Chronic meningitis in systemic lupus erythematosus: An unusual etiology

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Abstract

Chronic aseptic meningitis is a rare manifestation of systemic lupus erythematosus (SLE). Apart from immunological causes and drugs, the aseptic meningitis group can include some unidentified viral infections that cannot be detected by routine microbiological testing. It is imperative to do complete cerebrospinal fluid (CSF) workup before implicating the symptoms to disease activity or drugs, as untreated infections cause significant mortality in SLE. We present a case of young female with SLE who presented with chronic meningitis of an uncommon etiology.

Key Words

Herpes simplex virus, HSV-2, lupus, meningitis, systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease that can produce a wide range of neurological complications. Meningitis is not a common entity in patients with SLE and has been reported in 1.4-1.6% of studied cohorts (retrospective analysis of ~1400 SLE patients).[1,2] Aseptic meningitis accounts for 40-45% of the meningitis group.[1,2] It includes those patients whose cerebrospinal fluid (CSF) examination yields a typical "aseptic meningitis" picture (CSF pleocytosis > 5 cells/mm,[3] predominantly lymphocytic, no organisms on gram/acid fast /India ink stain, negative bacterial/mycobacterial/fungal cultures, negative polymerase chain reaction (PCR) for *Mycobacterium tuberculosis*, negative latex agglutination tests for bacterial antigens, normal or elevated protein concentration, normal or reduced glucose concentration).[1-3] Inevitably, there is some overlap between aseptic and septic meningitis clinically, making it essential to exclude conventional and opportunistic organisms. Further, aseptic meningitis is a conundrum with varying causes including immunological drugs and unidentified infections. It is imperative to do complete CSF workup before implicating the symptoms to disease activity or drugs, as untreated infections cause significant mortality in SLE.[1] We present, a case of young female with SLE who presented with chronic meningitis of an uncommon etiology.

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Case Report

A 30-year-old lady with a diagnosis of SLE, on oral prednisolone (10 mg OD) and hydroxychloroquine (400 mg OD) since 2 years, presented with a progressive neurological illness of 8 months duration. The illness heralded with holocranial-throbbing headache associated with photophobia and phonophobia. She also had history of intermittent fever (up to 103°F) with occasional chills and rigors for last 6 months. There was a history of slowly progressive painless diminution of vision in both eyes 4 months prior to admission. There was worsening in form of persistent vomiting for last 2 months along with reduced appetite and loss of weight. Examination was remarkable for pallor, neck stiffness and bilateral papilledema. Her visual acuity was 20/30 bilaterally using the Rosenbaum vision-screening chart. Confrontation testing revealed peripheral constriction of the visual fields. Rest of the general physical, neurological and systemic examination was normal. On investigations, she had bicytopenia {hemoglobin 80 g/L (8 g/dL), platelet count 76 × 10^9/L, WBC count 6.1 × 10^9/L}, low C3 levels {0.4 g/L (normal: 0.9-1.80 g/L)} and positive anti-double strand DNA antibodies.

Initial CSF analysis showed no cells, normal protein and low glucose {1.9 mmol/L (34 mg/dl), CSF/serum glucose ratio = 0.34}. CSF bacterial and fungal cultures, PCR for tuberculosis, VDRL, India ink staining and cryptococcal antigen test were negative and CSF adenosine deaminase (ADA) levels were 3 IU/L (normal <10 IU/L). The cranial MRI and MR venography were unremarkable. Contrast enhanced CT scan of chest and abdomen showed abdominal lymph adenopathy. Fine needle aspiration from these nodes revealed reactive lymphadenitis. Considering her diagnosis to be immune mediated aseptic meningitis, the dose of oral prednisolone was increased to 60 mg OD. This led to symptomatic improvement for 5 days but later there was worsening with increasing headache and vomiting. She was empirically started on anti-tubercular treatment (ATT) (isoniazid 300 mg, rifampicin 450 mg, pyrazinamide 1250 mg, ethambutol 800 mg, pyridoxine 20 mg daily) and dexamethasone 8 mg IV, 8 hourly, which led to transient symptomatic improvement for 4 days, after which her meningitic symptoms reappeared. A repeat CSF examination was conducted 10 days after the first CSF, which revealed 10 cells/μl, all lymphocytes, raised protein (2.39 g/L), low glucose {1.8 mmol/L (33 mg/dl), CSF/serum glucose ratio = 0.14} and adenosine deaminase of 7 IU/L. CSF was negative for cytomegalovirus (CMV) and Epstein-Barr virus (by PCR). Qualitative real time PCR was positive for HSV-2 DNA. ATT was stopped (received for a total of 10 days) and she was administered acyclovir 500 mg (10 mg/kg) IV 8 hourly for 14 days. Prednisolone was tapered off to 10 mg daily dosage. Her headache and fever subsided and vision improved (to 20/20 bilaterally) over the next 2 weeks. At 3-month follow-up visit patient was free of all symptoms and signs of chronic meningitis.

Discussion

SLE is an autoimmune disease with diverse clinical features and can inflict the nervous system by multiple mechanisms. Common manifestations include cerebrovascular disease and seizures with a cumulative incidence of >5%.[4] Aseptic meningitis, cognitive dysfunction, acute confusional state, peripheral nervous system disorders, major depression and psychosis are relatively uncommon. Secondary CNS syndromes, either iatrogenic (drug related complications), related to immune dysfunction (eg intracranial infection) or other organ dysfunction (eg hypertension secondary to lupus nephritis) are equally important and in fact close mimickers of neuropsychiatric lupus.[5,6]

This patient's presenting symptom was persistent headache, which was later followed by more ominous symptoms like fever, intractable vomiting and visual decline. The syndromic diagnosis of this patient was that of chronic meningitis with features of raised intracranial pressure and the differential diagnosis included aseptic versus septic meningitis. Intracranial space occupying lesion was excluded by the normal brain imaging.

It is pertinent to mention here that the diagnosis of septic meningitis is not always straightforward. Distinction from aseptic meningitis based on clinical manifestations alone is difficult. While lymphopenia, steroid use, chronic damage and systemic activity of SLE are common to both kinds of meningitis,[2] altered mental status, plasma leukocytosis, neutrophilia, and CSF pleocytosis with hypoglycorrhachia are more prominent in patients with septic meningitis.[1] As this patient's workup was negative for bacterial, mycobacterial and fungal causes, initially a possibility of aseptic meningitis due to immunological damage by the disease itself was thought of. CNS tuberculosis was also considered due to the high endemicity of this disease in this part of the world. When the patient worsened despite hiking of immunosuppressants and starting of anti-tubercular therapy, lumbar puncture was repeated, which revealed HSV-2 DNA positivity by real-time PCR study. The initial improvement of the patient with the anti-inflammatory and later anti-tubercular treatment and dexamethasone may be due to some decrease in the raised intracranial pressure due to corticosteroids (meningitis causes vasogenic edema and corticosteroids lower intracranial pressure in vasogenic edema through their beneficial effects on blood vessel permeability).

Thus, the diagnosis of HSV-2 meningitis and appropriate treatment were delayed because the initial CSF profile was inconclusive and the course of infection was atypical for HSV 2, perhaps because the patient was on prednisolone. The issue of reactivation of latent HSV 2, as a bystander (coinfection), in the setting of an immunocompromised status was also considered. However, rapid improvement of the patient's condition after initiation of anti-viral treatment argues effectively in the favor of HSV-2 as the cause of meningitis.

Herpes simplex virus-2 (HSV-2) typically causes mucocutaneous disease, encephalitis, and acute or benign recurrent meningitis. Many case series have analyzed the etiology of CNS infections in SLE patients,[1,2,7-10] but none reported HSV as a causative agent. *Cryptococcus neoformans* and *M. tuberculosis* were the most common etiologic agents found. While HSV-2 has not been reported as a cause of chronic meningitis in SLE, this has been reported in non-SLE patients.[11]

HSV-2 infection is usually seen in those immunocompromised hosts, who have impaired T lymphocyte/macrophage mediated cell immunity.[12] SLE patients are known to have functional alteration of phagocytic cells and cellular immunity defects with lymphopenia, CD4 lymphocytopenia and reduced cytokine production.[12] Use of corticosteroids and other immunosuppressive agents further increases the risk of infection.

Of note, CSF pleocytosis may be absent especially early in the course of CNS infection.[1] A repeat lumbar puncture is the most effective way to determine the nature of disease process if the suspicion of infection is high and the patient is not responding to initial treatment. The workup should include a thorough search for conventional and atypical organisms through nucleic acid amplification tests and cultures.

To conclude, the learning points from this case are

1. Infection is a close mimicker of neuropsychiatric SLE.
2. The slightest suspicion of CNS infection should entail a proactive approach for a spinal tap and dedicated CSF analysis.
3. HSV-2 should be considered as a cause in the work up of aseptic meningitis in SLE.

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