Neutrophilic Pleocytosis in Cerebrospinal Fluid: Adult-onset Still’s Disease

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Abstract

We describe a unique patient whose clinical and laboratory findings fulfill diagnostic criteria of adult onset Still’s disease and at the same time, this case was complicated by aseptic meningitis with neutrophilic pleocytosis in cerebrospinal fluid, as well as sensorineural hearing loss. The symptoms of the patient improved greatly with prednisolone therapy. Some studies in the literature suggest that this disease may lead to aseptic meningitis with neutrophilic pleocytosis. (Internal Medicine 42: 1039-1041, 2003)

Key words: adult-onset Still’s disease, aseptic meningitis, neutrophilic pleocytosis

Introduction

Adult-onset Still’s disease (AOSD), a systemic inflammatory disease which mimicks an infectious disease and is characterized by a high-grade fever, arthralgias, transient rash, hepatosplenomegaly, lymphadenopathy, and leukocytosis with neutrophilia (1). The diagnosis of AOSD is based on clinical findings that eliminate other diseases which may explain this clinical picture (2). Central nervous system involvement such as aseptic meningitis and sensorineural hearing loss in AOSD are rarely seen (3–5). To our knowledge, to date aseptic meningitis due to AOSD has been reported in eight patients (two episodes in one) and sensorineural hearing loss in only one patient (6–11).

Here, we describe a unique patient whose clinical and laboratory findings fulfill the criteria for a diagnosis of AOSD and whose course was complicated by aseptic meningitis and sensorineural hearing loss.

Case Report

A previously healthy 35-year-old female who had a history of fever, chill, weakness, and polyarthritis for 45 days, and unconsciousness for 2 days was admitted to the hospital. Physical examination revealed abnormal mentation, neck stiffness, transient macules and papules on the trunk emerging with fever. Arthritis was not noted, but she reported an arthralgia of 45 days. Fever was 39.1°C on admission, during the follow-up, it followed an intermittent course. Additionally, she developed hearing loss on the 14th day of hospitalization. Laboratory studies disclosed the following: erythrocyte sedimentation rate (ESR), 100 mm/h; C-reactive protein (CRP) level, 5 mg/dl (normal<0.5); white blood cell (WBC) count, 21.6x10³/l (90% neutrophil, 7% lymphocyte, 3% monocyte); AST, 47 U/l; ALT, 62 U/l; ferritin, 132 ng/ml (normal range 20–220) and negative PPD reaction, negative antinuclear antibodies (ANA) and negative rheumatoid factor (RF). Magnetic resonance imaging of the head, computed tomography of chest and abdomino-pelvic region revealed no abnormalities.

Analysis of cerebrospinal fluid (CSF) showed a high opening pressure (550 mm of H₂O), elevated WBC count (80/mm³) with mixed cellular response (62% neutrophil, 26% monocyte, 12% lymphocytes) and normal glucose and protein level.

The repeated examination at 10 days revealed similar findings. Acid-fast, Gram, and Indian ink staining and culture of CSF were negative. Six additional blood cultures remained negative. Serological tests for Lyme disease, brucellosis, syphilis and infections with Epstein-Barr virus, cytomegalovirus, herpes simplex virus, parvovirus B19, mumps virus, and human immunodeficiency virus were negative. Audiogram performed on the 18th day showed

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sensorineural hearing loss (52 dB for left ear; 55 dB for right ear).

A diagnosis of AOSD complicated by aseptic meningitis was made according to both the criteria for classification of AOSD that were defined by Yamaguchi et al (2) and also, the exclusion of similar underlying diseases. The present patient has 4 major (fever, arthralgia, typical rash, leukocytosis) and 2 minor criteria (negative RF and ANA, and mild liver dysfunction). She was initially treated with indomethacin. After sensorineural hearing loss developed, indomethacin therapy was switched to prednisolone (64 mg/day). She became asymptomatic and her fever resolved within 3 days. The dose of prednisolone was decreased to 32 mg/day and methotrexate (7.5 mg/week) was added to the therapy because of major organ involvement and hearing loss (12). She did not accept another control CSF analysis. In addition, audiometric control performed on the 40th day showed almost normal findings in both ears (27 dB for left ear; 27 dB for right ear). At a 3-year follow-up, she was asymptomatic and ESR, CRP and WBC count normalized.

Discussion

Central nervous system involvement is not a rare complication of AOSD. Different manifestations of the central nervous system in AOSD have been reported as follows: brain stem hemorrhage, seizures with fatal status epilepticus, transient cranial nerve paralysis, transient pyramidal tract signs, transient ptiosis and ophthalmoplegia associated with an inflammatory orbital pseudotumor, sensorineural hearing loss, aseptic meningitis, meningoencephalitis and encephalopathy (3-11). The prevalence of central nervous system involvement in AOSD has been reported as follows: there was no specific time during the disease course at which either complication was observed (6-11). The present case is unique in that uncommon forms of central nervous system involvement were simultaneously present early in the course of AOSD. Considering our patient and a review of the previously reported cases, the neutrophilic pleocytosis in almost all (9/10) of the cases with aseptic meningitis was due to AOSD.

We have measured the ferritin level as normal. In a series from Japan, 82% (28/34) of the patients have an increased level of ferritin (13). During the last 18 years, we have followed 20 patients with AOSD admitted with fever of unknown origin (excluding the present patient). Ferritin levels were measured in 16 and were higher in 14 (88%) (mean: 1,871±1,685 mg/dl, range: 102-5,000, normal range: 20-220) (14).

Despite microbiological studies, we could not find any relationship between aseptic meningitis and infectious diseases. We believe that the cause of neutrophilic pleocytosis was aseptic meningitis due to AOSD (6-8), so we did not start the patient on any antimicrobial therapy. The CSF findings of the other 8 patients and the present case are shown in Table 1. These CSF findings show that aseptic meningitis was due to AOSD is most often associated with a mixed cellular response and neutrophilic pleocytosis in CSF. Glucose in CSF is usually normal and protein is elevated. Other causes of neutrophilic pleocytosis with mixed cellular response are partially treated bacterial meningitis, syphilitic meningitis, Lyme disease, leptospiral meningitis, early viral or granulomatous meningitis, and non-infectious causes such as seizures, carcinomatous meningitis, drug-induced meningitis.

Table 1. CSF Findings of the Patients with Aseptic Meningitis Due to AOSD.

<table>
<thead>
<tr>
<th>Case (Reference)</th>
<th>Age/ Sex</th>
<th>WBC count (/mm³ in CSF (differential cell count)</th>
<th>Total protein in CSF (mg/dl)</th>
<th>CSF glucose level (mg/dl)</th>
<th>Gram/ EZN</th>
<th>Culture</th>
<th>CT/MRI</th>
<th>Antimicrobial therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (6)</td>
<td>20/M</td>
<td>236 (88% neutrophils)</td>
<td>45</td>
<td>42</td>
<td>–</td>
<td>–</td>
<td>N</td>
<td>Yes</td>
</tr>
<tr>
<td>2 (7)</td>
<td>16/M</td>
<td>615 (90% neutrophils)</td>
<td>48</td>
<td>63</td>
<td>–</td>
<td>–</td>
<td>+*/+†</td>
<td>Yes</td>
</tr>
<tr>
<td>3 (8)</td>
<td>20/F</td>
<td>200 (80% neutrophils)</td>
<td>72</td>
<td>57</td>
<td>–</td>
<td>–</td>
<td>N</td>
<td>Yes</td>
</tr>
<tr>
<td>4 (9)</td>
<td>17/M</td>
<td>25 (predominant lymphocytes)</td>
<td>100</td>
<td>70</td>
<td>–</td>
<td>–</td>
<td>N</td>
<td>Yes</td>
</tr>
<tr>
<td>5 (10)</td>
<td>14</td>
<td>291 (86% neutrophils)</td>
<td>138</td>
<td>35</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>6 (10)</td>
<td>17</td>
<td>138 (63% neutrophils)</td>
<td>241</td>
<td>42</td>
<td>–</td>
<td>–</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>7 (10)</td>
<td>19</td>
<td>691 (93% neutrophils)</td>
<td>175</td>
<td>66</td>
<td>–</td>
<td>–</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>8 (10)</td>
<td>15</td>
<td>580 (84% neutrophils)</td>
<td>135</td>
<td>55</td>
<td>–</td>
<td>–</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>9 (10)</td>
<td>27</td>
<td>1,370 (95% neutrophils)</td>
<td>107</td>
<td>51</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>10 (PR)</td>
<td>35/F</td>
<td>80 (62% neutrophils)</td>
<td>21</td>
<td>88</td>
<td>–</td>
<td>–</td>
<td>N</td>
<td>No</td>
</tr>
</tbody>
</table>

Aseptic Meningitis in AOSD

(non-steroid anti-inflammatory drugs, trimethoprim-sulfamethoxazole, anti-neoplastic agents), systemic lupus erythematosus and Behcet’s disease. The present patient did not have any finding consistent with these disorders and improved without any antibiotics, or antiviral drugs.

In a patient reported by Markusse et al (11) sensorineural hearing loss developed with an exacerbation in the 9th year of AOSD while taking indomethacin treatment. There is no information about the relationship between indomethacin and audiovestibular toxicity in humans. In experimental animal studies, reversible hearing loss due to indomethacin use has been demonstrated. This hearing loss due to indomethacin may be mediated by decreased prostaglandins and elevated leukotrienes (15).

AOSD should be considered in the differential diagnosis of all patients who present with aseptic meningitis, especially if there is neutrophilic pleocytosis in CSF and prolonged fever and rash. In addition, it should be kept in mind that aseptic meningitis with neutrophilic pleocytosis in CSF can be seen during the course of AOSD.

References