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TITLE: Infectious Lymphadenopathies

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Hello, my name is Teresa Scordino. I am a hematopathologist and medical director of the hematology laboratory at the University of Oklahoma Health Sciences Center. Welcome to this Pearl of Laboratory Medicine on "**Infectious Lymphadenopathies**."

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If you have not done so already, I suggest that you review the Pearl of Laboratory Medicine on normal Lymph Node Structure and Function. Understanding normal lymph node morphology is necessary so that you can recognize the architectural changes that occur with lymph node disease.

Lymphoid hyperplasia can occur for a wide variety of reasons, including infections, autoimmune diseases, and drug effect. Different stimuli may induce different patterns of hyperplasia, but overlapping patterns can also occur.

Follicular hyperplasia is an increase in the number and size of B cell follicles. Reactive germinal centers may be very large in size and irregularly shaped, but they maintain features of benign germinal centers: polarization into light and dark zones, tingible body macrophages, and preserved mantle zones. A predominantly follicular pattern of hyperplasia may be seen in nonspecific follicular hyperplasia, syphilis, and HIV infection.

Paracortical hyperplasia is an expansion of the paracortex, between follicles. A heterogeneous population of small lymphocytes, larger immunoblasts, and dendritic cells is present. Causes of lymphadenopathy showing a predominantly paracortical or mixed paracortical / follicular pattern of hyperplasia include EBV or HSV lymphadenitis, toxoplasmosis, dermatopathic lymphadenopathy, and granulomatous lymphadenitis.

Extensive necrosis may be seen in Kikuchi Fujimoto disease, lupus lymphadenitis, cat scratch disease, and systemic lupus erythematosus. A sinus pattern is seen in Rosai Dorfman disease, nonspecific sinus histiocytosis, and hemophagocytic lymphohistiocytosis. Diffuse effacement of the lymph node architecture is seen in occasional cases of HSV or EBV lymphadenitis.

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Bacterial infection can cause suppurative lymphadenitis. Acute bacterial lymphadenitis involving the cervical lymph nodes is often caused by *Streptococcus* or *Staphylococcus* infection. During the early stages, a neutrophilic infiltrate is present, and microabscesses may be seen. These microabscesses may coalesce into large abscesses. Over time, the neutrophilic infiltrate is replaced by chronic inflammatory cells and histiocytes. A high-power image of acute suppurative lymphadenitis is shown. Note the prominent neutrophilic infiltrate.

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The differential diagnosis for granulomatous lymphadenopathy is fairly broad. A number of different infections can cause granulomatous inflammation, including mycobacteria, *Leishmania*, fungi, and some bacteria. Non-necrotizing granulomas are a feature of sarcoidosis. Granulomas may also be seen in foreign body reactions.

Always keep in mind that granulomas may also occur in association with malignant processes, including classical Hodgkin or T cell lymphomas, some solid tumors, and rare cases of lymphoblastic lymphoma. Careful examination of the lymph node tissue between the granulomas is essential to exclude a partially obscured malignancy.

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Fungal lymphadenitis is generally associated with granulomatous inflammation.

Histoplasma lymphadenitis is caused by *Histoplasma capsulatum*, a dimorphic fungus endemic to the Ohio and Mississippi river valleys. Involved lymph nodes show granulomatous inflammation which is frequently necrotizing. GMS or PAS stains can be used to highlight yeast forms, 2-4 μm in diameter, with narrow-based budding, as seen in the top right image.

Cryptococcal lymphadenitis is caused by *Cryptococcus neoformans*, and is often seen in the setting of HIV/AIDS. Granulomatous inflammation is present. Yeast forms, surrounded by clear spaces corresponding to the mucopolysaccharide capsule, may be visible within histiocytes. A GMS or mucicarmine stain can help highlight yeast forms.

Coccidioides lymphadenitis is caused by *Coccidioides immitis* in the southwestern United States. Round spherules 10-100 μm in diameter, containing endospores measuring 2-5 μm in diameter, can be detected on GMS or PAS stains. In the early stages of disease, the inflammatory infiltrate consists predominantly of neutrophils; in later stages, granulomas develop. The H&E image at the bottom right shows an endospore containing small spherules, within a multinucleated giant cell.

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Mycobacterial lymphadenitis can be caused by *Mycobacterium tuberculosis*, or atypical /non-tuberculous mycobacteria.

The lymph nodes are the second most common site of *M. tuberculosis* infection, after the lungs. Involvement of the cervical lymph nodes is common. Histologic sections show necrotizing granulomas; multinucleated giant cells may be present. This case of *M. tuberculosis* lymphadenitis shows necrotizing granulomatous inflammation, with scattered multinucleated giant cells (arrow).

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Atypical mycobacteria can cause lymphadenitis in immunocompetent patients, especially children; however, disseminated disease is usually associated with HIV infection. Necrotizing and non-necrotizing granulomas may be present. Sheets of foamy macrophages containing mycobacterial organisms may be present. An acid-fast stain typically highlights more organisms in atypical mycobacterial infections than in tuberculosis. This figure shows an acid-fast stain highlighting multiple organisms within foamy macrophages in a case of disseminated *M. avium* infection in a patient with HIV.

Slide 8:
Cat scratch disease is caused by *Bartonella henselae*, a small gram negative bacillus. The organism is transmitted to cats by fleas, then transmitted to humans by a cat bite or scratch. Lymphadenopathy develops 1-3 weeks after exposure.

In early stages, affected lymph nodes develop follicular hyperplasia. Small areas of necrosis may be present around subcapsular sinuses. Later, small abscesses develop. These progress to form large stellate granulomas, with a rim of palisading epithelioid histiocytes surrounding areas of necrosis and neutrophilic debris. Organisms may be detected on Warthin-Starry or immunohistochemical stains. Serology and /or PCR studies are often necessary to confirm the diagnosis.

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Lymphogranuloma venereum is caused by the L1, L2, and L3 serovars of *Chlamydia trachomatis*. It often presents with unilateral tender enlargement of the regional lymph nodes near the site of primary infection. In men, the inguinal nodes are commonly affected, while involvement of deep pelvic and perianal nodes is more common in women. Patients may report a history of genital ulcer.

The classic lymph node morphology in LGV is nearly identical to the later stages of cat scratch disease, with stellate, necrotizing granulomas. Intracellular organisms may be visible within histiocytes. Warthin-Starry staining, PCR, and serology may aid in diagnosis.

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Bacillary angiomatosis is characterized by vascular lesions involving the skin and lymph nodes in immunosuppressed patients, and is associated with *Bartonella henselae* or *Bartonella quintana* infection. The lymph node is variably involved by a proliferation of small blood vessels with mild endothelial atypia, which may manifest as a nodular infiltrate (as shown in the top right image) or completely replace the lymph node parenchyma. Extravasated red blood cells and inflammatory cells may be present. Granular eosinophilic to faintly basophilic material may be visible on H&E stain; these contain aggregates of bacteria that may be highlighted with Warthin-Starry or immunohistochemical stains.

The differential diagnosis for a vascular lesion in an immunosuppressed patient includes Kaposi sarcoma. KS is characterized by a greater degree of endothelial atypia and positive staining for HHV-8.

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Syphilitic lymphadenitis is caused by *Treponema pallidum* infection. Lymphadenopathy associated with primary infection is usually confined to regional lymph nodes near the primary site of infection; inguinal adenopathy is most common, followed by cervical adenopathy. Secondary syphilis can present with generalized lymphadenopathy.

Involved lymph nodes show follicular hyperplasia. The paracortex is expanded, with small lymphocytes, plasma cells and immunoblasts. Epithelioid granulomas may be present. The lymph node capsule is thickened, with increased plasma cells; endarteritis may be present. In later stages, the capsular fibrosis may dip into the lymph node cortex, imparting a scalloped appearance. Increased numbers of plasma cells are present in the medulla. Serologic testing is used to confirm the diagnosis.

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Toxoplasma gondii is a parasite that infects cats as its definitive host. Humans are an intermediate host. Many infections are asymptomatic. *Toxoplasma* lymphadenitis typically involves cervical, occipital, or supraclavicular nodes. In contrast to systemic *Toxoplasma* infection, *Toxoplasma* lymphadenitis typically occurs in immunocompetent patients.

Histologically, *Toxoplasma* lymphadenitis is characterized by a triad of follicular hyperplasia, monocytoid B cell hyperplasia, and clusters of epithelioid histiocytes. The histiocytes may form loose granulomas and infiltrate germinal centers. Monocytoid B cells are slightly increased in size, with moderate amounts of clear cytoplasm, and are typically present around lymph node sinuses.

Although classic, this triad is not entirely sensitive or specific for *Toxoplasma* lymphadenitis; similar morphologic features may occasionally be seen in CMV or HIV lymphadenitis.

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The lymph node findings in HIV infection vary with the stage of disease. Patients with acute HIV infection may present with flulike symptoms, arthralgias, and generalized lymphadenopathy. In early HIV lymphadenopathy, follicular hyperplasia is the most common finding; monocytoid B

cells may be present (pattern A). In later stages, lymphocyte depletion may be seen. Follicles are small and regressed, and increased numbers of plasma cells are present between follicles (pattern C). Features intermediate between these patterns can be seen in intermediate stages of the disease.

Other causes of lymphadenopathy in HIV patients include lymphoma, HHV8-positive Castleman disease, and Kaposi sarcoma.

Slide 14:
Epstein-Barr virus causes infectious mononucleosis. EBV lymphadenitis commonly affects cervical lymph nodes. The lymph node architecture is preserved but distorted; follicular and paracortical hyperplasia are present. The paracortex contains a mixed population of small lymphocytes, plasma cells, and immunoblasts. Monocytoid B cells and areas of necrosis may be present.

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On the right is a low power image of a tonsil from a child with EBV infection. Reactive germinal centers are visible at the bottom of the image. There is marked expansion of the paracortex. The high-power image on the bottom left shows an increased number of immunoblasts, including rare multinucleated forms, which may mimic Reed-Sternberg cells. Areas of necrosis are present. In situ hybridization for EBV-encoded small RNA (EBER, top right) highlights EBV-infected cells, which may be numerous.

The presence of architectural distortion and necrosis in EBV lymphadenitis may raise concern for a malignant process. Sheets of immunoblasts may suggest a large cell lymphoma, or Reed-Sternberg-like cells may raise concern for classical Hodgkin lymphoma or T cell lymphoproliferative disorder. Like Reed-Sternberg cells, immunoblasts are positive for CD30; however, immunoblasts are negative for CD15, positive for CD45, and predominantly positive for CD20. Recognition of at least partial architectural preservation, and correlation with clinical and serologic data, can help prevent a misdiagnosis of lymphoma.

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Herpes simplex lymphadenitis can be caused by either HSV-1 or HSV-2 infection. Affected lymph nodes show paracortical expansion, with an increase in immunoblasts. Follicular hyperplasia may also be present. Areas of necrosis are often seen in interfollicular regions, associated with karyorrhectic debris and acute inflammation. HSV-infected cells show viral cytopathic effect, with ground-glass nuclear inclusions, multinucleation, and margination of chromatin. Immunohistochemical staining for HSV1/2 can be used to highlight infected cells.

Patients with chronic lymphocytic leukemia are at risk of developing HSV lymphadenitis. The presence of rapidly enlarging lymph nodes in these patients may raise clinical concern for Richter transformation.

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We have reviewed some of the more common causes of infectious lymphadenopathy. Familiarity with the characteristic features of these infectious processes is important to avoid misdiagnosis of malignancy, and to help guide further diagnostic testing and treatment.

Slide 18: References
The references listed here are excellent sources of additional information.

Slide 19: Disclosures
I have no conflicts of interest to disclose.

Slide 20: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on "**Infectious Lymphadenitis.**"