



Chapter 84

Lymphoproliferative, Leukemic and Histiocytic Lesions of the Orbit

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INTRODUCTION

Lymphoid tumors and leukemias constitute the largest sub-group among orbital tumors. Lymphoid tumor can occur in the orbit with or without associated systemic disease. Recent advances in diagnostic techniques have led to a better understanding of orbital lymphoproliferative lesions.

The most important differential diagnosis of orbital lymphoproliferative lesions is the group of inflammatory pseudotumor. In contrast to inflammatory pseudotumor, lymphoid tumor are predominantly composed of small lymphocytes. The inflammatory pseudotumors are also usually responsive to anti-inflammatory agents or to specific treatment directed towards the causative agents. It is important to establish the diagnosis by a biopsy. The preferred technique is to do an incisional biopsy with careful handling of the tissue and subjecting the sample to immunophenotyping and molecular studies. Fine needle aspiration biopsy (FNAB) is usually not done, as the tissue yield is not usually sufficient to confirm the diagnosis.

CLASSIFICATION

Due to the advent of newer immunodiagnostic techniques and understanding that these tumors arise

from the immune system, newer classifications have been proposed. Various systems of classification for Non-Hodgkin's lymphomas have been in vogue. Rappaport in 1966 proposed a classification based on the histologic differentiation of the lesions and this classification is still being used. About a decade later, the Lukes Collins and Kiel classification came into vogue.¹ In 1982 the Working Formulation was proposed for understanding the different classifications of Non Hodgkin's lymphomas.² In recent times this has been replaced by the Revised European American Lymphoma (REAL) classification system proposed by the International lymphoma study group (ILSG).³ A World Health Organization (WHO) classification based on the REAL system has also been proposed recently.⁴ The REAL classification system has replaced the Rappaport and Lukes Collins systems for the classification of orbital lymphomas (Table 84.1).

Rootman et al, have classified the lesions into 4 types based on the clinical presentation.⁵ Type 1 lesions have an insidious onset and are painless orbital masses. This is the largest group and consists of mainly low-grade lymphoproliferative lesions. Type 2 lesions include the fulminant lesions, which have a more rapid onset and are aggressive. In addition this group of patients are also prone to secondary infectious disorders. Type 3 lesions secondarily involve the orbit from the bone, the paranasal sinuses or the skin. Type

Table 84.1: REAL classification

- Clinically indolent (low-risk)
 - Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma
 - Lymphoplasmacytic lymphoma
 - Follicular lymphoma, grades I-II
 - Marginal-zone lymphoma, extranodal, nodal and splenic
 - Plasmacytoma/myeloma
 - Mycosis fungoides/Sezary syndrome
- Clinically aggressive (Intermediate risk)
 - Follicular lymphoma, grade III
 - Diffuse large B-cell lymphoma
 - DLBC lymphoma
 - Mantle cell lymphoma
 - B-cell prolymphocytic leukemia
 - Peripheral T-cell lymphomas (PTCL) and anaplastic large cell lymphoma
- Clinically very aggressive (High-risk)
 - Lymphoblastic lymphoma
 - Burkitt's lymphoma
 - Adult T-cell leukemia/lymphoma

4 patients present with neuroophthalmic complications due to the lymphoproliferative lesions.

For the purpose of simplicity and easy understanding, we will classify the lesions as suggested by Rootman et al.⁵

1. Lymphocytic tumor
 - a. Reactive lymphoid hyperplasia
 - b. Non Hodgkin's lymphomas
 - i. Small B cell lymphomas
 - ii. Diffuse large B cell lymphomas
 - iii. Burkitt's lymphoma
 - iv. T cell lymphomas
2. Leukemic lesions
 - a. Leukemia
 - b. Granulocytic sarcoma
3. Plasma cell tumors
 - a. Solitary plasma cell tumors
 - b. Multiple myeloma
4. Hodgkin's lymphoma
5. Histiocytoses
 - a. Langerhans' cell histiocytosis
 - b. Malignant histiocytosis
6. Miscellaneous lesion

Lymphocytic Lesions

These lesions usually have a gradual onset in the 6th or 7th decade of life with proptosis or diplopia. Visual acuity and ocular motility are usually only slightly impaired. The lesions are usually located in the

anterior orbit and may involve the conjunctiva, appearing as a pink fleshy mass ('Salmon patch' appearance). They mould the globe and are commonly found at an extraconal location. They usually have an oblong or pancake shape. On palpation they have a rubbery consistency. Bilateral lesions are found in one third of the cases and usually indicate a more aggressive course.⁶ These tumors also have a predilection for lacrimal gland involvement.⁷

Reactive Lymphoid Hyperplasia

These lesions are characterized by a polymorphous collection of lymphocytes and plasma cells. They show the presence of polyclonality, lymphoid follicles, vascular hyalinization, hemosiderin deposition and endothelial proliferation. Immunohistochemical methods show the polyclonal nature of the lesion with the presence of T and B-lymphocytes.⁸

Clinically these lesions have a more indolent course and appear as firm, rubbery lesions. They are usually painless and are usually in the anterior part of the orbit. The possibility of malignant transformation is rare and there is a 15 to 25% chance of eventual systemic involvement.⁹ These lesions are probably MALT (mucosa-associated lymphoid tissue) lymphomas and are not likely to progress.¹⁰

These lesions respond to steroids. Some of them need radiotherapy in the doses of 1500 to 2000 cGy. Those not responsive to steroid and radiotherapy need immunosuppression or cytotoxic therapy is usually indicated.¹¹ If future research shows that these tumors are actually MALT lymphomas, then it might be possible to spare the patients from radiation.¹²

Small B cell lymphomas

Most of the lymphoid lesions in the orbit belong to this group. The WHO classification of small cell lymphomas is given in Table 84.2.

Small lymphocytic lymphomas consist of normal appearing lymphocytes and are characterized by the presence of growth centers. The *lymphoplasmacytoid* lymphoma shows the presence of plasma cells and

Table 84.2: WHO classification of small cell lymphomas

- B-cell chronic lymphocytic leukemia/ small lymphocytic lymphoma
- Lymphoplasmacytic lymphoma
- Mantle cell lymphoma
- Follicular center lymphoma, follicular, grades I-II
- Diffuse follicular center lymphoma
- Extranodal marginal zone B cell lymphoma of MALT type

frequently Russell (intracytoplasmic inclusions of immunoglobulins) and Dutcher bodies (periodic acid Schiff positive intranuclear inclusions of immunoglobulins). The *mantle cell* lymphomas are more aggressive and show the presence of mitotic figures. The *follicle centre* lymphomas consist of small-cleaved cell lymphocytes. The *MALT* lymphomas have reactive lymphoid follicles and involve mucosal and epithelial surfaces throughout the body. These lesions are usually of a more benign nature.

These tumors show an insidious onset usually in the sixth or seventh decade of life. They are usually located in the anterior orbit and may be associated with subconjunctival lesions. They present with mild proptosis with the globe usually displaced inferomedially. Bilaterality is present in about 25% of the cases. Systemic involvement is likely to occur in nearly 60% of the patients over 10 years. CT scan reveals the presence of well-defined, homogeneous lesions usually in an extraconal location characteristically isodense to muscle. They mould to the globe or the adjacent structures. Though usually lobulated, they may sometimes assume a more nodular and infiltrative character. Lacrimal gland involvement is common. MRI is not very useful in the diagnosis of these lesions. On T1 weighted images these lesions are hypodense to the orbital fat. On T2 images the tumor is hyperintense to both fat and muscle. These lesions show gadolinium enhancement on T1 weighted images.

It is important to confirm the diagnosis by an orbital biopsy and stage the disease and look for any evidence of systemic involvement before starting treatment. Lesions localized to the orbit are best treated by radiotherapy at a dose of 2500 to 3000 cGy.¹³ If there is evidence of systemic lymphoma, it is best to administer chemotherapy and institute orbital radiotherapy for the orbital lesion. The prognosis after treatment is excellent.

Diffuse Large B Cell Lymphomas

These are the second most common form of Non-Hodgkin's lymphomas after the small cell variety in the orbit. It was previously believed to originate from the tissue histiocytes and was called as 'reticulum cell sarcoma' and 'histiocytic lymphoma'.¹⁴ They are rare; in the Mayo clinic series they comprised about 1.3% of the orbital lesions. Clinically these lesions are usually unilateral and present with eyelid swelling and proptosis. These are aggressive tumors and

systemic involvement occurs in most of the cases. They also tend to involve the central nervous system and sometimes affect the vitreous and the retina. They consist of large atypical lymphocytes and are sometimes poorly differentiated. Management is by systemic chemotherapy combined with radiotherapy for the orbital disease. The prognosis is usually poor owing to involvement of the central nervous system.¹⁴

Burkitt's Lymphoma

Denis Burkitt first described this in 1958.¹⁵ This tumor is endemic in Central Africa and has a predilection for the jaws and the abdomen.¹⁵ In addition there is a possible infectious etiology with involvement of the Epstein-Barr virus¹⁶ and chromosomal abnormalities involving translocation of the c-myc gene. It is also common in the presence of HIV infection.

The African form of the disease usually presents with rapidly progressive proptosis and upward globe displacement owing to the origin of the tumor from the maxillary bone. It frequently occurs in the first decade of life. The non-African form usually occurs in the first 3 decades of life and abdominal involvement is more common than facial tumors.

The clinical presentation of an abdominal tumor with proptosis especially upward globe displacement in an African child is suggestive of this lymphoma. CT scan usually demonstrates the maxillary lesion with secondary involvement of the orbit.

Histopathology reveals the presence of uniformly packed lymphocytes containing fat filled cytoplasmic vacuoles. Interspersed between these lymphocytes are phagocytic histiocytes, which impart a 'starry sky' appearance.¹⁴

Management involves a biopsy to confirm the diagnosis. Debulking can be attempted. This tumor shows a dramatic response to chemotherapy especially to cyclophosphamide, methotrexate and vincristine. Adjuvant radiotherapy can also be employed especially in cases refractory to chemotherapy.

The prognosis has greatly improved after the advent of chemotherapy. Favorable prognostic factors are localised disease and younger age.

T Cell Lymphomas

These can be classified as

1. Precursor T-cell lymphomas
2. Peripheral T-cell lymphomas

3. Cutaneous T-cell lymphomas
 - a. Mycosis fungoides
 - b. Sezary syndrome

The *precursor* T-cell group includes the subtype, lymphoblastic lymphoma that commonly involves the anterior mediastinum, central nervous system and the peripheral blood and rarely involves the orbit. The T/NK (T-cell/Natural Killer) lymphomas of the *peripheral* T-cell lymphoma group rarely involve the orbit and orbital involvement is usually secondary to spread from midfacial lesions.

The *cutaneous* T-cell lymphomas (CTCLs) includes two overlapping entities, Sezary syndrome and mycosis fungoides.¹⁷ Sezary syndrome presents with erythematous skin nodules, lymphadenopathy, abnormal lymphocytes in the blood and organomegaly. Mycosis fungoides is characterized by predominant skin involvement.

Diagnosis is by the identification of anaplastic large T lymphocytes which have irregular nuclear outlines and irregular indentations in their nuclear membrane called as Sezary cells.¹⁷ A complete blood count should also be performed to identify these abnormal cells. Skin lesions show these lymphocytes within the upper dermis and the epidermis and characteristic micro-abscesses (Pautrier's micro abscesses).

Clinically these tumors present mostly in males in the 4th decade of life. Orbital involvement occurs due to spread of the cutaneous disease and can affect the lids and conjunctiva as well. The T/NK lymphomas can secondarily involve the orbit and can cause cranial nerve palsies.

Management of these tumors is mainly by radiotherapy with occasional use of psoralen ultraviolet (PUVA) light therapy. Chemotherapy is given for widespread disease. The T/NK lymphomas are treated by irradiation.

Leukemic Lesions

Leukemia

Leukemia is a common childhood cancer and commonly involves the bone marrow. The eye and the adnexal tissue is rarely involved especially in the acute lymphoblastic form. It is usually unilateral and presents with a rapid onset of proptosis due to either soft tissue involvement or hemorrhage. Hemorrhages in the retina and leukemic infiltration of the uvea, optic nerve and meninges may be present. Orbital involvement indicates a grave prognosis. Systemic and

intrathecal chemotherapy with local irradiation may prolong survival.

Granulocytic sarcoma

Also called as chloroma, this usually is an extra-medullary form of acute myeloblastic leukemia or of chronic granulocytic leukemia entering blast crisis.¹⁸ It usually affects boys in the first decade of life. The orbit may be the initial site of presentation but usually progresses to systemic leukemia. It presents with a rapid onset and progression of unilateral proptosis.¹⁸ The mass typically involves the lateral walls of the orbit. Only 10% of the cases are bilateral. CT reveals the presence of a large irregular mass sometimes eroding the bone or extending into the temporal fossa.

Diagnosis is by a biopsy as this mimics inflammatory lesions owing to the rapidity of progression. Giemsa stained smears reveal the presence of cytoplasmic granules and Auer rods indicating the myeloid origin of the cells. The name chloroma is derived from the presence of myeloperoxidase in the tissue, which imparts a green color to the tissue. Immunohistochemical techniques with the use of the Leder stain in formalin fixed tissue for chloroacetate esterase can facilitate the diagnosis.

The prognosis is poor and treatment consists of local irradiation and intensive chemotherapy.

PLASMA CELL TUMORS

The plasma cell tumors are rare in and around the orbit. In conditions like Waldenstrom's macroglobulinemia there can be excess production of IgM paraproteins. Neuro-ophthalmic disorders and ocular lesions like retinal hemorrhages, microaneurysms and thrombosis can occur in multiple myeloma. Orbital involvement by these tumors is rare.

Histology reveals the presence of plasma cells, which are oval cells with an eccentric nucleus containing chromatin arranged in the form of a cartwheel and a paranuclear halo. Intracytoplasmic inclusions (Russell bodies) and intranuclear inclusions (Dutcher bodies) consisting of immunoglobulin deposits are also present.

Solitary Plasma Cell Tumors

These could be polyclonal or monoclonal. Polyclonal lesions consist of a mixed population of plasma cells and lymphocytes with reactive changes. Diagnosis is by identifying kappa and lambda light chains by

immunostaining. These lesions are commoner in the conjunctiva than the orbit. Treatment is by surgical excision followed by radiotherapy. The solitary extramedullary plasmacytomas are rare monoclonal infiltrates in soft tissue or bone. Orbital involvement is extremely uncommon and is usually secondary to paranasal sinus involvement. Radiotherapy is the mainstay of management, with surgery and chemotherapy being used in recurrent or unresponsive disease.

Multiple Myeloma

This condition commonly presents with bone pains, fractures, anemia and recurrent infections. It rarely involves the orbital tissues. It usually presents in the 7th decade of life and predominantly affects males. In most cases of ocular involvement, it presents initially as proptosis.¹⁹ Retinal vascular changes like cotton wool spots, retinal hemorrhages, microaneurysms and pars plana cysts can occur in patients with multiple myeloma. Central nervous system involvement can cause papilledema and cranial nerve palsies. Diagnosis is by immunostaining and detection of monoclonal light chains. Multiple osteolytic lesions, hypercalcemia, uremia, hyperglobulinemia and Bence Jones proteinuria are suggestive of this condition. Histology reveals the presence of large atypical plasma cells with giant cells and multinucleated cells. Treatment is with systemic chemotherapy and local radiation.

HODGKIN'S LYMPHOMA

This tumor commonly affects the lymph nodes and extranodal involvement is rare. The WHO classification of Hodgkin's lymphoma is given in Table 84.3. In Hodgkin's lymphoma orbital involvement follows systemic involvement and usually occurs in the advanced stages of the disease. It affects middle-aged adults with progressive proptosis.

The diagnostic feature is the presence of Reed Sternberg cells, which are large, irregular, binucleate

Table 84.3: Classification (World Health Organization) of Hodgkin's lymphoma

- Nodular lymphocyte-predominant Hodgkin's lymphoma
- Classical Hodgkin's lymphoma
 - Nodular sclerosis Hodgkin's lymphoma
 - Lymphocyte-rich classical Hodgkin's lymphoma
 - Mixed cellularity Hodgkin's lymphoma
 - Lymphocyte depletion Hodgkin's lymphoma

or multinucleate histiocytes with a foamy cytoplasm, in a matrix of lymphocytes, eosinophils, plasma cells and neutrophils.

The occurrence of an orbital mass in a patient with a previous diagnosis of Hodgkin's lymphoma should be viewed with suspicion.

The prognosis depends on the cytology and the staging of the lesion. The staging is commonly done by the Rye classification (Table 84.4).

Management includes a biopsy to confirm the diagnosis followed by orbital irradiation and systemic chemotherapy. The prognosis is guarded as orbital involvement usually indicates advanced disease.

HISTIOCYTOSES

Langerhans' Cell Histiocytoses

This entity was previously called as histiocytosis X and includes three disorders Hand-Schuller-Christian disease, Letterer Siwe disease and Eosinophilic granuloma.

This is a disease of young boys and ocular involvement occurs in about 10% of the cases. Most of the children present with bony involvement while one third of the patients present with disseminated disease.

There is an accumulation of dendritic histiocytes especially Langerhans' cells of the epidermis. These large mononuclear cells have an indented nucleus with a central striated line. On electron microscopy, the cells show the presence of characteristic 'racquet shaped' cytoplasmic granules called Birbeck granules.

Table 84.4: Staging of Hodgkin's lymphoma (Rye classification)

- *Stage I:* Disease limited to one anatomic region (stage I₁) or to two contiguous anatomic regions on the same side of the diaphragm (stage I₂)
- *Stage II:* Disease in more than two anatomic regions or in two non-contiguous regions on the same side of the diaphragm
- *Stage III:* Disease on both sides of the diaphragm but not exceeding beyond the involvement of lymph nodes, spleen or Waldeyer's ring
- *Stage IV:* Involvement of the bone marrow, lung parenchyma, pleura, liver, bone, skin, kidneys, gastrointestinal tract or any tissue or organ in addition to lymph nodes, spleen or Waldeyer's ring

*All stages are subclassified as A or B to indicate the absence or presence of systemic symptoms (fever, night sweats, weight loss > 10% of baseline).

Eosinophilic Granuloma

This is the most common variant and commonly presents with a painful swelling in the superolateral orbit with overlying skin erythema.²⁰ The frontal and zygomatic bones are most frequently involved.

Hand-Schuller-Christian Disease

The classical triad seen in this condition included bilateral proptosis, diabetes insipidus and multiple bony lesions of the skull but the complete picture is rarely seen.

Letterer-Siwe Disease

This entity shows the presence of hepatosplenomegaly, lymphadenopathy and osseous defects with occasional diffuse infiltration of the uveal tract.²¹

CT scan in cases of eosinophilic granuloma reveals the presence of an osteolytic lesion in the orbital bones superotemporally with irregular margins and hyperostosis.

Management of eosinophilic granuloma is by removal of the lesion by curettage followed by adjunctive radiotherapy. Intralesional methylprednisolone has been used for quicker resolution. Chemotherapy has also been tried in severe forms of the disease.

Eosinophilic granuloma has an excellent prognosis. Prognosis is poor in cases of Letterer-Siwe disease.

Malignant Histiocytosis

This is a rare condition characterized by an abrupt onset of fever, anemia, leukopenia and hepatosplenomegaly. Histology reveals diffuse infiltration by pleomorphic histiocytes showing erythrophagocytosis. Prognosis is poor, but some cases have shown remission with chemotherapy.

MISCELLANEOUS LESIONS

Sinus histiocytosis with massive lymphadenopathy This entity is also called as Rosai Dorfmann syndrome. This is a benign pseudolymphomatous entity characterized by infiltration of the lymph nodes and extranodal soft tissues by sheets of histiocytes. This usually occurs in the first decade of life and presents with cervical lymphadenopathy.²² Orbital involvement occurs in about 11% of the cases. This usually presents with proptosis, eyelid swelling and associated cervical lymphadenopathy. There is a painless, rubbery mass palpable in the superior orbit. Serum protein

abnormalities are sometimes present in this condition. Histology reveals the presence of lymphocytes and histiocytes, which have phagocytosed erythrocytes, lymphocytes and plasma cells, a phenomenon called as 'emperipoleisis'. This condition is often self-limiting. In localized disease surgical excision and low dose radiotherapy may be helpful. Systemic involvement is usually treated by a combination of radiotherapy, chemotherapy and corticosteroids.

Xanthogranulomas

These are histiocytic tumors in which the histiocytes contain lipid deposits. They are grouped into three categories—juvenile xanthogranulomas, Erdheim-Chester disease and necrobiotic xanthogranuloma. An immunologic basis has been suggested for the etiopathogenesis. It has been suggested that serum immunoglobulins are complexed with lipids and are deposited in the skin eliciting a giant cell foreign body reaction.

Histopathologically they are characterized by a granulomatous inflammation with histiocytes, lymphocytes and plasma cells. The distinctive feature is the presence of Touton Giant cells in which nuclei are arranged in a circular fashion around a central area of eosinophilic cytoplasm. Necrobiotic xanthogranulomas are characterized by the presence of areas of collagen destruction.

Juvenile xanthogranuloma usually presents in children with cutaneous eruptions and usually affects the anterior uveal tract; orbital involvement is rare. In cases of orbital involvement the presentation is usually during the first few weeks after birth with proptosis, without the typical skin lesions. These lesions are best managed by surgical excision followed by radiotherapy and steroids.

Erdheim Chester disease is the association of adult onset xanthogranulomas with systemic disease especially with diffuse sclerosis of the diaphysis and metaphysis of long bones and sometimes with hepatosplenomegaly, hepatic adenomas and infiltration of the lungs, kidneys and heart.²³ This condition is usually responsive to corticosteroids.

Necrobiotic xanthogranuloma is characterised by association with paraproteinemias and other entities like IgG monoclonal gammopathy, plasmacytosis, cryoglobulinemia, complement deficiency and leucopenia.²⁴ Multiple myeloma and non-Hodgkin's lymphoma have been associated with this condition.

The treatment modalities tried include steroids, chemotherapy and management of the associated diseases.

REFERENCES

1. Lukes RJ, Collins RD. New approaches to the classification of lymphomata. *Br J Cancer* 1975;31(suppl 2):1.
2. Non-Hodgkin's Lymphoma Pathologic Classification Project: National Cancer Institute-sponsored study of classifications of non-Hodgkin's lymphomas: Summary and description of a working formulation for clinical usage. *Cancer*; 1982; 49:2112.
3. Harris NL, Jaffe ES, Stein H et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International lymphoma Study Group. *Blood*; 1994;84:1361.
4. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee Meeting-Airlie House, Virginia, November 1997. *J Clin Oncol* 1999;17:3835.
5. Rootman J, White VA, Connors JM, Gascoyne RD. Lymphoproliferative, leukemic and Histiocytic lesions of the orbit. In Rootman J, ed. Diseases of the orbit. JB Lippincott Company: Philadelphia, 2001.
6. Jakobiec FA, McLean I, Font R. Clinicopathologic characteristics of orbital lymphoid hyperplasia. *Ophthalmology* 1979;86: 948.
7. Shields JA, Bakewell B, Augsburger JJ et al. Classification and incidence of space occupying lesions of the orbit: A survey of 645 biopsies. *Arch ophthalmol* 1984;102:1606.
8. Knowles DM, Jakobiec FA, Halper JP. Immunologic characterisation of ocular adnexal lymphoid neoplasms. *Am J Ophthalmol* 1979;87:603.
9. Knowles DM, Jakobiec FA. Orbital lymphoid neoplasms. A clinicopathologic study of 60 cases. *Cancer* 1980;46:576.
10. Lauer SA. Ocular adnexal lymphoid tumors. *Curr Opin in Ophthalmol* 2000;11:361-66.
11. Schick U, Lermen O, Unsold R, Hassler W. Treatment of primary orbital lymphomas. *Eur J Haematol* 2004 ;72:186.
12. Hardman-Lea S, Kerr-Muir M, Wotherspoon AC, et al. Mucosa-associated lymphoid tissue lymphoma of the conjunctiva. *Arch Ophthalmol* 1994;112:1207-12.
13. Hasegawa M, Kojima M, Shioya M et al. Treatment results of radiotherapy for malignant lymphoma of the orbit and histopathologic review according to the WHO classification. *Int J Radiat Oncol Biol Phys* 2003;57:172.
14. Henderson JW, Farrow GM. Orbital tumors (2nd Ed). New York, Brian C Decker (Thieme Stratton) 1980;344.
15. Burkitt D. A sarcoma involving the jaws in African children. *Br J Surg* 1958;46:218-223.
16. Henle W, Henle G. Evidence for an oncogenic potential of the Epstein-Barr virus. *Cancer Res* 1973;33:1419.
17. Meekins B, Proia AL, Klintworth GK. Cutaneous T cell lymphoma presenting as a rapidly enlarging ocular adnexal tumor. *Ophthalmology* 1985;92:1288-1293.
18. Zimmerman LE, Font RL. Ophthalmologic manifestations of granulocytic sarcoma. *Am J Ophthalmol* 1975;80:975-990.
19. Hamburger HA. Orbital involvement in multiple myeloma a new angiographic presentation. *J Clin Neuro Ophthalmol* 1984;25:4.
20. Baghdassarian SA, Shammas HF. Eosinophilic granuloma of orbit. *Ann Ophthalmol* 1977;9:1247.
21. Mittelman D, Apple DJ, Goldberg MF. Ocular involvement in Letterer Siwe disease. *Am J Ophthalmol* 1973;75:261-265.
22. Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy. A pseudolymphomatous benign disorder. A newly recognised benign clinicopathologic entity. *Arch Pathol* 1969;87:63-70.
23. Egan AJM, Boardman LA, Tazelaar HD et al. Erdheim-Chester disease: clinical, radiologic and histopathologic findings in five patients with interstitial lung disease. *Am J Surg Pathol* 1999;23:17-26.
24. Kossard S, Winkelmann RK. Necrobiotic xanthogranuloma with paraproteinemia. *J Am Acad Dermatol* 1980;3:257-270.



Chapter 108

Retinoblastoma

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This highly malignant tumor is the most common intraocular malignancy in children with a reported incidence averaging about 1 in 15,000 to 1 in 18,000 live births.¹ This lies second only to malignant melanoma of the uvea as the most common malignancy of the eye.

HISTORY

Petras Pawius from Amsterdam described the tumor as early as 1597.² In 1809, James Wardrop referred to the tumor as fungus hematodes and suggested enucleation as the mode of management.³ However von Graefe pointed out the need to remove a long section of the optic nerve at the time of enucleation.⁴

EPIDEMIOLOGY

There is no racial or sexual predisposition or any predilection for the right eye or left eye. Though mostly unilateral, it is bilateral in 25 to 35% of cases.⁵

AGE AT DIAGNOSIS

The average age at diagnosis is 18 months, unilateral cases being diagnosed later at 23 months and bilateral cases earlier at 12 months.⁵

PATHOGENESIS

Initially thought to be derived from the glial cells this was called a glioma of the retina by Virchow (1864). Flexner (1891) and Wintersteiner (1897) believed it to be a neuroepithelioma because of the presence of rosettes. Later there was a consensus that the tumor originated from retinoblasts and the American Ophthalmological Society officially accepted the term retinoblastoma in 1926.⁶

GENETICS

The suspicion that retinoblastoma could be hereditary arose quite late in the history of the disease. Stallard in 1962 reported on an infant with retinoblastoma with deletion of one of the D Group chromosomes, which included chromosome 13, 14 and 15.⁷ Later this chromosome was identified to be chromosome 13 and the syndrome named as the 13-deletion syndrome. The locus of deletion was the 14 band on the long arm (q) of the 13th chromosome. An intact gene protects against the development of retinoblastoma. This is a recessive tumor suppressor gene and for retinoblastoma to occur both the genes at the loci should be damaged.⁸

The 13-q deletion syndrome may be associated with many other phenotypic abnormalities, which include microcephaly, broad nasal bridge, hypertelorism, microophthalmos, micrognathia, lowset ears, anal and genital malformations and mental retardation.

Out of the newly diagnosed cases of retinoblastoma 6% have a family history (familial) while 94% do not have a family history (sporadic). Approximately 15% of unilateral sporadic retinoblastomas are caused by germline mutations affecting only one eye. The remaining 85% are nonhereditary. Bilateral retinoblastomas represent germline mutations in 100% of cases.⁹

In 1971, Knudson proposed the 2 hit hypothesis.¹⁰ He stated that for retinoblastoma to develop 2 chromosomal mutations are needed. In the case of hereditary retinoblastomas, the initial hit is a germline mutation, which is inherited and found in all cells. The second hit or mutation develops in somatic retinal cells leading to the development of retinoblastoma.

Therefore hereditary cases are predisposed to the development of second non-ocular tumors like osteosarcoma. In unilateral sporadic retinoblastoma, both the hits occur during the development of the retina and are somatic mutations. Therefore there is no risk of second nonocular tumors.

CLINICAL FEATURES

The most common presenting signs and symptoms include:

1. Leukocoria/cat's eye reflex 56%.
2. Strabismus 20%, exotropia 11%, esotropia 9%.
3. Red painful eye with glaucoma 7%.
4. Poor vision 5%.
5. None 3%.
6. Orbital cellulitis 3%.
7. Unilateral mydriasis 2%.
8. Heterochromia iridis 1%.
9. Hyphema 1%.
10. Strange expression 0.5%, nystagmus 0.5%, not eating 0.5%, failure to thrive 0.5%, white spots on the iris 0.5%.¹¹

Early Lesions

These are likely to be missed, unless an indirect ophthalmoscopy is done under anesthesia especially in familial cases. However the child may present with a strabismus if the tumor involves the macula or with reduced visual acuity. The tumors are transparent or white fluffy masses of the retina and become more white as the tumor grows.

Moderately Advanced Lesions

These usually present with leukocoria due to the reflection of light by the white mass in the retrobulbar area. As the tumor grows, 3 patterns are usually seen (Fig. 108.1).

1. Endophytic in which the tumor grows into the vitreous cavity. A white hazy mass fills the entire vitreous cavity and vitreous seeds occur. The tumor may extend into the anterior chamber and form anterior chamber tumor deposits forming a pseudohypopyon. The retinal vessels are not seen on the tumor surface.
2. Exophytic in which the tumor grows towards the subretinal space in which retinal vessels are seen over the tumor. Retinal detachment usually occurs and this condition may simulate Coats' disease.

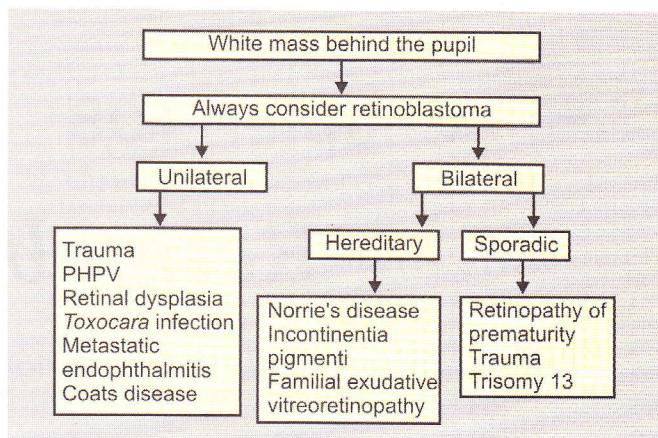


Fig. 108.1: Differential diagnosis of leukocoria

3. Diffuse infiltrating in which the tumor cells show a horizontal growth on the retina. This can mimic endophthalmitis. Usually there is a delay in diagnosis and this is seen in older children.

Spontaneous hyphema results from bleeding from the new vessels of the iris. New vessels develop due to posterior segment ischemia caused by the tumor. Any child with a spontaneous hyphema without trauma needs ultrasound examination to rule out retinoblastoma. Vitreous hemorrhage may sometimes occur from a necrotic tumor.

Pseudohypopyon could occur and may simulate intraocular inflammation but conjunctival injection or other inflammatory signs are usually absent. Preseptal or orbital cellulitis may occur in cases with necrotic retinoblastomas and may be associated with extraocular extension.

Advanced Lesions

These show optic nerve extension, orbital extension or distant metastasis. Retinoblastoma can spread through the optic nerve with relative ease especially once the lamina cribrosa is breached. Orbital extension may present with proptosis and is most likely to occur at the site of the scleral emissary veins. Distant metastasis is most likely to the brain, skull, distant bones and the lymph nodes.

Retinocytoma

This is the benign counterpart of retinoblastoma which is also called as retinoma.¹² It is a homogeneous, small, gray, slightly elevated tumor with normal caliber blood vessels leading into the tumor with varying

degrees of proliferation and migration of RPE in areas underlying or adjacent to the tumor. The eye is functional with clear media and no retinal detachment. This tumor also has a similar inheritance pattern like retinoblastoma.

Spontaneously regressed retinoblastoma. Retinoblastomas are known to undergo severe inflammation followed by phthisis bulbi. In any child with a phthisical eye of uncertain cause this should be considered.

PATHOLOGY

Gross

They appear as chalky white tumors with foci of calcification (Fig. 108.2). An endophytic retinoblastoma produces vitreous seeding while an exophytic tumor produces retinal detachment. Some tumors have both the components, while others are totally calcified due to marked necrosis.

Microscopy

Low Power

On low power basophilic areas of tumor are seen along with eosinophilic areas of necrosis and more basophilic areas of calcification within the tumor.

High Power

Poorly differentiated tumors consist of small to medium sized round cells with large hyperchromatic nuclei and scanty cytoplasm with mitotic figures.

Well differentiated tumors show the presence of rosettes and fleurettes. These can be of various types:

1. Flexner-Wintersteiner rosettes consist of columnar cells arranged around a central lumen. This is highly characteristic of retinoblastoma and is also seen in medulloepithelioma.
 2. Homer Wright rosettes consist of cells arranged around a central neuromuscular tangle. This is also found in neuroblastomas, medulloblastomas and medulloepitheliomas.
 3. Pseudorosette refers to the arrangement of tumor cells around blood vessels. They are not signs of good differentiation.
 4. Fleurettes are eosinophilic structures composed of tumor cells with pear shaped eosinophilic processes projecting through a fenestrated membrane.
- Rosettes and fleurettes indicate that the tumor cells show photoreceptor differentiation. In addition basophilic deposits which are precipitated DNA

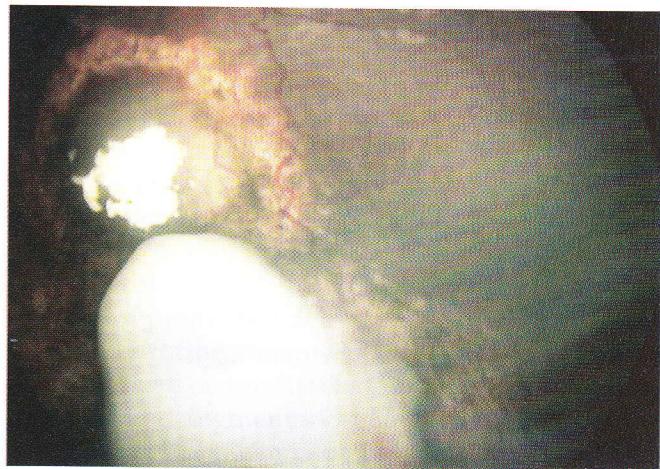


Fig. 108.2: Two endophytic tumors in the fundus, one of them showing the presence of calcification

(released after tumor necrosis) can be found in the walls of the lumen of blood vessels.

Retinocytomas show well differentiated retinoblastoma cells with smaller and less hyperchromatic nucleus, abundant cytoplasm without mitotic figures or necrosis.

DIFFERENTIAL DIAGNOSIS OF RETINOBLASTOMA

Various conditions can simulate retinoblastoma and lead to an erroneous diagnosis (Figs 108.3 and 108.4). The enucleation rates for these 'pseudoretinoblastomas' was 27% in 1977, however with newer diagnostic tools this is much lower.¹³

These conditions can be classified as follows.

Classification¹⁴

Hereditary

1. Norrie's disease
2. Congenital retinoschisis
3. Incontinentia pigmenti
4. Dominant exudative vitreoretinopathy.

Developmental Abnormalities

1. Persistent hyperplastic primary vitreous
2. Congenital cataract
3. Coloboma
4. Retinal dysplasia
5. Congenital retinal fold
6. Medullated nerve fibers.

Inflammatory Conditions

1. Ocular toxocariasis
2. Congenital toxoplasmosis
3. Congenital CMV retinitis
4. Herpes simplex retinitis
5. Metastatic endophthalmitis
6. Orbital cellulitis (Fig. 108.3).

Tumors

1. Retinal astrocytic hamartoma
2. Medulloepithelioma
3. Glioneuroma.

Miscellaneous Conditions

1. Coats' disease
2. Retinopathy of prematurity
3. Rhegmatogenous retinal detachment
4. Vitreous hemorrhage
5. Perforating ocular injury.

In a study of 500 patients by Shields et al,¹⁵ referred with a diagnosis of retinoblastoma, 58% were found to have retinoblastoma, while 42% had pseudoretinoblastomas. The 4 most common pseudoretinoblastomas were PHPV (27.8%), Coats' disease (16%), ocular toxocariasis (15.6%) and retinopathy of prematurity (4.7%).

HEREDITARY CONDITIONS

Norrie's disease is X linked recessive, occurs in males and is clinically apparent at birth. There is a bilateral white retrobulbar mass with elongated ciliary processes and total retinal detachment. Mental retardation is usually associated with this condition.

Congenital retinoschisis is an X linked recessive disorder occurring in males with the presence of retinoschisis and a stellate pattern at the fovea and occasional vitreous hemorrhage. *Incontinentia pigmenti* is characterized by proliferative retinal vascular abnormalities, total retinal detachment, cataract and RPE changes. *Familial exudative vitreoretinopathy* is a bilateral condition in which there is peripheral retinal avascularity and fibrovascular proliferation leading to retinal detachment and subretinal exudation.

DEVELOPMENTAL ABNORMALITIES

PHPV is usually unilateral and presents a few weeks after birth. There is a white reflex in a microphthalmic



Fig. 108.3: This child presented with features of orbital cellulitis in the left eye which on further investigation was diagnosed as retinoblastoma

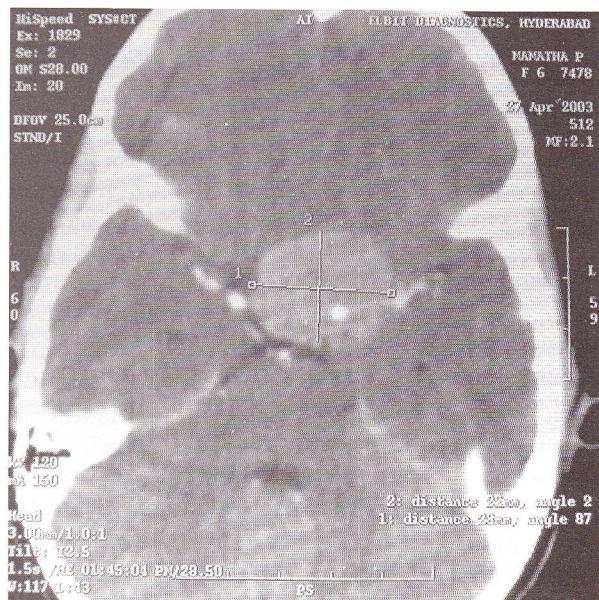


Fig. 108.4: Children with atypical presentation are also more likely to have extraocular spread. CT scan of the same child in Figure 108.3 showing the presence of a parasellar lesion

eye with occasional cataract. There is a retrobulbar mass into which the ciliary processes and peripheral retina is drawn. A persistent tunica vasculosa lentis is seen in some cases. *Congenital cataract* usually becomes apparent at an earlier age than retinoblastoma and there may be a history of maternal rubella or trauma.

A retinochoroidal coloboma may mimic retinoblastoma but can be differentiated by indirect ophthalmoscopy. *Retinal dysplasia* is characterized by

a malformed detached retina with other ocular abnormalities.

Congenital retinal fold consists of a ridge of abnormal retina, glia and blood vessels extending from the optic disc to the peripheral retina.

Medullated nerve fibers are seen as yellow white fluffy thickening of the nerve fibre layer and if extensive may cause leukocoria.

INFLAMMATORY CONDITIONS

Ocular toxocariasis is caused by the larva of the dog tapeworm *Toxocara canis*. There could be a history of contact with puppies or features like eosinophilia. A large retinal inflammatory mass could be present with severe cellular reaction and vitreous traction bands appearing like endophthalmitis or it may present as a solitary subretinal granuloma with much lesser vitritis. Eventually traction occurs with formation of a secondary falciform fold, retinal detachment and secondary cataract. Serological tests like ELISA may be helpful in making the diagnosis. The aqueous to plasma LDH is more than 1.0 and phosphoglucose isomerase is more than 2.0.¹⁵ *Congenital toxoplasmosis*, *congenital CMV retinitis* and *HSV retinitis* may produce severe inflammation with presence of vitreous cells and mimic retinoblastoma. Serology is useful in making the diagnosis. *Orbital cellulitis* may suggest retinoblastoma, however ethmoid sinus infection is usually associated.

TUMORS

Retinal astrocytomas can mimic a retinoblastoma. The calcification is usually yellow; while in retinoblastoma it is chalky white. In addition, these are usually associated with tuberous sclerosis or neurofibromatosis.

Medulloepithelioma is usually unilateral and affects older children. It can produce a yellow pink intraocular mass with leukocoria.

MISCELLANEOUS

Coats' disease is a unilateral vascular disorder characterized by retinal telangiectasia, intraretinal exudation and exudative retinal detachment occurring in young boys less than 10 years of age. Aneurysmal dilatation of the retinal blood vessels is present with occasional non-rhegmatogenous exudative retinal detachment and refractile particles, which correspond

to cholesterol crystals. NVI, hyphema and total retinal detachment may develop which may mimic retinoblastoma. Fluorescein angiography and ultrasound examination are useful in differentiation from retinoblastoma. Fluorescein angiography shows abnormal leakage and retinal telangiectasia. Ultrasound examination shows absence of a distinct tumor and echoes of moderate reflectivity corresponding to cholesterol crystals. In *retinopathy of prematurity* a history of premature delivery and receiving oxygen is usually forthcoming. This is a bilateral condition characterized on fundus examination by vitreoretinal traction and pigmentary changes. *Rhegmatogenous retinal detachment* can usually be differentiated from retinoblastoma based on B-scan which shows absence of tumor.

Diagnosis

The diagnosis of retinoblastoma is difficult because of numerous conditions which may mimic retinoblastoma. However with a high index of suspicion and using an array of diagnostic tools one can diagnose retinoblastomas.

History

When a child less than 3 years of age presents with a white pupillary reflex (leukocoria), strabismus or a red inflamed eye, retinoblastoma must be ruled out. A careful history can help rule out the mimics of retinoblastoma. The antenatal and neonatal histories are important. A history of prematurity, oxygen exposure, exposure to puppies or kitten, neonatal infection, trauma and maternal rubella should be enquired as these indicate conditions other than retinoblastoma. Retinal dysplasia is known to run in families. A detailed family history including any loss of eyes or deaths of children in the family should be sought.

Clinical Features

Any child presenting with leukocoria, squint or a red eye needs further evaluation, as these could be the presenting features of retinoblastoma. Less commonly the child could present with hyphema, glaucoma, rubeosis, phthisis bulbi or even with proptosis. Multiple white or pink tumors in one or both eyes are almost always retinoblastomas in children less than 5 years of age. A large unilateral tumor with a lumpy calcified consistency is virtually diagnostic.

External Ocular Examination

A white pupillary reflex is usually seen (Fig. 108.5). Anterior segment examination by slit lamp biomicroscopy may rarely show the presence of pseudohypopyon or tumor seeds and hyphema. Iris neovascularisation could be present.

Examination under Anesthesia

Any child presenting with leukocoria necessarily needs a dilated fundus examination under anesthesia. The intraocular pressure is measured and the anterior segment should be examined for neovascularization, pseudohypopyon, hyphema, and anterior chamber inflammation. Bilateral fundus examination with 360 degrees scleral depression is mandatory. Direct visualization of the tumor by an indirect ophthalmoscope is diagnostic of retinoblastoma in over 90% of cases.¹⁶ Based on the indirect ophthalmoscopy findings, the tumors are graded according to the Reese-Ellsworth classification (Table 108.1).

Investigations

Ultrasonography is useful in the diagnosis of retinoblastoma. A-scan shows high internal echoes within the tumor and rapid attenuation of the normal orbital pattern. B-scan shows a rounded or irregular intraocular mass with numerous highly reflective echoes within the lesion representing typical intralosomal calcification. These focal echoes, which represent calcification, persist even when the sensitivity is lowered. Computed tomography scores over ultrasound as it can delineate extraocular extension of tumor and detect the presence of an associated pinealoblastoma. Magnetic resonance imaging is specifically indicated if optic nerve invasion or intracranial extension is suspected. On fluorescein angiography the small intraretinal tumors show minimally dilated feeding vessels in the arterial phase, mild hypervascularity in the venous phase and late staining of the mass. Larger tumors show dilated feeding vessels and veins.

Laboratory tests like testing for elevated aqueous enzymes like lactate dehydrogenase and phosphoglucomutase isomerase have a minimal role to play in the diagnosis.

Management

Early diagnosis and recent advances in management have improved the prognosis of this potentially fatal



Fig. 108.5: Leukocoria is a common presentation of retinoblastoma. This photograph shows a white reflex in the left eye of the child

Table 108.1: Reese-Ellsworth classification

Group 1: Very favorable

1. Solitary tumor, less than 4 disk diameter in size, at or behind the equator.
2. Multiple tumors, none over 4 disk diameters in size, all at or behind the equator.

Group 2: Favorable

1. Solitary tumor, 4 to 10 disk diameters in size, at or behind the equator.
2. Multiple tumors, 4 to 10 disk diameters in size, behind the equator.

Group 3: Doubtful

1. Any lesion anterior to the equator
2. Solitary tumors larger than 10 disk diameters behind the equator.

Group 4: Unfavorable

1. Multiple tumors, some larger than 10 disk diameters
2. Any lesion extending anteriorly to the ora serrata

Group 5: Very unfavorable

1. Massive tumors involving over half the retina.
2. Vitreous seeding

tumor. The survival rate has improved from 30% in the 1930s to nearly 95% in the 1990s.

It is important to recognize the common pseudo-retinoblastomas, which include persistent hyperplastic primary vitreous, Coats' disease and ocular toxocariasis before embarking on the definitive treatment of retinoblastoma.

The primary goal of management of retinoblastoma is to safeguard the life of the child. Salvage of the eye and vision are the secondary and tertiary

goals respectively. The management involves a multidisciplinary approach with a team comprising of an ocular oncologist, pediatric oncologist, radiation oncologist, radiation physicist, pathologist and geneticist.

The most important factors that must be considered in the treatment are the tumor size, number, location, and laterality, condition of the other eye, threat of metastasis, risk for second malignant neoplasms and systemic status of the patient.

The treatment modalities currently available can be classified as focal, local, and systemic, and include cryotherapy, laser photocoagulation, thermotherapy, plaque brachytherapy, external beam radiotherapy, enucleation, orbital exenteration, and chemotherapy.

CRYOTHERAPY

Cryotherapy is performed for small equatorial or peripheral retinoblastomas measuring upto 4 mm in basal diameter and 2 mm in thickness. Tumor destruction is usually achieved with 2-3 sessions of triple freeze thaw cycles at 1-month intervals. The complications include transient serous retinal detachment, retinal tear, preretinal fibrosis and rhegmatogenous retinal detachment.

LASER PHOTOCOAGULATION

This modality of managing retinoblastoma has been sidelined with the advent of thermotherapy. This is usually done for small posterior tumors 4 mm in basal diameter and 2 mm or less in thickness. The treatment is directed to delimit the tumor and coagulate the blood supply to the tumor by surrounding the tumor with two rows of overlapping laser burns. The scar produced is consequently much larger than the tumor itself. The recurrence rate after treatment is as high at 20-30%. The common complications include transient serous retinal detachment, vascular occlusion, retinal traction, retinal hole and preretinal fibrosis.

THERMOTHERAPY

Thermotherapy is the delivery of heat using infrared radiation. The goal is to reach a subcoagulative temperature range of 40 to 60 degrees C, thus sparing the retinal vessels of photocoagulation. Transpupillary thermotherapy using infrared radiation from a semiconductor diode laser has become a standard practice. The large-spot-adapted indirect ophthalmo-

scope, operating microscope with a laser delivery system, or the transscleral route using a diopexy probe can be used to deliver it. The tumor is heated till it turns a subtle gray. Shields et al in their series could achieve complete tumor regression in 86% of tumors using 3-4 sessions of thermotherapy.¹⁷ The chief complications of thermotherapy are focal iris atrophy, peripheral focal lens opacity, retinal traction, retinal vascular occlusion and transient localized serous retinal detachment.

Thermotherapy alone can be performed for small tumors, measuring up to 4 mm in basal diameter and 2 mm in thickness. However, its major application is as an adjunct to chemoreduction. Heat has been observed to have a synergistic effect with chemotherapy facilitating greater uptake of the platinum group of drugs. This combination has been termed chemothermotherapy.

PLAQUE BRACHYTHERAPY

Retinoblastoma is a radiosensitive tumor. In plaque radiotherapy or brachytherapy, a radioactive implant is placed on the sclera over the base of the tumor to irradiate the tumor transsclerally. The goal is to deliver a radiation dose of 4000-5000 cGy to the apex of the tumor. The radioactive materials used commonly are ¹²⁵Iodine and ¹⁰⁶Ruthenium.

The advantages of plaque brachytherapy are the focal delivery of radiation with minimal damage to the "normal" structures, minimal periorbital tissue damage, minimal cosmetic abnormality, lesser risk of second malignant neoplasms in the irradiated area, and shorter duration of treatment.

Plaque brachytherapy can be performed as primary or as secondary treatment. It is generally reserved for tumors less than 16 mm in diameter and 8 mm in thickness, ideally situated > 3 mm from the optic nerve and fovea. It is most successful as secondary treatment in those eyes that fail to respond to cryotherapy, laser photocoagulation, thermotherapy, and chemoreduction, and is less successful in those that fail to respond to external beam radiotherapy.¹⁸ In one series, 90% of the eyes destined for enucleation could be salvaged with plaque brachytherapy.¹⁹ The radiation associated problems of papillopathy and retinopathy usually become clinically manifest at about 18 months after irradiation. Custom designs of plaques have reduced the incidence of radiation-induced complications.

EXTERNAL BEAM RADIOTHERAPY (EBRT)

This modality was started by Reese and Verhoeff and has been used extensively in the past in the management of retinoblastoma. Either the whole eye technique or the lens sparing technique can provide EBRT. The results of EBRT are gratifying (Table 108.2). EBRT, however, has some long-term complications such as impedance of orbital growth, midfacial dysmorphism, chronic dry eye, cataract, retinopathy and optic neuropathy. EBRT has been shown to induce second malignant neoplasms (SMN) in the field of irradiation. The 30-year cumulative incidence of SMN in patients of bilateral retinoblastoma increases to 35% in patients who received EBRT compared to 6% in those who did not.²⁰ Abramson²¹ found that the risk for SMN was greater in children less than 12 months of age.

EBRT was conventionally indicated for moderately advanced unilateral or bilateral retinoblastoma. It has now been observed that the combination of chemotherapy with local treatment is usually successful in salvaging eyes with Reese Ellsworth group 1 to 4 retinoblastomas (Table 108.2). Presently EBRT is indicated in eyes where chemoreduction and local therapy has failed, and in rare situations when chemotherapy is contraindicated because of poor systemic status. EBRT scores over enucleation in that it can help salvage the eye. However, an enucleation done after a failed EBRT may lead to socket contraction and poor cosmesis. The decision, therefore, has to be individualized in discussion with the patient's family. EBRT is also used as a standard adjunct following enucleation in patients with retinoblastoma with involvement of the optic nerve transection, scleral infiltration, and orbital extension.

ENUCLEATION

Just about 3 decades ago, a majority of patients with unilateral retinoblastoma and the worse eye in bilateral retinoblastomas underwent primary enucleation. However the advent of chemotherapy has changed this radical management of retinoblastoma. Chemotherapy with local therapy can prevent enucleation in a majority of Reese-Ellsworth groups 1-4 tumors, while enucleation may be necessary in about 50% patients with Reese-Ellsworth group 5 tumors. Enucleation is thus the second or third line of management and is reserved for patients who fail focal therapy, chemotherapy, and/or EBRT. However, eyes

Table 108.2: Eye salvage rates with external beam radiotherapy and chemoreduction

RE group	Ellsworth 1977 EBRT	Hungerford 1995 EBRT	Shields 1997 CRD + SALT
I	91%	100%	100%
II	83%	84%	100%
III	82%	43%	100%
IV	62%	43%	100%
V	29%	66%	78%

with neovascularization of iris, secondary glaucoma, anterior chamber tumor invasion, tumors occupying >75% of the vitreous volume, necrotic tumors with secondary orbital inflammation, and tumors associated with hyphema or vitreous hemorrhage where the tumor characteristics can not be visualized are primarily managed by enucleation.

Minimum-manipulation surgical technique should be necessarily practiced. It is important not to accidentally perforate the eye. The sclera is thin at the site of muscle insertions and the rectus muscles have to be hooked delicately. It is important to obtain a long stump of the optic nerve ideally more than 15 mm, but never less than 10 mm. Use of an enucleation spoon and a heavy scissors results in reduced space for manipulation and a shorter optic nerve stump. A straight blunt tip tenotomy scissors should be used for the medial approach and a gently curved blunt tip tenotomy scissors for the lateral approach. The optic nerve should be traced to the orbital apex with the scissors tip straddling the nerve and cut a little away from the apex to preserve structures passing through the superior orbital fissure. A snare or a clamp should not be used during optic nerve transection as it may induce crush artifacts making histopathological examination of the cut end for tumor invasion difficult.

Orbital implants were earlier thought to interfere with the detection of recurrence and impede EBRT. However imaging allows detailed evaluation in spite of the presence of an orbital implant. The orbital implant promotes orbital growth, provides better cosmesis and enhances prosthesis motility. The various implants available could be non-integrated like PMMA or silicon or bio-integrated like hydroxyapatite or Medpor. Bio-integrated implants are avoided in situations where postoperative adjunctive EBRT may be necessary.

ORBITAL EXENTERATION

Orbital exenteration is rarely performed for retinoblastomas. It is usually done for orbital recurrence after the child has received the maximum dose of radiation and chemotherapy.

CHEMOTHERAPY (Fig. 108.6)

Systemic Chemotherapy

With the advent of chemotherapy, radical methods of management like enucleation have been relegated to the second or third place. The introduction of newer chemotherapy protocols has dramatically improved the prognosis for life, eye salvage, and residual vision.

Chemotherapy could be local or systemic. Local chemotherapy is under trial. The role of systemic chemotherapy in the management of retinoblastoma includes chemoreduction, adjuvant chemotherapy, and treatment of metastasis.

Chemoreduction, defined as the process of reduction in the tumor volume with chemotherapy so that it becomes amenable to cure by local therapy, has become an integral part of the current management of retinoblastoma. With chemoreduction and sequential aggressive local therapy (SALT), it is now possible to salvage many an eye and maximize residual vision. There are different protocols in chemotherapy. The commonly used drugs are vincristine, etoposide and carboplatin, for 6 cycles (Table 108.3).

In patients with Reese-Ellsworth groups 1-4, chemoreduction coupled with SALT can minimize the need for enucleation or EBRT without significant systemic toxicity.²² Shields et al observed a globe salvage rate of 100% using chemoreduction and adjuvant treatment in Reese-Ellsworth groups 1 to 4.²³ Chemotherapy alone is however not curative and must be associated with intensive local therapy.

Table 108.3: Chemoreduction regimen and doses for intraocular retinoblastoma

Day 1: Vincristine + Etoposide + Carboplatin

Day 2: Etoposide

Standard dose: (3 weekly, 6 cycles): Vincristine 1.5 mg/m² (0.05 mg/kg for children \leq 36 months of age and maximum dose \leq 2 mg), etoposide 150 mg/m² (5 mg/kg for children \leq 36 months of age), carboplatin 560 mg/m² (18.6 mg/kg for children $<$ 36 months of age)

High-dose (3 weekly, 6-12 cycles): Vincristine 0.025 mg/kg, Etoposide 12 mg/kg, Carboplatin 28 mg/kg

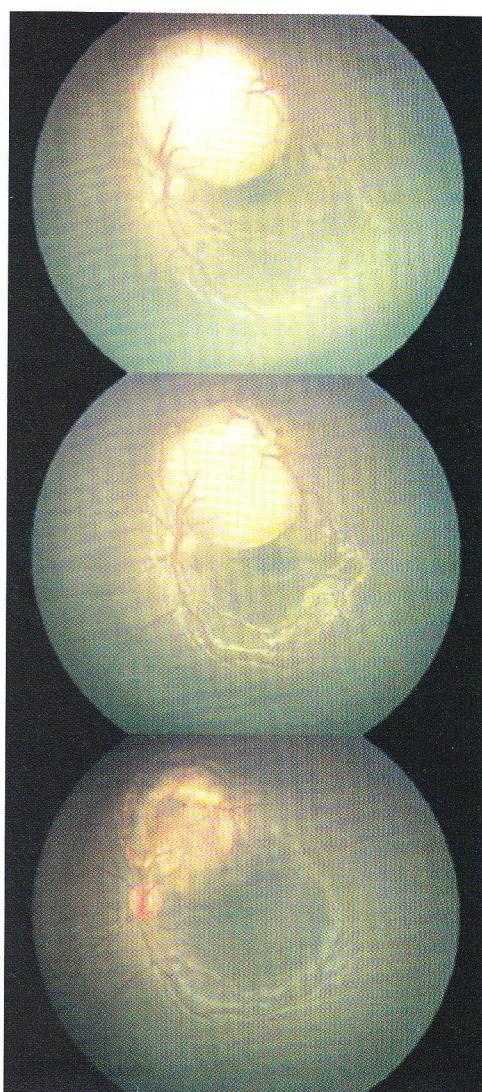


Fig. 108.6: Shows a tumor touching the foveola at presentation (top). There was remarkable tumor shrinkage after 3 cycles of chemotherapy (middle). With 6 cycles of chemotherapy and transpupillary thermotherapy, there was complete tumor regression (bottom). The resulting scar was much smaller than the original tumor with the foveola fully exposed, thus maximizing visual potential

In high dose chemoreduction, the dose of etoposide and carboplatin is increased (Table 108.3). This is indicated in Reese-Ellsworth group 5 tumors, recurrences, and metastasis. The recent application of high dose chemotherapy is in the management of orbital extension of retinoblastoma. Our unpublished early results indicate good response to a combination of initial 3 cycles of high dose chemotherapy, followed by enucleation, orbital EBRT, and continued chemotherapy for 12 cycles.

Standard dose adjuvant chemotherapy can be administered post enucleation in patients with high risk histopathologic characteristics that predispose to metastasis. The histopathologic high risk factors have been mentioned in Table 108.4. Honavar et al observed that the incidence of metastasis was 4% in the group which received post enucleation adjuvant therapy compared to 24% in the group which did not.²⁴ High-dose adjuvant chemotherapy is indicated in patients with extraocular extension of retinoblastoma, and those who have optic nerve invasion to transection. Patients with tumor cells in the cerebrospinal fluid get intrathecal methotrexate in addition to high-dose adjuvant chemotherapy.

It is important to be aware of the adverse effects and interactions of chemotherapeutic agents, which include myelosuppression, febrile episodes, neurotoxicity and non-specific gastrointestinal toxicity. Chemotherapy should be given only under the supervision of an experienced pediatric oncologist.

Periorcular Chemotherapy

Carboplatin delivered subconjunctivally has been demonstrated to be efficacious in the management of retinoblastoma especially in the presence of vitreous seeds because it can penetrate the sclera and achieve effective concentrations in the vitreous cavity. However the response may be short lived with tumor recurrences. This modality is currently under trial.

Follow up Schedule

The usual protocol is to schedule the first examination 3-6 weeks after the initial therapy. In cases where chemoreduction therapy has been administered, the examination should be done every 3 weeks with each cycle of chemotherapy. Patients under focal therapy are evaluated and treated every 4-8 weeks until complete tumor regression. Following tumor regression, subsequent examination should be 3 monthly for the first year, 6 monthly for three years or until the child attains 6 years of age, and yearly thereafter.

Genetic Counseling

This is often neglected in the management of retinoblastoma. In patients with a positive family history, 40% of the siblings would be at risk of developing retinoblastoma and 40% of the offspring of the affected patient may develop retinoblastoma. In patients with no family history of retinoblastoma,

Table 108.4. Histopathologic high-risk factors predictive of metastasis

- Anterior chamber seeding
- Iris infiltration
- Ciliary body infiltration
- Massive choroidal infiltration
- Invasion of the optic nerve lamina cribrosa
- Retrolaminar optic nerve invasion
- Invasion of optic nerve transection
- Scleral infiltration
- Extrascleral extension

Table 108.5: Current suggested protocol

- A. Intraocular tumor, Reese-Ellsworth Groups 1 to 4, Unilateral or Bilateral
 1. Focal therapy alone for smaller tumors if the standard tumor size indications are satisfied.
 2. Standard 6 cycle chemoreduction and sequential aggressive focal therapy for larger tumors and all tumors located in the macular area.
 3. Consider focal therapy for small residual tumor, and plaque brachytherapy/EBRT for large residual tumor if bilateral, and enucleation if unilateral.
- B. Intraocular tumor, Reese-Ellsworth Groups 5A and 5B, Unilateral
 - Primary enucleation
- C. Intraocular tumor, Reese-Ellsworth Groups 5A and 5B, Bilateral
 1. High dose chemotherapy and sequential aggressive focal therapy.
 2. Consider focal therapy for small residual tumor, and plaque brachytherapy/EBRT for large residual tumor.
- D. Advanced intraocular tumor, unilateral or bilateral, with neovascularization of iris, anterior segment seeds, iris infiltration, necrotic retinoblastoma with orbital inflammation, media opacity precluding tumor visualization, and eyes with no visual potential.
 - Primary enucleation
- E. Extraocular tumor
 1. Baseline CT scan/MRI, bone marrow and cerebrospinal fluid cytology.
 2. Intrathecal methotrexate if cerebrospinal fluid is positive for tumor cells.
 3. High dose chemotherapy for 6 cycles, followed by enucleation or exenteration, external beam radiotherapy, and continued chemotherapy for 12 cycles.
- F. High risk factors on histopathology
 1. Standard 6-cycle adjuvant chemotherapy.
 2. High dose adjuvant chemotherapy and orbital external beam radiotherapy in patients with scleral infiltration, extraocular extension, and optic nerve extension to transection.

if the affected child has unilateral retinoblastoma, 1% of the siblings are at risk and 8% of the offspring may develop retinoblastoma. In cases of bilateral retinoblastoma with no positive family history, 6% of the siblings and 40% of the offspring have a chance of developing retinoblastoma.

In summary, the current trend is to provide an individualized (Table 108.5) multispecialty management for patients with retinoblastoma. The recent advances in the management of retinoblastoma have yielded gratifying outcome in terms of preservation of life, salvage of the eye, and optimal residual vision.

REFERENCES

- Bishop JO, Madsen EC: Retinoblastoma. Review of current status. *Surv Ophthalmol* 1975;19:342.
- Albert DM: Historic review of retinoblastoma. *Ophthalmology* 1987;94:654.
- Wardrop J: Observations of fungus hematoles or soft cancer. Edinburgh : Archibald Constable & Co, 1809.
- von Graefe A: Enucleation ou exeneration du globe del'oeil. *Ann Oculistique* 1884;93:250.
- Shields JA, Shields CL. *Intraocular Tumors—A Text and Atlas*. WB Saunders Company 1992;18:306.
- Jackson E: Report of the committee to investigate and revise the classification of certain retinal conditions. *Trans Am Ophthalmol Soc* 1926;24:38.
- Stallard HB: The conservative treatment of retinoblastoma. *Trans Am Ophthalmol Soc UK* 1962;82:473.
- Murphree AL, Benedict WF: Retinoblastoma: Clues to human oncogenesis. *Science* 1984;223:1028.
- Shields JA, Shields CL. *Intraocular Tumors—A Text and Atlas*. WB Saunders Company 1992;19:337.
- Knudson AG: Mutation and cancer: Statistical study of retinoblastoma. *Proc Natl Acad Sci USA* 1971;68:820.
- Abramson DH, Frank CM, Susman M, Whalen MP, Dunkel IJ, Boyd NW 3rd. *J Pediatr* 1998;132 (3 Pt 1):505-8.
- Gallie BL, Phillips RA, Ellsworth RM et al. Significance of retinoma and phthisis bulbi for retinoblastoma. *Ophthalmology* 1982;89:1393.
- Margo CE, Zimmerman LE: The accuracy of clinical diagnosis in children treated by enucleation. *J Ped Ophthalmol Strab* 1983;20:227.
- Shields JA, Shields CL. *Intraocular Tumors—A Text and Atlas*. WB Saunders Company 1992;20:342.
- Felberg NT, Mc Fall R, Shields JA: Aqueous humor enzyme patterns in retinoblastoma. *Invest Ophthalmol* 1977;16:1039.
- Ellsworth RM. The practical management of retinoblastoma. *Trans Am Ophthalmol Soc* 67: 462, 1969
- Shields CL, Santos MC, Diniz W et al. Thermotherapy for retinoblastoma *Arch Ophthalmol* 1999;117:885.
- Shields CL, Shields JA, Cater J et al. Plaque radiotherapy for retinoblastoma, long-term tumor control and treatment complications in 208 tumors. *Ophthalmology* 2001;108:2116-21.
- Shields JA, Shields CL, Hernandez JC et al. Plaque radiotherapy for residual or recurrent retinoblastomas in 91 cases. *J Pediatr Ophthalmol Strabismus* 1994;31:242.
- Roarty JD, Mc Lean IW, Zimmerman LE. Incidence of second neoplasms in patients with retinoblastoma. *Ophthalmology* 1988;95:1583.
- Abramson DH, Frank CM. Second non ocular tumors in survivors of bilateral retinoblastoma; a possible age effect on radiation-related risk. *Ophthalmology* 1998;105:573.
- Friedman DL, Himelstein B, Shields CL et al. Chemoreduction and local ophthalmic therapy for intraocular retinoblastoma. *J Clin Oncol* 2000;18:12.
- Shields CL, Shields JA, Needle M et al. Combined chemoreduction and adjuvant treatment for intraocular retinoblastoma. *Ophthalmology* 1997;104:2101.
- Honavar SG, Singh AD, Shields CL et al. Post enucleation adjuvant therapy in high risk retinoblastoma. *Arch Ophthalmol* 2002;120:923.
- Hungerford JL, Toma NMG, Plowman PN, Kingston JE. External beam radiotherapy for retinoblastoma: I, whole eye technique. *Br J Ophthalmol* 1995;79:112.
- Ellsworth RM. Retinoblastoma. Modern problems in ophthalmology. 1977;96:1826.