



CASE REPORT

Can Aseptic Meningitis Present With Very High CSF Protein?

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Introduction

Cerebrospinal fluid (CSF) analysis commonly is performed to evaluate disease of the central nervous system (CNS). Protein concentration in the CSF varies with the type and degree of pathology in the CNS. Elevated CSF protein above 0.4 g/l and up to 4.5 g/l has been reported in viral and bacterial infections, intracranial hemorrhages, multiple sclerosis, Guillain Barre syndrome, malignancies, and inflammatory disease of the CNS.¹ On the other hand, very high levels above 4.5 g/l usually are seen only in suppurative bacterial meningitis and CNS malignancy.¹⁻³

Aseptic meningitis refers to cases with the clinical picture of meningitis and a CSF analysis revealing slightly elevated white blood cell count, usually lymphocytes, a slightly elevated protein level, and normal to slightly decreased glucose level. The CSF in these cases is with absence of bacterial or fungal colonies. We report a case of a patient with the clinical picture for aseptic meningitis except for a CSF protein above 5 g/l. Clinicians should be aware that in rare situations very high CSF protein can be seen in self-limiting aseptic meningitis.

Case Report

A 26-year-old male presented to the emergency department complaining of a severe generalized and pounding headache that started suddenly. He also reported associated abdominal pain, nausea, and vomiting. On physical examination, his vital

signs (blood pressure, pulse, and temperature) were normal. He was obtunded and had a depressed level of consciousness, but was arousable, responsive, oriented to time, person, and situation, withdrew to pain, and followed orders precisely. He had no focal motor deficits, no Babinski signs, and no limb ataxia. He had normal deep tendon reflexes. His cranial nerves were intact and his fundi were normal. His examination was pertinent for neck stiffness. Examination of the lungs, heart, and abdomen was normal. In view of these findings, the patient was suspected to be suffering from meningitis.

Routine CSF studies (cell count, protein, and sugar) are detailed in Table 1. CSF gram stain and culture for bacteria, mycobacterium, and fungal species were negative. Ziehl-Neelsen stain was negative. CSF cytology revealed numerous lymphocytes and macrophages, but no malignant cells. CSF PCR for human immunodeficiency virus (HIV 1 and 2), herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) were negative. No oligoclonal bands were detected.

Blood studies revealed an elevated white blood cell (WBC) count of 14,400 with lymphocyte predominance. His chemistry studies, including an amylase and lipase, were normal. His blood glucose was 98 mg/dl. Malaria smear was negative. Blood cultures did not grow any organism after five days of incubation. Carcino-embryonic

antigen (CEA) was 1.2 ng/ml and erythrocyte sedimentation rate (ESR) was 6 mm/hr. Urine analysis was normal. Other

serum studies were performed and were negative or normal (Table 2).

Table 1. CSF results during the patient's hospitalization.

| Date | Glucose (mg/dl) CSF / serum | Protein (g/l) CSF / serum | Cell count WBC/RBC | % Lymphocytes | % Monocytes |
|--------|--------------------------------|------------------------------|-----------------------|---------------|-------------|
| Day 1 | 25 / 96 | 4.45 / 36 | 3544 / 306 | 77 | 23 |
| Day 2 | 39 / 102 | 5.15 / 44 | 2880 / 43 | 92 | 8 |
| Day 8 | 41 / 104 | 2.03 / 39 | 350 / 30 | 80 | 20 |
| Day 13 | 43 / 101 | 1.27 / 41 | 174 / 2 | 96 | 4 |

Table 2. Serum tests performed and the results.

| Test | Results |
|--|-------------|
| Antinuclear antibodies (ANA) | Negative |
| Anti-neutrophil cytoplasmic antibodies | Negative |
| Angiotension converting enzyme (ACE) | Negative |
| Anti-cardiolipin antibodies | Negative |
| C3 & C4 complement levels | Normal |
| HIV 1 & 2 antibodies | Negative |
| Cryptococcus | Nonreactive |
| VDRL | Nonreactive |
| Brucella | Normal |
| Salmonella | Normal |
| Trypanosoma-brucei antibodies | Normal |
| Trypanosoma-cruzi antibodies | Normal |
| Flavivirus | Normal |
| West Nile virus | Normal |

Magnetic resonance imaging of the brain revealed leptomeningeal enhancement, but no evidence for pachymeningitis. Computed tomography of the chest, abdomen, and pelvis was normal.

The patient remained in the hospital for two weeks during which he gradually improved with decrease in the headache and lethargy and improvement in his level of consciousness and general well-being without any medical therapy.

Discussion

Cerebrospinal fluid analysis (CSF) analysis is an important step in the diagnosis

of central nervous system diseases. An elevated CSF white blood cell count is seen in infectious and inflammatory conditions. A protein level which rises in infectious, inflammatory, demyelinating, and malignant conditions usually reflects the disease process, and it may be elevated falsely by the presence of red blood cells (RBC) in a hemorrhagic tap.¹ The latter can be corrected by subtracting 1 mg/dl (0.01 g/l) of protein for every 1000 RBC/mm³.

A CSF protein level of 0.4 - 22.0 g/l has been reported in bacterial infections, 0.3 - 3.1 g/l in cryptococcal infections, and 0.2 - 11.4 g/l in tuberculosis meningitis.^{1,3,4} The

CSF protein level in brain tumors, whether primary or metastatic, has been reported between 0.15- 19 g/l.^{1,3} In leptomeningeal metastasis, the CSF protein is elevated in 80% of the cases with a median concentration of 1 g/l.⁴ Brain abscesses may raise the CSF protein between 0.16 - 2.88 g/l.¹ In demyelinating CNS disease, the CSF protein level rises to 0.13 - 1.33 g/l.^{1,3} Cerebral trauma and seizure disorder may raise the protein level to 0.1 - 2.0 g/l.

The blood-CSF barrier is a physical barrier consisting of different anatomical structures for the diffusion and filtration of molecules from the serum to the CSF. Elevated CSF protein can be either secondary to local synthesis of protein within the CNS, or impaired resorption of the CSF protein by the arachnoid villi, or increased entry of plasma proteins due to increased permeability of the blood brain barrier.³ The comparison of the CSF to serum protein usually reflects the type of pathology.

A significant increase in CSF protein level is seen in bacterial meningitis in comparison to viral meningitis.⁴ In viral or aseptic meningitis, the CSF glucose is

normal or low, the protein level is normal to elevated, the WBC count is elevated, and bacterial cultures are negative. The level of protein in these cases is usually between 0.1 - 4.0 g/l.^{1-3,5,6} In the majority of cases, no definite diagnosis is reached, and patients are labeled to have aseptic meningitis. No definite etiology usually is found in 75% of patients labeled to have aseptic meningitis.^{7,8} There are no reports in the literature whereby the CSF protein was above 4 g/l in cases of aseptic meningitis.⁹

The interesting aspect of this case was that the patient had elevated CSF WBC count, significantly elevated CSF protein, and significantly low sugar, absent bacterial cultures and viral PCRs, and spontaneous normalization of these results with no treatment. This picture is suggestive of aseptic meningitis rather than infectious meningitis and alerts clinicians to accept these CSF findings in certain cases of aseptic meningitis. Clinicians in general and neurologists in particular should be aware that, in exceptional cases, aseptic meningitis could present with very high levels of CSF protein up to 5 g/l.

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