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Case Report

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A young lady with fits and bleeding; a case of acquired hypodysfibrogenemia and cerebral lupus in a patient with systemic lupus erythematosis

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Abstract

Introduction: Systemic lupus erythematosis (SLE) is a multisystem disorder. Although Anti-Nuclear Antibody (ANA) positivity is described as an essential criterion of diagnosis in the 2019 EULAR guideline, ANA negative lupus is recognized up to 2% of all SLE patients who otherwise fulfil clinical and immunological criteria**.**

Case Presentation: We describe a 20-year-old female diagnosed with ANA negative SLE who presented with renal SLE relapse and adult-onset seizures with high blood pressures; MRI was more in favour of cerebral lupus than posterior reversible encephalopathy syndrome, facilities to detect CSF anti ribosomal P antibodies were not available. During hospital stay, she developed severe bleeding manifestations with normal prothrombin and activated partial thromboplastin time, prolonged thrombin time and fibrinogen clauss with low normal fibrinogen levels which partially corrected with cryoprecipitate. Clot solubility was not performed. A diagnosis of acquired hypodysfibrinogenemia with possible factor X111 deficiency was made.

Discussion: ANA-negative SLE is a clinical rarity. Differentiation between cerebral lupus and pure hypertensive encephalopathy may be challenging. Acquired coagulation disorders, which may exhibit diverse clinical and biochemical presentations, are well recognized in SLE.

Keywords: Systemic lupus erythematosis, acquired coagulation disorders, ANA negative lupus, cerebral lupus, hypertensive encephalopathy

INTRODUCTION

Systemic lupus erythematosis (SLE) is a multisystem disorder. Although Anti-Nuclear Antibody (ANA) positivity is described as an essential criterion of diagnosis in 2019 EULAR guideline[1], ANA negative lupus is recognized in up to 2% of all SLE patients who otherwise fulfil clinical and immunological criteria[2]. In addition to well-described major organ involvement, autoantibody formation may lead to a wide array of acquired coagulation disorders.

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CASE REPORT

A 20-year-old female patient presented with a history of generalized body swelling and reduced urine output for 4 days' duration. She carried a diagnosis of Systemic Lupus Erythematosis (SLE) from 2014. The initial diagnosis was made based on 2012 SLICC criteria with a biopsy-proven class 4 (DPGN) SLE nephritis. Her ANA by ELISA (enzyme-linked immunosorbent assay) was negative but there was dsDNA reactivity and hypocomplementemia. She also had photosensitivity and small joint arthritis at the time of diagnosis. She went into remission with intravenous methylprednisolone (MPP) and cyclophosphamide and was successfully maintained with oral prednisolone and mycophenolate mofetil. She experienced two renal relapses in 2016 and 2018 after defaulting. The patient had defaulted treatment for 2 months before this presentation. She was oliguric, acidotic and was managed as a renal relapse of SLE. She was treated with IV MPP and hemodialysis.

On examination, she was hypertensive with a blood pressure of 180/100mmHg and had generalized oedema. Laboratory investigations are as follows; ESR - 115mm/hr, ANA- Negative (by the indirect immunofluorescence assay (***IIFA***) on HEp-2 cells), DsDNA – positive, C3/C4 – low, UPCR – 17 (nephritic range), urine dysmorphic cells – 5%, serum creatinine – 5.6micmo/L, no microangiopathic hemolytic anaemia in the blood picture, mild thrombocytopenia, direct Coomb's test- negative, Anti Ro/Anti La – positive, Beta 2 microglobulin/ Anticardiolipin antibody – Negative, Lupus Anticoagulant – positive (ratio - 1.4), DRKVT/KCT for lupus anticoagulant – negative.

On the second day evening, she became acutely confused and was complaining of headache and started to vomit. Then she developed generalized tonic-clonic convulsions. Her blood pressure was 200/120mmHg, IV Glyceryl nitrate infusion was started to control the blood pressure. Her sensorium improved on controlling blood pressure, the non-contrast computed tomography of the brain was normal. There was no papilloedema and she was left with no neurological signs after this episode. MRI brain was performed; findings were consistent with cerebral lupus with T2/FLAIR changes involving the cortex and subcortical white matter of cerebral hemispheres predominantly in temporal and parieto-occipital lobes, bilateral caudate nucleus, L/posterolateral thalamus, splenium, brain stem and cerebellum. However, facilities to do CSF Ribosomal P antibodies were not available. She was pulsed with intravenous cyclophosphamide.

She developed uncontrollable vas-catheter site bleeding and per-vaginal bleeding on the fifth day. Her platelets were 126/µL (150-450) with normal prothrombin time and activated partial thromboplastin time. A rotational thromboelastometry (ROTEM) was performed which demonstrated slightly prolonged thrombin time and prolonged Fibrinogen clauss with low normal fibrinogen levels. Facilities to measure clot solubility were not available. She was successfully treated with cryoprecipitate with the presumptive diagnosis of acquired dysfibrogenemia and possible factor X111 deficiency.

DISCUSSION

SLE is a multisystem disease. 2019 EULAR/ACR criteria recognize ANA as an entry criterion[1]. However, with negative ANA and positive renal biopsy for lupus nephritis, our patient fulfils the 2012 SLICC criteria for SLE. The term "ANA negative lupus" was entertained since 1970; it was estimated that about 5% of patients with SLE were ANA-negative by indirect immunofluorescence back in the day. This negative finding occurred because sera were tested using rodent, not human tissues as the substrate for the indirect immunofluorescence test for ANA. With the use of human epithelial type 2 (Hep-2) cells in the indirect immunofluorescence, ANA assay has resulted in even fewer SLE patients with negative ANA. In addition, it was postulated that patients who have longstanding disease and/or have undergone treatment may lose ANA reactivity and become serologically negative over time. Current expert opinion suggests that ANA-negative lupus is a rarity, with an incidence of <2% in SLE patients[2].

The term lupus cerebritis/ cerebral lupus refers to neuropsychiatric manifestations of lupus that

appear to have an organic basis. The neurological manifestations in SLE are related to,

1) Vasculopathy; Accelerated atherosclerosis, lupus anticoagulant associated thrombosis, blood-brain permeability of immune complexes and plasmacytoid dendritic cells (pDC) activation

2) Autoantibodies; anti-ribosomal P antibodies and antineuronal antibodies

In addition to the above mechanisms, the patients with SLE may experience neurological symptoms secondary to infections associated with immunosuppressive therapy, metabolic complications of other organ system failure, such as uraemia, hypertension and toxic effects of therapy (particularly corticosteroids),

Differentiation between cerebral lupus and pure hypertensive encephalopathy may be challenging, as in our patient. This differentiation is of paramount significance as aggressive immunosuppression is the treatment of choice for cerebral lupus, whereas, blood pressure control is adequate for hypertensive encephalopathy. MRI is the most useful neuroimaging study in patients with SLE in this context. High signal intensity large lesions; their presence correlated with disease activity as assessed by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), diminished cerebral and corpus callosal volume, cytotoxic oedema are suggestive of cerebral lupus. T_2-weighted vasogenic oedema of the white matter of the parieto-occipital regions (reversible posterior leukoencephalopathy syndrome) or T2 pontine abnormalities (hypertensive brainstem encephalopathy) are in favour of hypertensive encephalopathy. Diffusion-weighted MRI (DWI) can help to distinguish between vasogenic oedema of RPLS and cytotoxic oedema more typical of lupus-related infarctions[3]. In addition, the presence of CSF antineuronal antibodies may favour cerebral lupus[4].

Autoantibodies that inhibit specific functions of fibrinogen which may interfere with fibrinopeptide release, fibrin monomer polymerization, or fibrin cross-linking are recognized in several conditions; Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ulcerative colitis, multiple myeloma, mitochondrial myopathy, medications i.e., isoniazid[5]. Our patient developed severe bleeding from the vascular catheter site after hemodialysis which was partially corrected by cryoprecipitate. This post-procedure bleeding was attributed to acquired hypodysfibrogenemia (with low normal fibrinogen levels and prolonged fibrinogen clauss). However, acquired factor 13 deficiency could not be ruled out since clot solubility was not performed.

CONCLUSION

ANA-negative SLE is a clinical rarity. Differentiation between cerebral lupus and pure hypertensive encephalopathy is challenging. Neuroimaging with MRI and detection of antineuronal antibodies may help in the process. Acquired coagulation disorders, which may exhibit diverse clinical and biochemical presentations, are well recognized in SLE.

Author declaration
Author contribution
All persons who have made substantial contributions to the work are reported in the manuscript.

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Ethics approval and consent to participate
Consent was taken from the patient to present the details

Competing interest
All authors disclose no competing interests

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