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CASE REPORT

ANA Negative (Ro) Lupus Erythematosus with Multiple Major Organ Involvement: A Case Report

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SUMMARY **Anti-nuclear antibody (ANA) negative systemic lupus erythematosus (SLE) occurs in about 4-13% of SLE cases. A small group of ANA negative SLE patients with positive anti-Ro antibodies usually present with typical vasculitic skin lesions which can be associated with photosensitivity, renal disease, congenital heart block or neonatal lupus. We present a case of a persistently ANA negative patient who presented with joint pain, rashes, mouth ulcer and alopecia. Clinical diagnosis of systemic lupus erythematosus was made even though ANA was negative. She was started on steroids and went into remission. Later, she developed several episodes of convulsions associated with fever and prominent vasculitic lesions. The patient was also found to have microscopic hematuria, proteinuria, anemia and thrombocytopenia. Renal biopsy showed lupus nephritis class 1B. Due to the prominent skin lesions, we performed anti-extractable nuclear antigens (ENA) antibodies test and anti-Ro turned out to be positive. The final diagnosis was ANA negative SLE (Ro lupus) with cutaneous, renal, musculoskeletal, hematological and cerebral involvement.**

Systemic lupus erythematosus (SLE) is a chronic, life long autoimmune or connective tissue disease characterized by a breakdown of tolerance and the presence of autoantibodies directed against cellular antigens resulting in inflammatory damage to multiple organ systems.[1] The incidence and prevalence varies according to ethnic background, age and sex.[1] The commonest age is between 20-40 years old with female predominance.[2] The etiology remains unknown. Genetic predisposition, sex hormones and environmental factors might play a role in the pathogenesis of SLE.[2] The diagnosis of SLE is made on clinical grounds with the support of laboratory investigations based on the America Rheumatism Association 1982 criteria (revised criteria for the classification of systemic lupus erythematosus).[3] The disease can be mild or severe with predilection for involvement of joints, skin, kidneys, brain, serosa, lungs, heart and the gastrointestinal tract.[2] There are several subsets of SLE such as discoid lupus, drug-induced lupus, neonatal lupus and Ro lupus.[1] Ro lupus is defined by the absence of ANA and the presence of partially photosensitive skin rash referred to as subacute cutaneous lupus erythematosus. ANA negative SLE seems to be a subgroup of SLE that is infrequently recognized. We report one persistently ANA negative SLE patient who presented with multiple joint pain, skin lesions, alopecia and mouth ulcers followed by hematological, cerebral and renal involvement and was later diagnosed as having Ro lupus.

CASE REPORT

A 22-year-old Chinese lady initially presented to Hospital Universiti Sains Malaysia in April, 1997 with multiple joint pain especially affecting the shoulders, elbows and knees. She also had a history of rashes on the face and the rest of the body, mouth ulcers and alopecia. On physical examination, her vital signs were normal. She had a malar rash on the face, alopecia and multiple mouth ulcers. The involved joints were tender but no swelling was noted. Other systems

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were normal.

Investigations revealed a hemoglobin of 11.4 g/dl, a white cell count of 7.0 x 10^9/l and platelets of 368 x 10^9/l. The erythrocyte sedimentation rate (ESR) was 130 mm/hour. A blood urea and serum electrolyte (BUSE) and renal function test were normal. Tests for antinuclear antibody (ANA) and rheumatoid factor (RF) done by indirect immunofluorescence (using Hep-2 cells substrate) and latex agglutination, respectively, were negative. The complement level C3 was 0.859 g/l (normal: 0.66-1.30 g/l) and C4 was 0.3 g/l (normal: 0.20-0.60 g/l). The international normalized ratio (INR) was 0.88 and the activated partial thromboplastin time (APTT) was 33.7 seconds with a control of 28.6 seconds. A diagnosis of systemic lupus erythematosus was made based on the clinical presentation. The patient was started on prednisolone 60 mg daily and went into remission. She was well during the follow-up period where ANA was persistently negative.

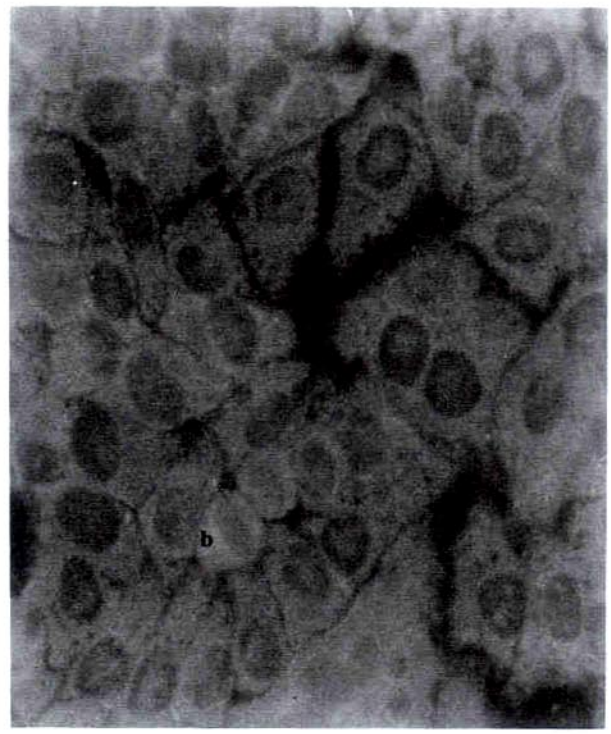

Fig. 1 Anti-nuclear antibody test result of the serum of the patient (400x magnification) (a: ANA negative; b: anti-cytoplasmic positive)

In July 2000, she was readmitted following 3 episodes of generalized seizures and fever of four days duration. She was again noted to have a malar rash, mouth ulcers, alopecia and multiple joint pain. The most prominent cutaneous manifestations during this admission were vasculitic lesions in the fingers and maculopapular lesions all over the body. During this admission, the investigation results were as follows: urine by dipstick and microscopic examination revealed proteinuria 2+ and microscopic hematuria, the 24-hour urine protein was 0.8 g/24 hours, the cerebrospinal fluid analysis was normal, the full blood count showed hemoglobin of 6.9 g/dl and peripheral blood film showed changes suggestive of iron deficiency with thrombocytopenia. Total white cell count was 6.5 x 10^9/l and platelet count was 33 x 10^9/l. No bone marrow study was performed since the anemia and thrombocytopenia were attributed to underlying SLE. The direct Coomb's test was positive (IgG 2+; C3d negative) but the indirect one was negative. However, the patient was transfused 2 units of packed cells without any problems. The serum ferritin level was 1,786 µg/l (normal range: 5-96 µg/l). The brain CT scan showed generalized cerebral atrophy without any focal lesions. The electroencephalogram showed changes of a mild encephalopathy compatible with cerebral lupus. The septic work up such as typhidot test, anti-streptolysin O titer (ASOT), widal weil-felix (WWF) and human immunodeficiency virus (HIV) tests were all negative. The blood urea and serum electrolyte (BUSE) analysis showed: sodium 137 mmol/l, potassium 3.7 mmol/l and urea 1.6 mmol/l. The serum creatinine was 67 µmol/l. Renal biopsy revealed lupus nephritis class 1B. Blood culture revealed growth of *Bacteroides fragilis*. The complement levels, INR and APTT were all normal. The VDRL was non-reactive. Anti-phospholipid and anti-dsDNA antibodies were not done. ANA remained negative but the cytoplasmic region was fluorescent (Fig. 1). In view of the prominent cutaneous manifestation, we performed anti-Ro and anti-La antibodies. Anti-Ro antibodies were found to be positive and anti-La antibodies were negative. The patient was diagnosed ANA negative SLE (Ro lupus) with involvement of the skin, joint, kidney, bone marrow and brain. The patient was treated with phenytoin and antibiotics. Intravenous methylprednisolone was given at a dose of 1 gram daily for 3 days followed by oral prednisolone. Her

condition improved and she was discharged well. She is still on follow-up at the Rheumatology and Nephrology outpatient clinics in our hospital and is currently in remission.

DISCUSSION

SLE is a multimeric condition of unknown atiology. It is often being called the great imposter because of its ability to occur in almost any system in the body. It occurs much more common in females than in males especially in women of child bearing age.[2] SLE is often associated with HLA-DR2 and DR3 or deficiencies of C2 or C4.[4] The diagnosis of SLE should be made on clinical grounds with the support of laboratory investigations. At least 4 out of 11 revised America Rheumatism Association (ARA) criteria should be fulfilled or present in order to make a diagnosis of SLE.[3] In our patient, seven criteria were present in the form of malar rash, photosensitivity, oral ulcers, thrombocytopenia, seizures, arthritis and proteinuria. Other features that have been reported in ANA negative SLE are Raynaud's phenomenon, oculo-motor palsy and penile ulcer.[5]

The types of autoantibodies that can be found in SLE patients are ANA, ds-DNA, anti-Sm, anti-RNP, anti-Ro/SSA, anti-La/SSB, rheumatoid factor, lupus anti-coagulant, anti-phospholipid etc. Antinuclear antibody (ANA) is important as a screening test for the diagnosis of SLE. Besides the immunoflourescence method, ANA can also be detected by an enzyme immunosorbent assay (ELISA).[6] However, immunofluorescence has been the gold standard method. ANA will be positive at a titer of 1/40 or more with a speckled, homogeneous or peripheral pattern. ANA negative SLE patients may show antibodies to dsDNA. Negative serological tests do not always exclude SLE as these tests may become positive at a later period.[5] ANA negative SLE is rare, occurring in only about 4-13% of all cases.[7] There are a few possibilities for ANA to be negative. The laboratory result for ANA may be false negative explicable on the basis of: (a) technical inaccuracy, (b) antibody is hidden within circulating immune complexes,[8] (c) prozone phenomenon as observed by Ritchie,[9] or (d) antibody which has been absorbed by tissues (e.g. ANA absorption by organs such as kidneys has been described in one case of ANA negative SLE where anti-cytidine antibodies were found in renal biopsy specimen).[10] ANA may also be negative if the patient is in clinical remission with treatment.[11] Whatever the ANA status of a patient, it must be emphasized that the diagnosis of SLE can be made as long as the patient fulfills at least four of the 11 ARA criteria.[12]

Detection of cytoplasmic antibodies (Ro and La) is an important serologic feature of ANA-negative SLE. Anti-Ro is found in 25-40% of SLE cases.[1] Usually this small group of patients with negative ANA but positive anti-Ro antibodies present with typical vasculitic cutaneous manifestations. Other clinical features include photosensitivity, renal disease, congenital heart block and neonatal lupus.[1] No previous case of central nervous system involvement in anti-Ro lupus has been reported. However in patients with central nervous system disease associated with Sjögren's syndrome, the subset of patients with positive anti-Ro antibodies have more serious and extensive central nervous system disease compared to anti-Ro antibody negative patients.[13] Excessive fetal morbidity and mortality have been noted in patients with systemic lupus erythematosus. The influence of anti-Ro antibodies on fetal outcome in SLE patients has rarely been reported, but its high association with congenital heart block or neonatal lupus syndrome is well known.[14] Although most women with systemic lupus erythematosus can achieve a successful pregnancy, fetal and maternal morbidity remain a major problem.[15] The majority of affected infants acquire anti-Ro antibodies transplacentally from the maternal circulation and these antibodies are pathogenic.[16] Early treatment with steroids and/or immunosuppressive drugs may minimize the damage and influence in a positive manner the significant morbidity and mortality observed in some anti-Ro antibody positive patients.[17]

ANA negative SLE seems to be a subgroup of SLE that has not been given adequate attention. It is important for the clinicians to be aware that some of the SLE patients may have persistently negative tests for ANA. Thus if a clinician suspects that his/her patient has SLE based on the clinical presentation, the first thing to do is to screen for ANA. A patient is suspected of suffering from SLE if ANA is positive accompanied by positive anti-dsDNA and/or positive anti-Sm. If ANA remains negative on repeat testing and the clinical suspicion of SLE is strong, tests to detect anti-Ro and anti-La antibodies should be performed which might reveal a small subgroup of patients with ANA negative (Ro lupus) as described here. But again, the final test is the presence of four out of the 11 ARA criteria.

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