ANA negative with Severe Lupus-like presentation: Is it lupus or not?

shuangxi li[1] and qi bian[1]

[1]Changhai Hospital Department of Nephrology

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Introduction

Systemic lupus erythematosus (SLE) is a protean disease. The classification criteria have been evolving to increase the sensitivity and specificity of SLE diagnosis. The American College of Rheumatology (ACR) criteria (1982 version [1]and 1997 revised version[2] have high specificity, but limited sensitivity. The Systemic Lupus International Collaborating Clinics (SLICC) 2012 criteria have increased sensitivity, but decreased specificity[3]. The 2019 EULAR/ACR SLE classification criteria have both high sensitivity and specificity, and advocated positive ANA (ever) as an entry criterion[4, 5]. Therefore, for patients with persistent ANA negative, it is difficult to diagnosis for SLE. Our report describes a young woman who presented an ANA negative and lack of typical clinical symptoms of SLE patient, but with severe lupus-like manifestations. At present, this is unique case report about severe lupus with ANA continued negative.

Case Report

On December 8, 2020, A 34-year-old Chinese woman was found to have renal failure (creatinine of 778.4 umol/L) due to frequent vomiting. She had not any medical history. Initial investigation showed renal failure, moderate anemia, abnormal calcium and phosphorus metabolism, normal complement and autoimmune antibodies test (supplementary table 1). A kidney biopsy was performed to confirm the etiology of the renal failure, which presented crescent glomerulonephritis, and multiple immune complexes deposition in the mesangial, subcutaneous and subepithelial areas with membranoproliferative and "full-house nephropathy" pattern (figure 1, 2).

She was initiated on peritoneal dialysis (PD) due to renal failure. After kidney biopsy, she received prednisone and intravenous cyclophosphamide monthly. On January18th, 2021, she had a sudden, unprovoked seizure with loss of consciousness that lasted about 6 minutes. She had no previous history of seizures. Susceptibility-Weighted Imaging (SWI) showed hemosiderosis deposits in cerebellar hemisphere and occipital lobe (figure 3). Immunoglobulin (IVIG) , methylprednisolone, and hydroxychloroquine (HCQ) was chonsen to treatment. But given that the subsequent serious pulmonary bacterial infection, fungal enteritis and severe myelosuppression, she was no longer treated with cyclophosphamide. After infection control, HCQ and low-dose mycophenolate mofetil (MMF) was chosen as maintenance treatment. The prednisolone taper was continued to a dose of 10mg/day. The treatment is effective and the brain lesion was obviously shrinked after 6 months (figure 3). She had no further seizures and no other specific clinical symptoms within more than 3 years of clinical follow-up .

Discussion

The patient was a young woman presenting with edema and renal failure. Initial investigation showed multiple serous effusion and double pneumonic exudation. Renal biopsy was chosen to confirm the diagnosis. It is confusing that renal pathology revealed lupus-like nephritis but this patient has not any typical lupus symptoms and all autoantibodies were negative. Therefore, we must deliberate this patient's diagnosis. SLE

was also considered in combination with the patient's clinical presentation (renal failure, multiple serous effusion and epilepsy) and persistent hypocomplementemia, as well as the renal pathology of type IV lupus-like changes. However, the 2019 EULAR/ACR SLE classification Criteria project proposed that ANA is an entry criterion for SLE[4, 5]. The patient's autoantibodies (including ANA, ds-DNA, ss-DNA, and Sm) were persistent negative. Hence, it proposed a question that ANA negative Lupus-like syndrome: Is it lupus or not?

The decision that ANA was used as a screening test and an entry criterion for SLE was made after the baseline facts had been worked up thoroughly. Nicolai Leuchten, et al. showed ANA at a titer of 1:80 have 98% sufficiently high sensitivity in a systematic literature review and meta-regression which included more than 13,000 SLE patients[6]. A report showed that only 6.2% of patients were ANA negative among more than 1000 SLE patients who fulfilled the ACR classification criteria[7]. Therefore, ANA is a useful and sensitive indicator for screening SLE. However, there are also a minority SLE patient with ANA negative[8, 9]. It has been reported that among patients with "full-house"or "Lupus-like" nephropathy but negative serology for lupus. Some of them developed autoantibodies and other clinical manifestations of SLE during the follow-up, while some of them remained seronegative and developed no clinical findings of SLE other than full-house nephropathy[8, 10]. Another report describes three processes of autoantibodies in the development of lupus[11]:Stage 1: patients had neither symptoms nor any detectable autoantibody levels; Stage 2: patients develop detectable autoantibodies without clinical manifestations; Stage 3: patients presented obvious clinical symptoms of lupus with autoantibodies positive[11]. According to the above description, ANA is not only a diagnostic indicator of lupus, but also related to the progression of the disease. Our patient presented with lupus-like pathological and devastating features of SLE, but persistent negative autoantibodies. This is different from the previous reports about ANA-negative lupus.

In this patient, renal pathology is an important basis for lupus diagnosis. SLICC (The Systemic Lupus International Collaborating Clinics) used full-house staining as the sole criteria to diagnose SLE[3]. However, It has been reported that the prevalence of no-lupus full house nephropathy was 20%-30%[12-15]. "No-lupus full house nephropathy" is an umbrella term for such patients who may exhibit "lupus-like" nephropathy, but without presenting any extrarenal symptoms or serologies suggestive of SLE. Pathologies of full-house nephropathy should also be considered in the differential diagnosis of SLE, including primary glomerular diseases (membranous nephropathy, C1q nephropathy, IgA nephropathy), infections (endocarditis, HIV, HBV, HCV, BK and CMV virus), diabetes mellitus, liver diseases[12-14]. This patient had none any evidence of these disease. For enhanced the sensitivity and specificity of stand-alone kidney biopsy to diagnose lupus nephritis, another report showed that five renal pathological features, which included "full-house" staining, intense C1q staining, extraglomerular deposits, combined subendothelial and subepithelial deposits, and tubuloreticular inclusions, were selected to create a scoring system to define lupus nephritis with reasonably high sensitivity and specificity[16]. According to this scoring system, this patient had 3 scores: "full-house" staining, subendothelial and subepithelial deposits, and tubuloreticular inclusions, with sensitivity of 80% and specificity of 95% for the diagnosis of lupus nephritis. However, there is still a certain bias in the diagnosis of LN by renal biopsy pathology alone. In the SLICC classification, If patients are ANA negative, however, they have to fulfill at least four of the other 10 (or 16) criteria, also biasing against ANA negative SLE[3]. At the onset, the patient presented with multiple serous effusion, renal failure, which had not yet met the diagnosis of ANA negative SLE. During the follow-up, the patient developed new signs: epilepsy and hypocomplement. Given excluding other possible diseases, combined with the patient's four clinical symptoms and lupus-like renal pathological findings, the diagnosis of ANA negative SLE is considered.

In conclusion, the patient presented with chronic renal failure at the time of diagnosis, and there was a lack of evidence and clinical manifestations of secondary renal failure. If the patient was directly treated with renal replacement therapy without renal biopsy, it would be more difficult to diagnose. Therefore, the auxiliary role of pathological manifestations in some intractable cases is crucial. ANA screening for SLE is a good tool, but autoantibody testing should not be overly relied upon when both pathological and clinical findings support the diagnosis of SLE. In conclusion, this patient is a unique case of ANA-negative severe lupus. For such cases, it is easy to be missed or misdiagnosed, which is a challenge in diagnosis and treatment. How to

detect these diseases early still needs more research.

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