

Overwhelming Leukoencephalopathy as the Only Sign of Neuropsychiatric Lupus

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ABSTRACT. We describe a patient with diffuse leukoencephalopathy, a rare central nervous system complication of systemic lupus erythematosus, who died of brain herniation despite aggressive management. Brain magnetic resonance imaging revealed diffuse white matter hyperintensities consistent with vasogenic edema. Autopsy revealed only widespread cerebral edema. Early recognition and persistent, aggressive treatment will be required to avoid this fatal and rare manifestation of neuropsychiatric lupus. (*J Rheumatol* 2005;32:1843–5)

Key Indexing Terms:

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AUTOANTIBODIES

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We describe a patient with systemic lupus erythematosus (SLE) who died with malignant intracranial hypertension and diffuse vasogenic edema. Although the incidence of central nervous system (CNS) involvement in patients with SLE — so-called neuropsychiatric SLE (NPSLE) — ranges from 18% to 69%¹, and the 5-year survival is 55% compared to 75% in those without neurological disease², the syndrome of diffuse leukoencephalopathy with massive cerebral edema is infrequently described^{1,3}.

CASE REPORT

A 38-year-old African American woman with SLE for 5 years had arthritis, a discoid rash, alopecia, Raynaud's phenomenon, positive antinuclear antibodies (ANA), leukopenia, and thrombocytopenia. She had no history of neurological disease. She had been treated with plaquenil for the previous 2 years and prednisone during a flare one year earlier. She was planning a pregnancy at the time of presentation and was taking no medicine.

She was admitted with severe headache and syncope. A head computerized tomographic (CT) scan revealed brain edema without hemorrhage or

infarct. Lumbar puncture showed an elevated opening pressure and cerebrospinal fluid (CSF) showed elevated protein without xanthochromia or pleocytosis. A CT angiogram showed no intracranial aneurysm, vasculopathy, or venous thrombosis. On the day after admission, she had another syncope episode characterized by initial slurred speech, followed by extensor posturing, fixed dilated pupils, and coma. Treatment with mannitol (50 g) reversed the coma, and within 20 minutes, she had a normal examination. Magnetic resonance imaging (MRI) of the brain showed diffuse T2 and fluid-attenuating inversion recovery (FLAIR) sequence hyperintensities that were nonenhancing on postgadolinium T1 images and involving the white matter bilaterally with sulcal effacement (Figure 1); diffusion-weight imaging was normal. Magnetic resonance venogram showed no cerebral venous thrombosis. Erythrocyte sedimentation rate was 29 mm/h and C-reactive protein < 0.3 mg/dl, but C3 and C4 complement had dropped to 54.9 and 5.0 mg/dl, respectively. ANA were strongly positive (1:2560 titer), but anti-double-stranded DNA was negative. Lupus anticoagulant and antiphospholipid antibodies were negative. CSF oligoclonal bands and JC virus by polymerase chain reaction were both negative. Magnetic resonance spectroscopy revealed a nonspecific elevation of choline and decrease of creatine peaks. Electroencephalogram showed normal organization and no seizure activity.

Over the next 3 days, she received pulse-dose corticosteroid (5 g over 3 days) and 3% hypertonic saline treatment, later changed to oral prednisone 60 mg qd and plaquenil 200 mg daily on Day 5. On hospital Day 7, she was discharged with a normal neurological examination, although repeat brain MRI showed persistence of severe edema.

One week after discharge, she had recurrent headaches and was suddenly unresponsive. She was admitted elsewhere with progressive herniation and expired within 48 h. Post mortem examination (limited to the brain) revealed uncal herniation and diffuse cerebral edema characterized by extensive perivascular pale eosinophilic fluid in the white matter, and nonspecific perivascular lymphocytic infiltration. This examination was remarkable for the absence of vascular hyalinization, petechial hemorrhages, microinfarcts, necrotizing vasculitis, and thrombotic microangiopathy (Figure 2).

DISCUSSION

This report describes a patient with a rare and malignant subtype of NPSLE who had a normal neurological examination followed by repeated episodes of syncope, obtunda-

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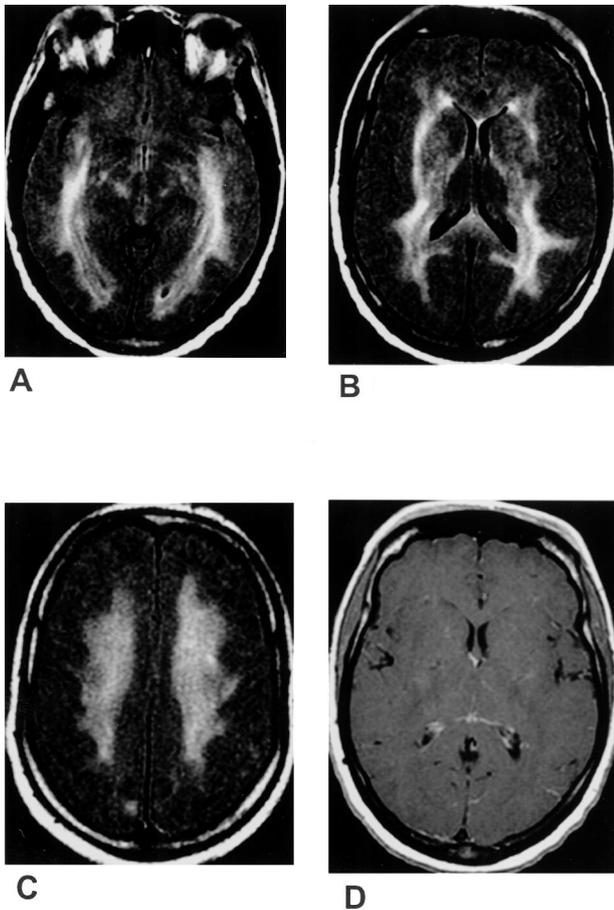


Figure 1. Panels A-C represent a FLAIR MRI sequence showing sulcal effacement and diffuse white matter hyperintensity. Panel D: gadolinium-enhanced T1 MRI showing no enhancement.

tion, and coma that were caused by intracranial hypertension and vasogenic edema. She had a rapid, albeit transient, beneficial response to aggressive treatment. Acute therapy for elevated intracranial pressure is critical in such patients. The mainstays of management are intensive monitoring for plateau waves, mannitol, hypertonic saline, and high-dose

corticosteroids to treat vasogenic edema. Prophylactic antiepileptic agents should also be considered, since a seizure in the setting of intracranial hypertension can precipitate brain herniation. In this patient, possibly more prolonged acute treatment for intracranial hypertension and brain edema (steroids and osmotherapy) could have prevented the subsequent fatal exacerbation.

In addition, when the course of disease is as malignant as in this patient, chronic immunosuppressive therapy might have been initiated early and maintained, despite the risk of complications. A recent randomized pilot trial in lupus patients with CNS disease found cyclophosphamide plus glucocorticoids improved outcomes and decreased disease activity compared to glucocorticoids or antimalarials alone⁴. Other potential immunotherapies might include plasmapheresis, intravenous immunoglobulin, azathioprine, mycophenolate, and methotrexate. Because of the diversity of CNS disease in lupus it is difficult to extrapolate confidently from observations in this study to the specific symptoms described in our patient.

On the MRI, there were striking bilateral, symmetric confluent nonenhancing white matter hyperintensities best appreciated on T2-weighted and FLAIR sequences. The differential diagnosis includes idiopathic intracranial hypertension and cerebral venous thrombosis. However, the diffuse MRI abnormalities and malignant course distinguish this patient from the former diagnostic possibility, and the normal magnetic resonance venogram and absent antiphospholipid antibodies discount the latter diagnostic possibility. Other differential diagnostic considerations like ischemic and inflammatory demyelination, or progressive multifocal leukoencephalopathy, were excluded, respectively, by the neuroimaging studies (in particular the diffusion-weight image) and from analysis of CSF, in which oligoclonal banding and JC virus were not found.

Isolated diffuse leukoencephalopathy in lupus has been rarely reported (Table 1): 2 patients with subacute cognitive decline^{5,6}; 3 others with probable idiopathic intracranial hypertension had hyperintense white matter lesions on

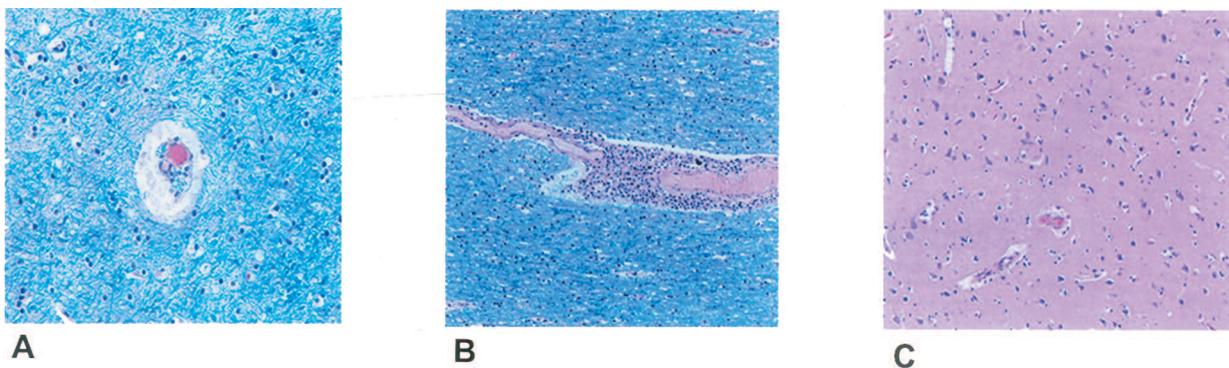


Figure 2. A. White matter shows nonspecific perivascular lymphocytic infiltrates (luxol fast blue, original magnification $\times 40$). B. Marked perivascular lymphocytic response in the white matter (luxol fast blue, original magnification $\times 20$). C. Cerebral cortex with a vessel surrounded by a clear area that suggests vasogenic edema (luxol fast blue, original magnification $\times 20$).

Table 1. Lupus patients with isolated diffuse leukoencephalopathy.

Patient	Age/Sex	Initial Presentation	Neuroimaging	Outcome
1 ¹¹	35 F	Headache, fever	CT: diffuse WM attenuation	Relapse in 6 mo
2 ⁶	56 F	Gradual cognitive decline	MRI: diffuse WM hyperintensities	Gradual improvement
3 ⁹	41 M	Headache, vertigo, papilledema	MRI: diffuse WM hyperintensities	Marked improvement
4 ¹⁰	47 F	Headache, mild R HP	MRI: diffuse WM hyperintensities	Marked improvement
5 ⁵	43 F	Gradual cognitive decline	MRI: diffuse WM hyperintensities; SPECT: diffuse hypoperfusion; cisternography: CSF resorption delay	Gradual improvement
6 ⁸	14 F	Headache, visual complaints	MRI: diffuse WM hyperintensities	Gradual improvement
7 ⁷	35 F	Headache, papilledema	MRI: diffuse WM hyperintensities; cisternography: CSF resorption delay	Gradual improvement
8 ¹²	33 F	Headache, nausea, vomiting, inattention	MRI: diffuse WM hyperintensities; SPECT: hypoperfusion	Death

HP: hemiparesis, CT: computed tomography, MRI: magnetic resonance imaging, SPECT: single photon emission computed tomography, WM: white matter.

FLAIR but benign outcomes⁷⁻⁹; and 2 with benign headache presentations^{10,11}. In all cases but one, the syndrome was reversible. In the other fatal case with similar MRI features, progressive herniation was cited as the cause of death¹². In none of these prior reports was neuropathology obtained. Previous autopsy cases of leukoencephalopathy involved deep gray structures and were complicated by prominent perivenous coagulation necrosis, thickened vein walls, and vacuolar demyelination^{13,14}.

Diffuse and severe vasogenic edema with perivascular lymphocytic infiltration was the sole histopathological finding in our patient. Leukoencephalopathy from brain edema is one of 4 different white matter pathologies described in NPSLE; the others are microinfarction, plaque-like demyelination, and vacuolar demyelination¹. Others have postulated that autoimmune disruption of CSF absorption leads to intracranial hypertension^{7,9}. Vascular endothelial growth factor (VEGF) and its receptors (VEGF-R) may be important in this process, mediating an increase in blood-brain barrier permeability via a nitric oxide-dependent pathway¹⁵. Serum concentrations of VEGF and VEGFR-1 have been shown to correlate directly with lupus disease activity; VEGFR-2 levels have an inverse correlation¹⁶.

CNS lupus has myriad presentations. While uncommon, the syndrome of diffuse malignant leukoencephalopathy needs to be recognized as a subtype of NPSLE and treated aggressively.

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