

Clinical Mimics of Lymphoma

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Determine when lymphadenopathy is of concern and merits biopsy.
2. Identify the benign causes of significant lymphadenopathy.
3. Identify the unusual lymphoproliferative disorders that can cause significant lymphadenopathy.

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ABSTRACT

Lymphadenopathy is a common clinical finding and is frequently benign. Warning signs suggestive of a malignant etiology include lymph nodes >2 cm in size, supraclavicular location, and generalized lymphadenopathy associated with hepatosplenomegaly or systemic symptoms. A metastatic solid tumor is always in the differential diagnosis of localized lymphadenopathy, particularly in older individuals. In the case of more generalized lymphadenopathy, in addition to the more common lymphomas, benign etiologies as well as benign and atypical lymphoproliferative disorders need to be considered. Benign etiologies of lymphadenopathy can include infections, autoimmune disorders, drug hypersensitivity reactions,

sarcoidosis, and amyloidosis. Rare but benign lymphoproliferative disorders include Kikuchi's disease, Rosai-Dorfman disease, and progressive transformation of germinal centers. Atypical lymphoproliferative disorders that bear close surveillance for evolution to a more aggressive malignancy include Castleman's disease, lymphomatoid granulomatosis, and lymphomatoid papulosis. Previously considered in this category but now classified as a true lymphoma is angioimmunoblastic lymphadenopathy with dysproteinemia. Physicians need to be aware of all of these disorders when evaluating suspicious lymphadenopathy, while also considering the more common lymphomas and leukemias. *The Oncologist* 2004;9:406-416

INTRODUCTION

Lymphadenopathy is a common clinical finding with a broad differential diagnosis. Isolated enlarged lymph nodes may be found in healthy adults, particularly in the cervical area, and are often without clinical significance [1]. In one

series of 543 patients referred by their primary care doctors for further evaluation of worrisome lymphadenopathy, only 17.5% had an underlying malignant disorder, with 11.4% having a lymphoproliferative disorder and 6.1% having a metastatic solid tumor [2]. Thirty-one percent of those

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patients had benign reactive lymphadenopathy and 26% had miscellaneous non-neoplastic diseases.

How, then, does one distinguish concerning from insignificant lymphadenopathy? Lymph nodes <1 cm in size are rarely malignant [3]. Single or localized lymph nodes may suggest a local infection, although even isolated enlarged supraclavicular, axillary, or epitrochlear lymph nodes have a greater probability of malignancy [3, 4]. Metastatic solid tumors are often associated with localized lymphadenopathy, particularly when the lymph nodes are firm, hard, and fixed to the adjacent tissue. Generalized lymphadenopathy, however, particularly if associated with hepatosplenomegaly, an abnormal complete blood count, or B symptoms, is particularly concerning for lymphoma or a systemic disease that mimics lymphoma. In this article, we review the diseases that can cause generalized lymphadenopathy and, therefore, mimic lymphoma (Table 1). We specifically do not address the common malignant lymphomas and leukemias themselves, although they often present with regional or generalized

lymphadenopathy. Instead, we focus on the clinical mimics of these lymphomas, which can be subdivided as follows: infections, particularly HIV or Epstein-Barr virus (EBV); autoimmune, hypersensitivity, or other benign disorders including sarcoidosis; benign reactive lymphadenopathies, like Kikuchi's disease; and atypical potentially malignant lymphoproliferative disorders, including Castleman's disease and lymphomatoid granulomatosis.

INFECTIONS

The range of infections that can cause significant lymphadenopathy is extensive. Acute bacterial infections, generally streptococcal or staphylococcal, are generally identified in the primary care setting. In the referral setting, in patients with persistent, multifocal lymphadenopathy, the most common infections identified are toxoplasmosis, tuberculosis, EBV, and HIV [2, 5]. EBV infection is associated with a clinical spectrum of lymphoproliferative disease ranging from infectious mononucleosis to polyclonal posttransplant lymphoproliferation to Hodgkin's disease (HD) [6] and non-Hodgkin's lymphomas (NHLs), particularly those that arise in immunodeficient patients including transplant recipients and HIV patients [7-9]. Similarly, although HIV is associated with benign lymphadenopathy, HIV disease is also highly associated with the development of NHLs, HD [10], Castleman's disease (see below), and Kaposi's sarcoma (KS). Therefore, even if EBV or HIV disease is identified, lymph node biopsy is still necessary for significantly enlarged or hard lymph nodes.

AUTOIMMUNE DISORDERS

Almost any autoimmune disorder can be associated with lymphadenopathy, but the most common associations are with rheumatoid arthritis, systemic lupus erythematosus (SLE), and Sjogren's syndrome [11]. Lymphadenopathy may occur in as many as 75% of rheumatoid arthritis patients at some time during the illness. Although the enlarged nodes may be related to inflamed joints, generalized adenopathy can also occur, often when the disease is active [11, 12]. Pathology generally shows reactive lymphoid hyperplasia with interfollicular plasmacytosis [12]. Lymphadenopathy in SLE is also quite common, occurring in 25%-67% of patients [13], and occasionally representing the presenting symptom [14]. Lymph node pathology in this case generally shows a diffuse hyperplasia with scarce follicles [11].

Sjogren's syndrome is characterized clinically by ocular and oral dryness, with lymphocytic infiltration of salivary and lacrimal glands and a polyclonal B cell activation [11]. Development of a lymphoproliferative disorder may be heralded by marked enlargement of the salivary glands or worsening lymphadenopathy [11]. Lymph node biopsies in Sjogren's

Table 1. Causes of lymphadenopathy

Miscellaneous benign causes	Lymphoproliferative disorders
Infections	Benign
Streptococcal, staphylococcal	Kikuchi's disease
Toxoplasmosis	Rosai-Dorfman disease
Cat-scratch disease	Vascular transformation of sinuses
Tuberculosis, atypical mycobacteria	Inflammatory pseudotumor of lymph nodes
EBV (infectious mononucleosis)	Progressive transformation of germinal centers
HIV	
	Atypical
Autoimmune	Polyclonal
Rheumatoid arthritis, SLE	Unicentric Castleman's disease
Sjogren's syndrome	Multicentric Castleman's disease
Drug hypersensitivity	
Anticonvulsants	Clonal
Phenytoin, carbamazepine	Lymphomatoid granulomatosis
Antibiotics	Lymphomatoid papulosis
Sulfas, penicillins, erythromycin	Angioimmunoblastic lymphadenopathy with dysproteinemia
Aspirin	
Allopurinol	
Sarcoidosis	Other malignant causes
Amyloidosis	Non-Hodgkin's lymphomas
Silicone	Hodgkin's lymphoma
Vaccine-induced	Acute and chronic leukemias
Storage diseases	Metastatic solid tumors
Gaucher's disease	

syndrome frequently show reactive adenitis or atypical lymphoid hyperplasia [15], although patients with Sjogren's syndrome do have an estimated 44-fold increase in risk for the development of NHL [16]. These lymphomas are most commonly marginal zone lymphomas [17-19] and most commonly located in the salivary glands. Rapid enlargement of the salivary glands, with or without persistent lymphadenopathy, again mandates a lymph node biopsy.

DRUG HYPERSENSITIVITY

Hypersensitivity reactions to drugs can cause diffuse lymphadenopathy, sometimes but not always in association with fever, rash, or eosinophilia [11, 20]. The classic culprits are anticonvulsants, particularly phenytoin, for which the syndrome was first described in 1959 [20], and carbamazepine. Other implicated drugs include sulfas, penicillins, allopurinol, aspirin, and erythromycin [11]. These reactions tend to occur within several months of initiation of the drug and tend to abate within a couple of weeks after discontinuation of the drug [11]. Biopsy most often shows features similar to viral-induced lymphadenopathy, with partial or complete effacement of nodal architecture by a polymorphous infiltrate of immunoblasts, small lymphocytes, eosinophils, and plasma

cells [21]. However, a wide range of pathologic abnormalities may be seen, from reactive hyperplasias to malignant lymphomas [11, 21, 22]. The pathogenesis of these lesions remains speculative but is thought to be related to drug-induced immunologic disturbances, including reduced cellular and humoral immunity [11].

MISCELLANEOUS BENIGN DISORDERS

A variety of other benign conditions is associated with lymphadenopathy. Sarcoidosis requires particular mention since it can quite easily mimic lymphoma with diffuse lymphadenopathy (Fig. 1). Generally this distinction requires a lymph node biopsy, which is definitive. Amyloidosis can also cause lymphadenopathy (Fig. 2), although generally not without other characteristic complications that include nephrotic syndrome, congestive heart failure, and neuropathy and help identify the disease. Silicone used in prosthetic joints and breast implants is associated with the development of regional lymphadenopathy up to 15% of the time [23]. A lymph node biopsy shows reactive lymphoid hyperplasia with multinucleated giant cells containing silicone particles or cystic spaces and vacuoles related to silicone liquid [24]. Finally, certain vaccines, particularly smallpox vaccine, may be associated

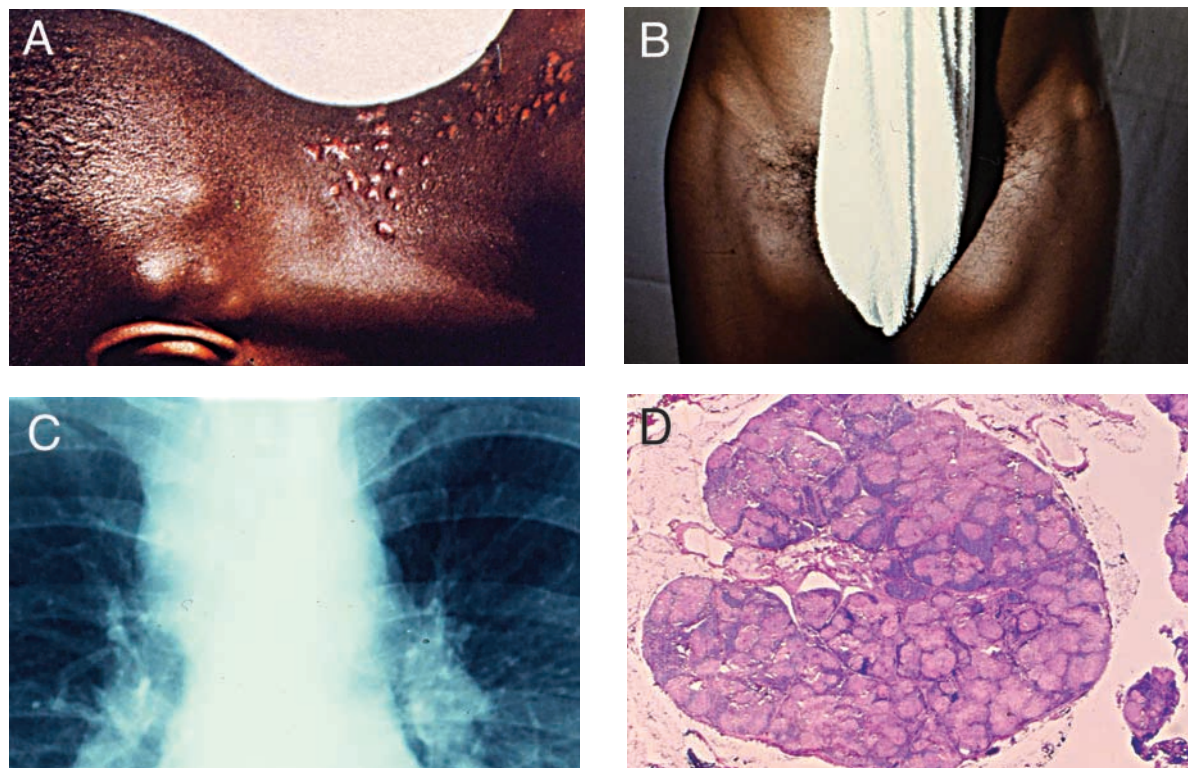


Figure 1. Sarcoidosis. A) Posterior auricular and suboccipital asymptomatic lymphadenopathy in an 18-year-old African-American male. Note the characteristic plaque-like skin lesions with flat, waxy tops. B) Same patient as in A, showing greatly enlarged inguinal and femoral nodes, originally thought to be hernias. C) X-ray from another patient, age 40, with asymptomatic bilateral hilar and mediastinal adenopathy. D) Low-power view of lymph node biopsy, showing characteristic numerous granulomas.

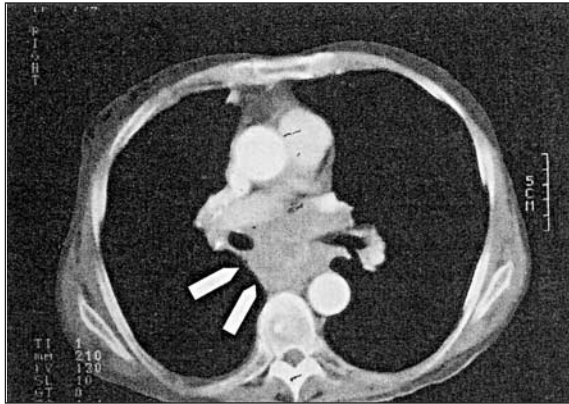


Figure 2. Amyloidosis. Magnetic resonance imaging scan of a 69-year-old man with newly diagnosed non-small cell lung cancer (NSCLC) who was found to have bulky mediastinal lymphadenopathy (subcarinal, arrows) on staging evaluation, suggesting regional metastases. Mediastinoscopy showed amorphous material exhibiting green birefringence of congo-red-stained tissue, diagnostic of amyloidosis. Reprinted with permission from Partridge et al. [108].

with lymphadenopathy, which histologically resembles a viral EBV-induced lymphadenopathy and can easily be confused with lymphoma. This “postvaccinial lymphadenitis” generally occurs 1-2 weeks following the vaccine and then resolves spontaneously [11].

BENIGN REACTIVE LYMPHOPROLIFERATIVE DISORDERS

This group of diseases comprises several rare reactive conditions with little or no potential for malignant transformation and includes Kikuchi’s disease, Rosai-Dorfman disease, vascular transformation of sinuses, inflammatory pseudotumor of lymph nodes, and progressive transformation of germinal centers.

KIKUCHI’S DISEASE

Kikuchi-Fujimoto disease, or histiocytic necrotizing lymphadenitis, is a self-limited disease first described in Japan in 1972 [25, 26]. Clinically, it is characterized most commonly by posterior cervical lymphadenopathy, fever, and leukopenia, which most commonly resolve spontaneously within about 3 months [27, 28]. The disease generally affects patients under the age of 40, with a variable female predominance reported to be 1.25-4 times that of males [27-30]. Although the lymphadenopathy is most commonly cervical and generally <2-4 cm in size, occasionally it can be generalized or result in larger lymph nodes [30]. Histologically, the lymph nodes contain foci of necrosis with nuclear debris (karyorrhexis) and a proliferation of histiocytes with eccentrically located, elongated nuclei (crescentic in appearance). Many immunoblasts can

sometimes be seen, of T cell lineage, but leading to the not uncommon confusion with lymphoma [29, 30]. Treatment is generally conservative, with resolution of symptoms most commonly starting a few weeks after onset. Steroids may be used for severe symptoms [29]. The etiology of Kikuchi’s disease remains unclear, with most speculation focused on an inciting viral infection or a possible autoimmune etiology related to SLE. No association has been found between Kikuchi’s disease and human herpesvirus (HHV)-8, HHV-6, parainfluenza, or EBV, however [27, 31-33]. An association with SLE has been reported in at least a handful of cases, but remains speculative [27, 28, 34].

ROSAI-DORFMAN DISEASE

Rosai-Dorfman disease, or sinus histiocytosis with massive lymphadenopathy, was first described as a clinical entity in 1969 [35]. Patients are generally healthy young adults who present with massive, matted cervical lymphadenopathy, sometimes associated with fever, polyclonal hypergammaglobulinemia, and an elevated sedimentation rate [29, 35, 36]. As many as 40% of cases are extranodal, with 75% of those occurring in the head and neck region [36, 37]. Pathology is characterized by distention of the lymph node capsule and histiocytic proliferation throughout the sinuses [29, 36, 37]. The histiocytes stain for S100, CD68, and other macrophage markers, but not for CD1a, and often show evidence of phagocytosis of lymphocytes or plasma cells [29, 36, 37]. The etiology of this disorder remains unclear; speculation has centered on a histiocytic reaction induced by cytokines or an as-yet-undefined infection [29]. HHV-6 and EBV have been associated with several cases, but a clear link remains to be confirmed [38]. The disease is generally self-limited, with about 50% of patients having spontaneous resolution [29, 37, 39]. In most other cases, the disease remains stable without regression or progression. Rare deaths do occur, due to visceral involvement or immune dysregulation, at a reported rate up to 7% [40]. Bulky or symptomatic lesions can be resected [39]. Little use has been found for radiotherapy or systemic chemotherapy, although steroids and single-agent chemotherapy have been used when necessary [29, 37, 39].

VASCULAR TRANSFORMATION OF SINUSES

Vascular transformation of sinuses is an uncommon reactive process characterized by transformation of lymph node sinuses into complex endothelial-lined channels [41, 42]. It is often found incidentally in surgical specimens of lymph nodes, but can also present as lymphadenopathy [29]. Most cases are thought to result from venous or lymphatic obstruction [41, 43]. Pathologically, the lymph node shows proliferated vessels within expanded, often sclerosed, sinuses, and the lymph node parenchyma may show atrophy;

the differential diagnosis can include Kaposi's sarcoma. Treatment is not indicated, but when vascular transformation is found, a search for occult cancer causing lymph node obstruction is warranted [29].

INFLAMMATORY PSEUDOTUMOR OF LYMPH NODES

Inflammatory pseudotumor of lymph nodes occurs mainly in young adults who present with enlarged lymph nodes in single or multiple sites, often associated with systemic complaints [44, 45]. The nodes may be quite large (>3 cm) and involve central as well as peripheral sites. Lymph node biopsy reveals activated histiocytes, inflammatory cells, and fibroblasts, with associated blood vessels, in a sclerotic stroma, mostly within the connective tissue framework of the lymph node [29]. The nodal parenchyma is often spared. Inflammatory pseudotumor of lymph nodes probably represents the end result of a response to infection, with reported association with toxoplasmosis [29, 44, 45]. Spontaneous regression occurs in almost all cases.

PROGRESSIVE TRANSFORMATION OF GERMINAL CENTERS

Progressive transformation of germinal centers (PTGC) was first described in 1975 [46] and is generally identified as unexplained, asymptomatic lymphadenopathy in young adults. Pathologically it is associated with follicular hyperplasia and characterized by the loss of a defined border between the germinal center and the lymphocytes of the mantle zone, which expand and replace the germinal center [47]. Overall lymph node architecture is preserved, however, in contrast to Hodgkin's disease [47]. The chief importance of the diagnosis of PTGC is that it may be associated with nodular lymphocyte-predominant Hodgkin's disease (NLPHD). Retrospective studies initially suggested that 1% of cases of NLPHD may be preceded by PTGC, and another 1.5% of cases may be simultaneously or subsequently diagnosed with NLPHD [47, 48]. Small prospective studies have shown that the diagnoses of PTGC and HD often coincide, but that only about 2.5% of patients with PTGC go on to develop HD [47]. The etiology of PTGC remains obscure, but may be related to immune dysregulation [49]. No therapy is required. Lymph nodes may remain stable for many years or regress spontaneously.

ATYPICAL LYMPHOPROLIFERATIVE DISORDERS

Unlike the last category of benign lymphoproliferative disorders, atypical lymphoproliferative disorders have significant potential for or have already acquired a malignant phenotype. Representative of this category is Castleman's disease, which likely is several different diseases, but presently is best subclassified as unicentric or

multicentric and by the presence or absence of HHV-8. Angioimmunoblastic lymphadenopathy with dysproteinemia (AILD) likely represents an evolving malignant T-cell clone, but because of its malignant clinical course is now classified as a true lymphoma. Finally, lymphomatoid granulomatosis and lymphomatoid papulosis represent atypical, frequently clonal lymphoproliferative disorders with high propensities to convert to malignant lymphoma.

UNICENTRIC CASTLEMAN'S DISEASE

Castleman's disease was first described in 1956 by *Benjamin Castleman* [50], who identified a series of solitary hyperplastic mediastinal lymph nodes with small atrophic germinal centers resembling Hassall's corpuscles of the thymus. Subsequent work identified two subtypes of the same disease, with Castleman's subtype being the hyaline vascular variant and the new subtype having more extensive plasmacytosis in the interfollicular regions and therefore being called the plasma cell variant [51]. All of these initially described patients had unicentric disease. Patients with unicentric Castleman's disease are often asymptomatic, with their disease found incidentally on imaging, and approximately 90% of cases are of the hyaline vascular variant. About 10%-20% of patients with unicentric disease present with the plasma cell variant, and their characteristics are similar to those of patients with the hyaline vascular type except that 50% have systemic symptoms. Overall, in unicentric disease, the lesion is located in the mediastinum or hilum 70% of the time, with the abdomen as the next most frequent site of lesions. Peripheral lymphadenopathy and laboratory abnormalities are uncommon, and complete resection is curative, with no reported recurrences in any series. For those patients whose lesions cannot be completely resected, outcomes remain favorable since the partially resected masses often remain stable and asymptomatic for many years [51-53].

MULTICENTRIC CASTLEMAN'S DISEASE

Multicentric Castleman's disease (MCD) was first described as an entity in 1978 [54]. MCD is a systemic disease with significant peripheral lymphadenopathy and hepatosplenomegaly, as well as frequent fevers, night sweats, fatigue, and weight loss [55]. Pathologically, it is generally of the plasma cell variant. The disease is more common in patients with HIV and Kaposi's sarcoma, a fact that led to the discovery of the association of MCD with HHV-8. HHV-8 is a human herpesvirus that was identified first as the causative agent of Kaposi's sarcoma, and since then as the causative agent of primary effusion lymphomas [56, 57]. Multiple studies have confirmed that HHV-8 is universally found in

HIV-associated MCD and present in approximately 40%-50% of cases of HIV-negative MCD [57, 58]. Thus far, only one case of unicentric Castleman's disease has been reported to be associated with HHV-8 [59-61], suggesting that, in fact, unicentric Castleman's disease may be a different disease from MCD.

Several different patterns of disease progression have been described in MCD [62, 63]. A rapidly progressive form can lead to death within weeks and may be more common in HIV-positive patients [64, 65]. A chronic persistent form of MCD is often of ill-defined, indolent onset and can persist for months to a few years without worsening. An episodic relapsing form may be aggressive for a short period and then remit spontaneously or in response to treatment, only to recur at a later time. Regardless of the pattern, however, median survival in the pre-HIV era was only 26-30 months [62, 63]. HIV-infected patients with MCD fare even more poorly, with an overall mortality rate of 70%-85% and a median survival time of only 8-14 months [65, 66].

Most patients die of fulminant infection or the development of other malignancies, particularly KS and NHL. KS was noted at some point in the clinical course of 13% of Castleman's cases historically [55]. In recently described HIV-positive patients with MCD, who are universally infected with HHV-8, fully 70% have also had KS [63-66]. NHL is also significantly associated with MCD, with approximately 15%-20% of MCD patients presenting with or developing intermediate- to high-grade NHL, most commonly the immunoblastic type [62, 63, 67-69]. A prospective cohort study of 60 HIV-positive patients with MCD found that 14 developed HHV-8⁺ NHL 0-76 months after MCD diagnosis, for an actuarial 2-year incidence of 24.3%, which is 15-fold greater than expected for HIV patients in general [70].

Treatment for MCD remains suboptimal. Steroids, single chemotherapy agents such as etoposide and vinblastine, and anti-human interleukin-6 antibody can temporarily mitigate symptoms but generally do not result in prolonged remissions [62, 66, 67, 71]. Recent interest has focused on rituximab, which has been able to induce 3-12 month remissions in four of six patients reported [72, 73], but whose safety and ultimate efficacy remain to be determined. Two patients treated with rituximab developed worsening of Kaposi's sarcoma [72], but the relationship of this worsening to rituximab is unclear.

ANGIOIMMUNOBLASTIC LYMPHADENOPATHY WITH DYSPROTEINEMIA

AILD is a lymphoproliferative disorder first described in 1974 [74-76]. Although affected patients present with signs and symptoms of malignant lymphoma, histologic features suggest a benign process [74, 76]. The clinical

course is malignant, however, and clonal T-cell populations can be identified, so the disorder is now properly classified as a T-cell lymphoma.

Patients are generally in their sixth or seventh decade of life and present with a several-week history of fever, night sweats, weight loss, pruritus, generalized lymphadenopathy, and often hepatosplenomegaly and skin rash [74, 76-78]. Coombs' positive hemolytic anemia and polyclonal hypergammaglobulinemia are common [74, 76-78]. Histologically, the lymph nodes are characterized by effacement of the nodal architecture by a pleomorphic cellular infiltrate that includes small and medium-sized lymphocytes, immunoblasts, plasma cells, histiocytes, and eosinophils [77, 79, 80]. Prominent vascular proliferation is seen throughout, with atrophic germinal centers. Immunoblasts are scattered throughout the cellular infiltrate; if sheets or clusters of immunoblasts are seen, the histologic appearance is consistent with frank malignant lymphoma, but this feature does not predict outcome and the disease is classified as a lymphoma regardless of the presence or absence of this feature [74, 80].

Determining the clonality of this lesion was initially challenging. Cytogenetic analysis identified a high incidence of trisomy 3, trisomy 5, and +X in patients with AILD, and in 47% of those cases, more than one clone was detected, suggesting that the disorder can, at least initially, be oligoclonal or polyclonal [81]. T-cell receptor (TCR) gene rearrangements can be identified in approximately 70% of cases, with occasional cases also showing immunoglobulin heavy chain gene rearrangement [80, 82-84]. Multiple TCR clones can appear and disappear with time in a single lesion [80, 82]. If histologic features of lymphoma emerge, often one dominant clone is seen, and that clone has the phenotype of a helper CD4⁺ T cell [83]. These findings suggest that AILD may begin as an abnormal immune response, with an impaired ability to regulate expansion of oligoclonal T-cell clones that then evolve into dominant monoclonal T-cell clones [80, 81].

The clinical course of AILD is aggressive, consistent with its classification as a lymphoma. Mortality rates range from 40%-73%, with median survival times of 13-48 months [74, 76, 85-87]. Up to half the patients die of infectious complications, including opportunistic infections [74, 76, 77, 80, 85-87]. Over the course of the disease, approximately 20% of patients develop histologic evidence of an aggressive lymphoma of B- or T-cell origin [77, 86]. The curability of the disorder is uncertain; 22%-29% of patients have been reported to be in persistent first complete remission at 4-5 year follow-up [86, 87].

Treatment recommendations are based on small series, and most of the options have 30%-60% response rates [77,

86]. Combination chemotherapy achieves a higher remission rate than steroids alone, but remissions are often short lived [85, 87]. Alpha-interferon, cyclosporin A, and the purine analogues fludarabine and cladribine have been reported to induce remission in a small number of patients [77, 88-90]. High-dose chemotherapy with autologous stem cell support has been reported to induce sustained remission in several patients [87, 91], but remains investigational. New approaches are clearly required to improve the outcome of this disorder.

LYMPHOMATOID GRANULOMATOSIS

Lymphomatoid granulomatosis (LG) was originally described as a form of pulmonary angiitis similar to Wegener's granulomatosis [92, 93]. The lesion demonstrates an angiocentric, angiodestructive polymorphous inflammatory infiltrate, with scattered large, atypical lymphoid cells. Although LG was originally believed to be of T-cell origin due to the abundance of T lymphocytes in the infiltrate, no evidence of clonal TCR gene rearrangements could be found [92, 94, 95]. The large atypical cells in the infiltrate were then noted to be EBV-infected B cells, at least some of which harbored clonal immunoglobulin gene rearrangements, thus identifying LG as an EBV-related B-cell lymphoproliferative disorder [92, 94-97].

Patients are generally in their fourth to sixth decade of life with a 2-3:1 male predominance [92, 98-100]. They most commonly present with cough, shortness of breath, or chest pain due to lung involvement, but also often have systemic symptoms including fevers, fatigue, and weight loss [92, 98-100]. Radiographically, pulmonary lesions generally appear as bilateral nodules favoring the lower lung fields. Skin lesions occur in 20%-50% of patients and may present as an erythematous rash, subcutaneous nodules, or indurated plaques [101]. Central nervous system (CNS) involvement occurs in up to one-third of patients and is a poor prognostic factor [100]; lumbar puncture is often nondiagnostic, but CNS imaging may show nodular lesion(s). Early in the disease course lymphoid tissues are often spared, but become involved with disease progression [92].

The clinical course of this disease is extremely variable, ranging from occasional spontaneous resolution to rapid fatality [92, 98-100]. The largest series, of 152 patients, reported a 67% mortality rate and a median survival time of 14 months [100], with patients dying of pulmonary complications, infection, CNS disease, or lymphoma. In an effort to better predict the disease course, histologic grading of the lesion based on the number of EBV-positive large atypical B cells is often used [92, 96, 97]. Grade I lesions have very rare EBV-positive

cells, grade II lesions contain scattered EBV-positive cells, and grade III lesions have sheets of large atypical EBV-positive cells and are histologically diagnostic of frank malignant lymphoma [92, 96, 97]. Many patients with rapid progression have this histologic evidence of large cell lymphoma on repeat biopsy or at autopsy [92, 98-100]. The grading likely reflects a progression of malignant transformation analogous to that seen in post-transplant EBV lymphoproliferative disorders.

The benefit of treatment has been difficult to establish in the early phases of the disease. The two largest older series failed to show a difference in outcome among patients treated with chemotherapy, steroids, or observation [98, 100]. The only prospective study did suggest that treatment with cyclophosphamide and steroids could induce prolonged complete remissions [99]. For asymptomatic patients with minimal disease burden and grade I or II disease, observation may be reasonable. For patients with more aggressive grade I or II disease, or with grade III disease, treatment for lymphoma with chemotherapy such as CHOP is appropriate [92].

LYMPHOMATOID PAPULOSIS

Lymphomatoid papulosis (LP) is a cutaneous T-cell lymphoproliferative disorder that is clinically indolent but histologically malignant [102, 103]. Patients present with multiple skin papules or nodules, generally <3 cm in size, which may wax and wane for years [102, 103]. Histologically, the lesion is characterized by a population of activated malignant-appearing CD4⁺ CD30⁺ helper T cells, which resemble Reed-Sternberg cells, in a background of small lymphocytes [104]. These CD30⁺ cells have now been clearly shown to share the same TCR gene rearrangement, which is not shared with the CD30⁻ cells [105, 106]. This finding establishes LP as a clonal T-cell lymphoproliferative disorder. Despite its indolent course, 20%-80% of LP patients eventually develop frank lymphoma, generally HD, cutaneous T-cell lymphoma, or anaplastic large cell lymphoma [102, 103, 106]. These lymphomas carry the same TCR gene rearrangement as the LP, which suggests clonal evolution and explains the high incidence of lymphomas in this disorder [102, 105, 107]. Treatment of the LP does not appear to alter the natural history of the disorder and therefore is generally reserved for symptoms [103].

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