

Initial Presentation of Systemic Lupus Erythematosus Masquerading as Bacterial Meningitis

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Neuropsychiatric manifestations of systemic lupus erythematosus (SLE) are well documented and recently reviewed.¹⁻⁵ As many as 14% to 75% of patients with SLE eventually develop various degrees of neuropsychiatric manifestations.⁴ It is relatively rare, however, for patients with SLE to have such manifestations initially. According to a retrospective study of 140 patients with SLE, only 5 patients (3%) initially had neuropsychiatric manifestations, and only 1 patient initially had aseptic meningitis.¹ Searching through MEDLINE, we were able to find only 10 cases of SLE-related aseptic meningitis from 1966 to 2000.⁶⁻¹³ We describe a case of SLE-related aseptic meningitis with fever, headache, neck rigidity, and laboratory findings otherwise typical of pyogenic meningitis.

Case Report

A 22-year old woman came to her physician complaining of acute onset of fever, headache, and blurry vision of 3 days' duration. Her history was notable for mild anemia since her last pregnancy 18 months earlier. She also complained of intermittently aching joints for 6 weeks. She had chronic back pain resulting from an injury of the lumbar spine 3 years earlier, for which she took propoxyphene and hydrocodone infrequently. When examined, she was an alert, oriented, but ill-looking woman. Her temperature was 104.9°F. There were multiple small and discrete cervical and axillary lymph nodes, the largest of which measured 1.5 cm. Her pupils were equal and reactive to light and accommodation. The extraocular movements of both eyes were intact. Horizontal nystagmus was

observed bilaterally. There was considerable nuchal rigidity and a positive Kernig sign. She had no skin rash or evidence of arthritis or joint deformities. There was no hepatosplenomegaly.

She was admitted to the hospital. Laboratory studies disclosed a white cell count of 8,400/ μ L, with 89% segmented neutrophils and 9% lymphocytes. The hemoglobin was 8.4 g/dL, and mean corpuscular volume was 81/ μ m³. Platelet count was 447,000/ μ L. Serum creatinine was 0.7 mg/dL, albumin 3.1 g/dL, and bilirubin 0.4 mg/dL. Serum alkaline phosphatase and liver transaminase values were within normal limits. Serum iron was less than 2 μ g/dL (normal 35–145 μ g/dL), and total iron-binding capacity was 253 μ g/dL (normal 250–400 μ g/dL). Serum ferritin was 643 ng/mL (normal 20–120 ng/mL). Prothrombin and activated partial thromboplastin times were normal. Urinalysis showed normal findings without casts, proteinuria, or leukocytes. A computerized tomograph of the brain was unremarkable. Cerebrospinal fluid analysis disclosed a white cell count of 975/ μ L and an erythrocyte count of 25/ μ L with 90% neutrophils. Cerebrospinal fluid protein and glucose levels were 465 mg/dL and 18 mg/dL, respectively.

In view of the possibility of bacterial meningitis, the patient was given ceftriaxone and ampicillin empirically. Cerebrospinal fluid studies were negative for group B streptococcus, pneumococcus, meningococcus, *Haemophilus*, and *Cryptococcus* antigens. All the blood, urine, and cerebrospinal fluid cultures for bacteria, acid-fast bacilli, and fungus were negative. Tests for antinuclear antibodies and human immunodeficiency virus 1 and 2 antibodies were negative. High swinging fever, headache, and nuchal rigidity persisted despite therapy. Doxycycline was also added after learning that the patient's dog recently died possibly of ehrlichiosis. Excisional biopsy of an axillary lymph node showed granulomatous lymphadenitis. Special staining for fungi and acid-fast bacilli was negative. The patient

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refused second lumbar puncture and left the hospital against medical advice 1 week later.

She returned to the hospital 2 days later with a high fever and general malaise. Laboratory studies at admission disclosed the following: her alkaline phosphatase was elevated to 715 IU/L, gamma-glutamyltransferase to 1,023 IU/L, alanine aminotransferase to 149 IU/L, and aspartate aminotransferase to 294 IU/L. Findings on a computerized tomographic scan of her body were unremarkable; there were no lung or liver lesions, nor was there any abdominal lymphadenopathy. In view of the lymph node biopsy showing granulomatous changes, empiric antituberculous therapy was started, but there was no response. A test for angiotensin-converting enzyme level was normal. Magnetic resonance imaging of the brain showed a nonspecific increase in T2-weighted signals in the periventricular areas. A repeat cerebrospinal fluid analysis showed a white cell count of 2/ μ L and an erythrocyte count of 11/ μ L. Cerebrospinal fluid protein and glucose levels were 217 mg/dL and 24 mg/dL, respectively.

Three days later she became confused and obtunded. An empiric trial of methylprednisolone, 100 mg every 8 hours, was given. The fever and mental condition improved drastically within 24 hours. A repeat antinuclear antibody test was positive at a titer of 1:5120 and anti-double-stranded DNA was positive at 1:160. Tests for anti-extractable nuclear antigens, antinuclear cytoplasmic, and antiphospholipid antibodies were negative. The patient was released from the hospital with a slowly tapering dose of prednisone. Her neurologic symptoms completely resolved. She stopped coming in for follow-up visits after 9 months. At her last clinic visit, she was asymptomatic and without any manifestations of SLE.

Discussion

Neuropsychiatric manifestations in patients with SLE have been reviewed recently.^{1,3-5} The common manifestations include, in order of frequency, cognitive dysfunction, dementia, altered consciousness, psychosis, generalized or focal seizures, strokes, and cranial and peripheral nerve palsies. These manifestations are for the most part secondary to infections or complications of therapy and, to a lesser extent, directly caused by the lupus disease. The latter is possibly mediated by a combination of

mechanisms, such as antineuronal antibody,¹⁴ antiphospholipid antibodies, immune complex-mediated vasculitis, and cytokines.

Infective meningitis has frequently been reported, usually as a complication of prolonged steroid and other immunosuppressive therapy in patients with SLE. Uncommon causative agents, such as *Cryptococcus*, aspergillus, mycobacterium, and *Neocardia*, have been reported not infrequently. Interestingly, a recent case of cryptococcal meningitis was reported at the initial diagnosis of SLE, underscoring the intrinsic immunologic defects of SLE.¹⁵

Aseptic meningitis has been reported in patients with SLE. Most of these cases are associated with drugs. Thorough reviews on drug-induced aseptic meningitis have been published recently.^{16,17} The incidence of drug-induced aseptic meningitis, a diagnosis of exclusion, is unknown. The clinical signs and cerebrospinal fluid findings vary widely. Many drugs have been implicated in causing drug-induced aseptic meningitis, and major categories, excluding intrathecal drugs that cause meningeal irritation, include nonsteroidal anti-inflammatory drugs (NSAIDs), antimicrobials (especially sulfa drugs), intravenous immunoglobulins, and OKT3 monoclonal antibodies. Among the NSAIDs, ibuprofen is the most frequently cited drug in patients both with SLE and without SLE.¹⁶ The pathogenetic mechanism of drug-induced aseptic meningitis is not fully understood. It is generally believed to be an immunologic hypersensitivity reaction; hence, patients with SLE have an underlying immune dysfunction and are more susceptible to the development of drug-mediated antibodies and immune complexes. The medications that our patient took before admission have not been reported to cause aseptic meningitis.

Aseptic meningitis primarily caused by SLE is very uncommon. Only 10 identified cases have been reported in the literature.⁶ These case reports are summarized in Table 1. Only four cases were diagnosed at the initial diagnosis of SLE. The cerebrospinal fluid findings varied widely, with white cell counts ranging from 14/ μ L to 874/ μ L and protein ranging from 21 to 293 mg/dL. Seven of the 10 cases showed predominantly lymphocytes in the cerebrospinal fluid (data not shown). Although spontaneous remission occurred in three of the cases, most of the patients who were given steroids responded.

Table 1. Case Reports of Aseptic Meningitis Directly Related to Systemic Lupus Erythematosus (SLE).

Case	Sex/Age (years)	SLE Diagnosed	Cerebrospinal Fluid Study			Serum ANA	Treatment
			WBC/ μ L	Protein mg/dL	Glucose mg/dL		
Keeffe et al ⁶	F/14	1 month	344	127	61	Positive	Prednisone with prompt response
Canoso & Cohen ⁷	F/17	3 years	31	104	65	NR	No treatment initially. Given prednisone at recurrence 2 months later with response
Canoso & Cohen ⁷	M/29	None	64	36	55	NR	Spontaneous remission without therapy. One year later, developed seizures
Canoso & Cohen ⁷	F/22	None	119	56	50	NR	Spontaneous remission without therapy and at recurrence 5 years later
Finelli et al ⁸	M/61	None*	801	212	55	Negative	Prompt response to prednisone
Welsby & Smith ⁹	M/54	3 years	150	†	NR	Positive	Prompt response to hydrocortisone
Sands et al ¹⁰	M/22	None	874	58	55	NR	Spontaneous remission without therapy. Transverse myelitis 3 months later
Lancman et al ¹¹	F/45	7 years	140	311	7	Positive	Not reported
Kanekura et al ¹²	F/46	8 years	14	21	39	Positive	Prompt response to methylprednisolone
Neumann-Anderson & Lindgren ¹³	M/28	15 years	780	293	NR	NR	Initial response to steroid. Developed transverse myelitis 2 months later
Dong et al	F/22	None	975	465	18	Positive	Prompt response to methylprednisolone

F—female, M—male, WBC—white cell count, ANA—antinuclear antibodies, NR—not reported.

*Treated as polymyalgia rheumatica for 2 months.

†Reported as 1,000 mmol/L (normal, < 700 mmol/L).

In our patient, the clinical signs and symptoms and cerebrospinal fluid findings, namely, markedly elevated protein, exceedingly low glucose levels, and high white cell counts with predominantly neutrophils, were typical of bacterial meningitis. All the cultures were negative, however, and the disease did not responded to antibiotics in our patient. The cerebrospinal fluid findings and the prompt response to steroids make viral meningitis very unlikely. The eye and magnetic resonance imaging findings, although nonspecific, have been reported in the patients with SLE.^{18,19} The cause of the moderately elevated liver transaminase levels during readmission is uncertain, because liver biopsy was not performed, although they were most likely due to autoimmune hepatitis. The serum ferritin was elevated probably as an acute phase reactant. The initial negative antinuclear antibody result is intriguing and is most likely due to laboratory error or prozone phenomenon caused by the extremely high titer.²⁰

In conclusion, SLE should be considered in differential diagnosis of meningitis with sterile cultures that fails to respond to antibiotics. An initial

negative antinuclear antibody titer does not exclude the possibility of SLE because false-negative results can occur.

References

1. Feinglass EJ, Arnett FC, Dorsch CA, Zizic TM, Stevens MB. Neuropsychiatric manifestations of systemic lupus erythematosus: diagnosis, clinical spectrum, and relationship to other features of the disease. *Medicine* 1976;55:323–9.
2. Sergeant JS, Lockshin MD, Klempner MS, Lipsky BA. Central nervous system disease in systemic lupus erythematosus. Therapy and prognosis. *Am J Med* 1975;58:644–54.
3. Wong KL, Woo EK, Yu YL, Wong RW. Neurological manifestations of systemic lupus erythematosus: a prospective study. *Q J Med* 1991;81:857–70.
4. West SG. Lupus and the central nervous system. *Curr Opin Rheumatol* 1996;8:408–14.
5. McLean BN. Neurological involvement in systemic lupus erythematosus. *Curr Opin Neurol* 1998;11:247–51.
6. Keeffe EB, Bardana EJ, Harbeck RJ, Pirofsky B, Carr RI. Lupus meningitis. Antibody to deoxyribonucleic acid (DNA) and DNA:anti-DNA complexes

- in cerebrospinal fluid. *Ann Intern Med* 1974;80: 58–9.
7. Canoso JJ, Cohen AS. Aseptic [sic] meningitis in systemic lupus erythematosus. Report of three cases. *Arthritis Rheum* 1975;18:369–74.
8. Finelli PF, Yockey CC, Herbert AJ. Recurrent aseptic meningitis in an elderly man. Unusual prodrome of systemic lupus erythematosus. *JAMA* 1976;235: 1142–3.
9. Welsby P, Smith C. Recurrent sterile meningitis as a manifestation of systemic lupus erythematosus [sic]. *Scand J Infect Dis* 1977;9:149–50.
10. Sands ML, Ryczak M, Brown RB. Recurrent aseptic meningitis followed by transverse myelitis as a presentation of systemic lupus erythematosus. *J Rheumatol* 1988;15:862–4.
11. Lancman ME, Mesropian H, Granillo RJ. Chronic aseptic meningitis in a patient with systemic lupus erythematosus. *Can J Neurol Sci* 1989;16:354–6.
12. Kanekura T, Mizumoto J, Setoyama M. A case of lupus meningitis treated successfully with methylprednisolone pulse therapy. *J Dermatol* 1993;20: 566–71.
13. Neumann-Andersen G, Lindgren S. Involvement of the entire spinal cord and medulla oblongata in acute catastrophic-onset transverse myelitis in SLE. *Clin Rheumatol* 2000;19:156–60.
14. Tishler M, Alosachie I, Chapman Y, et al. Anti-neuronal antibodies in antiphospholipid syndrome with central nervous system involvement: the difference from systemic lupus erythematosus. *Lupus* 1995;4:145–7.
15. Mok CC, Lau CS, Yuen KY. Cryptococcal meningitis presenting concurrently with systemic lupus erythematosus. *Clin Exp Rheumatol* 1998;16:169–71.
16. Moris G, Garcia-Monco JC. The challenge of drug-induced aseptic meningitis. *Arch Intern Med* 1999; 159:1185–94.
17. Jolles S, Sewell WA, Leighton C. Drug-induced aseptic meningitis: diagnosis and management. *Drug Saf* 2000;22:215–26.
18. Keane JR. Eye movement abnormalities in systemic lupus erythematosus. *Arch Neurol* 1995;52:1145–9.
19. Stimmler MM, Coletti PM, Quismorio FP Jr. Magnetic resonance imaging of the brain in neuropsychiatric systemic lupus erythematosus. *Sem Arthritis Rheum* 1993;22:335–49.
20. Koller SR, Johnston CL Jr, Moncure CW. Lupus erythematosus cell preparation-antinuclear factor incongruity. A review of diagnostic tests for systemic lupus erythematosus. *Am J Clin Pathol* 1976;66:495–505.