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CASE REPORT

Unusual co-existence of dural sinus thrombosis and aneurysmal subarachnoid hemorrhage in a patient with lupus

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Subarachnoid hemorrhage and dural sinus thrombosis are important manifestations of neuropsychiatric lupus erythematosus. We report the case of a woman with relapsed lupus nephritis, in partial remission, who presented with the unusual combination of dural sinus thrombosis (due to protein S functional deficiency) and aneurysmal subarachnoid hemorrhage. She had a fatal outcome, as has often been reported with subarachnoid hemorrhage in the context of active lupus. To our knowledge, this is the first report of such an unusual association in lupus, and highlights unique challenges in the management of intracranial hemorrhage in the context of dural sinus thrombosis. *Lupus* (2015) **24,** 994–997.

Key words: Neuropsychiatric lupus; thrombosis; systemic lupus erythematosus; nephritis; anticoagulation

Introduction

Neuropsychiatric lupus erythematosus (NPLE) can present as either thrombotic or hemorrhagic stroke.[1] Subarachnoid hemorrhage (SAH) in systemic lupus erythematosus (SLE) may occur due to vasculopathy or aneurysmal rupture, and predicts adverse prognosis in those with active disease.[2] Venous sinus thrombosis is another manifestation of NPLE, more common in patients with antiphospholipid antibodies, although resistance to anticoagulant protein S and protein C has also been reported.[3] Dural sinus thrombosis occurring concomitantly with SAH is extremely rare. We report a patient with relapsed lupus nephritis, who developed aneurysmal SAH along with dural sinus thrombosis. To our knowledge, this is the first report of such an unusual combination in SLE.

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Case report

A 39-year-old woman was admitted in March 2009 with polyarthritis for 2 years and recent onset of oral ulcers and alopecia. Investigations revealed Coomb's positive hemolytic anemia (hemoglobin 7.9 g%), active urinary sediments [red cells 20–30/high power field (HPF) and white blood cells 15–20/HPF], proteinuria of 700 mg/day, antinuclear antibody (ANA) positivity (4+ coarse speckled at 1:80 dilution), extractable nuclear antigen (ENA) profile showing antibodies to Sm and RNP, low serum complements (C3 27.9 mg%, normal 60–120 mg%; C4 <5.4 mg%, normal 15–25 mg%), elevated anti-dsDNA antibodies by ELISA (>200 IU/ml, normal <30 IU/ml), and normal serum creatinine (0.7 mg%). Activated partial thromboplastin time (APTT) was 26.1 s (control 29.8 s). IgM anticardiolipin antibody (ACLA) (6 MPL U/l) and IgG ACLA (13.8 GPL U/l) were negative. Renal biopsy showed active Class IIIA lupus nephritis. She was induced with six monthly pulses (750 mg/m^2) of intravenous cyclophosphamide (IVCY) and oral prednisolone in tapering doses, followed by oral azathioprine for maintenance. With this, she attained complete renal remission. In April 2013, she presented with lupus flare following drug default for 2 months (active urinary

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sediments: red cells 60–70/HPF, white blood cells 6–8/HPF, proteinuria 10.8 mg/g of creatinine, serum creatinine 0.71 mg%, low complements: C3 39 mg%, C4 <5.4 mg%, anti-dsDNA titers >150 IU/ml). Repeat renal biopsy showed Class IVA nephritis. She was treated with IVCY as per the Eurolupus Nephritis Trial protocol, followed by oral azathioprine. By October 2013, she had attained partial renal remission on azathioprine 100 mg/day, prednisolone 15 mg/day and HCQS 200 mg/day (proteinuria 588 mg/24 hours, SLEDAI-2 K 4, suggestive of active disease, SLICC damage index 0).

She presented in November 2013 with sudden onset of altered sensorium for 2 days along with a single episode of generalized tonic-clonic seizure. On examination, she was drowsy, and her blood pressure was 140/80 mm Hg. Neurological examination revealed left facial palsy with left hemiparesis and neck rigidity. Investigations revealed Hb 9.4 g%, total leucocyte count 9400/mm^3, platelet count 12,9000/mm^3, serum creatinine 1.6 mg%. Serum complements (C3 95 mg%, C4 18 mg%) were normal and anti-dsDNA antibodies were undetectable. Computed tomography of the head revealed intracerebral hemorrhage in the right temporoparietal region.

In view of intracerebral hemorrhage in the absence of thrombocytopenia, magnetic resonance angiography of the cerebral circulation was done suspecting an aneurysmal bleed. It showed hematoma in the right fronto-parietal region with extension into the right sylvian fissure and minimal subdural bleed (Figure 1), aneurysm at the trifurcation of the right middle cerebral artery (Figure 2) and thrombosis of right transverse and sigmoid sinus (Figure 3(a,b)). The latter prompted for a re-evaluation of pro-thrombotic state. There was no family history of ischemic stroke, venous sinus thrombosis or peripheral venous thrombosis at a younger age. Repeat values of IgM ACLA (<3 MPL U/l), IgG ACLA (<3 GPL U/l) and anti-β2GPI (<5 IU) were negative. APTT was normal (23 s; control 26.7 s), hence lupus anticoagulant was not done. Protein S functional activity was low (47%; range 65–140%); protein C functional assay showed normal activity (121%; range 70–130%). Anticoagulation was not started immediately in view of the recent intracerebral bleed. As she was being stabilized and awaiting a definitive surgical procedure for the aneurysm, she collapsed and died.

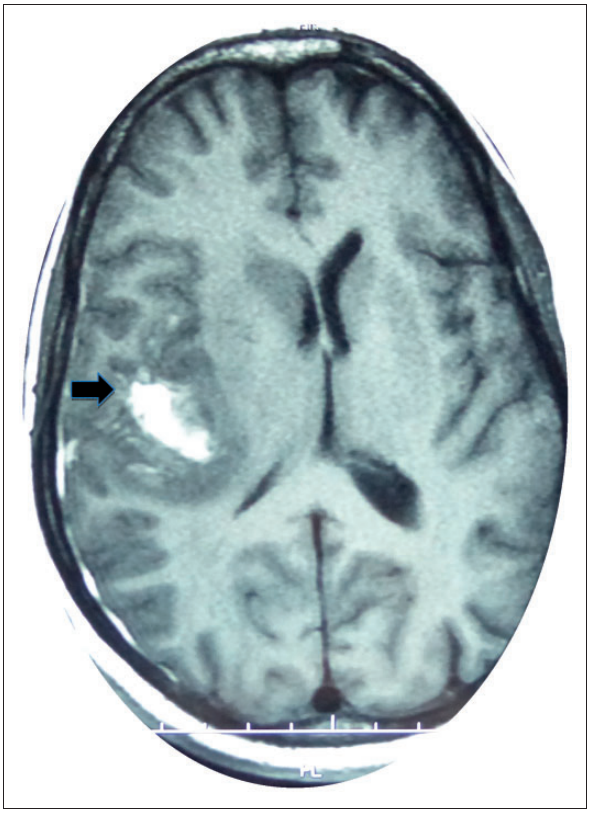

Figure 1 T1-weighted magnetic resonance image of brain showing bleed extending into right sylvian fissure (black arrow).

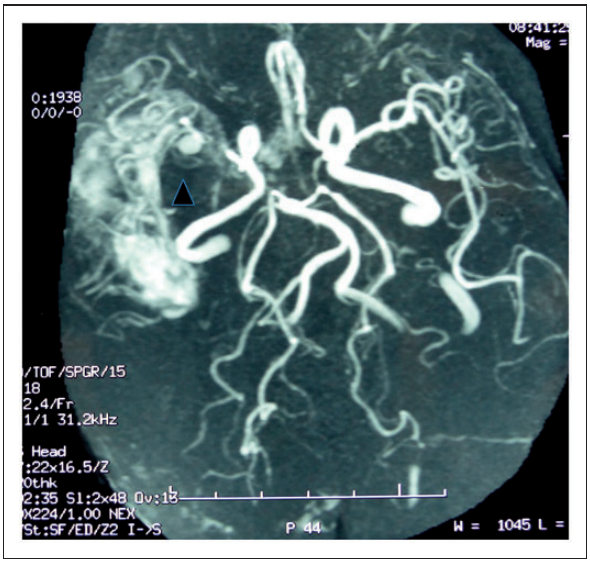

Figure 2 Magnetic resonance arteriogram showing aneurysm of the right middle cerebral artery (black arrowhead).

Discussion

The concomitant existence of dural sinus thrombosis and SAH is rare,[4–7] and challenging to manage. Our patient developed a SAH with intracerebral extension in the context of active lupus; the literature suggests a near-fatal outcome in such patients.[2] A possible explanation could be

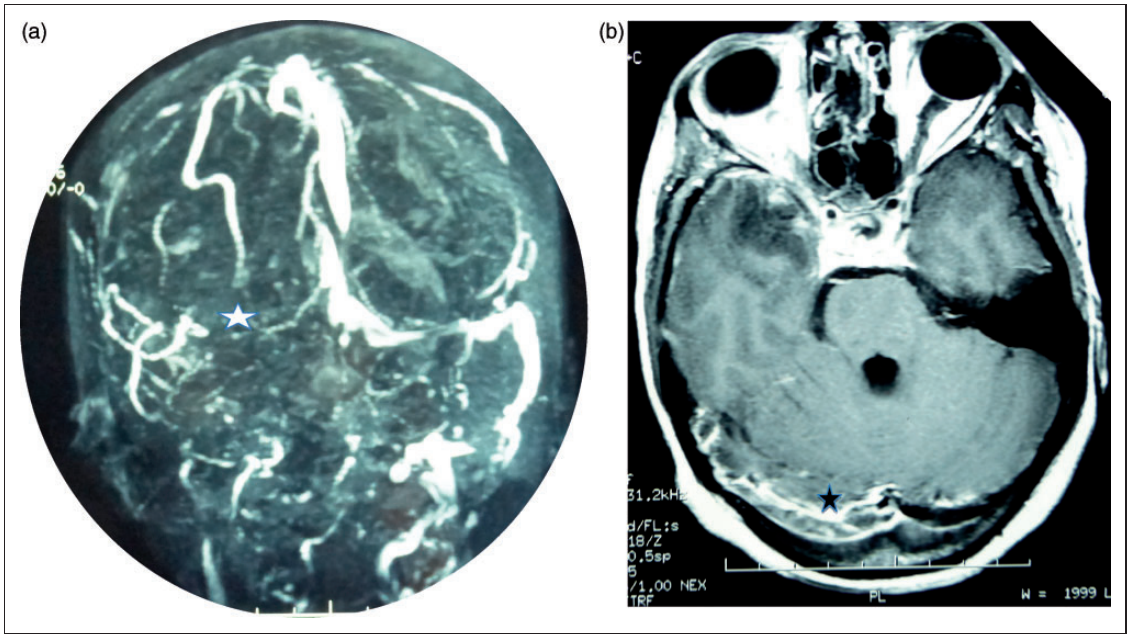

Figure 3 (a) Magnetic resonance venogram showing right transverse sinus thrombosis (white star), (b) Magnetic resonance venogram showing right transverse sinus thrombosis (black star).

occurrence of dural sinus thrombosis due to deficient protein S activity,[3,8] resulting in increased back pressure in the venous system which was transmitted back to the arterial system, causing rupture of a pre-existing aneurysm. Circulating antibodies to protein S form immune complexes, enhancing clearance of circulating protein S and interfering with the protein S–protein C anticoagulant cascade.[9] Interestingly, such interference with protein S function often occurs independently of antiphospholipid antibodies in patients with SLE,[10] as was found in our patient. Review of the literature suggests protein S levels should not be estimated in women during pregnancy or on hormone replacement therapy, as well as in those on oral vitamin K antagonists.[11] The presence of none of these in our patient lends reasonable confidence towards the validity of reduced functional protein S activity. Studies in patients with acute ischemic stroke have not shown a difference in protein S levels in the acute phase following the stroke or 3 or 6 months later,[12] hence the estimation of protein S function in close proximity to the vascular event was reliable. Anti-protein S antibodies, which should ideally have been estimated, were not available at our center. Lack of consent for this testing precluded estimation of protein S antigen levels or function in family members to look for evidence of familial protein S deficiency resulting from a heterozygous state.

This case poses an intriguing problem: concomitant dural sinus thrombosis and intracranial bleed. What are the therapeutic options to consider in such a case? In retrospect, a possible option could have been to anticoagulate this patient,[4] which may have reduced a chance of a re-bleed from the aneurysm until surgical intervention.

To conclude, this rare association of dural sinus thrombosis and aneurysmal subarachnoid bleed illustrates the complex interplay of autoimmunity in SLE, concomitantly affecting the integrity of the vasculature and interfering with coagulation cascade. Subarachnoid hemorrhage in the context of active SLE invariably has a fatal outcome and hence needs to be managed aggressively.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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