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TITLE: Lymphadenopathies Associated with Clinical Syndromes
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Slide 1:

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 "**Lymphadenopathies Associated with Clinical Syndromes**."

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.

Slide 2:

Progressive transformation of germinal centers is a benign process that can be seen in the setting of reactive follicular hyperplasia. It typically presents as localized lymphadenopathy, though a more generalized form may also occur. PTGC can occur at any age, though young adult males are more commonly affected. It often involves the cervical lymph nodes. The underlying cause is not well understood.

Slide 3:

In this image, we see progressively transformed germinal centers (outlined by the dashed lines). Note the reactive germinal centers in the background (arrows). In most cases, PTGC is a focal process, involving fewer than 5% of follicles in the involved lymph node. Rarely, more extensive involvement may be seen. Progressively transformed follicles are two or more times larger than the surrounding reactive germinal centers, and have a dark blue appearance on low power due to an influx of small, mantle zone-type B cells into the center of the follicle. The infiltration of

mantle zone type B cells leads to progressive disruption and fragmentation of the germinal center and its underlying follicular dendritic cell meshwork. In this image, residual germinal center elements are still visible as a pale area in the center of the progressively transformed follicle. These will become less apparent as the process progresses.

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There is an association between progressive transformation of germinal centers and nodular lymphocyte predominant Hodgkin lymphoma. The majority of patients with PTGC will not develop NLPHL. However, patients with a history of NLPHL have been reported to have an increased incidence of PTGC in subsequent biopsies, and PTGC can be present in lymph nodes involved by NLPHL. For these reasons, lymph nodes involved by PTGC should be carefully evaluated for evidence of NLPHL.

On low power examination, both PTGC and NLPHL are characterized by large, dark nodules of small lymphocytes.

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The presence of large, neoplastic lymphocyte predominant (LP) or “popcorn cells” within the nodules of small B cells distinguishes nodules of NLPHL from PTGC. LP cells usually have a single, large, often multilobated nucleus. They express B cell markers, including CD20 and CD79a. The B cell transcription factor OCT2 is often strongly expressed. Follicular helper T cells form rosettes around the LP cells, and can be highlighted with immunohistochemical stains for CD57 and PD-1 (CD279).

The top left image shows a large LP cell with a lobulated, “popcorn”-like nucleus. These cells are positive for CD20 (top right) and OCT2 (bottom right) and are surrounded by PD-1 positive T cell rosettes (bottom left).

Of note, the so-called floral variant of follicular lymphoma can also mimic progressive transformation of germinal centers on low-power examination. In this entity, benign mantle zone-type cells may infiltrate the malignant follicles. Absence of background follicular hyperplasia, coexpression of BCL2 with germinal center markers, and the presence of interfollicular CD10-positive cells are all clues to the diagnosis of follicular lymphoma.

Slide 6:

The next entity that we will discuss is Castleman disease. Castleman disease is a form of lymphoid hyperplasia that is further subclassified based on both the extent of disease – localized (unicentric) or widespread (multicentric) – and by its microscopic appearance.

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The majority of cases of unicentric Castleman disease are the hyaline vascular variant. Younger adults are most commonly affected. Hyaline vascular Castleman disease (HVCD) frequently involves lymph nodes of the mediastinum, neck, or abdomen. Surgical excision is generally curative for unicentric disease.

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Lymph nodes involved by HVCD have a nodular appearance from low power. The germinal centers are regressed, or depleted of lymphocytes, and are mostly made up of follicular dendritic cells. Sometimes more than one germinal center is present in a single follicle; this is called “twinning.” The mantle zone cells form concentric rings around the follicles, imparting an “onion-skin” appearance. Hyalinized vessels penetrate a subset of germinal centers at right angles; this is described as a “lollipop” pattern. There is increased vascularity in the interfollicular zone, with prominent high endothelial venules.

Slide 9:

On the left, there is a close-up image of a regressed germinal center, surrounded by concentric rings of mantle zone cells in an “onion skin” pattern. On the right, we see a “lollipop” follicle with a penetrating hyalinized vessel.

Follicular dendritic cells can show dysplastic features in HVCD, and cytogenetic and molecular abnormalities have been described. In rare cases, follicular dendritic cell tumors or follicular dendritic cell sarcomas can occur.

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The plasma cell variant of Castleman disease only makes up a minor subset of cases of unicentric CD; the majority of patients present with multicentric disease. In unicentric plasma cell variant of Castleman disease, lymph nodes show follicular hyperplasia with a prominent interfollicular plasma cell infiltrate.

Patients with multicentric Castleman disease present with systemic symptoms, including fevers, cytopenias, and weight loss. These inflammatory symptoms are related to elevated IL-6 levels. HHV-8 is positive in a subset of cases of multicentric Castleman disease; HHV-8 produces a viral homolog to human IL-6.

HHV-8 negative multicentric Castleman disease is also called idiopathic multicentric Castleman disease. Idiopathic multicentric Castleman disease may occur in the setting of multisystemic clinical syndromes, including POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) and TAFRO syndrome (Thrombocytopenia, Anasarca, Fevers, Reticulin myelofibrosis, Organomegaly).

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HHV-8 is present in essentially all cases of multicentric Castleman disease in HIV-positive patients, and about half of multicentric Castleman disease cases in HIV-negative patients. Patients present with lymphadenopathy and systemic symptoms; hepatosplenomegaly may be present. Involved lymph nodes are enlarged, typically with a mix of reactive and variably regressed germinal centers; focal “onion skinning” and/or penetrating vessels may be present. Scattered medium to large, HHV-8-positive plasmablasts are present at the periphery of mantle zones. The plasmablasts are positive for HHV-8 latency-associated nuclear antigen (LANA)-1, and are lambda light chain-restricted. Numerous mature plasma cells are present in the interfollicular zone.

It is important to be aware that lymph nodes involved by HHV-8-positive multicentric Castleman disease may also be involved by HHV-8 positive malignancies. In rare cases of HHV8+ MCD, the HHV-8+ plasmablasts proliferate to the extent that they efface the lymph node architecture and progress to HHV-8-positive diffuse large B cell lymphoma. Kaposi sarcoma can also occur in lymph nodes involved by HHV-8+ MCD; careful evaluation of the lymph node capsule is important, as the vascular proliferation can sometimes be subtle.

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Panel A shows a low power image of a case of HHV-8+ MCD in an HIV patient. Two partially regressed follicles are present; there is a hint of onion-skinning around the follicles. Panel B is an immunohistochemical stain for CD138, highlighting numerous interfollicular plasma cells. An HHV-8 (LANA) immunostain (panel C) shows a ring of HHV-8 positive plasmablasts surrounding a follicle, at the periphery of the mantle zone. Panel D shows a high-power image of Kaposi sarcoma, characterized by a proliferation of cytologically atypical endothelial cells and extravasated red blood cells. The malignant endothelial cells also express HHV-8 (LANA) by immunohistochemistry.

Slide 13:

The next entity we will discuss is Rosai-Dorfman disease. Rosai-Dorfman disease is also known as sinus histiocytosis with massive lymphadenopathy. It most commonly involves the cervical lymph nodes, but it can occur in many locations, including extranodal sites. Patients may have systemic symptoms, including fevers, night sweats, weight loss, and leukocytosis. Rosai-Dorfman disease is usually self-limited, but occasional patients have progressive disease, which can be fatal if vital organs are involved or compressed.

An association between Rosai-Dorfman disease and autoimmune lymphoproliferative syndrome (ALPS) has been reported. Rosai-Dorfman like changes may be seen in lymph node biopsies from ALPS patients, and *FAS* gene mutations similar to those seen in ALPS patients have been reported in lymph nodes involved by Rosai Dorfman disease, in the absence of other features of ALPS.

Mutations in *KRAS* or *MAP2K1* have been reported in approximately one third of cases of Rosai-Dorfman disease.

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The large image shows a lymph node with expanded sinusoids filled with numerous histiocytes, small lymphocytes, and plasma cells. Note that the contrast between the pale histiocytes and dark lymphocytes imparts a "mottled" appearance on low power.

The histiocytes have round nuclei with small nucleoli. A subset of histiocytes contains small lymphocytes or plasma cells, exhibiting a phenomenon called emperipolesis. Emperipolesis means "wandering in and about," and is characterized by the presence of intact cells within another cell (left inset). The process differs from phagocytosis in that the engulfed cells are not being digested. The histiocytes in Rosai Dorfman disease express S100 (right inset). An S100 stain can help to highlight emperipolesis.

Slide 15:

Kikuchi-Fujimoto lymphadenopathy, also known as Kikuchi disease, Kikuchi-Fujimoto disease (KFD) or necrotizing histiocytic lymphadenitis, is another benign cause of lymphadenopathy. KFD typically presents with tender cervical lymphadenopathy. The incidence is reported to be higher in females of Asian descent, though the disease can occur in males, at any age, and in diverse ethnic backgrounds. In rare cases, widespread lymphadenopathy is present. Patients may present with systemic symptoms, including fever, rash, and myalgia. Leukocytosis with reactive lymphocytes may be present.

Histologically, KFD is characterized by circumscribed areas of necrosis, with abundant karyorrhectic debris, and proliferation of histiocytes. Histiocytes may have crescentic nuclei or contain karyorrhectic debris, and express myeloperoxidase. There is a paucity of neutrophils, which can be helpful in excluding other causes of lymph node necrosis. Immunoblasts may be increased in number, and cause concern for lymphoma. Increased plasmacytoid dendritic cells are present at the edges of the necrotic areas. There is a predominance of CD8+ T cells.

Other causes of extensive lymph node necrosis, including infections, should be excluded when considering a diagnosis of KFD. Herpes lymphadenitis, in particular, may show similarly abrupt areas of necrosis. Systemic lupus erythematosus lymphadenopathy also has features that overlap with KFD, as will be described further in later slides.

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In the early stages of Kikuchi-Fujimoto lymphadenopathy, necrosis may be focal. Four histologic stages have been described: early proliferative or lymphohistiocytic, characterized by a proliferation of histiocytes, plasmacytoid dendritic cells, and immunoblasts; phagocytic, characterized by the presence of histiocytes containing phagocytosed apoptotic cells; necrotic; and xanthomatous or foamy cell, with clusters of foamy histiocytes around zones of necrosis.

The pictured case shows extensive necrosis, with abundant granular karyorrhectic debris. There is an absence of neutrophils. The inset image at the top right shows a histiocyte with a crescentic nucleus. The inset image on the bottom right is an immunohistochemical stain for CD123, highlighting clusters of plasmacytoid dendritic cells around an area of necrosis.

Slide 17:

Another cause of lymphadenopathy is lupus lymphadenitis. Patients with systemic lupus erythematosus may present with lymph node involvement; the cervical, inguinal, and axillary nodes are most commonly affected. Involved lymph nodes may show follicular and paracortical hyperplasia, with areas of necrosis surrounded by histiocytes. The morphologic features of lupus lymphadenopathy overlap with Kikuchi-Fujimoto disease, though in lupus, neutrophils may be present in necrotic areas, and hematoxylin bodies may be present. Hematoxylin bodies are basophilic, granular, DNA-containing aggregates that can be found in the lymph node sinuses or paracortex. Clinical and laboratory evaluation for other signs or serologic evidence of SLE aids in differentiation between lupus lymphadenopathy and KFD. It has been suggested that KFD may represent an early or incomplete form of lupus.

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Hematoxylin bodies are present in the sinus of this lymph node involved by lupus lymphadenopathy. Note the extensive necrosis in the right half of the image.

Slide 19:

Lymphadenopathy can also be seen in patients with sarcoidosis. Sarcoidosis is a systemic granulomatous disease of unclear etiology. Patients may present with constitutional symptoms. Any organ may be affected; pulmonary and skin involvement are common. Affected lymph nodes are extensively involved by granulomatous inflammation that is characteristically non-necrotizing; however, small areas of necrosis may be seen in rare cases. Multinucleated giant cells may be seen. Intracellular inclusions may be present, including Schaumann bodies (calcified inclusions), Hamazaki-Wesenberg bodies (yellow-brown, hemosiderin-containing granules) and asteroid bodies (star-shaped structures). None of these inclusions are specific for sarcoidosis.

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This lymph node shows the characteristic features of sarcoidosis lymphadenopathy. The node is extensively involved by non-necrotizing granulomatous inflammation. A Schaumann body is seen in the inset (arrow).

Infectious causes of granulomatous lymphadenitis, including fungal and mycobacterial infection, must be excluded. It is also important to evaluate the lymph node carefully for evidence of

metastatic tumor or lymphoma, especially given that patients with sarcoidosis have an increased risk of lymphoproliferative disorders.

Slide 21:

Dermatopathic lymphadenopathy may occur in lymph nodes that drain areas of chronic skin irritation. It can be seen in association with a wide array of skin conditions, including eczema, psoriasis, and other forms of dermatitis. Some patients with dermatopathic lymphadenopathy do not have a clinically evident skin condition.

Enlarged lymph nodes in mycosis fungoides patients often show dermatopathic lymphadenopathy. In these patients, careful evaluation for evidence of involvement by lymphoma is necessary. PCR and/or flow cytometry studies may be required to detect subtle involvement.

The lymph node architecture is preserved, but may be distorted, in dermatopathic lymphadenopathy. The paracortex is expanded, with an infiltrate of Langerhans cells, histiocytes, and interdigitating dendritic cells. A variable number of melanin pigment-laden macrophages are present.

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In this case of dermatopathic lymphadenopathy, the lymph node architecture is preserved. There is expansion of the paracortex, with an infiltrate of Langerhans cells, histiocytes, and dendritic cells; on low power, this infiltrate gives the paracortex a pale or mottled appearance (arrow). On high power, scattered pigment-containing histiocytes can be identified (top right); the pigment is mostly melanin.

Immunohistochemical staining for S100 will highlight the interdigitating dendritic cells and Langerhans cells in dermatopathic lymphadenopathy. Langerhans cells are also positive for CD1a and langerin. In this case, a CD1a stain (the bottom right) highlighted scattered Langerhans cells in the paracortex of the node.

Slide 23:

Drug-induced hypersensitivity syndrome is also known as DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome. In affected patients, exposure to a medication induces activation of T cells and macrophages, leading to cytokine release. Implicated drugs include phenytoin, trimethoprim/sulfamethoxazole, dapsone, minocycline, carbamazepine, allopurinol, and others. Patients typically present 2-8 weeks after drug exposure, with fever, rash, and evidence of organ dysfunction, which may manifest as liver dysfunction, renal insufficiency, CNS symptoms, pneumonitis, or neuropathy. Leukocytosis is generally present, with eosinophilia and/or reactive lymphocytosis. An association with infection or reactivation of HHV-6 or other herpesviruses has been described.

Lymphadenopathy is seen in about half of cases of DIHS. The lymphadenopathy can be localized or generalized. Patients presenting with generalized, hypermetabolic lymphadenopathy may raise clinical concern for lymphoma.

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The overall lymph node architecture is typically preserved but distorted in DIHS, with follicular and paracortical hyperplasia. In later stages, germinal centers may be atrophic. Vascular proliferation is typically seen; vasculitis may be present. The lymphoid proliferation may extend beyond the lymph node capsule.

This low-power image shows paracortical expansion and residual intact germinal centers (arrow).

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This is a high power image of the paracortical expansion in DIHS, showing an increase in eosinophils and scattered large immunoblasts. Immunoblasts express CD30 by immunohistochemistry (inset). The high power appearance may raise concern for classic Hodgkin or T cell lymphoma. However, the nodal architecture is preserved, the immunoblasts are negative for CD15 and positive for CD45, and flow cytometric immunophenotyping is negative for abnormal T or B cell populations, further supporting a benign diagnosis.

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We have reviewed some of the more common types of lymphadenopathies associated with clinical syndromes. Familiarity with the characteristic features of these processes can help prevent misdiagnosis of lymphoma. In addition, it allows us to give the clinician a more specific diagnosis beyond “lymphoid hyperplasia,” and helps to guide further diagnostic testing and management.

Slide 27: References

The references listed here are excellent sources of additional information.

Slide 28: Disclosures

I have no conflicts of interest to disclose.

Slide 29: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on "**Lymphadenopathy Associated with Clinical Syndromes.**"