

able to keep up.

Cancer Cells Refuse to Die

Cancer cells also don't die like normal cells do.

- Normal cells can only undergo a certain number of mitoses (usually around 60-70) before they die. But cancer cells are "**immortal**" and can replicate endlessly.
- Normal cells also have a preprogrammed script for a special kind of cell death called apoptosis—and they'll follow that script if they are told to do so. Cancer cells don't follow that script; they are able to **evade apoptosis**.
- Speaking of evasion, cancer cells are also able to **evade the host's immune response**, which typically kills any cell that displays abnormal antigens.

Cancer Cells Metastasize

One final hallmark of cancer is **metastasis**, which refers to the ability of cancer cells to spread throughout the body. This hallmark more than any other is diagnostic of cancer. Some of these other characteristics are present even in benign tumor cells—but with very few exceptions, benign tumors do not metastasize.

Cancer Cells Create the Right Conditions for Growth

Acquiring these eight hallmarks is not a simple or quick process. But cancer cells make this task easier by creating two cancer-enabling conditions:

- Genomic instability

- Genomic instability
- Cancer-enabling inflammation

Let's look at genomic instability first. As cancer cells evolve, they acquire gene mutations that enable them to bypass normal processes—such as DNA repair systems—that keep DNA intact and stable. As a result, the DNA of the cancer cell becomes even more susceptible to genetic mutations. This DNA condition is called genomic instability, and it paves the way for the cancer cell to acquire the hallmarks of cancer discussed above.

Another cancer-enabling condition is inflammation. As cancers invade tissues, they attract inflammatory cells such as lymphocytes and macrophages to the region of the tumor. Normally, inflammatory cells are very useful in the fight against foreign invaders. But in this scenario, the tumor manipulates the inflammatory cells into secreting factors that promote cancer cell growth, enhance the cancer cells' ability to resist death, and otherwise enable the cancer cell on its hallmark-acquiring path.

How Are Hallmarks Used in the Diagnosis and Treatment of Cancer?

We'll now go into more detail on four of those hallmarks of cancer that allow cancer to survive despite all of the checks and balances to prevent it:

- Altered metabolism
- Evasion of apoptosis
- Sustained angiogenesis
- Immortality

These four hallmarks merit a more in-depth discussion because they frequently are used as targets in the diagnosis and treatment of cancer. For example, the altered metabolism of cancer cells is the basis for positron

PET scan. In this scan, a radioactive tracer, such as 18F-

fluorodeoxyglucose (18F-FDG), an analog of glucose, is administered. This is taken up by cells as if it is glucose. Since cancer cells have higher glucose uptake than noncancerous cells, the tracer is significantly absorbed by cancer cells, leading to bright areas visible on the PET scan.

Evasion of Apoptosis

Apoptosis is programmed cell death, or cell suicide, and it is a normal cellular process. It often occurs when the cell is damaged. For example, when a cell has DNA damage that cannot be fixed, the cell will often induce apoptosis so as not to continue proliferating with this damage, because that could lead to cancer. Think of cancer cells as super cells that have bypassed this well-regulated process.

There are two different pathways to apoptosis: the extrinsic or death receptor-mediated pathway and the intrinsic mitochondrial pathway. Both pathways result in the production of caspases, protease enzymes that breakdown the nuclear and cytoplasmic components of the cell. Cancer cells can downregulate the expression of these caspases or modify their action through phosphorylation. In addition, the molecules in a normal cell that inhibit apoptosis such as the *Bcl-2* family of proteins and the inhibitor of apoptosis proteins (IAPs) are upregulated. This property can be used as a target for antitumor drugs, such as the *Bcl-2* inhibitor venetoclax, a treatment for hematologic malignancies.

How does a cancer cell avoid both the extrinsic and intrinsic pathways of apoptosis?

Sustained Angiogenesis

As cancer cells proliferate rapidly, avoiding apoptosis and shifting their metabolism to anaerobic pathways, they need to find a way to increase their access to energy, specifically glucose. To accomplish this task, they increase the number of avenues that can provide the nutrients they need. This process is called angiogenesis, or the creation of new blood vessels.

In normal physiology, angiogenesis is regulated. In cancers, this regulation is disrupted. One of the most common angiogenesis signals upregulated by cancer cells is *vascular endothelial growth factor* (VEGF). VEGF is a ligand to *VEGF receptor tyrosine kinase*. This signaling pathway initiates the production of new blood vessels, which will bring glucose and oxygen to growing cancer cells. In addition, these blood vessels create new avenues through which cancer cells can enter and travel to new parts of the body, a process known as metastasis. Several antitumor drugs take advantage of this upregulation of VEGF; *monoclonal antibodies* against VEGF are used in the treatment of many solid tumors, such as colorectal cancer.

Immortality

Most cells in the body have an internal limit to the number of times they

Figure 3

Two examples of tumor suppressor genes include retinoblastoma (RB) and p53. *RB* and *p53* encode proteins that impede the progression of the cell cycle from the G1 phase (ie, all cellular contents duplicate except the chromosomes) to the S phase (ie, synthesis phase or chromosome duplication phase). The Rb protein (product of the *RB* gene) acts as a growth suppressor, and its inactivation results in inappropriate cell proliferation. *p53* is activated when there are hyperproliferative signals, DNA damage, telomere shortening, or hypoxia and causes cell cycle arrest, senescence, or apoptosis. When inactivated, the cell continues to proliferate even with these issues.

INSTRUCTOR NOTE

There is a significant clinical correlation associated with the tumor suppressor gene *p53*. There are families in which some members inherit one mutated allele. Therefore, based on the "two-hit" hypothesis above, they only need one more hit for cancer to develop. These families usually have members who develop

carcinomas, sarcomas, leukemias, lymphomas, etc., before the age of 50 years. This is known as Li Fraumeni syndrome and is important to keep in mind.

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Oncogenes step on the gas (gain-of-function). Tumor suppressor genes remove the brakes (loss-of-function).

Genes That Regulate Programmed Cell Death (Apoptosis)

Remember discussing the avoidance of apoptosis by cancer cells? It turns out that there are two anti-apoptotic protein classes: certain members of the Bcl-2 family and the inhibitor of apoptosis proteins (IAPs) are critical for cancer cells to avoid apoptosis.

The Bcl-2 family of proteins has three groups, two pro-apoptotic and one anti-apoptotic. The anti-apoptotic group includes Bcl-2, Bcl-x_L, and Mcl-1.

	antineoplastic drugs, DS exonucleases	antineoplastic drugs, DS exonucleases
Key proteins/mechanism	BRCA1 and BRCA2, RAD51	BRCA1 and BRCA2, RAD51
Disease connections	Familial breast cancers and ovarian cancer	Severe combined immunodeficiency

Why Is Cancer So Difficult to Destroy?

Now that we have reviewed the events that can happen to turn a cell cancerous, let's take a look at how cancer becomes more than just one mutated cell. Typically, the mutation that a cancer cell acquires increases the cell's fitness. When a cell's fitness is improved, it has the ability to produce more daughter cells (ie, divide more rapidly) than a normal cell without the mutation. This process of one cell giving rise to many identical daughter cells is called **clonal expansion**.

Sometimes, cancer daughter cell clones develop additional mutations. These additional mutations make these cells even stronger and fitter than the original cancer cells. These cells are known as **subclones**. Subclones are one reason why treating cancer can be so difficult. One treatment may work on the original cancer cell and its clones. However, new subclone tumor cells may arise that are impervious to the original treatment, allowing these cells to continue to grow and metastasize despite treatment. This occurrence is one of the greatest challenges in treating cancer.

quickly?

You explain that cancer cells can shift their metabolism to generate more energy needed to grow, bypass normal conditions that lead to cell death, produce new blood vessels to bring them fuel, and develop the ability to divide forever. All of these factors make cancer cells invincible. "It sounds incredible, and sometimes like a science fiction movie, but it's true. But we can target your treatment to what we know is effective," you say.

Summary

- Nonlethal genetic damage is at the center of cancer pathogenesis.
- There are eight hallmarks of cancer cells that distinguish them from normal cells: those resulting in increased cell growth (autonomous cell proliferation, resistance to growth-suppressing signals, altered metabolism, angiogenesis), those resulting in decreased cell death (immortality, evasion of apoptosis, evasion of host immune response), and the ability to metastasize.
- Cancer cells acquire these eight hallmarks through the creation of genomic instability and cancer-enabling inflammation.
- Changes in metabolism (the Warburg effect), avoidance of apoptosis, stimulation of angiogenesis, and limitless replication are four critical hallmarks of cancer cells that can be targeted for cancer diagnosis and treatment.
- Growth-promoting proto-oncogenes, growth-inhibiting tumor suppressor genes, genes that regulate programmed cell death (apoptosis), and genes involved in DNA repair are all targets for cancer-related mutation and allow for cancer cells to continuously

grow and proliferate.

- Clonal expansion is the process by which a single cancer cell produces huge numbers of identical cancer cells.
- Tumor subclones with new mutations may emerge over time, and these new subclones may be resistant to the original treatment method; tumor subclones are one of the reasons why cancer is so difficult to treat.

B. *BRCA2*

C. p53

D. Ras

E. *RB*

Review Questions

Explanation (requires correct answer)

1. Which of the following changes in the cell prevents it from going through the process of cell suicide?

- A. Avoidance of apoptosis
- B. Changes in metabolism
- C. Limitless replication
- D. Stimulation of angiogenesis
- E. Warburg effect

Explanation (requires correct answer)

2. Which of the following is a proto-oncogene?

- A. *BRCA1*

3. Which of the following inhibits caspases, which effectively stops the process of apoptosis?

A. *BRCA1*

B. *BRCA2*

C. IAPs (inhibitors of apoptosis proteins)

D. p53

E. *RB*

Explanation (requires correct answer)

4. Which of the following terms describes cancerous cells that have additional mutations and are fitter compared with the original cancer cell?

Doubling Time

The doubling time is the amount of time it takes one cell to divide or a group of cells to double in quantity (Figure 1). The doubling time varies from one cancer to another and can vary even between cases of the same type of cancer. The clinical utility of doubling time is to estimate a prognosis based on how fast the tumor doubles in size. This is important because it correlates with the aggressiveness of the tumor. For example, when monitoring a lung nodule, if it was 1 cm in diameter and it grows to 2 cm within 4 years, the doubling time is 4 years. This tumor would not be considered very aggressive. In comparison, if the nodule was 1 cm in diameter and grew to 2 cm within 2 months, the outlook would be very different. This doubling time is 2 months, and the tumor is considerably more aggressive, which would warrant a more aggressive treatment course.

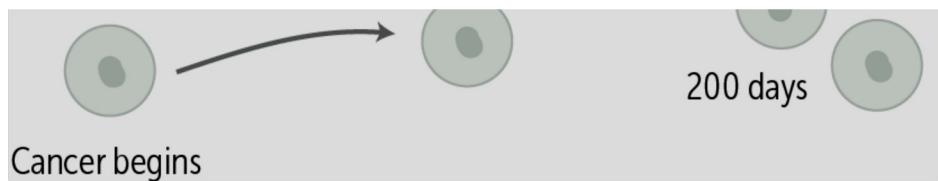


Figure 1

What is the doubling time shown in Figure 1?

Growth Fraction

The growth fraction is the amount of tumor cells that are within the **proliferative phase** of the cell cycle. Most of our cells are in the resting (nonproliferative) phase, which is G0. During periods of growth, cells leave the resting phase (G0) and enter into G1. The cell will proceed through the interphase (G1, S, G2) and M phase (mitosis, cytokinesis) to ultimately divide into two cells (Figure 2).

QUIZ

 Tap image for quiz

Figure 2

When the tumor is still in the early stages of growth, the majority of cells are in the proliferative phase. The interphase requires lots of nutrients, which are supplied by blood flow to the tumor. When a tumor grows too large, it outgrows its blood supply and is no longer able to maintain so many cells in the proliferative phase. As the tumor grows larger, more cells leave the proliferative phase and enter G0. This detail is clinically important because the majority of chemotherapy agents target cells in the proliferative phase of the cell cycle.

Cell Death Rate

There is a natural cycle of old cells dying and being replaced by new ones. This is true in tumors as well. The number of cells that turns over per unit time is known as the cell death rate.

How Do Subclones Increase Malignant Potential?

So how do some tumors decrease their doubling time and evade the immune system? Over time, some tumors acquire a greater malignant potential. This occurs incrementally. With each cell independently mutating, some mutations can prolong tumor cell survival, and others are detrimental to tumor cell survival.

A **subclone** (also known as a tumor cell variant) describes a tumor cell that has acquired additional mutations. Various tumor subclones will have different effects on growth, invasion, metastasis, and resistance to therapies (Figure 3).

through the extracellular matrix.

Step 2: Intravasation

Intravasation involves entry into the bloodstream or lymphatics. Many circulating tumor cells will die from shear stress from blood or lymphatic flow or apoptosis due to loss of adhesion. Tumor cells bind to each other or to platelets to survive in the bloodstream. They may activate coagulation factors, resulting in emboli. A tumor cell is significantly larger than most blood cells and for this reason will likely get stuck at the first capillary bed it crosses, getting closer to its final destination.

Step 3: Extravasation

Extravasation is the exit from the bloodstream and into the tissue. Adhesion molecules and anatomic location play a big role. However, some cancers prefer to metastasize to organs that are not nearby. One example of distant metastasis is the predilection of lung cancer to metastasize to the adrenal glands. This may be due to specific adhesion molecules on target endothelium. Tumor cells may express specific ligands (binding molecules) for certain endothelium.

Step 4: Growth at Secondary Site

Growth at a secondary site can only occur if the surrounding tissue of the target organ is favorable. Metastasis will not occur if the stromal environment is not conducive to the tumor's growth, for example, if certain growth factors are not present. A growing tumor requires certain factors to survive.

What are the four steps of tumor cell metastasis?

How Does Cancer Evade the Immune System?

As previously noted, as a tumor grows it develops subclones, each with its own unique features. One such feature is immune evasion. Mechanisms for immune evasion include:

- Antigen masking
- Outgrowth of antigen variants
- Loss of major histocompatibility complex (MHC) molecules
- Lack of co-stimulation
- Immunosuppression
- Apoptosis of cytotoxic T cells

Antigen Masking

Antigen masking is one way that tumor cells hide from the immune

Figure 11

Immunosuppression

The immune response is regulated by cytokines, which are small proteins that function as signaling molecules. One of these cytokines is transforming growth factor β (TGF- β), a potent immunosuppressant capable of suppressing the activities of B cells, T cells, dendritic cells, and macrophages. Some tumor cells secrete TGF- β in large quantities, suppressing the immune system (Figure 12).

What potent immunosuppressant do tumor cells use to evade immune system defenses?

Apoptosis of Cytotoxic T Cells

Apoptosis (programmed cell death) is basically a self-destruct button. This process can occur via two different mechanisms: the intrinsic or extrinsic pathway. Tumor cells such as melanoma and hepatocellular carcinoma express a receptor that leads to apoptosis via the extrinsic pathway. They express FasL, which binds to the Fas-receptor on T cells, leading to apoptosis of cytotoxic T cells.

What Are the Different Pathways of Metastasis?

There are three main pathways by which tumor cells can metastasize. Tumors can spread lymphatically (through the lymphatic system), hematogenously (through the circulatory system), or by seeding (directly

Figure 12

By which pathway do carcinomas typically metastasize?

CASE CONNECTION

[BACK TO INTRODUCTION ↑](#)

Thinking back to TF, what are the likely locations and sources of TF's metastases?

Unfortunately, TF has stage IV breast cancer, with involvement of her lymph nodes and lungs. You now know that breast cancer can spread to the axillary lymph nodes directly and to the lungs via the superior vena cava through the process of intravasation and extravasation. You spend a good deal of time with TF, answering her questions and supporting her through the discussion. After discussing things with her family, TF decides to undergo chemotherapy. You call her on the phone the next day to see how she is doing. "Not bad. Today is better than yesterday. I have a wonderful and supportive family," TF says.

Summary

- Doubling time is the amount of time it takes a group of cells to double in size; this varies between different types of cancers.
- The growth fraction corresponds to the number of tumor cells within the proliferative phase, which includes any stage of the cell cycle other than G₀; this indicates that cells are dividing.
- Tumor subclones occur when some of the tumor cells acquire mutations; these mutations can benefit the tumor and lead to immune evasion and eventual metastasis.
- Immune evasion is achieved by antigen masking, outgrowth of antigen variants, loss of MHC molecules, lack of co-stimulation, immunosuppression, and apoptosis of cytotoxic T cells.
- The steps of metastasis are invasion, intravasation, extravasation, and growth at secondary sites.
- Intravasation corresponds to tumor cell invasion through the extracellular matrix, into the bloodstream, and travel to a secondary site.
- In extravasation, tumor cells exit the bloodstream or lymphatics and infiltrate outside of the capillaries.
- Growth of a tumor at a distant site relies on the environment of that tissue; without the proper stromal environment, such as cytokines and growth factors, survival of the tumor cannot occur.
- A tumor can metastasize lymphatically, hematogenously, or by seeding.
- Carcinomas are associated with lymphatic spread.
- Sarcomas are associated with hematogenous spread.
- Seeding occurs within open spaces such as the peritoneal cavity, subarachnoid space, pleural space, and joint cavities.

Viruses: The Front Runner

That common cold you have had for the last 2 weeks because you were too tired to go to the doctor? Watch out! Just kidding—sort of. The common cold probably will not cause cancer, but 12% of cancers are caused by viruses. Viruses typically target specific cell types. They take over the machinery of the cells and can alter genes. When this occurs, the cell can be turned toward the path of cancer. Let's take a look at a few of the most common oncoviruses (ie, viruses that cause cancer).

Epstein-Barr Virus

Epstein-Barr virus (EBV), also called human herpesvirus 4 (HHV-4), is best known as the cause of mononucleosis or “mono.” Mononucleosis is often referred to as the “kissing disease” because it is most commonly transmitted by salivary contact during the teenage years. Although mononucleosis itself does not cause cancer, EBV can lead to its development.

How does this happen? EBV targets B lymphocytes. It often remains latent in these cells for a very long time, binding to the CD21 cell marker. With the affinity for this cell type, this virus is more likely to infect these cells and alter their genetic make-up. This action increases the chances for two types of cancers that are associated with B cells: Hodgkin lymphoma and Burkitt lymphoma.

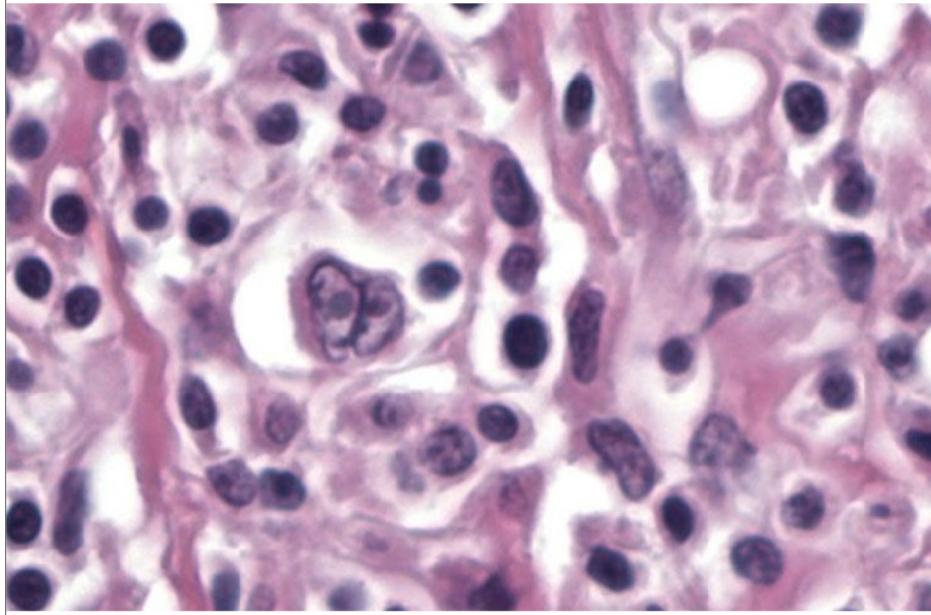
Which cancers are associated with EBV infections?

Hodgkin lymphoma cases are related to infection with EBV about 50% of the time. Risk factors for developing Hodgkin lymphoma include immunosuppression and a family history of the disease. On histology, this cancer is typified by the presence of Reed-Sternberg cells, colloquially referred to as “owl eye” cells because they typically have a bilobed nucleus with prominent eosinophilic inclusion-like nucleoli ([Figure 1](#)).

INSTRUCTOR NOTE

We will discuss this further in Lymphomas. For now just know the association between EBV and Hodgkin Lymphoma and Burkitt lymphoma

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QUIZ

Tap image for quiz

Figure 1

CLINICAL CORRELATION

An important difference between Hodgkin and non-Hodgkin lymphoma on light microscopy, which can be seen in [Figure 1](#) with an H&E (hematoxylin and eosin) stain, is the presence of Reed-Sternberg cells in the former condition.

Burkitt lymphoma is a type of [non-Hodgkin lymphoma](#). About 75% of cases have a t(8;14) translocation, resulting in translocation of c-MYC and [immunoglobulin heavy-chain locus](#) (IgH), which causes increased constitutive levels of c-MYC. c-MYC signaling helps the cancer cells survive and proliferate. Under a light microscope, neoplastic B lymphocytes of Burkitt lymphoma appear monomorphic and highly mitotically active.

LECTUROR NOTE

This will be discussed at a later session. The details of Burkitt lymphoma are not necessary at this point.

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There are three subtypes of Burkitt lymphoma:

- African (endemic) Burkitt lymphoma
- Sporadic (nonendemic) Burkitt lymphoma
- Burkitt lymphoma occurring in patients with [HIV](#) infection

The African subtype is, as the name suggests, endemic to certain parts of Africa. It is virtually always positive for EBV and typically presents in children or young adults as a large mandibular mass ([Figure 2](#)). The sporadic subtype also occurs mainly in children and typically presents with a fast-growing mass involving the ileocecum. EBV is found in only 15% of sporadic cases and 25% of HIV-associated cases.

changes can cause the development of hepatocellular carcinoma as well.

Human Papillomavirus

Did you have to get the Gardasil shot when you were a teenager? Both females and males ages 9-26 years can receive this shot to “guard” against human papillomavirus (HPV). HPV is a virus that can cause warts and cancer. It comes in several serotypes. HPV serotypes 1 and 4 cause warts in children, known as verruca vulgaris. HPV-6 and HPV-11 can present as genital warts or recurrent respiratory papillomatosis (skin surface elevations in the larynx).

Several HPV serotypes—most notably HPV-16, -18, -31, and -33—are considered “high-risk” serotypes because they frequently are associated with specific types of cancer, most notably cervical carcinoma, but also certain cancers of the vagina, vulva, penis, anus, rectum, and oropharynx. Let’s take a look at how these strains cause this type of cancer.

The key players affected by HPV are the tumor suppressor proteins p53 and Rb (Rb is the retinoblastoma protein encoded by the RB gene). p53 and Rb are crucial regulators of the cell cycle, specifically the transition from the G1 phase to the S phase. G1 is the phase where most of the cell and its components double in size, except for DNA. S is the phase where the DNA “doubles” or a second set is synthesized from the original strands. p53 and Rb inhibit the progression of the cell cycle from the G1 to S phase.

Arresting this process gives the cell time to correct any issues in duplication of cellular components and any problems found in the DNA before the DNA is synthesized in the S phase. HPV stops this process.

How does HPV stop these tumor suppressor genes from performing their function? HPV encodes for two molecules: E6 and E7. E6 has an affinity for and destroys p53. E7 does the same but with Rb. When p53 and Rb are

destroyed, the cell cycle can continue without any checks from the G1 to S phase. This event permits the multiplication of cells with mutations. These mutated cells eventually become cancer.

INSTRUCTOR NOTE

This will be discussed in Female Reproductive Pathology, year 2. Details are not necessary now except to know that HPV (especially types 16 and 18) is associated with squamous cell carcinoma of the cervix, as well as other types of squamous cell carcinomas to be discussed in the future.

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What is the mechanism of oncogenesis in HPV infection?

			into hepatocyte
HPV	Squamous cells	E6 inactivates p53 E7 inactivates Rb	Cancers of the cervix, vagina, vulva, penis, anus, rectum, and oropharynx
HTLV-1	CD4 T cells	Tax protein	Adult T-cell leukemia/ lymphoma
Bacteria			
<i>H pylori</i>	Gastric epithelial cells Lymphocytes in mucosa-associated lymphoid tissue	Chronic inflammation	Gastric adenocarcinoma Lymphoma
Parasites			
<i>S haematobium</i>	Bladder epithelial cells	Chronic inflammation	Bladder carcinoma

CASE CONNECTION

[BACK TO INTRODUCTION ↑](#)

Thinking back to RS, what is his diagnosis?

RS has Kaposi sarcoma due to HHV-8. HHV-8 allows for continuous activation of VEGF, resulting in an increase in the formation of blood vessels. These new blood vessels bring nutrients to the skin, which is responsible for the physical appearance of the lesion. RS responds to the treatment for his Kaposi sarcoma and continues taking his multidrug regimen to treat his HIV infection.

Summary

- Viruses, bacteria, and parasites can cause cancer.
- Each of these microorganisms has a specific affinity for a certain cell type.
- The microorganisms have unique mechanisms of action to infect the human host and initiate the development of cancer.
- Viruses cause 12% of all cancers.
- EBV can cause Hodgkin lymphoma, Burkitt lymphoma, and nasopharyngeal carcinoma because of its affinity for B cells.
- HHV-8 causes Kaposi sarcoma and primary effusion lymphoma because of its deregulatory effects on VEGF.
- HBV and HCV target hepatocytes and cause hepatocellular carcinoma.
- HPV uses E6 and E7 to inhibit p53 and Rb, respectively, causing anogenital carcinomas, especially cervical cancer.
- HTLV-1 uses the Tax protein to mutate CD-4 T cells, resulting in adult T-cell leukemia/lymphoma.
- The main cancer-causing bacteria is *H pylori*, which is associated with gastric adenocarcinoma and MALT lymphoma.
- Parasites, like bacteria, cause chronic inflammation and can lead to cancer, such as bladder carcinoma from *S haematobium*.

Review Questions

1. A 13-year-old child presents to you with a large tumor on his jaw. He and his family recently emigrated from Uganda in the hopes of finding him better care. What organism most likely caused this child's tumor?
 - EBV
 - H pylori*

~~Limbic encephalitis can be fatal if not treated. Immediate treatment includes steroids, intravenous immunoglobulins (IVIG), plasmapheresis, and supportive measures.~~ The offending tumor should be resected as soon as possible. Even with appropriate treatment, cognitive deficits, sleep disturbances, and behavioral abnormalities can persist for years.

What tumor is most commonly associated with anti-NMDA receptor encephalitis?

Limbic Encephalitis

Limbic encephalitis is an immune-mediated paraneoplastic syndrome that is characterized by inflammation of the structures that compose the limbic system. The typical presentation involves subacute onset of symptoms classically associated with the limbic system. These include short-term memory loss (a hallmark symptom), seizures, personality changes, olfactory and gustatory hallucinations, headaches, agitation, and sleep disturbance.

CLINICAL CORRELATION

Recall that the hippocampus, amygdala, cingulate gyrus, and mammillary bodies are components of the limbic system. The limbic system is responsible for the famous five Fs: feeding, fleeing, fighting, feeling, and sex.

The cancer most commonly associated with limbic encephalitis is SCLC. The underlying mechanism involves an autoimmune attack targeted at neurons in the limbic system. Antibodies against a neuronal antigen called Hu (anti-Hu antibodies) play an important role in this mechanism. While treatment of the underlying cancer is of primary importance, if symptoms are particularly troublesome, immunosuppressive treatment may provide some relief.

Which cancer is most commonly associated with limbic encephalitis?

Paraneoplastic Syndromes That Affect the Endocrine System

Tumors sometimes do strange things for reasons that aren't entirely clear. One of these strange activities is hormone secretion (by tumors that have no business making hormones). We're not talking about a thyroid cancer secreting thyroid hormones. That makes sense. But a squamous cell lung cancer that makes parathyroid hormone? That's just strange. To be fair, these "hormones" are often not structurally identical to their normal counterparts (so we often call them hormone-like substances). But they're similar enough to the normal hormones that the body reacts to them as if they were real hormones, and patients end up with all kinds of hormone-related symptoms, sometimes well before the cancer itself makes an appearance.

It's important to note that in these hormone-related paraneoplastic syndromes, the tumor cells are just sitting there making hormone on their own, and they don't respond to any outside signals telling them to stop. This type of secretion is called ectopic, meaning that it's outside of the normal axis of hormonal control.

Normal hormone secretion is responsive to inhibiting signals. When the serum calcium level is low, the parathyroids release parathyroid hormone (PTH); when the serum calcium level reaches normal levels, PTH is no longer released. Ectopic hormone secretion is unresponsive to inhibiting signals. When a tumor cell secretes a PTH-like substance, it doesn't care about the serum calcium level! The serum calcium can be markedly elevated, and the tumor cell will keep on secreting its PTH-like substance.

There are many paraneoplastic syndromes involving the endocrine system.

Here, we'll touch on Cushing syndrome, but because of its importance and breadth, it will be covered in more depth in another brick. Then we'll focus on two of the more common syndromes: hypercalcemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH). Once you understand how these syndromes work, you can apply that knowledge to any of the other hormone-related paraneoplastic syndromes you may encounter.

Cushing Syndrome

Cushing syndrome is a common disorder caused by high levels of serum cortisol. Patients develop characteristic signs and symptoms such as deposition of adipose tissue in the upper back and neck region ("buffalo hump") and around the face ("moon facies") along with a number of metabolic derangements, including hyperglycemia.

Although there are other, more common, causes of Cushing syndrome, a small but significant number of cases are caused by a paraneoplastic syndrome. The most common culprit is SCLC, which can secrete a substance so similar to adrenocorticotrophic hormone (ACTH) that it acts just like ACTH and stimulates the production of cortisol by the adrenal gland.

Hypercalcemia

There are many causes of hypercalcemia (serum calcium >10.2 mg/dL). When a patient is found to have hypercalcemia on a routine laboratory assay but has no clinical signs or symptoms of hypercalcemia, the most common cause is a primary hyperparathyroidism (something in the parathyroid gland itself is causing excess PTH secretion). When patients with hypercalcemia are symptomatic however that's a different story. the

With hypercalcemia are symptomatic, however, that's a different story, the most common cause of symptomatic hypercalcemia is malignancy.

Hypercalcemia is one of the most common paraneoplastic syndromes. Most malignant tumors that cause hypercalcemia do so by secreting a substance called parathyroid hormone-related protein (PTHrP), which, like normal PTH, causes the serum calcium level to increase. A number of cancers are highly associated with the production of PTHrP: most commonly squamous cell carcinoma of the lung and head and neck as well as carcinomas of the breast, ovaries, bladder, and kidneys.

Malignant tumors can also cause hypercalcemia by secreting calcitriol (the active form of vitamin D), which raises serum calcium by several different mechanisms. This is a much less common mechanism of paraneoplastic hypercalcemia, and it's seen primarily in patients with lymphoma.

What cancers are associated with paraneoplastic hypercalcemia?

CLINICAL CORRELATION

Recall that parathyroid hormone ultimately increases serum calcium levels and lowers serum phosphate levels. Vitamin D3 (calcitriol) ultimately increases both serum calcium and serum phosphate.

Recall that squamous cell carcinoma of the lung and SCLC are strongly associated with smoking.

Hypercalcemia can present with a variety of signs and symptoms, and key symptoms can be remembered by organ system.

To recall the key symptoms of hypercalcemia: stones, bones, groans, and psychiatric overtones.

Renal: kidney stones, polyuria, nocturia (urinating excessively at night, usually disturbing sleep), dehydration.

Musculoskeletal: Bone pain and muscle weakness.

Gastrointestinal (GI): constipation, GI upset, nausea, vomiting.

Neuropsychiatric: depression, confusion, lethargy, fatigue.

When hypercalcemia occurs as part of a paraneoplastic syndrome, calcium levels can increase to dangerously high levels. In these cases, managing the calcium level is the first priority: a search for the cause can be

the calcium level is the first priority, a search for the cause can be undertaken once the patient is stable.

Syndrome of Inappropriate Antidiuretic Hormone

As its name implies, the paraneoplastic syndrome of inappropriate antidiuretic hormone (SIADH) results from increased levels of antidiuretic hormone (ADH) because of ectopic production by a tumor. SCLC is by far the most commonly associated cancer. ADH normally stimulates the reabsorption of water in the collecting ducts of kidney, and its action is tightly controlled by physiologic feedback mechanisms. In SIADH, however, the offending tumor releases ADH in an unregulated fashion. This excess ADH causes hyponatremia (decreased serum sodium, <135 mEq/L) through a dilutional effect in the serum and by increasing sodium excretion.

Watch for neurologic symptoms: decreased consciousness, malaise, weakness, seizures, headaches, and memory impairment. Laboratory studies will show hyponatremia, hypo-osmolality (<275 mOsm/kg), and urine that is less dilute than expected (>100 mOsm/kg).

What cancer is most commonly associated with paraneoplastic SIADH?

The immediate management of SIADH is centered on correcting serum sodium levels mainly through fluid restriction and pharmacologic intervention. As with all the paraneoplastic syndromes, the optimal treatment addresses the underlying tumor.

Paraneoplastic Syndromes That Affect the Skin and Musculoskeletal System

Paraneoplastic syndromes that affect the skin often precede a diagnosis of cancer and are often the first symptoms of an underlying malignancy.

Acanthosis Nigricans

• TRUCTOR NOTE

Will be discussed further in Skin pathology sessions

MARIA PLUMMER

Acanthosis nigricans (AN) refers to thickened, black or brown hyperpigmentation of the skin that often has a velvety texture, seen here on the neck ([Figure 1](#)) and axilla ([Figure 2](#)), the most common sites. Most cases of acanthosis nigricans are associated with conditions such as

CASE CONNECTION

[BACK TO INTRODUCTION ↑](#)

Thinking back to AH, what is the diagnosis? What is the etiology of the elevated calcium level?

You suspect that AH has squamous cell carcinoma of the lung due to his tobacco use and that the hypercalcemia is due to ectopic production of PTH. You admit AH to the hospital, begin antibiotics for his pneumonia, and administer IV fluids as initial management of his hypercalcemia. “We have a few problems here,” you explain to AH. “You have pneumonia, but more seriously, you have a lung mass that I think is cancer. Your symptoms are related to an elevated calcium level that can be associated with certain lung cancers. Once the pneumonia is treated, we’ll be able to address these issues more thoroughly.”

Summary

- Paraneoplastic syndromes are groups of signs and symptoms that happen in patients with cancer but are not directly related to the growth of the tumor itself.
- There are many such syndromes, some of which can be fatal if not treated.
- Paraneoplastic syndromes often result from immune cross-reactivity or production of hormone by the tumor cells.
- Paraneoplastic neurologic syndromes include anti-NMDA receptor encephalitis, limbic encephalitis, Lambert-Eaton myasthenic syndrome, and myasthenia gravis. Each of these syndromes is associated with specific cancers.

- Paraneoplastic endocrine syndromes result from the secretion of hormone-like substances by tumor cells. Examples include Cushing syndrome, hypercalcemia, and SIADH.
- Paraneoplastic syndromes that affect the skin include acanthosis nigricans and the sign of Leser-Trélat. Both are associated with GI adenocarcinomas.
- Some paraneoplastic syndromes, such as SIADH, require specific, urgent treatment. Overall, however, the focus of treatment is the underlying malignancy.

Review Questions

1. A 20-year-old female is brought to the emergency department by her roommate. The roommate says the patient has been acting bizarre lately, and she is afraid her friend might be taking psychedelic drugs. She also mentions that over the last few days, the patient had what she thought was the flu. The patient is admitted to the hospital, and a week later her blood pressure becomes unstable, she spikes a fever, and she becomes obtunded. Assuming this constellation of symptoms is all attributable to one underlying cancer, what malignancy would you be most concerned for?

- A. Gastric adenocarcinoma
- B. Lymphoma
- C. Ovarian teratoma
- D. Small cell lung cancer