Hemophagocytic Syndrome and Adult Still’s Disease Associated with Meningoencephalitis and Unconsciousness

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Abstract

We describe a 19-year-old woman with hemophagocytic syndrome and adult Still’s disease who showed rare features of central neurological involvement, including cerebellar symptoms and the sudden onset of unconsciousness with pleocytosis in the cerebrospinal fluid during the early course of the illness. As this patient’s serum showed a high level of interferon-γ and soluble interleukin 2 receptor, this might play a pathologic role in the development of central nervous system symptoms. Intensive treatment consisting of methylprednisolone pulse therapy followed by the oral administration of methylprednisolone and cyclosporine, as well as plasma exchange, was found to achieve good results. (Internal Medicine 40: 1037-1040, 2001)

Key words: cytokine, plasma exchange, cerebellar symptoms

Introduction

Hemophagocytic syndrome (HPS) is characterized by high fever, cytopenia, hepatosplenomegaly, liver dysfunction, hypoferritinemia, coagulopathy, and the presence of hemophagocytosis in the bone marrow and/or reticuloendothelial systems (1). On the other hand, adult Still’s disease (ASD) is a systemic inflammatory disorder of unknown etiology characterized by a spiking fever, evanescent rash, polyarthralgia and liver dysfunction (2). Recent case reports indicate that HPS and ASD occasionally occur simultaneously (3). However, no neurological complications have been reported in such cases.

We present a case of HPS and ASD accompanied by rare neurological features, such as cerebellar signs with pleocytosis for short periods followed by sudden bouts of unconsciousness. Although the neurological symptoms of this case were severe, intensive treatment including corticosteroid pulse, plasma exchange, and intravenous immunoglobulin provided good results. In addition we also estimated the levels of some cytokines, which were suggested to play a pathologic role in the development of the neurological symptoms in this case.

Case Report

A 19-year-old woman was admitted to our hospital in October 1997 because of fever, sore throat, and myalgia of 19 days duration, and also dysarthria, vertigo, and dizziness of 4 hours duration. From five days before admission, she had demonstrated a spiking fever of up to 39.5°C without headache. She had a past history of allergic reactions to clarithromycin. Her mother had primary biliary cirrhosis, and her grandmother also suffered from rheumatoid arthritis.

A physical examination upon admission (=day 1) yielded the following data: height, 164 cm; weight, 57 kg; temperature, 39.1°C; pulse rate, 102 beats/min; blood pressure, 134/52 mmHg. The oropharynx was reddened. She was anemic, but no jaundice, swollen lymph nodes, goiter or skin rash were noted. An examination of the chest revealed no abnormalities. The liver edge was palpable for 4 cm at the midclavicular line. Her consciousness was clear. A neurological examination revealed direction-changing nystagmus with a rapid phase to the left on left gaze and a rapid upward phase on upward gaze. On gazing to the right, vertigo, dizziness and nausea all worsened. Ataxic dysarthria and ataxia of the bilateral extremities were all observed. There were no signs of limb muscle weakness or sensory disturbance. She was unable to sit, stand, or walk because of ataxia. The deep tendon reflexes were normal without any pathological reflexes. In addition, nuchal rigidity and Kernig’s sign were absent.

A laboratory test on admission revealed the following: a C-reactive protein level of 3.3 mg/dl; a white blood cell count of 17.6×10³/µl (neutrophils 89%); a hemoglobin level of 10.3 g/dl; a platelet count, 12.8×10⁴/µl; aspartate aminotransferase (AST), 136 IU/l; alanine aminotransferase (ALT), 142; lactate dehydrogenase (LDH), 1,363 IU/l (normal; 100–225); serum ferritin, 6,228 ng/ml (normal; 3.4–120). Soluble interleukin 2 receptor (sIL-2R) was elevated to 2,240 U/ml (normal; <519). Antinuclear antibody, rheumatoid factor, and antineutrophil...
cytoplasmic antibody were all negative. Immunoglobulin (Ig) G was 1,625 mg/dl; IgA, 268; IgM, 189. The prothrombin time was 13.1 seconds, with a control of 10.4 seconds; the activated partial thromboplastin time, 37.8 seconds, with a control of 30.3 seconds. Fibrinogen was 257 mg/dl; the fibrinogen degradation product (FDP), 17 μg/ml (normal; 1–12); D-dimer, 19 (normal; <1.0); heparplastin test, 49.3%. The titers of anti-influenza A virus antibodies in the serum showed an increase from 1: 32 at admission to 1: 128 at two weeks after the first measurement. Other titers of anti-virus antibodies, such as anti-Epstein-Barr virus and anti-human parvovirus B19, were low and did not increase even 2 weeks after the first measurement. The urinalysis findings were normal. The cerebrospinal fluid (CSF) on admission showed an opening pressure of 18 cmH2O with lymphocyte dominant marked pleocytosis (1,008/μl); total protein, 178 mg/dl; glucose, 49 mg/dl. Bacterial cultures of CSF were negative, and the cytology of CSF was class 2.

The brain magnetic resonance imaging (MRI) findings on the 4th day were normal; no gadolinium-DTPA enhancement was seen. A single photon emission computed tomography (SPECT) on the 10th day revealed cortical hypoperfusion in the left antero-parietal lobe and normal perfusion in the cerebellum. The electroencephalogram (EEG) on the 9th day showed diffuse slow α and θ waves despite that she was alert. Shortly after admission, we made a tentative diagnosis of meningitis associated with cerebellitis and encephalitis (Fig. 1). Glycerol was administered to decrease the intracranial pressure. The intravenous administration of antibiotics, fluconazole, acyclovir and isoniazid was initiated under suspicion of either a viral or some other type of infection. Despite these therapies, the high spiking fever persisted. Both the symptoms of anemia and thrombocytopenia worsened, while the AST, ALT, LDH and serum ferritin levels all increased. In addition, slightly itchy maculopapular, salmon-pink rashes ranging from 3 to 8 mm in diameter appeared mainly on the trunk on the 10th day and thereafter soon became generalized in distribution. Bone marrow aspiration on the 11th day revealed hypercellularity without blastoid proliferation, and histiocytes that ingested either erythrocytes or mature polymorphonuclear cells. As she began to show probable signs of disseminated intravascular coagulation (DIC) according to the criteria established by the Japanese Ministry of Health and Welfare, nafamostat mesilate (a protease inhibitor), 100 mg/day was first started, and later was switched to gabexate mesilate (another protease inhibitor), 1,200 mg/day because of hyperkalemia caused by an adverse effect to nafamostat mesilate.

Although the CSF findings on the 12th day revealed a remarkable improvement; the cell count had decreased markedly (cell count, 41/μl with 2% of polymorphonuclear cells and 98% of mononuclear cells; protein, 72 mg/dl), her neurological symptoms persisted. Antibiotics, fluconazole, acyclovir and isoniazid were all tapered. Instead, on the 12th through 14th day, methylprednisolone pulse therapy (1,000 mg/day) was introduced to suppress the disease activity. Despite the therapy, a clouding of consciousness suddenly developed on the morning of the 15th day. She lost her ability to speak even though her eyes opened spontaneously. The deep tendon reflexes were normal without any pathological reflexes. The patient could not remember anything regarding these incidents after she recovered. Plasma exchange was performed using 40 units of fresh frozen plasma on the 15–17th days, and cyclosporine treatment (250 mg/day) was also started. Due to these therapies, her level of consciousness suddenly improved on the 16th day. From that time, the symptoms of nystagmus, ataxia, and rash all began to improve gradually. The bone marrow on the 19th day still showed the findings of hemophagocytosis. On the 19th through 23rd day, high-dose intravenous immunoglobulins (20 g/day) were administered. The CSF findings on the 23rd day returned to normal (cell count, 11/μl with 100% of mononuclear cells; protein, 41 mg/dl). The features of hemophagocytosis in a bone marrow smear almost disappeared on the 25th day. Dysarthria, ataxia and rash almost diminished, and she thereafter was able to walk without any assistance. In addition to persistent fever, bilateral knee joint pain and swelling appeared on the 26th day. In addition, whenever the fever was high, a macropapular nonpruritic salmon-pink rash appeared temporarily on her chest and hands on the 30th and 31st day. She was therefore diagnosed to have ASD because of fever, arthralgia, typical rash, leukocytosis, sore throat, splenomegaly, liver dysfunction, and the absence of rheumatoid factor and antinuclear antibody (2). Oral methylprednisolone was started at an initial dose of 24 mg/day on the 32nd day. MRI findings on the 33rd day and EEG findings on the 37th day were normal. The dose of methylprednisolone was tapered after 4 weeks, since the clinical symptoms including rash and arthralgia, and the laboratory data all began to improve. She made a complete recovery and was discharged from the hospital in January 1998.

Discussion

According to previous reports, patients with adult Still’s disease complicated by HPS primarily present with ASD symptoms, followed by HPS symptoms (3). In contrast, HPS in children complicated by Still’s disease primarily presented with HPS symptoms (4–8). This 19-year-old patient, who was an adolescent and not a child, revealed symptoms of HPS, followed by those of ASD. In spite of suffering from HPS, the peripheral WBC in this case was elevated throughout the course. HPS in children complicated by Still’s disease also shows an elevated WBC (8). Therefore, this 19-year-old patient’s clinical characteristics were similar to those of children’s HPS followed by Still’s disease.

This patient with HPS and ASD presented with such neurological symptoms as dizziness, nystagmus, dysarthria, and ataxia at first, and the sudden onset of a clouded consciousness during the course. From 20–33% of all HPS cases are reported to show neurological disorders such as a disturbance of consciousness, convulsions, increased intracranial pressure or meningeal irritation (1). On the other hand, a multicenter survey of Japanese patients with ASD demonstrated that 7 in 90 patients (8%) showed central nervous system (CNS) involvement, such as aseptic meningitis, delirium, convulsion, and ri-
CNS Symptoms in HPS and ASD

rigidity (9). Most HPS patients who demonstrated neurological symptoms were children. Regarding this point, the patient’s clinical features were similar to those of HPS in children. Moderate pleocytosis in CSF was frequently noted and was due predominantly to small lymphocytes in such patients (1). The pleocytosis in this case was more remarkable (1,008 cells/μl) than that in the previously reported cases; they rarely exceeded 100 cells/μl (10). Despite the presence of pleocytosis, symptoms of headache or signs of meningeal irritation were all absent during her entire clinical course. In addition, the pleocytosis disappeared rapidly.

There is a possibility that the influenza A virus might induce initially HPS and acute cerebellitis, because a significant increase in the titers of anti-influenza A virus in serum was noted in this case. In addition to the cerebellar sign, unconsciousness also suddenly appeared when the activity of HPS and ASD was still at a high level based on the clinical symptoms as well as the AST, ALT, and serum ferritin levels. In the present case, an electrolyte disturbance, steroid psychosis, and hepatic encephalopathy were all ruled out based on the CSF findings, clinical symptoms, and laboratory data. Moreover, no abnormal findings were obtained on MRI and CT. MRI and EEG could not be performed during the unconscious state: day 15–day 16. Stephan et al reported three cases of HPS in children complicated by Still’s disease, who showed comatose states in which two cases recovered, but one case died (6). We therefore considered both her disturbance of consciousness as well as meningoencephalitis to be a part of the neurological symptoms in HPS and/or ASD.

The etiology of neurological manifestations in HPS and/or ASD has not yet been clarified precisely. Recently, hypercytokinemia has been pointed out to be a common abnormality underlying HPS, ASD, and Still’s disease in children. Concentrations of cytokines and its receptor, such as TNF-α, IFN-γ, M-CSF, G-CSF, IL-1β, IL-6, IL-10, and sIL-2R were reported to be elevated in the serum of patients with these diseases (6, 11–13). In fact, the IFN-γ and sIL-2R levels in the serum of our patient were high. CNS symptoms such as coma, confusion, blurred vision, and headache have been noted when IL-2 and IFN-γ were administered to patients with malignancies (14, 15). Her consciousness was restored after undergoing plasma exchange therapy that brought a rapid reduction of the elevated cytokines in the peripheral blood. Plasma exchange therapy might therefore be a preferential treatment modality in patients with HPS and/or ASD when they fall into a state of unconsciousness due to such diseases.

References