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Review article

Autoimmune and medication-induced lymphadenopathies

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ABSTRACT

This article will provide a discussion of some common autoimmune disorders that could affect the lymph nodes and potentially mimic B and T-cell lymphomas. Some of these disorders are more characteristic of individuals in the pediatric age group (autoimmune lymphoproliferative syndrome, Kawasaki disease), while others present in older individuals (rheumatoid arthritis, lupus erythematosus, sarcoidosis). A common finding that groups all of these disorders together is the overall relative preservation of the architecture, a feature that can be particularly helpful to distinguish them from many B and T-cell lymphomas. Another area of interest, that will be discussed in this review, is the pathologic manifestations that can be present in lymph nodes secondary to medications. Such alterations range from 'reactive' forms of follicular, interfollicular or paracortical hyperplasia, to specific B and T-cell lymphoproliferative disorders (particularly documented in association with methotrexate and TNF-inhibitors).

Autoimmune lymphoproliferative syndrome (ALPS)

This is a disease that arises from a disruption in the immune system secondary to a defective mechanism of FAS-mediated apoptosis[1]. There are many different types of mutations that have been associated with ALPS, and all of them share an autosomal dominant pattern of inheritance. The two most common mutations involve the *FAS (TNFRSF6)*, accounting for 65% of cases of ALPS, and *CASP10*, affecting 25% of patients[2,3].

Clinically, most patients present with symptoms within the 1st year of life: patients with ALPS have chronic or recurrent lymphadenopathy (80% of cases), hepatosplenomegaly (85% of cases), and pneumonia. Approximately 70% of cases have autoimmune manifestations: autoimmune hemolytic anemia, immune thrombocytopenia, neutropenia, etc. Many cases present with the Evans syndrome (autoimmune destruction of red blood cells and platelets). Other immunologic reactions include autoimmune hepatitis, glomerulonephritis, thyroiditis and colitis; vasculitis; uveitis. Patients with ALPS have an increased risk for developing malignancies of different types: the risk of Hodgkin lymphoma (51x) and non-Hodgkin lymphomas (14x) is particularly increased[2–4].

Laboratory findings include a peripheral blood lymphocytosis. By flow cytometry, there is a distinctive increased number of double negative (CD4-CD8-) T-cells (required for the diagnosis > 2.5% of T-cells), increased number of TCR-γδ T-cells, decreased CD4 + CD25 + T_{regs}, and increased CD5 + B-cells (activated B1a cells). Other findings include the presence of autoimmune antibodies, anti-smooth muscle, antiphospholipid antibodies, antinuclear and rheumatoid factor[1,3].

The affected lymph nodes show marked paracortical expansion of T-cells. Lymphocytes at different stages of immunoblastic transformation are present (small, intermediate and large cells). There is often an increased number of immunoblasts and frequent mitotic figures. Scattered plasma cells in the background are present. Some cases can show prominent postcapillary venules. The germinal centers show a spectrum of reactive changes that vary from florid follicular hyperplasia, progressive transformation of germinal centers, and atrophic follicles that can mimic those seen in Castleman disease (Fig. 1). The bone marrow shows a lymphocytosis in 75% of cases. By immunohistochemistry there is a marked increased number of double-negative T-cells (CD45RA + ,CD45RO-,CD3 + ,CD4-,CD8-), increased number of CD57 + , TIA-1 + and perforin + T-cells. No clonal rearrangements of T or B-cell genes are present[1,5].

Differential diagnostic considerations could include the presence of thymic tissue or a thymona, particularly on lesions from the head and neck area. Most thymomas and thymic elements contain epithelial cells which are positive for CK, a feature that could help distinguish from ALPS. T-cell lymphomas can also be included in the differential diagnosis, particularly in view of the negative expression of CD4 and CD8. As opposed to T-cell lymphomas, the architecture of ALPS is preserved. Additionally, T-cell lymphomas will typically show loss of common T-cell antigens (CD2, CD5, CD7). Peripheral T-cell lymphomas in general are also very uncommon in the pediatric setting, with the exception of

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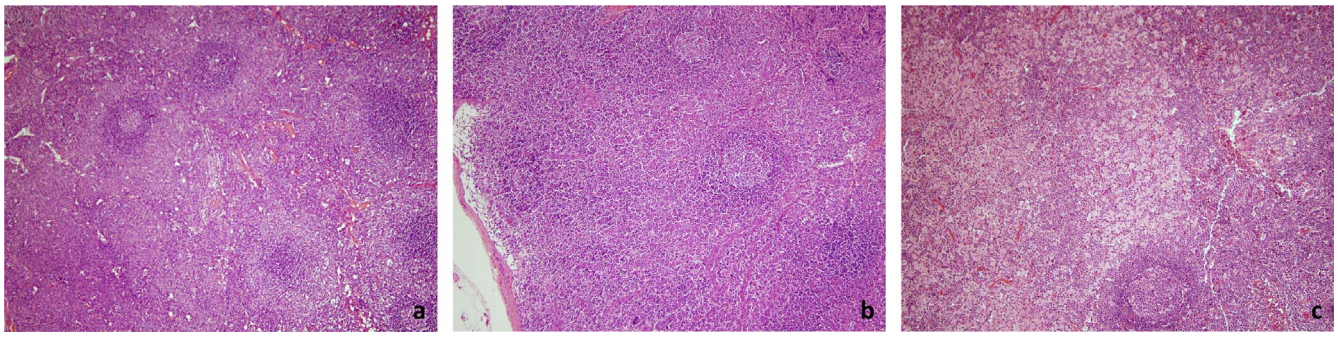

Fig. 1. Autoimmune lymphoproliferative syndrome (ALPS). Paracortical hyperplasia is noted, with a variation in size of germinal centers, some of which appear atrophic (1a and 1b, 40x and 200x)). A paracortical expansion of immunoblasts is shown (1c, 200x).

ALK+ anaplastic large cell lymphoma, a subtype that will not be considered in the differential diagnosis of ALPS. Classic Hodgkin lymphoma (CHL) can also occur in children and the background could be very rich in T-cells. As opposed to ALPS, CHL has the presence of the characteristic Reed-Sternberg cells and variants, CD30+, CD15+, PAX5+ (dim) and CD45-. The reactive immunoblasts of ALPS are CD15-, PAX5-, and CD45+. A viral lymphadenitis can also mimic the paracortical hyperplasia and immunoblastic reaction of ALPS. However, the dual CD4-/CD8- T-cells are not seen in the setting of a viral infection.

Sarcoidosis

This is a multisystemic chronic granulomatous disease. (? Comment on unknown etiology?) Sarcoidosis can present at any age, but its peak occurs at the ages of 20–39. Constitutional symptoms are common (fatigue, malaise, weight loss, night sweats), in addition to those related to organ involvement: lungs (dyspnea, cough); eyes (keratoconjunctivitis, uveitis, retinal vasculitis), skin (rashes, erythema nodosum)[6]; musculoskeletal (arthritis); etc. Peripheral blood cytopenias are relatively uncommon but can sometimes occur. Hypercalcemia and hypercalciuria can be seen, and approximately 75% of patients have elevations of the serum angiotensin-converting enzyme (ACE)[7]. The latter finding is not specific, though. Very frequently, a bronchioalveolar lavage will show a lymphocytic pleocytosis, characterized by a significant increased in CD4: CD8 ratio on flow cytometry. Frequently, sarcoidosis shows bilateral hilar lymphadenopathy on CT scans with associated reticular opacities[8].

The affected lymph nodes show focal, firm nodules (granulomas) or are diffusely replaced (Fig. 2). The cut surface of the noncaseating granulomas is firm and white to yellow, and typically has well-circumscribed borders. Histologically the disease is characterized by the presence of distinctive non-necrotizing non-caseating granulomata. The granulomas are composed of epithelioid histiocytes with scattered Langhans type giant cells and small lymphocytes. While the absence of necrosis is the classic finding, small central foci of fibrinoid necrosis can be present in approximately 10% of cases. Schaumann bodies (round with concentric laminations of calcium), asteroid bodies (star-like structures with calcium), and Hamazaki-Weisenberg inclusions (yellow-brown, ovoid, large lysozomes with hemosiderin) can also be present, but are not specific. Special stains for microorganisms (GMS, AFB, Fite) are negative in sarcoidosis[7,9].

Differential diagnostic considerations include infectious lymphadenitis, particularly from fungal or mycobacterial organisms. The use of fungal (PAS, GMS) and mycobacterial (AFB, FITE) stains can help distinguish those apart. Immunostains for mycobacterial organisms are also currently available. Most infectious granulomatous lymphadenitis shows the presence of suppurative granulomas with necrosis, features not typically seen in sarcoidosis. Chronic granulomatous disease (CGD) can also occur in children and is associated with recurrent bacterial and fungal infections, in the setting of mutations in various genes that encode the subunits of the superoxide-generating phagocyte NADPH oxidase system. Various organs and systems can be affected including the lymph nodes. When LN involvement is present, non-necrotizing and necrotizing granulomas can be present. The diagnosis is made on the basis of the abnormal Nitroblue Tetrazolium (NBT) reduction test.

Systemic lupus erythematosus/Kikuchi Fujimoto disease

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by auto-antibodies production, and has significant systemic symptoms, in addition to frequent involvement of the lymph nodes and spleen. In SLE the auto-antibodies against double-stranded DNA (dsDNA) appear to have a primary pathogenic role. The impaired clearance of the autoantibodies by the macrophages appear to lead to the development of the disease. Clinically, SLE presents with protean manifestations: malar rash, photosensitivity, ulcers in the mucous membranes, arthritis,serositis, etc. Virtually, any organ or system could be affected by SLE. Lymph node involvement is present in 12–78% of patients with SLE (cervical, inguinal and axillary are the most affected sites). The laboratory diagnosis of SLE relies on the demonstration of the auto-antibodies (ANA, anti dsDNA, etc.)[10].

Histopathologically, the affected lymph nodes show follicular hyperplasia, necrosis (sometimes large, geographic areas), and various proliferations of macrophages, immunoblasts, and plasma cells (Fig. 3). In most cases, the areas of necrosis show neutrophils and neutrophilic debris. Interfollicular polyclonal plasmacytosis can be seen, in addition to the presence of plasma cells within the follicles. Such pattern is strikingly similar to the changes seen in Kikuchi-Fujimoto disease (KFD, described below). Indeed, many have postulated that KFD is a 'forme-fruste'(incomplete form) of SLE[11,12]. Hematoxylin bodies (amorphous aggregates of basophilic material, PAS+) in the sinuses, paracortex, or vessel walls is considered diagnostic of SLE (Fig. 4). However, hematoxylin bodies are extraordinary rare in typical diagnostic evaluations. Other histologic patterns in SLE lymphadenopathy have also been reported and those include: Castleman-like changes, follicular hyperplasia with vascular proliferation, and marked interfollicular hyperplasia of polyclonal plasma cells. Follicle-lysis with mantle cells intruding on the germinal centers, and proliferations of follicular dendritic cells (CD21, CD23, CD35, D2-40) can also be seen[13–17]. Such cases can sometimes be confused with angioimmunoblastic T-cell lymphoma or polymorphous post-transplant lymphoproliferative disorders. Similarly to KFD, clusters of plasmacytoid dendritic cells which are positive for CD123 can be seen in the lymph nodes of SLE patients.

Kikuchi-Fujimoto disease (KFD) is a necrotizing lymphadenitis without neutrophilic infiltration (in contrast to SLE lymphadenopathy) that presents in individuals under the age of 30. Women are more frequently affected than men (4:1). Many patients are of Asian descent. The most common affected site is the cervical lymph nodes. Many patients present with fever, upper respiratory symptoms, and very tender