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Case Report

Fulminant Hemophagocytic Syndrome with a High Interferon γ Level Diagnosed as Macrophage Activation Syndrome

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Abstract

A 26-year-old woman presented with general fatigue, persistent fever, nuchal lymphadenitis, thrombocytopenia, and liver damage. From the bone marrow finding, we diagnosed her condition as hemophagocytic syndrome. Steroid pulse therapy, cyclosporin A treatment, and combined chemotherapy generated no response. The patient showed severe mucosal bleeding, rapidly experienced multiple organ failure, and finally died of a brain hemorrhage on the 13th hospital day. Epstein-Barr virus, cytomegalovirus, human herpes virus type 6, human parvovirus B19, and herpes simplex virus were not detected. Autopsied samples of the spleen, bone marrow, and liver showed extreme proliferation of activated macrophages, so-called histiocytes, without lymphoid malignancy. The interferon γ level at presentation was prominently high. The continuously elevated levels of ferritin and soluble interleukin 2 receptor were correlated with the catastrophic outcome. The disease in our case mimicked infantile hemophagocytic lymphohistiocytosis. However, there was neither a family history of the disease nor a mutation in the perforin gene. So, it is reasonable to categorize our case as macrophage activation syndrome. Although our patient lacked arthritis or eruption, we cannot deny the possibility that an oligoarthritis type of systemic-onset juvenile rheumatoid arthritis or, considering the patient's age, adult-onset Still disease lies at the base of our case.
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Key words: HPS; MAS

1. Introduction

Hemophagocytic syndrome (HPS) is defined as a reactive proliferation of histiocytes with hemophagocytosis [1]. Clinical features are characterized by high fever, hepatosplenomegaly, pancytopenia, hypofibrinogenemia, hypertriglyceridemia, and hyperferritinemia [2]. HPS has been complicated with various diseases. Virus-associated HPS (VAHS), first described by Risdall et al [3], is sometimes fatal and difficult to distinguish clinically from malignant histiocytosis [4,5]. Herpes simplex virus [6], varicella-zoster virus [7], cytomegalovirus [2], human parvovirus B19 [8], human herpes virus type 6 [9], adenovirus [10], rubella virus [11], and influenza virus [3] all can induce VAHS. Epstein-Barr virus (EBV)-associated HPS, called EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH), develops mostly in children and young adults and shows fulminant and severe manifestations, including systemic organ failure with vascular damage [12,13]. Fatal HPS in early infancy caused by impaired natural killer (NK) cell activity is called HLH [14]. Macrophage activation syndrome (MAS) is a life-threatening complication caused by excessive activation and proliferation of well-differentiated macrophages [15]. MAS also shows the same characteristics of HPS mentioned above, and MAS becomes complicated by association with infections, neoplasms, and rheumatologic diseases, such as systemic-onset juvenile rheumatoid arthritis [15].

Here we describe a case of fatal HPS. The clinical manifestations in our case had mimicked VAHS, HLH, or MAS, so we evaluated the differential diagnosis from the analysis of serum and autopsied samples with immunologic and genetic methods.

2. A Case Report

A 26-year-old woman presented to a home doctor with a fever of 12 days, fatigue, weight loss, and pain on the left side of the neck. She had no arthralgia. The patient had 3

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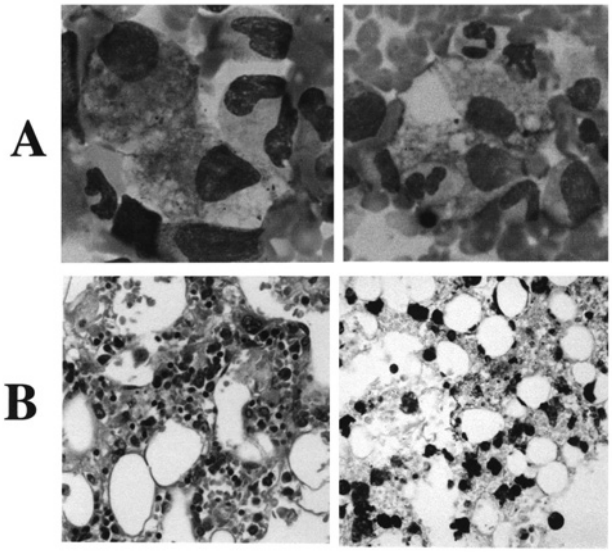

Figure 1. A, A bone marrow aspirate from the patient on admission showed scattered histiocytes with abundant cytoplasm, oval or indented nuclei, and indistinct nucleoli. Hemophagocytosis was apparent but was not prominent (Wright-Giemsa stain, original magnification ×1000). B, Histologic examination of the autopsied bone marrow specimens showed proliferation of histiocytes with hemophagocytosis. Left, hematoxylin and eosin (original magnification ×250); right, anti-CD68 staining (original magnification ×250).

healthy siblings. She had neither persistent febrile episodes nor arthralgia following presentation and did not regularly use any medicines. Investigation of blood samples at that time showed a glutamic-oxaloacetic transaminase (GOT) level of 51 IU/L, a glutamic-pyruvic transaminase (GPT) level of 46 IU/L, and a lactate dehydrogenase (LDH) level of 639 IU/L. Three days later, the patient's body temperature went up to 40.2°C and held there, so she was admitted to our hospital. Physical examination showed painful swelling of left submandibular fat tissue and a painful small lymph node. The liver was palpable by 3 finger breadths. Laboratory test results on patient admission showed a white blood cell count of 11,400/μL (with 55.5% granulocytes, 19% monocytes, 9% lymphocytes, and 20% atypical lymphocytes), a red blood cell count of $4.20 \times 10^6/\mu L$, and a platelet count of $61 \times 10^3/\mu L$. Biochemical data showed 705 IU/L GOT, 420 IU/L GPT, 5697 IU/L LDH (19.9% LDH4 and 38.6% LDH5), 1.03 mg/dL serum creatinine, 11.99 mg/dL C-reactive protein, and 21,423 ng/mL ferritin (normal values, 27-320 ng/mL). Reduction in the CD4/CD8 lymphocyte ratio (0.79) was observed. A coagulation study showed a pattern of disseminated intravascular coagulation. The bone marrow smear showed hypercellularity with a few histiocytes (Figure 1A). A naphthyl acetate esterase assay of the histiocytes yielded positive results. A diagnosis of HPS was made. Steroid pulse therapy with dexamethasone was administered. At 48 hours after admission, the patient's liver damage, renal dysfunction, and acute respiratory distress syndrome had progressively advanced. Symptoms of a problem with the central nervous system, including irritability, confusion, and hallucination, developed. An immunologic analysis on patient admission revealed 16,800 U/mL soluble interleukin 2 receptor (sIL-2R) (normal values, 220-530 U/mL), 170 IU/mL interferon γ (IFN-γ) (normal values, <0.1 IU/mL), 1090 mg/dL immunoglobulin G (IgG), 334 mg/dL IgA, 136 mg/dL IgM, 30 IU/mL total serum hemolytic complement (CH_{50}) (normal range, 30-40 IU/mL), no detectable rheumatoid factor, and no detectable antinuclear factor. A serologic test on admission revealed that the patient had previously had infections of EBV, herpes simplex virus, cytomegalovirus, and human parvovirus B19. Test results were negative for hepatitis viruses, adult T-cell leukemia virus, and human immunodeficiency virus. Using polymerase chain reaction (PCR) methods with the DNA derived from peripheral blood mononuclear cells, we did not detect EBV DNA, cytomegalovirus DNA, or human herpes virus type 6 DNA. EBV DNA was not detected in cell-free serum with PCR methods. Southern blot analysis revealed no monoclonal rearrangements of the αβ receptor of T-lymphocytes. The patient's acute respiratory distress syndrome and acute renal failure had advanced by 60 hours after admission, so we intubated the patient and administered mechanical ventilation. Transient administration of cyclosporin A on the third hospital day had no effect. On the fourth hospital day, chemotherapy with a reduced CHOP-like regimen (cyclophosphamide, hydroxydaunomycin, vincristine [Oncovin], and prednisone) was administered. The patient underwent hemodialysis from the fifth to the 12th hospital day. On the fifth hospital day, severe mucosal bleeding occurred from erosions in the pharynx. While hemostasis procedures were followed, the mucosal lymphoid tissue of the pharyngeal tonsil was biopsied. On the eighth hospital day, ferritin and sIL-2R levels became elevated to 77,604 ng/mL and 18,900 U/mL, respectively. Multiple organ failure had progressed, and the patient died of a brain hemorrhage on the 13th hospital day.

The autopsy revealed an enlarged liver weighing 1650 g and a swollen spleen weighing 140 g. No lymph nodes were enlarged. Bilateral pulmonary edema, mucosal bleeding from multiple gastroenteric erosions, and an intracranial hemorrhage also were apparent.

Histopathologic analysis of the biopsied pharyngeal tonsil showed infiltrating histiocytes with abundant cytoplasm and oval or lobated nuclei with prominent nucleoli. Most of the histiocytes showed phagocytosis of blood cells. The lymphocytes were small and mature without morphologic atypia. There were a few scattered immunoblasts and plasmacytes. There was no infectious component in the specimen. The proliferated histiocytes were positive for both anti-CD68 and lysozyme and negative for CD3, CD56, and S-100 protein. Staining for B-cells and T-cells was limited to small background lymphocytes with no atypia. No cells tested positive for CD21, CD30, or CD56. An in situ hybridization analysis revealed no detectable EBV early region protein (EBER) in either the lymphocytes or the histiocytes. Autopsied samples of the spleen (Figure 2A) and the liver (Figure 2B) revealed necrotic changes and infiltration of histiocytes. Widespread infiltration of histiocytes and marked hypocellularity of other cellular elements were shown in the bone marrow (Figure 1B).

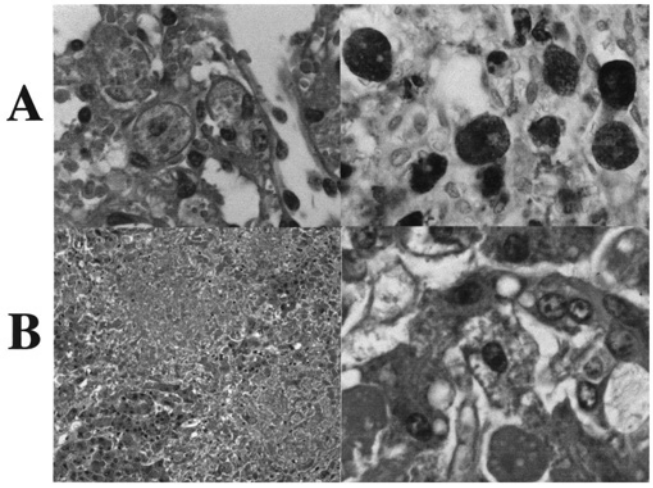

Figure 2. A, The spleen specimens showed diffuse tissue necrosis. Sinusoidal infiltrating histiocytes showed round or indented nuclei, small but distinct nucleoli, and abundant eosinophilic cytoplasm. Histiocytes proliferated individually and sometimes in clusters. Hemophagocytosis was frequent. Left, hematoxylin and eosin (original magnification ×330); right, anti-CD68 staining (original magnification ×330). B, The liver specimen showed numerous necrosis foci, which were located in pericentral, periportal, and occasional intralobular areas. Sinusoidal infiltration of histiocytes showed bizarre nuclei and distinct nucleoli. Left, hematoxylin and eosin (original magnification ×40); right, hematoxylin and eosin, (original magnification ×330).

3. Discussion

Our case met the diagnostic criteria for HPS [1,2]. Major viruses with the ability to induce VAHS were not detected. The possibility of EBV-HLH is quite low because EBV DNA was not detected in the peripheral blood and EBER was not detected in the biopsied samples. The pathologic analysis showed the absence of T-cell, B-cell, null, and NK cell lymphoma, which led us to exclude the possibility of lymphoma-associated hemophagocytosis. Some of the histiocytes in our patient showed prominent nucleoli and minimal atypia, which indicated the extreme activation of histiocytes, such as seen with severe VAHS [16]. Our patient showed prominent hepatosplenic and bone marrow necroses, which were also indicated in a fatal case of VAHS [3]. Our case also mimics the clinical manifestations of HLH [14]. Approximately one third of HLH cases were recently shown to have perforin gene abnormalities that lead to an impairment of the cytolytic function of NK cells [17]. HLH has been described in 6 adult patients [18,19], 2 of whom carried a perforin gene mutation [19]. Consequently, we investigated the possibility of a perforin gene mutation in our patient but found no such mutation. Thus, we failed to diagnose late-onset HLH in this patient. Because of these excluding diagnoses, it is better to categorize our case as MAS. A recent study revealed that MAS had decreased NK cell activity associated with low levels of perforin expression in all of the cytotoxic cells, which were indistinguishable from those of perforin-deficient familial HLH [20]. This finding explained why MAS and HLH had overlapped pathophysiologically, as previously indicated [21]. Adult-onset Still disease (AOSD) is a subtype of systemic-onset rheumatoid arthritis that consists of fever, arthritis, and rash [22], but approximately 1 of the 10 cases described in the literature lacked either arthritis or rash [22,23]. So, we cannot deny the possibility that AOSD may lie at the base of our case. IFN-γ, an antiviral inhibitor, is produced by activated T-cells and is one of the most potent activators of macrophages [24]. The elevation of IFN-γ levels reveals a serious clinical condition in cases of reactive histiocytosis [25-28], and it is also the key to the pathogenesis of MAS [15]. Serum levels of IFN-γ also were elevated in a serious case of AOSD [29]. In our case, the extremely high elevation of IFN-γ levels explains the prominent activation of macrophages. Ferritin is produced by activated macrophages and is the marker of activated histiocytes [30]. High serum ferritin levels also indicate disease activity in MAS cases [31]. As for AOSD, very high serum ferritin levels reflect the presence of an extreme activation of histiocytes that can sometimes lead to HPS [32]. In our case, the ferritin levels continued to elevate even after the chemotherapy, indicating the persistent activation of macrophages. An extreme elevation of sIL-2R levels indicates prominent T-lymphocyte activation [25]. In our case, the level of sIL-2R was elevated continuously, indicating the persistent activation of T-lymphocytes. Serum levels of sIL-2R are significantly higher in patients with HLH [33] and severe AOSD [29]. As for the therapeutic aspects, MAS is sometimes resistant to high doses of corticosteroids [15], as was seen in our case. Cyclosporin A seems to be effective therapy for MAS [15]. We also administered cyclosporin A transiently but reluctantly stopped because of the progressive hepatorenal failures. There may be difficulty in diagnosing and treating the acute fulminant state of MAS arising primarily prior to either arthritis or eruption.

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