meningiomas, spinal cord ependymoma, spinal cord astrocytoma, hamartomas	22q12	*NF2*
von Hippel-Lindau (autosomal dominant)	Hemangioblastoma	3p25-26	*VHL*
Tuberous sclerosis (autosomal dominant)	Subependymal giant cell astrocytoma, cortical tubers	9q34 16q13	*TSC1* *TSC2*
Li-Fraumeni (autosomal dominant)	Astrocytoma, primitive neuroectodermal tumor	17q13	*TP53*
Cowden (autosomal dominant)	Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease)	10q23	*PTEN*
Turcot (autosomal dominant)	Medulloblastoma	5q21	*APC*
	Glioblastoma	3p21 7p22	*hMLH1* *hPSM2*
Nevoid basal cell carcinoma Gorlin (autosomal dominant)	Medulloblastoma	9q31	*PTCH1*

Modified from Kleihues P, Cavenee WK. *World Health Organization Classification of Tumors: Pathology and Genetics of Tumors of the Nervous System*. Lyon: IARC Press, 2000.

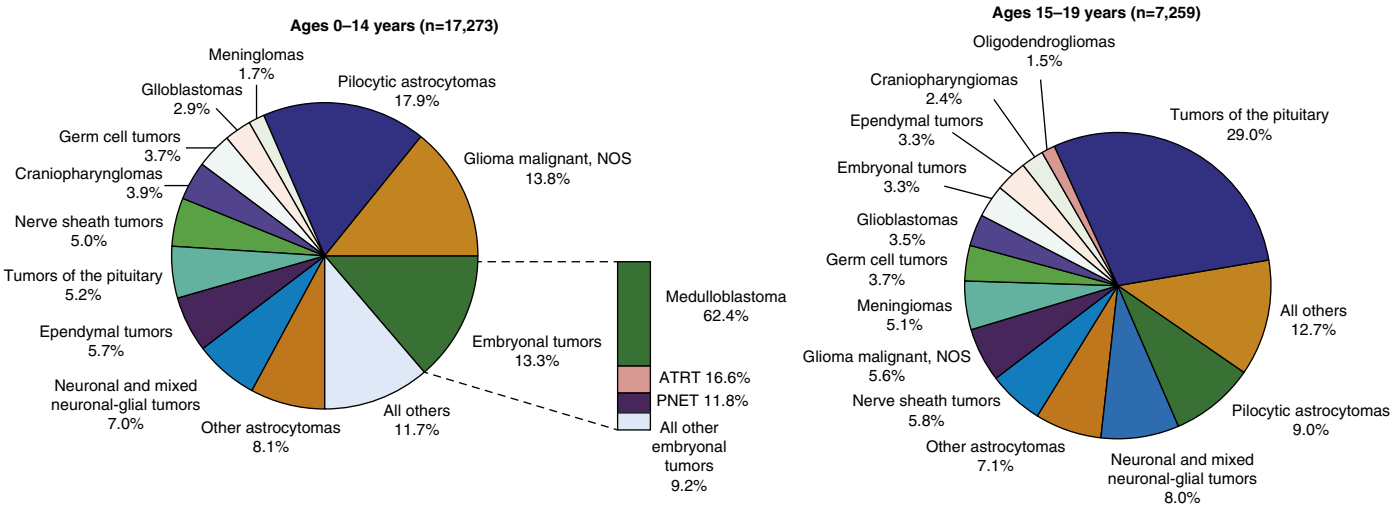

Fig. 546.1 Distribution of childhood primary brain and central nervous system (CNS) tumors by histology. ATRT, Atypical teratoid rhabdoid tumor; NOS, not otherwise specified; PNET, primitive neuroectodermal tumor. *(From Ostrom QT, Patil N, Cioffi G, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2013-2017. Neuro Oncol. 2020;30;22:iv1–iv96.)*

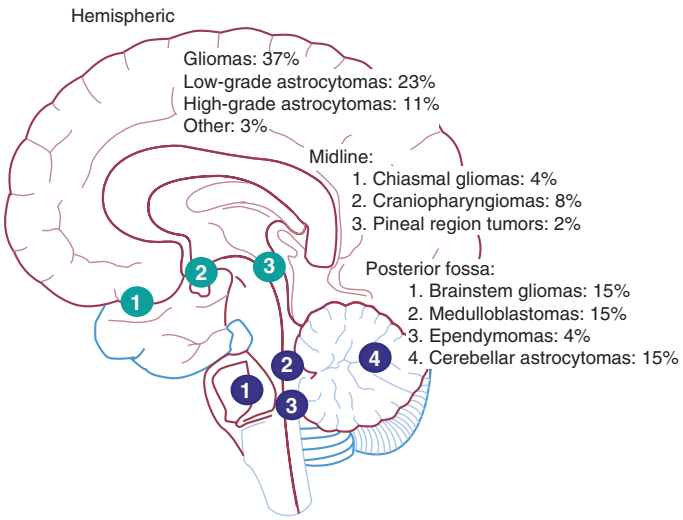

Fig. 546.2 Childhood brain tumors occur at any location within the central nervous system. The relative frequency of brain tumor histologic types and the anatomic distribution are shown. *(Redrawn from Albright AL. Pediatric brain tumors. CA Cancer J Clin 1993;43:272–288.)*

CLINICAL MANIFESTATIONS

The clinical presentation of the patient with a brain tumor depends on the tumor location, the tumor type, and the age of the child. Signs and symptoms are related to obstruction of cerebrospinal fluid (CSF) drainage paths by the tumor, leading to **increased intracranial pressure (ICP)** or causing focal brain dysfunction. In young children, the diagnosis of a brain tumor may be delayed because the symptoms are similar to those of more common illnesses, such as gastrointestinal disorders, with associated vomiting. Infants with open cranial sutures may present with signs of increased ICP, such as vomiting, lethargy, and irritability, as well as the later finding of macrocephaly. The **classic triad** of headache, nausea, and vomiting as well as papilledema is associated with midline or infratentorial tumors. Disorders of equilibrium, gait, and coordination occur with infratentorial tumors. **Torticollis** may occur in cases of cerebellar tonsil herniation. Blurred vision, diplopia, and nystagmus also are associated with infratentorial tumors. Tumors of the brainstem region may be associated with gaze palsy, multiple cranial nerve palsies, and upper motor neuron deficits (e.g., hemiparesis, hyperreflexia, and clonus). **Supratentorial tumors** are more commonly associated with focal motor weakness, focal sensory changes, language disorders, focal seizures, and reflex asymmetry. Infants with supratentorial tumors may present

Table 546.2 Posterior Fossa Tumors of Childhood

TUMOR	RELATIVE INCIDENCE (%)	PRESENTATION	DIAGNOSIS	PROGNOSIS
Medulloblastoma	35-40	2-3 mo of headaches, vomiting, truncal ataxia	Heterogeneously or homogeneously enhancing fourth ventricular mass; may be disseminated	65–85% survival; dependent on stage/type; poorer (20–70%) in infants
Cerebellar astrocytoma	35-40	3-6 mo of limb ataxia; secondary headaches, vomiting	Cerebellar hemisphere mass, usually with cystic and solid (mural nodule) components	90–100% survival in totally resected pilocytic type
Brainstem glioma	10-15	1-4 mo of double vision, unsteadiness, weakness, and cranial nerve dysfunction, including facial weakness, swallowing dysfunction, and oculomotor abnormalities	Diffusely expanded, minimally or partially enhancing mass in 80%; 20% more focal tectal or cervicomedullary lesion	>90% mortality in diffuse tumors; better in localized
Ependymoma	10-15	2-5 mo of unsteadiness, headaches, double vision, and facial asymmetry	Usually enhancing, fourth ventricular mass with cerebellopontine predilection	>75% survival in totally resected lesions
Atypical teratoid/rhabdoid	5–10% of infantile malignant tumors	As in medulloblastoma, but primarily in infants; often associated facial weakness and strabismus	As in medulloblastoma, but often more laterally extended	≤20% survival in infants

Modified from Packer RJ, MacDonald T, Vezina G. Central nervous system tumors. *Pediatr Clin North Am.* 2008;55:121–145.

with premature hand preference. **Optic pathway tumors** manifest as visual and/or afferent oculomotor disturbances, such as decreased visual acuity, Marcus Gunn pupil (afferent pupillary defect), nystagmus, and/or visual field defects. Suprasellar region tumors and third ventricular region tumors may manifest initially as **neuroendocrine deficits,** such as subacute development of obesity, abnormal linear growth velocity, diabetes insipidus, galactorrhea, precocious puberty, delayed puberty, and hypothyroidism. In fact, signs of endocrine dysfunction preceded symptoms of neuroophthalmologic dysfunction by an average of 1.9 years, and their recognition as a possible sign of hypothalamic or pituitary neoplasm can hasten diagnosis and improve outcome. The **diencephalic syndrome,** which manifests as failure to thrive but normal linear growth, emaciation despite normal caloric intake, and inappropriately normal or happy (euphoric) affect, occurs in infants and young children with tumors (most often low-grade hypothalamic or thalamic glioma). **Parinaud syndrome** is seen with pineal region tumors and is manifested by paresis of upward gaze, pupillary caliber reactive to accommodation but not to light (pseudo-Argyll Robertson pupil), nystagmus to convergence or retraction, and eyelid retraction. **Spinal cord tumors** and spinal cord dissemination of brain tumors may manifest as long nerve tract motor and/or sensory deficits often localized to below a specific spinal level, bowel and bladder deficits, resistance to back flexion, scoliosis, bowel and bladder dysfunction, and back or radicular pain. The signs and symptoms of meningeal metastatic disease from brain tumors or leukemia include head or back pain and symptoms referable to compression of cranial nerves or spinal nerve roots.

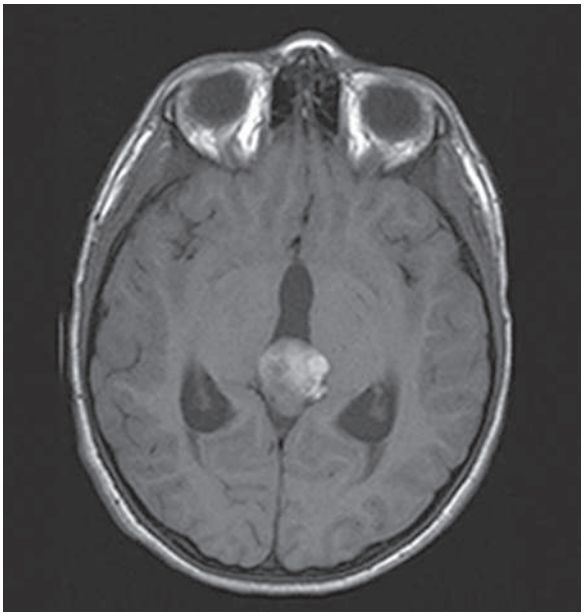

Fig. 546.3 Axillary T1 weighted MR image with gadolinium of a 10-yr-old male presenting with **mixed germ cell tumor** of the pineal region, with early onset of puberty, headaches, and elevated α-fetoprotein and β-human chorionic gonadotropin in the spinal fluid and serum.

DIAGNOSIS

The evaluation of a patient when a CNS tumor is suspected is an emergency. Initial evaluation should include a complete history (including endocrine), physical (including ophthalmic) examination, and full neurologic assessment with neuroimaging. For primary brain tumors, **MRI** with and without gadolinium is the neuroimaging standard. Tumors in the pituitary/suprasellar region, optic pathway, and infratentorium are better delineated with MRI than with CT. Patients with tumors of the midline and the pituitary/suprasellar/optic chiasmal region should undergo evaluation for **neuroendocrine dysfunction.** Formal ophthalmologic examination is beneficial in patients with optic path region tumors to document the impact of the disease on oculomotor function, visual acuity, and fields of vision. The suprasellar and pineal regions are preferential sites for germ cell tumors (Fig. 546.3). Both serum and CSF measurements of β-**human chorionic gonadotropin** and α-**fetoprotein** can assist in the diagnosis of germ cell tumors. In tumors with a propensity for spreading to the leptomeninges, such as medulloblastoma/PNET, ependymoma, and germ cell tumors, lumbar puncture with cytologic analysis of the CSF is indicated; lumbar puncture is contraindicated in individuals with newly diagnosed hydrocephalus secondary to CSF flow obstruction, in tumors that cause supratentorial midline shift, and in individuals with

infratentorial tumors. Lumbar puncture in these individuals may lead to brain herniation, resulting in neurologic compromise and death. Therefore, in children with newly diagnosed intracranial tumors and signs of increased ICP, the lumbar puncture usually is delayed until surgery or shunt placement.

SPECIFIC TUMORS

Astrocytoma

Astrocytomas are a heterogeneous group of tumors that account for approximately 40% of pediatric CNS malignancies. These tumors occur throughout the CNS.

Low-grade astrocytomas (LGAs), the predominant group of astrocytomas in childhood, are characterized by an indolent clinical course. **PA** is the most common astrocytoma in children, accounting for approximately 15.2% of all brain tumors (Fig. 546.4). Based on clinicopathologic features using the WHO Classification System, PA is classified as a WHO grade I tumor. Although PA can occur anywhere in the CNS, the classic sites are the **cerebellum followed by the optic pathway region** (Fig. 546.5A-B). The classic but not exclusive neuroradiologic finding in PA is the presence of a contrast-enhancing nodule within the wall of a cystic mass (Fig. 546.5A). The microscopic findings include the biphasic appearance of bundles of compact fibrillary tissue interspersed with loose microcystic, spongy areas. The presence of **Rosenthal fibers,** which are condensed masses of glial filaments occurring in the compact areas, with low mitotic potentials helps establish the diagnosis. A small proportion of these tumors can progress and develop leptomeningeal spread, particularly in the optic path region and very rarely transform to higher grade aggressive type. A PA of the optic nerve and chiasmal region is a relatively common finding in patients with neurofibromatosis type 1 (15% incidence). Molecularly, PA has activation of the **MAPK** pathway in the form of **BRAF** fusion or duplication and less commonly BRAF pathogenic variant (V600E) (see Fig. 546.4). Other low-grade tumors occurring in the pediatric age-group with clinic pathologic characteristics similar to PA include pleomorphic xanthoastrocytoma, pilomyxoid astrocytoma, and subependymal giant cell astrocytoma.

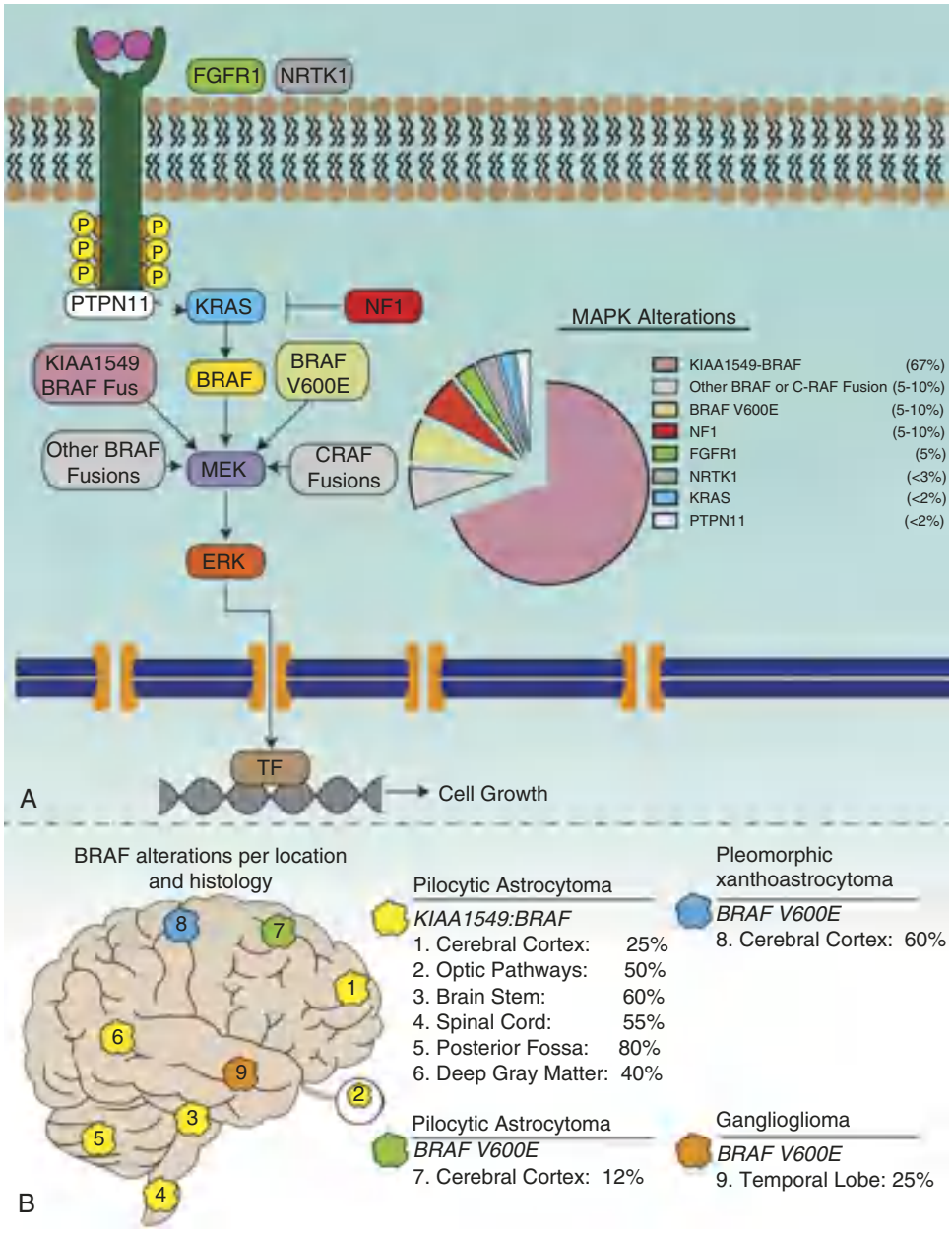

Fig. 546.4 A, Schematic of the frequency of MAPK pathway alterations detected by biopsy of pilocytic astrocytomas. This underestimates the frequency of NF1 pathogenic variants among children with low-grade gliomas (LGGs) because the tumors in patients affected by NF1 often do not undergo biopsy. Although BRAF fusions (BRAF Fus) constitute the majority of alterations in pilocytic astrocytoma, BRAF pathogenic variants are more commonly observed in pleomorphic xanthoastrocytomas and gangliogliomas. B, Frequency of the different BRAF abnormalities as a function of tumor location and histological diagnosis. *(From Pollack IF, Agnihotri S, Broniscer A. Childhood brain tumors: current management, biological insights, and future directions. J Neurosurg Pediatr. 2019;23:261–273. Fig. 1.)*

The second most common astrocytoma is **DA,** which consists of a group of tumors characterized by a pattern of diffuse infiltration of tumor cells amidst normal neural tissue. Histologically, these low-grade tumors demonstrate greater cellularity, with few mitotic figures, nuclear pleomorphism, and microcysts. They occur anywhere in the CNS with predilection to supratentorial location. The characteristic MRI finding is a lack of enhancement after contrast agent infusion. Molecular genetic abnormalities found in DA include pathogenic variants of *P53* and overexpression of platelet-derived growth factor receptor-α. Evolution of DA into malignant astrocytoma is associated with cumulative acquisition of multiple molecular abnormalities. Overactivation of the MAPK pathway has been detected in DA in the form of the ***BRAF V600E*** pathogenic variant and **FGFR1** duplication.

Pilomyxoid astrocytoma occurs most commonly in the hypothalamic/optic chiasmic region and carries a high risk of local as well as cerebrospinal spread. This astrocytoma affects young children and infants. It is classified as a WHO grade II tumor.

The clinical management of LGAs focuses on a multimodal approach incorporating surgery if feasible as the primary treatment as well as radiation therapy and chemotherapy. With complete surgical resection, the overall survival approaches 80–100%. In patients with partial resection, overall survival varies from 50–95%, depending on the anatomic location of the tumor. In the patient who has undergone partial tumor resection and has stable neurologic status, the current approach is to follow the patient closely by examination and imaging. With evidence of progression, a second surgical resection should be considered. In patients in whom a second procedure was less than complete or is not feasible, radiation therapy is beneficial. Radiation therapy is delivered to the tumor bed at a total cumulative dose ranging from 50-55 Gy. Modern surgical techniques and innovative radiation therapy methodology, *including proton-beam radiation,* may have a positive impact on the survival and clinical outcome of these patients. Chemotherapy for LGAs has become the standard of care for progressive LGAs. Because of concerns regarding morbidity from radiation therapy in young children, several chemotherapy approaches have been evaluated, especially in children younger than 10 years of age. Complete response to chemotherapy is uncommon; however, these approaches have yielded durable control of disease in 70–100% of patients with clinical improvement. Patients with midline tumors in the hypothalamic/optic chiasmatic region (see Fig. 546.5B) have tended to do less well. The chemotherapy approaches have permitted delay and, potentially, avoidance of radiation therapy. Chemotherapy agents given singly or in combination for LGA include carboplatin, vincristine, lomustine, procarbazine, temozolomide, and vinblastine. Observation is the primary approach in clinical management of selected patients with LGAs that are biologically indolent (neurofibromatosis type 1 and tectal gliomas and indolent LGA variants like angiocentric gliomas). *Astrocytomas associated with tuberous sclerosis have responded to everolimus, a mammalian target of rapamycin inhibitor.*

Malignant astrocytomas are less common in children and adolescents than in adults, accounting for 7–10% of all childhood brain tumors. Among this group, **anaplastic astrocytoma** (WHO grade III; Fig. 546.6) is more common than **glioblastoma multiforme** (WHO grade IV). The histopathology of anaplastic astrocytomas demonstrates greater cellularity than that of LGA, with cellular and nuclear atypia, and the presence of mitoses. Characteristic histopathologic findings in glioblastoma multiforme include dense cellularity, high mitotic index, microvascular proliferation, and foci of tumor necrosis with pseudopalisading. Genome-wide DNA methylation patterns have identified five molecular subgroups of pediatric high-grade glioma. These subgroups appear to have distinct cellular origins and biological drivers. Common genetic alterations include gene pathogenic variants in ***histone H3.3*** or ***H3.1, p53,*** and ***BRAF*** in addition to focal amplifications of oncogene (***PDGFRA*** and ***EGFR***) and deletions of tumor-suppressor genes ***(CDKN2A, CDKN2B, PTEN).***

Optimal therapeutic approaches for malignant astrocytomas have yet to be defined. Standard therapy continues to be surgical resection followed by involved-field radiation therapy with evolving role of maintenance alkylator chemotherapy (temozolomide ± lomustine). A study of adult glioblastoma showed significantly better survival with temozolomide during and after irradiation than with irradiation alone. Current therapeutic approaches incorporate novel chemotherapeutic agents with radiation therapy.

Oligodendrogliomas are uncommon tumors of childhood. These infiltrating tumors occur predominantly in the cerebral cortex and originate in the white matter. Histologically, oligodendrogliomas consist of rounded cells with little cytoplasm and microcalcifications. Observation of a **calcified cortical mass** on CT in a patient presenting with a seizure is suggestive of oligodendroglioma. The definition of oligodendroglioma requires two diagnostic genotypic features: pathogenic gene variants in isocitrate dehydrogenase (IDH) and the co-deletions of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). Treatment approaches are similar to those for infiltrating astrocytomas.

Ependymal Tumors

Ependymal tumors are derived from the ependymal lining of the ventricular system. Cellular ependymoma (WHO grade II) is the most common of these neoplasms, accounting for 5% of childhood CNS tumors. Approximately 70% of ependymomas in childhood occur in the posterior fossa. The mean age of patients is 6 years, with approximately

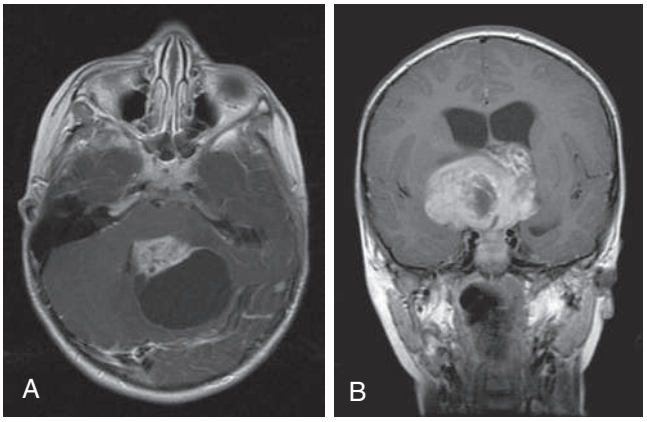

Fig. 546.5 A, Gadolinium-enhanced axial T1-weighted MR image in a 4-yr-old child with cerebellar **pilocytic astrocytoma** presenting with headaches, emesis, and ataxia demonstrates a predominantly cystic mass with enhancement of the solid component and enhancement of the capsule. B, Gadolinium-enhanced coronal view of a cystic juvenile pilocytic astrocytoma of the suprasellar region from a 4-yr-old child presenting with visual loss and headaches.

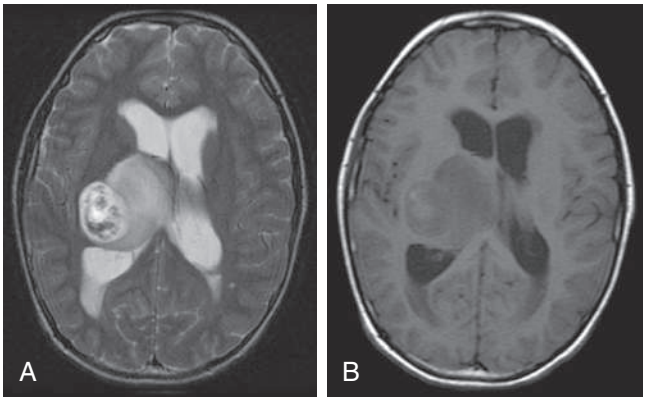

Fig. 546.6 A, Nonenhanced axial T2-weighted MR image of **grade III astrocytoma** of the right thalamus demonstrating diffuse hyperintensity and area of necrotic cyst formation. B, Gadolinium-enhanced sagittal T1-weighted MR image showing slight enhancement and hypodensity of **grade III astrocytoma** of the thalamus. This 14-yr-old child presented with left arm and leg numbness and weakness and right-sided headaches.

40% of cases occurring in children younger than 4 years of age. The incidence of leptomeningeal spread approaches 10% overall. Clinical presentation can be insidious and often depends on the anatomic location of the tumor. MRI demonstrates a well-circumscribed tumor with variable and complex patterns of gadolinium enhancement, with or without cystic structures (Fig. 546.7). These tumors usually are noninvasive, extending into the ventricular lumen and/or displacing normal structures, sometimes leading to significant obstructive hydrocephalus. Histologic characteristics include perivascular pseudorosettes, ependymal rosettes, monomorphic nuclear morphology, and occasional nonpalisading foci of necrosis. Other histologic subtypes include **anaplastic ependymoma** (WHO grade III), which is much less common in childhood and is characterized by a high mitotic index and histologic features of microvascular proliferation and pseudopalisading necrosis. **Myxopapillary ependymoma** (WHO grade II) is a slow-growing tumor arising from the filum terminale and conus medullaris and appears to be a biologically different subtype. Preliminary studies suggest that there are genetically distinct subtypes of ependymoma, exemplified by an association between alterations in the ***NF2*** gene and spinal ependymoma. Surgery is the primary treatment modality, with extent of surgical resection a major prognostic factor. Two other major prognostic factors are age, with younger children having poorer outcomes, and tumor location, with localization in the posterior fossa, which often is seen in young children, associated with poorer outcomes. Surgery alone is rarely curative. Multimodal therapy incorporating irradiation with surgery has resulted in long-term survival in approximately 40% of patients with ependymoma undergoing gross total resection. Recurrence is predominantly local. The role of chemotherapy in multimodal therapy of ependymoma is still unclear. Current investigations are directed toward identification of optimal radiation dose, surgical questions addressing the use of second-look procedures after chemotherapy, and further evaluation of classic as well as novel chemotherapeutic agents. Genome-wide DNA methylation patterns have identified nine molecular subgroups in these tumors across three anatomic compartments including supratentorial (ST), posterior fossa (PF), and the spinal locations (Fig. 548.8). Two subgroups (group A and B) of PF ependymoma have been identified with distinct molecular and clinical characteristics, and the use of targeted chemotherapy against these subtypes is being evaluated.

Choroid Plexus Tumors

Choroid plexus tumors account for 2–4% of childhood CNS tumors. They are the most common CNS tumors in children younger than 1 year of age and account for 10–20% of CNS tumors in infants. These tumors are intraventricular epithelial neoplasms arising from the choroid plexus. Children present with signs and symptoms of increased ICP. Infants may present with macrocephaly and focal neurologic deficits. In children, these tumors predominantly occur supratentorially in the lateral ventricles. The group of choroid plexus tumors is made up of **choroid plexus papillomas** (WHO grade I), **atypical choroid plexus papillomas** (WHO grade II), and **choroid plexus carcinomas** (WHO grade III). Choroid plexus papilloma, the *most common of this group*, is a well-circumscribed lesion with focal calcification on neuroimaging. *Choroid plexus carcinoma* is a malignant tumor with metastatic potential to seed into the CSF pathways. This malignancy has the following histologic characteristics: nuclear pleomorphism, high mitotic index, necrosis, and increased cell density. MRI typically demonstrates a large, hyperdense, contrast-enhancing, intraventricular mass with peritumoral edema, hemorrhage, and hydrocephalus. The tumor suppressor p53 is crucially involved in the biology of this cancer and may contribute to aggressive tumor behavior. Molecular data subclassify choroid plexus tumors into three distinct subgroups with different molecular aberrations and clinical outcomes. These tumors are associated with the Li-Fraumeni syndrome. After complete surgical resection, the frequency of cure for choroid plexus *papilloma* approaches 100%, whereas the frequency of cure for choroid plexus *carcinoma* approaches 20–40%. Reports suggest that radiation therapy and/or chemotherapy may lead to better disease control for choroid plexus carcinoma.

Embryonal Tumors

Embryonal tumors or **primitive neuroectodermal tumors (PNETs)** are one of the most common groups of *malignant* CNS tumors of childhood, accounting for approximately 9% of pediatric CNS tumors. They have the potential to metastasize to the neuraxis and extracranial tissues. The group includes medulloblastoma, supratentorial PNET, atypical teratoid/rhabdoid tumor, and other rare embryonal tumors, all of which are histologically classified as WHO grade IV tumors.

Medulloblastoma, which accounts for ~62% of embryonal CNS tumors, is a cerebellar tumor occurring predominantly in males and at a median age of 5-7 years. CT and MRI demonstrate a solid, homogeneous, contrast medium–enhancing mass in the PF causing fourth ventricular obstruction and hydrocephalus (Fig. 546.9). Up to 30% of patients with medulloblastoma present with neuroimaging evidence of leptomeningeal spread. Among a variety of diverse histologic patterns of this tumor, the most common is a monomorphic sheet of undifferentiated cells classically noted as small, blue round cells. Neuronal differentiation is more common among these tumors and is characterized

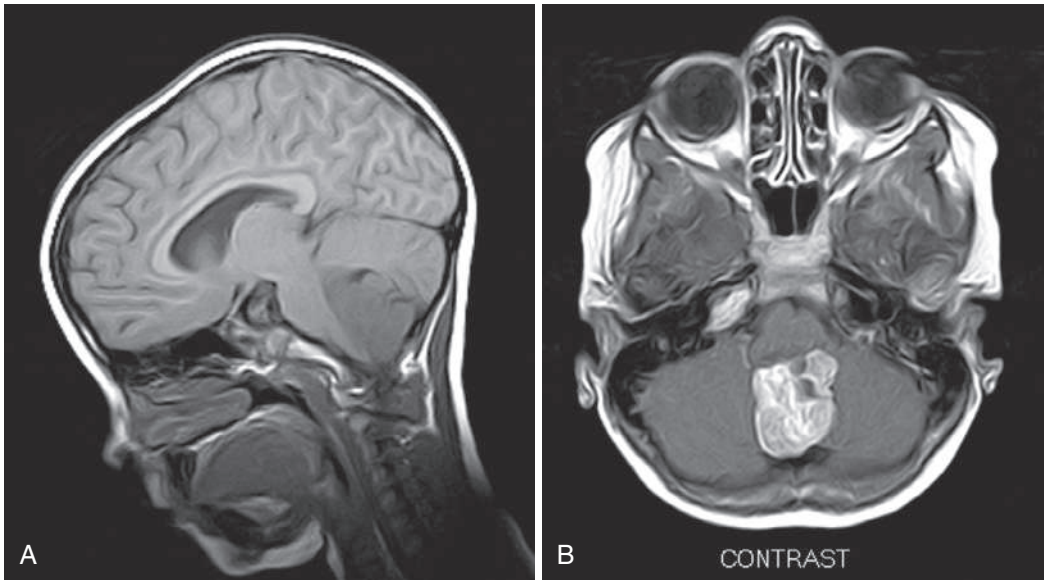

Fig. 546.7 A, Sagittal T1-weighted MR image of a 6-yr-old patient with **ependymoma**, demonstrating a hypointense mass within the fourth ventricle compressing the brainstem. B, Gadolinium-enhanced axial T1-weighted image of an ependymoma showing an enhancing mass within the fourth ventricle.

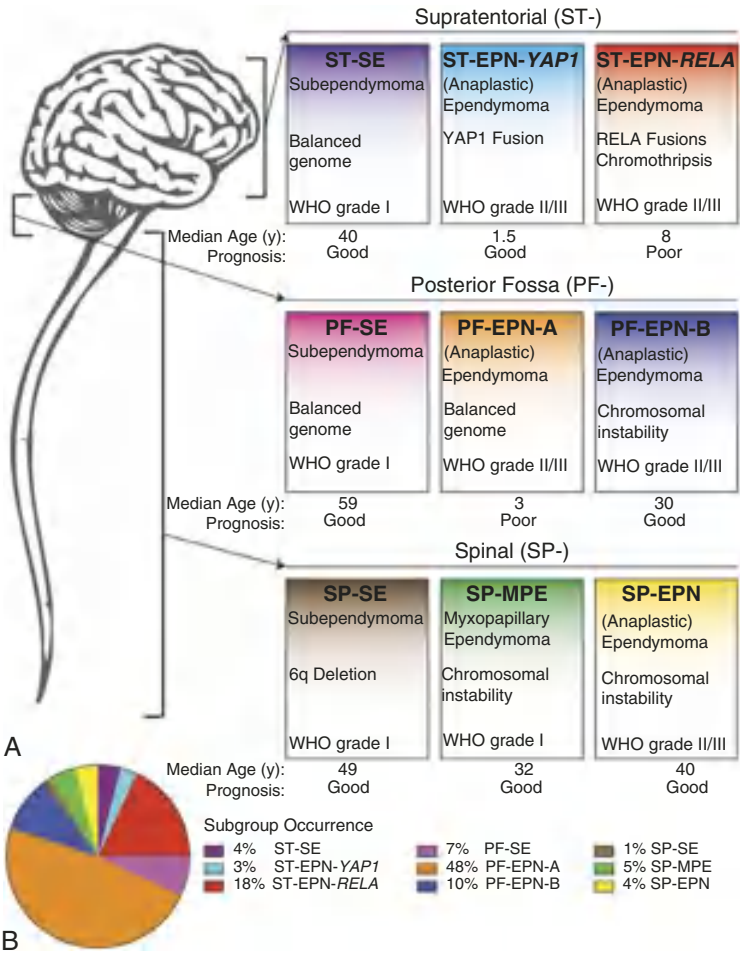

Fig. 546.8 A, Illustration of the nine recognized subsets of **ependymomas**. Only four of these subsets (ST-EPN-YAP1, ST-EPN-RELA, PF-EPN-A, and PF-EPN-B) typically occur during the childhood years. The subependymoma (SE) groups typically affect middle-age or older adults, and the spinal lesions, although occasionally encountered in children, are largely seen in adults. B, Estimate of the overall frequency of the different subtypes of ependymomas. *(From Pollack IF, Agnihotri S, Broniscer A. Childhood brain tumors: current management, biological insights, and future directions. J Neurosurg Pediatr. 2019;23:261–273. Fig. 3.)*

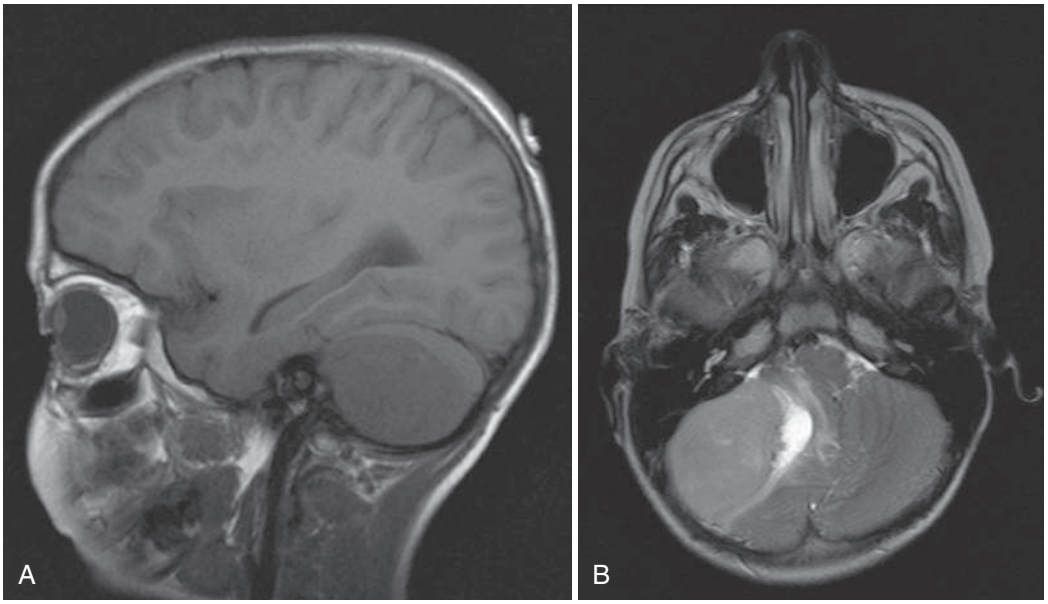

Fig. 546.9 A, Sagittal T1-weighted MR image shows hypointense mass involving the cerebellar hemisphere in a 6-yr-old child with desmoplastic variant of **medulloblastoma**. B, Axial T2-weighted image of the same child shows hyperintense mass involving the cerebellar hemisphere.

histologically by the presence of Homer Wright rosettes and by immunopositivity for synaptophysin. An anaplastic variant is often more aggressive and may be associated with poorer prognosis. Patients present with signs and symptoms of increased ICP (i.e., headache, nausea, vomiting, blurring of vision, mental status changes, and hypertension) and cerebellar dysfunction (i.e., ataxia, poor balance, dysmetria, dysarthria). Clinical staging evaluation includes MRI of the brain and spine, both preoperatively and postoperatively, as well as lumbar puncture after the increased ICP has resolved. Clinical features that have consistently demonstrated prognostic significance include age at diagnosis,

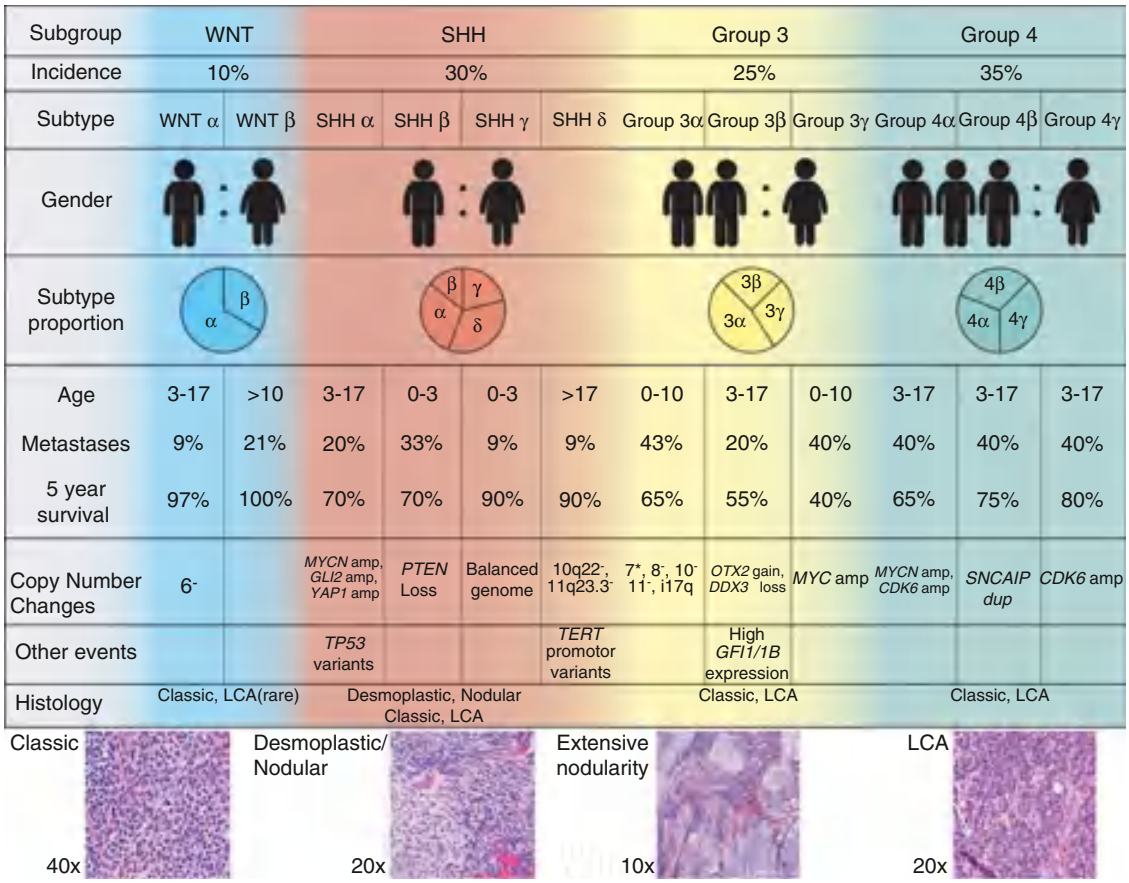

Fig. 546.10 Schematic *(upper)* depicting the four WHO-recognized subgroups of medulloblastoma, as well as the additional subtypes noted more recently and their distinguishing characteristics in terms of amplifications (amp) and duplications (dup). The figure *(lower)* also depicts the histological diversity of medulloblastomas: WNT tumors most commonly have a classic histology, whereas SHH tumors have desmoplastic histology with varying degrees of nodularity. Large cell/anaplastic (LCA) histology is most commonly seen in group 3 and less commonly in group 4 tumors. *(From Pollack IF, Agnihotri S, Broniscer A. Childhood brain tumors: current management, biological insights, and future directions. J Neurosurg Pediatr. 2019;23:261–273. Fig. 2.)*

extent of disease, and extent of surgical resection. Patients younger than 4 years of age have a poor outcome, partly as the result of a higher incidence of disseminated disease on presentation and past therapeutic approaches that have used less intense therapies. Patients with disseminated disease at diagnosis (M > 0), including positive CSF cytologic result alone (M1), have a markedly poorer outcome than those patients with no dissemination (M0). Similarly, patients with gross residual disease after surgery have poorer outcomes than those in whom surgery achieved gross total resection of disease.

Cytogenetic and molecular genetic studies have demonstrated multiple abnormalities in medulloblastoma (Fig. 546.10). The most common abnormality involves chromosome 17p deletions, which occur in 30–40% of all cases. Several signaling pathways have been shown to be active in medulloblastomas, including the sonic hedgehog **(SHH)** pathway, predominately associated with the desmoplastic variants, and the **WNT** pathway, which can occur in up to 15% of cases and has been associated with improved survival. Integrative genomic studies have identified at least four distinct molecular subgroups of medulloblastoma—**WNT**, **SHH**, **group 3**, and **group 4**—that exhibit highly discriminate transcriptional, cytogenetic, and mutational spectra, in addition to divergent patient demographics and clinical behavior (see Fig. 546.10). These prognostic groups still must be validated in larger prospective studies, though the WNT subgroup is known to have the most favorable outcome. A multimodal treatment approach is pursued in medulloblastoma, with surgery as the starting point of treatment. Medulloblastoma is sensitive to both chemotherapy and radiation therapy. With technologic advances in neurosurgery, neuroradiology, and radiation therapy, as well as identification of chemotherapy as an effective modality, the overall outcome among all patients approaches 60–70%. Standard radiation treatment in standard risk medulloblastoma incorporates craniospinal radiation at a total cumulative dose of 24 Gy, with a cumulative dose of 50-55 Gy to the tumor bed. Craniospinal radiation at this dose in children younger than 3 years of age results in severe late neurologic sequelae, including microcephaly, learning disabilities, cognitive impairment, neuroendocrine dysfunction (growth failure, hypothyroidism, hypogonadism, and absence/delay of puberty), and/or second malignancies. Similarly, in older children, late sequelae, such as learning disabilities, neuroendocrine dysfunction, and/or second malignancies, can occur. These observations have resulted in stratification of treatment approaches into the following three strata: (1) patients younger than 3 years of age, (2) standard-risk patients older than 3 years of age with surgical total resection and no disease dissemination (M0), and (3) high-risk patients older than 3 years of age with disease dissemination (M > 0) and/or bulky residual disease after surgery. With the risk-based approach to treatment, children with high-risk medulloblastoma receive high-dose cranial–spinal radiation (36 Gy) with chemotherapy during and after radiation therapy. As the dose of radiation depends on the risk stratification, complete staging with MRI of the spine before starting treatment is essential for the best chance of survival. Approaches in young children (usually younger than 3 years of age) incorporate high-dose chemotherapy with peripheral stem cell reinfusion to avoid radiation therapy.

Overall survival in children with nonmetastatic medulloblastoma and gross total tumor resection approaches 85%. The presence of bulky residual tumor (56% survival) or metastases (38% survival) confers a poor prognosis. The molecular classification is being evaluated to stratify risk groups and tailor therapy accordingly. The WNT subgroup and nonmetastatic group 4 tumors are recognized as low-risk tumors that may qualify for reduced therapy. High-risk groups were defined as patients with metastatic SHH or group 4 tumors, where intensification of therapy is being profiled.

Supratentorial primitive neuroectodermal tumors (SPNETs) account for approximately 1% of childhood CNS tumors, primarily in children within the first decade of life. These tumors are similar histologically to medulloblastoma and are composed of undifferentiated or poorly differentiated neuroepithelial cells. Historically, patients with SPNETs have had poorer outcomes than those with medulloblastoma after combined-modality therapy. Children with SPNETs are considered among the high-risk group and receive dose-intense chemotherapy with craniospinal radiation therapy.

Atypical teratoid/rhabdoid tumor is a very aggressive embryonal malignancy that occurs predominantly in children younger than 5 years of age and can occur at any location in the neuraxis. The histology demonstrates a heterogeneous pattern of cells, including rhabdoid cells that express epithelial membrane antigen and neurofilament antigen. The characteristic cytogenetic pattern is partial or complete deletion of chromosome 22q11.2 that is associated with pathogenic variants in the *INI1* gene. The relation between this variant and tumorigenesis is unclear. Though the overall prognosis remains poor, intensive chemotherapy, focal radiation, and high-dose chemotherapy with stem cell rescue have shown a trend toward improved survival. This is noted more in patients who undergo complete resection of tumor and focal radiation.

Pineal Parenchymal Tumors

The pineal parenchymal tumors are the most common malignancies after germ cell tumors that occur in the pineal region. These include **pineoblastoma**, occurring predominantly in childhood, **pineocytoma**, and the **mixed pineal parenchymal tumors**. The therapeutic approach in this group of diseases is multimodal. There was significant concern regarding the location of these masses and the potential complications of surgical intervention. With developments in neurosurgical technique and surgical technology, the morbidity and mortality associated with these approaches have markedly decreased. Stereotactic biopsy of these tumors may be adequate to establish diagnosis; however, consideration should be given to total resection of the lesion before institution of additional therapy. Pineoblastoma, the more malignant variant, is considered a subgroup of childhood PNETs. Chemotherapy regimens incorporate cisplatin, cyclophosphamide (Cytoxan), etoposide (VP-16), and vincristine and/or lomustine. The survival outcome of combined chemotherapy and radiation therapy in pineal-region PNETs approaches 70% at 5 years. Pineocytoma usually is approached with surgical resection.

Craniopharyngioma

Craniopharyngioma (WHO grade I) is a common tumor of childhood, accounting for 3–10% of all CNS childhood tumors. Two histological subtypes have been identified, adamantinomatous and papillary craniopharyngiomas (CP), each with specific origin and genetic alterations. ***BRAFV600E*** pathogenic variants are solely found in the papillary CP subgroup, which is the common type in adults, whereas ***CTNNB1*** pathogenic variants are exclusively detected in adamantinomatous CP, which is common in children. Children with CP often present with endocrinologic abnormalities (growth failure and delayed sexual maturation) and/or visual changes (decreased acuity or visual field abnormalities). These tumors are often large and heterogeneous, displaying both solid and cystic components, and occur within the suprasellar region. They are minimally invasive, adhere to adjacent brain parenchyma, and engulf normal brain structures. MRI demonstrates the solid tumor with cystic structures containing fluid of intermediate density, and CT may show calcifications. Surgery is the primary treatment modality, with gross total resection being curative. Controversy exists regarding the relative roles of surgery and radiation therapy in large, complex tumors. Significant morbidity (panhypopituitarism, growth failure, visual loss) is associated with these tumors and their therapy, owing to the anatomic location.

Germ Cell Tumors

Germ cell tumors of the CNS are a heterogeneous group of tumors that are primarily tumors of childhood, arising predominantly in midline structures of the pineal and suprasellar regions (see Fig. 546.3). They account for 3–5% of pediatric CNS tumors. The peak incidence of these tumors is in children 10-12 yr of age. Overall, there is a male preponderance, although there is a female preponderance for suprasellar tumors. Germ cell tumors occur multifocally in 5–10% of cases. This group of tumors is much more prevalent in Asian populations than European populations. Delays in diagnosis can occur because these tumors have a particularly insidious course; the initial presenting symptoms may be subtle. Similar to peripheral germ cell tumors, the analysis of protein markers, **α-fetoprotein,** and **β-human chorionic gonadotropin** may be useful in establishing the diagnosis and monitoring treatment response. Surgical biopsy is recommended to establish the diagnosis; however, secreting **germinomas** and **nongerminomatous germ cell tumors** may be diagnosed based on protein marker elevations. Therapeutic approaches to germinomas and nongerminomatous germ cell tumors are different. The survival proportion among patients with pure germinoma exceeds 90%. The postsurgical treatment of pure germinomas is somewhat controversial in defining the relative roles of chemotherapy and radiation therapy. Clinical trials have investigated the use of chemotherapy and reduced-dose radiation and field after surgery in pure germinomas. The therapeutic approach to nongerminomatous germ cell tumors is more aggressive, combining more intense chemotherapy regimens with craniospinal radiation therapy. Survival rates among patients with these tumors are markedly lower than those noted in patients with germinoma, ranging from 70–80% at 5 years. Trials have shown the benefit of the use of high doses of chemotherapy with peripheral blood stem cell rescue specially at metastatic and relapse groups.

Tumors of the Brainstem

Tumors of the brainstem are a heterogeneous group of tumors that account for 10.9% of childhood primary CNS tumors. Outcome depends on tumor location, imaging characteristics, and the patient's clinical status. Patients with these tumors may present with motor weakness, cranial nerve dysfunction, cerebellar dysfunction, and/or signs of increased ICP. On the basis of MRI evaluation and clinical findings, tumors of the brainstem can be classified into four types: focal (5–10% of patients), dorsally exophytic (5–10%), cervicomedullary (5–10%), and diffuse intrinsic pontine glioma **(DIPG)** (70–85%) (Fig. 546.11). Surgical resection is the primary treatment approach for focal and dorsally exophytic tumors and leads to a favorable outcome. Histologically, these two groups usually are low-grade gliomas. *Cervicomedullary tumors, because of their location, may not be amenable to surgical resection but are sensitive to radiation therapy*. DIPG, characterized by the diffuse infiltrating grade II-IV glioma, is associated with a very poor outcome independent of histologic diagnosis. These tumors are not amenable to surgical resection. Biopsy in children in whom MRI shows DIPG is controversial and is not recommended unless there are atypical radiographic findings suspicious for another diagnosis, such as infection, vascular malformation, myelination disorder, or metastatic tumor. Studies have identified the unique genetic makeup of this fatal brain cancer, with nearly 80% found to harbor pathogenic variants in histone ***H3.3*** or ***H3.1 (H3-K27M)*** and 20% pathogenic variants affecting the activin receptor gene ***(ACVR1);*** three molecularly distinct subgroups have been identified (H3-K27M, silent and MYCN).

The standard treatment approach has been palliative radiation therapy, and median survival with this treatment is 12 months, at best. Use

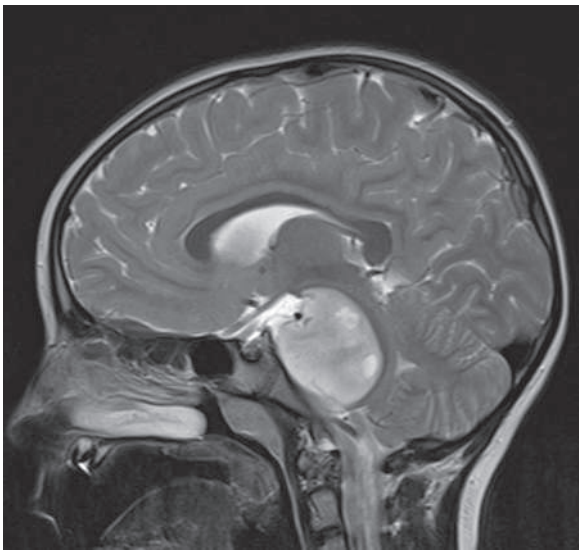

Fig. 546.11 T2-weighted sagittal MR image of a diffuse infiltrating pontine glioma in a 5-yr-old child presenting with headaches, left facial droop, and lethargy.

of chemotherapy, including high-dose chemotherapy with peripheral blood stem cell rescue, has not yet been of survival benefit in this group of patients. Experimental approaches have included the use of immunotherapy with oncolytic herpes simplex virus (HSV) or adenoviruses.

Metastatic Tumors

Metastatic spread of other childhood malignancies to the brain is uncommon. Childhood acute lymphoblastic leukemia and non-Hodgkin lymphoma can spread to the leptomeninges, causing symptoms of communicating hydrocephalus. **Chloromas,** which are collections of myeloid leukemia cells, can occur throughout the neuraxis. Rarely, brain parenchymal metastases occur from lymphoma, neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, and clear cell sarcoma of the kidney. Therapeutic approaches are based on the specific histologic diagnosis and may incorporate radiation therapy, intrathecal administration of chemotherapy, and/or systemic administration of chemotherapy. Medulloblastoma is the childhood brain tumor that most commonly metastasizes extraneurally. Less commonly, extraneural metastases from malignant glioma, PNET, and ependymoma can occur. Ventriculoperitoneal shunts have been known to allow extraneural metastases, primarily within the peritoneal cavity but also systemically.

COMPLICATIONS AND LONG-TERM MANAGEMENT

Data from the National Cancer Institute Surveillance, Epidemiology, and End Results Program indicate that more than 70% of patients with childhood brain tumors will be long-term survivors. At least 50% of these survivors will experience chronic problems as a direct result of their tumors and treatment. These problems include chronic neurologic deficits such as focal motor and sensory abnormalities, seizure disorders, neurocognitive deficits (e.g., developmental delays, learning disabilities), and neuroendocrine deficiencies (e.g., hypothyroidism, growth failure, delay or absence of puberty). These patients are also at significant risk for secondary malignancies, hearing deficit, and early cataract from radiation therapy. Supportive multidisciplinary interventions for children with brain tumors both during and after therapy may help improve the ultimate outcome. Optimal seizure management, physical therapy, endocrine management with timely growth hormone and thyroid replacement therapy, tailored educational programs, and vocational interventions may enhance the childhood brain tumor survivor's quality of life.

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Chapter 547

Neuroblastoma

Fiorela N. Hernandez Tejada and Douglas J. Harrison

Neuroblastomas are embryonal cancers of the peripheral sympathetic nervous system with heterogeneous clinical presentation and course, ranging from tumors that undergo spontaneous regression to very aggressive tumors unresponsive to very intensive multimodal therapy. The causes of most cases remain unknown. Advances have been made in the treatment of children with these tumors, which have improved outcomes, although many with aggressive forms of neuroblastoma still succumb to their disease despite intensive therapy.

EPIDEMIOLOGY

Neuroblastoma is the most common extracranial solid tumor in children and is the most commonly diagnosed malignancy in the first year of life. Approximately 600 new cases are diagnosed each year in the United States, accounting for 8–10% of childhood malignancies and one-third of cancers in infants. Neuroblastoma accounts for >15% of the mortality from cancer in children. The median age of children at diagnosis of neuroblastoma is 18 months, and 90% of cases are diagnosed in children who are <10 years of age. The incidence is slightly higher in males and in the White population.

PATHOLOGY

Neuroblastoma tumors, which are derived from primordial neural crest cells, form a spectrum with variable degrees of neural differentiation, ranging from tumors with primarily undifferentiated small round cells (neuroblastoma) to tumors consisting of mature and maturing Schwannian stroma with ganglion cells (ganglioneuroblastoma or ganglioneuroma). The tumors may resemble other **small, round blue cell tumors,** such as rhabdomyosarcoma, Ewing sarcoma, and non-Hodgkin lymphoma. The prognosis of children with neuroblastoma varies with the histologic features of the tumor as dictated by the presence and amount of Schwannian stroma, the degree of tumor cell differentiation, and the mitosis-karyorrhexis index.

PATHOGENESIS

The etiology of neuroblastoma in most cases remains unknown. Familial neuroblastoma is rare but accounts for 1–2% of all cases, is associated with a younger age at diagnosis, and is linked to germline gain-of-function pathogenic variants in the *ALK* gene. The *BARD1* gene has also been identified as a major genetic contributor to neuroblastoma risk. Germline gain-of-function pathogenic variants in *PHOX2B* predisposes to most of the syndromic neuroblastoma cases, including Hirschsprung disease and central congenital hypoventilation syndrome. Neuroblastoma is associated with other neural crest disorders, such as neurofibromatosis type 1, and potentially congenital cardiovascular malformations (Table 547.1). Children with Beckwith-Wiedemann syndrome and hemihypertrophy also have a higher incidence of neuroblastoma. Increased incidence of neuroblastoma is associated with some maternal and paternal occupational chemical exposures, maternal drug use, farming, and work related to electronics, although no single environmental exposure has been shown to directly cause neuroblastoma.

Genetic characteristics of neuroblastoma tumors that are of prognostic importance include amplification of the *MYCN (N-myc)* protooncogene and tumor cell DNA content, or ploidy (Tables 547.2-547.4). Amplification of *MYCN* is strongly associated with advanced tumor stage and poor outcomes. Other genetic alterations have been identified

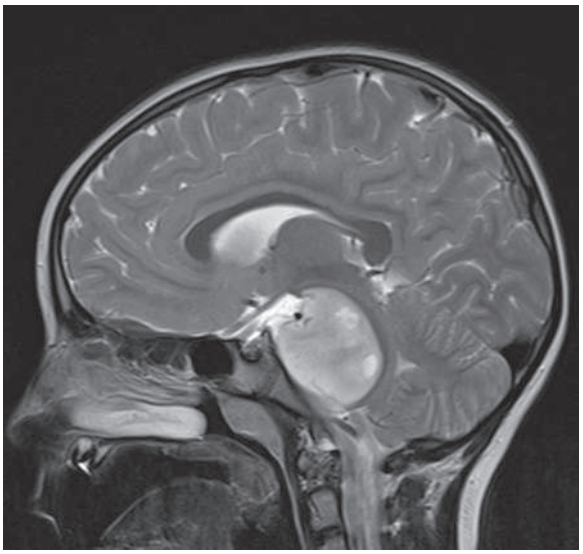

Fig. 546.11 T2-weighted sagittal MR image of a diffuse infiltrating pontine glioma in a 5-yr-old child presenting with headaches, left facial droop, and lethargy.

of chemotherapy, including high-dose chemotherapy with peripheral blood stem cell rescue, has not yet been of survival benefit in this group of patients. Experimental approaches have included the use of immunotherapy with oncolytic herpes simplex virus (HSV) or adenoviruses.

Metastatic Tumors

Metastatic spread of other childhood malignancies to the brain is uncommon. Childhood acute lymphoblastic leukemia and non-Hodgkin lymphoma can spread to the leptomeninges, causing symptoms of communicating hydrocephalus. **Chloromas,** which are collections of myeloid leukemia cells, can occur throughout the neuraxis. Rarely, brain parenchymal metastases occur from lymphoma, neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, and clear cell sarcoma of the kidney. Therapeutic approaches are based on the specific histologic diagnosis and may incorporate radiation therapy, intrathecal administration of chemotherapy, and/or systemic administration of chemotherapy. Medulloblastoma is the childhood brain tumor that most commonly metastasizes extraneurally. Less commonly, extraneural metastases from malignant glioma, PNET, and ependymoma can occur. Ventriculoperitoneal shunts have been known to allow extraneural metastases, primarily within the peritoneal cavity but also systemically.

COMPLICATIONS AND LONG-TERM MANAGEMENT

Data from the National Cancer Institute Surveillance, Epidemiology, and End Results Program indicate that more than 70% of patients with childhood brain tumors will be long-term survivors. At least 50% of these survivors will experience chronic problems as a direct result of their tumors and treatment. These problems include chronic neurologic deficits such as focal motor and sensory abnormalities, seizure disorders, neurocognitive deficits (e.g., developmental delays, learning disabilities), and neuroendocrine deficiencies (e.g., hypothyroidism, growth failure, delay or absence of puberty). These patients are also at significant risk for secondary malignancies, hearing deficit, and early cataract from radiation therapy. Supportive multidisciplinary interventions for children with brain tumors both during and after therapy may help improve the ultimate outcome. Optimal seizure management, physical therapy, endocrine management with timely growth hormone and thyroid replacement therapy, tailored educational programs, and vocational interventions may enhance the childhood brain tumor survivor's quality of life.

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Chapter 547

Neuroblastoma

Fiorela N. Hernandez Tejada and Douglas J. Harrison

Neuroblastomas are embryonal cancers of the peripheral sympathetic nervous system with heterogeneous clinical presentation and course, ranging from tumors that undergo spontaneous regression to very aggressive tumors unresponsive to very intensive multimodal therapy. The causes of most cases remain unknown. Advances have been made in the treatment of children with these tumors, which have improved outcomes, although many with aggressive forms of neuroblastoma still succumb to their disease despite intensive therapy.

EPIDEMIOLOGY

Neuroblastoma is the most common extracranial solid tumor in children and is the most commonly diagnosed malignancy in the first year of life. Approximately 600 new cases are diagnosed each year in the United States, accounting for 8–10% of childhood malignancies and one-third of cancers in infants. Neuroblastoma accounts for >15% of the mortality from cancer in children. The median age of children at diagnosis of neuroblastoma is 18 months, and 90% of cases are diagnosed in children who are <10 years of age. The incidence is slightly higher in males and in the White population.

PATHOLOGY

Neuroblastoma tumors, which are derived from primordial neural crest cells, form a spectrum with variable degrees of neural differentiation, ranging from tumors with primarily undifferentiated small round cells (neuroblastoma) to tumors consisting of mature and maturing Schwannian stroma with ganglion cells (ganglioneuroblastoma or ganglioneuroma). The tumors may resemble other **small, round blue cell tumors,** such as rhabdomyosarcoma, Ewing sarcoma, and non-Hodgkin lymphoma. The prognosis of children with neuroblastoma varies with the histologic features of the tumor as dictated by the presence and amount of Schwannian stroma, the degree of tumor cell differentiation, and the mitosis-karyorrhexis index.

PATHOGENESIS

The etiology of neuroblastoma in most cases remains unknown. Familial neuroblastoma is rare but accounts for 1–2% of all cases, is associated with a younger age at diagnosis, and is linked to germline gain-of-function pathogenic variants in the *ALK* gene. The *BARD1* gene has also been identified as a major genetic contributor to neuroblastoma risk. Germline gain-of-function pathogenic variants in *PHOX2B* predisposes to most of the syndromic neuroblastoma cases, including Hirschsprung disease and central congenital hypoventilation syndrome. Neuroblastoma is associated with other neural crest disorders, such as neurofibromatosis type 1, and potentially congenital cardiovascular malformations (Table 547.1). Children with Beckwith-Wiedemann syndrome and hemihypertrophy also have a higher incidence of neuroblastoma. Increased incidence of neuroblastoma is associated with some maternal and paternal occupational chemical exposures, maternal drug use, farming, and work related to electronics, although no single environmental exposure has been shown to directly cause neuroblastoma.

Genetic characteristics of neuroblastoma tumors that are of prognostic importance include amplification of the *MYCN (N-myc)* protooncogene and tumor cell DNA content, or ploidy (Tables 547.2-547.4). Amplification of *MYCN* is strongly associated with advanced tumor stage and poor outcomes. Other genetic alterations have been identified

Table 547.1 Syndromes Due to or Associated with Neuroblastoma

EPONYM	FEATURES
SYNDROMES CAUSED BY NEUROBLASTOMA	
Pepper syndrome	Massive involvement of the liver with metastatic disease with or without respiratory distress
Horner syndrome	Unilateral ptosis, myosis, and anhidrosis associated with a thoracic or cervical primary tumor; symptoms do not resolve with tumor resection
Hutchinson syndrome	Limping and irritability in young child associated with bone and bone marrow metastases
Opsoclonus-myoclonus-ataxia syndrome	Myoclonic jerking and random conjugate eye movements with or without cerebellar ataxia; often associated with a biologically favorable and differentiated tumor; the condition is likely immune mediated, may not resolve with tumor removal, and often exhibits progressive neuropsychologic sequelae
Kerner-Morrison syndrome	Intractable secretory watery diarrhea due to tumor secretion of vasointestinal peptides; tumors are generally biologically favorable
ROHHAD	Approximately 40% may have neural crest-derived tumors. Obesity and neurologic issues may be part of a paraneoplastic syndrome
SYNDROMES PREDISPOSING TO NEUROBLASTOMA	
Neurocristopathy syndrome	Neuroblastoma associated with other neural crest disorders, including congenital hypoventilation syndrome or Hirschsprung disease; germline pathogenic variants in the paired homeobox gene *PHOX2B* have been identified in a subset of patients with this disease
Beckwith-Wiedemann syndrome	Macrosomia, hyperinsulinemic hypoglycemia, omphalocele
Costello syndrome (faciocutaneo-skeletal syndrome)	Autosomal dominant, pathogenic variant in *HRAS*, intellectual disability, delayed development, cardiomyopathy
Familial pheochromocytoma/paraganglioma syndrome	Autosomal dominant, pathogenic variant in *MAX* and other genes
Fanconi anemia	Autosomal recessive, congenital anomalies, aplastic anemia, pathogenic variants in *FANCA*, *FANCC*, *FANCG*
Neurofibromatosis type 1	*NF1* pathogenic variants
Noonan syndrome	Ras-MAPK pathway (RASopathies) pathogenic variant
Turner syndrome	Partial or complete deletion of X chromosome, short-webbed neck, short stature

ROHHAD, Rapid-onset obesity, hypothalamic dysfunction, hypoventilation, autonomic dysregulation.
Modified from Park JR, Eggert A, Caron H. *Neuroblastoma*: biology, prognosis, and treatment. *Pediatr Clin North Am*. 2008;55:97–120.

Table 547.2 Children's Oncology Group Neuroblastoma Risk Stratification

RISK GROUP	STAGE	AGE	*MYCN* AMPLIFICATION STATUS	PLOIDY	SHIMADA
Low	1	Any	Any	Any	Any
Low	2A/2B	Any	Not amplified	Any	Any
High	2A/2B	Any	Amplified	Any	Any
Intermediate	3	<547 days	Not amplified	Any	Any
Intermediate	3	≥547 days	Not amplified	Any	FH
High	3	Any	Amplified	Any	Any
High	3	≥547 days	Not amplified	Any	UH
High	4	<365 days	Amplified	Any	Any
Intermediate	4	<365 days	Not amplified	Any	Any
High	4	365 to <547 days	Amplified	Any	Any
High	4	365 to <547 days	Any	DNA index = 1	Any
High	4	365 to <547 days	Any	Any	UH
Intermediate	4	365 to <547 days	Not amplified	DNA index > 1	FH
High	4	≥547 days	Any	Any	Any
Low	4S	<365 days	Not amplified	DNA index > 1	FH
Intermediate	4S	<365 days	Not amplified	DNA index = 1	Any
Intermediate	4S	<365 days	Not amplified	Any	UH
High	4S	<365 days	Amplified	Any	Any

FH, Favorable histology; UH, unfavorable histology.
Data from Irwin MS, Naranjo A, Zhang FF, et al. Revised neuroblastoma risk classification system: a report From the Children's Oncology Group. *J Clin Oncol*. 2021;39(29):3229–3241.

Table 547.3 International Neuroblastoma Staging System

STAGE	DEFINITION	INCIDENCE (%)	SURVIVAL AT 5 YR* (%)
1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive)	5	≥90
2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically	10	70-80
2B	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor; enlarged contralateral lymph nodes must be negative microscopically	10	70-80
3	Unresectable unilateral tumor infiltrating across the midline,† with or without regional lymph node involvement; *or* localized unilateral tumor with contralateral regional lymph node involvement; *or* midline tumor with bilateral extension by infiltration (resectable) or by lymph node involvement	25	40-70
4	Any primary tumor with dissemination to distant lymph nodes; bone, bone marrow, liver, skin, and other organs (except as defined for stage 4S)	60	85-90¶ 30-40#
4S	Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and bone marrow‡ (limited to infants <1 yr of age)	5	>80

*Survival is influenced by other characteristics, such as *MYCN* amplification. Percentages are approximate.
†The *midline* is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the other side of the vertebral column.
‡Marrow involvement in stage 4S should be minimal (i.e., <10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate). More extensive marrow involvement would be considered stage 4. Results of the metaiodobenzylguanidine (MIBG) scan (if performed) should be negative in the marrow.
¶If age at diagnosis is <18 mo.
#If age at diagnosis is >18 mo.
Modified from Kliegman RM, Marcdante KJ, Jenson HB, et al., eds. *Nelson Essentials of Pediatrics*. 5th ed. Philadelphia: WB Saunders; 2006. p 746; and Brodeur GM, Pritchard J, Berthold F, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. *J Clin Oncol*. 1993;11:1466–1477.

Table 547.4 Phenotypic and Genetic Features of Neuroblastoma, Treatment, and Survival According to Prognostic Category

	PROGNOSTIC CATEGORY*			
VARIABLE	LOW RISK	INTERMEDIATE RISK	HIGH RISK	TUMOR STAGE 4S
Pattern of disease	Localized tumor	Localized tumor with locoregional lymph node extension; metastases to bone marrow and bone in infants	Metastases to bone marrow and bone (except in infants)	Metastases to liver and skin (with minimal bone marrow involvement) in infants
Tumor genomics	Whole-chromosome gains	Whole-chromosome gains	Segmental chromosomal aberrations	Whole-chromosome gains
Treatment	Surgery†	Moderate-intensity chemotherapy; surgery†	Dose-intensive chemotherapy, surgery, and external-beam radiotherapy to primary tumor and resistant metastatic sites; myeloablative chemotherapy with autologous hematopoietic stem cell rescue; isotretinoin with anti-ganglioside GD2 immunotherapy	Supportive care‡
Survival rate	>98%	90–95%	40–50%	>90%

*Patients are assigned to prognostic groups according to risk, as described by the Children's Oncology Group, with the level of risk defining the likelihood of death from disease. Stage 4S disease is considered separately here because of the unique phenotype of favorable biologic features and relentless early progression but ultimately full and complete regression of the disease.
†The goal of surgery is to safely debulk the tumor mass and avoid damage to surrounding normal structures while obtaining sufficient material for molecular diagnostic studies. Some localized tumors may spontaneously regress without surgery.
‡Low-dose chemotherapy or radiation therapy, or both, is used in patients with life-threatening hepatic involvement, especially in infants <2 mo of age, who are at much higher risk for life-threatening complications from massive hepatomegaly.
From Maris JM. Recent advances in neuroblastoma. *N Engl J Med*. 2010;362:2202–2210.

in patients with neuroblastoma using whole genome sequencing such as loss of function in *ATRX* and *TERT*. Hyperdiploidy confers better prognosis if the child is younger than 18 months of age at diagnosis if amplification of *MYCN* is not present. Other chromosomal abnormalities, including loss of heterozygosity of 1p, 11q, and 14q, and gain of 17q, may be found in neuroblastoma tumors and have been associated with worse outcomes. In addition, many other biologic factors are associated with neuroblastoma outcomes, including tumor vascularity and the expression levels of nerve growth factor receptors (TrkA, TrkB), ferritin, lactate dehydrogenase, ganglioside GD2, neuropeptide Y, chromogranin A, CD44, multidrug resistance–associated protein, and telomerase.

CLINICAL MANIFESTATIONS

Neuroblastoma may develop at any site of sympathetic nervous system tissue. Approximately half of neuroblastoma tumors arise in the adrenal glands, and most of the remainder originate in the paraspinal sympathetic ganglia. Metastatic spread, which is more common in children older than 1 year of age at diagnosis, occurs via local invasion or distant hematogenous or lymphatic routes. The most common sites

of metastasis are the regional or distant lymph nodes, long bones and skull, bone marrow, liver, and skin. Lung and brain metastases are rare, occurring in less than 3% of cases.

The signs and symptoms of neuroblastoma reflect the tumor site and extent of disease and may mimic other disorders, which can result in a delayed diagnosis. Metastatic disease can cause a variety of signs and symptoms, including fever, irritability, failure to thrive, bone pain, cytopenias, bluish subcutaneous nodules, orbital proptosis, and periorbital ecchymoses (Fig. 547.1). Localized disease can manifest as an asymptomatic mass or can cause symptoms due to mass effect, which can in certain cases result in spinal cord compression, bowel obstruction, and superior vena cava syndrome.

Children with neuroblastoma can also present with associated neurologic signs and symptoms (see Table 547.1). Neuroblastoma originating in the superior cervical ganglion can result in **Horner syndrome.** Paraspinal neuroblastoma tumors can invade the neural foramina, causing spinal cord and nerve root compression. Neuroblastoma can also be associated with a paraneoplastic syndrome of autoimmune origin, termed **opsoclonus-myoclonus-ataxia syndrome**, in which patients experience rapid, uncontrollable jerking eye and body movements, poor coordination, and cognitive dysfunction. Some tumors produce catecholamines that can cause increased sweating and hypertension, and some release vasoactive intestinal peptide, causing a profound secretory diarrhea. Children with extensive tumors can also experience tumor lysis syndrome and disseminated intravascular coagulation. Infants younger than 18 months of age also can present in unique fashion, termed *stage MS* (previously 4S; see later), with widespread subcutaneous tumor nodules, massive liver involvement, limited bone marrow disease, and a small primary tumor without bone involvement or other metastases. The stage MS disease can spontaneously regress. The enigmatic characteristics of neuroblastoma with paraneoplastic syndromes and spontaneous regression under some circumstances have led some researchers to suggest that neuroblastoma may originate as a neurodevelopmental disorder.

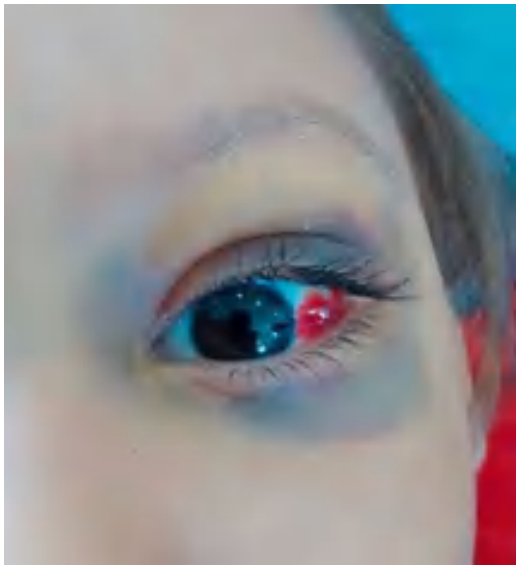

Fig. 547.1 Neuroblastoma. Periorbital ecchymosis, proptosis, and subconjunctival hemorrhage of the left eye. *(From Mota EB, Penna CRR, Marchiori E. Metastatic dissemination of a neuroblastoma. J Pediatr. 2017;189:232–232.e1. Fig. 1.)*

DIAGNOSIS

Neuroblastoma is usually discovered as a mass or multiple masses on plain radiography, CT, or MRI (Fig. 547.2A). The mass often contains calcification and hemorrhage that can allow it to be appreciated on plain radiography or CT (Fig. 547.3). Prenatal diagnosis of perinatal neuroblastoma on maternal ultrasound scans is sometimes possible. Tumor markers, including catecholamine metabolites homovanillic acid and vanillylmandelic acid, are elevated in the urine of approximately 95% of cases and help to confirm the diagnosis. A pathologic diagnosis is established from tumor tissue obtained by biopsy. Neuroblastoma can be confirmed without a primary tumor biopsy if small, round, blue tumor cells are observed in bone marrow samples (Fig. 547.4) and the levels of vanillylmandelic acid or homovanillic acid are elevated in the urine.

Evaluations for metastatic disease should include CT or MRI of the chest and abdomen, bone scans to detect cortical bone involvement, and at least two independent bone marrow aspirations and biopsies to evaluate for marrow disease. **Iodine-123 metaiodobenzylguanidine (^{123}I-MIBG)** studies should be used when available to better define the extent of disease. Some centers use gallium-68 dotatate PET/MRI or CT scans, especially if the MIBG scan is negative (Fig. 547.5). MRI of the spine should be performed in cases with suspected or potential spinal cord compression, but imaging of the brain with

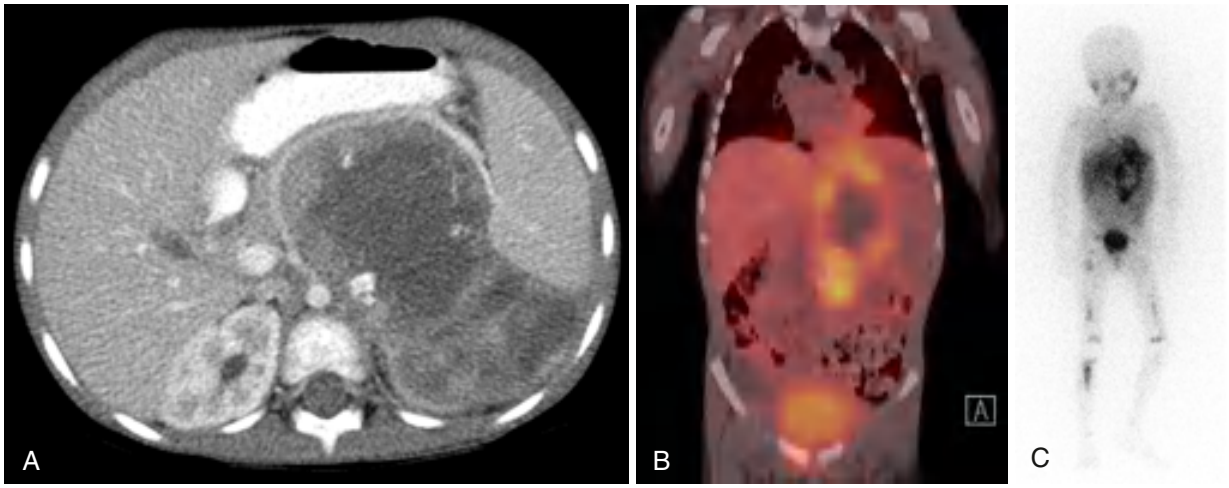

Fig. 547.2 A, CT scan of an abdominal neuroblastoma with central necrosis at diagnosis. B, Coronal fused CT and metaiodobenzylguanidine (MIBG) image of the same child with extensive retroperitoneal mass and central necrosis, probably an adrenal primary with extensive lymph node involvement. C, MIBG avid neuroblastoma with increased uptake of radiolabeled tracer can be detected in multiple sites of disease, including bone and soft tissue.

either CT or MRI is not routinely performed unless dictated by the clinical presentation.

The **International Neuroblastoma Risk Group (INRG) Staging System (INSS)** is currently used to stage patients with neuroblastoma and is based on the extent of disease as determined by imaging at diagnosis. Extent of locoregional disease is based on specific local image-defined risk factors (IDRFs) (see Table 547.3). L1 tumors (previously classified as INSS stage 1) are localized and confined to one body compartment without any IDRFs. L2 tumors (previously classified as INSS stages 2 and 3) refer to localized tumors with the presence of IDRFs. Disseminated tumors with metastases to bones, bone marrow, liver, distant lymph nodes, and/or other organs are staged as M (previously classified as INSS stage 4). Stage MS (previously stage 4S) refers to neuroblastoma in children younger than 18 months of age with dissemination to liver, skin, and/or bone marrow without bone involvement and with a primary tumor that would otherwise be staged as L1 or L2. This new INSS was recently developed to allow for more effective comparisons of treatments and outcomes worldwide.

TREATMENT

Treatment strategies for neuroblastoma have changed with significant reduction in treatment intensity for children who have localized low-risk tumors and with continued increased treatment intensity and the addition of novel agents for treatment of children who have high risk or recurrent disease. The patient's age and tumor stage are combined with cytogenetic and molecular features of the tumor to determine the treatment risk group and estimated prognosis for each patient (see

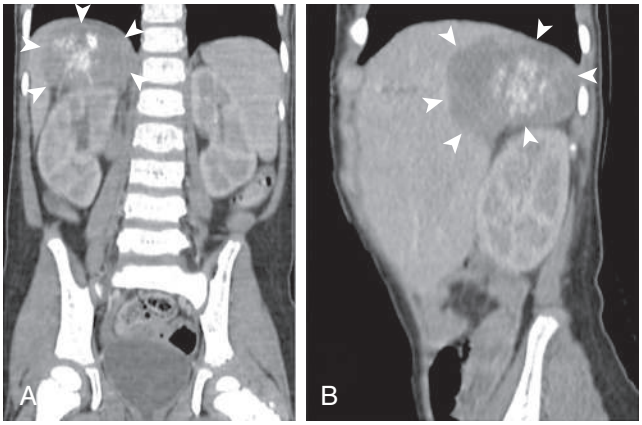

Fig. 547.3 Neuroblastoma. CT images of the abdomen with coronal (**A**) and sagittal (**B**) reconstructions showing a large low-density tumor in the right suprarenal region *(arrowheads)*. Note the neoplastic calcifications inside the mass. *(From Mota EB, Penna CRR, Marchiori E. Metastatic dissemination of a neuroblastoma. J Pediatr. 2017;189:232–232.e1. Fig. 3.)*

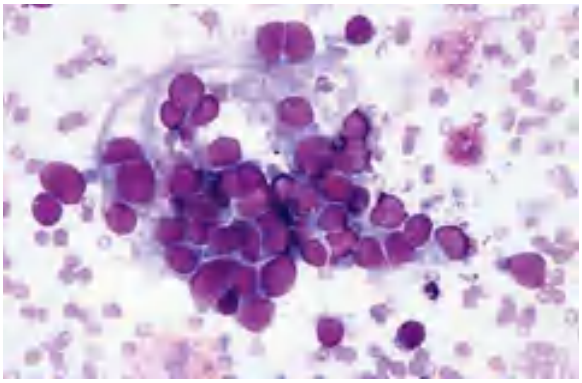

Fig. 547.4 Neuroblastoma cells aspirated from the bone marrow. Clumps of cells often contain ≥3 cells with or without evidence of rosette formation. Rosettes of cells surrounding an inner mass of fibrillary material are characteristic of neuroblastoma.

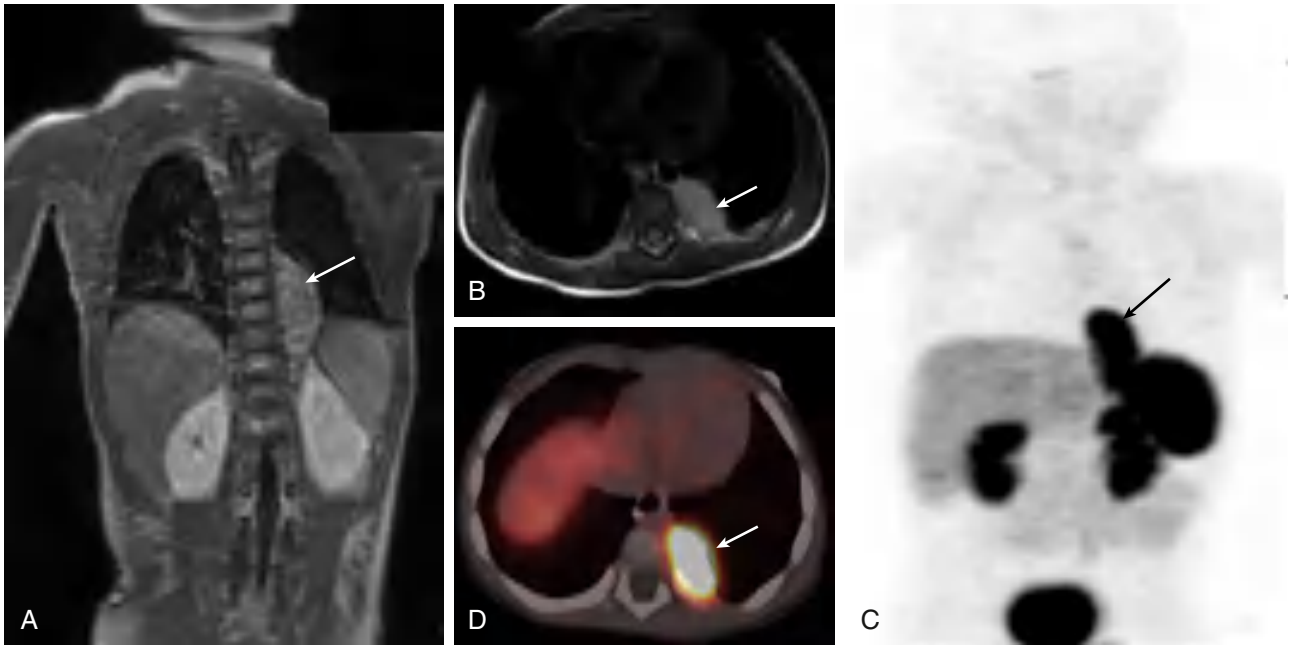

Fig. 547.5 Neuroblastoma. MRI and gallium-68 DOTANOC PET/CT scan of chest and abdomen reveal a mass in left posterior mediastinum (likely neuroblastoma). **A**, Coronal T1-weighted postcontrast image (**A**) and axial T2-weighted image (**B**) reveal a well-defined isointense lesion (42 × 26 × 27 mm) in the left posterior mediastinum extending from D7-D11 vertebrae. **C**, PET/CT maximum intensity projection image shows increased uptake in left lower thoracic paraspinal region. **D**, Axial fused PET-CT image shows somatostatin-receptor expressing mass (maximum standardized uptake value, 21; *arrow in A–D*) in the same location. *(From Kaur A, Bhagwat C, Madaan P, et al. Dancing eyes. J Pediatr. 2019;214:231.)*

Tables 547.2-547.4). Treatment for children with low-risk neuroblastoma typically includes surgery for stages L1 and L2 and observation for asymptomatic stage MS with cure rates generally >90% without further therapy. Treatment with chemotherapy or radiation for the rare child with local recurrence can still be curative. Children with spinal cord compression at diagnosis may require urgent treatment with chemotherapy, surgery, or radiation to avoid neurologic damage. Stage MS neuroblastomas have a very favorable prognosis, and many regress spontaneously without therapy. Chemotherapy or resection of the primary tumor does not improve survival rates, but for infants with massive liver involvement and respiratory compromise, chemotherapy or radiation is used to alleviate symptoms. For children with stage 4S neuroblastoma who require treatment for symptoms, the survival rate is 81%.

Treatment of intermediate-risk neuroblastoma includes surgery, chemotherapy, and, in some cases, radiation therapy. The chemotherapy usually includes moderate doses of cisplatin or carboplatin, cyclophosphamide, etoposide, and doxorubicin given over several months. Radiation therapy is used for tumors with incomplete response to chemotherapy. Children with intermediate-risk neuroblastoma, including children with L2 disease and infants with M disease both with favorable characteristics, have an excellent prognosis and >90% survival with this moderate treatment. In this intermediate-risk group, obtaining adequate diagnostic material for determination of the underlying biologic features of the tumor, such as the Shimada pathologic classification and *MYCN* gene amplification, is critical, so that children with unfavorable characteristics can receive more-aggressive treatment and those with favorable features can be spared excessive toxic therapy.

Children with high-risk neuroblastoma historically have had poor long-term survival rates of 25–35% despite intensive treatment consisting of induction chemotherapy, high-dose chemotherapy with autologous stem cell rescue, surgery, radiation, and 13-*cis*-retinoic acid. Induction chemotherapy for children with high-risk neuroblastoma includes combinations of cyclophosphamide, topotecan, doxorubicin, vincristine, cisplatin, and etoposide. After completion of induction chemotherapy, resection of the residual primary tumor is followed by high-dose chemotherapy with autologous stem cell rescue and focal radiation therapy to tumor sites. A national cooperative group trial demonstrated significantly better survival with chemotherapy plus autologous stem cell rescue than with chemotherapy alone. The further addition of the differentiating agent, 13-*cis*-retinoic acid, following autologous stem cell transplantation, resulted in further improvements in survival rates. In addition, a national clinical trial has demonstrated an increase in short-term survival rates with the addition of the monoclonal antibody ch14.18 **(dinutuximab)** to 13-*cis*-retinoic acid therapy. This monoclonal antibody targets a disialoganglioside, GD2, which has ubiquitous expression on neuroblastoma cells. In this large, randomized, clinical trial of high-risk neuroblastoma patients sponsored by the Children's Oncology Group, incorporation of the antibody into consolidative therapy following autologous stem cell transplant improved the 2-year event-free survival from 46.5–66.5%. The incorporation of tandem autologous stem cell transplant (two separate autologous stem cell transplants with differing conditioning regimens) may further improve outcomes for patients with high-risk disease.

Cases of high-risk neuroblastoma are associated with frequent relapses, and children with recurrent neuroblastoma have a <50% response rate to alternative chemotherapy regimens. New treatment strategies and agents are needed for children with both high-risk and recurrent neuroblastoma. Therapies currently under investigation include new chemotherapeutic agents as well as novel therapies directed against critical intracellular signaling pathways, radiolabeled targeted agents (such as *therapeutic* ^{131}I-MIBG), immunotherapy, and antitumor vaccines.

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Chapter 548

Neoplasms of the Kidney

548.1 Wilms Tumor

Najat C. Daw and Dristhi S. Ragoonanan

Wilms tumor **(nephroblastoma)** is the most common primary malignant *renal* tumor of childhood. It is the second most common malignant abdominal tumor in childhood after neuroblastoma. The most common sites of metastases are the lungs, regional lymph nodes, and liver. Histologically, the classic Wilms tumor is made up of varying proportions of blastemal, stromal, and epithelial cells, recapitulating stages of normal renal development. The use of multimodality treatment and multi-institutional cooperative group trials has dramatically improved the cure rate of Wilms tumor from <30% to >90% (Table 548.1).

EPIDEMIOLOGY

Wilms tumor accounts for 6% of pediatric malignancies and >95% of kidney tumors in children. In the United States, incidence of Wilms tumor is approximately 7 cases per 1 million children <15 years of age per year, and about 650 new cases are diagnosed each year. Approximately 75% of the cases occur in children <5 years old, with a peak incidence at 2-3 years. It can arise in one or both kidneys; the incidence of bilateral Wilms tumors is 7%. The male/female ratio is 0.92 to 1 in unilateral disease and 0.6 to 1 in bilateral disease. Most cases are sporadic, but approximately 2% of patients have a family history. In 8–10% of patients, Wilms tumor is observed in the context of hemihypertrophy, aniridia, genitourinary anomalies, and a variety of rare syndromes, including **Beckwith-Wiedemann syndrome (BWS)** and **Denys-Drash syndrome** (Table 548.2). An earlier age at diagnosis and an increased incidence of bilateral disease are generally observed in syndromic and familial cases.

ETIOLOGY: GENETICS AND MOLECULAR BIOLOGY

Wilms tumor is thought to be derived from incompletely differentiated renal mesenchyme, and tumors are typically composed of cells reminiscent of the undifferentiated and partially differentiated cells that normally arise from renal mesenchyme. Foci of benign, undifferentiated mesenchyme **(nephrogenic rests)** that persist abnormally in the kidney into postnatal life are observed in approximately 1% of children in the general population but are present in up to 90% of children who have a family history of Wilms tumor, develop bilateral tumors, or display features of Wilms tumor–related syndromes. Nephrogenic rests usually regress or differentiate, but those that persist can become malignant.

Wilms tumor has been associated with genetic abnormalities. The first identified Wilms tumor gene, *WT1*, located at 11p13, is a homozygous gene variant in 10–15% of tumors, resulting in loss of function of the encoded zinc finger transcription factor. The majority of *WT1* pathogenic variants are somatic; however, *WT1* pathogenic variants can also be germline. The type of WT1 pathogenic variant affects the disease phenotype. Germline truncating variants are usually associated with Wilms tumor in the context of genitourinary anomalies or the **WAGR syndrome** (Wilms tumor, aniridia, genitourinary anomalies, mental retardation) as it involves the deletion of several contiguous genes at 11p13. Missense germline variants are usually observed in children with Denys-Drash syndrome, resulting in early-onset renal failure. In instances of germline variant, the wild-type allele present in the germline is altered or lost in the tumor, resulting in loss of *WT1* function.

Tables 547.2-547.4). Treatment for children with low-risk neuroblastoma typically includes surgery for stages L1 and L2 and observation for asymptomatic stage MS with cure rates generally >90% without further therapy. Treatment with chemotherapy or radiation for the rare child with local recurrence can still be curative. Children with spinal cord compression at diagnosis may require urgent treatment with chemotherapy, surgery, or radiation to avoid neurologic damage. Stage MS neuroblastomas have a very favorable prognosis, and many regress spontaneously without therapy. Chemotherapy or resection of the primary tumor does not improve survival rates, but for infants with massive liver involvement and respiratory compromise, chemotherapy or radiation is used to alleviate symptoms. For children with stage 4S neuroblastoma who require treatment for symptoms, the survival rate is 81%.

Treatment of intermediate-risk neuroblastoma includes surgery, chemotherapy, and, in some cases, radiation therapy. The chemotherapy usually includes moderate doses of cisplatin or carboplatin, cyclophosphamide, etoposide, and doxorubicin given over several months. Radiation therapy is used for tumors with incomplete response to chemotherapy. Children with intermediate-risk neuroblastoma, including children with L2 disease and infants with M disease both with favorable characteristics, have an excellent prognosis and >90% survival with this moderate treatment. In this intermediate-risk group, obtaining adequate diagnostic material for determination of the underlying biologic features of the tumor, such as the Shimada pathologic classification and *MYCN* gene amplification, is critical, so that children with unfavorable characteristics can receive more-aggressive treatment and those with favorable features can be spared excessive toxic therapy.

Children with high-risk neuroblastoma historically have had poor long-term survival rates of 25–35% despite intensive treatment consisting of induction chemotherapy, high-dose chemotherapy with autologous stem cell rescue, surgery, radiation, and 13-*cis*-retinoic acid. Induction chemotherapy for children with high-risk neuroblastoma includes combinations of cyclophosphamide, topotecan, doxorubicin, vincristine, cisplatin, and etoposide. After completion of induction chemotherapy, resection of the residual primary tumor is followed by high-dose chemotherapy with autologous stem cell rescue and focal radiation therapy to tumor sites. A national cooperative group trial demonstrated significantly better survival with chemotherapy plus autologous stem cell rescue than with chemotherapy alone. The further addition of the differentiating agent, 13-*cis*-retinoic acid, following autologous stem cell transplantation, resulted in further improvements in survival rates. In addition, a national clinical trial has demonstrated an increase in short-term survival rates with the addition of the monoclonal antibody ch14.18 **(dinutuximab)** to 13-*cis*-retinoic acid therapy. This monoclonal antibody targets a disialoganglioside, GD2, which has ubiquitous expression on neuroblastoma cells. In this large, randomized, clinical trial of high-risk neuroblastoma patients sponsored by the Children's Oncology Group, incorporation of the antibody into consolidative therapy following autologous stem cell transplant improved the 2-year event-free survival from 46.5–66.5%. The incorporation of tandem autologous stem cell transplant (two separate autologous stem cell transplants with differing conditioning regimens) may further improve outcomes for patients with high-risk disease.

Cases of high-risk neuroblastoma are associated with frequent relapses, and children with recurrent neuroblastoma have a <50% response rate to alternative chemotherapy regimens. New treatment strategies and agents are needed for children with both high-risk and recurrent neuroblastoma. Therapies currently under investigation include new chemotherapeutic agents as well as novel therapies directed against critical intracellular signaling pathways, radiolabeled targeted agents (such as *therapeutic* ^{131}I-MIBG), immunotherapy, and antitumor vaccines.

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Chapter 548

Neoplasms of the Kidney

548.1 Wilms Tumor

Najat C. Daw and Dristhi S. Ragoonanan

Wilms tumor **(nephroblastoma)** is the most common primary malignant *renal* tumor of childhood. It is the second most common malignant abdominal tumor in childhood after neuroblastoma. The most common sites of metastases are the lungs, regional lymph nodes, and liver. Histologically, the classic Wilms tumor is made up of varying proportions of blastemal, stromal, and epithelial cells, recapitulating stages of normal renal development. The use of multimodality treatment and multi-institutional cooperative group trials has dramatically improved the cure rate of Wilms tumor from <30% to >90% (Table 548.1).

EPIDEMIOLOGY

Wilms tumor accounts for 6% of pediatric malignancies and >95% of kidney tumors in children. In the United States, incidence of Wilms tumor is approximately 7 cases per 1 million children <15 years of age per year, and about 650 new cases are diagnosed each year. Approximately 75% of the cases occur in children <5 years old, with a peak incidence at 2-3 years. It can arise in one or both kidneys; the incidence of bilateral Wilms tumors is 7%. The male/female ratio is 0.92 to 1 in unilateral disease and 0.6 to 1 in bilateral disease. Most cases are sporadic, but approximately 2% of patients have a family history. In 8–10% of patients, Wilms tumor is observed in the context of hemihypertrophy, aniridia, genitourinary anomalies, and a variety of rare syndromes, including **Beckwith-Wiedemann syndrome (BWS)** and **Denys-Drash syndrome** (Table 548.2). An earlier age at diagnosis and an increased incidence of bilateral disease are generally observed in syndromic and familial cases.

ETIOLOGY: GENETICS AND MOLECULAR BIOLOGY

Wilms tumor is thought to be derived from incompletely differentiated renal mesenchyme, and tumors are typically composed of cells reminiscent of the undifferentiated and partially differentiated cells that normally arise from renal mesenchyme. Foci of benign, undifferentiated mesenchyme **(nephrogenic rests)** that persist abnormally in the kidney into postnatal life are observed in approximately 1% of children in the general population but are present in up to 90% of children who have a family history of Wilms tumor, develop bilateral tumors, or display features of Wilms tumor–related syndromes. Nephrogenic rests usually regress or differentiate, but those that persist can become malignant.

Wilms tumor has been associated with genetic abnormalities. The first identified Wilms tumor gene, *WT1*, located at 11p13, is a homozygous gene variant in 10–15% of tumors, resulting in loss of function of the encoded zinc finger transcription factor. The majority of *WT1* pathogenic variants are somatic; however, *WT1* pathogenic variants can also be germline. The type of WT1 pathogenic variant affects the disease phenotype. Germline truncating variants are usually associated with Wilms tumor in the context of genitourinary anomalies or the **WAGR syndrome** (Wilms tumor, aniridia, genitourinary anomalies, mental retardation) as it involves the deletion of several contiguous genes at 11p13. Missense germline variants are usually observed in children with Denys-Drash syndrome, resulting in early-onset renal failure. In instances of germline variant, the wild-type allele present in the germline is altered or lost in the tumor, resulting in loss of *WT1* function.

Table 548.1 Treatment and Four-Year Outcomes for Patients with Wilms Tumor

STUDY	STAGE/HISTOLOGY	TREATMENT	EFS (%)	OS (%)
NWTS-5	Stage I or II FH; no LOH	Regimen EE4A	91	98
COG AREN0532	Stage I FH (age <24 mo, tumor weight <550 g)	Nephrectomy alone	90	100
	Stage I or II FH; +LOH	Regimen DD4A	87	100
	Stage III FH; no LOH	Regimen DD4A Flank radiation*	88	97
COG AREN0533	Stage III or IV FH; +LOH	Regimen M Radiation to flank per local stage Radiation to metastatic sites	90	96
	Stage IV FH with lung metastases only and complete response at 6 weeks; no LOH	Regimen DD4A Radiation to flank per local stage Omit radiation to whole lung	80	96
	Stage IV FH with lung metastases only and incomplete response at 6 weeks; no LOH	Regimen M Radiation to flank per local stage Radiation to whole lung	89	95
COG AREN0534	Stage V FH	Chemotherapy Radiation per local stage	82	95
COG AREN0321	Stage I FA + DA	Regimen DD4A Radiation to flank	100	100
	Stage II DA	Regimen UH-1 Radiation to flank	87	86
	Stage III DA	Regimen UH-1 Radiation to flank*	81	89
	Stage IV DA	Regimen UH-1/UH-2 Radiation to flank per local stage Radiation to metastatic sites	42	49
COG AREN0534	Stage V DA	Chemotherapy Radiation to flank per local stage Radiation to metastatic sites	58	68
	Unilateral Wilms tumor with bilateral predisposition	EE4A followed by treatment per stage/histology Radiation to flank per local stage	94	100

*Whole-abdomen radiation therapy indicated for patients with diffuse intraperitoneal tumor rupture, peritoneal tumor seeding, and cytology-positive ascites

NWTS-5, National Wilms Tumor Study-5; COG, Children's Oncology Group; EFS, event-free survival; OS, overall survival; FH, favorable histology; LOH, loss of heterozygosity at both 1p and 16q; FA, focal anaplasia; DA, diffuse anaplasia; EE4A, vincristine/dactinomycin × 19 weeks; DD4A, vincristine/dactinomycin/doxorubicin × 25 weeks; M, vincristine/dactinomycin/doxorubicin/cyclophosphamide/etoposide × 31 weeks; revised UH-1, vincristine/doxorubicin/cyclophosphamide/carboplatin/etoposide × 30 weeks; revised UH-2, revised UH-1 with vincristine/irinotecan × 36 weeks.

Table 548.2 Wilms Tumor Predisposing Conditions

SYNDROME	GENETIC LESION	ESTIMATED WT RISK	PHENOTYPE
WT1-ASSOCIATED WILMS TUMOR PREDISPOSITION SYNDROMES			
Denys-Drash syndrome (DDS)	*WT1* pathogenic variant affecting exon 8 or 9	~75%	Ambiguous genitalia, diffuse mesangial sclerosis
Frasier syndrome	*WT1* pathogenic variant affecting intron 9 donor splice site	Low; 1 case reported	Ambiguous genitalia, streak gonads, focal segmental glomerulosclerosis
WAGR syndrome (Wilms tumor, aniridia, genital anomalies, retardation)	Deletion of 11p13 containing *WT1*	~50%	Aniridia, genitourinary anomalies, delayed-onset renal failure
WT1-associated WT predisposition	*WT1* pathogenic variant	~30%	Median age at WT diagnosis is 1.3 yr (range: 0.6-4.5)
OTHER SYNDROMES THAT PREDISPOSE TO WILMS TUMOR			
Beckwith-Wiedemann syndrome (BWS)	LOM at maternal IC2 at 11p15.5 GOM at maternal IC1 at 11p15.5 Paternal UPD at 11p15.5 Pathogenic variant in *CDKN1C* Negative molecular test	~0.2% ~24% ~8% ~1.4% ~4%	Organomegaly, large birth weight, macroglossia, omphalocele, hemihypertrophy, ear pits and creases, neonatal hypoglycemia
Bloom syndrome	Biallelic *BLM* pathogenic variants	~3%	Short stature, microcephaly, growth deficiency, immune abnormalities, sensitivity to sunlight

Continued

Table 548.2 Wilms Tumor Predisposing Conditions—cont'd

SYNDROME	GENETIC LESION	ESTIMATED WT RISK	PHENOTYPE
Fanconi anemia	Biallelic *BRCA2* or *PALB2* pathogenic variants	20–40%	Short stature, abnormal skin pigmentation, skeletal malformations, microcephaly, bone marrow failure
Hyperparathyroid-jaw tumor syndrome	*CDC73* pathogenic variant	~3%	Primary hyperparathyroidism, ossifying fibroma of the maxilla and/or mandible
Mosaic variegated aneuploidy	Biallelic *BUB1B* or *TRIP13* pathogenic variants	>85%	Microcephaly, growth deficiency, developmental delay, eye anomalies, mild dysmorphism
Perlman syndrome	Biallelic *DIS3L2* pathogenic variants	~65%	Organomegaly, large birth weight, developmental delay
Simpson-Golabi-Behmel syndrome	*GPC3* pathogenic variant	4–9%	Overgrowth, congenital heart defects
CLOVES syndrome	*PIK3CA* pathogenic variant	<5%	Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal/spine anomalies
Sotos syndrome	*NSD1* pathogenic variant	<5%	Cerebral giantism, macrocephaly, intellectual disability, advanced bone age, poor coordination
Trisomy 18	Trisomy 18	<5%	Cognitive impairment, hypertonia, overlapping fingers, congenital heart disease, micrognathia
GENETIC VARIANTS THAT PREDISPOSE TO NONSYNDROMIC WILMS TUMOR			
CTR9-associated WT predisposition	*CTR9* pathogenic variant	4 families reported; 9/14 individuals with a pathogenic *CTR9* variant developed WT	Median age at WT diagnosis is 1.3 yr (range: 0.6-3.3). All reported variants are paternally inherited
DICER1 syndrome	*DICER1* pathogenic variant	Low; 5 families in which 6/22 individuals with a pathogenic *DICER1* variant developed WT	Lung cysts, cystic nephroma, nodular hyperplasia of the thyroid, nasal chondromesenchymal hamartoma, ciliary body medulloepithelioma and increased cancer risks including pleuropulmonary blastoma (PPB), ovarian sex cord-stromal tumors, pineoblastoma, and pituitary blastoma
Li-Fraumeni syndrome (LFS)	*TP53* pathogenic variant	Low; 12 cases reported	Around 50% of individuals with LFS develop cancer by the age of 30 yr, with a lifetime risk of >70% The tumors most closely associated with LFS include soft tissue sarcomas, osteosarcoma, premenopausal breast cancer, brain tumors, and adrenocortical carcinoma
REST-associated WT predisposition	*REST* pathogenic variant	4 families reported; 7/14 individuals with a pathogenic *REST* variant developed WT Ten presumed sporadic cases reported	Median age at WT diagnosis is 3 yr (range: 0.5-6) Other clinical features reported include primary ovarian failure, café-au-lait macules, and mild developmental delay
TRIM28-associated WT predisposition	*TRIM28* pathogenic variant	9 families reported; 18/24 individuals with a pathogenic *TRIM28* variant developed WT; however, few unaffected family members were tested 17 presumed sporadic cases reported	Median age at WT diagnosis is 1.1 yr (range: 0.4-9.8) All reported variants are maternally inherited Histology is frequently epithelial type

GOM, Gain of methylation; IC, imprinting center; LOM, loss of methylation; UPD, uniparental disomy; WT, Wilms tumor.
Modified from Maciaszek JL, Oak N, Nichols KE. Recent advances in Wilms' tumor predisposition. *Hum Mole Genetics.* 2020;29(R2):R138–R149. Table 1, p. R139–R140.

Consistent with the etiology of Wilms tumor being grounded in aberrant kidney development, genes that regulate the proliferation and differentiation of kidney progenitors have been identified to be mutated in tumors. One class of genes that encodes proteins essential for the biogenesis of mature miRNAs are altered in one fifth to one third of Wilms tumors. These include *DROSHA* missense variants that occur in approximately 10% of tumors, and *DICER, DGCR8, XPO5*, and *TARBP2* variants. Of note, germline *DICER1* variants are observed, albeit infrequently, in Wilms tumor families and, more frequently, in families with pleuropulmonary blastoma (see Table 548.2).

The **Wnt signaling pathway** plays a critical role in regulating the differentiation of the fetal kidney. Somatic pathogenic variants in *CTNNB1* and *WTX*, both of which play a role in the Wnt pathway regulation, are observed in approximately 15% and 20% of Wilms tumors,

Table 548.3 Differential Diagnosis of Abdominal and Pelvic Tumors in Children

TUMOR	PATIENT AGE	CLINICAL SIGNS	LABORATORY FINDINGS
Wilms tumor	Preschool	Unilateral flank mass, aniridia, hemihypertrophy	Hematuria, polycythemia, thrombocytosis, elevated partial thromboplastin time
Neuroblastoma	Preschool	Gastrointestinal/genitourinary obstruction, raccoon eyes, myoclonus-opsoclonus, diarrhea, skin nodules	Increased urinary vanillylmandelic acid, homovanillic acid, or ferritin; stippled calcification in the mass
Non-Hodgkin lymphoma	>1 yr	Intussusception in >2 yr old	Increased lactate dehydrogenase; blood cytopenia caused by bone marrow involvement
Rhabdomyosarcoma	All	Gastrointestinal/genitourinary obstruction, abdominal pain, vaginal bleeding, paratesticular mass	Hypercalcemia; blood cytopenia caused by bone marrow involvement
Germ cell tumor/ teratoma	Preschool, teenage	*Females:* Abdominal pain, vaginal bleeding *Males:* Testicular mass, new-onset hydrocele, sacrococcygeal mass/dimple	Increased β-human chorionic gonadotropin, increased α-fetoprotein
Hepatoblastoma	Birth-3 yr	Right upper quadrant mass, jaundice Early puberty in males	Increased α-fetoprotein
Hepatocellular carcinoma	School age, teenage	Right upper quadrant mass, jaundice, hepatitis B, cirrhosis	Increased α-fetoprotein

respectively. Somatic variants in genes that are critical for regulating progenitor proliferation and differentiation (*MYCN, SIX1,* and *SIX2*) are observed in approximately 10% of tumors. Other somatic variants, including *MLLT1, ARID1A,* and *SMARCA4,* occur at a frequency of approximately 4–5% each. Importantly a somatic variant of the p53 gene, *TP53*, is observed in approximately 5% of tumors and is associated with **anaplastic tumor** histology, a poor prognostic feature of Wilms tumor.

Loss of heterozygosity (LOH; usually copy number neutral) or loss of imprinting at imprinted loci at 11p15 is observed in approximately 70% of Wilms tumors. This epigenetic alteration often results in biallelic expression of *IGF2,* a normally imprinted gene that encodes insulin-like growth factor 2, in addition to the loss of imprinting of other 11p15 genes. BWS, a somatic overgrowth syndrome with predisposition to embryonal tumors (including Wilms tumor), has been linked to 11p15, and microdeletions within the *IGF2* imprinting control region are present in BWS families in whom Wilms tumor is observed.

Allelic imbalances have been identified in Wilms tumors, particularly LOH at 1p and 16q, which has been associated with increased risk of recurrence. Gain of chromosome 1q was found to be associated with inferior survival in unilateral favorable-histology Wilms tumor.

In patients with a family history of Wilms tumor, predisposition is inherited as an autosomal dominant trait with incomplete penetrance. Predisposition to other tumor types or other phenotypes is not observed in most of these families. Germline pathogenic variants have been identified in a minority of families, and each of those genes identified (e.g., *WT1, DICER1, MYCN, REST, BRCA2*) is altered in <5% of Wilms tumor families.

CLINICAL PRESENTATION

The most common initial clinical presentation for Wilms tumor is the incidental discovery of an asymptomatic **abdominal mass** by parents while bathing or clothing an affected child or by a physician during a routine physical examination (Table 548.3). At presentation, the mass can be quite large, because retroperitoneal masses can grow unhampered by strict anatomic boundaries. Functional defects in paired organs such as the kidney, with good functional reserve, are also unlikely to be detected early. Physical exam findings include a firm, nontender, smooth abdominal mass that rarely crosses the midline. Care should be taken to avoid vigorous palpation to prevent the risk of renal capsule rupture. Children with direct access to pediatricians vs generalists as primary caregivers are more likely to be diagnosed early and to have smaller tumors and less advanced stage at diagnosis. Hypertension is present in about 25% of patients at presentation and has been attributed to increased renin activity. Abdominal pain (40%), gross painless hematuria (18%), and constitutional symptoms such as fever, anorexia, and weight loss are other findings at diagnosis. Occasionally, rapid abdominal enlargement and anemia occur because of bleeding into the renal parenchyma or pelvis. Wilms tumor thrombus extends into the inferior vena cava (IVC) in 4–10% of patients and rarely into the right atrium; dislodgment of the intravascular tumor may produce a fatal occlusive **pulmonary embolism**. Patients might also have microcytic anemia from iron deficiency or anemia of chronic disease, polycythemia, elevated platelet count, and acquired deficiency of von Willebrand factor or factor VII deficiency.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

An abdominal mass in a child should be considered malignant until diagnostic imaging, laboratory findings, and pathology can define its true nature (see Table 548.3). Imaging studies include plain abdominal radiography, abdominal ultrasonography (US), and CT of the abdomen to define the intrarenal origin of the mass and differentiate it from adrenal masses (e.g., neuroblastoma) and other masses in the abdomen. Abdominal US helps differentiate solid from cystic masses. Wilms tumor might show focal areas of necrosis or hemorrhage and hydronephrosis because of obstruction of the renal pelvis by the tumor. US with Doppler imaging of renal veins and the IVC is a useful first study to identify Wilms tumor, evaluate the collecting system, and demonstrate tumor thrombi in the renal veins and IVC. However, its routine use after CT has been performed is not required.

CT is useful to define the extent of the disease, integrity of the contralateral kidney, and metastasis (Figs. 548.1 and 548.2). MRI requires sedation in young children and is not routinely used. However, MRI may be helpful in defining an extensive tumor thrombus that extends up to the level of the hepatic veins, or even into the right atrium, and to distinguish Wilms tumor from nephrogenic rests. Chest CT is more sensitive than chest radiography to screen for pulmonary metastasis and is preferably performed before surgery because effusions and atelectasis can confound the interpretation of postoperative imaging studies. A bone scan is performed if the histologic diagnosis confirms clear cell sarcoma of the kidney (CCSK) or rhabdoid tumor of the kidney, to look for bone metastasis. Brain imaging with CT or MRI is also obtained in cases of clear cell sarcoma or rhabdoid tumor of the kidney because these tumors can spread to the brain.

Wilms tumor lesions are metabolically active and concentrate fluorodeoxyglucose (FDG). Regional spread and metastatic lesions can

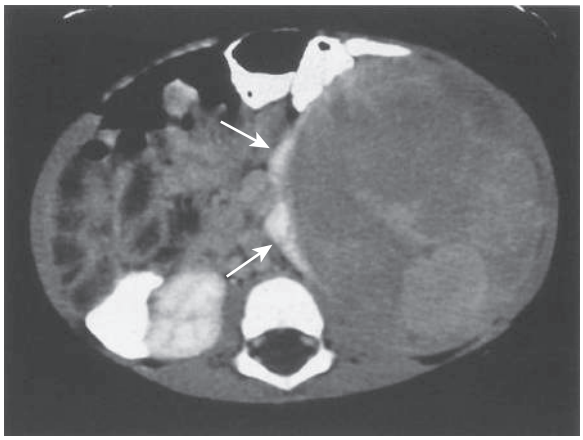

Fig. 548.1 Large heterogeneous Wilms tumor in left kidney. The residual renal parenchyma is displaced medially *(arrows). (From Haaga JR, Boll DT, eds. CT and MRI of the Whole Body. 6th ed. Philadelphia: Elsevier; 2017: Fig. 54-84, p. 1816.)*

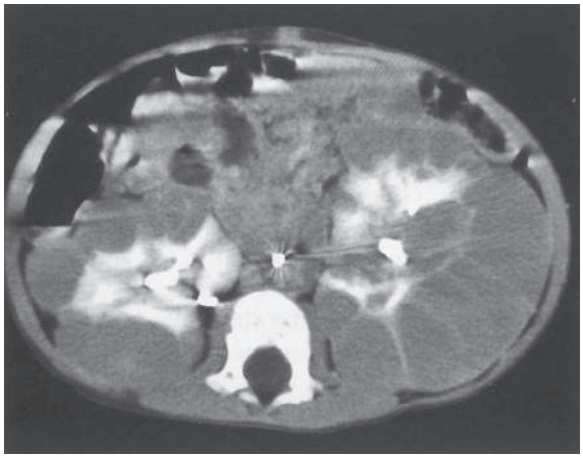

Fig. 548.2 Multicentric and bilateral Wilms tumors. The tumors have a low density and compress residual enhancing renal tissue. *(From Haaga JR, Boll DT, eds. CT and MRI of the Whole Body. 6th ed. Philadelphia: Elsevier; 2017: Fig. 54-86, p. 1817.)*

be visualized on PET/CT scanning. The diagnosis is usually made by imaging studies and confirmed by histology at the time of nephrectomy. Although biopsy is a reliable diagnostic tool, it is discouraged because it results in disease upstaging according to the Children's Oncology Group (COG) staging system. A core needle biopsy obtained through a posterior approach (to limit contamination of the peritoneal cavity) should be performed in cases of unusual presentation (>10 years old, signs of infection, inflammation) or unusual imaging findings (significant adenopathy, no renal parenchyma seen, intratumoral calcification).

Patients with Wilms tumor associated syndromes should undergo routine screening with serial abdominal US to allow for early detection and treatment.

TREATMENT

The COG protocols and the **International Society of Pediatric Oncology (SIOP)** protocols differ in their initial treatment approach. *COG advocates upfront surgery* prior to initiating treatment, whereas *SIOP recommends preoperative chemotherapy.* Each approach has advantages and limitations, but they have similar outcomes. Early surgery provides accurate diagnosis and staging and can facilitate *risk-adapted therapy*. Preoperative chemotherapy can make surgery easier and reduces the risk of intraoperative tumor rupture and hemorrhage. Surgery entails a radical nephrectomy, with meticulous dissection to avoid rupture of the tumor capsule, and lymph node sampling despite the absence of abnormal nodes on preoperative imaging studies or intraoperative assessment. Partial nephrectomy is performed in patients with bilateral disease or those with unilateral Wilms tumor and predisposing syndrome such as the Denys-Drash and WAGR syndromes to minimize the risk of future renal failure.

Table 548.4 Children's Oncology Group Staging of Wilms Tumor

STAGE	DESCRIPTION
I	Tumor *confined to the kidney* and completely resected Renal capsule or sinus vessels not involved Tumor not ruptured or biopsied Regional lymph nodes examined and negative
II	Tumor extends *beyond the kidney* but is completely resected with negative margins and lymph nodes At least one of the following has occurred: (a) penetration of renal capsule, (b) invasion of renal sinus vessels
III	*Residual tumor* present following surgery confined to the abdomen, including gross or microscopic tumor; spillage of tumor preoperatively or intraoperatively; biopsy prior to nephrectomy, regional lymph node metastases; tumor implants on the peritoneal surface; extension of tumor thrombus into the inferior vena cava, including thoracic vena cava and heart
IV	*Hematogenous metastases* (lung, liver, bone, brain, etc.) or lymph node metastases outside the abdominopelvic region
V	*Bilateral* renal involvement by tumor

Prognostic factors for risk-adapted therapy include age, stage, histology, tumor weight, LOH at chromosomes 1p and 16q, and metastatic lung nodule response (Table 548.4). Histology plays a major role in risk stratification of Wilms tumor. Absence of anaplasia is considered a favorable histologic finding. Presence of anaplasia is further classified as focal or diffuse, both of which are unfavorable histologic findings.

The COG has very specific drug dose and schedule recommendations for risk-adapted treatment of Wilms tumor. Patients with *favorable-histology* Wilms tumor have a good outcome and are generally treated in the outpatient setting. Nephrectomy alone is sufficient for patients with very low risk disease (<2 years old with stage I disease and a tumor weight <550 g), resulting in a 4-year event-free survival of 90% and a 4-year overall survival of 100%. Patients with stage I and II disease receive chemotherapy with two drugs, vincristine and actinomycin D (also called dactinomycin), every 1-3 weeks for a total of 18 weeks (regimen **EE4A**). Patients with stage III or stage IV disease receive chemotherapy with three drugs (vincristine, doxorubicin, and actinomycin D) every 1-3 weeks for a total of 24 weeks (regimen **DD4A**) and radiation therapy. Patients with regional lymph node metastases, residual disease after surgery, or tumor rupture receive radiation therapy to the flank or abdomen, and those with lung metastases receive radiation therapy to the lungs. Rapid response of lung metastases to chemotherapy may eliminate the need for lung radiation. In patients with stage III or stage IV disease and LOH at both 1p and 16q or in those with lung metastases only who have incomplete response at 6 weeks of DD4A, therapy is augmented by adding cyclophosphamide/etoposide to DD4A (Regimen M). The LOH of both 1p and 16q and gain of 1q confers an adverse prognosis and deserves treatment intensification.

For patients with bilateral Wilms tumor, three-drug preoperative chemotherapy, surgical resection within 12 weeks of diagnosis, and histology-based postoperative therapy improves survival outcomes and feasibility of nephron-sparing surgery.

Anaplastic histology (focal and diffuse) accounts for approximately 11% of Wilms tumor cases. Patients with *diffuse anaplasia* have worse outcome than patients with favorable histology and receive more

intensive therapy. Patients with stage 1 anaplastic Wilms tumor treated with regimen DD4A and flank radiation had excellent survival outcomes. Patients with stage II-IV disease are treated more intensively with multiagent chemotherapy including vincristine, cyclophosphamide, doxorubicin, etoposide, carboplatin, and irinotecan, in addition to radiotherapy. Despite some improvement in survival outcomes, patients with stage IV disease continue to fare poorly.

RECURRENT DISEASE

Approximately 15% of favorable-histology and 50% of anaplastic-histology Wilms tumors relapse; most relapses occur early (within 2 years of diagnosis). Factors associated with a favorable outcome after relapse include low stage (I/II) at diagnosis, treatment with vincristine and actinomycin D only, no prior radiotherapy, favorable histology, relapse to lung only, and interval from nephrectomy to relapse ≥12 months. Patients with recurrent Wilms tumor who previously received only vincristine and actinomycin D had a 4-year survival of approximately 80%, whereas those who previously received the three-drug regimen of vincristine, actinomycin D, and doxorubicin had a 4-year survival of only 50%. Other agents used to treat recurrent Wilms tumor include doxorubicin, carboplatin, cyclophosphamide, ifosfamide, etoposide, irinotecan, and topotecan. *Metachronous* Wilms tumor may not represent tumor relapse but development of a new tumor in the opposite kidney.

PROGNOSIS

Despite some adverse risk factors that decrease prognosis (presence of metastasis, unfavorable histology, recurrent disease, incomplete lung nodule response at 6 weeks of chemotherapy, LOH of both 1p and 16q and gain of 1q), most children with Wilms tumor have a very favorable prognosis. Overall survival of children with Wilms tumor exceeds 90%, with some prognostic factors (low stage, favorable histology, young age, low tumor weight) conferring even better outcomes. Wilms tumor tops the list of common pediatric solid tumors in terms of favorable outcome.

LATE EFFECTS

Current strategies are successful with relatively few long-term effects of therapy. Generally, late complications are a consequence of treatment type and intensity; the use of radiotherapy and anthracyclines increase the risk of these complications. Clinically significant late sequelae include musculoskeletal effects, cardiac toxicity, pulmonary disease, reproductive problems, renal dysfunction, and development of second malignant neoplasms such as leukemia and cancer of the digestive organs and breast (in females).

548.2 Other Pediatric Renal Tumors

Najat C. Daw and Dristhi S. Ragoonanan

MESOBLASTIC NEPHROMA

Mesoblastic nephroma is the most common solid renal tumor identified in the *neonatal period* and the most frequent benign renal tumor in childhood. It represents approximately 5% of all pediatric renal tumors. ETV6-NTRK3 fusion pathogenic variant is the most common molecular alteration seen in these tumors. Many cases are diagnosed with prenatal US and can manifest as polyhydramnios, hydrops, and premature delivery. Most patients are diagnosed before 3 months of age, whereas Wilms tumor is *rarely diagnosed* before 6 months. Male/female ratio is 1.5:1. Radical nephrectomy is the treatment of choice and may be sufficient by itself. Local recurrence is uncommon. Although rare, malignant variants do occur, marked by metastases to the lung, liver, heart, and brain.

CLEAR CELL SARCOMA OF THE KIDNEY

CCSK is an uncommon renal neoplasm of childhood, with approximately 20 new cases diagnosed each year in North America. Peak incidence is between 1 and 4 years of age with a male/female ratio of 2:1. It usually presents with abdominal distention, abdominal mass, or gross hematuria. Gene expression profiles of CCSK suggest the cell of origin to be a renal mesenchymal cell with neural markers, and *BCOR* gene duplication is the most common molecular alteration seen. Bone is the most common site of distant metastasis, followed by lung, abdomen, retroperitoneum, brain, and liver. Therefore the staging workup should include a bone scan. With modern therapy, patients with stage I and II disease have an excellent prognosis (4-year overall survival of 97–100%), whereas those with stage III and IV disease have a 4-year overall survival of 89% and 45%, respectively.

RHABDOID TUMOR OF THE KIDNEY

Malignant rhabdoid tumor of the kidney **(MRTK)** has rhabdomyoblast-like morphology and is a rare but aggressive cancer. The median age of presentation is 11 months, and hematuria is a common presenting feature. Both rhabdoid tumor of the kidney and central nervous system (CNS) atypical teratoid/rhabdoid tumors have deletions and pathogenic variants of the *SMARCB1/hSNF5/INI1* gene and are considered related. Germline pathogenic variants in *SMARCA4* or *SMARCB1* have been linked to rhabdoid tumor predisposition syndrome, an autosomal dominant disorder that results in the increased risk of developing rhabdoid tumors predominantly in infants and children younger than 3 years of age. MRTKs tend to metastasize to the lungs and brain. Prognosis is poor with current therapeutic protocols. Younger age at diagnosis, advanced-stage disease, and CNS involvement are associated with a worse prognosis. The outcome of patients with MRTK is poor. Both the 4-year relapse-free survival and overall survival for patients treated on the National Wilms Tumor Study-5 (NWTS-5) were 50% for stage I, 33% for stages II and III, and 21% for stage IV.

RENAL CELL CARCINOMA

Although renal cell carcinoma **(RCC)** is the most prevalent renal tumor in adults, it is extremely rare in children, accounting for <10% of pediatric renal tumors. The annual incidence rate is approximately four cases per 1 million children. Although Wilms tumor is the predominant renal tumor in childhood, it is rare past early childhood, and RCC is the most prevalent renal malignancy during the second decade of life. Several **genetic disorders** are associated with a predisposition to RCC, including von Hippel-Lindau disease, tuberous sclerosis, and hereditary leiomyomatosis. The most common subtype of RCC in children, the **translocation-type RCC**, is characterized by translocations most frequently involving the *TFE3* gene on chromosome Xp11.2 or the *TFEB* gene on chromosome 6p21. *Renal medullary carcinoma is seen typically in young patients with sickle cell trait.*

Children with RCC may present with frank hematuria, flank pain, and/or a palpable mass, although RCC can be asymptomatic and detected incidentally. RCC has a propensity to metastasize to the lungs, liver, and bone. Although local lymph node involvement is a poor prognostic indicator in adult RCC, the importance of nodal status in pediatric RCC is controversial. Nephrectomy alone may be adequate for early-stage RCC. Along with surgery, there is no established optimal treatment for childhood RCC; neither chemotherapy nor radiation therapy has demonstrated significant activity. Localized pediatric RCC has an excellent outcome without adjuvant therapy; however, the outcomes remain poor for metastatic RCC and renal medullary carcinoma.

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Chapter 549

Soft Tissue Sarcomas

Wendy A. Allen-Rhoades and Carola A.S. Arndt

The annual incidence of soft tissue sarcomas is 11 cases per 1 million children younger than 14 years of age and 17.4 cases per 1 million adolescents age 15-19 years. Rhabdomyosarcoma accounts for more than 50% of soft tissue sarcomas. The prognosis most strongly correlates with age and extent of disease at diagnosis, primary tumor site and histology, and presence of translocations involving the *FOXO1* and *PAX* genes.

RHABDOMYOSARCOMA

Epidemiology

The most common pediatric soft tissue sarcoma, rhabdomyosarcoma, accounts for approximately 3.5% of childhood cancers. These tumors may occur at any anatomic site (Table 549.1) including the head and neck, orbit, genitourinary tract, and extremities; retroperitoneal and other sites account for the remainder of primary sites. The incidence at each anatomic site is related to both patient age and tumor type. Extremity lesions are more likely to occur in older children and to have alveolar histology and harbor a fusion oncoprotein. Rhabdomyosarcoma occurs with increased frequency in patients with neurofibromatosis, Costello syndrome, and other family cancer predisposition syndromes such as Li-Fraumeni syndrome (Table 549.2).

Table 549.1 Common Presenting Signs and Symptoms by Primary Site

PRIMARY SITE (%)	SYMPTOMS AND SIGNS
Head and neck (40%)	Painless or painful swelling Proptosis Ptosis Ophthalmoplegia Headache Vomiting Cranial nerve palsy Other cranial nerve palsies Nasal discharge Nasal/sinus congestion Trismus Systemic hypertension
Limbs/trunk (30%)	Asymptomatic swelling
Genitourinary tract/pelvis (20%)	Painless scrotal lesions Hematuria Urinary retention/dribbling Vulval nodule Polypoid vaginal lesions Vaginal bleeding/discharge Constipation
Abdomen/liver/biliary (~10%)	Asymptomatic swelling Abdominal pain Intestinal obstruction Jaundice Cholangitis
Metastatic disease (20% at diagnosis) Bone Bone marrow Lung Lymph nodes	Otherwise unexplained: Poor feeding Seizures Pain Irritability Pancytopenia

Modified from Rogers TN, Dasgupta R. Management of rhabdomyosarcoma in pediatric patients. *Surg Oncol Clin N Am.* 2021;30(2):339–353. Table 2.

Pathogenesis

Rhabdomyosarcoma is thought to arise from the same embryonic mesenchyme as striated skeletal muscle although a large percentage of these tumors arise in areas lacking skeletal muscle (e.g., bladder, prostate, vagina). On the basis of light microscopic appearance, it belongs to the general category of small, round, blue cell tumors that includes Ewing sarcoma, neuroblastoma, and non-Hodgkin lymphoma. Definitive diagnosis of a pathologic specimen requires immunohistochemical studies using antibodies to skeletal muscle (desmin, muscle-specific actin, myogenin) and reverse transcription polymerase chain reaction, next generation sequencing, or fluorescent in situ hybridization for *FOXO1* rearrangements.

Determination of the specific histologic subtype and fusion status is important in treatment planning and assessment of prognosis. There are four recognized histologic subtypes. The **embryonal type** accounts for approximately 60% of all cases and does not typically harbor a genetic translocation. The rare **spindle/sclerosing** subtype that accounts for approximately 3–4% of all children with rhabdomyosarcoma. It is characterized by a sclerosing (microalveolar) pattern that can mimic the alveolar subtype, but it does not harbor the characteristic PAX/FOXO translocation seen in the alveolar subtype. The **alveolar type** accounts for approximately 25–40% of cases and is characterized by the presence of a chromosomal translocation. Over 80% of *FOXO1* translocations in the alveolar subtype involve a translocation between *FOXO1* and *PAX3*, but other rare variants exist such as *PAX3-NCOA2*. The tumor cells tend to grow in nests that often have cleft-like spaces resembling alveoli. Alveolar tumors occur most often in the trunk and extremities and carry the poorest prognosis. The **pleomorphic type** (adult form) is rare in childhood, accounting for <1% of cases.

Table 549.2 Genetic Disorders Associated with Rhabdomyosarcoma

DISORDER	GENETIC VARIANTS
Beckwith-Wiedemann syndrome	Deletions and loss of heterozygosity at chromosome 11p15, particularly affecting *IGF2*, *CDKAIC*, *H19*, and/or *LIT1*
Gorlin syndrome (basal cell nevus syndrome)	*PTCH*
Costello syndrome	*H-RAS*
Neurofibromatosis 1	*NF1*
Li-Fraumeni syndrome	*TP53*
Mosaic variegated aneuploidy syndrome	*BUB1B*
Nijmegen breakage syndrome (ataxia-telangiectasis syndrome variant 1)	*NBS*
Rubinstein-Taybi syndrome	*CREBBP*
Constitutional mismatch-repair/deficiency syndrome	*PSM2*
Adenomatous polyposis coli	*APC*
Hereditary retinoblastoma	*RB1*
Familial pleuropulmonary blastoma syndrome	*DICER1*
Noonan syndrome	*PTPN11*
Werner syndrome	*RECOL2*

From Parham DM, Alaggio R, Coffin CM. Myogenic tumors in children and adolescents. *Pediatr Dev Pathol.* 2012;15(1):S211–S236. Table 3.

Clinical Manifestations

The most common presenting feature of rhabdomyosarcoma is a mass that may or may not be painful. Symptoms are caused by displacement or obstruction of normal structures. Origin in the **nasopharynx** may be associated with nasal congestion, mouth breathing, epistaxis, and difficulty with swallowing and chewing. Regional extension into the cranium can produce cranial nerve paralysis, blindness, and signs of increased intracranial pressure with headache and vomiting. When the tumor develops in the face or cheek, there may be swelling, pain, trismus, and, as extension occurs, paralysis of cranial nerves. Tumors in the **neck** can produce progressive swelling with neurologic symptoms after regional extension. **Orbital** primary tumors are usually diagnosed early in their course because of associated proptosis, periorbital edema, ptosis, change in visual acuity, and local pain. When the tumor arises in the **middle ear**, the most common early signs are pain, hearing loss, chronic otorrhea, or a mass in the ear canal; extensions of the tumor produce cranial nerve paralysis and signs of an intracranial mass on the involved side. An unremitting croupy cough and progressive stridor can accompany rhabdomyosarcoma of the **larynx**. Because most of these signs and symptoms also are associated with common childhood conditions, clinicians must be alert to the possibility of tumor.

Rhabdomyosarcoma of the trunk or extremities often is first noticed after trauma and initially may be regarded as a hematoma. If the swelling does not resolve or increases, malignancy should be suspected. Involvement of the genitourinary tract can produce hematuria, obstruction of the lower urinary tract, recurrent urinary tract infections, incontinence, or a mass detectable on abdominal or rectal examination. Paratesticular tumor usually manifests as a painless, rapidly growing mass in the scrotum. Vaginal rhabdomyosarcoma may manifest as a grapelike mass of tumor tissue bulging through the vaginal orifice, known as **sarcoma botryoides**, and can cause urinary tract or large bowel symptoms. Vaginal bleeding or obstruction of the urethra or rectum may occur. Similar findings can be noted with tumors arising from the uterus.

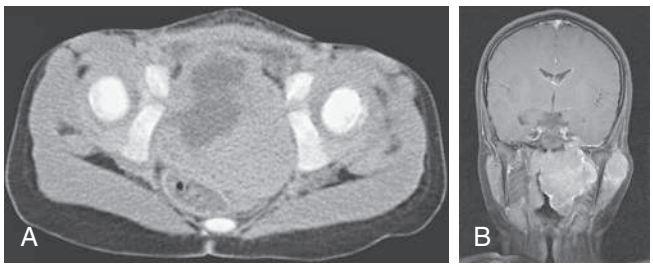

Fig. 549.1 A, Pelvic CT scan of a child with a bladder rhabdomyosarcoma. B, MR image of a child with a parameningeal rhabdomyosarcoma.

Tumors in any location may disseminate early and cause symptoms of pain or respiratory distress associated with pulmonary metastases. Extensive bone involvement can produce symptomatic hypercalcemia or bony pain. In such cases, it may be difficult to identify the primary lesion.

Diagnosis

Early diagnosis of rhabdomyosarcoma requires a high index of suspicion. The microscopic appearance is that of a small, round blue cell tumor. Neuroblastoma, lymphoma, and Ewing sarcoma also are **small, round blue cell tumors** from which suspected rhabdomyosarcomas must be differentiated. The differential diagnosis depends on the site of presentation. Definitive diagnosis is established by biopsy, microscopic appearance, and results of immunohistochemical stains and analysis of *PAX/FOXO1* expression. A lesion in an extremity may be thought to be a hematoma or hemangioma, an orbital lesion resulting in proptosis may be treated as an orbital cellulitis, or bladder-obstructive symptoms may be missed. Adolescents may ignore or be embarrassed to mention paratesticular lesions for a long time. Unfortunately, several months often elapse between initial symptoms and biopsy. Diagnostic procedures are determined mainly by the area of involvement. CT or MRI is necessary for evaluation of the primary tumor site. With signs and symptoms in the head and neck area, MRI should be performed to identify intracranial extension or meningeal involvement and also to reveal bony involvement or erosion at the base of the skull. For abdominal and pelvic tumors, CT with a contrast agent or MRI can help delineate the tumor (Figs. 549.1 and 549.2). A radionuclide bone or fluorodeoxyglucose PET (FDG-PET) scan, chest CT, and bilateral bone marrow aspiration and biopsy should be performed to evaluate the patient for the presence of metastatic disease and to plan treatment. Some low-risk patients may not need bone marrow evaluation. The most critical element of the diagnostic workup is examination of tumor tissue by an experienced sarcoma pathologist, which includes the use of special histochemical stains and immunostains along with molecular genetics to detect fusion transcripts as described earlier. Lymph nodes also should be sampled for the presence of disease spread, especially in tumors of the extremities and in males older than 10 years of age with paratesticular tumors.

Treatment

Treatment is multidisciplinary and includes the pediatric oncologist, pediatric surgeon or other surgical subspecialist, and often a radiation oncologist. Only if the tumor is able to be completely resected, with negative margins, without loss of function or major cosmetic deformity, should this be attempted initially. Unfortunately, most rhabdomyosarcomas are not completely resectable at initial diagnosis. Treatment is based on risk classification of the tumor, which is determined by the stage of tumor, the tumor histology and/or fusion status, and the amount of tumor that was surgically resected prior to chemotherapy ("surgical group"). Stage is dependent on primary site

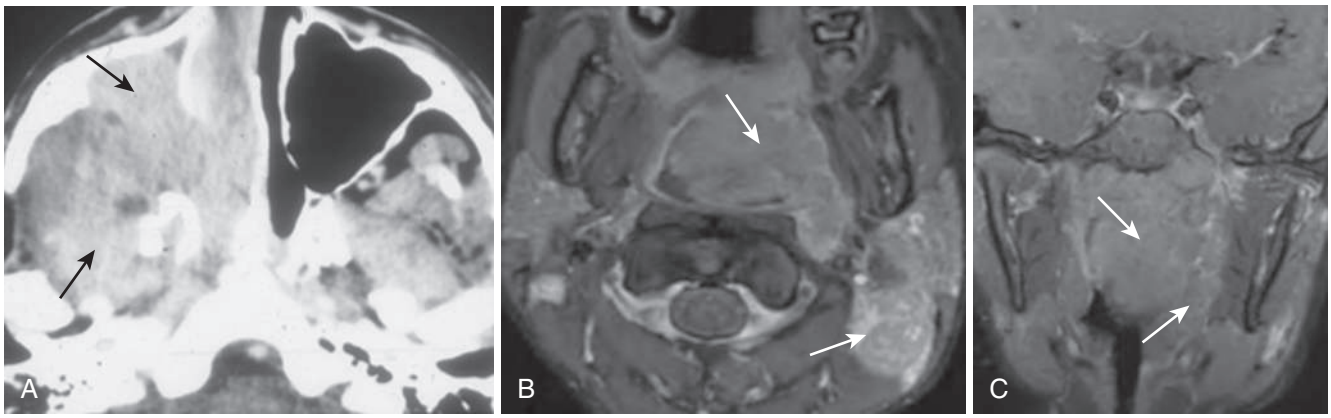

Fig. 549.2 Rhabdomyosarcoma. A, Axial contrast-enhanced CT scan at the level of the nasal cavity demonstrates a large, enhancing aggressive soft tissue mass involving the right maxillary sinus and the infratemporal fossa *(arrows)*. Axial MR image (B) and coronal contrast-enhanced T1-weighted MR image (C) demonstrate an infiltrative mass involving the pharyngeal mucosal space, left infratemporal masticator space, skull base, and sphenoid sinus *(arrows)*. *(From Haaga JR, Boll DT, eds. CT and MRI of the Whole Body. 6th ed. Philadelphia: Elsevier; 2017: Fig. 26-16, p. 769.)*

(favorable vs unfavorable), tumor invasiveness (T1 or T2), lymph node status, tumor size, and presence of metastasis. Favorable sites include female genital, paratesticular, and head and neck (nonparameningeal) regions; all other sites are considered unfavorable. Table 549.3 shows the Children's Oncology Group staging system for rhabdomyosarcoma.

Patients should be offered enrollment in clinical trials. Table 549.4 shows current risk stratification and outcome based on results of recent studies. Patients with low-risk disease can be cured with minimal therapy consisting of vincristine and actinomycin with or without lower doses of cyclophosphamide; radiation therapy can be used in the case of residual disease after initial surgery. Treatment for patients with intermediate-risk disease consists of vincristine, actinomycin, and cyclophosphamide along with radiation. The addition of irinotecan has recently been studied in intermediate risk rhabdomyosarcoma, and the current trial for patients with intermediate risk disease is exploring the role of maintenance chemotherapy. For patients with high-risk disease, approaches using intensive multiagent chemotherapy have not improved the outcome and new approaches are being investigated.

Prognosis

Prognostic factors include age, stage, histology/fusion status, and primary site. Among patients with resectable tumor and favorable histology, 80–90% have prolonged disease-free survival. Unresectable tumor localized to certain favorable sites, such as the orbit, also has a high likelihood of cure. Approximately 65–70% of patients with incompletely resected tumor also achieve long-term disease-free survival. Patients with disseminated disease have a poor prognosis; only approximately 50% achieve remission, and fewer than 50% of these are cured. Older children have a poorer prognosis than younger children. For all patients, surveillance for late effects of cancer treatment is extremely important. Some examples of late effects include infertility from cyclophosphamide, late effects in the radiation field such as bladder dysfunction, infertility, cataracts, impaired bone growth, and secondary malignancies.

OTHER SOFT TISSUE SARCOMAS

The nonrhabdomyosarcoma soft tissue sarcomas constitute a heterogeneous group of tumors that account for 3% of all childhood malignancies (Table 549.5). Because they are relatively rare in children, much of the information about their natural history and treatment has been derived from studies in adult patients. In children, the median age at diagnosis is 12 years, with a male:female ratio of 2.3:1. These tumors commonly arise in the trunk or lower extremities. The most common histologic types are synovial sarcoma (42%), fibrosarcoma (13%), malignant fibrous histiocytoma (12%), and neurogenic tumors (10%). Molecular genetic studies often prove useful in diagnosis, because several of these tumors have characteristic chromosomal translocations. Tumor size, stage (clinical group), invasiveness, and histologic grade correlate with survival.

Surgery remains the mainstay of therapy, but a careful search for lung and bone metastases should be undertaken before surgical excision. Chemotherapy and radiation therapy should be considered for large, high-grade, and/or unresectable tumors. The role of chemotherapy for nonrhabdomyosarcoma soft tissue sarcomas is not as well defined as for rhabdomyosarcoma. Patients with large (>5 cm) high-grade, or unresectable or metastatic disease are treated with multiagent chemotherapy in addition to irradiation and/or surgery. Patients with completely resected small (<5 cm) tumors are generally treated with surgery alone and can be expected to have an excellent outcome regardless of whether the tumor is high or low grade.

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Table 549.3 Staging System for Rhabdomyosarcoma

STAGE	SITE	T STAGE	SIZE	NODE STATUS	METASTASIS
1	Favorable	T1 or T2	a or b	N0 or N1 or Nx	M0
2	Unfavorable	T1 or T2	a	N0 or Nx	M0
3	Unfavorable	T1 or T2	a b	N1 N0 or N1 or Nx	M0
4	Any	T1 or T2	a or b	N0 or N1 or Nx	M1

T1, confined to anatomic site of origin; T2, extension and/or fixative to surrounding tissue.
Size: a, <5 cm in diameter; b, ≥5 cm in diameter.
Nodes: N0, regional nodes not involved; N1, regional nodes involved; Nx, regional node status unknown.
Metastases: M0, no distant metastases; M1, metastases present (includes positive cytology in cerebrospinal, pleural, or peritoneal fluid).

Table 549.4 Risk Groups and Outcome for Rhabdomyosarcoma, Children's Oncology Group

RISK GROUP	STAGE	CLINICAL GROUP	MOLECULAR FINDINGS	AGE	LONG-TERM EFS (%)*
Very Low	1	I	FOXO1 -, wildtype P53, wildtype MYOD1	Any	92
Low	1	II, III (orbit only)	FOXO1-, wildtype P53, wildtype MYOD1	Any	87
Low	2	I, II	FOXO1 -, wildtype P53, wildtype MYOD1	Any	87
Intermediate	1	III (non orbit)	FOXO1-	Any	70-85
Intermediate	1, 2, 3	I, II, III	FOXO1+	Any	63-93
Intermediate	2, 3	III	FOXO1 -	Any	63-93
Intermediate	3	I, II	FOXO1-	Any	63-93
Intermediate	4	IV	FOXO1-	<10 yr	60-64
High	4	IV	FOXO1-	≥10 yr	35
High	4	IV	FOXO1+	Any	9†

*4–5-year EFS based on D9602, D9803, ARST0331, ARST0431, and ARST0531 studies.
†From Rudzinski ER, Anderson JR, Chi YY, et al. Histology, fusion status, and outcome in metastatic rhabdomyosarcoma: A report from the Children's Oncology Group. *Pediatr Blood Cancer.* 2017;64(12):10.1002/pbc.26645.
EFS, event-free survival,
Modified from Oberoi, S, Crane, JN, Haduong, JH, et al. Children's Oncology Group's 2023 blueprint for research: Soft tissue sarcomas. *Pediatr Blood Cancer.* 2023;70(Suppl. 6):e30556. https://doi.org/10.1002/pbc.30556.

Table 549.5 Clinical and Biological Features of the Nonrhabdomyosarcoma Soft Tissue Sarcomas

TUMOR*	CELL ORIGIN AND CYTOGENETICS/ PRODUCT	COMMON SITES	COMMON AGES	GOOD PROGNOSTIC FACTORS†	OUTCOME	THERAPY
Synovial sarcoma	Mesenchymal cells/t(X;18) (p11q11)/*SSX1–SYT*(seen in biphasic tumors) *SSX2–SYT*(seen in monophasic tumors)/ translocation present in >90%, MYCN over-expression	Extremities (lower twice as common as upper extremity)	Adolescence/ young adult-hood, accounts for 30% of pedi-atric NRSTS	Age ≤14 years, size <5 cm, calcification, chemosensi-tive	Stages I and II, 70%; stages III and IV, poor	WLE with/without RT chemo: ifosfa-mide/doxorubicin
Dermatofibrosar-coma protuber-ans (DFSP)	Dermis/t(17;22) (q21;q13) ring chromosome/*COL1A1–PDGFB*	Trunk and proximal limbs, rare head and neck	20-50 years, rare in childhood	Complete exci-sion, local recurrence 60% with incomplete resection		WLE (3 cm) margin pseudopod-like projections with Mohs micrographic surgery; RT has been used when WLE not possible, imatinib for unresectable; locally advanced, recurrent, or metastatic disease
MFH aka undif-ferentiated pleomorphic sarcoma	Unknown/19p+, complex abnormalities	Lower extremity, trunk, head and neck	In children, 10-20 years, 40-60 years common radiation-induced sarcoma	Extremity site	5-year survival, 27–53%	WLE chemo: ifosfamide/ doxorubicin
Angiomatoid fibrous histiocy-toma	Fibroblast/t(2;22)(q34;q12) t(12;16)(q13;p11) t(12;22) (q13;q12)/*EWSR1–CREB1 TLS–ATF1 EWSR1–ATF1*	Extremity, trunk and head and neck (subcutis may infiltrate dermis or muscle)	Young children and young adults	Much less aggressive than MFH	Excellent with surgery alone	WLE
MPNST	Schwann cell or fibroblast/17q;22q loss or rearrangement, complex abnormalities in high-grade tumors	Extremity, retroperito-neum trunk	Younger patients with neurofi-bromatosis (NF1) develop in 10% patients with *NF1* and 20–60% cases of MPNST occur in association with *NF1*	Size <5 cm, no *NF1*	53% survival without NF, 16% with NF	WLE with/without RT chemo: neoadjuvant role, ifosfamide/ doxorubicin
Fibrosarcoma	Fibroblast/t(X;18), t(2;5), t(7;22)	Truncal/proxi-mal site	Adolescence		5-year survival 34–60%	WLE with/without RT chemo: no established role
Infantile fibro-sarcoma	Fibroblast/t(12;15) (p13;q25)/*ETV6–NTRK3*	Distal extremity	Most <2 years	<5 years	5-year survival 84%	WLE, RT/chemo if WLE not possible historically, neoad-juvant chemo-therapy (with VA ± C). However, the use of molecular targeting with NTRK inhibitor for up to 26 cycles has had dramatic results and should be considered first-line therapy

Table 549.5 Clinical and Biological Features of the Nonrhabdomyosarcoma Soft Tissue Sarcomas—cont'd

TUMOR*	CELL ORIGIN AND CYTOGENETICS/ PRODUCT	COMMON SITES	COMMON AGES	GOOD PROGNOSTIC FACTORS†	OUTCOME	THERAPY
Leiomyosarcoma	Deletion 1p, other complex abnormalities, smooth muscle-uterine t(12;14)(q15;q24); *HMGA2* rearrangement	Retroperitoneum GI tract, any soft-tissue or vascular area	40-70 years, when in children, any age, associated with human immunodeficiency virus related to EBV infection, reported in patients who received RT for retinoblastoma and Carney triad‡	<5 cm	33% disease-free survival at 1-5 years	WLE chemo: ifosfamide/ doxorubicin or gemcitabine/ docetaxel
Alveolar soft part sarcoma	der(17)t(X;17)(p11;25)/*ASPSCR1–TFE3*	Orbit, head and neck, lower extremity	15-35 years	Young age, orbital site, <5 cm	5-year survival 27–59% (indolent; death from disease after 10-20 years) 79% metastatic disease, including brain	WLE chemo or RT only after recurrence chemo: no clear role Possible role of vascular endothelial growth factor inhibitors being explored
Hemangiopericytoma infantile form (<1 year of age)	Pericytes/t(12;19)(q13;q13)/t(13;22)(q22;q11)	Extremity, retroperitoneum head and neck extremity, trunk	20-70 years, when in children, 10-20 years rare, but typically 1 year	Low stage, <5 cm, infantile form	Stages I and II, 30–70% 5-year survival with adjuvant therapy stages III and IV, poor infantile—excellent with surgery alone	WLE, with/without RT chemo: no established role but can be chemoresponsive, infantile form responds more favorably to chemotherapy
Liposarcoma (myxoid)	Primitive mesenchyme/t(12;16)(q13p11)/*FUS–DDIT3*	Extremity, retroperitoneum	0-2 years and second decade; sixth decade most common	Child, myxoid type	Very good with WLE, rarely metastasizes	WLE, with/without RT RT important in retroperitoneal lesion chemo: no established role
Clear cell sarcoma	Mesoderm, melanin deposits t(12;22)(p13;q12)/*EWSR1–ATF1*	Tendons and aponeuroses of lower extremity	Young adults, females	<5 cm, no necrosis, nonmetastatic	Adverse prognosis; 5-year survival rates of 60–70%. However, only 30–40% are long-term survivors due to late recurrences	WLE with sentinel node biopsy no clear role for adjuvant chemotherapy Potential role for immunotherapy (e.g., translocation-targeted vaccines, interferon, GM-CSF-secreting vaccine)
Epithelioid sarcoma	Inactivation of INI1 (hSNF5/SMAR CB1) located on chromosome 22q11.2	Distal extremities (especially hands)	Young adult	Younger age, distal tumor location, no necrosis or vascular invasion, negative nodal status, and microscopic complete resection	Tumor is highly aggressive and has a propensity for lymph node metastases Localized smaller tumors have better prognosis	WLE with sentinel lymph node biopsy ± RT and/or chemo: ifosfamide/ doxorubicin Clinical trial for use of tazemetostat recently completed Approval for patients with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection

*Listed in order of decreasing incidence.
†Low histologic grade and low stage are good prognostic factors.
‡Carney triad: A condition consisting of gastric epithelioid leiomyosarcoma, pulmonary chondroma, functioning extraadrenal paraganglioma.
NRST, Nonrhabdomyosarcoma soft tissue sarcoma; GI, gastrointestinal; EBV, Epstein-Barr virus; MFH, malignant fibrous histiocytoma; MPNST, malignant peripheral nerve sheath tumor; NF, neurofibromatosis; V, vincristine; C, cyclophosphamide; NTRK, neurotrophic tyrosine receptor kinase; RT, radiation therapy; WLE, wide local excision; GM-CSF, granulocyte-macrophage colony-stimulating factor.
From Amin S, Levy CF. Rhabdomyosarcoma and other soft-tissue sarcomas. In: Fish JD, Lipton JM, Lanzkowsky P, eds. *Lanzowsky's Manual of Pediatric Hematology and Oncology*. 7th ed. London: Elsevier; 2022: Table 25.1, p. 543–544.

Chapter 550
Neoplasms of Bone

550.1 Malignant Tumors of Bone

Wendy A. Allen-Rhoades and Carola A.S. Arndt

The annual incidence of malignant bone tumors in the United States is approximately 8.2 cases per 1 million children younger than 14 years and 14.7 per 1 million for adolescents age 15-19. **Osteosarcoma** is the most common primary malignant bone tumor in children and adolescents, followed by **Ewing sarcoma** (Table 550.1, Fig. 550.1). In children <10 years old, Ewing sarcoma is more common than osteosarcoma. Both tumor types are most likely to occur in the second decade of life.

OSTEOSARCOMA

Epidemiology

The annual incidence of osteosarcoma in the United States is 5.7 cases per 1 million children 0-19 years old. The highest risk period for development of osteosarcoma is during the adolescent growth spurt, suggesting an association between rapid bone growth and malignant transformation. Patients with osteosarcoma are taller than their peers of similar age.

Pathogenesis

Although the cause of osteosarcoma is unknown, certain genetic or acquired conditions predispose patients to development of osteosarcoma. Patients with **hereditary retinoblastoma** have a significantly increased risk for development of osteosarcoma. The sites of osteosarcoma in these patients include previously irradiated areas but also sites far from the original retinoblastoma radiation field. Predisposition to development of osteosarcoma in these patients may be related to loss of heterozygosity of the *RB* gene. Osteosarcoma also occurs in **Li-Fraumeni syndrome**, which is a familial cancer syndrome associated with germline pathogenic variants of the *P53* gene. Kindreds with Li-Fraumeni syndrome have a spectrum of malignancies in first-degree relatives, including carcinoma of the breast, soft tissue sarcomas, brain tumors, leukemia, adrenocortical carcinoma, and other malignancies. **Rothmund-Thomson syndrome** is a rare condition associated with short stature, skin telangiectasia, small hands and feet, hypoplasticity or absence of the thumbs, and a high risk of osteosarcoma. **Diamond-Blackfan anemia** is also a risk factor for osteosarcoma. Osteosarcoma can also be induced by irradiation for Ewing sarcoma, craniospinal irradiation for brain tumors, or high-dose irradiation for other malignancies. Other benign conditions that can be associated with malignant transformation to osteosarcoma include Paget disease, enchondromatosis, multiple hereditary exostoses, and fibrous dysplasia (see Chapter 550.2).

The pathologic diagnosis of osteosarcoma is made by demonstration of a highly malignant, pleomorphic, spindle cell neoplasm associated with the formation of malignant osteoid and bone. There are four pathologic subtypes of conventional high-grade osteosarcoma: osteoblastic, fibroblastic, chondroblastic, and telangiectatic. No significant differences in outcome are associated with the various subtypes, although the chondroblastic component of that subtype may not respond as well to chemotherapy.

Telangiectatic osteosarcoma may be confused with aneurysmal bone cyst (ABC) because of its lytic appearance on radiography. High-grade osteosarcoma typically arises in the diaphyseal region of long bones and invades the medullary cavity. It also may be associated with a soft tissue mass. Two variants of osteosarcoma, parosteal and periosteal, should be distinguished from conventional osteosarcoma because of their characteristic clinical features. **Parosteal osteosarcoma** is a low-grade, well-differentiated tumor that does not invade the medullary cavity and most frequently is found in the posterior aspect of the distal femur. Surgical resection alone often is curative in this lesion, which has a low propensity for metastatic spread. **Periosteal osteosarcoma** is a rare variant that arises on the surface of the bone but has a higher rate of metastatic spread than the parosteal type and an intermediate prognosis.

Clinical Manifestations

Pain, limp, and swelling are the most common presenting manifestations of osteosarcoma. Because these tumors occur most often in active

Table 550.1 Comparison of Features of Osteosarcoma and the Ewing Family of Tumors

FEATURE	OSTEOSARCOMA	EWING FAMILY OF TUMORS*
Age	Second decade	Second decade
Ethnicity	All	Primarily Whites
Sex (M:F)	1.5:1	1.5:1
Predisposition	Retinoblastoma, Li-Fraumeni syndrome, Rothmund-Thomson syndrome, Paget disease, radiotherapy	None known
Site	Metaphyses of long bones	Diaphyses of long bones, flat bones, soft tissues
Presentation	Local pain and swelling; often history of injury; pathologic fracture	Local pain and swelling; fever, palpable mass, pathologic fracture
Radiographic findings	Sclerotic destruction (less often lytic); sunburst pattern, Codman triangle	Primarily lytic, multilaminar periosteal reaction ("onion-skinning"), "moth-eaten," Codman triangle
Differential diagnosis	Ewing sarcoma, osteomyelitis, hematoma	Osteomyelitis, eosinophilic granuloma, lymphoma, neuroblastoma, rhabdomyosarcoma, FUO
Metastasis	Lungs, bones	Lungs, bones, bone marrow
Treatment	Chemotherapy	Chemotherapy
	Ablative surgery of primary tumor	Radiotherapy and/or surgery of primary tumor
Outcome	Without metastases, 70% cured; with metastases at diagnosis, ≤20% survival	Without metastases, 65–75% cured; with metastases at diagnosis, 20–30% survival

FUO, Fever of unknown origin.
*Ewing family of tumors includes: (1) Ewing sarcoma of bone; (2) extraosseous (extraskeletal) Ewing tumor; (3) peripheral primitive neuroectodermal tumor (PPNET). A PPNET arising from the chest wall is an Askin tumor.

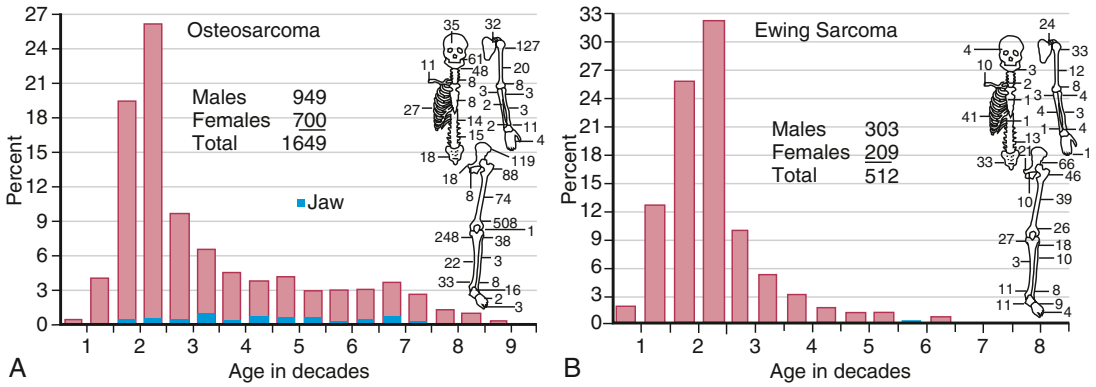

Fig. 550.1 A, Age and skeletal distribution of 1,649 cases of osteosarcoma in the Mayo Clinic files. B, Age and skeletal distribution of 512 cases of Ewing sarcoma in the Mayo Clinic files. *(From Unni KK, ed. Dahlin's Bone Tumors: General Aspects and Data on 11,087 Cases. 5th ed. Philadelphia: Lippincott-Raven; 1996. Reprinted by permission of the Mayo Foundation.)*

adolescents, initial complaints may be attributed to a sports injury or sprain; any bone or joint pain not responding to conservative therapy within a reasonable time should be investigated thoroughly. Additional clinical findings may include limitation of motion, joint effusion, tenderness, and warmth. Results of routine laboratory tests, such as a complete blood cell count and chemistry panel, are usually normal, although alkaline phosphatase or lactate dehydrogenase values may be elevated.

Diagnosis

Bone tumor should be suspected in a patient who presents with deep bone pain, often causing nighttime awakening, and has a palpable mass with radiographs that demonstrate a lesion. The lesion may be mixed lytic and blastic in appearance, but new bone formation is usually visible. The classic radiographic appearance of osteosarcoma is the *sunburst pattern* (Fig. 550.2). When osteosarcoma is suspected, the patient should be referred to a center with experience in managing bone tumors. The biopsy and the surgery should be performed by the same surgeon so that the incisional biopsy site can be placed in a manner that will not compromise the definitive surgical procedure. Tissue usually is obtained for molecular and biologic studies at the time of the initial biopsy. Before biopsy, MRI of the primary lesion and the entire bone should be performed to evaluate the tumor for its proximity to nerves and blood vessels, soft tissue and joint extension, and skip lesions. The metastatic workup includes CT of the chest and radionuclide bone scanning or positron emission tomography (PET) scan to evaluate for lung and bone or soft tissue metastases, respectively. The **differential diagnosis** of a lytic bone lesion includes histiocytosis, Ewing sarcoma, lymphoma, and bone cyst.

Fig. 550.2 Radiograph of an osteosarcoma of the femur with typical sunburst appearance of bone formation.

Treatment

With chemotherapy and surgery, 5-year disease-free survival of patients with nonmetastatic extremity osteosarcoma is 65–75%. Complete surgical resection of the tumor is important for cure. The current approach is to treat patients with preoperative chemotherapy in an attempt to facilitate limb salvage operations and to treat micrometastatic disease immediately. Up to 80% of patients are able to undergo limb salvage operations after initial chemotherapy. It is important to resume chemotherapy as soon as possible after surgery. Lung metastases present at diagnosis should be resected by thoracotomies at some time during treatment. Active agents in use in multidrug chemotherapy regimens for conventional osteosarcoma include doxorubicin, cisplatin, methotrexate, and ifosfamide.

One of the most important prognostic factors in osteosarcoma is the *histologic response to chemotherapy;* a poor histologic response is ≥10% viable tumor (<90% necrosis in resected tissue). **MAP** (methotrexate, doxorubicin, cisplatin) is the standard chemotherapy regimen for osteosarcoma. After limb salvage surgery, intensive rehabilitation and physical therapy are necessary to ensure maximal functional outcome. Intensification of therapy by addition of ifosfamide and etoposide in patients with poor histologic response after induction chemotherapy with MAP has not improved outcome.

For patients who require amputation, early prosthetic fitting and gait training are essential to enable patients to resume normal activities as soon as possible. Before definitive surgery, patients with tumors on weight-bearing bones should be instructed to use crutches to avoid stressing the weakened bones and causing pathologic fracture. The role of chemotherapy in parosteal and periosteal osteosarcomas is not well defined, and chemotherapy is generally reserved for use in patients with tumors that have a high-grade microscopic appearance.

Prognosis

Surgical resection alone is curative only for patients with low-grade parosteal osteosarcoma. Conventional high-grade osteosarcoma requires multiagent chemotherapy. Up to 75% of patients with nonmetastatic extremity osteosarcoma are cured with current multiagent treatment protocols. The prognosis is not as favorable for patients with pelvic tumors as for those with primary tumors in the extremities. From 20–30% of patients who have limited numbers of pulmonary metastases also can be cured with aggressive chemotherapy and resection of lung nodules. Patients with bone metastases and those with widespread lung metastases have an extremely poor prognosis. Long-term follow-up of patients with osteosarcoma is important to monitor for late effects of chemotherapy, such as cardiotoxicity from anthracycline and hearing loss from cisplatin. Patients in whom late, isolated lung metastases develop may be cured with surgical resection of the metastatic lesions alone.

EWING SARCOMA

Epidemiology

The incidence of Ewing sarcoma in the United States is 3.1 cases per 1 million children ages 0-19 years. It is rare among Black children. Ewing sarcoma, an undifferentiated sarcoma of bone, also may arise from soft tissue. Treatment protocols for these tumors are the same whether the tumors arise in bone or soft tissue. Anatomic sites of primary tumors arising in bone are distributed evenly between the extremities and the central axis (pelvis, spine, and chest wall). Primary tumors arising in the chest wall are often referred to as **Askin tumors**.

Pathogenesis

Immunohistochemical staining assists in the diagnosis of Ewing sarcoma to differentiate it from **small, round, blue cell tumors** such as lymphoma, rhabdomyosarcoma, and neuroblastoma. Histochemical stains may react positively with certain neural markers on tumor cells (neuron-specific enolase and S-100), especially in peripheral primitive neuroectodermal tumors. Reactivity with muscle markers (e.g., desmin, actin) is absent. Additionally, MIC-2 (CD99) staining is usually positive. A specific chromosomal translocation, t(11;22) (q24;q12), or a variant is found in most of the Ewing sarcoma family of tumors. Analysis for the translocation by next generation sequencing, fluorescence in situ hybridization (FISH), or polymerase chain reaction (PCR) analysis for the chimeric fusion gene products *EWS*/*FLI1* or *EWS*/*ERG* (or other variants) are used routinely in diagnosis.

Clinical Manifestations

Symptoms of Ewing sarcoma are similar to those of osteosarcoma. Pain, swelling, limitation of motion, and tenderness over the involved bone or soft tissue are common presenting symptoms. Patients with large chest wall primary tumors may present with respiratory distress. Patients with paraspinal or vertebral primary tumors may present with symptoms of cord compression. Ewing sarcoma often is associated with **systemic manifestations**, such as fever and weight loss, and may be accompanied by elevated inflammatory markers; patients may have undergone treatment for a presumptive diagnosis of osteomyelitis or a fever of unknown origin. Patients also may have a delay in diagnosis when their pain or swelling is attributed to a sports injury. Biopsy and tissue diagnosis should be considered for patients presenting with suspicious bone lesions, because even the gross appearance of Ewing sarcoma can appear similar to infection and the time course can be rapid. Surgical procedures for treatment of infection can contaminate the surgical field and impact treatment outcomes.

Diagnosis

The diagnosis of Ewing sarcoma should be suspected in a patient who presents with pain and swelling, with or without systemic symptoms, and with a radiographic appearance of a primarily lytic bone lesion with periosteal reaction, the characteristic **onion-skinning** (Fig. 550.3). A large, associated soft tissue mass often is visualized on MRI or CT (Fig. 550.4). The **differential diagnosis** includes osteosarcoma,

Fig. 550.3 Radiograph of tibial Ewing sarcoma showing periosteal elevation or "onion-skinning."

Fig. 550.4 MR image of tibial Ewing sarcoma showing a large associated soft tissue mass.

osteomyelitis, Langerhans cell histiocytosis, primary lymphoma of bone, metastatic neuroblastoma, or rhabdomyosarcoma in the case of a pure soft tissue lesion. Patients should be referred to a center with experience in managing bone tumors for evaluation and biopsy. Thorough evaluation for metastatic disease includes CT of the chest, radionuclide bone scan, or PET scan. Bone marrow aspiration and biopsy specimens from at least two sites are generally required but can be omitted for certain lower risk patients. MRI of the tumor and the entire length of involved bone should be performed to determine the exact extension of the soft tissue and bony mass and the proximity of tumor to neurovascular structures. Studies are also using fluorodeoxyglucose (FDG) PET to evaluate response to therapy.

To avoid compromising an ultimate potential for limb salvage by a poorly planned biopsy incision, the same surgeon should perform the biopsy and the surgical procedure. CT-guided biopsy of the lesion often provides diagnostic tissue. It is important to obtain adequate tissue for special stains and molecular studies.

Treatment

Tumors of the Ewing sarcoma family are best managed with a comprehensive multidisciplinary approach in which the surgeon, chemotherapist, and radiation oncologist plan therapy. Multiagent chemotherapy is important because it can shrink the tumor rapidly and is usually given before local control is attempted. In North America, standard **chemotherapy** for nonmetastatic Ewing sarcoma includes vincristine, doxorubicin, cyclophosphamide, etoposide, and ifosfamide. Chemotherapy usually causes dramatic shrinkage of the soft tissue mass and rapid, significant pain relief. Patients with nonmetastatic Ewing sarcoma have a better outcome when treated on a 14-day rather than on a 21-day schedule. An international cooperative group trial found that myeloablative chemotherapy and stem cell rescue was not superior to chemotherapy with lung irradiation for patients with pulmonary metastases.

Ewing sarcoma is considered a radiosensitive tumor, and local control may be achieved with **irradiation** or **surgery**. Radiation therapy is associated with a risk of radiation-induced second malignancies, especially osteosarcoma, as well as failure of bone growth in skeletally immature patients. It is important to provide the patient with crutches if the tumor is in a weight-bearing bone to avoid a pathologic fracture before definitive local control. Many centers prefer surgical resection, if possible, to achieve local control. Chemotherapy should be resumed as soon as possible after surgery.

Prognosis

Patients with small, nonmetastatic, distally located extremity tumors have the best prognosis, with a cure rate of up to 75%. Patients with pelvic tumors have, until recently, had a much worse outcome. Patients with metastatic disease at diagnosis, especially bone or bone marrow metastases, have a poor prognosis, with <30% surviving long term.

Long-term follow-up of patients with Ewing sarcoma is important because of the potential for late effects of treatment, such as anthracycline-induced cardiotoxicity, infertility, and second malignancies, especially in the radiation field, and late relapses, even as long as 10 years after initial diagnosis.

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550.2 Benign Tumors and Tumor-Like Processes of Bone

Carola A.S. Arndt and A. Noelle Larson

Benign bone lesions in children are common compared with the relatively rare malignant neoplasms of bone. A broad range of diagnostic possibilities must be considered when the physician is confronted with an undiagnosed bone lesion (Table 550.2). Some, although histologically benign, can be life-threatening, while others can be locally destructive to bone. Many represent an incidental finding that, if asymptomatic, can be observed. A group of benign characteristic lesions including osteochondroma, nonossifying fibroma, unicameral bone cyst, and enchondroma may occur in 19% of children in a historic cohort of children and can readily be diagnosed on standard radiographs without additional imaging studies. Other conditions require further study to determine a diagnosis where no single element in the history or diagnostic test is sufficient to rule out malignancy. Benign lesions are usually painless but may be painful, especially if the lesion is causing local bone destruction or there is an impending pathologic fracture. Night pain that awakens a child suggests malignancy, but relief of such pain with aspirin is common with osteoid osteomas. Rapidly enlarging lesions usually are associated with malignancy, but several benign lesions, such as ABCs, can enlarge faster than most malignancies. Several conditions, such as osteomyelitis, can simulate the appearance of bone tumors.

Many benign bone tumors are diagnosed incidentally or after pathologic fracture. Initial management of these fractures is similar to that of nonpathologic fractures in the same location. It is unusual for benign bone tumors to interfere with fracture healing, but the area of weakness typically remains, and refracture is common. Fractures rarely result in resolution of the tumor, which usually is treated after the fracture has healed. Fractures around the hip, however, frequently require immediate treatment to stabilize the femoral neck and restore anatomic alignment.

Radiographs of any suspected bone lesion should always be obtained in two planes. Additional studies may be necessary to help arrive at the correct diagnosis and to guide treatment. Although these lesions are benign, selected lesions require intervention. If biopsy is performed, both microbiology and pathology evaluations should always be obtained.

Osteochondroma (exostosis) is one of the most common benign bone tumors in children. Because many are completely asymptomatic and unrecognized, the true incidence of this lesion is unknown. Osteochondromas develop in childhood, arising from the metaphysis of a long bone, particularly the distal femur, proximal humerus, and proximal tibia. The lesion enlarges with the child until skeletal maturity. Children commonly present at 5-15 years of age, when the child or parent notices a bony, nonpainful mass. Some are discovered because they are irritated by soft tissues rubbing over the lesion during athletic or other activities. Fracture is rare. Osteochondromas appear radiographically as stalks or broad-based projections from the surface of the bone, usually in a direction away from the adjacent joint (Fig. 550.5A). The bone is in continuity with the medullary canal. Invariably, the lesion is radiographically smaller than suggested by palpation because the cartilage cap covering the lesion is not seen. This cartilage cap may be up to 1 cm thick. Both the cortex of the bone and the marrow space of the involved bone are continuous with the lesion. Malignant degeneration of a chondrosarcoma is rare in children but occurs in as many as 1% of adults. Routine removal is not performed unless the lesion is large enough to cause symptoms, such as pain or nerve compression, most commonly presenting as foot drop. Osteochondromas can be diagnosed by radiographs alone, and unless patients present with unusual symptoms such as night pain, further studies such as CT or MRI are not typically indicated. Patients should be referred to an orthopedic practice for counseling, but routine radiographic follow-up and treatment should be based on symptoms.

Multiple hereditary osteochondrosis (exostoses) is a related but rare condition characterized by the presence of multiple osteochondromas (see Fig. 550.5B). This is an autosomal dominant disorder due to pathogenic variants in *EXT1* or *EXT2*. Severely involved children can have short stature, limb-length inequality, premature partial physeal arrests, deformity of both the upper and lower extremities including genu valgum, dislocation of the radial head at the elbow, and neurovascular impingement or entrapment in areas adjacent to the tumor and neurovascular compartments. These children must be monitored carefully during growth by a pediatric orthopedist. Malignant transformation may occur but is rare. Screening MRI of the entire spine is recommended during childhood to detect bony lesions growing into the

Table 550.2 Features of Pediatric Benign Bone Tumors

LESION	TYPICAL COURSE	MOST COMMON WORKUP TO CONFIRM DIAGNOSIS
Fibroma (nonossifying fibroma, fibrous cortical defect, metaphyseal fibrous defect)	Observation; surgery to treat fracture/impending fracture (rare, large lesions)	Radiographs
Enchondroma	Observation; treat if symptomatic	Radiographs, occasionally MRI
Osteochondroma	Observation; excise if symptomatic	Radiographs
Subungual exostosis	Symptoms warrant excision for most patients	Radiographs
Unicameral/simple bone cyst	Observation; treat if fracture occurs to prevent further fractures	Radiographs, occasionally MRI
Osteoid osteoma	NSAIDs; but symptoms warrant percutaneous ablation for most patients	Radiographs, CT
Heterotopic ossification	Observation; if symptomatic, excise after bone is mature (>6 mo)	Radiographs, ± MRI, CT
Fibrous dysplasia	Observation; treat if pain or bony deformities	Radiographs, ± MRI, ± biopsy
Chronic regional multifocal osteomyelitis (reactive bone condition)	Observation; medical treatment available if symptomatic; pathology is identical to osteomyelitis	Radiographs, MRI; bone scan to look for other lesions; antibiotics to rule out osteomyelitis; biopsy
Langerhans cell histiocytosis	Variable; depends on extent of disease	Skeletal survey, MRI, biopsy, workup to rule out systemic disease
Infection	Treat with prolonged antibiotics, typically some intravenously; surgery for joint/growth plate involvement, abscess, and chronic disease	CRP, sedimentation rate, CBC with differential, blood cultures, radiographs, ± MRI, ± biopsy
Osteoblastoma	Locally aggressive, treat	Radiographs, CT, MRI, biopsy
Aneurysmal bone cyst	Locally aggressive, treat	Radiographs, MRI, biopsy
Chondroblastoma	Locally aggressive, treat	Radiographs, MRI, biopsy
Chondromyxoid fibroma	Locally aggressive, treat	Radiographs, MRI, biopsy
Osteofibrous dysplasia	Possibly locally aggressive; variable	Radiographs, MRI, biopsy
Adamantinoma	Malignant, treat	Radiographs, MRI, biopsy

CBC, Complete blood count; CRP, C-reactive protein; CT, computed tomography; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal antiinflammatory drugs.

canal, which can result in spinal cord compression which may occur in up to 20–30% of patients (see Fig. 550.5C).

SUBUNGUAL EXOSTOSIS

This lesion is an osteochondroma that forms underneath the nailbed in an otherwise healthy child. The nailbed may become discolored or raised, and the condition is typically painful (Fig. 550.6). It can be differentiated from a paronychia or ingrown toenail by findings of an osteochondroma on radiographs. Radiographs should be taken, which will show a bony protuberance under the nailbed. Treatment should be nailbed removal and surgical excision with nailbed repair. Despite surgical excision, recurrence can occur up to 5% of the time.

Enchondroma is a benign lesion of hyaline cartilage that occurs centrally in the bone. These lesions are asymptomatic and frequently occur in the hands. Most are discovered incidentally, although pathologic fractures often lead to the diagnosis. Radiographically, the lesions occupy the medullary canal, are radiolucent, and are sharply marginated. Punctate or stippled calcification may be present within the lesion, but this is much more common in adults than in children. Almost all enchondromas in children are solitary and small. Most can simply be observed, with curettage and bone grafting reserved for lesions that are symptomatic or large enough to weaken the bone structurally. Large lesions with extensive involvement may represent low-grade chondrosarcoma. Multifocal involvement is referred to as **Ollier disease** and can result in bone dysplasia, short stature, limb-length inequality, and joint deformity. Surgery may be necessary to correct or prevent such deformities. When multiple enchondromas are associated with angiomas of the soft tissue, the condition is referred to as **Maffucci syndrome**. A high rate of malignant transformation has been reported in both of these multifocal conditions.

Chondromyxoid fibroma is an uncommon benign bone tumor in children. This metaphyseal lesion usually causes pain and local tenderness. The lesion occasionally is asymptomatic. Chondromyxoid fibroma appears radiographically as eccentric, lobular metaphyseal radiolucency with sharp, sclerotic, and scalloped margins. The lower extremity is involved most often. Treatment usually consists of curettage and bone grafting or en bloc resection.

Osteoid osteoma is a small benign bone tumor typically found in the proximal tibia and femur and the posterior elements of the spine. Most of these tumors are diagnosed between 5 and 20 years of age. The clinical pattern is characteristic, consisting of unremitting and gradually increasing pain that often is worst at night and is relieved by NSAIDs. Boys are affected more often than girls. Vertebral lesions can cause scoliosis or symptoms that mimic a neurologic disorder. Examination can reveal a limp, atrophy, and weakness when the lower extremity is involved. Palpation and range of motion do not alter the discomfort. Radiographs may show cortical thickening, and CT shows distinctive findings, with a round or oval metaphyseal or diaphyseal lucency (0.5-1.0 cm in diameter) surrounded by dense sclerotic bone (Fig. 550.7). The central lucency, or nidus, shows intense uptake on bone scan. Approximately 25% of osteoid osteomas are not visualized on plain radiographs but can be identified with CT. Because of the small size of the lesion and its location adjacent to thick cortical bone, MRI is poor at diagnosing osteoid osteomas, revealing only extensive T2

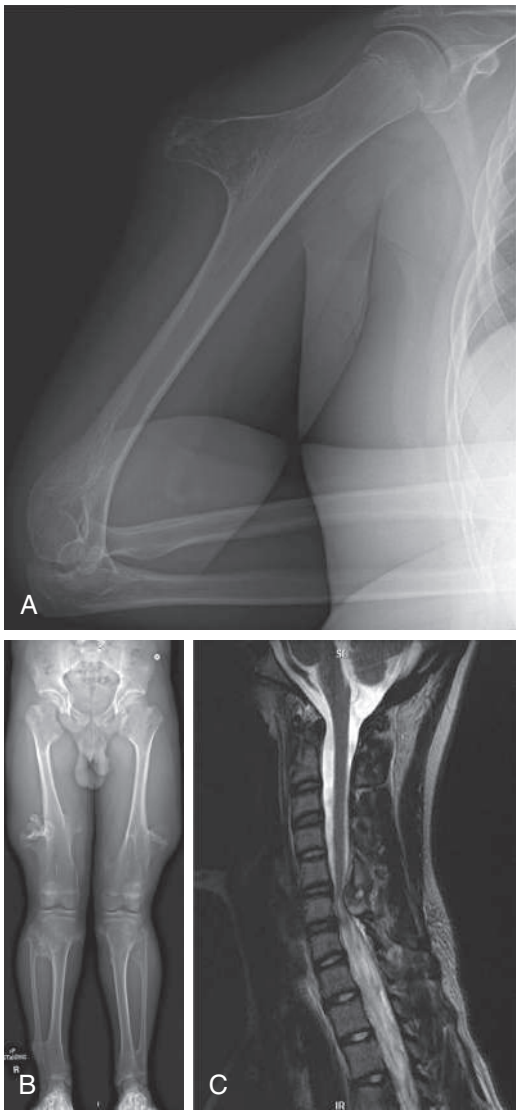

Fig. 550.5 A, Lateral radiograph of the right humerus showing isolated osteochondroma. Bone lesion is in continuity with the medullary canal and points away from the growth plate. B, Hip-to-ankle radiograph in a child with multiple hereditary exostoses (MHE) showing many osteochondromas about the knees and ankles. C, Sagittal T2 weighted MR image of the cervical spine in a 15-yr-old female with MHE who underwent routine cervical screening MRI, which detected asymptomatic spinal stenosis caused by C6 osteochondroma. She underwent urgent decompression.

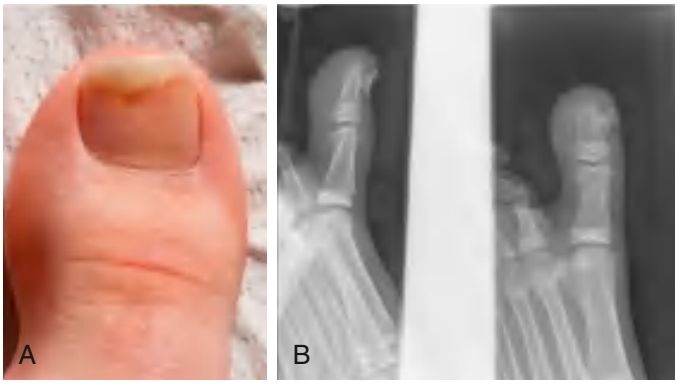

Fig. 550.6 A, Photograph of the great toe showing nailbed abnormality. B, Lateral and oblique views of the left great toe showing subungual exostosis. These lesions are typically painful and require surgical removal.

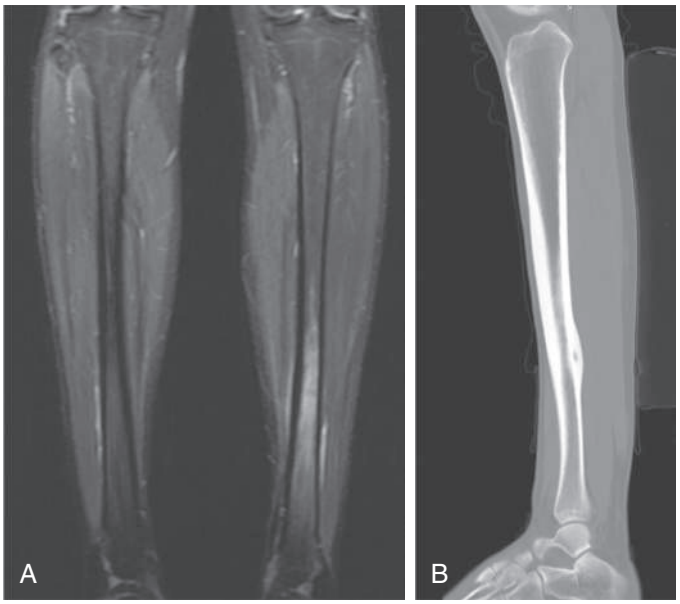

Fig. 550.7 MRI and CT in 15-yr-old female with left tibial night pain. A, Coronal T2 weighted MR of the bilateral tibias shows increased T2 signal change in the left tibia diaphysis. B, Sagittal CT scan shows cortically based lesion <1 cm typical for osteoid osteoma. Patient was treated with percutaneous radiofrequency ablation.

signal change throughout the region. Treatment is directed at removing the lesion. Patients may be treated with NSAIDs, and the symptoms typically resolve within 1-2 years. Most patients and families elect for treatment. Percutaneous treatments such as radiofrequency ablation and cryoablation have become the standard of care for routine lesions. There is still an occasional role for open surgical resection, if there is concern for osteomyelitis (Brodie's abscess), or the lesion is in close proximity to articular cartilage or neurovascular structures.

Osteoblastoma is a locally destructive, progressively growing lesion of bone with a predilection for the vertebrae, although almost any bone may be involved. Most patients note the insidious onset of dull aching pain, which may be present for months before patients seek medical attention. Spinal lesions can cause neurologic symptoms or deficits. The radiographic appearance is variable and less distinctive than that of other benign bone tumors. CT or MRI is indicated. Approximately 25% show features suggesting a malignant neoplasm, making biopsy necessary in many cases. Expansile spinal lesions often involve the posterior elements. Treatment involves curettage and bone grafting or en bloc excision; care must be taken to preserve nerve roots when treating spinal lesions. Surgical stabilization of the spine may be necessary.

Fibromas (nonossifying fibroma, fibrous cortical defect, metaphyseal fibrous defect) are fibrous lesions of bone that occur in up to 40% of children older than 2 years of age. They most likely represent a defect in ossification rather than a neoplasm and usually are asymptomatic. Most are discovered incidentally when radiographs are taken for other reasons, usually to rule out a fracture after trauma. Occasional pathologic fractures can occur through large lesions. Physical examination usually is unrevealing. Radiographs show a sharply marginated eccentric lucency in the metaphysis or metaphyseal cortex (Fig. 550.8). Lesions may be multilocular and expansile, with extension from the cortex into the medullary bone. The long axis of the lesion runs parallel to that of the bone. Approximately 50% are bilateral or multiple. Because of the characteristic radiographic appearance, most lesions do not require axial imaging, biopsy, or treatment. If the child is asymptomatic, no further monitoring is needed for characteristic lesions. Spontaneous regression can be expected after skeletal maturity. Curettage and bone grafting may be considered for symptomatic lesions or lesions occupying >50% of the bone diameter due to the risk of a pathologic fracture.

Fig. 550.8 Anteroposterior radiograph of the knee showing nonossifying fibroma, which was discovered incidentally.

Fig. 550.9 External rotation view of the left humerus in a 9-yr-old female who presented with pain after falling off her bicycle. Imaging is consistent with simple bone cyst.

Unicameral bone cysts can occur at any age in childhood but are rare in children younger than 3 years of age and after skeletal maturity. The cause of these fluid-filled lesions is unknown. Spontaneous resolution after skeletal maturity is expected, although pathologic fracture can be a significant problem in the interim. Diagnosis usually follows a pathologic fracture (Fig. 550.9). Such fractures can occur with relatively minor trauma, such as with throwing or catching a ball. Unicameral bone cysts appear radiographically as solitary, centrally located lesions within the medullary portion of the bone. These cysts are most common in the proximal humerus or femur. They often extend to (but not through) the physis and are sharply marginated. The cortex expands, but that does not exceed the width of the adjacent physis. Treatment involves allowing the pathologic fracture to heal. Subsequently, humerus lesions can be observed or treated. Proximal femoral lesions are typically treated due to the risk of pathologic fracture. Treatments include aspiration and injection with methylprednisolone or calcium phosphate. A randomized controlled trial (RCT) showed 42% healing rate with steroid injections (1-3, mean 1.7 injections) compared with injection of bone marrow aspirate (23% healing rate, 1-3 injections, 2.1 mean). Open biopsy and bone grafting with or without internal fixation can also be performed. Recurrence is common despite surgical treatment. Repeat injections are frequently necessary to treat recurrent lesions. Healing rates are higher with injection or surgical treatment compared with observation, and internal fixation is recommended for proximal femoral lesions given the high risk of fracture.

Fibrous dysplasia is a developmental abnormality characterized by fibrous replacement of cancellous bone. Lesions may be solitary or multifocal (polyostotic). Lesions may progress over time or may be stable. Some children are asymptomatic, although others have bone pain. Those with skull involvement might have swelling or exophthalmos. Pain and limp are characteristic of proximal femoral involvement, which also may indicate impending pathologic fracture. Limb-length discrepancy, bowing of the tibia or femur, and pathologic fractures may be presenting complaints. The triad of polyostotic disease, precocious puberty, and cutaneous pigmentation is known as McCune-Albright syndrome. Radiographic features of fibrous dysplasia include a lytic or ground-glass expansile lesion of the metaphysis or diaphysis. The lesion is sharply marginated and often is surrounded by a thick rim of sclerotic bone. Bowing, especially of the proximal femur, may be present. Treatment usually involves observation for asymptomatic lesions. Surgery is indicated for patients with progressive deformity, pain, or impending pathologic fractures. Bone grafting is not as successful in the treatment of fibrous dysplasia, because the lesion recurs within the grafted bone. Reconstructive surgical techniques with metal implants often are necessary to provide stability and treat pain, particularly in the proximal femur. In addition to surgical stabilization, bisphosphonate therapy has been used to treat bone pain, although a recent RCT showed improvement in regional bone mineral density but no change in pain scores.

LOCALLY AGGRESSIVE LESIONS

Aneurysmal bone cyst (ABC) is a reactive lesion of bone seen in persons younger than 20 years of age. The lesion is characterized by cavernous spaces filled with blood and solid aggregates of tissue. Although the femur, tibia, and spine are commonly involved, this progressively growing, expansile lesion can develop in any bone. Radiographs show eccentric lytic destruction and expansion of the metaphysis surrounded by a thin sclerotic rim of bone. Expansion of the bone frequently extends beyond the diameter of the physis. Pain and swelling are common. Spinal involvement can lead to cord or nerve root compression and associated neurologic symptoms, including paralysis. Posterior elements of the spine are involved more commonly than the vertebral body. Unlike most other benign bone tumors, which usually are confined to a single bone, ABCs can involve adjacent vertebrae. Spinal lesions can require stabilization after excision. As with other benign tumors, attempts are made to preserve nerve roots and other vital structures. Rapid growth is characteristic and can lead to confusion with malignant neoplasms (Fig. 550.10). ABCs can occur with concomitantly with neoplasms, confounding pathology results from biopsy. Treatment consists of percutaneous injection, curettage and bone grafting, or excision. Recurrence after surgical treatment occurs in 20–30% of patients, is more common in younger than older children, and usually occurs in the first 1-2 years after treatment. Treatment approaches also include percutaneously treatment with polidocanol or doxycycline, which targets the specific matrix metalloproteinase upregulation pathway seen in ABCs and has shown promising results.

CHARACTERISTIC LESIONS OF THE TIBIA

Osteofibrous dysplasia affects the tibia in children. Most children present with anterior swelling or enlargement of the leg. Radiographs show solitary or multiple lucent cortical diaphyseal lesions surrounded by sclerosis. Anterior bowing of the tibia often is present, and pathologic fracture can occur. The radiographic appearance closely resembles that

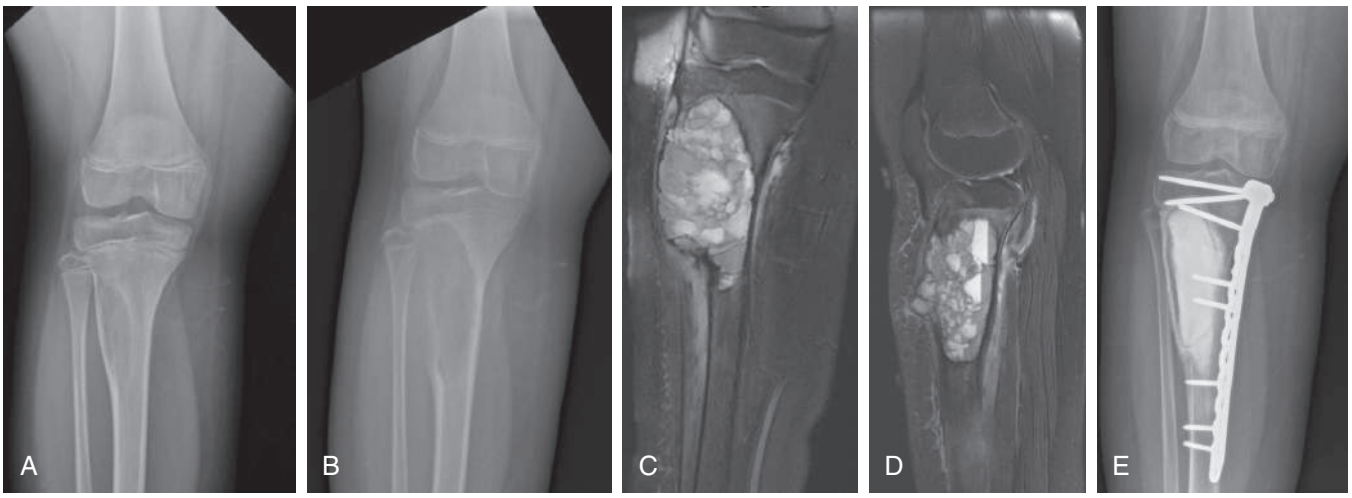

Fig. 550.10 Aneurysmal bone cyst. **A**, A 10-yr-old female presents with right tibia pain after playing softball. PA radiograph of the right proximal tibia reveals an eccentric, lytic lesion. **B**, Repeat imaging 4 months later shows rapid expansion. **C**, Coronal T2 MR image. **D**, Sagittal T2 MR image shows fluid-fluid levels classically seen with aneurysmal bone cysts. **E**, The patient was treated with curettage, bone grafting, and plate fixation to prevent fracture.

Table 550.3 Summary of Prognosis and Treatment of Vascular Bone Tumors

CLASSIFICATION	ENTITY	PROGNOSIS	TREATMENT
Benign	Hemangioma	100% survival, 0% metastasis	Treat symptoms
Intermediate	Epithelioid hemangioma	100% survival, 2% metastases, 9% local recurrence	Curettage or marginal excision
	Pseudomyogenic hemangioendothelioma	Limited follow-up, stable or progressive osseous disease	
Malignant	Epithelioid hemangioendothelioma	85% survival, 25% metastases	Wide resection
	Angiosarcoma	30% survival	Wide resection, consider systemic therapy

From van IJzendoorn DGP, Bovee JVMG. Vascular tumors of bone: the evolvement of a classification based on molecular developments. *Surg Pathol Clin.* 2017;10:621–635. Table 1.

of adamantinoma, a malignant neoplasm, making biopsy more common than with other benign bone tumors. Some believe osteofibrous dysplasia is a precursor lesion to adamantinoma. Treatment options include observation, excision and bone grafting, or wide resection.

Adamantinoma is a rare malignancy, typically found in adults, but occasionally in children. In contrast to osteofibrous dysplasia, the lesion involves the medullary canal. Resection is indicated, as there are no known benefits to radiation or chemotherapy for this slow-growing tumor.

Langerhans cell histiocytosis is a monostotic or polyostotic disease that can also involve the skin, liver, or other organs. Single-site disease should be distinguished from the other forms of Langerhans cell histiocytosis (Hand-Schüller-Christian or Letterer-Siwe variants), which can have a less favorable prognosis (see Chapter 556.1). Langerhans cell histiocytosis usually occurs during the first 3 decades of life and is most common in males 5-10 years of age. The skull is commonly affected, but any bone may be involved. Patients usually present with local pain and swelling. Marked tenderness and warmth often are present in the area of the involved bone. Spinal lesions can cause pain, stiffness, and occasional neurologic symptoms. Vertebra plana with uniform compression or flattening of the vertebral body is commonly but not always associated with Langerhans cell histiocytosis. The radiographic appearance of the skeletal lesions is similar in all forms of Langerhans cell histiocytosis but is variable enough to mimic many other benign and malignant lesions of bone as well as infection. The radiolucent lesions have well-defined or irregular margins with expansion of the involved bone and periosteal new bone formation. A skeletal survey is warranted as lesions may not be apparent on bone scan. Polyostotic involvement and the typical skull lesions strongly suggest the diagnosis of eosinophilic granuloma. Biopsy often is necessary to confirm the diagnosis because of the broad radiographic differential diagnosis. Treatment for isolated bone lesions includes curettage and bone grafting, or observation for asymptomatic lesions because most osseous lesions heal spontaneously and do not recur. All children with bone lesions should be evaluated for visceral involvement because multisystem organ disease may exist with the bone lesion and may not be obvious. Treatment of multisystem disease is more complex and often systemic and may require chemotherapy. For multisystem disease, bone lesions frequently improve with systemic chemotherapy, and operative treatment may not be necessary.

VASCULAR TUMORS OF BONE

There is a wide spectrum of vascular bone tumors (Table 550.3), which, depending on severity, may produce local sclerosis or osteopenia (see also Chapter 554). More severe lesions are locally aggressive and result in cortical destruction.

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Chapter 551

Retinoblastoma

Cynthia E. Herzog

Retinoblastoma is an embryonal malignancy of the retina and the most common intraocular tumor in children. Although the survival rate of children with retinoblastoma in the United States and developed countries is extremely high, retinoblastoma progresses to metastatic disease and death in >40% of children in low income countries. Furthermore, the associated loss of vision and side effects of therapy are significant problems that remain to be addressed.

EPIDEMIOLOGY

Approximately 200-300 new cases of retinoblastoma are diagnosed each year in the United States, with no known racial or gender predilection. The cumulative lifetime incidence of retinoblastoma is approximately 1 in 20,000 live births, and retinoblastoma accounts for 2% of all pediatric malignancies. The median age at diagnosis is approximately 2 years, and >90% of cases are diagnosed in children <5 years old. Overall, 66–75% of children with retinoblastoma have unilateral tumors, with the remainder having bilateral retinoblastoma. Bilateral involvement is more common in younger children, particularly in those diagnosed before age 1 year, and is always heritable. Risk of retinoblastoma may be increased in children conceived by in vitro fertilization.

Retinoblastoma can be either hereditary or sporadic. **Hereditary** cases usually are diagnosed at a younger age and are multifocal and bilateral, whereas **sporadic** cases are usually diagnosed in older children who tend to have unilateral, unifocal involvement. The hereditary form is associated with loss of function of the **retinoblastoma gene *(RB1)*** via a pathogenic variant or deletion. *RB1* is located on chromosome 13q14 and encodes the retinoblastoma protein, a tumor-suppressor protein that controls cell cycle phase transition and has roles in apoptosis and cell differentiation. Children with **13q deletion syndrome** are at increased risk to develop retinoblastoma. Many different causative pathogenic variants have been identified, including translocations, deletions, insertions, point pathogenic variants, and epigenetic modifications such as gene methylation. The nature of the predisposing pathogenic variant can affect the penetrance and expressivity of retinoblastoma development.

According to Knudson's "2-hit" model of oncogenesis, two pathogenic variant events are required for retinoblastoma tumor development (see Chapter 541). In the hereditary form of retinoblastoma, the first pathogenic variant in *RB1* is inherited through germinal cells, and a pathogenic variant occurs subsequently in somatic retinal cells. Second pathogenic variants that lead to retinoblastoma often result in the loss of the normal allele and concomitant loss of heterozygosity. Parents and siblings of a child with a germline pathologic genetic variant should be referred to a genetic specialist for testing; most children with hereditary retinoblastoma have spontaneous new germinal pathogenic variants, and both parents have wild-type retinoblastoma genes. All first-degree relatives of children with known or suspected hereditary retinoblastoma should have retinal examinations to identify retinomas or retinal scars, which may suggest hereditary retinoblastoma even though malignant retinoblastoma did not develop. In the sporadic form of retinoblastoma, the two pathogenic variants occur in somatic retinal cells. Heterozygous carriers of oncogenic *RB1* pathogenic variants demonstrate variable phenotypic expression.

PATHOGENESIS

Histologically, retinoblastoma appears as a small, round blue cell tumor with rosette formation **(Flexner-Wintersteiner rosettes)**. It may arise in any of the nucleated layers of the retina and exhibit various degrees of differentiation. Retinoblastoma tumors tend to outgrow their blood supply, resulting in necrosis and calcification.

Endophytic tumors arise from the inner surface of the retina and grow into the vitreous and can also grow as tumors suspended within the vitreous itself, known as **vitreous seeding**. *Exophytic* tumors grow from the outer retinal layer and can cause retinal detachment. Diffuse infiltrating tumors grow intraretinally and remain flat; these are less common and can cause iris neovascularization. Tumors can also be both endophytic and exophytic. These tumors can also spread by direct extension to the choroid or along the optic nerve beyond the lamina cribrosa to the central nervous system, or by hematogenous or lymphatic spread to distant sites, including bones, bone marrow, and lungs.

SCREENING

Children with a positive family history of retinoblastoma should undergo a dilated eye examination under general anesthesia early in life and at regular intervals until genetic testing is performed and results are available. Infants with a negative genetic test require no further screening; infants with a positive genetic test require regular screening ophthalmologic examinations until age 7 years.

CLINICAL MANIFESTATIONS

Retinoblastoma classically presents with **leukocoria,** a *white pupillary reflex*, which often is first noticed when a red reflex is not present at a routine newborn or well-child examination or in a flash photograph of the child (Fig. 551.1). Strabismus often is an initial presenting complaint. Decreased vision, orbital inflammation, hyphema, and pupil irregularity can occur with advancing disease. Pain can occur if secondary glaucoma is present. Only about 10% of retinoblastoma cases are detected by routine ophthalmologic screening in the context of a positive family history.

DIAGNOSIS

The diagnosis is established by the characteristic ophthalmologic findings of a chalky, white-gray retinal mass with a soft, friable consistency. Imaging studies are not diagnostic, and biopsies are contraindicated. Indirect ophthalmoscopy with slit-lamp evaluation can detect retinoblastoma tumors, but a complete evaluation requires an examination

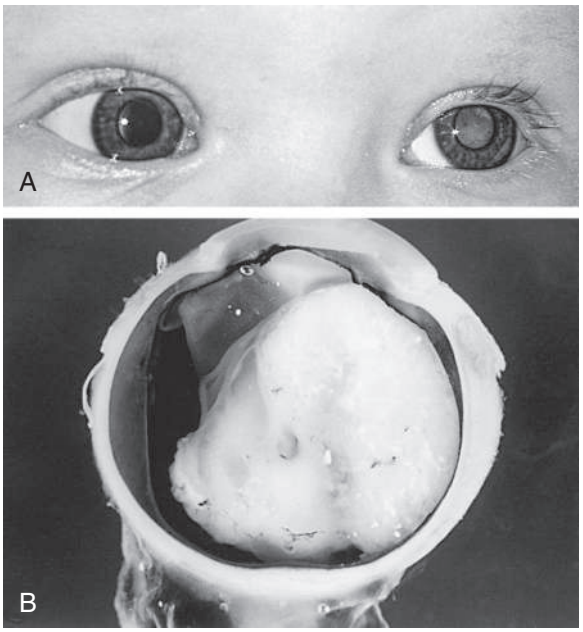

Fig. 551.1 A, Leukocoria noted in the left eye of a child presenting with retinoblastoma. B, A large white tumor mass noted within the posterior chamber of the enucleated eye. *(From Shields JA, Shields CL. Current management of retinoblastoma. Mayo Clin Proc. 1994;69:50–56.)*

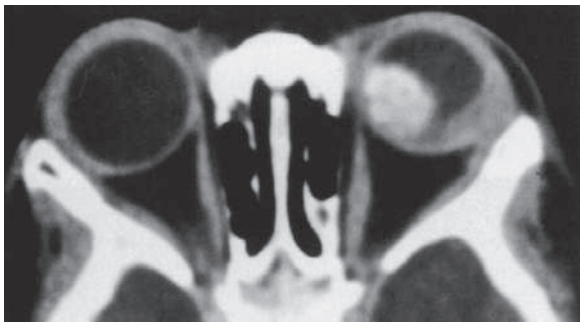

Fig. 551.2 Axial contrast-enhanced CT scan shows calcified retinoblastoma of the left eye. *(From Haaga JR, Boll DT, eds. CT and MRI of the Whole Body. 6th ed. Philadelphia: Elsevier; 2017. Fig. 20-32.)*

under general anesthesia by an experienced ophthalmologist to obtain complete visualization of both eyes, which also facilitates photographing and mapping of the tumors. Retinal detachment or vitreous hemorrhage can complicate the evaluation.

Orbital ultrasonography, CT, or MRI is used to evaluate the extent of intraocular disease and extraocular spread (Fig. 551.2). In approximately 5% of cases, a pineal area (primitive neuroectodermal) tumor is detected in a child with hereditary and bilateral retinoblastoma, a phenomenon known as **trilateral retinoblastoma**. MRI allows for better evaluation of optic nerve involvement. Metastatic disease is rarely present at diagnosis; evaluation of the cerebrospinal fluid and bone marrow for tumor metastasis and radionuclide bone scan are required only if indicated by other clinical, laboratory, or imaging findings.

The **differential diagnosis** of retinoblastoma includes other causes of leukocoria, including persistent hyperplastic primary vitreous, Coats disease, vitreous hemorrhage, cataract, endophthalmitis from *Toxocara canis*, choroidal coloboma, retinopathy of prematurity, and familial exudative vitreoretinopathy.

TREATMENT

Treatment is determined by the size and location of the tumors, if the disease is localized to the eye or has spread either to the brain or to the rest of the body, and whether the child has hereditary or sporadic disease. The primary goal of treatment is always cure; the secondary goals include preserving vision and the eye itself and decreasing the risk of late side effects, mainly secondary malignancies. With current modalities for local control of intraocular tumors and more effective systemic chemotherapy, primary enucleation is being performed less often.

Most unilateral disease presents with a solitary, large tumor. **Enucleation** is performed if useful vision cannot be salvaged. With bilateral disease, chemoreduction in combination with **focal therapy** (laser photocoagulation or cryotherapy) has replaced the traditional approach of enucleation of the more severely affected eye and irradiation of the remaining eye. If feasible, small tumors can be treated with focal therapy with careful follow-up for recurrence or new tumor growth. Larger tumors often respond to multiagent **chemotherapy**, including carboplatin, vincristine, and etoposide given intravenously. However, systemic therapy is generally reserved for patients with unilateral disease when high-risk features are noted after enucleation, or in very young patients with bilateral disease that are at higher risk of complications with intraarterial chemotherapy. The delivery of chemotherapy via the ophthalmic artery is becoming more common, as is delivery of intravitreal chemotherapy. If these approaches fail, **external-beam irradiation** should be considered, although this approach may result in significant orbital deformity and increased incidence of second malignancies in patients with germline *RB1* pathologic genetic variants. **Brachytherapy**, or *episcleral plaque radiotherapy,* is an alternative with less morbidity. Enucleation may be required for unresponsive or recurrent tumors. Intense multiagent chemotherapy with autologous stem cell rescue may be used for patients with metastatic disease.

PROGNOSIS

Approximately 95% of U.S. children with retinoblastoma are cured with modern treatment. Current efforts using chemotherapy in combination with focal therapy are intended to preserve useful vision and avoid external-beam radiation or enucleation. Unfortunately, the diagnosis of retinoblastoma in many children from resource-poor countries is delayed, resulting in spread of the tumor outside the orbit. The prognosis for children with retinoblastoma that has spread outside the eye is poor. Trilateral retinoblastoma, disease involving both eyes and the pineal region, is almost universally fatal.

Children with germline *RB1* pathologic genetic variants are at significant risk for development of *second malignancies*, especially osteosarcoma, as well as soft tissue sarcomas and malignant melanoma. The risk of second malignancies is further increased by the use of radiation therapy. Other radiation-related late adverse effects include cataracts, orbital growth deformities, lacrimal dysfunction, and late retinal vascular injury.

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Chapter 552

Gonadal and Germ Cell Neoplasms

Cynthia E. Herzog and Winston W. Huh

EPIDEMIOLOGY

Malignant **germ cell tumors (GCTs)** and gonadal tumors are rare, with an incidence of 12 cases per 1 million persons younger than 20 years. Most malignant tumors of the gonads in children are GCTs. The incidence varies according to age and sex, although the incidence of GCTs in adolescent males has increased over time. **Sacrococcygeal** tumors occur predominantly in infant females. **Testicular** GCTs occur predominantly before age 4 years and after puberty. Klinefelter syndrome is associated with an increased risk of **mediastinal** GCTs. Trisomy 21, undescended testes, infertility, testicular atrophy, testicular microlithiasis, testicular dysgenesis syndrome, and inguinal hernias are associated with an increased risk of **testicular cancer**. The risk of testicular cancer in patients with cryptorchidism is reduced but not eliminated if orchiopexy is performed before 13 years of age. The risk of testicular GCT is increased in first-degree relatives and is highest among monozygotic twins.

PATHOGENESIS

The GCTs and non-GCTs arise from primordial germ cells and coelomic epithelium, respectively. Testicular and sacrococcygeal GCTs arising during early childhood characteristically have deletions at chromosome arms 1p and 6q and gains at 1q, and they lack the isochromosome 12p that is highly characteristic of malignant GCTs of adults. Testicular GCTs also may demonstrate loss of imprinting. Ovarian GCTs from older females characteristically have deletions at 1p and gains at 1q and 21. Dysregulation of microRNAs have been linked to GCTs. Because GCTs may contain benign and mixed malignant elements in different areas of the tumor, extensive sectioning is essential to confirm the correct diagnosis. The many histologically distinct subtypes of GCTs include **teratoma** (mature and immature), endodermal sinus tumor, and embryonal carcinoma (Fig. 552.1). Non-GCTs of the

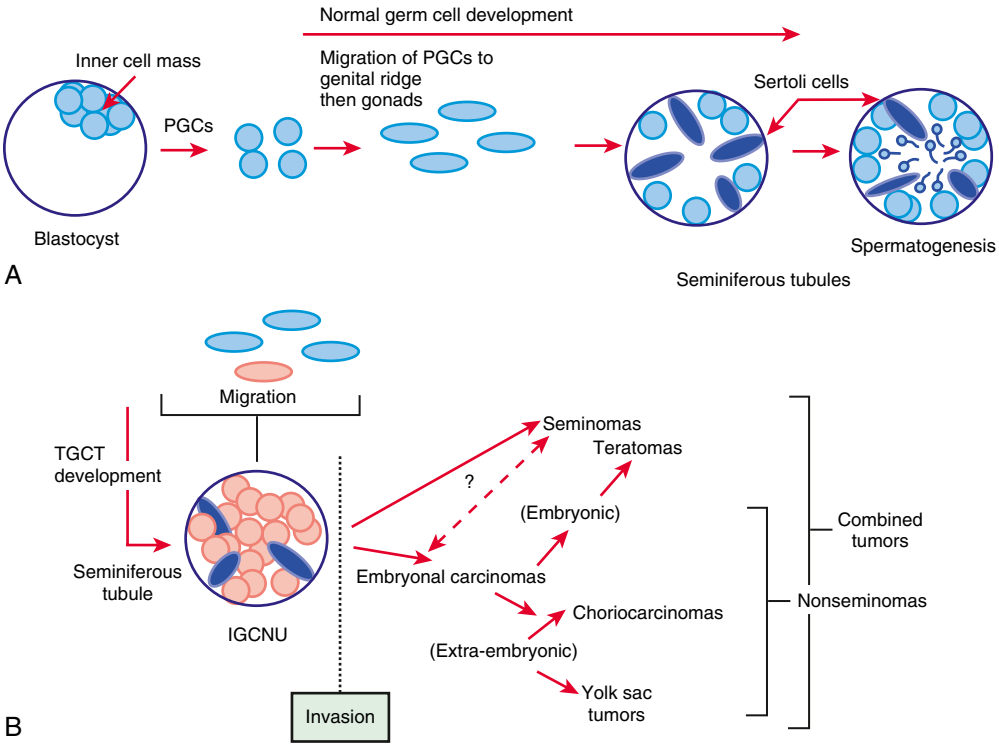

Fig. 552.1 A, Normal germ cell development. B, Model for the origin and histogenesis of different subtypes of testicular germ cell tumors. IGCNU, Intratubular germ cell neoplasia unclassified; PGCs, primary germ cells; TGCT, testicular germ cell tumor.

Table 552.1 Main Histologic Types of Testicular Germ Cell Tumors*

NONINVASIVE GERM CELL NEOPLASIA
Germ cell neoplasia in situ (GCNIS; previous synonyms: carcinoma in situ testis, intratubular germ cell neoplasia unclassified)
Gonadoblastoma (in patients with disorders of sex development; tumor also contains sex cord–stromal elements)
GERM CELL TUMORS DERIVED FROM GCNIS
Seminoma
Nonseminoma (nonseminomatous germ cell tumors)
Embryonal carcinoma
Teratoma (postpubertal type)
Yolk sac tumor (postpubertal type)
Choriocarcinoma and other trophoblastic tumors
GERM CELL TUMORS UNRELATED TO GCNIS
Childhood tumors
Teratoma (prepubertal type)
Yolk sac tumor (prepubertal type)
Spermatocytic tumor (median age at diagnosis: approximately 50 yr)

*Based on updated WHO classification of tumors of the testis and paratesticular tissue. Adapted from Raypert-De Meyts E, McGlynn KA, Okamoto, et al. Testicular germ cell tumours, *Lancet* 2016;387:1762–1770.

ovary include epithelial (serous and mucinous) and sex cord–stromal tumors; non-GCTs of the testicle include sex cord–stromal (e.g., Leydig cell, Sertoli cell) tumors. *DICER1* pathogenic variants have been observed in nonepithelial ovarian cancers, especially in Sertoli-Leydig tumors. Table 552.1 provides a histologic classification of testicular GCTs.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The clinical presentation of germ cell neoplasms depends on location (Table 552.2). Ovarian tumors often are quite large by the time they are diagnosed (Fig. 552.2). Extragonadal GCTs occur in the midline, including the suprasellar region, pineal region, neck, mediastinum, and retroperitoneal and sacrococcygeal areas (Fig. 552.3). Symptoms relate to mass effect, but the intracranial GCTs often present with anterior and posterior pituitary deficits (see Chapter 546).

The serum α-fetoprotein **(AFP)** level is elevated with endodermal sinus tumors and may be minimally elevated with teratomas (Table 552.3). Infants normally have higher levels of AFP, which usually falls to normal adult levels by about age 8 months; consequently, high AFP levels must be interpreted with caution in this age-group. Elevation of the β subunit of human chorionic gonadotropin (β-**hCG**), which is secreted by syncytiotrophoblasts, is seen with choriocarcinoma and germinomas. Lactate dehydrogenase, although nonspecific, may be a useful marker. If elevated, these markers provide important confirmation of the diagnosis and provide a means for risk stratification and to monitor the patient for tumor response and recurrence. Both serum and cerebrospinal fluid (CSF) should be assayed for these markers in patients with intracranial lesions. MicroRNA-371 is a superior tumor marker in GCT, but its use is still limited.

Diagnosis begins with physical examination and imaging studies, including plain radiographs of the chest and ultrasonography of the abdomen. CT or MRI can further delineate the primary tumor. If germ cell malignancy is strongly suggested, preoperative staging with CT of the chest and bone scan is appropriate. Primary surgical resection is indicated for tumors deemed resectable. For older patients with testicular tumors, ipsilateral retroperitoneal lymph node sampling may be required to determine extent of the disease and aid in treatment planning. Ovarian tumors also require detailed surgical evaluation, including lymph node removal and pelvic washings for cytologic analysis for peritoneal spread. Diagnosis of intracranial lesions can be established with imaging and AFP or β-hCG determinations of serum and CSF.

Gonadoblastomas often occur in patients with gonadal dysgenesis and all or parts of a Y chromosome. **Gonadal dysgenesis** is characterized by failure to fully masculinize the external genitalia. If this syndrome is diagnosed, imaging of the gonad with ultrasonography or CT is performed, and surgical resection of the tumor usually is curative. Prophylactic resection of dysgenetic gonads at the time of diagnosis is recommended, because gonadoblastomas, some of which contain malignant GCT elements, often develop. Gonadoblastomas may produce abnormal amounts of estrogen.

Table 552.2 Clinical Features of Germ Cell Tumors

	CLINICAL FEATURES	
TUMOR TYPE	**FEMALE**	**MALE**
Mature/immature teratoma	Abdominal pain, abdominal mass 10% bilateral Gliomatosis peritonei does not affect prognosis	Nontender scrotal mass Excellent survival with surgery alone in prepubertal males
Dysgerminoma/seminoma	Rapidly developed intraabdominal mass 20% bilateral 14–25% mixed with other germ cell elements	Virtually not seen in children, most common testicular tumor in adult males. Most patients present in their 30s
YST	Most common malignant histology 75% stage I	Most common malignant histology, most pediatric tumors are pure YST 85% stage I
Embryonal carcinoma	Associated with precocious puberty, amenorrhea, and hirsutism	Higher incidence of metastatic disease at presentation, patients can present with retroperitoneal mass
Choriocarcinoma	Rare in children, when present in infants related to maternal metastatic disease	Frequent pulmonary metastatic disease at presentation, patients can present with hemoptysis due to hemorrhage of metastases
Gonadoblastoma	Associated with gonadal dysgenesis Presents mostly in phenotypical females with a Y chromosome	Very rare

YST, Yolk sac tumor.
Modified from Fonseca A, Olson TA. Extracranial germ cell tumors. In: Fish JD, Liptin JM, Lanzkowsky P, eds. *Lanzkowsky's Manual of Pediatric Hematology and Oncology*. 7th ed. London: Elsevier; 2022: Table 28.2, p. 600.

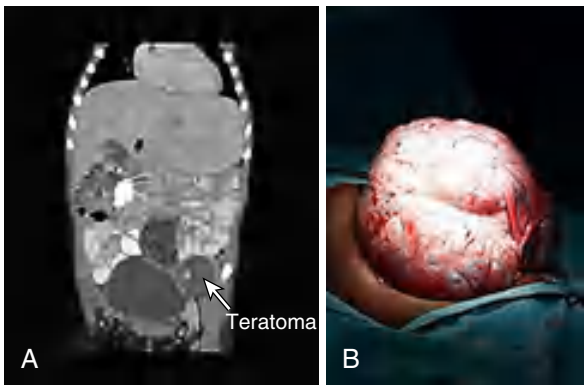

Fig. 552.2 A, Postnatal MR image showing a left ovarian teratoma with bony calcification. B, Massive ovarian teratoma. *(From Lakhoo K. Neonatal teratomas. Early Hum Dev. 2010;86:643–647.)*

Table 552.3 Serum Tumor Marker Levels for Pediatric GCTs

GCT TYPE	AFP	β-hCG	LDH
MT	-	-	-
IT	+/–	-	+/–
Seminoma/dysgerminoma	-	-	+
Yolk sac tumor	+	-	-
Choriocarcinoma	-	+	-
Embryonal carcinoma	+	+	+/–

+, Usually elevated; +/–, may be elevated; -, usually not elevated.
GCT, Germ cell tumor; AFP, α-fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; MT, mature teratoma; IT, immature teratoma.
From Weil BR, Billmire DF. Management of germ cell tumors in pediatric patients. *Surg Oncol Clin N Am*. 2021;30:325–338. Table 1.

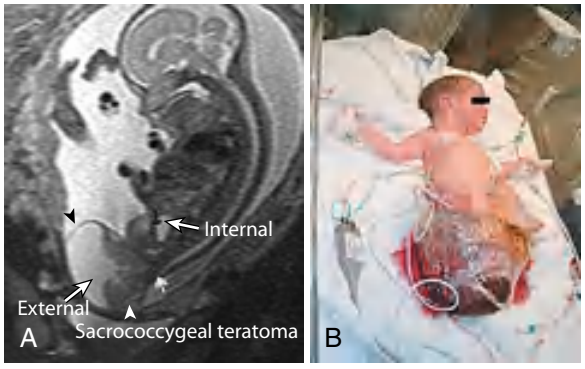

Fig. 552.3 A, Prenatal MR image showing sacrococcygeal teratoma with a small internal and large external component. B, Postnatal large, bleeding sacrococcygeal teratoma. *(From Lakhoo K. Neonatal teratomas. Early Hum Dev. 2010;86:643–647.)*

Teratomas occur in many locations, presenting as masses. They are not associated with elevated markers unless malignancy is present. The sacrococcygeal region is the most common site for teratomas. Sacrococcygeal teratomas occur most commonly in infants and may be diagnosed in utero or at birth, with most found in girls. The rate of malignancy in this location varies, ranging from <10% in children younger than 2 months to >50% in children older than 4 months.

Germinomas occur intracranially, in the mediastinum, and in the gonads. In the ovary, they are called **dysgerminomas,** and in the testis, they are called **seminomas.** They usually are tumor-marker–negative masses despite being malignant. Endodermal sinus or yolk sac tumor and choriocarcinoma appear highly malignant by histologic criteria. Both occur at gonadal and extragonadal sites. Embryonal carcinoma most often occurs in the testes. Choriocarcinoma and embryonal carcinoma rarely occur in the pure form and are usually found as part of a mixed malignant GCT.

Non–germ cell gonadal tumors are very uncommon in pediatrics and occur predominantly in the ovary. Epithelial carcinomas (usually an adult tumor), Sertoli-Leydig cell tumors, and granulosa cell

tumors may occur in children. Carcinomas account for ~30% of ovarian tumors in females <20 years old; most of these occur in older teens and are of the serous or mucinous subtype. **Sertoli-Leydig cell tumors** and **granulosa cell tumors** produce hormones that can cause virilization, feminization, or precocious puberty, depending on pubertal stage and the balance between Sertoli cells (estrogen production) and Leydig cells (androgen production). Diagnostic evaluation usually focuses on the chief complaint of inappropriate sex steroid effect and includes hormone measurements, which reflect gonadotropin-independent sex steroid production. Appropriate imaging also is performed to rule out a functioning gonadal tumor. Surgery usually is curative. No effective therapy for nonresectable disease has been found.

TREATMENT

Complete surgical excision of the tumor usually is indicated, except for patients with intracranial tumors, for whom the primary therapy consists of radiation therapy and chemotherapy. For testicular tumors, an inguinal approach is indicated, and complete resection should include the entire spermatic cord. When complete excision cannot be accomplished, preoperative chemotherapy is indicated, with second-look surgery, especially if retroperitoneal lymph node enlargement persists. For teratomas, both mature and immature, and completely resected malignant tumors of the testes and ovary, surgery alone is the treatment. For ovarian tumors, unless the contralateral ovary is obviously also involved by tumor, a fertility-sparing surgery should be performed. Cisplatin-based chemotherapy regimens usually are curative in GCTs that cannot be completely resected, even if metastases are present. However, sex cord–stromal tumors tend to be refractory to chemotherapy. Except for GCTs of the central nervous system, radiation therapy is limited to those tumors that are not amenable to complete excision and are refractory to chemotherapy. High-dose chemotherapy followed by autologous stem cell rescue is an option in those with refractory disease.

PROGNOSIS

The overall cure rate for children with GCTs is >80%. Age is the most predictive factor of survival for extragonadal GCTs. Children >12 years old have a fourfold higher risk of death and a sixfold higher risk if the tumor is thoracic. Histology has minimal effect on prognosis. Patients with nonresected extragonadal GCTs have a slightly worse prognosis.

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Chapter 553

Neoplasms of the Liver

Fiorela N. Hernandez Tejada and Cynthia E. Herzog

Hepatic tumors are rare in children. Primary tumors of the liver account for approximately 1% of malignancies in children younger than 15 years, with an annual incidence of 1.5 cases per 1 million children in the United States (Table 553.1). Between 50% and 60% of hepatic tumors in children are malignant, with >65% of these malignancies being **hepatoblastomas** and most of the remainder being **hepatocellular carcinomas (HCCs)**. Rare **hepatic malignancies** include embryonal sarcoma, angiosarcoma, malignant germ cell tumor, rhabdomyosarcoma of the liver, and undifferentiated sarcoma. More common childhood malignancies, such as neuroblastoma, Wilms tumor, and lymphoma, can metastasize to the liver. **Benign liver tumors**, which usually present in the first 6 months of life, include hemangiomas, hamartomas, and hemangioendotheliomas.

Table 553.1 Pediatric Liver Tumors Consensus Classification

Epithelial tumors Hepatocellular	**Benign:** Hepatocellular adenoma, focal nodular hyperplasia (FNH), regenerative nodules, and dysplastic nodules **Malignant:** Hepatoblastoma (various types), hepatocellular carcinoma (classic HCC and fibrolamellar HCC), hepatocellular malignant neoplasm not otherwise specified (NOS)
Biliary	**Benign:** Bile duct adenoma, biliary hamartoma **Malignant:** Cholangiocarcinoma, combined HCC-cholangiocarcinoma
Mesenchymal tumors	**Benign:** Hemangioma, mesenchymal hamartoma **Malignant:** Embryonal sarcoma, rhabdomyosarcoma, malignant vascular tumors (epithelioid hemangioendothelioma, angiosarcoma)
Other rare malignancies	Malignant rhabdoid tumor, germ cell tumors, desmoplastic small round cell tumor, peripheral primitive neuroectodermal tumor
Metastases (and secondary)	From solid tumors: neuroblastoma, Wilms, acute myeloid leukemia, Langerhans cell histiocytosis, hemophagocytic lymphohistiocytosis

Modified from Chavhan GB, Siddiqui I, Ingley KM, Gupta AA. Rare malignant liver tumors in children. *Pediatr Radiol*. 2019;49:1404–1421. Table 1.

HEPATOBLASTOMA

Epidemiology

Approximately 100 new cases of hepatoblastoma are diagnosed each year in the United States. The incidence of hepatoblastoma has increased over the last 30 years by as much as 2.7% per year, probably related to increasing survival of very low birthweight premature infants. Hepatoblastoma occurs predominantly in children <3 years old, and the median age of diagnosis is 1 year. The etiology is unknown. Hepatoblastomas are associated with **familial adenomatous polyposis**. Alterations in the antigen-presenting cell/β-catenin pathway have been found in most of the tumors evaluated. Hepatoblastomas are also associated with **Beckwith-Wiedemann syndrome** (BWS), **hemihyperplasia**, and other somatic overgrowth syndromes. Increased expression of insulin-like growth factor 2 secondary to genetic pathogenic variants or epigenetic changes is implicated in hepatoblastoma development in patients with BWS. All children with BWS or hemihyperplasia should be routinely screened with α-fetoprotein (AFP) levels and abdominal ultrasounds. Prematurity/low birthweight is associated with increased incidence of hepatoblastoma, with the risk increasing as birthweight decreases. Aicardi syndrome, trisomy 18, other trisomies, Li-Fraumeni syndrome, Prader-Willi syndrome, Alagille syndrome, glycogen storage disease (type 1), Simpson-Golabi-Behmel syndrome, and fetal alcohol syndrome have also been associated with increased risk of hepatoblastoma.

Pathogenesis

Hepatoblastoma arises from precursors of hepatocytes and is histologically classified as *whole epithelial* type, containing fetal or embryonal malignant cells (either as a mixture or as pure elements), and *mixed* type, containing both epithelial and mesenchymal elements. Histologic classification has a direct correlation with clinical outcome. *Pure fetal histology* and low mitotic activity predicts the best outcome, and the *small cell undifferentiated* subtype associated with normal AFP levels predicts the worse outcome.

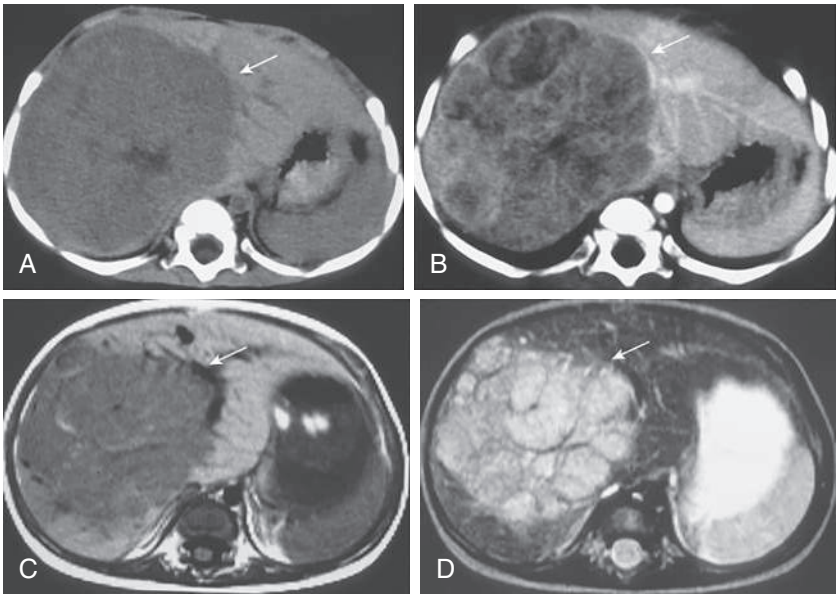


Fig. 553.1 Hepatoblastoma in a 3-yr-old child. **A,** Precontrast CT scan shows well-demarcated, heterogeneous hypodense mass *(arrow).* **B,** Postcontrast CT scan shows heterogeneous internal enhancement *(arrow).* **C** and **D,** The mass *(arrow)* demonstrates heterogeneous hypointensity on T1-weighted **(C)** and hyperintensity on T2-weighted **(D)** MR images.

Clinical Manifestations

Hepatoblastoma usually presents as a large, asymptomatic abdominal mass, with no associated systemic symptoms. Jaundice is uncommon. It arises from the right lobe three times more often than the left and usually is unifocal. When the disease progresses, fatigue, fever, weight loss, anorexia, vomiting, and abdominal pain may ensue. Rarely, hepatoblastoma presents with hemorrhage secondary to trauma or spontaneous rupture. Metastatic spread of hepatoblastoma most often involves regional lymph nodes and the lungs.

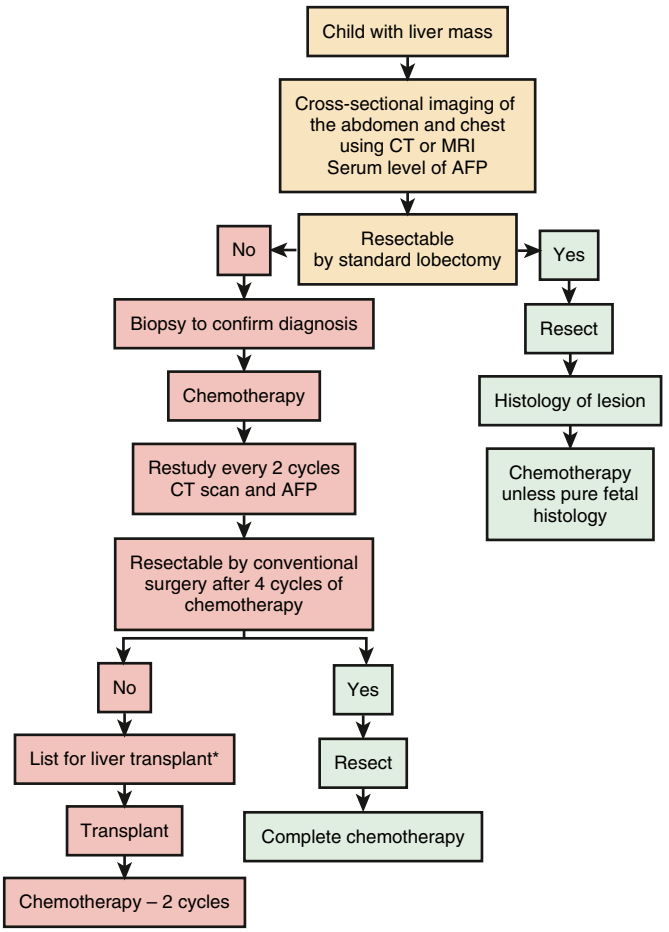
Diagnosis

A biopsy of liver tumors is necessary to establish the diagnosis. A valuable serum tumor marker, AFP, is used in the diagnosis and monitoring of hepatic tumors. AFP is normally elevated in the newborn period and then declines to <10 ng/mL by 1 year of age. The AFP levels are elevated in almost all hepatoblastomas. Bilirubin and liver enzymes usually are normal. Anemia is common, and thrombocytosis occurs in approximately 30% of patients. Serologic testing for hepatitides B and C should be performed, but the results usually are negative in hepatoblastoma.

Diagnostic imaging should include plain radiographs and ultrasonography of the abdomen to characterize the hepatic mass. US can differentiate malignant hepatic masses from benign vascular lesions. Either CT or MRI is an accurate method of defining the extent of intrahepatic tumor involvement and the potential for surgical resection. Evaluation for metastatic disease should include CT of the chest (Fig. 553.1).

Treatment

Treatment is guided by the degree of local tumor burden determined by the pre- and posttreatment extent of disease. In general, the cure of malignant hepatic tumors in children depends on complete resection of the primary tumor (Fig. 553.2); as much as 85% of the liver can be resected, with hepatic regeneration noted within 3-4 months after surgery. Treatment of hepatoblastoma is based on surgery and **systemic chemotherapy** using cisplatin in combination with vincristine and 5-fluorouracil (5-FU), and for intermediate- and high-risk patients, doxorubicin is also used. The role of **radiation therapy** is questionable, because the effective antitumor dose exceeds the hepatic tolerance. Radiation therapy may have a role in shrinking unresectable disease or managing incompletely resected tumors. In 30% of cases, tumors are resectable at diagnosis; a safe attempt for initial gross total resection should be made, followed by adjuvant chemotherapy. Unresectable tumors with or without metastatic disease at presentation usually respond to chemotherapy; preresection chemotherapy is indicated, and excision of the primary tumor and



*Consider continuation of chemotherapy or living-related liver transplantation if cadaveric liver transplant not available in a timely fashion

Fig. 553.2 Algorithm for the management of a child who presents with a hepatoblastoma. AFP, α-Fetoprotein. *(From Tiao GM, Bobey N, Allen S, et al. The current management of hepatoblastoma: a combination of chemotherapy, conventional resection, and liver transplantation. J Pediatr. 2005;146:204–211.)*

extrahepatic disease should be attempted as soon as it becomes feasible, followed by additional chemotherapy. Orthotopic **liver transplant** is a viable option for unresectable primary hepatic malignancies and results in good long-term survival. The pretransplant medical condition is an important predictor of outcome, and thus transplant is much more effective as the primary surgery than as salvage therapy. Alternative treatment options currently under investigation include other systemic chemotherapy agents such as carboplatin, ifosfamide, etoposide, irinotecan, and temsirolimus. Other treatment approaches include transarterial chemoembolization, cryoablation, and radiofrequency ablation (RFA).

Prognosis

In low-stage tumors, survival rates >90% can be achieved with multimodal treatment, including surgery and adjuvant chemotherapy. With tumors unresectable at diagnosis, survival rates of approximately 60% can be obtained. Metastatic disease further reduces survival, but complete regression of disease often can be obtained with chemotherapy and surgical resection of the primary tumor and isolated pulmonary metastatic disease, resulting in survival rates of approximately 25%. Treatment-related long-term adverse effects include cardiac toxicity with doxorubicin and renal and ototoxicity with cisplatin.

HEPATOCELLULAR CARCINOMA

Epidemiology

HCC occurs mostly in adolescents and often is associated with perinatal acquired hepatitis B infection and tyrosinemia. It is more common in East Asia and other areas where hepatitis B is endemic; the incidence has decreased following the introduction of hepatitis B vaccination. In these areas, HCC also tends to occur in a bimodal pattern, with the younger age peak overlapping the age of hepatoblastoma presentation. HCC also occurs in the chronic form of glycogen storage disease, α_1-antitrypsin deficiency, biliary atresia, progressive familial intrahepatic cholestasis, Alagille syndrome, congenital portosystemic shunts, Budd-Chiari syndrome, status postirradiation for liver metastatic Wilms tumor, and with other liver diseases producing chronic inflammation or cirrhosis (Fig. 553.3).

Pathogenesis

Pediatric HCC arises in cirrhotic and noncirrhotic backgrounds and presents as a multicentric, invasive tumor consisting of large pleomorphic cells of epithelial origin. Compared to adults, cirrhosis in children is less common, and congenital liver disorders are more common. HCCs are classified as **classical** or **fibrolamellar**. The fibrolamellar variant occurs more often in adolescent and young adult patients, is not associated with cirrhosis, and represents one fourth of the pediatric

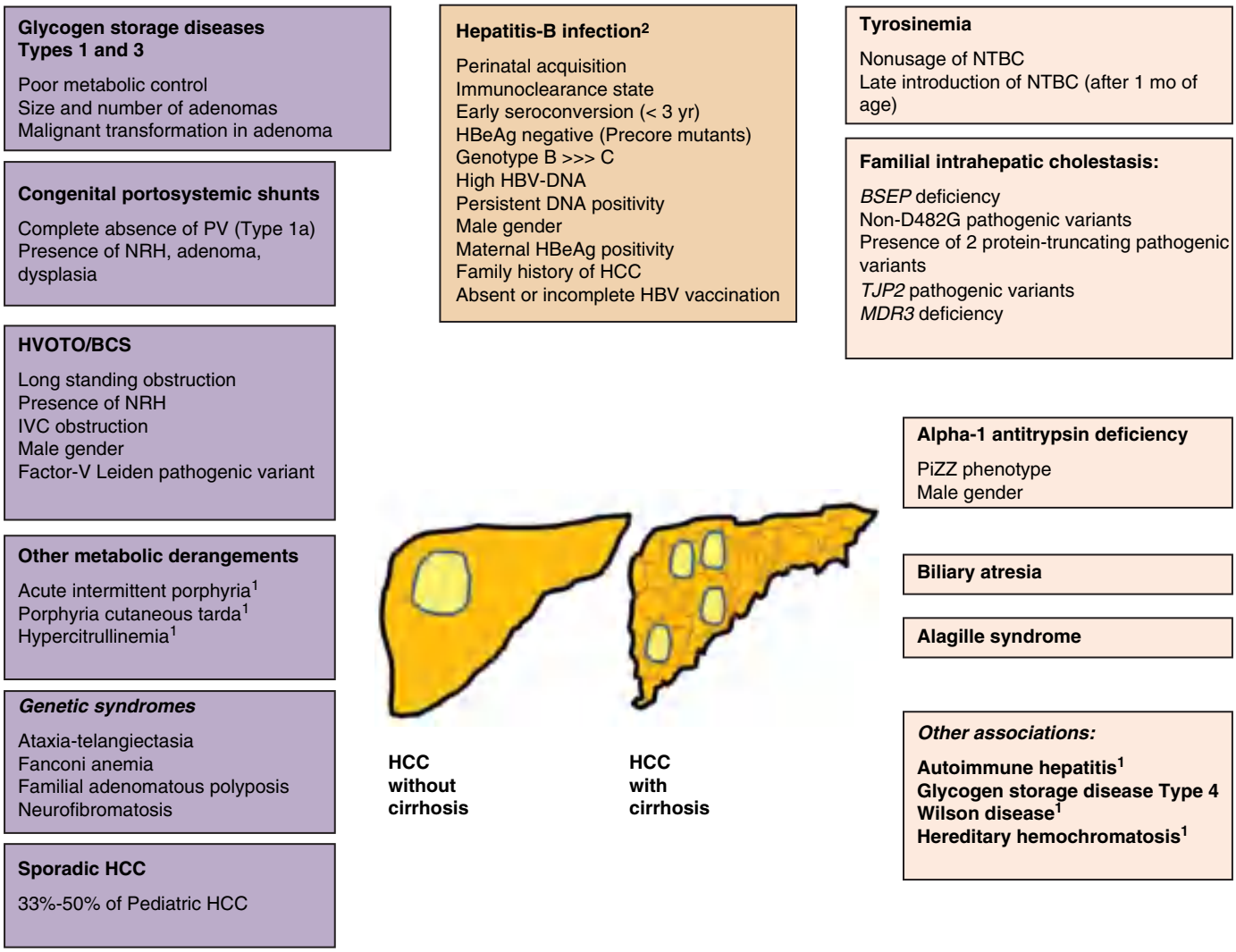


Fig. 553.3 Risk factors for pediatric hepatocellular carcinoma (HCC). [1]Conditions cause HCC in adults, and very rarely in children; [2]Hepatitis B virus (HBV)-related HCC may occur in the presence or absence of cirrhosis. BCS, Budd-Chiari syndrome; HVOTO, hepatic venous outflow tract obstruction; IVC, inferior vena cava; NRH, nodular regenerative hyperplasia; BSEP, bile salt export pump; MDR3, multidrug resistance protein-3; NTBC, [2-(2-nitro4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (Nitisinone); PiZZ, homozygous PiZ phenotype of α_1-antitrypsin; PV, Portal vein; TJP: tight junction protein. *(From Khanna R, Verma SK. Pediatric hepatocellular carcinoma. World J Gastroenterol. 2018;24[35]:3980–3999. Fig. 1.)*

HCC cases. This variant has been reported to have a distinct translocation, *DNAJB1-PRKACA*. A rare subtype called **transitional liver tumor** occurs in older children and has clinical and histopathologic findings of both hepatoblastoma and HCC.

Clinical Manifestations

HCC usually presents as a hepatic mass with abdominal distention and symptoms of anorexia, weight loss, jaundice, and abdominal pain. HCC can present as an acute abdominal crisis with rupture of the tumor and hemoperitoneum. Metastatic spread usually involves regional lymph nodes and the lungs. The AFP level is elevated in approximately 60% of children with conventional HCC, but not in the fibrolamellar variant. Evidence of hepatitis B usually is found in endemic areas but not in Western countries or with the fibrolamellar type. Liver enzymes may be abnormal.

Diagnostic imaging should include plain radiographs and US of the abdomen to characterize the hepatic mass. US can differentiate malignant hepatic masses from benign vascular lesions. Either CT or MRI is an accurate method of defining the extent of intrahepatic tumor involvement and the potential for surgical resection. Evaluation for metastatic disease should include CT of the chest.

Treatment

Complete tumor resection is crucial for curative treatment. Because of the multicentric origin of HCC and underlying liver disease, complete resection is accomplished in only 20–30% of cases. A gross total resection should be attempted at diagnosis when possible; if not, neoadjuvant chemotherapy should be given to convert nonresectable tumors into resectable ones. Combination chemotherapy following surgery is necessary. For unresectable tumors, **chemotherapy** followed by surgical assessment is essential, and **liver transplant** should be decided individually for each patient with HCC. Chemotherapy, including cisplatin, carboplatin, doxorubicin, and etoposide, has shown activity against this tumor, but improved long-term outcome has been difficult to achieve if tumor is not completed resected. **Sorafenib**, a small inhibitor of several tyrosine protein kinase showed antitumoral activity in adult patients with HCC, and initial studies have been published in the pediatric population with encouraging results. Other techniques are under study in adults, including cryosurgery, RFA, transarterial chemoembolization, and radiation therapy.

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Chapter 554

Complex Vascular Anomalies

Alexandra J. Borst and Denise M. Adams

Vascular anomalies in children encompass a spectrum of disorders that may be divided into **vascular malformations** and vascular tumors (Tables 554.1-554.4; see Chapter 691). **Vascular malformations** are developmental disorders of blood vessel formation. Malformations do not regress; rather, they slowly enlarge. They should be named after the predominant vessel(s) forming the lesion: arterial, capillary, lymphatic, or venous, or combinations of these (see Table 554.1). Vascular tumors exhibit endothelial cell hyperplasia and proliferation. The International Society for the Study of Vascular Anomalies (ISSVA) continues to update the classification structure for vascular disorders as new disorders are identified and as the biology and genetic causes for established disorders are found. The complete classification, associated syndromes, and causative pathogenic variants can be found at www.issva.org. The discovery of the molecular basis of many **vascular malformations** and tumors has allowed for improved understanding of the etiology of these disorders as well as new **targeted therapeutic approaches** for management.

GENETIC BASIS FOR VASCULAR ANOMALIES

Two key intracellular signaling pathways have been implicated in the pathogenesis of most **vascular malformations**, syndromes, and tumors. The RAS/MAPK and PI3K/AKT/mTOR pathways are crucial for cell cycle regulation, proliferation, and migration (Fig. 554.1). Pathogenic, *somatic* variants in the *PIK3CA* gene have been identified in patients with **venous malformations**, **lymphatic malformations**, and several vascular anomalies and overgrowth syndromes (see Table 554.4). Pathogenic variants in the RAS/MAPK pathway have been identified in **capillary and arteriovenous malformations (AVMs)**, central conducting lymphatic anomalies, as well as many of the vascular tumors.

Discovery of the molecular basis for **vascular malformations** and tumors has led to the ability to find **targeted therapies** for management of these conditions. **Sirolimus** has been utilized successfully in vascular malformations and tumors. The identification of the crucial role of *PIK3CA* pathogenic variants in vascular anomalies has led to the investigation of **PI3K inhibitors** as important targeted therapies. Agents that target the RAS/MAPK pathway, such as **MEK inhibitors**, have also been trialed in complicated AVMs as well as Kaposiform lymphangiomatosis (KLA).

COMPLEX LYMPHATIC ANOMALIES

Lymphatic anomalies represent a rare disease entity, with an estimated incidence of 1:10,000 for the most common form of lymphatic malformations, but with only a few hundred case reports in the literature for *complex* lymphatic anomalies. Lymphatic anomalies arise from developmental defects in lymphangiogenesis. They carry significant risk for comorbidities, including pain, infection, disfigurement, and life-threatening organ dysfunction. Lymphatic anomalies encompass a broad range of developmental and functional defects in lymphatic vessels that range from discrete malformations to complex anomalies (generalized lymphatic anomaly [GLA], KLA, and Gorham-Stout disease [GSD]) and primary lymphedema syndromes.

Most lymphatic anomalies are thought to arise from *somatic* pathogenic variants in genes involved in lymphangiogenesis, but germline predispositions also exist. Pathogenic variants in the PIK3CA/AKT/mTOR and VEGFC/VEGFR3 pathways have been found in many isolated lymphatic malformations; variants in the RAS/MAPK pathway have been identified in patients with *complex lymphatic anomalies* (Fig. 554.2). However, most patients remain without a genetic diagnosis.

Generalized Lymphatic Anomaly

Previously known as lymphangiomatosis, GLA is characterized by a nonneoplastic, multicentric proliferation of dilated lymphatic vessels, with multiple sites resembling common lymphatic malformations (Fig. 554.3). The lesions are present since birth but generally become clinically apparent within the first 2 decades of life. The lesions can affect the bones, liver, spleen, mediastinum, lung, and soft tissues. Bone involvement is typically osteolytic, with punched out lesions and intact cortex. Clinical response depends on location and extent of disease, with thoracic involvement having the poorest prognosis. Patients with GLA most commonly have pathogenic somatic variants in *PIK3CA* leading to overactivity in the PI3K/AKT/mTOR pathway and disrupted lymphatic development and growth. Many patients have been successfully managed with sirolimus.

Gorham-Stout Disease

GSD (also known as *vanishing bone disease*) has significant clinical overlap with GLA but tends to involve a single site or adjacent sites. Patients may present with adjacent soft tissue mass or small areas of

Table 554.1 Overview of Vascular Anomalies

	VASCULAR MALFORMATIONS			
VASCULAR TUMORS	**SIMPLE**	**COMBINED***	**OF MAJOR NAMED VESSELS**	**ASSOCIATED WITH OTHER ANOMALIES**
Benign	Capillary malformations Lymphatic malformations	CMV, CLM LVM, CLVM	See Table 554.2	See Table 554.3
Locally aggressive or borderline	Venous malformations Arteriovenous malformations†	CAVM† CLAVM†		
Malignant	Arteriovenous fistula†	Others		

*Defined as two or more vascular malformations found in one lesion.
†High-flow lesions.
A list of casual genes and related vascular anomalies is available in Tables 554.3 and 554.4
CVM, Capillary venous malformation; CLM, capillary lymphatic malformation, LVM, lymphatic venous malformation, CLVM, capillary lymphatic venous malformation, CAVM, capillary arteriovenous malformation; CLAVM, capillary lymphatic arteriovenous malformation.
From ISSVA Classification for Vascular Anomalies (Approved at the 20th ISSVA Workshop, Melbourne, April 2014, last revision May 2018) https://www.issva.org/UserFiles/file/ISSVA-Classification-2018.pdf

Table 554.2 Anomalies of Major Named Vessels (Also Known as "Channel Type" or "Truncal" Vascular Malformations)

Affect
Lymphatics
Veins
Arteries
Anomalies of
Origin
Course
Number
Length
Diameter (aplasia, hypoplasia, stenosis, ectasia / aneurysm)
Valves
Communication (AVF)
Persistence (of embryonal vessel)

AVF, Arteriovenous fistula.
From ISSVA Classification for Vascular Anomalies (Approved at the 20th ISSVA Workshop, Melbourne, April 2014, last revision May 2018) https://www.issva.org/UserFiles/file/ISSVA-Classification-2018.pdf

microcystic lymphatic malformation. The upper axial skeleton is commonly affected, and there is osteolysis of both the medullary and cortical bone (Fig. 554.4). This osteolysis can be profound and result in significant morbidity, including dysfunction of an appendage or even spinal column instability. Some molecular findings in patients with GSD have suggested that somatic activating variants in *KRAS* and dysfunction of the RAS/MAPK signaling pathway drive the pathogenesis of GSD. Many patients have been treated with sirolimus with adjunctive bisphosphonate therapy.

Kaposiform Lymphangiomatosis

KLA has been considered an aggressive subtype of GLA but is histologically and molecularly distinct. Many patients with KLA harbor *somatic* activation variants in the RAS pathway, rather than the PI3K/AKT/mTOR pathway identified as causative in GLA. KLA presents with distinct foci of spindled endothelial cells on a background of malformed lymphatic vessels. KLA can affect multiple organs and sites but primarily affects the thoracic cavity with patients presenting with life-threatening, and frequently hemorrhagic, pleural effusions (Fig. 554.5). Patients often have a coagulopathy at presentation due to the same **Kasabach-Merritt phenomenon (KMP)** seen in patients with **Kaposiform hemangioendothelioma**. Patients typically present at a younger age than those with GLA or GSD; the mortality has been reported as high as 50–60% prior to the introduction of sirolimus.

Central Conducting Lymphatic Anomaly

Central conducting lymphatic anomaly (CCLA), also known as *lymphangiectasia*, is classified as a channel-type lymphatic anomaly. CCLA is caused by lymphatic channel dysmotility and distal obstruction/malformation affecting lymphatic drainage and leading to recurrent effusions (Fig. 554.6). Patients with other complex lymphatic anomalies may have a component of CCLA. Pathogenic variants in *EPHB4* and *ARAF* have been identified in patients with CCLA and both mTOR and MEK inhibition have been used in its management with mixed success. Patients frequently needed targeted interventional procedures to embolize abnormal lymphatic vessels.

Treatment of Complex Lymphatic Anomalies

Management of complex lymphatic anomalies is principally aimed at control, not cure. This can include a variety of medical, surgical, and interventional procedures to control symptoms and prevent morbidity. Sirolimus, an mTOR inhibitor, has been shown to decrease symptoms of lymphatic leak such as lymphatic blebs, decrease the size of macrocystic and microcystic malformations, decrease chylous production, and may slow the pathologic dissolution of bone by lymphatic malformation. MEK inhibition has shown promise in the management of KLA and CCLA, both found to be driven more by perturbations affecting RAS/MAPK signaling. Adjunctive therapy with bisphosphonates is often used in GSD and in patients with GLA and KLA with bony vertebral lesions.

COMPLEX VENOUS ANOMALIES

Venous anomalies are slow-flow lesions that represent abnormal or excessive growth of venous structures. **Venous malformations** are the most common vascular malformations with an incidence of 1 in 5,000 to 10,000. Due to the slow and sometimes turbulent flow, they commonly are associated with pain, swelling, and intralesional thrombosis. Venous malformations have been found to have *somatic* pathogenic variants in both *PIK3CA* and *TIE2/TEK*, an endothelial cell–specific tyrosine kinase receptor that functions through the PI3K/AKT/mTOR pathway (see Fig. 554.1).

Blue Rubber Bleb Nevus Syndrome

Blue rubber bleb nevus syndrome (BRBNS) is characterized by multiple cutaneous and internal venous malformations, primarily hepatic and intestinal (Fig. 554.7). Many cases have been found to be due to gain-of-function

Table 554.3 Vascular Malformations Associated with Other Anomalies

SYNDROME	LESIONS	GENES
Klippel-Trenaunay syndrome*:	CM + VM +/– LM + limb overgrowth	*PIK3CA*
Parkes-Weber syndrome:	CM + AVF + limb overgrowth	*RASA1*
Servelle-Martorell syndrome:	limb VM + bone undergrowth	
Sturge-Weber syndrome:	facial + leptomeningeal CM + eye anomalies +/– bone and/or soft tissue overgrowth	*GNAQ*
Limb CM + congenital nonprogressive limb overgrowth		*GNA11*
Maffucci syndrome:	VM +/– spindle-cell hemangioma + enchondroma	*IDH1/IDH2*
Macrocephaly-CM (M-CM/MCAP)*		*PIK3CA*
Microcephaly-CM (MICCAP)		*STAMBP*
CLOVES syndrome*:	LM + VM + CM +/– AVM + lipomatous overgrowth	*PICK3CA*
Proteus syndrome:	CM, VM, and/or LM + asymmetrical somatic overgrowth	*AKT1*
Bannayan-Riley-Ruvalcaba syndrome:	AVM + VM + macrocephaly, lipomatous overgrowth	*PTEN*
CLAPO syndrome*:	lower lip CM + face and neck LM + asymmetry and partial/generalized overgrowth	*PIK3CA*

*These lesions belong to the PIK3CA-related overgrowth spectrum (PROS)
CM, Capillary malformation; VM, venous malformation; LM, lymphatic malformation; AVF, arteriovenous fistula; M-CM, macrocephaly-capillary malformation; MCAP, megalocephaly-capillary-malformation-polymicrogyria; MICCAP, microcephaly-capillary malformation; CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, skeletal/scoliosis/spinal anomalies; CLAPO, lower lip CM + face and neck LM + asymmetry and partial/generalized overgrowth.
From ISSVA Classification for Vascular Anomalies (Approved at the 20th ISSVA Workshop, Melbourne, April 2014, last revision May 2018) https://www.issva.org/UserFiles/file/ISSVA-Classification-2018.pdf

Table 554.4 PIK3CA-Related Overgrowth Spectrum

PIK3CA-related overgrowth spectrum (PROS) group lesions with heterogeneous segmental overgrowth phenotypes with or without vascular anomalies due to somatic PIK3CA activating variants.

This spectrum includes:

- Fibroadipose hyperplasia or overgrowth (FAO)
- Hemihyperplasia multiple lipomatosis (HHML)
- Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, scoliosis/skeletal, and spinal (CLOVES) syndrome
- Macrodactyly
- Fibroadipose infiltrating lipomatosis/facial infiltrative lipomatosis
- Megalencephaly-capillary malformation (MCAP or M-CM)
- Dysplastic megalencephaly (DMEG)
- Klippel-Trenaunay syndrome

From ISSVA Classification for Vascular Anomalies (Approved at the 20th ISSVA Workshop, Melbourne, April 2014, last revision May 2018) https://www.issva.org/UserFiles/file/ISSVA-Classification-2018.pdf

TIE2/TEK pathogenic variants; both sporadic and autosomal dominant inheritance have been described. Significant morbidity can arise due to intestinal venous malformations, which can lead to severe bleeding and secondary iron deficiency anemia. Patients must be monitored closely for signs and symptoms of bleeding. The mainstay of management is control of disease with sirolimus and supportive care for anemia.

Glomuvenous Malformation (Glomangioma)

Glomuvenous malformations, also known as *glomangiomas* or *glomus tumors*, are one of the rare germline conditions in vascular anomalies. Glomuvenous malformations result from an autosomal dominant loss-of-function variant in the *GLMN* gene, which encodes a protein essential for normal vascular development. Patients present with multiple superficial cutaneous lesions with a cobblestone appearance (Fig. 554.8). There is 100% penetrance but variable expressivity. Painful lesions can be treated with surgical resection, laser, or sclerotherapy.

SYNDROMES ASSOCIATED WITH VASCULAR ANOMALIES

PIK3CA-Related Overgrowth Spectrum Disorders

PIK3CA-related overgrowth spectrum (PROS) encompasses a group of disorders caused by somatic mosaic mutations in the PI3K/AKT/mTOR pathway (see Table 554.4). The *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α) gene encodes a group of lipid kinases (PI3 kinases) that are key to regulating cell proliferation and survival via the PI3K/AKT/mTOR pathway. Patients with PROS present with a wide spectrum of clinical phenotypes, but progressive segmental overgrowth and vascular malformations are key components.

Klippel-Trenaunay Syndrome

Klippel-Trenaunay syndrome (KTS) is characterized by overgrowth of one lower extremity in combination with combined slow-flow vascular malformation (capillary, venous, and/or lymphatic). Complications include lymphatic overgrowth, infection, oozing and/or bleeding from lymphatic blebs, and thromboembolism (Fig. 554.9). Patients with KTS have an anomalous venous return system composed of dilated and incompetent veins, often with a larger marginal vein. The deep venous system may also be poorly developed. Patients can have lymphatic involvement of the skin, musculature, and intestinal tract. Venous malformation may affect the bladder and urethra. Due to variability in diagnostic criteria and identification of KTS over the years, the genetic etiology of KTS is not completely confirmed, but many patients have been identified to have a *somatic* variants in *PIK3CA*; KTS is considered part of PROS disorders. Surgical and interventional procedures may be important for some patients with KTS. Medical management currently includes sirolimus and anticoagulation therapy.

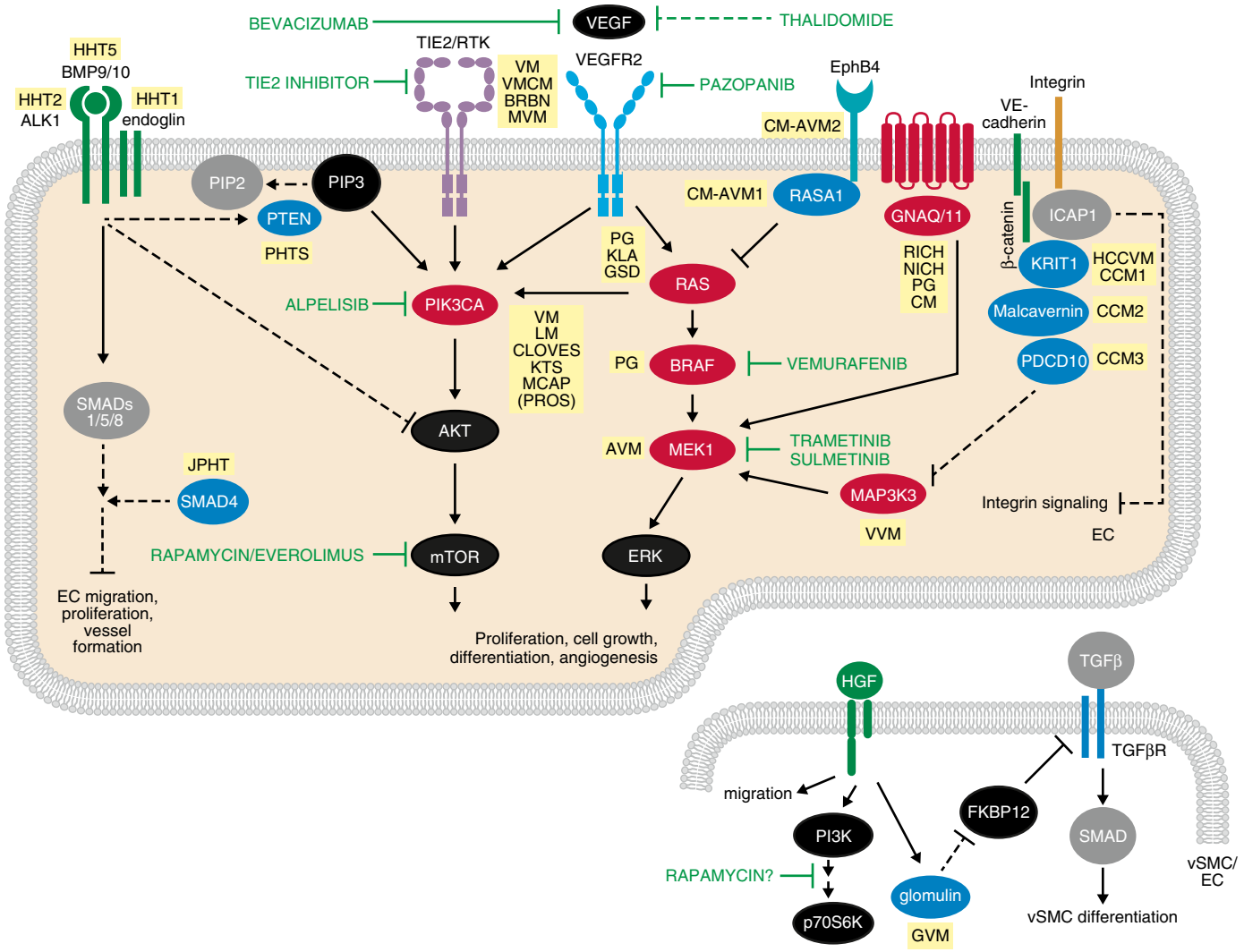

Fig. 554.1 PI3K/AKT/mTOR signaling and RAS/MAPK signaling in vascular anomalies. Red, gain of function; blue, loss of function; black, enhanced signaling; gray, decreased signaling. *(From Queisser A, Seront E, Boon LM, Vikkula M. Genetic basis and therapies for vascular anomalies. Circ Res. 2021;129[1]:155–173. Fig. 3.)*

CLOVES

CLOVES, or congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis/spinal/skeletal anomalies, is a disorder that results from an early embryonic pathogenic variant in *PIK3CA*. In addition to extremity hypertrophy, patients can have significant fatty lipomatous overgrowth (Fig. 554.10). Spinal involvement is common. Patients with vascular malformations usually have a combination of capillary, venous, and lymphatic malformations. AVMs are less common but have been reported with spinal involvement. Deep venous anomalies increase the risk for venous thromboembolism. Patients with CLOVES have an increased risk of Wilms tumor and require serial monitoring with abdominal ultrasonography in early childhood. Patients may require sclerotherapy, surgery, and other interventional procedures depending on symptoms. Patients have also been successfully managed with sirolimus.

Macrocephaly-Capillary Malformation

Macrocephaly-capillary malformation (M-CM) syndrome is a PROS disorder characterized by macrocephaly, brain abnormalities, CM (often in a reticular pattern), overgrowth, and developmental delays (Fig. 554.11). Neurologic manifestations can include hydrocephalus, cortical dysplasia, polymicrogyria, and posterior fossa crowding with cerebellar tonsillar herniation. Patients require supportive care for overgrowth and other vascular anomalies, as well as close monitoring of brain growth and development.

AKT-RELATED OVERGROWTH SPECTRUM

Proteus Syndrome

Proteus is an overgrowth disorder caused by a *somatic* mosaic pathogenic variant in the PI3K/AKT/mTOR pathway. Clinical features include overgrowth (including lipomatous), bony abnormalities, cerebriform connective tissue nevus, vascular malformations (capillary, venous, lymphatic), epidermal nevi, cerebral abnormalities and accompanying intellectual disability, and increased risk for secondary neoplasms and venous thromboembolism. Management of proteus disorders has primarily been supportive, although use of AKT1 inhibition is currently being evaluated.

RASopathies

RASopathies refers to a group of medical conditions caused by pathogenic variants in the RAS/MAPK pathway. It includes both germline conditions, as well as *somatic* variants. The RAS/MAPK pathway is important in cell cycle regulation, proliferation, migration, and stress response. RAS/MAPK pathway pathogenic variants have been identified in patients with solitary CMs and AVMs, GLA, KLA, verrucous venous malformation, cerebral CM, pyogenic granuloma (PG), and congenital hemangiomas.

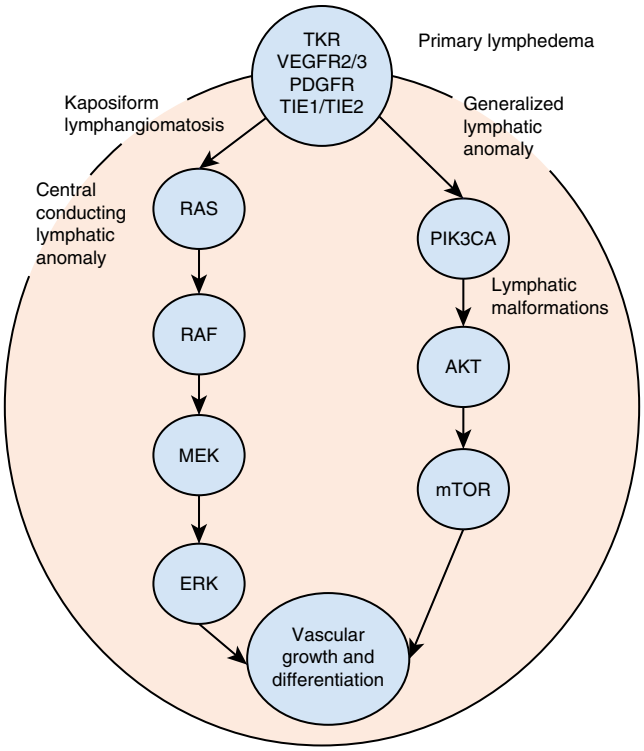

Fig. 554.2 Molecular pathways identified in lymphatic anomalies.

Capillary Malformation-Arteriovenous Malformation Syndrome

Capillary malformation-arteriovenous malformation (CM-AVM) is an autosomal dominant disorder characterized by diffuse, circumscribed CMs and increased risk for intra- or extracranial AVMs. AVMs are found in ~80% of patients. The CMs have a distinct appearance with a round or ovoid shape and surrounding pale halo. Most cases of CM-AVM are caused by a loss-of-function pathogenic variant in *RASA1*, but variants in *EPHB4* have also been reported (CM-AVM type 2). Familial penetrance is high, and screening is important due to the high risk for life-threatening complications from AVMs. AVMs may require treatment with a combination of interventional and surgical procedures.

Parkes-Weber Syndrome

Parkes-Weber syndrome (PKWS) is associated with pathogenic variants in *RASA1*. The syndrome includes multiple microscopic arteriovenous fistulae in association with a CM. PKWS is also associated with soft tissue and bony overgrowth of an extremity.

KAPOSIFORM HEMANGIOENDOTHELIOMA

Kaposiform hemangioendothelioma (KHE) is a rare and potentially life-threatening vascular tumor. KHE classically presents as a red to purple firm plaque on the lateral neck, axilla, trunk, or extremities. Visceral tumors occur as well. Lesions may occasionally get smaller over time but rarely resolve completely. **Tufted angioma,** once thought to be a separate tumor on the same clinical spectrum as KHE, is considered under the umbrella term of KHE (Fig. 554.12). The main complication of these tumors is the development of **KMP**, which may be fatal; therefore early diagnosis and treatment is important. Retroperitoneal or intrathoracic lesions in the absence of cutaneous lesions are uncommon but are often associated with KMP.

Kasabach-Merritt Phenomenon

KMP is a life-threatening combination of a rapidly enlarging KHE, thrombocytopenia, microangiopathic hemolytic anemia, and an acute or chronic consumption coagulopathy. The clinical manifestations are usually evident during early infancy. The vascular lesion is usually cutaneous and is only

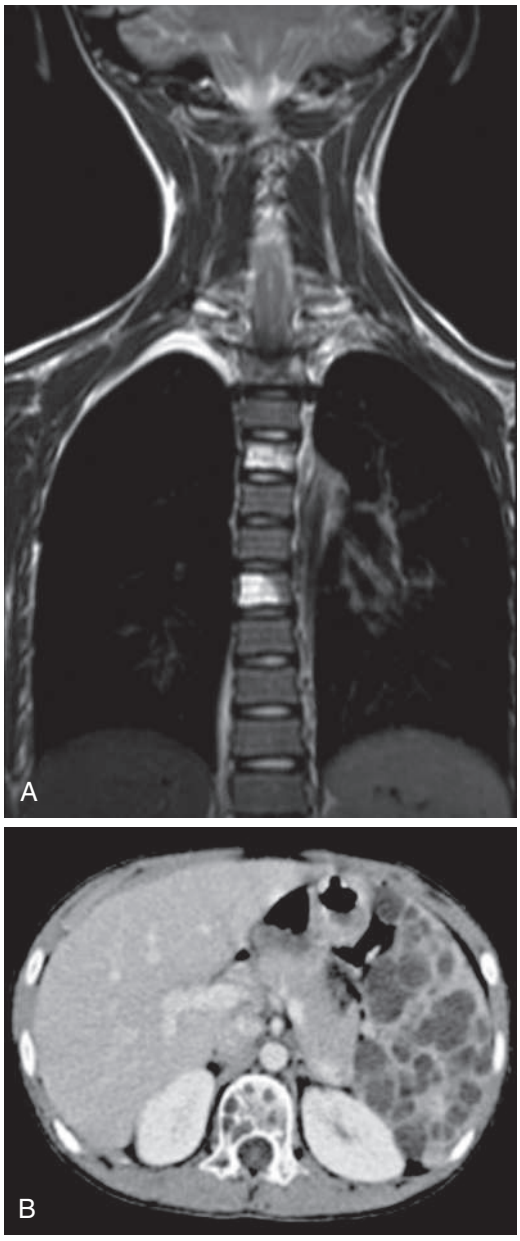

Fig. 554.3 **A**, MRI imaging of vertebral body **lymphatic malformations** in a patient with generalized lymphatic anomaly (GLA). **B**, Splenic and vertebral body lesions in a patient with GLA. (***B*** *from Joshi M, Phansalkar DS. Simple lymphangioma to generalized lymphatic anomaly: role of imaging in disclosure of a rare and morbid disease. Case Rep Radiol. 2015;2015:603859.)*

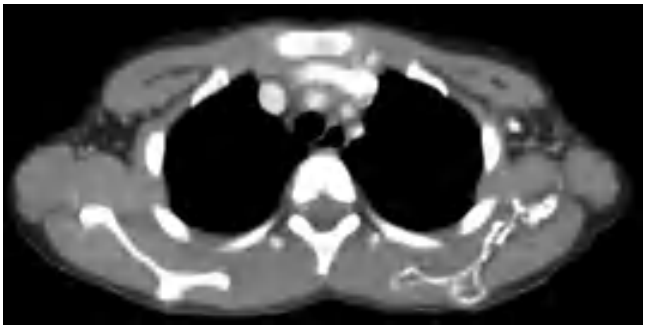

Fig. 554.4 Osteolytic destruction of the left scapula in a patient with Gorham-Stout disease (GSD). Axial CT image of the left scapula demonstrates intramedullary lucent lesions with cortical thinning.

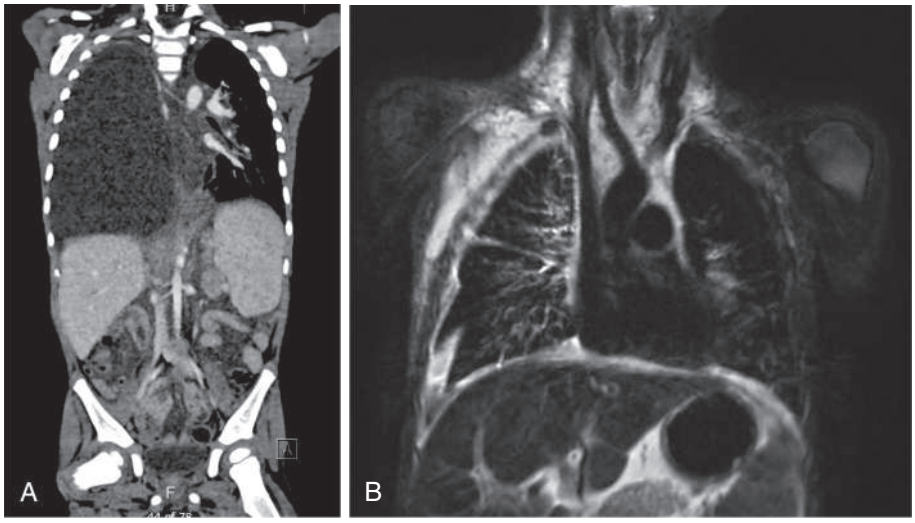

Fig. 554.5 A, Large hemorrhagic pleural effusion in a patient with Kaposiform lymphangiomatosis (KLA). B, Abnormal lymphatic fluid distribution and central lymphatic drainage in a patient with KLA.

Fig. 554.6 MR lymphangiography study showing a dilated and malformed thoracic duct and central lymphatics with retrograde flow into the mediastinum and pericardium *(arrows)* in a patient with central conducting lymphatic anomaly (CCLA).

Fig. 554.7 Multiple **venous malformations** on the tongue (A) and subcutaneous tissues of the foot (B) in a patient with blue rubber bleb nevus syndrome (BRBNS).

rarely located in viscera. The associated thrombocytopenia may lead to precipitous hemorrhage accompanied by ecchymoses, petechiae, and a rapid increase in the size of the vascular lesion. Severe anemia from hemorrhage or microangiopathic hemolysis may ensue. The thrombocytopenia has been attributed to sequestration or increased destruction of platelets within the lesion. Hypofibrinogenemia and decreased levels of consumable clotting factors are relatively common (see Chapter 533.6). KMP is seen in KHE or tufted angioma, as well as to a milder extent in very large congenital and hepatic hemangiomas *but not* in infantile hemangiomas.

Treatment includes surgical excision of small lesions, although this is often difficult because of coagulopathy and the infiltrative nature of the tumor. Additional pharmacologic treatments include systemic steroids with or without vincristine as first-line therapy in most cases. mTOR inhibition with sirolimus has been found to be successful as an alternative first-line treatment for KHE. The optimal initial combination of medical therapies is not yet known. Antiplatelet, antifibrinolytic, and other chemotherapeutic agents have been used with mixed results. The mortality rate overall once patients have KMP is high.

OTHER RARE VASCULAR TUMORS

Benign Tumors (Other Than Infantile Hemangiomas) (see Chapter 691)

Epithelioid Hemangiomas

Epithelioid hemangioma (EH) is a very rare vascular tumor, usually occurring in the skin or subcutaneous tissues, but occasionally occurring

Fig. 554.8 Cobblestoned appearance of a patient with a glomangioma, or glomuvenous malformation, caused by a germline pathogenic variant in the glomulin gene *(GLMN)*. Family members all with similar appearing lesions.

Fig. 554.9 Overgrown right lower extremity with **capillary-venous-lymphatic malformation** in a patient with Klippel-Trenaunay syndrome.

in other sites such as bone. They may be mistaken for infantile hemangiomas or PGs and can be reactive due to trauma or infection. EHs are well-circumscribed proliferations of capillaries that stain for endothelial cell and lymphatic markers but are without any cytologic atypia or mitoses. Primary treatment is with surgical excision, though they can recur locally. *FOS* gene rearrangements have been identified in some EHs.

Pyogenic Granuloma (Lobular Capillary Hemangioma)

A PG is a small red, glistening, sessile, or pedunculated papule that often has a discernible epithelial collarette (see Fig. 691.16). The surface may be weeping and crusted or completely epithelialized. PGs initially grow rapidly, may ulcerate, and bleed easily when traumatized because they consist of exuberant granulation tissue. They are relatively common in children, particularly on the face, arms, and hands. Such a lesion located on a finger or hand may appear as a subcutaneous nodule. PGs may arise at sites of injury, but a history of trauma often cannot be elicited.

PGs are benign but a nuisance because they bleed easily with trauma and may recur if incompletely removed. Numerous satellite papules have developed after surgical excision of PGs from the back, particularly in the interscapular region. Small lesions may regress after cauterization with silver nitrate; larger lesions require excision and electrodesiccation of the base of the granuloma. Small (<5 mm) lesions may be treated successfully with **pulsed dye laser** therapy.

Spider Angioma

A vascular spider (nevus araneus) consists of a central feeder artery with many dilated radiating vessels and a surrounding erythematous flush, varying from a few millimeters to several centimeters in diameter (see Fig. 691.17). Pressure over the central vessel causes blanching; pulsations visible in larger nevi are evidence for the arterial source of the lesion. Spider angiomas are associated with conditions in which there are increased levels of circulating estrogens, such as cirrhosis and pregnancy, but they also occur in up to 15% of normal preschool-age children and 45% of school-age children. Sites of predilection in children are the dorsum of the hand, forearm, nose, infraocular region, lips, and ears. Lesions often regress spontaneously after puberty. If removal is desired, pulsed dye laser therapy is the mode of choice; resolution is achieved in 90% of cases with a single treatment.

Maffucci Syndrome

The association of spindle cell hemangiomas with nodular enchondromas in the metaphyseal or diaphyseal cartilaginous portion of long bones is known as Maffucci syndrome. Maffucci syndrome is caused by *somatic* mosaic pathogenic variants in the *IDH1* and *IDH2* genes. Vascular lesions are typically soft, compressible, asymptomatic blue to purple subcutaneous masses that grow in proportion to a child's growth and stabilize by adulthood. Mucous membranes or viscera may also be involved. Onset occurs during childhood. Bone lesions may produce limb deformities and pathologic fractures. Malignant transformation of enchondromas (chondrosarcoma, angiosarcoma) or primary malignancies (ovarian, fibrosarcoma, glioma, pancreatic) may be a complication (see Chapter 550).

LOCALLY AGGRESSIVE RARE VASCULAR TUMORS

Retiform Hemangioendothelioma

Retiform hemangioendothelioma (RHE) is an intermediate, or rarely metastasizing, vascular tumor. They usually present as a slow-growing mass with plaque-like or nodular appearance. They can involve the entire dermis and extend into the subcutaneous tissue. Histologically, hobnail endothelial cells are found, but only variably lymphatic endothelial cell markers. Treatment is with surgical excision, though local recurrence is common and regional lymph node metastases have been reported.

Papillary Intralymphatic Angioendothelioma

Papillary intralymphatic angioendothelioma (PILA), also referred to as *Dabska tumor,* is a locally aggressive hemangioendothelioma. PILA occur within the dermis and superficial soft tissues of the head, neck, trunk, or extremities. On occasion they have been reported to arise from preexisting lymphatic or venolymphatic malformations, or within an extremity affected by lymphedema. They appear as violaceous nodules similar to RHE but histologically appear similar to lymphatic malformations and contain hobnail endothelial cells. Primary treatment is with excision, but regional lymph node metastasis and even death due to distant metastasis have been reported. Systemic chemotherapy based on sarcoma treatment may be used in recurrent or refractory cases.

Composite Hemangioendothelioma

Composite hemangioendotheliomas (CHE) contain overlapping histologic features with epithelioid, retiform, and spindle-cell hemangioendotheliomas. Some also contain angiosarcoma-like features within the same tumor. Fewer than 40 cases have been reported in the literature, and they can present at any age and in association with other vascular anomalies. Treatment options include surgical excision, chemotherapy, and radiation therapy.

Fig. 554.10 A, Soft tissue and bony overgrowth of the digits of the bilateral hands in a patient with CLOVES. Also noted is overlying capillary malformation (CM). B, Overgrowth of digits of the feet and right sandal-toe gap deformity in a patient with CLOVES. Also noted are CM and dilated venous pattern from underlying bilateral **venous malformation** of the lower extremities.

Fig. 554.11 Infant with macrocephaly, prominent forehead, depressed nasal bridge, short neck, bluish white iris, and reticulated port-wine stains over body, consistent with macrocephaly-capillary malformation (M-CM). *(From Panigrahi I, Bhushan M, Yadav M, Khandelwal N, Singhi P. Macrocephaly-capillary malformation syndrome: three new cases. J Neurol Sci. 2012;313:178–181. Fig. 5.)*

Pseudomyogenic Hemangioendothelioma (Epithelioid Sarcoma-Like Hemangioendothelioma)

Pseudomyogenic hemangioendothelioma (PMH) is a rare vascular tumor that presents more commonly in males than females (4:1 predominance) and usually in young adulthood (<40 years). The typical presentation is multifocal presentation within one extremity, and it does frequently have bony involvement. Histologically, it shares some features with epithelioid sarcoma, with myoid-appearing spindle cells, but has very low metastatic potential. Primary treatment is with surgical resection, but local recurrence is common, and mTOR inhibition with sirolimus has shown promise in its management.

MALIGNANT TUMORS

Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma (EHE) is variant of *angiosarcoma*, which is locally aggressive and has metastatic potential. It usually occurs in middle-age adults and presents as a solitary mass in the soft tissues, viscera, or bone, with liver as the most common site. Thirty

Fig. 554.12 A, Patient with **Kaposiform hemangioendothelioma** (KHE) of the thigh who presented with **Kasabach-Merritt phenomenon** (KMP) with thrombocytopenia and hypofibrinogenemia unresponsive to all therapy until introduction of sirolimus. B, Premature infant with KHE of the arm who presented with KMP.

percent present with metastases, and occasionally patients present with hemolytic anemia or consumptive coagulopathy. EHE is characterized by the WWTR1/CAMTA1 translocation, with some also expressing a *YAP1-TFE3* gene fusion. Histologically, EHE are epithelioid tumors arranged in nests or cords. They may contain spindle endothelial cells and express Fli-1 and CD31. Treatment depends on location and metastatic pattern but includes surgery, radiotherapy, and chemotherapy. Overall survival for those with progressive disease is quite poor.

Angiosarcoma

Angiosarcomas account for ~2% of all soft tissue sarcomas, occur mostly in adults, and very rarely affect children. In children, they may be cutaneous or in the deep tissues or viscera. Angiosarcomas present as rapidly enlarging purplish plaques or nodules that ulcerate and can leak serosanguinous fluid. Necrosis and hemorrhage within the tumor are common. Due to risk for rapid progression and metastasis, multimodal therapy including resection and intensive chemotherapy is generally pursued. Combined treatment with mTOR and MEK inhibition has shown some promise, but progression-free and overall survival remain very poor.

Hepatic angiosarcomas appear to be a distinct subtype of angiosarcoma, presenting in earlier childhood, usually between age 1 and 5 years (Fig. 554.13). There is sometimes a history of infantile hepatic hemangioma, although cutaneous infantile hemangiomas do not appear to progress to angiosarcoma. Patients can present with anemia and thrombocytopenia due to intratumoral bleeding. Liver function tests may be abnormal, but α-fetoprotein is normal or only minimally elevated. Risk of local invasion and metastasis is quite high, so rapid diagnosis, surgical resection, and initiation of sarcoma-based chemotherapy is important. Unfortunately, complete cure is very rare.

Lymphangiosarcoma is a distinct subtype of angiosarcoma arising from the lymphatic endothelium of a site of lymphedema. Lymphangioma resembles angiosarcoma both clinically and histologically and appears to harbor the same c-myc amplification seen in postradiation angiosarcoma of the breast. Similar to the "hemangiosarcoma" form of angiosarcoma, lymphangiosarcomas are managed similarly and have similar overall poor prognosis.

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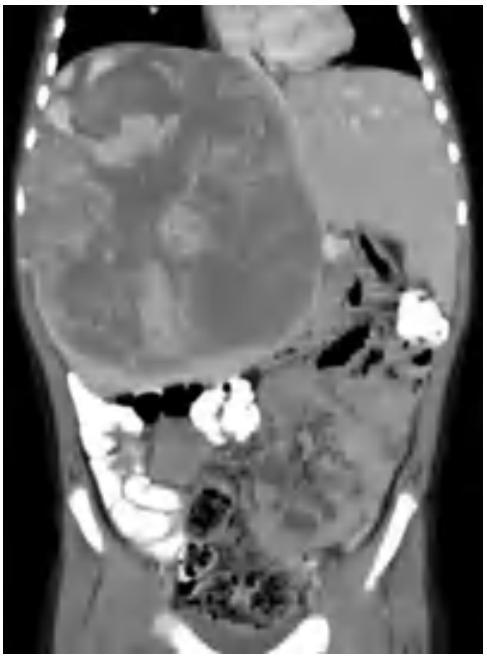

Fig. 554.13 Angiosarcoma of the liver. *(From Potanos KM, Hodgkinson N, Fullington NM, et al. Long-term survival in pediatric hepatic angiosarcoma (PHAS): a case report and review of the literature. J Pediatr Surg Case Rep. 2015;3:410–413. Fig. 1.)*

Chapter 555
Rare Tumors

555.1 Thyroid Tumors

Jonathan D. Wasserman

See Chapter 607.

BENIGN THYROID TUMORS

Benign thyroid tumors represent approximately 75% of all thyroid nodules presenting in the pediatric population and generally require no treatment unless they result in compressive symptoms or thyroid hormone hypersecretion. The workup of a suspected thyroid nodule includes the laboratory assessment of thyroid function (thyroid-stimulating hormone [TSH]), ultrasound (US) to assess characteristics of the nodule(s) and regional lymph nodes, and US-guided fine-needle aspiration biopsy (of the primary nodule and suspicious lymph nodes) for cytopathologic diagnosis if imaging is suspicious for malignancy. Nuclear scintigraphy using radioactive iodine (^{123}I) or technetium 99m (^{99m}Tc)-pertechnetate are not recommended in the initial diagnostic evaluation, except in the event of a suppressed TSH level.

MALIGNANT THYROID TUMORS

Pediatric thyroid malignancies are rare tumors that include medullary thyroid carcinoma (MTC) and the differentiated thyroid carcinomas (DTCs), namely, papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma. Findings suggestive of a thyroid malignancy are noted in Table 555.1.

PTC represents the majority of thyroid cancers in children. The incidence of pediatric thyroid cancer has been rising, with the highest rate in adolescence, and a female predominance emerges around the time of puberty. With few exceptions, children with PTC have a highly favorable prognosis, with anticipated survival over decades, even in the presence of distally metastatic disease at diagnosis. *The major established risk factor for development of PTC is exposure to ionizing radiation, typically in the context of antineoplastic therapy.*

MTC is an uncommon disease in childhood that usually occurs in the context of **multiple endocrine neoplasia type 2a (MEN2A) or type 2b (MEN2B),** autosomal dominant, hereditary endocrine tumor syndromes that arise secondary to activating variants in the *RET* proto-oncogene. In addition to the almost complete penetrance of MTC in patients with the most common *RET* variants, patients with MEN2A and MEN2B have up to a 50% lifetime risk of developing pheochromocytomas (PHEOs). Up to 20% of MEN2A patients also develop primary hyperparathyroidism. Patients with MEN2B do not develop hyperparathyroidism but have a distinct clinical phenotype that includes a characteristic facial appearance, marfanoid body habitus, aerodigestive tract ganglioneuromatosis, and **oral and ocular mucosal neuromas** (Fig. 555.1). The diagnosis of MEN2B is often delayed (usually after the MTC has already metastasized) because its pathognomonic features are not apparent in very early childhood, although an inability to cry tears (alacrimia) and constipation represent the earliest clues to diagnosis. MTC may be sporadic or familial without features of MEN 2A or 2B; it may also be associated with **Hirschsprung disease**.

Children with sporadic **DTC** typically present with an asymptomatic thyroid mass and/or cervical lymphadenopathy. Lymph node metastases are present in most PTC cases, and lung metastases are identified in up to 20% of patients, primarily in those children with a high burden of neck disease. In contrast, children with MEN2-related **MTC** are often diagnosed only after a positive genetic test result or, in the case of MEN2B, after the clinical phenotype is recognized. When

Table 555.1 Clinical Findings Associated with Malignant Thyroid Nodules

HISTORIC FEATURES
Neck irradiation during childhood or adolescence
Rapid growth
Recent, persistent changes in speaking, breathing, or swallowing
Family history of multiple endocrine neoplasia type 2
PHYSICAL EXAMINATION
Firm, fixed, and irregular consistency of nodule
Vocal cord paralysis or hoarseness
Persistent regional lymph adenopathy

Modified from Melmed S, Auchus RJ, Goldfine AB, et al., eds. *Williams Textbook of Endocrinology*. 14th ed. Philadelphia: Elsevier; 2020: Table 14.3, p. 439.

Fig. 555.1 Classic appearance of oral mucosal neuromas on the tongue in a boy with multiple endocrine neoplasia type 2b (MEN2B) secondary to the typical M918T variant in the *RET* protooncogene.

a family history is known, presymptomatic surveillance may identify MTC at earlier stages. As with PTC, MTC also frequently metastasizes to cervical lymph nodes.

There are well-documented genotype-phenotype correlations in MEN2, and the biologic aggressiveness of MTC depends on the hereditary setting in which it develops. With the availability of genetic testing for *RET* variants, MTC has become one of the few malignancies that can be prevented by *prophylactic thyroidectomy*.

The age at which prophylactic thyroidectomy is recommended is determined based on the specific *RET* variant, serum calcitonin levels, and parent and child preference.

The **primary therapy** for thyroid cancer, regardless of histologic type, is thyroidectomy and, if there is evidence of lymph node metastasis, a compartment-oriented lymph node dissection performed by a highly experienced thyroid cancer surgeon. In **DTC**, adjuvant radioactive iodine (^{131}I) may be used postoperatively to treat iodine-avid distant metastasis and unresectable residual neck disease. The use of ^{131}I is limited to children at higher risk for residual or recurrent disease who are most likely to benefit from treatment. Children with **MTC** do not require ^{131}I therapy.

In children with DTC, the TSH level is initially suppressed by giving supraphysiologic levothyroxine, because TSH may stimulate DTC tumor growth; the TSH level is kept normal in MTC.

Oral multikinase inhibitors and oncogene-targeted therapy (for children with tumors driven by *BRAF*, *RET*, or *NTRK* substitutions or oncogenic fusions) have demonstrated benefit for the treatment of advanced MTC and DTC in adults. These are rarely indicated in pediatric patients but may be considered for symptomatic and/or progressive disease.

Long-term follow-up of thyroid cancer survivors involves monitoring of tumor markers (thyroglobulin/thyroglobulin antibody in DTC, calcitonin/carcinogenic embryonic antigen in MTC) and routine imaging, primarily neck US.

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555.2 Nasopharyngeal Carcinoma

Cynthia E. Herzog

Nasopharyngeal carcinoma is rare in the pediatric population, but it is one of the most common nasopharyngeal tumors in pediatric patients. In adults, the incidence is highest in South China, but it is also high among the Inuit people and in North Africa and Northeast India. In China, this diagnosis is rare in the pediatric population, but in other populations, a substantial proportion of cases occur in the pediatric age-group, primarily in adolescents. It occurs in males twice as often as in females and is more common in Black people. In the pediatric population, the tumors are more frequently of undifferentiated histology and associated with **Epstein-Barr virus (EBV)**. Nasopharyngeal carcinoma is associated with specific human leukocyte antigen (HLA) types; other genetic factors may play a role, especially in low-incidence populations.

Most pediatric patients present with advanced locoregional disease manifesting as cervical lymphadenopathy. Epistaxis, trismus, and cranial nerve deficits also may be present. The diagnosis is established from biopsy of the nasopharynx or cervical lymph nodes. In most cases the lactate dehydrogenase level is elevated, but this finding is nonspecific. CT or MRI evaluation of the head and neck is performed to determine the extent of locoregional disease. Chest radiography, CT, bone scan, and liver scan are used to evaluate for metastatic disease. PET scans appear to be useful for monitoring primary disease and looking for metastases. EBV DNA levels correlate with disease stage, have prognostic value, and can be used to monitor for recurrence.

Treatment is a combination of chemotherapy and irradiation. Cisplatin, given concurrently with radiation, with either neoadjuvant or adjuvant cisplatin-based chemotherapy, is the standard treatment. The outcome depends on the extent of disease; patients with distant metastases have a very poor prognosis. Using intensity-modulated radiation therapy improves local control and reduces the late adverse effects associated with radiation therapy, including hormonal dysfunction, dental caries, fibrosis, and second malignancies. Use of proton therapy may result in further reduction of adverse effects.

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555.3 Adenocarcinoma of the Colon and Rectum

Cynthia E. Herzog and Winston W. Huh

Colorectal carcinoma (CRC) is rare in the pediatric population, with an estimated incidence rate of approximately one case per 1 million. Even in patients with predisposing conditions, CRC usually does not present until late adolescence or adulthood; only 35–40% of CRC in this age-group are association with a known predisposition factor. **Hereditary nonpolyposis colon cancer (HNPCC) (Lynch Syndrome)** is an autosomal dominant disorder, with germline pathogenic variants in DNA mismatch repair genes *(MMR)* causing DNA repair errors and microsatellite instability (MSI). *MYH*-associated polyposis, Peutz-Jeghers syndrome, and juvenile polyposis also predispose to CRC.

Genetic testing is available, and screening for cancer in HNPCC and familial adenomatous polyposis (FAP) should begin during childhood or adolescence. Likewise, genetic evaluation for these conditions should be pursued in young patients presenting with colon cancer, even when there is no history of predisposing genetic conditions.

Presenting symptoms include bloody stools or melena, abdominal pain, weight loss, and changes in bowel patterns. In many cases, signs are vague, often resulting in a delay in diagnosis, sometimes not until the disease has reached an advanced stage. The histologic subtype differs from that seen in adults, with most pediatric tumors being either mucinous adenocarcinoma or signet ring cell carcinoma. Pediatric patients tend to have tumors with MSI and tend to present with more advanced disease. Treatment is based on guidelines used in adults with CRC and consists of surgical resection when possible with chemotherapy for unresectable tumors. Adequate lymph node removal should be performed at surgical resection of primary tumor. Radiation therapy is useful in select cases. Pediatric patients have a worse overall prognosis compared with adult patients, but the reasons for this discrepancy are not clear.

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555.4 Adrenal Tumors

Jonathan D. Wasserman

See Chapters 617-621.

The adrenal gland is comprised of two embryologically distinct layers, the steroid-secreting outer cortex and the catecholamine-secreting inner medulla. **Adrenocortical tumors (ACTs)** arise from the cortex, whereas pheochromocytomas (**PHEOs**) derive from the chromaffin cells of the adrenal medulla. Additionally, catecholaminergic tumors arising from the parasympathetic and sympathetic ganglia *outside* the adrenal medulla are called **paragangliomas (PGLs)**. Both ACTs and PHEOs are strongly associated with hereditary tumor predisposition syndromes, and thus diagnosis of either in childhood should initiate a thorough family history and referral to an expert in cancer genetics for counseling and germline testing.

ACTs are very rare and, in children, tend to present before age 10 years. They have a female predominance and are functional (hormone secreting) in >90% of cases, primarily producing androgens and/or glucocorticoids and causing clinically apparent **virilization** with or without **Cushing syndrome** (see Chapter 619). ACTs may also present as an abdominal mass or pain. In children, ACTs are most frequently associated with **Li-Fraumeni syndrome** (germline inactivating variants in the *TP53* tumor-suppressor gene) and **Beckwith-Wiedemann syndrome** (BWS), but they can also be seen in hemihyperplasia other than that seen as part of BWS, MEN1, McCune-Albright syndrome, FAP, and very rarely, congenital adrenal hyperplasia. Unusual causes of bilateral nodular adrenocortical disease, which also typically present with Cushing syndrome, include the Carney complex and macronodular adrenocortical hyperplasia.

PHEOs/PGLs are rare tumors that are more likely to be bilateral, malignant, and secondary to a heritable tumor syndrome when diagnosed in childhood compared with adulthood (see Chapter 621). **Von Hippel-Lindau disease** is the most common genetic association in the pediatric population, followed by the **familial PGL syndromes (1, 2, 3, 4)** caused by variants in the succinate dehydrogenase *(SDHx)* genes. MEN2 (types 2A and 2B) and neurofibromatosis type 1 *(NF1)* are also included in the differential diagnosis but are more often associated with a PHEO diagnosis during adulthood (Table 555.2). Overall, germline pathogenic variants in at least 16 different genes have been associated with predisposition to PHEO/PGL. PHEO/PGL is also associated with congenital cyanotic heart disorders (somatic gain-of-function variant in *EPAS1*). *Hypertension is usually sustained* in pediatric patients with PHEO/PGL, who may also lack the triad of intermittent headache, palpitations, and diaphoresis typically seen in adults. Nonetheless, PHEO/PGL accounts for <1% of pediatric hypertension. Additional manifestations may include chest pain, pallor, tremor, fever, cardiomyopathy, or exacerbations with exercise; flushing is not typical of PHEO/PGL. The differential diagnosis is noted in Table 555.3. The most appropriate screening test for PHEO/PGL is measurement of fractionated plasma and/or urine **metanephrine** levels. Initial imaging studies, when metanephrine levels are elevated, include CT or MRI. When indicated, to confirm abnormal biochemistry and/or cross-sectional imaging, ^{18}F-DOPA and ^{68}Ga-DOTATATE (DOTA-octreotate) PET/MRIs are the functional imaging modalities of choice given greater sensitivity and specificity than earlier radioisotopes (Fig. 555.2). ^{131}I-Metaiodobenzyguanidine (MIBG) imaging may also be considered in such circumstances.

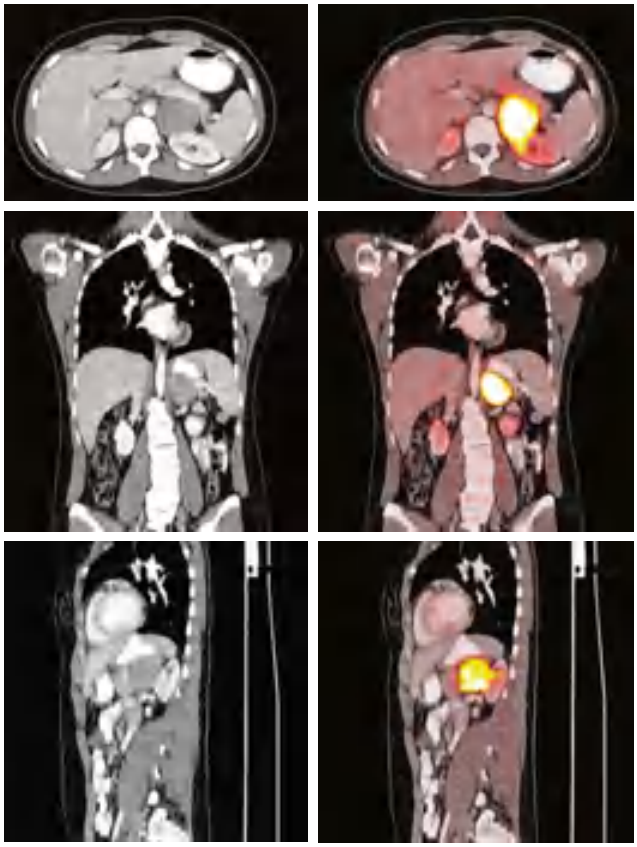

Fig. 555.2 Appearance of pheochromocytoma on functional imaging (^{18}F-l -dihydroxyphenylalanine [^{18}F-DOPA] PET/CT). Focal uptake is seen in the left suprarenal fossa. *(From Duh QY, Livhits M, Yeh MW. The adrenal glands. In: Mattox KL, Townsend CM, Beauchamp RD, Evers BM, eds. Sabiston Textbook of Surgery. 21st ed. Philadelphia: Elsevier; 2022. Fig. 40.18A.)*

Table 555.2 Germline Pathogenic Variants Associated with Pheochromocytoma and Paraganglioma

SYNDROME/NAME	GENE	TYPICAL TUMOR LOCATION AND OTHER ASSOCIATIONS
HYPOXIC PATHWAY: CLUSTER 1*		
SDHD (familial paraganglioma type 1)†	*SDHD*	Primarily skull base and neck; occasionally adrenal medulla, mediastinum, abdomen, pelvis; GIST; possible pituitary adenoma
SDHAF2 (familial paraganglioma type 2)†	*SDHAF2*	Primarily skull base and neck; occasionally abdomen and pelvis
SDHC (familial paraganglioma type 3)	*SDHC*	Primarily skull base and neck; occasionally abdomen, pelvis, or chest; GIST; possible pituitary adenoma
SDHB (familial paraganglioma type 4)	*SDHB*	Abdomen, pelvis, and mediastinum; rarely adrenal medulla, skull base, and neck; GIST; renal cell carcinoma; possible pituitary adenoma
SDHA	*SDHA*	Primarily skull base and neck; occasionally abdomen and pelvis; GIST; possible pituitary adenoma
VHL disease	*VHL*	Adrenal medulla, frequently bilateral; occasionally paraganglioma that may be localized from skull base to pelvis
Hereditary leiomyomatosis and renal cell carcinoma (Reed syndrome)—fumarate hydratase variant	*FH*	Multifocal and metastatic; associated with hereditary leiomyomatosis, uterine fibroids, and renal cell cancer
Hypoxia-inducible factor (HIF) 2α	*HIF2A*	Paraganglioma, polycythemia, and rarely somatostatinoma
Familial erythrocytosis associated with pathogenic variant in prolyl hydroxylase isoform 1 (PDH1)	*EGLN2*	Polycythemia associated with pheochromocytoma and paraganglioma
Familial erythrocytosis associated with pathogenic variant in prolyl hydroxylase isoform 2 (PDH2)	*EGLN1*	Polycythemia associated with pheochromocytoma and paraganglioma
KIF1B	*KIF1B*	Neuroblastoma
KINASE SIGNALING PATHWAY: CLUSTER 2‡		
MEN2A and MEN2B	*RET*	Adrenal medulla, frequently bilateral
Neurofibromatosis type 1 (NF1)	*NF1*	Adrenal or periadrenal
MAX†	*MAX*	Adrenal medulla
Familial pheochromocytoma	*TMEM127*	Adrenal medulla; possible renal cell carcinoma

*Cluster 1 tumors are mostly extraadrenal paragangliomas (except in VHL, where most tumors are localized to the adrenal) and nearly all have a noradrenergic biochemical phenotype.
†Associated with maternal imprinting.
‡Cluster 2 tumors are usually adrenal pheochromocytomas with an adrenergic biochemical phenotype.
GIST, Gastrointestinal stromal tumor; MEN, multiple endocrine neoplasia; SDH, succinate dehydrogenase; VHL, von Hippel-Lindau disease.
Modified from Melmed S, Auchus RJ, Goldfine AB, et al., eds. *Williams Textbook of Endocrinology*. 14th ed. Philadelphia: Elsevier; 2020: Table 16.4, p. 550.

Table 555.3 Differential Diagnosis of Pheochromocytoma-Type Spells

ENDOCRINE CAUSES
Carbohydrate intolerance
Hyperadrenergic spells
Hypoglycemia
Pancreatic tumors (e.g., insulinoma)
Pheochromocytoma
Thyrotoxicosis
CARDIOVASCULAR CAUSES
Orthostatic hypotension
Paroxysmal cardiac arrhythmia
Pulmonary edema
Renovascular disease
Syncope (e.g., vasovagal reaction)
PSYCHOLOGIC CAUSES
Factitious (e.g., drugs, Valsalva maneuver)
Hyperventilation
Severe anxiety and panic disorders
Somatization disorder
PHARMACOLOGIC CAUSES
Chlorpropamide-alcohol flush
Combination of a monoamine oxidase inhibitor and a decongestant
Illegal drug ingestion (cocaine, phencyclidine, lysergic acid diethylamide)
Sympathomimetic drug ingestion
Vancomycin (red man syndrome)
Withdrawal of adrenergic inhibitor
NEUROLOGIC CAUSES
Autonomic neuropathy
Diencephalic epilepsy (autonomic seizures)
Migraine headache
Postural orthostatic tachycardia syndrome
Stroke
OTHER CAUSES
Carcinoid syndrome
Mast cell disease
Recurrent idiopathic anaphylaxis
Unexplained flushing spells

Modified from Melmed S, Auchus RJ, Goldfine AB, et al., eds. *Williams Textbook of Endocrinology*. 14th ed. Philadelphia: Elsevier; 2020: Table 16.3, p. 547.

The initial treatment of ACT and PHEO/PGL is *resection by a surgeon experienced in the management of these tumors.* Children with suspected or confirmed PHEO/PGL require preoperative medical management with α-adrenergic blockade (and sometimes β-blockade) to mitigate risk of hypertensive crisis.

Medical therapy for metastatic ACT includes mitotane and chemotherapy with cisplatin, etoposide, and doxorubicin. Endocrine therapy targeting hormonal overproduction may also be needed to palliate symptoms and improve quality of life. Metastatic PHEO/PGL has historically been poorly responsive to cytotoxic chemotherapy. Kinase inhibitor therapy and peptide-receptor radiotherapy (such as ^{177}Lu-DOTATATE) have demonstrated promise in some studies.

Long-term follow-up is warranted for both ACTs and PHEOs to monitor for recurrence, particularly in the context of hereditary tumor predisposition syndromes.

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555.5 Desmoplastic Small Round Cell Tumor

Cynthia E. Herzog

Desmoplastic small round cell tumor **(DSRCT)** is a very rare and aggressive mesenchymal tumor that occurs predominantly in adolescent and young adult males. It is associated with a diagnostic chromosomal translocation between the Ewing tumor gene and the Wilms tumor gene, t(11;22) (p13;q12), creating a chimeric gene *(EWS-WT1)* that encodes a chimeric protein with oncogenic properties. Patients typically present at advanced stage with a bulky abdominal mass, multiple peritoneal and omental implants, and symptoms of abdominal sarcomatosis, including pain, ascites, intestinal obstruction, hydronephrosis, and weight loss. DSRCT mainly involves the abdominal cavity but can spread to the lymph nodes, liver, lungs, and bones, and in ~10% of cases, arise outside of the abdomen. There is no standard treatment approach. Aggressive treatment with combination chemotherapy, debulking surgery, and whole abdominopelvic irradiation results almost universally in a poor outcome. Median survival ranges between 17 and 25 months, and the 5-year overall survival remains <20%. Hyperthermic intraperitoneal chemotherapy may be of benefit but requires further study. Novel targeted agents and radioimmunotherapy with monoclonal antibodies targeting different surface antigens on tumor cells are being studied.

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Chapter 556
Histiocytosis Syndromes of Childhood

Stephan Ladisch

INTRODUCTION

Childhood histiocytoses constitute a diverse group of disorders that are frequently severe in their clinical expression. These disorders are individually rare and are grouped together because they have in common a prominent proliferation or accumulation of cells of the monocyte-macrophage system of bone marrow (myeloid) origin. Although these disorders sometimes are difficult to distinguish clinically, accurate diagnosis is essential for facilitating progress in treatment. A current systematic classification of histiocytoses is based on histopathologic, clinical, and genetic findings (Tables 556.1-556.3) A thorough, comprehensive evaluation of a biopsy specimen obtained at diagnosis is critical. This evaluation includes studies such as immunostaining, molecular genetic analyses, and electron microscopy that may require special sample processing.

CLASSIFICATION AND PATHOLOGY

Three classes of childhood histiocytosis are defined, based on histopathologic findings. The first and best known is **Langerhans cell histiocytosis (LCH)**, previously called *histiocytosis X.* LCH includes the clinical entities of bone or skin limited disease (**eosinophilic granuloma**), **Hand-Schüller-Christian disease,** and **Letterer-Siwe disease.** The normal Langerhans cell is an antigen-presenting cell (APC) of the skin. The hallmark of LCH in all forms is the presence of a clonal proliferation of cells of the monocyte–dendritic cell lineage containing the characteristic electron microscopic findings of a Langerhans cell, the **Birbeck granule**. This tennis racket–shaped bilamellar granule, when seen in the cytoplasm of lesional cells in LCH, is diagnostic of the disease. The Birbeck granule expresses a newly characterized antigen, *langerin* (CD207), which itself is involved in antigen presentation to T lymphocytes. CD207 expression has been established to be uniformly present in LCH lesions and thus becomes an additional reliable diagnostic marker. However, it is now clear that the LCH cell is not actually a (differentiated) Langerhans cell but rather an immature cell of myeloid origin, possibly in an arrested state of development. The definitive diagnosis of LCH is established by demonstrating CD1a positivity of lesional cells, which can be done using fixed tissue (Fig. 556.1). Lesional cells must be distinguished from normal Langerhans cells of the skin, which are also CD1a positive but are only sparsely distributed and are not diagnostic of LCH. The peripheral lesions usually leading to the diagnosis of LCH (e.g., skin, lymph node, bone) contain various proportions of Birbeck granule–containing CD1a-positive cells, lymphocytes, granulocytes, monocytes, and eosinophils.

Clonality of individual lesions exists in some cases of LCH. Importantly, an activating *somatic* pathogenic variant of the *BRAF* gene *(V600E)* (part of the mitogen-activated protein kinase [MAPK] cell signaling pathway: Fig. 556.2) has been identified in many patients with LCH. Studies in patients negative for *BRAFV600E* have revealed pathogenic variants in other genes of the MAPK pathway, including *MAP2K1* and *ARAF.* With the majority of LCH patients having one or another of these activating variants in the MAPK pathway (see Fig. 556.2), it has been suggested that LCH is driven by a disorder in MAPK signaling affecting cell migration and resulting in an accumulation of LCH cells in the lesions.

In contrast to the prominence of an APC in LCH, the other common form of histiocytosis is characterized by accumulation of activated macrophages and lymphocytes and is known as **hemophagocytic lymphohistiocytosis (HLH)**. This diagnosis is the result of uncontrolled hemophagocytosis and uncontrolled activation (upregulation) of inflammatory cytokines driven by an abnormality of T cells. It has some similarities to the **macrophage activation syndrome**. Tissue infiltration by activated CD8 T lymphocytes, activated macrophages, and hypercytokinemia are classic features (Fig. 556.3). With the characteristic morphology of normal macrophages by light microscopy, these phagocytic cells (see Fig. 556.1) are CD163 positive but negative for the markers that are characteristic of LCH cells (Birbeck granules, CD1a, CD207).

The two major forms of HLH, primary and secondary, have indistinguishable pathologic findings but are important to differentiate because of implications for treatment and prognosis. **Primary HLH**, originally named *familial erythrophagocytic lymphohistiocytosis,* is now known as **familial hemophagocytic lymphohistiocytosis (FHLH)**. This disease is an autosomal recessive disorder and represents approximately 25% of patients with HLH (see Table 556.3).

Table 556.1 Main Types of Histiocytosis Disease

DISEASE	HISTIOCYTOSIS CLASSIFICATION GROUP
LANGERHANS CELL HISTIOCYTOSIS	L
Single system	L
Pulmonary	L
Multisystem with no risk organ involvement	L
Multisystem with risk organ involvement	L
ERDHEIM-CHESTER DISEASE	L
Mixed H	L
Indeterminate H	L
Extracutaneous/disseminated JXG with MAPK pathogenic variant (including LALK + H. and other genetic alterations)	L
ROSAI-DORFMAN-DESTOMBES DISEASE	R
Familial	R
Sporadic classical with or without IgG4 infiltration	R
Sporadic extranodal with or without IgG4 infiltration	R
MALIGNANCY HISTIOCYTOSES	M
Primary, phenotypic subtypes	M
Secondary, phenotypic subtypes	M
Histiocytoses with cutaneous or mucosal involvement	C
LYMPHOHISTIOCYTOSES	M
Primary	M
Sporadic	M
Unknown	M

L, Langerhans; R, Rosai-Dorfman-Destombes; M, Malignant, C, cutaneous; H, hemophagocytic; JXG, juvenile xanthogranuloma; MAPK: mitogen-activated kinase.
From Emile JF, Cohen-Aubart F, Collin M, et al. Histiocytosis. *Lancet*. 2021;398:157–168. Supplementary Appendix, Table 1.

Genes are known for four of five familial HLH syndromes and other hereditary causes of HLH; these pathogenic variants affect the ability of T lymphocytes and natural killer (NK) cells to synthesize and release perforin and granzymes, thus reducing cytotoxic granule formation (Fig. 556.4). **Secondary HLH** includes other forms of the syndrome triggered by a separate pathologic process, such as infection *(infection-associated hemophagocytic syndrome),* tumor *(malignancy-associated HLH),* or primary immunodeficiency diseases and metabolic disorders (Tables 556.4 and 556.5). Both primary and secondary HLH affect multiple organs and are characterized by massive infiltrates of hyperactivated lymphocytes and activated phagocytic macrophages in the involved organs, with the lymphocytes serving as the driver of the resulting disease process.

In primary HLH, genetic pathogenic variants in multiple different steps in granule formation and release by cytotoxic T cells have been identified (Fig. 556.5, *bottom*). Pathogenic variants in the *PRF1* perforin gene or the *MUNC13-4* gene are the most common causes of defective function of the cytotoxic lymphocytes whose activity is inhibited in primary HLH. In an analogous way, a trigger can result in secondary HLH (see Fig. 556.5, *top*). A myriad of both infectious and noninfectious processes can trigger secondary HLH (Fig. 556.6; see Table 556.4 and Fig. 556.11). Examples of noninfectious triggers include drugs (e.g., phenytoin, Lamictal, highly active antiretroviral therapy), hematopoietic stem cell transplantation, chemotherapy, autoimmune diseases, inflammatory bowel disease, cancer, and immunodeficiency states (e.g., DiGeorge syndrome, Bruton agammaglobulinemia, severe combined immunodeficiency syndrome, chronic granulomatous disease). A complicating factor in diagnosis is the realization that there are also both mixed genetic variants causing primary HLH and heterozygotic variants (therefore not strictly primary HLH) also causing disease, particularly triggered by infection.

In addition to these two most common forms of childhood histiocytosis (LCH and HLH), rarer diseases are included under this rubric (see Table 556.2). **Juvenile xanthogranuloma (JXG)** is characterized by vacuolated histiocytes with foamy cytoplasm in lesions that evolve into mixed granulomas also containing eosinophils, lymphocytes, and other cells. **Erdheim-Chester disease (ECD)** predominantly affects adults. Surface markers suggest a link among LCH, JXG, and ECD; all three are dendritic cell diseases, and represent a spectrum, or continuum, of differentiation stages of the abnormal dendritic cell precursors, frequently with *BRAFV600E* pathogenic variants in the affected cells. Another rare form of histiocytosis is **Rosai-Dorfman disease**, also known as **sinus histiocytosis** with massive lymphadenopathy. Rosai-Dorfman disease is characterized by packing of sinusoids of the lymph nodes with hemophagocytic histiocytes, although extranodal involvement may also be present. Last, there is a group of unequivocal **malignancies** of cells of monocyte–macrophage lineage. By this definition, acute monocytic leukemia and true malignant histiocytosis are included among the class III histiocytoses (see Chapter 544). True neoplasms of Langerhans cells have been reported but are extremely rare.

556.1 Langerhans Cell Histiocytosis

Stephan Ladisch

CLINICAL MANIFESTATIONS

LCH has an extremely variable presentation. The skeleton is involved in 80% of patients and may be the only affected site, especially in children >5 years old. **Bone lesions (eosinophilic granuloma)** may be single or multiple and are seen most often in the skull (Fig. 556.7). Other sites include the pelvis, femur, vertebra, maxilla, and mandible. Lesions may be asymptomatic or associated with pain and local swelling. Involvement of the spine may result in collapse of the vertebral body, which can be seen radiographically and may cause secondary compression of the spinal cord. In flat and long bones, osteolytic lesions with sharp borders occur, and no evidence exists of reactive new bone formation until the lesions begin to heal. Lesions that involve weight-bearing long bones may result in pathologic fractures. Chronically draining, infected ears are usually associated with destruction in the mastoid area. Bone destruction in the mandible and maxilla may result in teeth that appear to be free floating on radiographs. With response to therapy, healing of bone lesions is usually complete.

Approximately 50% of patients experience **skin involvement** (isolated or part of multisystem disease) at some time during the course of disease. This is a frequently difficult-to-treat scaly, papular, seborrheic dermatitis of the scalp, diaper, axillary, or posterior auricular regions (see Fig. 556.7; Figs. 556.8 and 556.9). The lesions may spread to involve the back, palms, and soles. The exanthem may be petechial or hemorrhagic, even in the absence of thrombocytopenia. Localized or disseminated **lymphadenopathy** is present in approximately 33% of patients. **Hepatosplenomegaly** occurs in approximately 20% of patients. Various degrees of hepatic malfunction may occur, including jaundice and ascites.

Gastrointestinal involvement, more common than previously appreciated**,** can present as vomiting, abdominal pain, bloody diarrhea, and/or failure to thrive.

Exophthalmos, when present, may be bilateral and is caused by retroorbital accumulation of granulomatous tissue. Gingival mucous membranes may be involved with infiltrative lesions that appear superficially like candidiasis. Otitis media is present in 30–40% of patients; deafness may follow

Table 556.2 Clinical Features, Investigations, and Treatment of Langerhans Cell Histiocytosis, Erdheim-Chester Disease, and Rosai-Dorfman-Destombes Disease

	MOST FREQUENT REVEALING CLINICAL FEATURES	INITIAL INVESTIGATIONS* WHEN DIAGNOSIS IS CONFIRMED BY BIOPSY	MOST FREQUENT FIRST-LINE SYSTEMIC THERAPIES FOR MULTIORGAN OR DISSEMINATED FORMS	MOST FREQUENT SYSTEMIC SECOND-LINE AND SALVAGE THERAPIES
Childhood Langerhans cell histiocytosis	Bone pain or fracture; vertebra plana†; skin papules; lymphadenomegaly; palpable tumor; diabetes insipidus†; exophthalmos†; deafness or chronic otorrhea; systemic symptoms with fever, hepatosplenomegaly, or hematologic cytopenia (risk organs); pneumothorax	For all patients: blood tests (full blood count, erythrocyte sedimentation rate or CRP, albumin, renal function tests, liver function tests, coagulation tests); chest and skeletal radiographs According to initial investigations: CT scan or MRI focused on involved area; brain MRI when diabetes insipidus or any sign of CNS involvement or visual or hearing dysfunction; chest high-resolution CT scan when signs of lung involvement	Vinblastine combined with corticosteroids	Should be decided according to initial extension and risk-organ involvement status, as assessed by a trained team With risk organ involvement: BRAF or MEK inhibitors‡ Without risk organ involvement: monotherapy or combined chemotherapies with cladribine, and, in less documented approaches, cytarabine or clofarabine
Adult Langerhans cell histiocytosis	Bone pain or fracture; skin papules; lymphadenopathy; palpable tumor; diabetes insipidus†; exophthalmos†; repeated dental loss; pneumothorax; dyspnea, dry cough	^{18}F-FDG-PET (full body); chest, abdomen, and pelvis CT scan; brain MRI; blood tests (full blood count, CRP, albumin, renal function tests, liver function tests)	Cytarabine, alone or combined with methotrexate; vinblastine combined with corticosteroids; cladribine	BRAF or MEK inhibitors
Erdheim-Chester disease	Lower limb pain; general symptoms (fatigue, weight loss, fever); xanthelasma; diabetes insipidus†; exophthalmos†; dyspnea, dry cough; signs of cardiac involvement (e.g., tamponade); signs of CNS involvement (degenerative or tumoral)	^{18}F-FDG-PET (full body); chest, abdomen, and pelvis CT scan; brain MRI; cardiac MRI; blood tests (full blood count, CRP, albumin, renal function tests, liver function tests)	Interferon alfa-2a or pegylated interferon alfa-2a; other potential options are anakinra, infliximab, or sirolimus plus corticosteroids; BRAF or MEK inhibitors for life-threatening cases (e.g., CNS or heart involvement)	BRAF or MEK inhibitors
Rosai-Dorfman-Destombes disease	Lymphadenopathy; skin nodules; nasal obstruction, epistaxis, nasal dorsum deformity; dyspnea, dry cough; signs of CNS or nerve root involvement; testicular enlargement	Children: chest x-ray with neck and abdominal ultrasound scans Adults: neck, chest, abdomen, and pelvis CT scan; ^{18}F-FDG-PET is recommended by some experts All patients: brain MRI when signs of orbital or CNS involvement; blood tests (full blood count, CRP, albumin, renal function tests, liver function tests)	Corticosteroids; sirolimus; methotrexate; azathioprine	Several drugs or combined chemotherapies or MEK inhibitors reported to be active in case reports or small case series

^{18}F-FDG-PET, ^{18}F-fluorodeoxyglucose PET; CNS, central nervous system..
*Aimed to determine the extent of the disease; thus each clinical feature drives specific investigation of the potentially involved organ(s), including for any signs of endocrine dysfunction or autoimmunity.
†Features that are suggestive of the disease.
‡BRAF inhibitors: vemurafenib, dabrafenib, encorafenib. MEK inhibitors: cobimetinib, trametinib, binimetinib, selumetinib.
From Emile JF, Cohen-Aubart F, Collin M, et al. Histiocytosis. *Lancet*. 2021;398:157–168. Fig. 1, p. 158.

destructive lesions of the middle ear. In 10–15% of patients, **pulmonary infiltrates** are found on radiography. The lesions may range from diffuse fibrosis and disseminated nodular infiltrates to diffuse cystic changes (Fig. 556.10). Rarely, pneumothorax is a complication. If the lungs are severely involved, tachypnea and progressive respiratory failure may result.

Pituitary dysfunction or hypothalamic involvement in patients often presents as diabetes insipidus and may also cause growth retardation. Patients suspected of having LCH should demonstrate the ability to concentrate their urine before going to the operating room for a biopsy. Rarely, panhypopituitarism may occur, as may primary hypothyroidism as a result of thyroid gland infiltration.

Patients with multisystem disease who are affected more severely are those who have systemic manifestations, including fever, weight loss, malaise, irritability, and failure to thrive. These systemic manifestations will distinguish patients at high risk of mortality (i.e., risk organ–positive, or RO+, patients) from patients at low risk of mortality (i.e., without systemic

Table 556.3 Hemophagocytic Lymphohistiocytosis

DISEASE	GENE	PROTEIN	PERCENTAGE OF FHLH	IMMUNE IMPAIRMENT	UNIQUE CLINICAL CHARACTERISTICS
FHLH-1	Unknown		Rare	Cytotoxicity	
FHLH-2	*PRF1*	Perforin	~20–37, 50delT mainly in African American/ African descent	Cytotoxicity; forms pores in APCs	
FHLH-3	*UNC13D*	Munc13–4	20–33	Cytotoxicity; vesicle priming	Increased incidence of CNS HLH
FHLH-4	*STX11*	Syntaxin	<5	Cytotoxicity; vesicle fusion	Mild recurrent HLH, colitis
FHLH-5	*STXBP2*	Syntaxin-binding protein 2	5–20	Cytotoxicity; vesicle fusion	Colitis, hypogammaglobulinemia
SYNDROMES WITH PARTIAL OCULOCUTANEOUS ALBINISM					
Griscelli syndrome	*RAB27A*	Rab27A	~5	Cytotoxicity; vesicle docking	Partial albinism, silver-gray hair
Chédiak-Higashi syndrome	*LYST*	Lyst	~2	Cytotoxicity; heterogeneous defects in NK cells	Partial albinism, bleeding tendency, recurrent infections
Hermansky-Pudlak syndrome type II	*AP3B1*	AP-3 complex subunit β_1	Rare	Cytotoxicity; vesicle trafficking	Partial albinism, bleeding tendency
EBV-DRIVEN AND RARE CAUSES					
XLP1	*SH2D1A*	SAP	~7	Signaling in cytotoxic NK and T cells	Hypogammaglobulinemia, lymphoma
XLP2	*BIRC4*	XIAP	~2	NK T-cell survival and NF-κB signaling	Mild recurrent HLH, colitis
ITK deficiency	*ITK*	ITK	Rare	IL-2 signaling in T cells	Hypogammaglobulinemia, autoimmunity, Hodgkin lymphoma
CD27 deficiency	*CD27*	CD27	Rare	Signal transduction in lymphocytes	Combined immunodeficiency, lymphoma
XMEN syndrome	*MAGT1*	MAGT1	Rare	Magnesium transporter, induced by TCR stimulation	Lymphoma, recurrent infections, CD4 T-cell lymphopenia
NLRC4 GOF	*NLRC4* Somatic or germline variants	NLRC4 inflammasome	Rare	↑ IL-18	Responds to recombinant IL-18BP
CDC42	*CDC42*	CDC42	Rare	↑ IL-18, variants interfere with binding and localization of CDC42	Neonatal cytopenias, hepatosplenomegaly, fevers, urticaria-like rashes, facial dysmorphisms
CD70	*CD70*	CD70 interaction with CD27	Rare	↓ expression and ↓ cytotoxicity of T cells	EBV susceptibility to HLH
CTPS1	*CTPS1*	Cytidine nucleotide triphosphate synthesis	Rare	Impaired proliferation of NKT cells	EBV susceptibility
RASGRP1	*RASGRP1*	RASGRP1	Rare	Activates RAS; defects in T-cell activation, migration, proliferation ↓ cytotoxicity ↓ NKT cells	EBV susceptibility to HLH

APCs, Antigen-presenting cells; CNS, central nervous system; EBV, Epstein-Barr virus; FHLH, familial hemophagocytic lymphohistiocytosis; GOF, gain of function; HLH, hemophagocytic lymphohistiocytosis; ITK, interleukin (IL)-2–inducible T-cell kinase; NF-κB, nuclear factor–kappa B; NK, natural killer; TCR, T-cell receptor; XLP-1, 2-X-linked lymphoproliferative diseases.

Adapted from Erker C, Harker-Murray, Talano JA. Usual and unusual manifestations of familial hemophagocytic lymphohistiocytosis and Langerhans cell histiocytosis. *Pediatr Clin North Am.* 2017;64:91–109. Table 1.

manifestations; risk organ–negative patients). The **risk organs** are liver, spleen, and the hematopoietic (bone marrow) system. The lung is not considered a risk organ. The distinction of risk-organ involvement is important for deciding the intensity of the treatment approach and has been addressed in standard treatment approaches for LCH, as delineated in the Histiocyte Society protocols. Bone marrow involvement may cause anemia and thrombocytopenia. Two uncommon but serious manifestations of LCH are hepatic involvement (leading to fibrosis and cirrhosis) and a peculiar central nervous system (CNS) involvement characterized by ataxia, dysarthria, and other neurologic symptoms. **Hepatic involvement** is associated with multisystem disease that is often already present at diagnosis. In contrast, neurodegenerative **CNS involvement**, which is progressive and

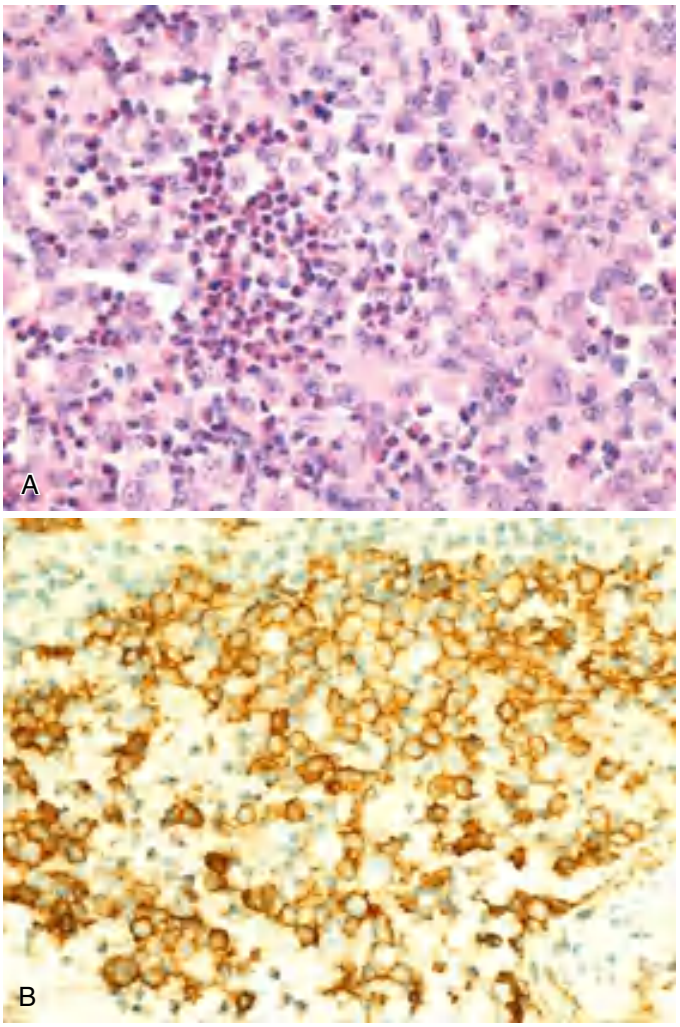

Fig. 556.1 A, Histopathology of Langerhans cell histiocytosis (LCH) shows eosinophilic granuloma of a lytic bone lesion of the femoral head. Multiple LCH cells with characteristic grooved nuclei, as well as numerous eosinophils, are visible in this mixed infiltrate. B, CD1a staining, characteristic and diagnostic of lesions with LCH cells.

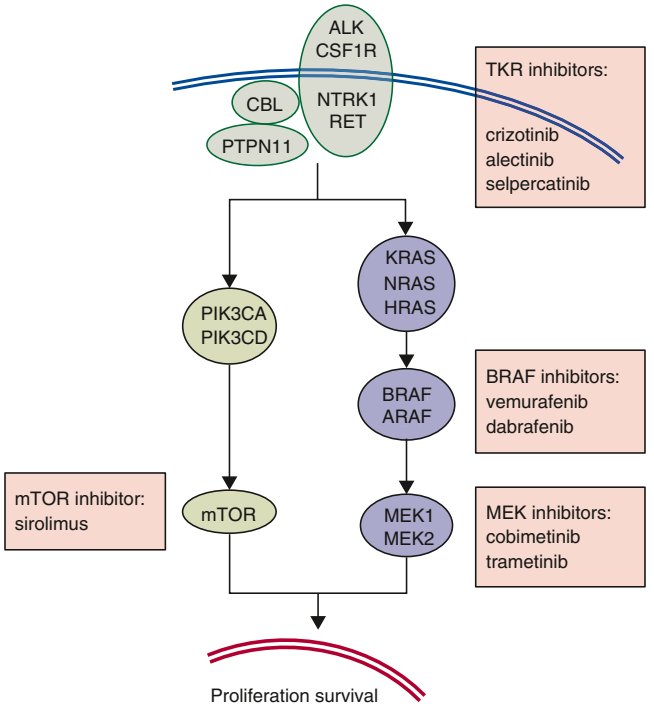

Fig. 556.2 Proteins of the MAP kinase cell-signaling pathway involved by activating pathogenic variants, and inhibitors already reported to benefit patients with histiocytosis. *(From Emile JF, Cohen-Aubart F, Collin M, et al. Histiocytosis. Lancet. 2021;398:157–168. Fig. 1.)*

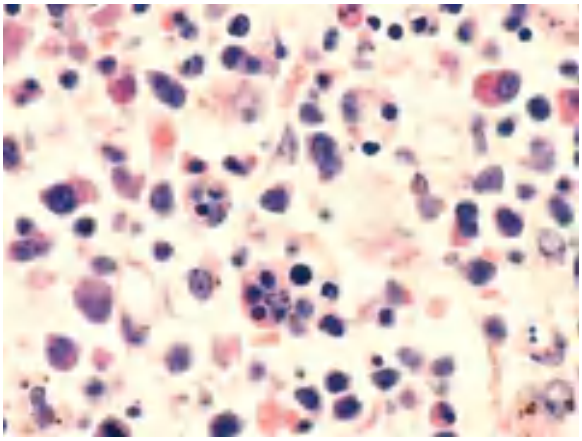

Fig. 556.3 Bone marrow aspirate of a child with familial (genetically confirmed) hemophagocytic lymphohistiocytosis. Numerous characteristic hemophagocytic cells (which are CD163-positive macrophages) are seen ingesting various blood elements.

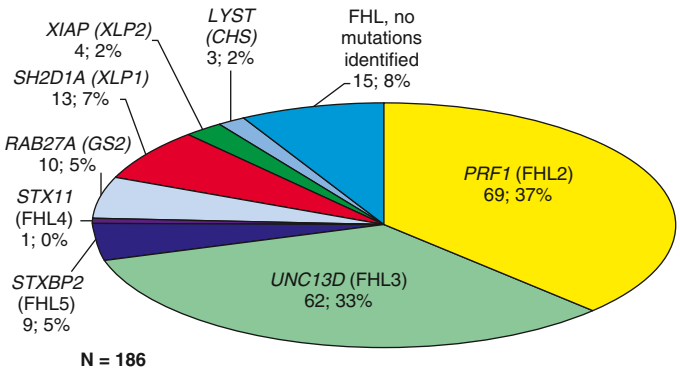

Fig. 556.4 Different genetic subtypes in 171 patients with familial hemophagocytic lymphohistiocytosis (FHL) or FHL-related disease. For each subtype, the name of the gene, the abbreviation of the disease subtype, the absolute number, and the percentage are shown. Furthermore, we include as FHL one subgroup of 15 patients with either familial recurrence or refractory/recurrent disease despite specific therapy and/or repeatedly documented severe functional defect in degranulation or cytotoxicity assays. *(From Cetica V, Sieni E, Pende D, et al. Genetic predisposition to hemophagocytic lymphohistiocytosis: Report on 500 patients from the Italian registry. J Allergy Clin Immunol. 2016;137:188–196. Fig. 2, p. 191.)*

histopathologically characterized by gliosis and has no definitive treatment, may be observed only many years after the initial diagnosis of LCH. These manifestations are not known to be associated with LCH cells, Birbeck granules, CD1a positivity, or any other indication of LCH cell infiltration, raising questions about their pathogenesis and the suggestion that they may be cytokine-mediated.

After tissue biopsy, which is diagnostic of LCH and is easiest to perform on skin or bone lesions, a comprehensive clinical and laboratory evaluation is essential and should be undertaken. This should include a series of studies in all patients: CBC, liver function tests, coagulation studies, skeletal survey, chest radiograph, and measurement of urine osmolality. In addition, detailed evaluation of any organ system shown to be involved by physical examination or by these studies should be performed to establish the extent of disease before initiation of treatment.

TREATMENT AND PROGNOSIS

The clinical course of **single-system disease** (usually bone, lymph node, or skin) generally is benign, with a high chance of spontaneous remission. Therefore treatment should be minimal and should be directed at arresting the progression of a bone lesion that could result in permanent damage before it resolves spontaneously. Curettage or, less often but especially

Table 556.4 Infections Associated with Hemophagocytic Syndrome

VIRAL
Adenovirus
Cytomegalovirus (CMV)
Dengue virus
Epstein-Barr virus (EBV)
Enteroviruses
Herpes simplex viruses (HSV1, HSV2)
Human herpesviruses (HHV6, HHV8)
HIV
Influenza viruses
Parvovirus B19
Varicella-zoster virus (VZV)
Hepatitis viruses
Measles
Parechovirus
BACTERIAL
Babesia microti
Brucella abortus
Enteric gram-negative rods
Haemophilus influenzae
Mycoplasma pneumoniae
Staphylococcus aureus
Streptococcus pneumoniae
Ehrlichia chaffeensis
FUNGAL
Candida albicans
Cryptococcus neoformans
Histoplasma capsulatum
Fusarium
MYCOBACTERIAL
Mycobacterium tuberculosis
RICKETTSIAL
Coxiella burnetii
Other rickettsial diseases
PARASITIC
Leishmania donovani
Plasmodium

From Nathan DG, Orkin SH, Ginsburg D, et al., eds. *Nathan and Oski's Hematology of Infancy and Childhood*. 6th ed. Philadelphia: Saunders; 2003, p. 1381.

Table 556.5 Other Primary Immunodeficiency and Inherited Metabolic Diseases That May Be Complicated (Rarely) by Hemophagocytic Lymphohistiocytosis

PRIMARY IMMUNODEFICIENCY DISEASES
SCID
CIDs
DiGeorge syndrome
Wiskott-Aldrich syndrome
Ataxia telangiectasia
Dyskeratosis congenita
ORAI-1 deficiency
Chronic granulomatous disease
Other PIDs
X-linked agammaglobulinemia
Autoimmune lymphoproliferative syndrome
STAT1 gain of function
CTLA4
GATA2
TRAPS
FMF
NEMO
TIM3
DOCK8
STAT2
STAT3
PIK3CD
INBORN ERRORS OF METABOLISM
Lysinuric protein intolerance
Multiple sulfatase deficiency
Biotinidase deficiency
Lysosomal acid lipase deficiency/Wolman disease
Methylmalonic acidemia
Galactosemia
Gaucher disease
Pearson syndrome
Galactosialidosis
Propionic acidemia
Cobalamin C disease
Niemann-Pick disease
LCHAD deficiency
CONGENITAL DISORDERS OF GLYCOSYLATION
COG6

From Canna SW, March RA. Pediatric hemophagocytic lymphohistiocytosis. *Blood*. 2020;135(16):1332–1343. Table 5.

when a weight-bearing bone is involved, corticosteroid injection or low-dose local radiation therapy (5-6 Gy) may accomplish this goal.

In contrast, **multisystem disease** requires treatment with systemic multiagent chemotherapy. Several different regimens have been proposed, but central elements are the inclusion of vinblastine and corticosteroids, both of which have been found to be very effective in treating LCH. Etoposide has been excluded from the standard treatment of multisystem LCH, which is treated with multiple agents, designed to reduce mortality, reactivation of disease, and long-term consequences. The response rate to therapy is quite high, and mortality in severe LCH has been substantially reduced by multiagent chemotherapy, especially if the diagnosis is made accurately and expeditiously. The most recent treatment results associated with lengthened continuation therapy (HS LCH-III) show a greater than 85% survival rate in severe (RO+) multisystem disease and a reduced rate of reactivation.

Experimental therapies are suggested only for unresponsive disease (often in very young children with multisystem disease and organ dysfunction who have not responded to multiagent initial treatment) and reactivation of RO+ disease in risk organs but not in reactivation of mild disease (any risk organ–negative reactivations) (see Fig. 556.2). The approaches include immunosuppressive therapy with cyclosporine/antithymocyte globulin and possibly imatinib, 2-chlorodeoxyadenosine, and clofarabine. With the discovery of the *BRAFV600E* pathogenic variant causing hyperactivation of the MAPK pathway in LCH cells, pharmacologic inhibition of BRAF and pharmacologic inhibition of MEK are currently the subject of clinical trials as therapeutic approaches for resistant disease.

Late (fibrotic) complications, whether hepatic or pulmonary, are irreversible and require organ transplantation to be definitively treated. Current treatment approaches and experimental protocols for both LCH and HLH can be obtained at the Histiocyte Society website (http://www.histiocytesociety.org). An unresolved problem is treatment of the (usually late-onset) severe, progressive, and intractable LCH-associated **neurodegenerative** syndrome. This is also under investigation for response to experimental therapies, including the pharmacologic inhibitors of the MAPK pathway. Regarding current treatment recommendations for LCH as well as HLH, the continuing rapid advances in understanding of their pathogeneses is likely to result in further rapid development and validation of new therapeutic approaches.

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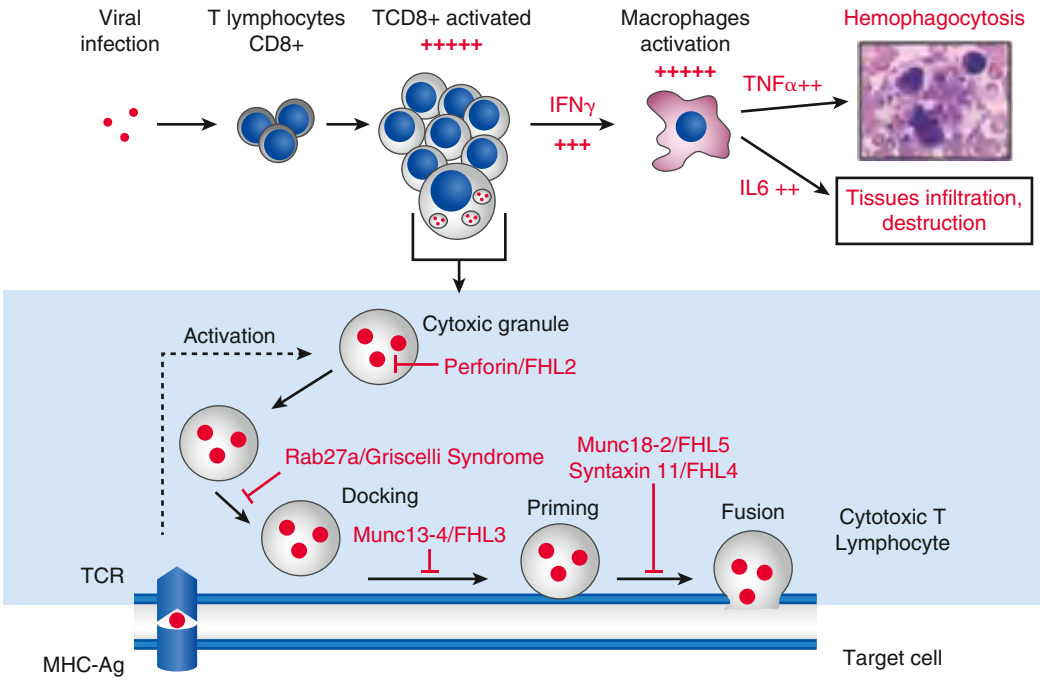

Fig. 556.5 Inborn errors in the cytotoxic activity of lymphocytes. **Top,** Immune mechanisms leading to the occurrence of a hemophagocytic syndrome. Following a viral infection, antigen-specific $CD8^+$ T lymphocytes undergo massive expansion and activation and secrete high levels of interferon (IFN)-γ. The overwhelming activated effector cells induce excessive macrophage activation and proinflammatory cytokine production, including tumor necrosis factor (TNF)-α and interleukin-6 (IL-6). Macrophages spontaneously phagocytose blood elements (platelets, red blood cells, and a polymorphonuclear cell shown here). Activated lymphocytes and macrophages infiltrate various organs, resulting in massive tissue necrosis and organ failure. **Bottom,** Genetic variants causing hemophagocytic lymphohistiocytic syndrome (HLH) affect a precise step of the cytotoxic machinery: granule content, docking, priming, or fusion. Only the defects causing Griscelli syndrome and familial hemophagocytic lymphohistiocytosis (FHL) are shown. MHC-Ag, Major histocompatibility complex antigen; TCR, T-cell receptor. *(From Pachlopnik Schmid J, Cote M, Menager MM, et al. Inherited defects in cytotoxic lymphocyte activity. Immunol Rev. 2010;235:10–23.)*

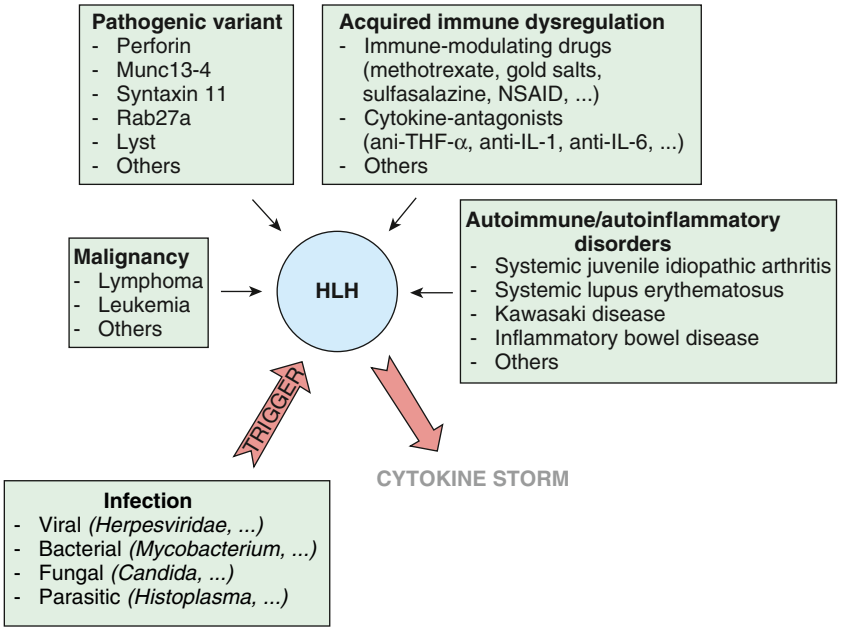

Fig. 556.6 Hemophagocytic lymphohistiocytosis (HLH) comprises a heterogeneous spectrum of disorders that all present with severe cytokine storm and life-threatening immunopathology. HLH can be caused by pathogenic variants in genes involved in granule-mediated cytotoxicity but can also be acquired on a multitude of underlying autoimmune/autoinflammatory diseases or malignancies, with possible facilitation by immunomodulating therapies. Clinical manifestations of HLH are generally precipitated by an infection. IL, Interleukin; NSAID, nonsteroidal antiinflammatory drugs. *(From Brisse E, Wouters CH, Matthys P. Hemophagocytic lymphohistiocytosis (HLH): a heterogeneous spectrum of cytokine-driven immune disorders. Cytokine Growth Factor Rev. 2015;26:263–280. Fig. 2, p. 267.)*

Fig. 556.7 Langerhans cell histiocytosis. **A,** Young child with disseminated Langerhans cell histiocytosis (LCH) skin lesions. **B,** Chest CT scan showing multiple cysts. **C,** X-rays showing LCH involvement of the skull. **D,** X-rays showing LCH involvement of the mandible, as revealed by so-called floating teeth. **E,** MRI showing a femoral lesion revealed by a fracture. **F,** CT scan showing the spinal column. **G and H,** MRI showing degenerative neuro-LCH on axial T2 spin echo-weighted images, which reveal symmetrical hyperintensities within the cerebellar corpus medullare *(arrows). (From Emile JF, Cohen-Aubart F, Collin M, et al. Histiocytosis. Lancet. 2021;398:157–168. Fig. 2.)*

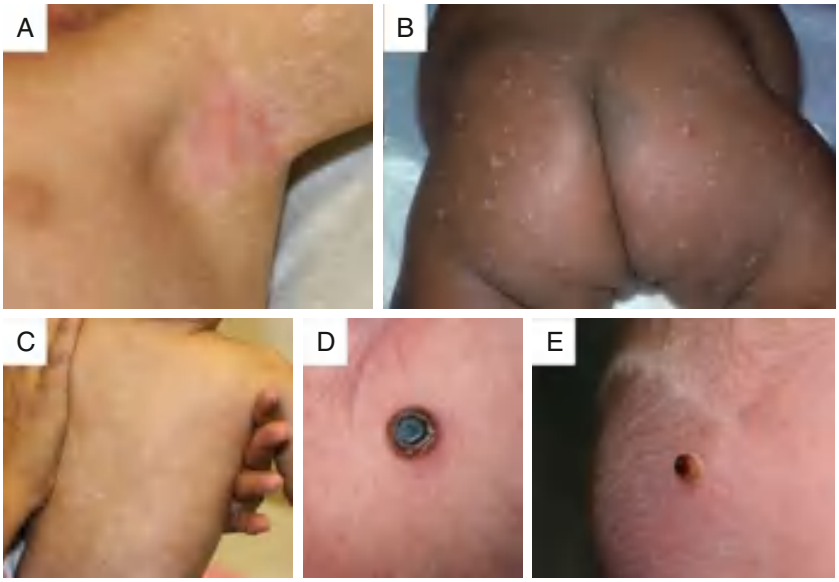

Fig. 556.8 Variable appearance of Langerhans cell histiocytosis of skin. **A,** Eczematous dermatitis. **B,** Hypopigmented, eroded papules. **C,** Hypopigmented macules. **D** and **E,** Crusted papulonodules. Presentation does not reflect presence or absence of multisystem disease. Despite similar appearance, the patient in **D** had a single lesion, whereas the patient in **E** had organ involvement. *(From Simko SJ, Garmezy B, Abhyankar H, et al. Differentiating skin-limited and multisystem Langerhans cell histiocytosis. J Pediatr. 2014;165:990–996. Fig. 3.)*

Fig. 556.9 Langerhans cell histiocytosis presenting as "blueberry muffin" rash in neonate. Multiple firm, nonblanching, purple papules affecting the head and neck (A) and the body (B). *(From Schmitt AR, Wetter DA, Camilleri MJ, et al. Langerhans cell histiocytosis presenting as a blueberry muffin rash. Lancet. 2017;390:155.)*

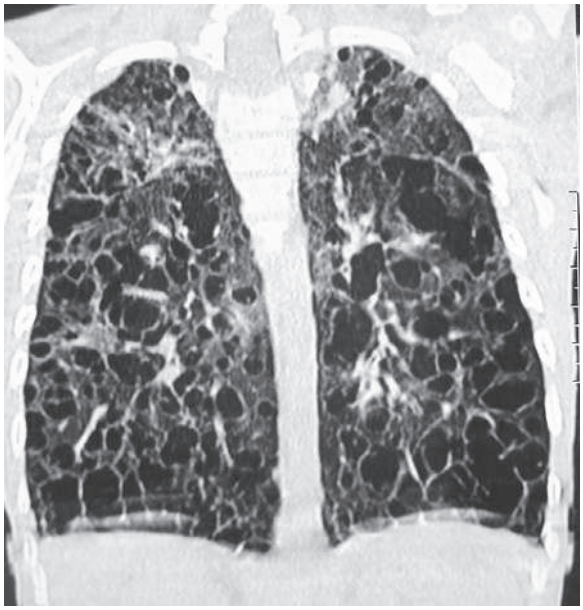

Fig. 556.10 High-resolution coronal CT image (lung window) reveals diffuse lung cysts with parenchymal destruction in bilateral lung fields. *(From Chauhan L, Aggarwal N. Honey-comb Langerhans cell histiocytosis. J Pediatr. 2016;168:248. Fig. 2.)*

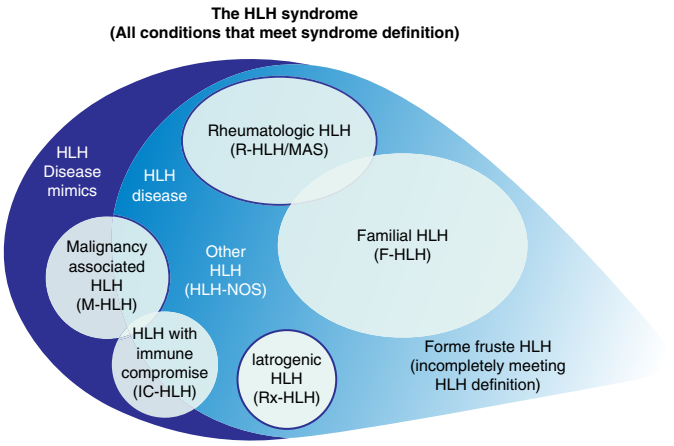

Fig. 556.11 Spectrum of the hemophagocytic lymphohistiocytosis (HLH) syndrome. The HLH syndrome includes all conditions meeting consensus diagnostic criteria. This syndrome includes conditions that would benefit from HLH-directed immunosuppressive therapies, which are termed "HLH disease," and those conditions that would not benefit from such therapy or require entirely different treatments, termed "HLH disease mimics." HLH disease includes recognizable subgroups: familial HLH with clear genetic etiology, HLH associated with malignancy, HLH associated with rheumatologic conditions (also called MAS), HLH observed after immune-activating therapies (iatrogenic HLH, also called cytokine release syndrome), HLH associated with immune compromise (either primary immune deficiency or treatment-related immune suppression), and HLH not associated with other specific conditions. Recognition of these subcategories is valuable as this may alter treatment. *(From Jordan MB, Allen CE, Greenberg J, et al. Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: Recommendations from the North American Consortium (NACHO). Pediatr Blood Cancer. 2019;66:e27929.)*

556.2 Hemophagocytic Lymphohistiocytosis

Stephan Ladisch

See the previous section on "Classification and Pathology," Table 556.3, and Chapter 174.

CLINICAL MANIFESTATIONS

Primary FHLH and secondary HLH have a remarkably similar, clinically indistinguishable presentation (Fig. 556.11). It consists of a generalized disease process, most often with fever (90–100%), maculopapular and/or petechial rash (10–60%), weight loss, and irritability. The initial clinical presentation can vary but is usually severe. In the case of secondary HLH, onset may be camouflaged by a primary disease process. Acute presentations of HLH include a hyperferritinemic septic shock–like picture, acute respiratory distress, seizures, ataxia, focal lesions, or coma (because of CNS infiltration). Other features that are frequently present result from bone marrow involvement and pancytopenia or hepatic dysfunction.

Children with primary HLH are generally <1-2 years old, and children with secondary HLH typically present at an older age, but both forms may present at any age. **Physical examination** often reveals hepatosplenomegaly (70–100%), lymphadenopathy (20–50%), respiratory distress (40–90%), jaundice, and symptoms of CNS involvement (50%) that are not unlike those of aseptic meningitis, CNS vasculitis, or acute demyelinating encephalomyelitis. MRI may demonstrate systemic T2 weighted/fluid-attenuated inversion recovery (FLAIR) hyperintensities in gray and white matter and in supratentorial and infratentorial regions (Fig. 556.12). The cerebrospinal fluid (CSF) pleocytosis (50–90%) associated with CNS involvement in primary HLH is characterized by cells that are the same phagocytic macrophages found in the peripheral blood or bone marrow. HLH may initially or only manifest CNS symptoms. Isolated neuroinflammation may be present in the absence of cytopenias, splenomegaly, or other systemic features. Approximately 35% will eventually develop diagnostic features of HLH (Table 556.6). The interval from neurologic onset to eventual diagnosis often exceeds 2 years. In CNS isolated disease, the diagnosis of familial HLH is often made by whole exome sequencing for other diseases.

The **diagnosis** of HLH is arrived at in two stages. The first stage is based on a set of eight clinical and laboratory findings, with the presence of five of the eight being diagnostic of HLH. The eight findings, formulated by the Histiocyte Society, are fever, splenomegaly, cytopenia of two cell lines (in 90–100%), hypertriglyceridemia (80–100%) or hypofibrinogenemia (65–85%), hyperferritinemia (≥500 but often >10,000), extremely elevated soluble CD25 (interleukin-2 receptor), reduced or absent NK cell activity, and bone marrow, CSF, or lymph node evidence of hemophagocytosis (see Table 556.6). The second stage involves genetic analysis and is undertaken as quickly as possible but generally requires ~2 weeks to complete and should not interfere with initiation of treatment (Fig. 556.13). The genetic findings and family history will determine whether the diagnosis is (autosomal

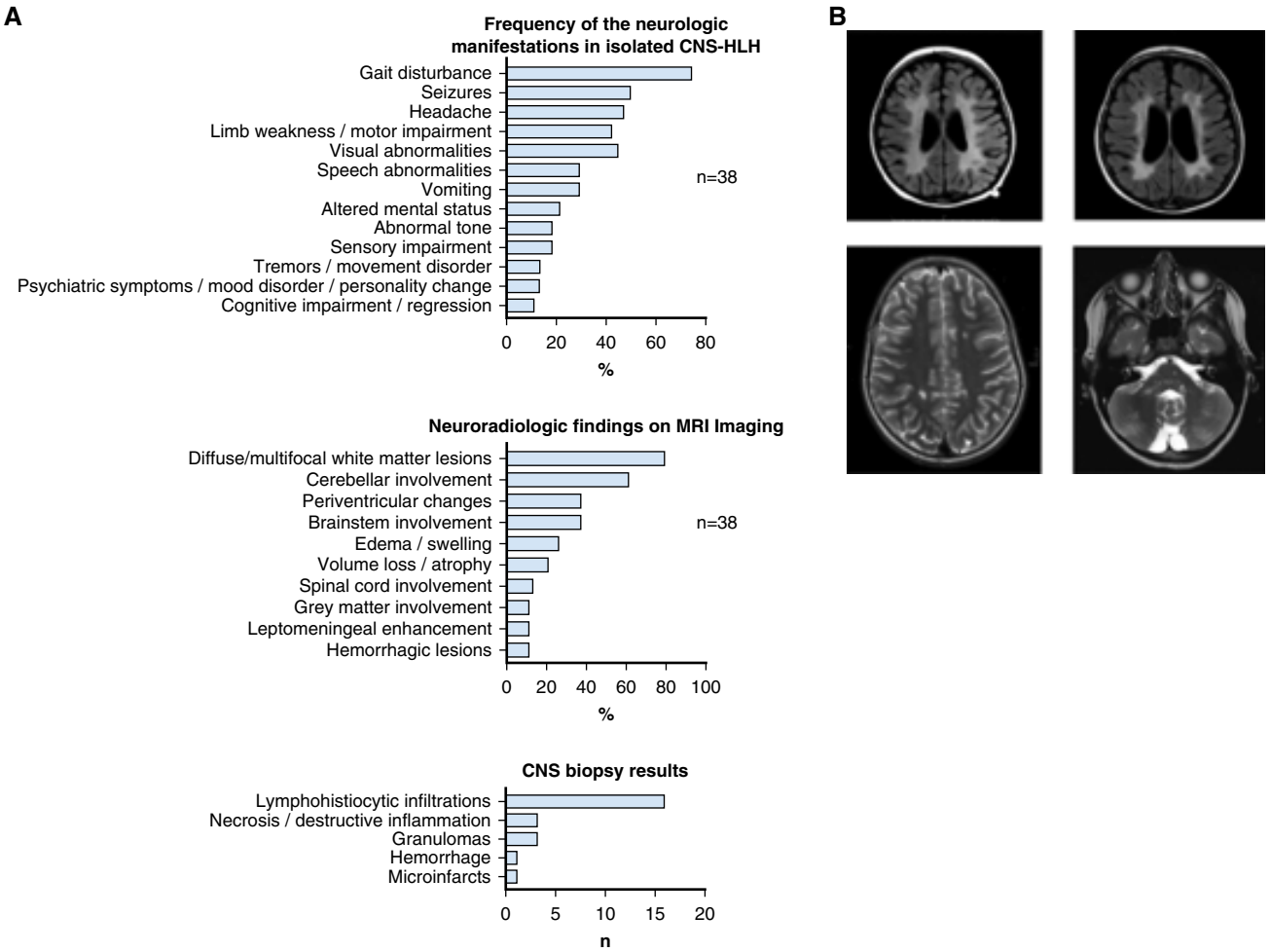

Fig. 556.12 A, Frequencies of neurologic manifestations, neuroradiologic findings, and histopathologic central nervous system (CNS) biopsy results in 38 patients with isolated CNS hemophagocytic lymphohistiocytosis (HLH). B, Examples of CNS MRI imaging in patients with isolated CNS-HLH. *Upper panels*, T2 images in one patient from 2016 *(left)* and 2017 *(right)* demonstrate cerebral atrophy with diffuse white matter involvement. Neuroradiologic findings on MRI show imaging abnormalities. *Lower panels*, T2 images from another patient reveal multiple nodular lesions in the pons, cerebellum, and white matter. *(From Blincoe A, Heeg M, Campbell PK, et al. Neuroinflammatory disease as an isolated manifestation of hemophagocytic lymphohistiocytosis. J Clin Immunol. 2020;40:901–916. Fig. 1.)*

recessive) primary HLH, secondary HLH, or a genetic hybrid form of HLH.

Hemophagocytosis is not specific for HLH and should be considered only in the context of the diagnostic criteria. No absolute clinical or laboratory distinction can be made between primary HLH and secondary HLH. In some subgroups of HLH, perforin assays may be normal. Similarly, some patients with primary FHLH have no known identifiable pathogenic variant, while new genetic variants associated with HLH continue to be discovered.

In the absence of either (1) a documented genetic defect coupled with defective NK cell cytotoxicity or (2) frank hemophagocytosis, care should be taken in making the diagnosis of secondary HLH, given the implication to use cytotoxic chemotherapy. The nonspecific criteria (indicative of inflammation) used to diagnose HLH can also be seen in diseases that are not always associated with hemophagocytosis (e.g., overwhelming acute viral infection with appropriate T-cell activation), in which the cytotoxic and immunosuppressive therapy used in treating HLH might be contraindicated.

Macrophage activation syndrome, particularly in the context of systemic-onset juvenile idiopathic arthritis (JIA) or infection, has many similarities to HLH (see Chapter 196). Indeed, whole exome sequencing of patients with systemic-onset JIA or those with fatal influenza has revealed a higher than expected incidence of HLH genes.

TREATMENT AND PROGNOSIS

Therapy for **primary HLH** (autosomal recessive genetic disease or familial occurrence) consists of a combination of etoposide, dexamethasone, cyclosporine, and intrathecal methotrexate. It should be stressed that pancytopenia and the presence of an infection are *not* contraindications to cytotoxic or immunosuppressive therapy (etoposide and steroid, cyclosporine or antithymocyte globulin for maintenance therapy). Paradoxically they ameliorate the HLH. Emapalumab, a monoclonal antibody against interferon-γ, is approved for recurrent, refractory, or progressive familial HLH or for patients who cannot tolerate chemotherapy. The goal for all therapies is to reach the point of initiating **stem cell transplantation,** to date the only known potentially curative treatment for primary HLH, effective in achieving cure in >60% of patients. Chemotherapy is inadequate for sustained cure of primary HLH, which is ultimately fatal without transplantation.

In **secondary HLH**, it is critical that the underlying disease (e.g., infection, malignancy) be identified and successfully treated. The diagnostic distinction between primary HLH and secondary HLH sometimes can be based on the acute onset of secondary HLH in the presence of an already documented infection or cancer, including leukemia, and certain autoimmune or immunodeficiency disorders. In this case, treatment of the underlying infection is coupled with supportive care. If the diagnosis is made in the setting of iatrogenic immunodeficiency, immunosuppressive

Table 556.6 Diagnostic Criteria for the HLH-2004 Trial and Their Relevance for Clinical Diagnosis

HLH2004 ENTRY CRITERIA	COMMENT
A. Molecular diagnosis consistent with HLH: Pathogenic variants of *PRF1, UNC13D, STXBP2,* Rab27a, *STX11, SH2D1A,* or *XIAP* or	In a patient with known variants, treatment before full development of HLH may be appropriate, but genetic studies usually just help to define HLH recurrence risk, not the presence of an active disease state.
B. Five of the eight criteria listed below are fulfilled	
1. Fever ≥38.3°C	Nearly universal in untreated HLH.
2. Splenomegaly	Although splenomegaly and hepatomegaly are very common in HLH, adenopathy is not.
3. Cytopenias (affecting at least two of three lineages in the peripheral blood): Hemoglobin <9 g/dL (in infants <4 wk: hemoglobin <10 g/dL), platelets <100 × 10^3/mL, neutrophils <1 × 10^3/mL	Cytopenias are ubiquitous in HLH. Lack of cytopenias should make one doubt a diagnosis of HLH, except in the special case of isolated, CNS-only disease.
4. Hypertriglyceridemia (>265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL)	Low fibrinogen in the context of inflammation is paradoxical and one of the more distinctive features of HLH.
5. Hemophagocytosis in bone marrow or spleen or lymph nodes or liver	Not specific to HLH, or essential for the diagnosis, but helpful as a disease marker. Of note, it is often not evident early after disease onset.
6. Low or absent NK-cell activity	More modern and robust assays measuring perforin levels and its degranulation should replace this assay for reliable diagnosis of HLH. This assay is not specific for primary HLH.
7. Ferritin >500 ng/mL	Most patients have much higher levels than this threshold suggests.
8. Elevated soluble CD25 (soluble IL-2 receptor α)	As HLH is a T-cell driven disease, this assay is extremely informative for diagnosis and response to therapy.

HLH, Hemophagocytic lymphohistiocytosis; NK, natural killer; IL, interleukin; CNS, central nervous system.
From Jordan MB, Allen CE, Greenberg J, et al. Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: Recommendations from the North American Consortium (NACHO). *Pediatr Blood Cancer.* 2019;66(11):e27929. Table 1.

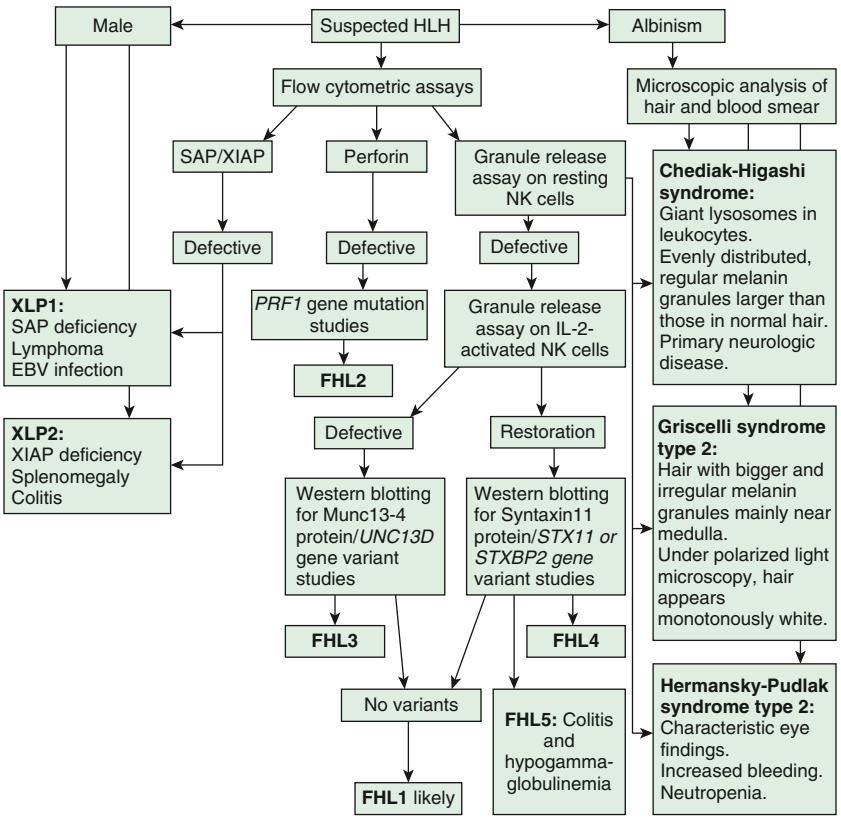

Fig. 556.13 Algorithm for identification of genetic causes of hemophagocytic lymphohistiocytosis (HLH). The HLH algorithm is based on flow cytometry assays: all the patients fitting into HLH criteria, irrespective of age and clinical presentations, should be screened for perforin expression and granule release assay. All male patients should be screened for signaling lymphocyte activation molecule–associated protein (SAP) and X-linked inhibitor of apoptosis protein (XIAP) expression. For patients clinically presenting with albinism, microscopic analysis of hair and blood smear is essential for differential diagnosis of Chédiak-Higashi syndrome, Griscelli syndrome, and Hermansky-Pudlak syndrome. Based on the defect in expression of a particular protein identified, molecular characterization for the respective gene should be performed for confirmation of diagnosis. EBV, Epstein-Barr virus; FHL, familial hemophagocytic lymphohistiocytosis; IL, interleukin; NK, natural killer. *(Adapted from Madkaikar M, Shabrish S, Desai M. Current updates on classification, diagnosis and treatment of hemophagocytic lymphohistiocytosis (HLH). Indian J Pediatr. 2016;83:434–443.)*

treatment should be withdrawn and supportive care instituted along with specific therapy for the underlying infection. In many patients the prognosis is excellent without additional specific treatment other than treating the triggering infection. However, when a treatable infection or other cause cannot be documented, and when the clinical presentation is severe, the prognosis for secondary HLH is as poor as for primary HLH. These patients should receive the identical initial 8-week chemotherapeutic approach, including etoposide, even in the face of cytopenias. In both primary and secondary HLH, the cytotoxic effect of etoposide on macrophages interrupts cytokine production and the consequent cytokine storm, the hemophagocytic process, and the accumulation of macrophages, all of which may contribute to the pathogenesis of **infection-associated hemophagocytic syndrome**. A broad spectrum of infectious agents, including viruses (e.g., cytomegalovirus, Epstein-Barr virus, human herpesvirus 6), fungi, protozoa, and bacteria, may trigger secondary HLH, often in the setting of immunodeficiency (see Table 556.3). A thorough evaluation for infection should be undertaken in immunodeficient patients with hemophagocytosis. The same syndrome may be identified in conjunction with a rheumatologic disorder (e.g., systemic lupus erythematosus, Kawasaki disease) or a neoplasm (e.g., leukemia). In these patients, effective treatment of the underlying disease (e.g., infection, cancer) is critical and may itself lead to ultimate resolution of the hemophagocytosis. In addition anakinra or ruxolitinib (JAK inhibitors) has been used in patients with secondary HLH.

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556.3 Other Histiocytoses

Stephan Ladisch

Other rare histiocytoses that have been named for their clinical presentation include xanthogranuloma in JXG, ECD, and striking lymphadenopathy in Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy). JXG and ECD may require systemic treatment with cytotoxic chemotherapy or potentially MAPK pathway inhibitors, reflecting the presence of a *BRAF* pathogenic variant. Rosai-Dorfman disease usually is not treated, although the massive lymphadenopathy may require intervention because of its tendency to cause physical obstruction.

Rare histiocytic malignancies include acute monocytic leukemia, true malignant histiocytosis, and histiocytic sarcoma. Also included is the more recently identified histiocytic malignancy, ALK+ histiocytosis, which is a systemic histiocytic proliferation presenting as disseminated disease in infants. The cells bear histiocytic markers (CD68, CD163) but not those of LCH (CD1a, BRAF V600E). Whereas all these rare histiocytic malignancies are referred to as histiocytoses because of their monocyte-macrophage lineage, they are better considered under the rubric of true proliferative malignancies of the monocyte–macrophage lineage.

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