Clinical Case Report

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Castleman disease mimicking systemic lupus erythematosus

A case report

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Abstract

Rationale: Castleman disease (CD) is a nonclonal lymphoproliferative disorder sometimes manifested systemic inflammatory symptoms. Systemic lupus erythematosus (SLE) is an autoimmune disease characterized with multi-system involvement as well as broad spectrum of serum autoantibodies. When these two conditions happened to have similar clinical spectrum features, the confusion with each other occurred.

Patient Concerns: A 46-year-old man suffered from chronic fever, nephrotic syndrome, acute kidney injury, anemia, thrombocytopenia and serositis, as well as hypocomplementemia and negative anti-nuclear antibody.

Diagnoses: Meeting the classification criteria for SLE, the patient was diagnosed as SLE at first. The renal biopsy showed that he had endocapillary proliferative glomerulonephritis with negative immunofluorescence. Finally, he was diagnosed with CD after lymph nodes biopsy.

Interventions: The patient was treated with oral prednisone (50 mg daily) but got poor response. After being proved to have CD, he was treated with CHOP chemotherapy.

Outcomes: His condition was controlled by CHOP chemotherapy. After six course of chemotherapy, the proteinuria disappeared.

Lessons: If patients, even qualified by classification criteria of SLE, had negative autoantibody or unsatisfied response to the standard treatment, the original diagnosis should be suspected. The biopsy may be help to identify the final criminals, such as CD.

Abbreviations: Anti-dsDNA = anti-double-stranded DNA antibody, Anti-RNP = anti-u1 small-nuclear RNA-protein antibody, Anti-rRNP = anti-ribosomal RNA-protein antibody, Anti-Sm = anti-Smith antibody, Anti-SSA = anti-SSA antibody, Anti-SSB = anti-SSB antibody, APL = anti-phospholipid antibody, CD = Castleman disease, CHOP = cyclophosphamide + adriamycin + vincristine + predinisone, IgA = immunoglobulin A, IgG = immunoglobulin G, IgM = immunoglobulin M, LDH = lactate dehydrogenase, POEMS = polyneuropathy + organomegaly + endocrinopathy + M protein + skin changes, RF = rheumatic factor, SLE = systemic lupus erythematosus, SLICC = Systemic Lupus International Collaborating Clinics, TMA = thrombotic microangiopathy, VEGF = vascular endothelial growth factor.

Keywords: Castleman disease, erythematosus, lupus

1. Introduction

Systemic lupus erythematosus (SLE) is a heterogeneous, systemic autoimmune disease associated with the production of multiple antibodies against self-antigens. It often affects childbearing-age women and commonly presents as mucocutaneous, hematologic, musculoskeletal, renal, and neurologic manifestations. Its pathologic basis is autoantibody-induced complement-dependent vasculitis. Now, the SLICC classification criteria[1] for SLE could be summarized into a simple rule: the patient must satisfy at least

Editor: Raouf Hajji.

LW and HC contributed equally to this article.

All interventions given were part of normal health care and thus ethical approval was neither obliged, nor sought. However, the patient had given informed consent already and approval from the patient was also obtained to publish the case report.

This study was supported by the Chinese National High Technology Research and Development Program, Ministry of Science and Technology (2014AA020527), the Chinese Medical Association (12040670367), and the National Natural Science Foundation of China (81501414, 81571598, 81571594).

The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:38(e12291)

Received: 3 March 2016 / Accepted: 17 August 2018

http://dx.doi.org/10.1097/MD.0000000000012291

4 criteria, including at least 1 clinical criterion and 1 immunologic criterion or the patient must have biopsy-proven lupus nephritis in the presence of antinuclear antibodies (ANA) or anti-dsDNA antibodies. The requirement reflects that both clinical features and positive serologic autoantibodies are indispensable to diagnostic of SLE, because SLE is ultimately an autoantibody-driven clinical disease.

Multiple autoantibodies could be found in the serum of patients with SLE. The more antibodies were detected, the higher possibility of SLE the patient had. The presence of ANA is one of the criteria for the diagnosis of SLE, but the sensitivity of ANA testing can be as low as 70%, especially early in the disease.[2] Some patients might be diagnosed with SLE according to the classification criteria, even though they are ANA negative (titer <1:80 by immunofluorescence) at initial presentation or, rarely, throughout the course of the disease.[3]

The typical cases may be diagnosed without any doubt. But, in some cases, only a few features are present at disease process, and these features can resemble other autoimmune, infectious, or hematologic diseases.[4] Moreover, some other patients can present with a combination of clinical findings suggestive of SLE and even qualify by classification criteria as having the disease but do not have SLE. These SLE "mimics" often puzzle clinicians and should be excluded. Otherwise, the patients may be misdiagnosed or even treated improperly.

2. Case report

A 46-year old Chinese man, presented with fever for 4 months and low extremities edema for 3 months. Four month ago, he developed a daily moderate fever of 38.5°C with fatigue. One month later, he found that there were lots of foam in his urine and pitting edema in lower limbs. Lab tests revealed anemia (96 g/L), thrombocytopenia (62×10^9/L), as well as nephrotic syndrome which manifested as proteinuria (4.9 g/24 h), hematuria (200/μL, with 80% dysmorphic cells), hypoalbuminemic (25 g/L), and injured renal function (blood creatinine 295 μmol/L). Erythrocyte sedimentation rate (ESR) and C-reactive protein were elevated (30 mm/h and 49.1 mg/L, respectively), and hypocomplementemia (C3 0.89 g/L, C4 0.15 g/L) was also noted. Serum gamma globulin, immunoglobulin (Ig) G, A, and M levels were normal. Serum protein electrophoresis revealed no monoclonal spike. Autoantibodies profile, including ANA, anti-DNA, anti-Sm, anti-SSA, anti-phospholipid antibody (APL), anti-u1 small-nuclear RNA-protein antibody (anti-RNP), and rheumatic factor (RF), were negative. Computed tomography showed moderate bilateral pleural effusions and massive ascites. Bone marrow analysis revealed active proliferation and few platelet-producing megakaryocytes.

In the absence of any clue of infectious or malignancy diseases, the patient was diagnosed to have SLE by doctors of the local hospital and was treated with oral prednisone (50 mg daily). The proteinuria and elevated serum creatinine level responded well, but fever persisted.

Therefore, this patient was admitted to our hospital in October 2012. Physical examination revealed he had several palpable lymphonodes in the neck and axilla. The serum autoantibodies profiles were rechecked and still negative, as well as the testing of human immune deficiency virus, hepatitis B virus, hepatitis C virus, CytoMegalo Virus, Epstein-Barr virus, and malignancy markers. The diagnosis of SLE seems questionable.

To identify the exact causes of his renal disease, the patient was recommended to undergo kidney biopsy, which proved that he had endocapillary proliferative glomerulonephritis (Fig. 1). Instead of a "full-house" immunofluorescence pattern from typical lupus nephritis, the immunofluorescence of kidney specimens was negative.

Finally, lymph nodes biopsy showed that the histologic findings consistent with Castleman disease (CD) (Fig. 2). Then, he was treated with CHOP (cyclophosphamide + adriamycin + vincristine + predinisone) chemotherapy. Only after one course of chemotherapy, his temperature becomes normal. Six courses later, the proteinuria disappeared.

3. Discussion

Multisystem involvement is not specific for SLE and can be seen in many other diseases including systemic vasculitis, general infections, and some malignancy. Comparatively speaking, presence of differential autoantibodies is more reliable diagnostic significance. Generally, the more antibodies were detected, the higher probability of SLE. That may be an important reason why rheumatologists switched the 1997 classification criteria[5] for SLE to 2012 SLICC, which more emphasized the indispensable role of related antibodies in the diagnosis of SLE.

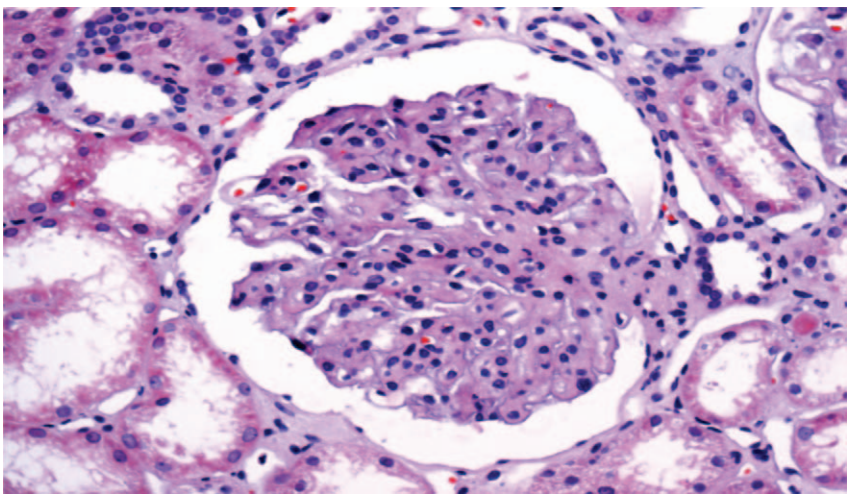

Figure 1. Kidney biopsy: endocapillary proliferative glomerulonephritis.

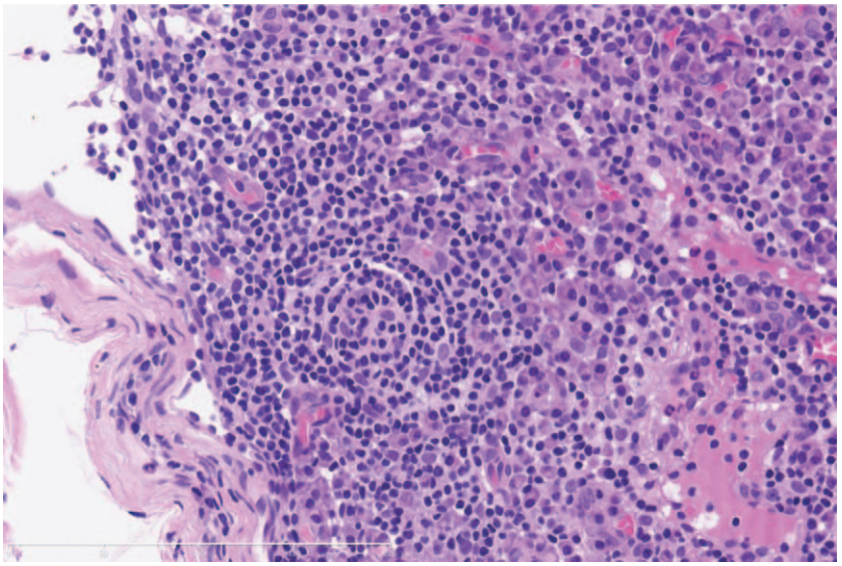

Figure 2. Lymph node biopsy: Castleman disease. Immunohistochemistry: CD20 (+), CD23 (+), CD3(+), CD34(+), S-100(−), CD138 (+), CD38(+), PC (+), Ki-67 index 10%.

This case mimicked SLE by its systemic clinical manifestations, including constitutional symptoms (fever and fatigue), renal involvement (acute kidney injury and nephrotic syndrome), hematologic changes (anemia, thrombocytopenia, and lymphadenectasis), and even multiple serositis. All of which were common and characteristic in SLE. That is the main reason why the patient was initially diagnosed as SLE. However, there were several doubts in identifying SLE. The deadly defect was lack of ANA and other diagnostic antibodies, since SLE was considered to be an autoantibody-driven disease. Additionally, his renal biopsy was not full-house staining but blank pattern on the immunofluorescence. The last but not the least, 1 month of high-dose glucocorticoid therapy had not improved his fever.

The ANA-negative SLE does exist. In some active SLE cases, almost all the antibodies combined with their self-antigens and then formed into the immune complex which deposited in the gaps of capillary endothelium and other tissues; therefore, there were not enough remaining free antibodies to be detected. Caltik et al[6] had reported such an ANA-negative SLE presented with vasculitis, serositis, and full-house nephropathy. However, our patient's renal biopsy did not reveal the classic full-house immunofluorescence staining patterns, which suggested extremely unlikely of SLE.

There were many other possibilities of patients with SLE who were ANA-negative. For example, in patients with significant hypoalbuminemia and(or) hypoimmunoglobulinemia due to lupus protein-losing enteropathy[7] or membranous nephropathy, nonselective protein loss could cause low-titer or undetectable serum ANAs. Interestingly, we found high-titer urine ANA in an ANA-negative case with renal biopsy proved Class V lupus nephritis and nephrotic syndrome (24-hour-urine-protein >20 g). Additionally, the serum level of ANA turns positive in some cases that respond to treatment. Moreover, if the patients had APL, their ANAs could be negative. ANA test could be false-negative, because Hep-2 cells, the substrates of ANA test, are scarce of cytoplasm, which is enriched with auto-antigen such as ribosomal RNP and SSA.[8] If these antigens are responsible for positive ANA, the test could mistakenly negative. Finally, the titer of ANA may decrease to undetectable in long-term remission patients. Obviously, our reported case met none of the reasons mentioned earlier. At this moment, we had to ask for the renal biopsy, which subsequently proved that it was an endocapillary proliferative glomerulonephritis.

The spectrum of endocapillary proliferative glomerulonephritis is classified by immunofluorescence. When typical "full-house" appeared, it hinted the possibility of lupus nephritis. When the immune deposits distributed like stars in the night sky, the patient maybe suffered from acute poststreptococcal glomerulonephritis.[9] If there was no subendothelial deposit at all, the glomerulonephritis might be caused by proangiogenic cytokines like vascular endothelial growth factor (VEGF),[10] which could proliferate endotheliocytes and increase vascular permeability.[11] Indeed, VEGF-signaling inhibition could also induce nephritic syndrome and/or thrombotic microangiopathy (TMA).[12,13] Elevated VEGF levels were commonly reported in malignancies and lymphoproliferative disorders,[14] especially in POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes)[15] and CD.[16] Given the marked lymphadenopathy in this case, the lymph nodes biopsy was conducted and eventually revealed the typical histologic findings of CD.

The CD is a nonclonal lymphoproliferative disorder characterized as either unicentric or multicentric. Unicentric CD is localized and carries an excellent prognosis, whereas multicentric CD is a systemic disease that commonly manifested as diffuse lymphadenopathy, splenomegaly, anemia, and systemic inflammatory symptoms.[17] Given its diverse and broad-spectrum manifestations, CD is a great mimic of both benign and malignant conditions.[18] CD may mimic systemic autoimmune diseases such as adult onset still disease, rheumatoid arthritis, systemic vasculitis, IgG_4-related diseases, etc. Cytokine overproduction (IL-6, VEGF, etc) is an important pathogenetic factor in the development and mimicking of CD, especially in those who had renal complications. Yuan et al[19] had analyzed 75 cases of CD with renal involvements. Their renal pathology could commonly manifest as amyloidosis, TMA, membranoproliferative glomerulonephritis, mesangial proliferative glomerulonephritis, focal glomerulosclerosis. Endocapillary proliferative glomerulonephritis was 1 rare type of renal manifestations in CD.

In this case, despite of systemic manifestations, the absence of serum ANAs and immunofluorescence of renal biopsy finally ruled out the diagnosis of lupus. However, if the lymphadenopathy was noted early, the patient may avoid misdiagnosis.

4. Conclusion

Autoantibodies play an important role in diagnosing SLE. Patients with multisystemic involvement but absence of ANAs response to standard treatment was poor and should be cautiously identified as SLE, especially those whose renal biopsy was not supportive. CD could be one of the mimics of SLE.

Acknowledgments

The authors thank Lijuan Gou, Yubing Wen, Dachun Zhao, Tienan Zhu, Qiang Wang, Chao Li, Xiaohong Fan, Bing Han, and all the residents and attendings, who were in charge of the cases we studied, for their contributions to save the patient's live and improve his life quality.

Author contributions

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