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Diffuse Lymphadenopathy as the Presenting Manifestation of SLE

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Abstract

We report the case of a 27 year old African-American man who presented with 6 months of generalized lymphadenopathy and nothing in his history or examination to suggest systemic lupus erythematosus. He was thought to have lymphoma, syphilis or tuberculosis and an extensive work up was done. Laboratory investigation finally revealed leukopenia (4.0), proteinuria (1.87grams), ANA (640 speckled), anti-dsDNA (640) , anticardiolipin IgG and IgM, anti-Smith, Coombs, anti-Ro, anti-La, CK (531U/L), aldolase (8.5 U/L), high erythrocyte sedimentation rate (130) and low complement (C3 15mg/dl and C4 3mg/dl). A kidney biopsy showed diffuse proliferative glomerulonephritis, ISN class IV. Generalized lymphadenopathy as the first and only manifestation for 6 months made the diagnosis of SLE challenging. Generalized diffuse lymphadenopathy has been associated with SLE, but is much less frequent now than in the past. The differential diagnosis of lymphadenopathy relevant to rheumatologists, includes Kikuchi histiocytic necrotizing lymphadenitis, Castleman disease, syphilis, tuberculosis, sarcoidosis and lymphoma.

Keywords

Systemic Lupus Erythematosus; Lymphadenopathy

CASE DESCRIPTION

A 27-year-old African-American male presented to the emergency room with a six month history of generalized lymphadenopathy (preauricular, supraclavicular, occipital and inguinal lymph nodes). He also had malaise, weight loss and left sided severe and recurrent

Disclosures: None

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abdominal pain. He had been treated twice for syphilis with penicillin because of positive serologies. CT of the chest, abdomen and pelvis confirmed supraclavicular nodes (1.6 to 2.1 cm), subcarinal (2.1 cm), periaortic (1.3 cm) and inguinal nodes (1.5 cm). There was splenomegaly with a wedge-shaped hypodense area. The suspected diagnosis was lymphoma. An occipital node biopsy showed reactive lymphoid hyperplasia, and an atypical lymphoid infiltrate. The cells were phenotypically large but did not have the typical morphology of Reed-Sternberg cells. They were not bi-nucleated and did not stain for CD15 or CD30. Therefore, there was no definite evidence of Hodgkin lymphoma. Smaller cells of B-cell lineage stained positive for CD 45. They were immunoblasts. Other immunoblasts stained for CD30 which was still highly suspicious for malignancy. LE cells were not seen. It was recommended that another node be biopsied to rule out malignancy.

He was readmitted to the hospital one week later, with profound weakness, malaise, left sided abdominal pain, pleuritic chest pain and night sweats. The differential diagnosis considered included Kikuchi histiocytic necrotizing lymphadenitis, Castleman (angiofollicular lymph node hyperplasia) and, because of the persistence of the lymphadenopathy, malignancy remained high on the differential. Viral infections, human immunodeficiency virus, syphilis (given the history of a positive rapid plasma reagin (1:4) with positive fluorescent treponemal antibody), tuberculosis and sarcoidosis were also considered. Tests for cytomegalovirus, HHV-6 human herpes virus-6, adenovirus, herpes simplex virus, and streptococcus and toxoplasma gondii were negative. Sputum microscopy and culture for acid-fast bacilli were negative.

A large inguinal lymph node was biopsied and revealed benign follicular hyperplasia with no evidence of Kikuchi, Castleman or sarcoidosis. No Reed-Sternberg cells were identified. Stains showed an appropriate pattern of B- and T-cells (CD20 and CD3). No atypical CD30-positive cells (found in Hodgkin and large cell non-Hodgkin lymphoma) were seen. There were increased follicular dendritic cells consistent with a reactive pattern. CD1a (expressed by Langerhans cells), was negative. In situ hybridization for Epstein-Barr virus encoded RNA was negative. The lymph node stain for acid fast bacilli was negative. The Gomori-Grocott methenamine silver stains were also negative for fungi. Flow cytometry studies showed no evidence of lymphoma. There were no hematoxylin bodies suggestive of SLE. A bone marrow biopsy and aspirate were normocellular. The suspicion by the team was still extremely high for malignancy. Therefore, a positron emission tomography scan was ordered. Compared with CT, positron emission tomography scans detect more lymphoma lesions, and particularly extra-nodal lesions in the liver, spleen and bone marrow [1]. His positron emission tomography (PET) scan found hypermetabolic adenopathy, which is a non-specific finding. Hypermetabolic adenopathy can be seen in infections, inflammatory conditions or malignancy.

CT scan of the chest revealed bilateral pleural effusions. Pleural fluid analysis revealed prominent lymphocytosis and reactive mesothelial cells and histiocytes. The pattern of lymphocytosis was concerning for tuberculosis or a viral illness. The pleural fluid was negative for acid fast bacilli. A transthoracic right upper lobe ultrasound guided core fine needle aspiration was negative for acid fast bacilli by fluorochrome stain.

A week after admission, 6 months into the illness, a rheumatology consultation was requested. He was found to have an erythematous macular rash on his cheeks, forehead and biceps. On his scalp there was non-scarring, moderate patchy alopecia. Dry scaling skin was noted on the second digits bilaterally on the lateral palmar aspect of the hand. There was synovitis involving the metacarpophalangeal joints, wrists and a large knee effusion. His muscle strength was 3/5 in the upper and lower extremities. Laboratory tests included leukopenia (4.0). There were 9% bands, 66% PMN, 7% lymphocytes, 7% monocytes, 9% atypical lymphocytes and 2% eosinophils. The absolute neutrophil count was 3510 and the absolute lymphocyte count was 748. He had proteinuria (1.87grams). The serum creatinine 0.6mg/dl, ANA (1:640 speckled), anti-dsDNA (1:640), anticardiolipin IgG (21 GPL units), anti-Smith, positive Coombs, anti-Ro, anti-La, CK (531 U/L), normal aldolase (8.5 U/L), high erythrocyte sedimentation rate (130), low complement (C3 15 mg/dl and C4 3mg/dl) and a low 25(OH)vitamin D level (less than 5). Skin biopsy revealed a superficial and deep perivascular lymphoplasmacytic infiltrate, as well as a dyskeratotic keratinocyte background with vacuolar changes at the dermal-epidermal junction. These findings were consistent with a connective tissue disease such as dermatomyositis or systemic lupus erythematosus. MRI with T2 STIR imaging of the lower extremity showed evidence of diffuse lower extremity edema. An electromyogram and nerve conduction study revealed a severe irritable myopathy. A muscle biopsy was suggested to evaluate for a myositis overlap, as severe myositis is rare in SLE [2]. Muscle biopsy found perivascular inflammation, perifascicular atrophy, and varying size of the muscle fibers.

When he was admitted to our institution he had pre-renal azotemia, BUN 39 and creatinine 1.0 mg/dl, which improved with hydration to 17 mg/dl and 0.7 mg/dl, respectively. Urinalyses revealed moderate blood and protein. The 24-hour urine protein was 1.87g. His urine protein/creatinine ratio was 4.7 grams. Kidney biopsy revealed ISN class IV (diffuse proliferative glomerulonephritis). The activity score was 3/24. There were diffuse wire loops and hyaline thrombi. There was minimal endocapillary hypercellularity. The chronicity score was 0/12. There was no tubular atrophy, interstitial fibrosis, fibrous crescents or global glomerular sclerosis.

He was finally diagnosed with SLE seven months after the onset of lymphadenopathy. Intravenous “pulse” methylprednisolone (1000mg for 5 days) was started. He was transitioned to 1mg/kg methylprednisolone after 5 days. His muscle strength, rash and arthralgias improved. The lymphadenopathy also improved with high dose corticosteroid treatment. On discharge, he was prescribed prednisone 80mg daily, hydroxychloroquine 400 mg daily, mycophenolate mofetil 1 gram by mouth two times a day, and Vitamin D 50,000 units weekly. His follow up spot urine protein/creatinine ratio three weeks later had improved to 1.32 grams. The anti-dsDNA remained positive. Both C3 and C4 remained low for 3 months after the initial admission. The creatinine kinase returned to within normal limits 6 weeks after discharge. The lymphadenopathy resolved completely once he was treated with hydroxychloroquine and mycophenolate mofetil.

Discussion

The differential for generalized diffuse lymphadenopathy is complex and was particularly challenging diagnostically in our patient. The differential diagnosis included Kikuchi histiocytic necrotizing lymphadenitis, Castleman disease, malignancy (lymphoma in particular), syphilis, tuberculosis, and rheumatic (sarcoidosis, SLE).

Kikuchi histiocytic necrotizing lymphadenitis was first described in Japan in 1972. It is a non-malignant and self-limited lymphadenopathy that is most common in young Asian females. Patients can present with fever, chills, upper respiratory tract symptoms, and leukopenia. Lymphadenopathy is the classic feature, with cervical adenopathy being the most common. Generalized lymphadenopathy has been reported in 1% to 22% of cases [3]. .

Histopathologically, there are areas of coagulative necrosis in the paracortex. There are typically no neutrophils in Kikuchi histiocytic necrotizing lymphadenitis, as opposed to SLE. Immunohistochemical stains are positive for CD68. Kikuchi histiocytic necrotizing lymphadenitis has an excellent prognosis, but relapse is common. Kikuchi histiocytic necrotizing lymphadenitis has been reported to coincide with, precede, or follow the diagnosis of SLE [4,5]. The pathogenesis and etiology of Kikuchi histiocytic necrotizing lymphadenitis is not known. It is thought to be an immune mediated response due to infection [6]. Immunohistochemical stain for CD 68 was not done on our patient. Viruses, including human herpes virus-6, Epstein–Barr virus, cytomegalovirus, and human immunodeficiency virus have been considered as potential causes.

Castleman Disease, also called angiofollicular lymph node hyperplasia, is a rare lymphoproliferative neoplasm characterized by large non-malignant tumors in lymphoid tissues. It can begin as a soft tissue mass within the neck or mediastinum. Unicentric Castleman disease is a localized process. Multicentric Castleman disease is systemic. It can present with peripheral lymphadenopathy, hepatosplenomegaly, fevers, night sweats and a low CD4. Fifty percent of cases may be caused by human herpes virus-8 [7]. Human herpes virus-8 levels may be a potential biomarker for a clinical diagnosis of HIV-associated Castleman disease [8]. Human herpes virus-8 levels were ordered but never done in our patient. A lymph node biopsy in Castleman shows a reactive lymph node with prominent follicles, sheets of plasma cells in the inter-follicular regions, vascular proliferation with endothelial hyperplasia, and human herpes virus-8 DNA.

Infectious causes were particularly of concern in our patient, who had positive syphilis serology. Secondary syphilis is apparent four to ten weeks after a chancre. Approximately 25 percent of individuals with untreated syphilis will develop a systemic illness that presents with lymphadenopathy [9] involving the cervical, axillary, inguinal, and femoral nodes. The diagnosis is based on dark field examination of motile *Treponema pallidum*, positive direct fluorescent antibody staining for *Treponema pallidum* in the fluid from a lesion or modified silver staining showing spirochetes. Hyperplasia of the lymphoid follicles is seen on biopsy. There is expansion of the capsule by chronic inflammation and fibrosis.

In tuberculosis, lymph nodes are usually non-tender and may enlarge over weeks to months. Tuberculin lymphadenitis commonly affects the cervical lymph nodes (63%), followed by

mediastinal (26.7%), and then axillary and inguinal nodes [10]. Our patient's sputum, lymph node, pleural fluid and lung biopsy acid fast bacilli stains and culture were all negative for acid fast bacilli.

Sarcoidosis is a multi-system granulomatous disorder. The classic presentation is bilateral hilar adenopathy. Patients can present with reticular opacities in the lung, skin findings of erythema nodosum or lupus pernio, sarcoid arthropathy and anterior (iridocyclitis or iritis) or posterior uveitis (chorioretinitis). Some patients have rare manifestations of the disease with splenic infarcts, cardiac involvement and peripheral adenopathy [11]. Our patient did have a splenic infarct, but no non-caseating granulomas in the lymph node biopsies. The granulomas in sarcoid are commonly found in lymph nodes and in the lung. They do not contain necrosis and are surrounded by concentric fibrosis.

Malignancy was a major concern in our patient, especially given his constitutional symptoms. Lymphoma typically features cytological atypia and monomorphic cells. Features of Kikuchi histiocytic necrotizing lymphadenitis that may help prevent its misdiagnosis as malignant lymphoma include the absence of Reed-Sternberg cells [12]. . Immunohistochemical stains are helpful in distinguishing SLE from lymphoma. In our patient, we originally thought that a lymph node biopsy would reveal the diagnosis. The first biopsy did not provide definitive evidence of a specific disease process. The proliferation of immunoblasts and atypical lymphoid infiltrate heightened the concern for a malignant process. Therefore a second biopsy of an inguinal node was performed. Stains showed an appropriate pattern of B and T cells (CD 20 and CD 3). No atypical CD 30 cells were seen, thus excluding the possibility of lymphoma. Ultimately the lymph node biopsy did not provide information to bring us closer to the correct diagnosis.

Our patient was particularly challenging, as he presented with severe generalized diffuse lymphadenopathy and no other detected signs of SLE for 6 months. His lymph node biopsies did not show the classic SLE finding of hematoxylin bodies. In 1954 Harvey et al published a case series of 138 patients with SLE [13]. Lymphadenopathy was diagnosed based on clinical observation and biopsy and 105 of 138 patients had generalized lymphadenopathy. Regional or generalized adenopathy was observed in 76 percent of the patients. Cervical and axillary nodes were the most common. In 1964 Dubois et al reviewed 520 cases of lupus over 13 years [14]. Lymphadenopathy was found in approximately 56 percent. Estes et al performed a prospective analysis of SLE patients in 1971 [15]. Generalized lymphadenopathy was found in 36 percent of their patients.

In contrast, more recent series have found generalized lymphadenopathy in SLE to be both less common and less severe. The prevalence of lymphadenopathy in 90 SLE patients in the Shapira series was 25 percent, half of whom had only mild lymphadenopathy [16]. Twelve patients (13%) had lymphadenopathy involving only 1 lymph chain. Only nine patients (10%) had lymphadenopathy involving 2-3 lymph chains or lymphadenopathy greater than 1 cm x 1.5 cm in one chain. Only two patients (2.2%) had generalized lymphadenopathy. SLE patients with lymphadenopathy were significantly younger than the non-lymphadenopathy patients. Shapira et al also reported that SLE patients with lymphadenopathy had significantly more constitutional symptoms of fatigue, fever, weight loss, more cutaneous

findings, as well as increased anti-dsDNA and decreased complement levels. Lymphadenopathy is both less common and less severe in SLE today for many reasons. It may not be as thoroughly evaluated on physical examination (as it is not included in the formal criteria for SLE). Importantly, corticosteroid therapy improves lymphadenopathy nonspecifically [16]. Hydroxychloroquine, now used in most SLE patients early in their course, is helpful for lymphadenopathy [17].

In SLE, lymph nodes biopsies often reveal follicular hyperplasia and foci of necrosis with blastoid cells, karyorrhectic debris, macrophages and histiocyte necrosis. Hematoxylin bodies are not always present, but when they are, they are considered characteristic of lupus lymphadenitis [18]. Our patient's lymph node biopsy did not contain hematoxylin bodies.

Extensive generalized diffuse lymphadenopathy as the presenting feature of SLE is not common today; in fact it is so rare that it was rejected by the Systemic Lupus International Collaborating Clinics in their new classification criteria for SLE [19]. However, our case demonstrates that this rare presentation of SLE should not be forgotten.

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