Hematologic Infections

I. Introduction

Certain infectious diseases are of particular interest to the hematologist/hematopathologist, because

1) they produce clinical or hematologic manifestations that simulate hematologic neoplasms (such as lymphoma and leukemia),

2) they directly or indirectly cause anemia or other abnormalities on peripheral blood counts, or

3) they involve direct infection of hematopoietic or lymphoid tissues as specific targets of infections.

Some of these infections have been dealt with in great depth elsewhere in the curriculum and will be mentioned only briefly here. The conditions we discuss may be conveniently divided into 1) those that produce findings related to the lymphoid tissues, usually lymph node enlargement (referred to clinically as "lymphadenopathy") and 2) those that manifest themselves as abnormalities of peripheral blood or bone marrow findings.

II. Infections Related to Lymphoid Tissues

Lymph node enlargement may be one of the predominant manifestations of most of these diseases. Other clinical findings that pertain to nodes include pain (classically, pain characterizes infectious and reactive conditions, while painless lymphadenopathy is more characteristic of neoplasms, with numerous glaring exceptions) and the formation of buboes (purulent or liquefactive necrosis of enlarged nodes which may penetrate the lymph node capsule and surrounding tissues, including skin, to produce draining sinuses).

A. **Granulomatous lymphadenitis** is a morphologic category that describes any condition in which epithelioid granulomas are found in lymph nodes. As you have learned in General Pathology, granulomas are not etiologically specific but tend to be found in selected infections due to a limited number of pathogenic species.

1. Tuberculosis

The most important of these are mycobacterial infections and deep fungal infections. Mycobacterial infections may involve nodes either primarily or as part of a general systemic infection (miliary tuberculosis, for example). Secondary node involvement may also be seen locally, where a drainage of a primarily-infected organ (such as lung) produces infection of the nodes in the path of the lymphoid drainage of that organ (pulmonary hilar nodes, in the case of the lung). Primary tuberculous lymphadenitis of the neck is referred to by the clinical term **scrofula**. As in mycobacterial infections elsewhere, the morphologic hallmark is the tuberculoid granuloma, consisting of

clusters of polyhedral and/or spindle-shaped histiocytes with abundant, eosinophilic cytoplasm. Central necrosis of the granulomas and Langhans' multinucleated giant cells may or may not be present. The diagnosis can be made by examination of sections or smears stained with the acid-fast technique, which may demonstrate the characteristic beaded bacillus. Identification of the organisms by culture is slower (taking up to eight weeks) but is more sensitive and allows identification of the exact species of mycobacterium and determination of its sensitivity to a panel of antimicrobial drugs.

2. Histoplasmosis

The classic deep fungal infection associated with granuloma formation is histoplasmosis, caused by the dimorphic[1] mold, *Histoplasma capsulatum* (also called *Emmonsiella capsulata).* Like mycobacterial infections, the lymph node involvement may be localized or part of a systemic infection. The budding yeast form of the organism may be seen in routine hematoxylin/eosin-stained sections but can be made more easily visible with silver impregnation stains, of which Gomori methenamine silver ("GMS") is most widely used.

3. Coccidioidomycosis

The other main fungal infection associated with a tuberculoid granulomatous response is **coccidioidomycosis**, caused by *Coccidioides immitis,* another dimorphic mold. Histoplasmosis is extremely common in the Mississippi river valley, while coccidioidomycosis is more common in the desert Southwest.

4. Other fungal infections

a. Some fungal infections may produce a peculiar reaction characterized by a mixture of loosely arranged granulomas admixed with a prominent suppurative (neutrophilic) exudate. This so-called suppurative granulomatous response is characteristic of **sporotrichosis** (caused by the mold *Sporothrix schenckii)* and **North American blastomycosis** (caused by the dimorphic mold

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[1]Dimorphic molds are: those that tend to grow as fuzzy molds at room temperature but as smooth, shiny colonies of yeast when incubated at 37°C. For microbiology labs to identify one of these pathogenetic dimorphic molds in culture, they must first grow the mold form at room temperature (which takes several weeks) and then try to convert it to the yeast form. This conversion process again takes weeks, sometimes months. For this reason, fungal cultures, which are the gold standard for accuracy, may not help you until the patient is m extremis or dead.

Blastomyces dermatitidis). Both of these infections may be localized or systemic.

b. ***Cryptococcus neoformans*** is an encapsulated yeast that can cause meningoencephalitis in normal individuals but more frequently in immunocompromised hosts (patients with AIDS, leukemia, lymphoma, SLE, sarcoidosis or transplant recipients). *C. neoformans* is present in the soil and in bird (particularly pigeon) droppings and infects patients when it is inhaled. Although the lung is the primary site of localization, pulmonary infection with *C. neoformans* is usually mild and asymptomatic, even while the fungus is spreading to the central nervous system. It may form a solitary pulmonary granuloma similar to the coin lesions caused by Histoplasma. The major pathology of *C. neoformans* is in the CNS with variable tissue response ranging from virtually no inflammatory reaction to chronic granulomatous reaction. In severly immunosuppressed persons, it may disseminate widely to the skin, liver, spleen, adrenals, and bones.

c. ***Aspergillus*** is an ubiquitous mold that causes allergies (brewer's lung) in otherwise healthy persons and serious sinusitis, pneumonia, and fungemia in neutropenic persons. *Aspergillus* species secrete three toxins that may be important in human disease. The carcinogen aflatoxin is made by *Aspergillus* species growing on the surface of peanuts and may be a major cause of liver cancer in Africa. Mitogillin is a potent inducer of IgE and so may be involved in host allergic responses to Aspergillus. Sensitization to the *Aspergillus* spores produces an allergic alveolitis by inducing Type III and Type IV hypersensitivity reactions. Allergic bronchopulmonary aspergillosis, which is associated with hypersensitivity arising from superficial colonization of the bronchial mucosa and often occurs in asthmatic patients, may eventually result in chronic obstructive lung disease.

Colonizing aspergillosis (aspergilloma) implies growth of the fungus in pulmonary cavities wit minimal or no invasion of the tissues. Proliferating masses of fungal hyphae called "fungus balls" form brownish masses lying free within the cavities. Patients with aspergillomas frequently have recurrent hemoptysis. Invasive aspergillosis is an opportunistic infection confined to immuno-suppressed and debilitated hosts. The primary lesions are usually in the lung, but widespread hematogenous dissemination with involvement of the heart valves, brain, and kidneys is common. The pulmonary lesions take the form of necrotizing pneumonia with sharply delineated, rounded, gray foci with hemorrhagic borders, often referred to as target lesions. *Aspergillus* forms fruiting bodies (particularly in cavities) and septate filaments, branching at acute

angles, 45 degrees). *Aspergillus* has a tendency to invade blood vessels.

d. **Mucormycosis** is an opportunistic infection of neutropenic persons and ketoacidotic diabetics, caused by "breadmold fungi," including *Mucor*, *Absidia*, *Rhizopus*, and *Cunninghamella*, which are collectively referred to as the Phycomycetes. These fungi, which are widely distributed in nature, infect immunosuppressed patients. The three primary sites of *Mucor* invasion are the nasal sinuses, lungs, and gastrointestinal tract, depending on whether the spores are inhaled or ingested. In diabetics, the fungus may spread from nasal sinuses to the orbit and brain, giving rise to rhinocerebral mucormycosis. The phycomycetes cause local tissue necrosis, invade arterial walls, and penetrate the periorbital tissues and cranial vault.

B. Cat scratch disease is an infectious form of lymphadenitis that has been known for a long time (although the popular description by Nugent in 1977 is among the most memorable literature on the subject). The disease is caused by inoculation through the skin or mucous membrane of a small, pleomorphic, cell wall-deficient Gram-negative rod. More than one species may be involved, but the most important one is *Bartonella henselae* (formerly *Rochalimaea henselae*). The organism's natural habitat is the claws of house cats, as most patients give a history of having been scratched by one of their furry friends. However, some patients insist that there was no such feline contact prior to their developing the lymphadenopathy that is characteristic of the disease. Classically, there is enlargement of a cervical or axillary node draining the area of inoculation. The disease is more common in children, but adults may be affected. The patient is brought to the doctor for evaluation of the lump, which, on excision, is shown to be a lymph node occupied by broad, stellate areas of necrosis surrounded by epithelioid histiocytes admixed with neutrophils. Using difficult-to-perform silver impregnation stains, such as the Warthin-Starry technique, the node may be found to contain the organisms. Culture is not yet routinely available outside a few research labs.

Cat scratch disease is almost always benign clinically, remains localized to a node or node group, and resolves without treatment. The minority of cases may develop complications, in-cluding encephalitis, retinitis, osteomyelitis, arthritis, hepatitis, and pleuritis. The use of gentamicin, a parental-only antibiotic—and not an innocuous one at that—has been advocated for treatment of these complicated infections.

Parenthetically, the *Bartonella henselae* can show a very ugly face when infecting an AIDS patient. Severe skin infections and deep soft tissue

masses may result. Microscopically, the lesions are characterized by proliferation of small blood vessels lined by very, plump, almost carcinomatous-appearing endothelial cells that are stuffed with myriad's of the bacilli. The term for this condition is **bacillary angiomatosis.** A related condition caused by the same organism is **bacillary peliosis**, in which the liver (and occasionally spleen) develops large blood-filled cystic structures associated with heavily-infected stromal cells.

C. **Toxoplasmosis** is caused by *Toxoplasma gondii,* which is classified as a protozoan — at least this week (specifically, a true coccidium, phylum Apicomplexas, suborder Eimeriina). Infection is usually via the ingestion of uncooked meat or by contact with the feces of infected cats. The latter may be extremely casual. A local pathologist recently reported a case of *Toxoplasma* lymphadenitis in a family of three, all adults, who had some days before gone to an animal shelter to look at a cat with the intention of adopting it. The cat was noted to be ill by the shelter veterinarian. The human contacts developed febrile symptoms almost simultaneously. One of them developed lymphadenopathy and had an inguinal node biopsied to rule out malignant neoplasm. The characteristic microscopic picture of *Toxoplasma* lymphadenitis was seen. Careful attention to the clinical history may have saved this patient the trauma, inconvenience, and expense of an excisional lymph node biopsy. The acute human infection in immunocompetent, nonpregnant adults is generally mild and self-limited, not requiring any specific treatment.

Microscopically, *Toxoplasma* lymphadenitis shows marked follicular hyperplasia with reactive germinal center formation. There is the formation of nests of epithelioid histiocytes, some of which intrude into the germinal centers. The actual organisms are almost never seen in infections of immunocompetent hosts. Therefore, the diagnosis is usually made clinicopathologically from the morphology of the lymph node reaction together with the history and results of serologic studies.

D. **Human immunodeficiency virus infection** is characterized by a generalized lymphadenopathy that clinically may simulate malignant lymphoma, which is also a common complication of AIDS. For this reason, AIDS patients are often called upon to undergo excisional node biopsy. In early stages of the infection, there is marked hyperplasia of the follicular B-lymphocytes, producing a follicular hyperplasia. The follicles gradually decrease in size as the parafollicular B-cells undergo blast transformation and proliferate, producing a pattern of hyperplastic parafollicular areas surrounding relatively atrophic follicles. At this stage, the presence of diffusely proliferating, parafollicular, blast-transformed lymphocytes throughout the node may morphologically simulate a large cell lymphoma, so potential for pathologic diagnostic

error exists here. The final stage of HIV infection is that of totally atrophic lymphoid tissue depleted of lymphocytes.

E. **Epstein-Barr virus** (EBV), a troublesome and ubiquitous DNA virus, is a member of the herpesvirus group. It rightly or wrongly suffers the blame for a variety of conditions, from chronic fatigue syndrome to certain malignant lymphomas. We will leave out chronic fatigue syndrome, since the majority of cognoscenti now believe that EBV is not responsible for this condition. The most commonly diagnosed EBV-caused condition is infectious mononucleosis.

1. **Infectious mononucleosis** is classically an acute viral infection characterized by severe pharyngitis, prostration, lymphadenopathy, and fever. Inoculation of the virus has clasically been blamed on intimate contact involving transfer of saliva, typically, as one author put it, "in kissing of greater than filial intensity." However, it has become clear that the virus can spread among non-intimate household members (e.g., dorm roomates) just as well. The disease occurs most commonly in teenagers and young adults. The majority of the American population — and the overwhelming majority of the world population — show serological evidence of infection by age thirty. Most cases are never diagnosed as "mono," because either they are so mild as to be subclinical, or they impersonate some other mild acute upper respiratory infection, such as those caused by rhino-, echo-, coxsackie-, or adenoviruses. Although most cases are self-limited and benign (if acutely debilitating), there may be complications, including, hepatitis, splenic rupture, and myocarditis. Despite these, fatalities are rare.

   EBV targets the B lymphocyte, which it infects, stimulating the production and transformation of T-killer lymphocytes. These T-cells appear in great numbers in the peripheral blood and have been referred to as "virocytes," "transformed lymphocytes," "atypical lymphocytes," and "Downey cells." The cells are large and have abundant cytoplasm which is "busier" and more opaque than that of normal lymphocytes. The nucleus is also larger has more finely dispersed chromatin. The resemblance of these to monocytes resulted in the mistaken belief at one time that they were in fact monocytes, thus the misnaming of the disease, which, like many other misnomers, has stuck. Actually, these cells are not specific for mononucleosis and may be seen in a variety of reactive states, including other viral infections, bacterial infections, and allergic hypersensitivity states. Therefore, although examination of the peripheral blood smear is helpful in evaluating a case of suspected mono, there are no morphologic findings that are diagnostic.

The reactive lymph nodes seen in these cases show proliferation of blast-transformed lymphocytes (immunoblasts) that may be so striking as to morphologically mimic malignant lymphoma. Incorrect pathologic diagnosis of lymphoma has occurred. This may be avoided by a high index of suspicion on the part of the surgical pathologist. It is important for the clinician to relate to the pathologist clinical information regarding any findings suggestive of infectious mono, so as to minimize the likelihood of such a mistake.

The serologic findings in infectious mononucleosis have been the subject of much hazing of medical students for decades, with talk of heterophile antibodies, Forssman antigen, Guinea pig kidney, and beef red blood cells. No one uses or even remembers any of this. Since one can now measure specific IgM-class antibodies to the virus itself, or measure the mononucleosis-associated heterophile antibody with simple, one-step procedures, all the details of the heterophile reaction are generally relegated to the dusty tomes of medical history. However, you may want to read about it the night before National Boards, in case one of the Mesozoic urine-tasting-and-Bunsen-burner crowd slips a Forssman antigen question into the exam. Generally, the serologic diagnosis is made with one of the easily performed tests which are readily available in essentially all hospitals and outpatient labs. These tests utilize proprietary technology, under such names as "MonoTest," "MonoSpot," and "MonoLert." Incidentally, a minority of cases of a clinical syndrome otherwise indistinguishable from infectious mononucleosis show no antibody response to EBV and are sometimes referred to as "heterophile-negative mono." Most of these cases have been found to be due to infection by the cytomegalovirus (CMV).

2. **Burkitt's Lymphoma** is a high-grade malignant neoplasm of B-lymphocytes that has possibly the fastest rate of growth of any human cancer. It has been said that the physician may detect a palpable increase in tumor size between morning and evening hospital rounds on the same day. There are two epidemiologic/clinical varieties of this tumor, the African Burkitt's lymphoma, and the non-African, or "American," Burkitt's lymphoma. About 98% of tumors of the African type carry the EBV genome, while only a minority of the non-African cases do. The clinical difference between the two types is significant and will be discussed in the class material on lymphomas. The Robbins textbook has an excellent (and laudably brief) discussion on the association of EBV and Burkitt' s Lymphoma, which will not be parroted here.

3. **Post-transplant lymphoproliferative disorder** is a multisystem, Lymphomalike proliferation of immunoblasts and plasmacytoid lymphocytes in iatrogenically immunosuppressed organ transplant patients. It is thought to be caused by EBV infection of B-lymphocytes in combination with loss of host T-cell function brought on by immunosuppressive therapy. Morphologically, it is generally indistinguishable from malignant lymphoma. However, while some of the cases behave like high-grade lymphomas and kill the patient, others respond to antiviral therapy and regress. Also, some are clearly monoclonal proliferations of lymphocytes (thus fitting the classic concept of cancer),while others are shown to be polyclonal and therefore conceptually more akin to the reactive lymphoproliferation seen in infectious mono (above). Although this disease is a subject of a highly specialized area of medicine (transplantation science), it is important in that it illustrates that the distinction between lymphocyte *cancer* and lymphocyte *reactive states* can be a blurry one, and that a definition of cancer by the classic criteria of morphology and clonality is not impeccable.

F. **Visceral leishmaniasis** (kala-azar[2]) is a mainstay of tropical medicine, but it has taken on new importance in the Western world recently, because 1) American service personnel returning from the Persian Gulf War (1990-91) have been found to be infested, and 2) the disease has arisen as an opportunistic infection in AIDS patients in western Europe. The disease is caused by one of several species of the genus *Leishmania*, most notably *L. donovani* (*L. tropica* in Gulf War veterans), which are flagellated protozoa that live in histiocytes/macrophages in the human host. The parasite is vectored by the sandfly, genus *Phlebotomus*. The condition is of interest to hematopathologists, because the reticuloendothelial system is the target of parasitization. The spleen, in particular, becomes massively enlarged. Microscopically, smear preparations of infested tissues show huge numbers of parasites, in their **amastigote** (without flagella) stage. Other clinical manifestations include hepatomegaly, fever, and a peculiar gray discoloration of the skin of the hands, feet, abdomen, and face (which gave the name "kala-azar," or "black disease," to the condition).

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[2]"Kala-azar" is a Hindi word of mixed parentage. "Kala," meaning "black" is from Sanskrit (an Indo-European language), but is borrowed from Dravidic (a non-Indo-European language). "Azar," meaning "disease," is from Persian. Our English term for the disease shows no less linguistic immiscibility, combining elements of Latin ("visceral"), German ("leishman-"), and Greek ("-iasis").

The variant of leishmaniasis afflicting American servicemen is not the same clinically as kala-azar. These individuals suffered from fatigue, low-grade fever, malaise, and occasionally, diarrhea.

III. Infections Related to Blood and Bone Marrow

A. Malaria is the most common cause of hemolytic anemia in the world. It is seen occasionally in our local area, but almost always in individuals who have traveled from one of the endemic areas (Central and South America, Hispaniola, sub-Saharan Africa, the Indian Subcontinent, Southeast Asia, the Middle East, and Oceania). The causative agents are the four species of the parasite genus *Plasmodium* (*P. falciparum, P. vivax, P. ovale, P. malariae),* all vectored by the female *Anopheles* mosquito. The life cycles and morphologic stages of these parasites constitute a complex subject that makes ideal material for hazers of medical students. Basically the only thing the practicing physician need know about the life cycles of *Plasmodium* is that *P. falciparum* does not produce a dormant liver stage (called **hypnozoites**), so it cannot cause a late relapse of disease, unlike *P. vivax* and *P. ovale*, which can.[3] Also, *P. falciparum* produces a more severe clinical disease than the others and must be managed accordingly. Therefore, a lab result of "*Plasmodium* species, *not falciparum"* is generally adequate for practical purposes.

The pathologic findings are the subject of an enormous volume of knowledge, but from an operational standpoint, the diagnosis in the living patient is almost always made by examination of the peripheral blood smear (either the routine Wright-stained smear, or the expert level, hemolyzed thick smear), where one looks for the parasitized erythrocytes. This is a bit more difficult than it sounds, since the changes may be seen in only a rare red cell, and the changes in the abnormal cells may be quite subtle. It is probably not necessary for most doctors practicing in the U.S. to acquire facility in looking for malarial parasites in blood, but you should be sure that you are supported by a lab that employs personnel who have demonstrated the necessary skill. This is definitely a "kids, do not try this at home" procedure.

Clinically, the disease is characterized by fever, chills, myalgia, malaise, prostration, and headache. Death may occur as a result of anemia or

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[3]The fine print: *P. malariae* is the least important of the four malarial species. It *can* cause persistent disease, but it remains in the bloodstream at low levels (for up to thirty years), and does not hide out in the liver, like *P. vivax* and *P. ovale*. Don't worry though — no one ever asks National Board questions about *P. malariae*. This is probably some kind of unwritten law in the microbiologist's code of honor, or something.

renal failure. Rare cases of falciparum malaria are complicated by an acute, very severe, catastrophic hemolytic anemia called **blackwater fever.** The rate of hemolysis is far in excess of the degree of red cell parasitization, so there must be some explanation other than direct parasite-induced lysis for this phenomenon. The pathogenesis of blackwater fever is still unresolved.

B. Lymphatic filariasis is caused by two major species of nematode, *Wuchereria bancrofti* and *Brugia malayi,* both vectored by *Culex* mosquitoes. The macroscopic adults live in the human lymphatic vessels and produce tremendous lymphedema in the areas drained by the occupied lymphatics. The lymphedema is especially severe in the scrotum and lower extremities and is referred to as **elephantiasis,** not only because of the huge size of the affected members, but also for the pachyderm-like, hyperkeratotic, fibrotic skin that covers them. Filarial elephantiasis is extremely common in India. The male victims obviously cannot wear trousers because of their commodious scrota, so they wear a skirt-like garment. This is such a badge of being an unprivileged, regular kind of guy, that an image-conscious, otherwise healthy politician may dress similarly to show that he is just one of the common people.

Lymphatic filariasis is of interest to hematologists, since the microscopic larval forms shed by the adults in the lymphatics may appear in the routine peripheral blood smear. These microfilariae may be distinguished by species on routine examination. A related nematode, the eye worm, *Loa loa,* may also shed microfilariae into the circulation. All forms of filariasis are associated with eosinophilia of the peripheral blood, as would generally be expected in any tissue-invasive parasitosis.

C. Human immunodeficiency virus infection obviously results — directly and indirectly — in many pathological effects throughout the body. One that may be less well appreciated is **myelodysplastic syndrome.** Clinically this may produce pancytopenia in excess of that expected by zidovudine effect. The pathogenesis is unknown. Morphologically, the HIV-related myelodysplastic syndrome is indistinguishable from that seen idiopathically in non-HIV-infected individuals. The classification of these syndromes is covered elsewhere in this course block.

D. Human T-cell Lymphotropic Virus Type I (HTLV-I) is a taxonomic cousin of HIV-1 (formerly called HTLV-III) and probably has similar modes of transmission. This retrovirus infects T-Lymphocytes and causes adult T-cell leukemia/lymphoma. It is also associated with a transverse myelopathy that produces spastic paraparesis. Although

these conditions are relatively rare in the United States (compared with Japan and the Caribbean), the incidence of HTLV-I infection is rather alarming in American intravenous drug users and female prostitutes. The overall proportion of infected prostitutes in the U.S. is 6.7%. Interestingly, there is geographic variation. In southern Nevada, where prostitution is legal, the rate of infection is 0%, while that of Newark, where it is illegal, is 25%.

HTLV-II has not been clearly associated with human disease — yet.

E. **Parvovirus B19** is the etiologic agent of **erythema infectiosum,** also called **fifth disease**, a relatively mild viral exanthem of childhood. It is also associated with fetal death due to nonimmune hydrops fetalis. It is of hematologic concern because of its association with transient aplastic crisis. This may be a great problem in individuals with preexisting chronic hemolytic conditions (such as sickle cell anemia and hereditary spherocytosis), who normally have a shortened rbc life span and tolerate poorly even a transient and otherwise self-limited episode of erythropoietic shutdown. In immunodeficient patients, a chronic hyporegenerative anemia may occur.