

Massive Abdominal Lymphadenopathy as a Manifestation of Connective Tissue Diseases. Report of Two Cases and Review of the Literature

Keywords: Massive abdominal lymphadenopathy; Systemic lupus erythematosus (SLE); Mixed connective tissue disease (MCTD);

Reactive lymphadenitis

Abstract

In this report, massive abdominal lymphadenopathy of the reactive type, related to the underlying disease activity, was described in a patient with systemic lupus erythematosus and another one with mixed connective tissue disease. The diagnosis of this very rare clinical presentation was made after appropriate and meticulous work up that ruled out other possibilities such as infectious or lymphoproliferative diseases. Clinicians should be aware of this rare occurrence and, when faced with such a picture, they should appropriately rule out other more serious pathologies, before administering moderate steroid doses targeting the underlying disease.

Abbreviations

CTD: Connective Tissue Disease; ANA: Antinuclear Antibodies; anti-dsDNA antibodies: Anti-Double Stranded DNA Antibodies; SACE: Serum Angiotensin Converting Enzyme; CT: Computed Tomography; HRCT: High Resolution Computed Tomography; IBD: Inflammatory Bowel Disease; ILD: Interstitial Lung Disease; PPD: Purified Protein Derivative

Introduction

Lymphadenopathy is a relatively common manifestation of connective tissue diseases (CTD), particularly rheumatoid arthritis [1-4], and systemic lupus erythematosus (SLE) [4-7]. The clinically palpable nodes are predominantly located in the axillary and cervical areas and are usually non tender and discrete, varying in size from a few millimeters to 3-4 centimeters. However, massive abdominal / retroperitoneal lymphadenopathy, as a manifestation of the disease itself, is extremely rare and very few cases have been described so far [8,9]. When such a massive lymphadenopathy, especially in the abdomen, is encountered in a CTD patient, the physician's main concern is to rule out infectious causes [10-16], granulomatous diseases [17], but also malignant, and rarely benign [18-22], lymphoproliferative disorders. We present herein two patients with CTD, one with SLE and the other with mixed connective tissue disease (MCTD), in whom massive abdominal lymphadenopathy was directly related to activity of the underlying disease and not to another cause. The purpose of this presentation, besides reporting a very rare



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manifestation of CTD activity, is the sensitization of the physician to this rare occurrence which should be included in the differential diagnosis of similar cases, without of course underestimating the importance of prompt and appropriate study to rule out other more serious possibilities.

Presentation of cases

1st Case: A 48 year old caucasian male was diagnosed with SLE 15 years ago, when he presented with fever, serositis, autoimmune hemolytic anemia and flushing, and positive ANA (1/640 homogeneous), anti-dsDNA, and anticardiolipin antibodies. During follow up, he had experienced two recurrences of his disease with low grade fever and serositis, treated by the addition of small doses of steroids to his regular hydroxychloroquine treatment. Moderate interstitial lung disease had also been detected and he had been regularly followed with pulmonary function testing and HRCT. In May 2010, after an asymptomatic period of 6 years, he presented with

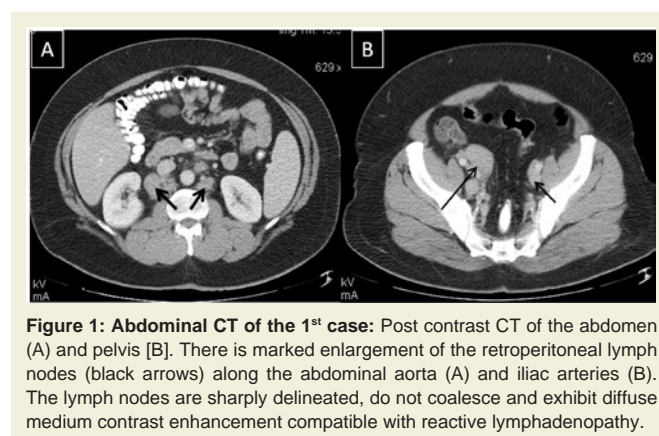


Figure 1: Abdominal CT of the 1st case: Post contrast CT of the abdomen (A) and pelvis [B]. There is marked enlargement of the retroperitoneal lymph nodes (black arrows) along the abdominal aorta (A) and iliac arteries (B). The lymph nodes are sharply delineated, do not coalesce and exhibit diffuse medium contrast enhancement compatible with reactive lymphadenopathy.

fatigue, fever up to 38°C, abdominal pain and nausea. An abdominal CT (Figure 1A and 1B) was reported as showing markedly enlarged and sharply delineated retroperitoneal lymph nodes along the abdominal aorta and the iliac arteries. Inguinal lymph nodes (up to 2.5 cm) were also detected, along with a small pleural effusion. No other significant pathology of the abdominal viscera was present, except for a slightly swollen spleen. HRCT confirmed the presence of enlarged axillary lymph nodes, which had been clinically palpated, and showed minor fibrotic lesions in the lung parenchyma. Upper and lower gastrointestinal endoscopy revealed no abnormality. Serologic profile included positive ANA at a 1:1280 titer and of homogeneous pattern, positive anti-dsDNA 300 units (normal up to 15 units) and low C3 60mg% and C4 10mg% complement levels (normal 79-152mg% and 16-38mg% respectively). Hematology showed a mild anemia with normal reticulocyte count, lymphopenia (900 cells/mm³) and mild thrombocytopenia (115000/mm³), whereas ESR was 60mm in the first hour. During hospitalization no focus of infection was found, whereas a meticulous search for viral infection was negative. Serum angiotensin converting enzyme (SACE) level was normal. An axillary lymph node biopsy did not reveal any specific pathology and the histologic picture was consistent with reactive lymphadenitis. In order to further exclude any infectious, lymphoproliferative or metastatic disease, the patient underwent laparoscopic biopsy of a lymph node block (Figure 2). Both lymph node biopsies (axillary and abdominal) displayed similar histological findings. In more detail, the abdominal lymph node architecture was preserved, although there was an expansion of the interfollicular zone with prominent postcapillary venules. The follicles were small or regressed with only few large secondary follicles with germinal centers present. No granulomas or metastatic epithelial elements were observed. The immunohistochemical evaluation confirmed the reactive nature of the follicles which were CD20 and CD79A positive, with CD10/bcl-6 positive and bcl-2 negative germinal center cells, and a network of CD23 positive dendritic cells. The expansion of the

T-cell interfollicular zone was underlined by the expression of all T-cell markers (CD3, CD5, CD2, CD7), with predominance of CD4 T-cells and the presence of scattered CD30 positive immunoblasts. In this zone, there was neither CD23 and CD10 expression to suggest an angioimmunoblastic T-cell lymphoma, nor presence of CD15 positive cells or Reed-Sternberg/Hodgkin-like cells. The diagnosis was reactive lymphadenitis of interfollicular type, without any findings compatible with lymphoproliferative, metastatic malignant or granulomatous disease. Appropriate stains and cultures did not reveal any infectious agent. Based on the above, an underlying disease exacerbation was diagnosed and the patient was treated with prednisolone (20 mg / day) with gradual dose reduction. Two days later, the patient's condition significantly improved with disappearance of his fever and fatigue, whereas laboratory values began to normalize. Five months after discharge and off steroids, he was in good condition, without symptoms and with normal laboratory tests except for positive ANA and slightly low complement. The size of lymph nodes was reduced in a repeat abdominal CT. Since then and up to now, the patient has remained in good health on hydroxychloroquine 200mg daily.

2nd Case: A 47 year old Caucasian lady was diagnosed with MCTD 11 years ago, on the basis of interstitial lung disease (ILD), symmetric polyarthrititis, myositis with elevation of muscle enzymes and compatible electromyographic findings, Raynaud's phenomenon and high titre anti-U1RNP Abs. During the first 2 years after diagnosis, she had received six monthly IV cyclophosphamide pulses and IV methylprednisolone pulses, for treatment of her ILD with favourable response (improvement of pulmonary function and HRCT picture). In early 2005, during an episode of diarrhea, which lasted for 10 days, appropriate investigation including endoscopy did not show findings suggestive of inflammatory bowel disease (IBD) or another specific pathology. This disappeared without modification of her low dose steroid treatment (5mg of prednisone daily). For the next 5 years on regular follow up on an outpatient basis, she had been feeling well on this regimen. In April 2010, she presented with mild-moderate

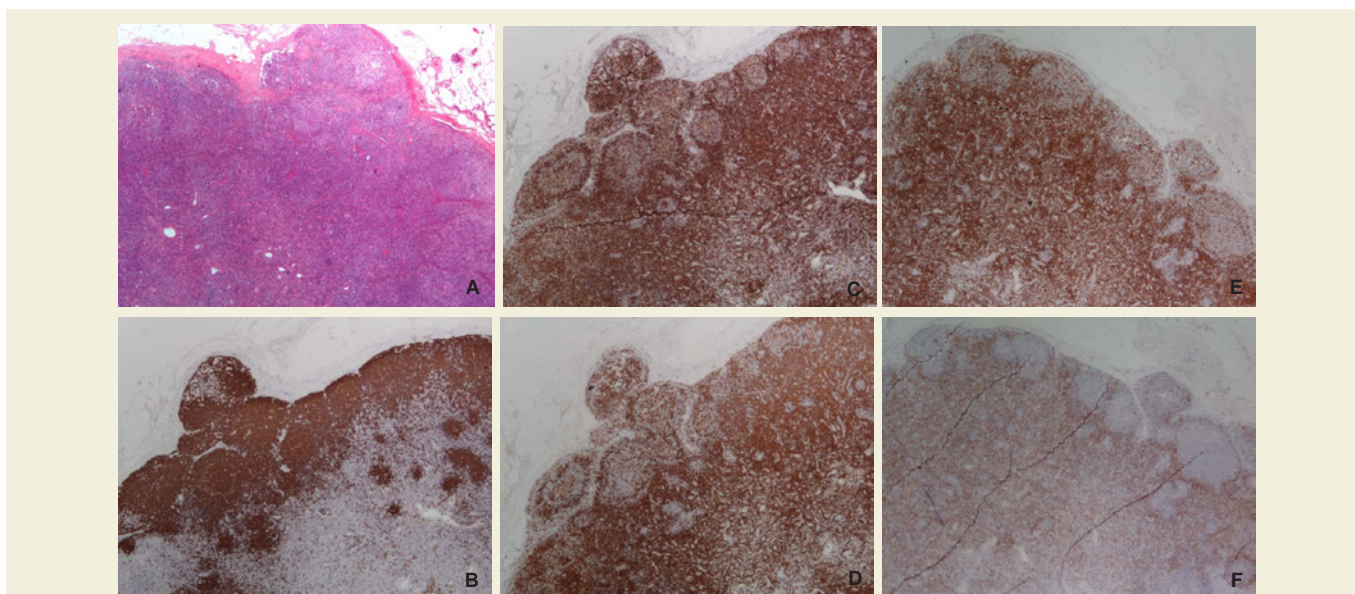


Figure 2: Abdominal lymph node pathology of the 1st case: A. Hematoxylin-eosin stain of the lymph node (X2) showing expansion of the interfollicular zone. B. CD20 positive (brown) reaction of the follicles. C. CD3 positive reaction of the interfollicular T-cell zone as well as intrafollicular T-cells. D. CD5 positive reaction of the interfollicular T-cell zone as well as intrafollicular T-cells. E. CD2 positive reaction of the interfollicular T-cell zone as well as intrafollicular T-cells. F. CD7 positive reaction of the interfollicular T-cell zone as well as intrafollicular T-cells.

arthritis in the small joints of her hands and atypical abdominal pain, accompanied by elevated serum indices of inflammation. SACE level was normal. Because of the previously suspected IBD, a new lower gastrointestinal endoscopy was performed which was unrevealing. An abdominal CT though showed multiple enlarged lymph nodes, with a diameter more than 3cm along the iliac vessels bilaterally (Figure 3). No other pathology of the abdominal organs was seen, while a chest CT showed no significant findings. In order to exclude a lymphoproliferative process - that might have been related to the previously administered cyclophosphamide - or a specific infection such as extrapulmonary tuberculosis - in view of a positive PPD skin test that the patient exhibited-, she underwent laparoscopic lymph node biopsy. The histologic diagnosis was reactive lymphadenitis with follicular hyperplasia (Figure 4). Appropriate stains and cultures did not reveal any infectious agent, whereas immunohistochemistry

ruled out a lymphoproliferative process. On the basis of the above, the whole picture was attributed to the patient's underlying CTD. She improved immediately after increasing the dose of prednizone to 20mg/d with prompt resolution of the arthritis and disappearance of the abdominal pain. At the same time, the patient was placed on antituberculous chemoprophylaxis for six months with isoniazid because of the positive PPD skin test. Since then she has remained asymptomatic with gradual decrease of prednisone dose to 5mg/d, whereas an abdominal MRI has shown reduction in the size of the lymph nodes.

Discussion

We have presented two cases of massive abdominal lymphadenopathy of which, one was observed in a patient with SLE and the other in a patient with MCTD. The lymphadenopathy was proven to be related directly to the underlying CTD, since a meticulous search for any other possible cause was unrevealing. The purpose of this presentation was mainly to report a seemingly very rare occurrence, since such lymphadenopathy has been only twice reported in SLE [8,9] and never in MCTD. This, despite the fact that clinically palpable lymphadenopathy is a well recognized manifestation of rheumatoid arthritis and systemic lupus erythematosus [1-7]. In rheumatoid arthritis, the axilla is the most common site of palpable lymphadenopathy, most likely because these nodes drain the inflamed joints of the upper extremities. In SLE, lymphadenopathy may be more generalized and is more common in children. It has been suggested that in both diseases, lymph node enlargement accompanies disease activity [4].

On the other hand, the detection of unusually large lymph nodes in the abdomen poses an important diagnostic challenge to the physician. In such cases, a laparoscopic surgical biopsy has proven to be the most yielding diagnostic procedure [10], and this was performed in our two cases. The differential diagnosis in these situations includes mycobacterial [10-12] and fungal infections including among others histoplasmosis [13,14] and cryptococcosis [15,16], sarcoidosis [17], metastatic carcinoma and most importantly malignant and more rarely benign [18-22] lymphoproliferative disorders. The frequency of these diagnoses depends on the epidemiologic features of the populations studied, with tuberculosis being the leading cause in endemic areas [10-12] and immunosuppressed individuals, such as those suffering from AIDS [23], whereas lymphomas predominate in the developed world.

In the present report, two such cases of CTD patients, characterized by impressive abdominal lymphadenopathy, creating serious differential diagnostic problems, have been described. Massive abdominal lymphadenopathy has been described in SLE only twice [8,9] and never in MCTD so far. In the cases presented, the possibility of an infectious process was initially excluded, since mycobacterial and fungal infections are not an uncommon cause of massive abdominal lymphadenopathy. The possibility of lymphoma was appropriately excluded as well. Furthermore, the histological examination of excised lymph nodes ruled out the possibility of sarcoidosis or benign lymphoproliferative diseases, such as Rosai - Dorfman disease (sinus hyperplasia massive lymphadenopathy) [18,19], Kikuchi-Fujimoto disease [20,21] and Castleman disease [22], that can rarely coexist with SLE. The lymphadenopathy of our patients seemed to correlate with activity of the underlying autoimmune process, since in both patients it coexisted with evidence



Figure 3: Abdominal CT of the 2nd case: Post contrast CT of the pelvis. There are numerous enlarged lymph nodes (black arrows) along the iliac arteries. Open arrows point to the external iliac arteries. The lymph nodes are sharply delineated, do not coalesce and exhibit diffuse medium contrast enhancement compatible with reactive lymphadenopathy.

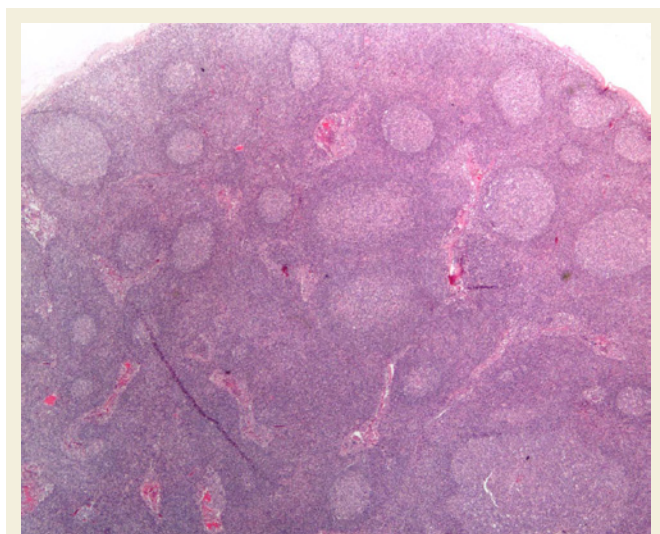


Figure 4: Abdominal lymph node pathology of the 2nd case: Hematoxylin-eosin stain of the lymph node (x2) showing reactive lymphadenopathy with follicular hyperplasia.

of disease exacerbation and showed improvement after the disease was put into remission with moderate dose steroid administration.

In summary, in the present communication we have reported a very rare manifestation, i.e. massive abdominal lymphadenopathy, of connective tissue diseases, and as a matter of fact the first such case in MCTD. Clinicians should be aware of this rare occurrence in the fore mentioned connective tissue diseases, which seems to coexist with activity of the underlying disease. However, appropriate work up should be undertaken in such cases to rule out the presence of an infectious or neoplastic process that necessitate specific treatment, whereas the administration of a moderate steroid dose is adequate for CTD related lymphadenopathy .

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