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Transient Life-Threatening Cerebral Edema in a Patient with Systemic Lupus Erythematosus

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Abstract

Central nervous system symptoms occur in a substantial portion of patients with systemic lupus erythematosus. However, coma is a rare presentation and is usually secondary to complications such as subarachnoid hemorrhage, seizure, or ischemia. Here, we present a 49-year-old woman with lupus erythematosus and a history of recurrent aseptic meningitis and mild subarachnoid hemorrhage who presented with altered mental status and lethargy that progressed rapidly over hours to the herniation syndrome of coma, extensor posturing, and unilateral pupillary dilation. Spinal fluid showed massive protein elevation (>1600), and head computed tomography revealed global cerebral edema. The clinical and radiologic findings rapidly reversed with intravenous corticosteroids and mannitol within 24 hours, and her mental status improved to baseline.

Her course was complicated by 2 episodes of recurrent encephalopathy when corticosteroids were tapered; these resolved after resuming high dosing. Because of ongoing pancytopenia, chemotherapy immunosuppression was delayed, and instead she received intravenous immunoglobulin with improvement in the pancytopenia. She remained cognitively intact during subsequent corticosteroid tapering. Rapid development of coma in lupus patients may be due to a primary process of the disease impacting blood brain barrier integrity. Although rare, this potentially fatal complication may be reversible with acute corticosteroid administration.

Keywords

corticosteroids; reversible; blood brain barrier; coma; encephalopathy

Systemic lupus erythematosus causes a broad range of nervous system dysfunction.^{1–3} The mechanism of central nervous system involvement may include complications of treatment (corticosteroid side effects; infection in the setting of immunosuppression), complications of systemic effects of the disease (uremia; hypertension; hypercoagulability causing stroke), or

a direct consequence of autoimmune mechanisms directed at the central nervous system or the blood brain barrier.⁴⁻⁶ The spectrum of neuropsychiatric lupus encompasses headache, psychiatric disturbances, seizures, cognitive impairment, confusion, meningitis (infectious or aseptic), neuropathy, demyelination, movement disorder, and cerebral ischemia (see the American College of Rheumatology definitions for neuropsychiatric lupus).^{7,8} Despite evidence for over 100 different auto-antibodies identified in lupus patients (including for example, antineuronal, antiphospholipid, and antiribosomal),⁹ their specific roles in the pathophysiology of neuropsychiatric lupus remain controversial.

Although the neurologic and psychiatric manifestations of lupus present a treatment challenge and contribute significantly to the morbidity of the disease, only in rare instances are these presentations acutely life threatening. For example, there have been case reports of severe neurologic compromise, some of which are reversible, including bilateral thalamic hypodensities that might represent reversible focal cerebral edema.¹⁰ A case series reported that 8 of 82 neurologic events in 71 lupus patients manifested as coma, and these were associated with metabolic (renal or hepatic) failure, severe hypertension, severe thrombocytopenia, or high corticosteroid dosing.¹¹ In that series, half of the computed tomography (CT) scans showed hemorrhage and half were unremarkable; none showed diffuse cerebral edema. In another series, of 36 neuropsychiatric events in 33 patients, coma was the manifestation in 2 patients.¹² Other case series involving 40 to 128 subjects revealed no instances of coma.^{3,8,13-15} Two cases of coma associated with seizures,^{16,17} and 1 case of acute coma in a pediatric patient¹⁸ resolved with intravenous corticosteroids, but cerebral edema was not present in any of these cases (cerebrospinal fluid [CSF] showed either normal or moderately elevated total protein). Fatal leukoencephalopathy with edema and herniation has also been described,¹⁹ with pathologic confirmation of diffuse edema in a similar case.²⁰ Subarachnoid hemorrhage (SAH) is a rare but potentially life threatening complication of lupus,²¹ and concurrent global cerebral edema portends a higher mortality.²²

Here, we present the case of a 49-year-old woman with long-standing lupus who presented with altered mental status that rapidly deteriorated to coma, decerebrate posturing, and global cerebral edema, which was rapidly responsive to corticosteroids and mannitol therapy.

Case Description

A 49-year-old woman with a history of migraines was initially diagnosed with lupus erythematosus (SLE) at age 31 based on the constellation of 4 miscarriages, hemolytic anemia, arthralgias, and a positive antinuclear antibody. She was subsequently found to have serum antiphospholipid antibodies, but had no clotting events. She was maintained on hydroxychloroquine and intermittent low dose corticosteroids for more than 15 years, without neuropsychiatric symptoms. Her systemic manifestations were limited to hemolytic anemia and thrombocytopenia. At age 47, she developed facial weakness and dysarthria from a small corona radiata ischemic stroke, with workup revealing a patent foramen ovale, right femoral deep venous thrombosis (DVT), and confirming antiphospholipid antibodies. Anticoagulation with warfarin was initiated, and later changed to enoxaparin injections due to International Normalized Ratio variability. She experienced several episodes of headache

with mental status change, and on one occasion had inflammatory CSF findings of 210 WBC (lymphocytic predominance), and total protein elevation of 715 with normal glucose and negative infectious workup, and was presumed to represent lupus meningitis. She received rituximab treatment for anemia that was unresponsive to corticosteroids, with minimal improvement.

Five weeks prior to presentation, she developed subacute onset of constant headache. She was admitted after emergency department evaluation revealed a small right cortical convexity SAH (Fig. 1, left column). CT angiography was negative for aneurysm, and the bleeding was attributed to anticoagulation, which was held for 2 weeks. Her headaches persisted but repeat CT scans were stable or improved. On the seventh day after discharge, she presented with altered mental status, then somnolence requiring intubation, without focal neurologic deficits. Edema and venous congestion of the right arm was later confirmed as new DVT. Cranial CT revealed diffuse cerebral edema and a small amount of SAH (Fig. 1, second column), but CT angiography (and subsequent conventional angiography) were negative. Venous sinus thrombosis was also not seen on either of those 2 imaging studies. Urgent "hairline" EEG revealed theta and delta slowing but no epileptiform activity. CSF studies showed an opening pressure of 18, 133 WBC (68% PMN), 27000 RBC, 1610 total protein, and glucose 40, and negative infectious studies. Serum testing revealed the following: Na 144, Cr 1.7, BUN 24, WBC 6.6, HCT 32.3, PLT 166, glucose 101, and troponin peak of 5.5. Complement panel revealed CH50 123, C2 1.10, C3 86, C4 10, and the DS-DNA was 37.

In the neurologic intensive care unit, she deteriorated rapidly (within hours) to coma, bilateral extensor posturing, and the left pupil dilated, without other cranial nerve findings or papilledema. She urgently received 1 g intravenous methylprednisolone and 75 g of intravenous mannitol. Repeat CT-confirmed diffuse edema with effacement of the sulci and basal cisterns, and extravasation of contrast received for CT-angiography several hours prior (Fig. 1, third column). This extravasation supports the idea that blood brain barrier has been compromised. The posturing and pupil dilation resolved within 2 hours of treatment. She was extubated the next day and her mental status returned to baseline by the second day. Repeat imaging revealed resolution of the edema (Fig. 1, right column), but MRI showed diffuse sulcal T2 hyperintensity consistent with diffuse high protein signal in the subarachnoid space, without new T2 hyperintensity in the white matter or cortex (not shown).

When daily high dose corticosteroids were tapered to 60 mg prednisone orally, encephalopathy recurred within 24 hours. Repeat head CT revealed no new bleeding and was otherwise stable. Reinitiation of corticosteroid treatment with 1 g intravenous methylprednisolone improved her mental status within hours. After a 5 day course, she again deteriorated with encephalopathy within 24 hours of taper initiation. Cranial CT was again without edema or new hemorrhage, and repeat CSF revealed 2 WBC, 72 RBC, total protein of 1075, and glucose of 38. High dose intravenous corticosteroids were again restarted, with rapid improvement in mental status.

Immunosuppression with cyclophosphamide was postponed because of pancytopenia, including frank neutropenia and hemolytic anemia requiring transfusion of 5 units of red blood cells. Bone marrow aspiration revealed nonspecific suppression. Instead, intravenous immunoglobulin was initiated (5 doses of 0.4g/kg), and her pancytopenia gradually resolved over the subsequent week. Her corticosteroid dosing was then successfully tapered over the next 2 weeks without incident. On follow-up 4 weeks later, her serum testing included WBC 10.9, HCT 34, and PLT 246.

Discussion

The case describes a patient with longstanding SLE mainly manifested by recurrent miscarriages, anemia, and thrombocytopenia in the context of antiphospholipid antibodies who developed multiple complications including embolic stroke (possibly paradoxical in the setting of patent foramen ovale and DVT), recurrent aseptic meningitis, and SAH (in the setting of anticoagulation). The most dramatic complication was the rapid development of diffuse life-threatening cerebral edema, which rapidly reversed with corticosteroid and mannitol treatment. There was no evidence for hypertension, metabolic or electrolyte derangement, infection, seizure, anoxia, ischemia, or venous sinus thrombosis. There was, however, severe protein elevation in the CSF, as well as contrast extravasation on CT scans, suggesting profound blood brain barrier (BBB) compromise. Although there was evidence for mild subarachnoid hemorrhage, we do not feel this accounted for the diffuse edema. In one study, the clinical severity and edema was related to aneurysm size, coma on presentation, and use of pressor agents.²² In our case, the initial SAH occurred at an unknown time during 2 weeks of subacute antecedent headache, and there was no evidence of aneurysm or diffuse blood to explain her presentation. It is also unknown whether a single event or repeated leakages occurred in the context of inflamed BBB and ongoing anticoagulation. Although we cannot completely rule out a contribution of the SAH to edema and inflammation, the global edema was out of proportion to the small amount of SAH, and it resolved rapidly with anti-inflammatory and antiedema treatments, neither of which is compatible with SAH as the cause. We attribute the improvement to corticosteroids, as opposed to the mannitol, because of (a) the evidence of massive inflammation; (b) intact blood brain barrier is required for osmotic therapy efficacy; and (c) the recurrence of encephalopathy immediately upon weaning corticosteroids.

The spectrum of neuropsychiatric complications of lupus and other rheumatologic diseases is diverse,^{1,2} but coma from cerebral edema is a rare event. The most common causes of cerebral edema in the ICU setting are subarachnoid hemorrhage, trauma, global hypoxia (for example, after cardiac arrest), infection, or severe metabolic derangements (electrolyte, liver, or renal dysfunction). None of these mechanisms were present in our case. Lupus cerebritis is thought to be an inflammatory process, involving loss of blood brain barrier integrity, resulting in high CSF protein levels, and cerebral edema. Blood brain barrier mechanics and breakdown in disease states involving inflammatory processes has been reviewed by Petty and Lo.²³ Whether water transport via aquaporins is specifically involved in lupus cerebritis remains unknown, but the increasingly large number of lupus-related antibodies⁹ and the recent evidence from a mouse model of lupus implicating aquaporins²⁴ raises the possibility of brain aquaporin regulation²⁵ as a potential diagnostic or therapeutic

target. In one study, progesterone decreased the edema and aquaporin expression found in an animal model of traumatic brain injury.²⁶ Similarly, serum levels of adhesion molecules have been correlated with central nervous system disease activity, as well as antiphospholipid antibody levels, in lupus patients.²⁷ Mechanisms of vascular permeability and BBB compromise might be more likely than a possible transient (and FLAIR-negative) vasculitis process, although pathologic analysis would complement these measures. Although a nonvasculitic autoimmune inflammatory meningoencephalitis syndrome has been described,²⁸ the onset ranged from 3 weeks to >1 year of cognitive changes, in contrast to our case (< 18 hours onset). SLE comprises one of many diseases increasingly recognized to affect the nervous system through autoimmune mechanisms.²⁹ Further understanding of the effects of inflammation on blood brain barrier function may improve diagnosis and treatment of this spectrum of disorders.³⁰

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Figure 1.

Axial computed tomography images of the brain. CT scan images illustrate several findings in this patient over time. Column 1: the initial small subarachnoid hemorrhage (left column, with white arrows showing subarachnoid blood). Column 2: the diffuse cerebral edema seen during her acute presentation of lethargy and coma (2nd column), with arrows indicating edema-related effacement of the basal cisterns (top image), Sylvian fissure (second image), and cortical sulci (third image from top; compare with right column of images), and the asterisk indicating a small amount of subarachnoid hemorrhage. Column 3: contrast extravasation in a scan taken several hours after iodinated contrast was administered intravenously (arrows show deep and superficial locations of contrast material). Column 4: A repeat CT scan 7 days later showed complete resolution of edema.