21 The Lymphatic and Immune Systems

Objectives
In this chapter we will study
• lymphatic and immune disorders;
• some diseases of the lymph nodes and lymphoid tissues—metastatic cancer, lymphomas, and lymphadenitis;
• tonsillitis;
• infectious mononucleosis;
• autoimmune diseases, particularly systemic lupus erythematosus; and
• how the body’s natural immune response affects tissue grafts and transplants.

Diagnosis of Lymphatic and Immune Disorders
The lymphatic and immune systems work together to detect and destroy foreign substances and microorganisms that may disturb homeostasis. In addition, the lymphatic system aids the cardiovascular system in maintaining fluid balance. Disorders of the lymphatic system are therefore often associated with disorders of immunity and fluid balance. Such interactions must be kept in mind in the diagnosis of lymphatic and immune disorders.

Signs of lymphatic system disorders include the following:
• Fever indicates infection, while weakness and fatigue both suggest altered homeostasis.
• Splenomegaly (enlargement of the spleen) is common in infections and hematologic disorders. It can be detected by palpation, and an enlarged spleen typically produces a dull sound on percussion.
• Lymphadenitis (inflammation of the lymph nodes) usually results from an infection elsewhere in the body, and is marked by enlargement and tenderness of a lymph node. Clinicians palpate the lymph nodes to assess their texture, size, relative mobility, and degree of tenderness. These variables help narrow down the diagnosis.
• Lymphangitis (inflammation of the lymphatic vessels) is indicated by the presence of red streaks on the skin (erythematous), which often radiate from the site of inflammation. Lymphangitis is commonly seen in the lower limbs and was once used to identify “blood poisoning” (now called septicemia—bacteria in the bloodstream).
• Edema is often an indication of impaired lymphatic drainage of tissue fluid.
• Respiratory disorders such as coughing, wheezing, dyspnea, and runny nose are common indicators of immune hypersensitivity (allergy).
• Skin lesions (see chapter 7 of this manual) are also seen in response to allergic reactions. The most common type of skin lesion is hives (urticaria).
• Recurrent infections indicate that the immune system may not be functioning adequately.

The results of a physical examination may indicate the need for additional testing. Possible diagnostic procedures include blood analysis (CBC, immunoglobulin electrophoresis, and identification of specific antibodies), imaging techniques (CT, MRI, and X ray), skin tests to identify allergic reactions, biopsy of the lymphoid tissues, and lymphangiography, a test similar to angiography in which dye is used to visualize the lymph nodes and lymphatic ducts.

Disorders of the Lymphatic System
Although the lymphatic system serves largely to protect us from disease, it sometimes contributes to the spread of disease, and it is also subject to diseases of its own. Here, we consider the role of the lymphatic system in the spread of cancer and examine some
diseases of the lymph nodes and tonsils. Lymph node disease in general is called lymphadenopathy.

Lymph Nodes and Cancer Metastasis

Because one of the roles of the lymph nodes is to remove foreign substances, the nodes are predisposed to cancer metastasis. When a cancer metastasizes, some of the tumor cells enter the blood and tissue fluid. From the latter site, they are easily picked up by the lymphatic capillaries and transported in the lymph until they lodge in a nearby lymph node. If the cancer cells are not destroyed in the node, they can seed the growth of a metastatic tumor. The degree of metastasis can be determined by finding the lymph nodes most distant from the original site of the cancer that are “normal.” This is also the reason the lymph nodes draining the site of a malignant tumor are removed and examined for the presence of abnormal cells at the same time the tumor itself is excised.

Lymphomas

Lymphoma is a collective term for both benign and malignant neoplasms of the lymphoid tissues, although the word is often used alone to mean malignant lymphoma. It is estimated that between 50,000 and 80,000 new cases of lymphoma are diagnosed annually in the United States. Malignant lymphomas are divided into three different types based on cell appearance and origin: Hodgkin disease, non-Hodgkin lymphoma, and Burkitt lymphoma.

Hodgkin disease is a malignant lymphoma first characterized in 1832 by British physician Thomas Hodgkin. It usually affects lymph nodes in the mediastinal, supraclavicular, or cervical region. It occurs almost equally in males and females and is seldom seen before the age of 10. Incidence peaks in people 15 to 34 years of age and again in those over 60. The incidence of Hodgkin disease in the United States in females and males, respectively, is 26 and 35 cases per million. It is apparently caused by an oncogene.

The signs and symptoms of Hodgkin disease include painless swelling of the lymph nodes, splenomegaly, hepatomegaly (liver enlargement), fever, anorexia (loss of appetite), weight loss, night sweats, and pruritis (severe itching). Laboratory analysis reveals thrombocytosis, leukocytosis, eosinophilia, an elevated RBC sedimentation rate, and elevated serum alkaline phosphatase. Diagnosis is made by combining the findings of the physical examination, imaging techniques, and laboratory tests. The disease is confirmed by the presence of characteristic Reed-Sternberg cells in a lymph node biopsy. Hodgkin disease is treated with radiation and chemotherapy, with a survival rate of 70% to 80%.

Non-Hodgkin lymphomas are a group of lymphomas in which Reed-Sternberg cells are not observed upon biopsy. Otherwise, the signs and symptoms are similar to those of Hodgkin lymphoma. In non-Hodgkin lymphoma, the lymphadenopathy is not always localized to the cervical and mediastinal lymph nodes, but can include the axillary, inguinal, and femoral lymph nodes. Additionally, these cancers sometimes develop in extranodal sites, including the nasopharynx, bone, thyroid, testes, and gastrointestinal tract.

Non-Hodgkin lymphoma is more common than Hodgkin lymphoma, and its etiology is usually unknown. Patients on immunosuppressive drugs, however, have a 100 times greater risk of developing non-Hodgkin lymphoma than other people. It is thought that the drugs activate a virus which, in turn, causes the genetic transformation to a cancer cell. Diagnosis and treatment methods are similar to those for Hodgkin disease. Monoclonal antibodies against the tumor cells are also effective. Slightly more than half of patients survive, but mortality is higher than for Hodgkin disease. The median time of death ranges from 6 months to 7.5 years after the first symptoms appear, depending on how advanced the lymphoma is when treatment begins.

Burkitt lymphoma affects predominantly children and young adults in central Africa, where it is thought to involve an insect-borne virus. It is rare in the United States. Burkitt lymphoma causes bone-destroying lesions of the jaw and face. It is treated with chemotherapy and is highly curable if treated early, although it disproportionately affects people with little access to the necessary health care.

Lymphadenitis

Lymphadenitis can be triggered by a wide variety of pathogens, including bacteria, viruses, fungi, and protozoans. Streptococcal infections, tuberculosis, cat-scratch disease, primary syphilis, and genital herpes, among other disorders, cause regional lymphadenitis (inflammation of lymph nodes in selected areas), while infectious mononucleosis, cytomegalovirus, secondary syphilis, and other conditions cause generalized lymphadenitis. The
Lymph node enlargement is a result of edema and infiltration of the node with leukocytes. Lymphadenitis usually subsides when the underlying cause, such as an infection, is cured, but inflamed, abscessed lymph nodes sometimes require drainage.

**Tonsillitis**

Tonsillitis (inflammation of the tonsils) usually results from streptococcal or viral infections. The pharyngeal and palatine tonsils are most often involved. Signs and symptoms include a sore throat, redness, difficulty swallowing, high fever, headache, malaise, and vomiting. As the tonsils swell with inflammation, they may obstruct breathing. Tonsillitis is most often diagnosed through a physical examination and patient history. A throat culture is often done to determine whether the cause is viral or bacterial and to rule out other disorders. If the tonsillitis has a bacterial cause, an appropriate antibiotic is prescribed; viral tonsillitis is treated with bed rest and aspirin to relieve the pain. Tonsillectomy (removal of the tonsils) is nowadays performed only in the event of frequently recurring tonsillitis.

**Infectious Mononucleosis**

Infectious mononucleosis is an acute infection of the B lymphocytes with Epstein-Barr virus (EBV). It usually affects young adults between the ages of 15 and 33 years, with peak incidences at the ages of 18 to 23 in males and 15 to 16 in females. At ages younger than these, children in lower socioeconomic groups are most likely to contract EBV, and it is estimated that up to 85% of them do so by the age of 4. However, at this age, children are usually asymptomatic and gain some immunity to further exposure. Most people have acquired an EBV infection by early adulthood, but only a minority of them develop any clinical signs. After the initial infection, the virus remains in the body for life, but is normally kept in check by the immune system.

EBV initially replicates in the nasopharynx, oropharynx, and salivary glands before invading the B lymphocytes. People transmit the virus to others through close contact, usually by exchanging saliva, so mononucleosis is sometimes called the “kissing disease.” The incubation period of approximately 30 to 50 days allows time for considerable transmission.

Patients with infectious mononucleosis usually exhibit four signs and symptoms: fatigue, fever, pharyngitis, and lymphadenopathy. The individual may also have malaise, headache, anorexia, and dysphagia. Approximately 50% of all patients have splenomegaly and mild hepatomegaly. Diagnosis is confirmed through blood tests that show leukocytosis, lymphocytosis, and antigens against specific EBV proteins.

Mononucleosis is usually self-limiting, lasting only a few weeks after diagnosis. Treatment is therefore primarily supportive and includes bed rest, analgesics for pain, and antipyretics for fever. In rare cases, death occurs from splenic rupture or airway obstruction. Strenuous physical activity should be restricted for about 2 months to avoid the last of these complications.

**Autoimmune Diseases**

Autoimmune diseases are disorders in which the immune system mistakenly recognizes normal tissues as foreign and initiates immune-mediated destruction of the tissue cells. Virtually every body system is affected by autoimmune diseases, some of which have been discussed in previous chapters of this manual (for example, rheumatoid arthritis in chapter 10; myasthenia gravis, chapter 12; and Graves disease, chapter 17). Most autoimmune disorders appear to involve a genetic predisposition. They affect more women than men.

Systemic lupus erythematosus (SLE), is one of the most serious autoimmune diseases. Approximately 90% of SLE patients are women between the ages of 20 and 40, blacks are affected more frequently than whites. In SLE, autoantibodies are produced against a wide variety of substances, including blood cells (erythrocytes, platelets, and lymphocytes), clotting proteins, phospholipids, and especially nuclear contents such as the nucleic acids and histones. Thus, virtually every cell of the body is subject to attack. Tissue damage most often occurs when antibody-antigen complexes are deposited in body tissues. The most common site of deposition is the basement membrane of the glomerulus in the kidney, leading to renal complications.

Manifestations of SLE include arthralgia (joint pain) or arthritis, vasculitis (inflamed blood vessels), rash, renal and cardiovascular dysfunction, and anemia or other blood disorders. Diagnosis is complicated by the fact that there are periods of remission during which the patient is asymptomatic.
There are 11 clinical indicators of SLE; a patient must present with at least four of these to be diagnosed with the disease:

1. malar rash (a rash confined to the cheeks);
2. discoid rash (showing raised, scaly patches);
3. photosensitivity (a rash triggered by sunlight);
4. oral or nasopharyngeal ulcers;
5. arthritis in at least two joints;
6. inflammation of the serous membranes;
7. renal dysfunction (often with protein in the urine);
8. neurologic dysfunctions such as seizures or psychosis;
9. hematologic disorders such as anemia, leukopenia, or thrombocytopenia;
10. presence of antibody against nuclear contents; and
11. various other abnormal antibodies and serological signs.

Treatment and prognosis for SLE depend on the severity of the symptoms and the systems that are affected. In most countries, the 10-year survival rate exceeds 95% if diagnosis is made promptly. Treatment is aimed at managing the signs and symptoms, and includes steroidal anti-inflammatory and analgesic medications.

Transplant Rejection

As with autoimmune diseases, clinicians might wish for a less active immune system when transplanting tissues and organs into a patient because a normal, healthy immune system does its best to destroy transplanted foreign tissues.

Transplant rejection is an example of alloimmunity—immune responses to cells that are genetically different from the host body but belong to the same species. To minimize this reaction, it is necessary to have a tissue donor who is antigenically compatible with the recipient. Tissue compatibility is determined by HLAs (an abbreviation for either human leukocyte antigens or histocompatibility locus antigens), coded for by genes called the major histocompatibility complex (MHC). A perfect HLA match is possible only between identical twins; other siblings have just a 1 in 4 chance of being antigenically compatible. The greater the difference in HLAs, the greater is the probability that the transplant will be rejected. Finding a compatible donor is difficult and important.

When the transplant recipient’s immune system detects the nonself antigens on the transplanted tissue, immune responses are triggered. These rejection responses are characterized as hyperacute, acute, or chronic, depending on the time course. Hyperacute rejection is rare, but occurs almost immediately after blood perfusion to the transplanted organ is established. It occurs in recipients who already have antibodies against antigens of the transplanted tissue. Acute rejection occurs about 2 weeks after the transplant as the recipient develops antibodies against the donor’s HLA antigens. Chronic rejection occurs after months to years of normal transplant function as a result of a weak immune response against minor HLA antigens in the transplant. It results in slow, progressive organ failure.

With improved medical technology, including advances in surgical techniques and the development of immunosuppressive drugs, the number of successful transplants has increased. Immunosuppressive drugs allow for transplants between less compatible donors and recipients, although a certain degree of compatibility is still required. By suppressing the immune system, these drugs lessen the likelihood of rejection and give the transplanted tissue time to become established. However, immunosuppressive drugs also make the patient more susceptible to opportunistic infections, and it may be months before normal immune function returns. To minimize the development of infections, patients on immunosuppressive drugs are often treated with immunoglobulins (gamma globulins) and antibiotics.
Zach is a 28-year-old graduate student working in a laboratory that studies the genetics of the human immunodeficiency virus (HIV). He has recently noticed that he is losing weight, his lymph nodes are swollen, and he has been experiencing night sweats. He also seems to be scratching more often than normal. Zach is concerned that he may have contracted HIV through his research project.

Zach is married, monogamous, and has never received a blood transfusion or used intravenous drugs. Physical examination reveals pallor, lymphadenopathy, splenomegaly, and an abnormal mass in his abdomen. Zach’s heart and respiratory sounds are normal, but his body temperature is slightly elevated (99°F). Blood analysis is done, with the following results.

- Hematocrit (Hct) = 35%
- Hemoglobin (Hb) = 9.5 g/dL
- RBC count = 3.5 x 10^6/µL
- WBC count = 22,000/µL
- Platelet count = 450,000/µL
- Alkaline phosphatase = 120 IU/L
- HIV antibodies = Negative
- IgA = 300 mg/dL
- IgG = 1,500 mg/dL
- IgM = 65 mg/dL
- Erythrocyte sedimentation rate = 23 mm/hr

**Differential WBC count:**
- Neutrophils = 65%
- Eosinophils = <1%
- Basophils = 1%
- Lymphocytes = 30%
- Monocytes = 3%

Suspecting a lymphoma, the physician suggests a lymph node biopsy. Results of the biopsy show fibrosis, few lymphocytes, and the presence of Reed-Sternberg cells. These results confirm a diagnosis of Hodgkin disease.

**Based on this case study and other information in this chapter, answer the following questions.**

1. Other than his occupation, what symptoms lead Zach to suspect HIV infection?
2. What signs, symptoms, and test results lead his physician to suspect a lymphoma?
3. Why is Zach diagnosed specifically with the Hodgkin form of lymphoma?
4. What treatment will likely be prescribed for Zach? What is his prognosis?
5. Marcy has been diagnosed with renal failure and is admitted to the hospital for a kidney transplant. What postsurgical treatment should be initiated to prevent rejection of the organ?
6. What complication of the postsurgical treatment in the previous question would be of greatest concern to Marcy?
7. Why is infectious mononucleosis more prevalent in adolescents and young adults than in other age groups?
8. Suppose a man had an autoimmune disease in which his body produced autoantibodies against sperm cells. What would you expect to be the chief complaint?
9. Sandra presents to her physician complaining of fever, headache, and painful swellings in her armpits. During the physical examination, the doctor notices that her hands are covered with scratches. He asks about these, and Sandra says they’re from a kitten that she found wandering along a country road 2 weeks earlier and adopted as a pet. What disorder do you think her physician might suspect?
10. Why are antibiotics prescribed for bacterial tonsillitis but not for viral tonsillitis?
**Selected Clinical Terms**

**infectious mononucleosis**  An acute infection of the B lymphocytes with the Epstein-Barr virus, found mostly in adolescents and young adults and typically causing a few weeks of malaise, headache, anorexia, and dysphagia.

**lymphadenitis**  Inflammation of a lymph node, marked by swelling and tenderness; usually indicative of an infection in a region of the body whose lymphatic drainage leads to that node.

**lymphadenopathy**  A collective term for all diseases of the lymph nodes.

**lymphangitis**  Inflammation of a lymphatic vessel.

**lymphoma**  Any neoplasm of the lymphoid tissues, especially malignant neoplasms.

**septicemia**  The presence of bacteria in the bloodstream; formerly called blood poisoning.

**systemic lupus erythematosus**  An autoimmune disease that involves widespread immune attack on the body’s tissues, producing renal complications, connective tissue disease, a characteristic facial rash, and other pathologies.

**tonsillitis**  Inflammation of the tonsils.