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CASE REPORT

A case report of systemic lupus erythematosus combined with Castleman's disease and literature review

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Abstract Although lymph node enlargement is common in active systemic lupus erythematosus (SLE), lymph node examination is frequently ignored in the diagnosis of SLE. Clinical presentation and abnormal laboratory findings are often sufficient for SLE diagnosis, not to mention that the specific histological finding of lymph node necrosis in SLE is rarely seen, and the follicular hyperplasia is usually considered as nonspecific. However, since the late 1990s, a few cases of SLE lymphadenopathy have been reported exhibiting a Castleman's disease (CD) morphology, which was discovered in lymph node biopsies. Here we report a similar case of SLE combined with CD in a 23-year-old girl who displayed systemic symptoms, including systemic lymphadenopathy and abnormal laboratory findings indicating the active phase of SLE. A biopsy of neck lymph-nodes showed histopathological features of CD. The patient responded very well to the prednisolone treatment. Based on the related literature review, we would like to stress the possibility of CD in patients with SLE lymphadenopathy.

Keywords Systemic lupus erythematosus · Lymphadenopathy · Castleman's disease

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Introduction

Localized or generalized lymphadenopathy occurs in about 60% of patients with systemic lupus erythematosus (SLE) at some stage during the evolution of the disease. Histologically, the varying degrees of coagulative necrosis with hematoxylin bodies in lymph node lesions are described to be unique to SLE. However, this characteristic histological finding is rarely seen in biopsy. Except for necrosis, lymph node changes in SLE are generally characterized by follicular hyperplasia which is usually considered to be nonspecific. As a result, little attention has been paid to the histopathological or immunohistochemical examination of lymph nodes in patients with SLE [1]. However, since the late 1990s, a number of cases of SLE lymphadenopathy have been reported exhibiting a Castleman's disease (CD) morphology, which was discovered in lymph node biopsies for the purpose of excluding malignant lymphoma. CD, which also refers to giant lymph node hyperplasia, is described as an atypical lymphoproliferation disorder that may present with or without systemic symptoms. Some reports have showed that multicentric CD has a close association with several autoimmune conditions such as thrombocytic thrombocytopenic purpura, rheumatoid arthritis, pemphigus vulgaris and membranous nephropathy [2, 3]. In this report, we present a patient with SLE combined with CD morphology.

Case report

A 23-year-old girl complained of chest pain for 10 days as admitted to hospital in July 2007. She described the left chest pain as continuous dull, mild to moderate in intensity, without radiating to other areas. The pain would get more severe while she was inhaling or lying on her right side. Five days before admission, the patient contracted a recurrent fever, with a temperature as high as 38.8°C. She denied chills, cough or sputum production, shortness of breath or palpitation. The patient was treated with clindamycin and levofloxacin in a local hospital, without noticeable improvement in her symptoms. She had a history of drug allergies to penicillin and cephamycin. The patient also had a history of epilepsia and had been treated with carbamazepine.

On physical examination, her temperature was 38°C, heart rate 108 bpm, blood pressure 102/70 mmHg and respiratory rate 24 per min and her oxygen saturation rate was 98% while breathing room air. A diffused distribution of red rashes, without pruritus, was seen on the skin of the extremities and the back. All the rashes exhibited color fading when pressed. Swollen lymph nodes were palpated at the neck, infraclavicula, axillary fossa, and inguinal groove. The biggest lymph nodes were measured as 2 × 3 cm at inguinal groove and 1 × 2 cm at the neck. All the swollen lymph nodes were moveable, with clear boundary, and without pain while pressed. No other abnormalities were found.

In laboratory tests, white blood cell counts were 3,800/μL, with 51.1% of neutrophils, and the hemoglobin concentration was 90 g/L. Liver function tests showed an albumin level of 3.08 g/L, an aspartate aminotransferase level of 118 U/L, and a lactate dehydrogenase level of 258 U/L, while the alanine aminotransferase value and total and direct bilirubin values were normal. A titer of anti-nuclear antibody (ANA) was 1:320, anti-double stranded DNA antibody (ds-DNA) and anti-extractable nuclear antigen antibody (ENA) were both positive, whereas antinuclear cytoplasmic antibody (ANCA) was negative. Urinary examination showed that microglobulin was 315.2 U, immunoglobulin G 103.1 U, α-globulin 29.55 U, N-acetyl-β-D-glucosaminidase 40.91 U and the urinary protein excretion rate was 936.8 mg/day. The C-reactive protein level was 32.2 mg/L and the erythrocyte sedimentation rate was 130 mm/h, rheumatoid factor 27.3 IU/ml and anti-streptolysin "O" (ASO) 183 IU/ml. Both anti-tuberculosis antibody and purified protein derivative of tuberculin (PPD) test were negative. The Ig M and Ig G against *Chlamydia pneumoniae* were positive. Chest X-ray revealed infiltrating inflammation in both lung bases with mild pleural effusion in the left, which was also found in computed tomography (CT) of the chest. Based on the physical examination and laboratory tests, the patient was diagnosed as in the active phase of SLE. During hospitalization, the right neck lymph node was removed and the histological examination showed reactive proliferation of folliculus lymphaticus, with partial fibrosis in the interstitial tissue. There was hyalinization in some of the small vessels (Fig. 1). Immunohistochemical detection showed that CD20, CD3, CD43, CD79a, S-100, CD68 were positive, whereas CD30, CD15, CD21, CD5 were negative, indicating a diagnosis of CD (Fig. 2). Polymerase chain reaction (PCR) analysis showed T-cell receptor gene rearrangement was negative. The patient was treated with prednisolone (40 mg/days for 10 days) and received a marked decrease in size of the swelled lymph nodes.

Discussion

The histopathological findings of CD in patients with SLE have been relatively rarely reported. During recent years, the frequency of lymph node biopsy for patients with SLE

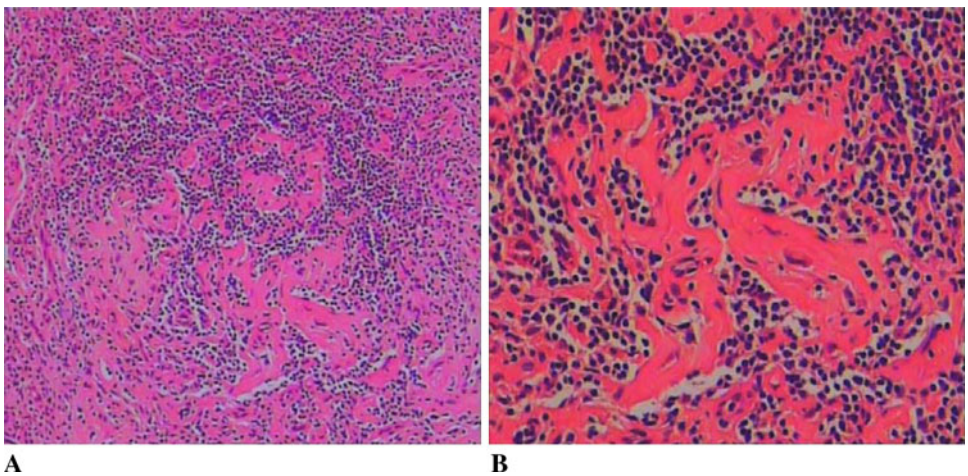

Fig. 1 Histological examination in neck lymph node showed reactive proliferation of folliculus lymphaticus and hyalinization in some of the small vessels **a** HE × 100; **b** HE × 200

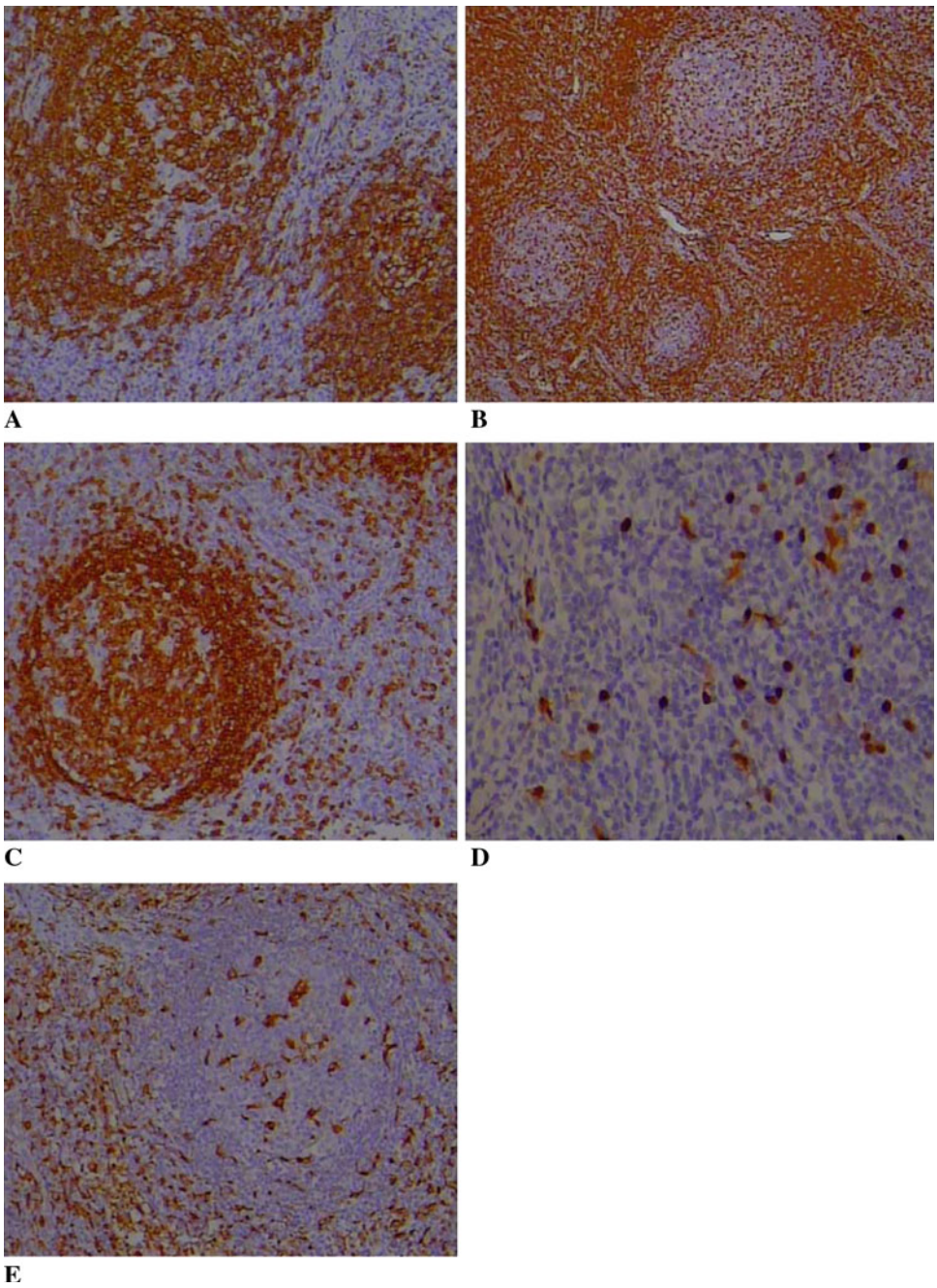

Fig. 2 Immunohistochemical detection showed positive staining for CD20, CD3, CD79a, S-100, and CD68 **a** CD20 × 40; **b** CD3 × 40; **c** CD79a × 100; **d** S-100 × 100; **e** CD68 × 100

exhibiting lymphadenopathy has increased in order to exclude the possibility of lymphoma, which leads to the accumulation of case reports about CD morphology presenting in SLE lymphadenopathy. In a previous study, 5 of 19 (26%) patients with SLE lymphadenopathy showed similar histological features to CD, which indicates a close association between these two diseases [4].

In fact, the multicentric form of CD often presents with a systemic illness that manifests as disseminated enlarged lymph nodes, constitutional symptoms, autoimmune abnormalities, recurrent infections, or other laboratory abnormalities, and some of these overlapping signs and symptoms with autoimmune diseases most closely resemble SLE [5, 6]. Frizzera et al. [7] reported that 6 of 15 (40%) cases with CD manifested two or three of the clinical characteristics of SLE, but did not completely fulfill the four or more items of diagnostic criteria. Based upon physical examination, laboratory tests and histological examination, our case was diagnosed as SLE. Simultaneously, this patient manifested CD morphology in lymphadenopathy of the neck and constitutional symptoms such as fatigue, fever, weight loss and sweats, and laboratory abnormalities such as anemia, hypoalbuminemia, and an increased erythrocyte sedimentation rate. All these

suggested that the SLE patient with CD in our report might share the same clinicopathologic features to those with multicentric CD.

CD has been occasionally discovered presenting in SLE lymphoadenopathy since the 1990s. CD, together with three other types of lymphoproliferative disorders (LPDs) includes: (1) reactive follicular hyperplasia with giant follicles (RFHGFs) [8]; (2) atypical paracortical hyperplasia with lymphoid follicles (APHLFs) [9]; and (3) atypical lymphoplasmacytic and immunoblastic proliferation (ALPIBP) [10], which have been described as atypical LPDs, because these disorders closely mimic malignant lymphomas both clinically and pathologically, but they do not demonstrate all of the characteristics of malignancy (e.g. monoclonality). These atypical LPDs have occasionally been demonstrated in lymph node lesions of SLE in some studies [1, 8].

As mentioned earlier, SLE lymphadenopathy sometimes poses serious problems in diagnosis. In the differentiation diagnosis, besides SLE lymphadenopathy and hematologic malignancies, other diseases which may be manifested by lymphadenitis should also be taken into consideration, such as tuberculosis, sarcoidosis, metastasis, Kikuchi-Fujimoto disease, and infection processes such as infectious mononucleosis and toxoplasmosis. All aforementioned diseases may cause lymphadenopathy, but they are usually distinguishable based on clinical and laboratory findings [11–13]. The most reliable way to establish a definitive diagnosis is by surgical resection and histopathologic confirmation. Besides fine-needle aspiration cytology, CT, MRI and ECT are less reliable and of little help in definitive diagnosing CD. CD exhibits a polyclonal lymphoproliferative process. When monoclonality develops, transformation to a malignant lymphoma must be suspected. Immunohistochemical and gene-rearrangement studies can be used to identify such clonal cell populations [14]. Decreased CD57-positive cells in the germinal centers and increased CD21-positive follicular dendritic cell networks in the mantle zone supported the diagnosis of CD. Differential diagnoses were mainly low-grade malignant lymphomas including follicular lymphoma, mantle cell lymphoma, extranodal marginal zone B-cell lymphoma or mucosa-associated lymphoid tissue (MALT) lymphoma, and small lymphocytic lymphoma. The germinal center cells were negative for bcl-2, excluding follicular lymphoma. There were no bcl-1–positive atypical lymphoid cells in the mantle zone, which excluded mantle cell lymphoma. The absence of clonal gene rearrangement by PCR, the lack of abnormal MALT gene after FISH study and the absence of an aberrant CD43-positive B-cell population excluded extranodal marginal zone B-cell lymphoma as well. The lack of abnormal B-cells coexpressing CD20 and CD5, CD23, or CD43 also made the diagnosis of small lymphocytic lymphoma unlikely [15].

Generally, treatment options including high-dose steroids, radiation therapy and systemic chemotherapy are adopted according to the different types of CD. Most patients with localized CD can be treated with complete surgical ablation, or radiation therapy. In contrast, corticosteroids are recommended to treat multicentric CD with systemic manifestations. In our case, the patient responded very well to prednisolone treatment. In more recent research, immunotherapy has received intensive attention and rituximab has been demonstrated to be effective in some cases. After 18 months of follow-up, the patient recovered well and was still treated with oral prednisolone at a low dosage. Follow-up is particularly important for patients with multicentric disease because of the potential for development of malignancy or a fatal infection.

In conclusion, the histological changes in SLE lymphadenopathy are extremely variable, such as nonspecific lymphadenitis and lymph node necrosis. Therefore, the differential diagnosis of any benign or malign lymphadenopathy is of great importance. From a therapeutic perspective, we would like to stress the possibility of CD morphology in patients with SLE lymphadenopathy.

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