Autoimmune-associated Hemophagocytic Syndrome Originating from Autoimmune Hepatitis with a Successful Response to Therapy

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Abstract

The patient was a 15-year-old girl with severe acute hepatitis. A liver biopsy showed the typical findings of autoimmune hepatitis (AIH). Subsequently, two lineages of cytopenia were found in the patient’s peripheral blood. Hemophagocytosis by macrophages was observed in the bone marrow. Virus-, drug- and lymphoma-associated hemophagocytic syndrome (HPS) was ruled out. Therefore, the patient was diagnosed with autoimmune-associated HPS (AAHS). Following the administration of combination therapy with prednisolone and cyclosporine A, both the AAHS and AIH improved. This is the first report of AAHS originating from AIH. The patient was followed up for five years after treatment, and no disease recurrence was detected.

Key words: autoantibody, cytopenia, hemophagocytosis, macrophage activation syndrome


Introduction

Hemophagocytic syndrome (HPS) is a clinicopathological entity characterized by a high-grade fever, hepatosplenomegaly, cytopenia, a high ferritin level and increased proliferation and activation of benign macrophages with hemophagocytosis in the bone marrow or other reticuloendothelial systems (1). HPS is classified as genetic (primary) or acquired (secondary). Primary HPS includes familial hemophagocytic lymphohistiocytosis, X-linked lymphoproliferative syndrome, Chediak-Higashi syndrome and Griscelli syndrome (2). Secondary HPS includes infection-associated HPS (IAHS), malignancy-associated HPS, autoimmune-associated HPS (AAHS) and drug-associated HPS (3-9).

AAHS is frequently observed in patients with systemic lupus erythematosus (SLE) or adult-onset Still’s disease (AOSD). Its prevalence has been found to be 4.6% in SLE patients and 7.7% in AOSD patients (10). On the other hand, AAHS is rarely observed in patients with juvenile idiopathic arthritis or multicentric Castleman’s disease (11) and has not been reported in patients with autoimmune hepatitis (AIH). Almost all cases of HPS in patients with systemic autoimmune diseases other than SLE or AOSD have been shown to be complicated by infectious events or malignancy (5). This paper is the first to report a case of AAHS originating from AIH that was not complicated by infection or malignancy. Moreover, the patient was followed up for a long period after treatment.

Case Report

The patient was a 15-year-old girl with general fatigue that began on January, 2008. She had no past medical or family history, including liver diseases. She also had no his-
tory of medication use, including health food supplements or blood transfusions. On an examination performed at a local hospital on the beginning of January (day 0), 2008, her bulbar conjunctiva was icteric, and blood tests showed liver dysfunction, as follows: total bilirubin (T-Bil), 9.9 mg/dL; aspartate aminotransferase (AST), 1,774 IU/L; alanine aminotransferase (ALT), 1,301 IU/L; lactate dehydrogenase (LDH), 215 IU/L; alkaline phosphatase, 415 IU/L; and prothrombin time (PT), 69%. Therefore, she was admitted to our hospital for a further evaluation.

At admission on day 7, the patient’s consciousness was clear, and her body temperature was 37.1°C. Her body height and weight were 154 cm and 42 kg, respectively. Her body mass index was 17.7 kg/m². Her abdomen was soft and flat without tenderness, and bowel sounds were normal. The liver was palpable 3 cm below the costal margin. The blood test results obtained on admission were as follows: white blood cells, 8,000/μL; red blood cells (RBC), 434×10⁴/μL; hemoglobin, 12.3 g/dL; platelet count, 24.4×10⁴/μL; prothrombin time (PT), 51.1%; prothrombin time-international normalized ratio (PT-INR), 1.50; C-reactive protein, 0.25 mg/dL; albumin, 3.6 g/dL; T-Bil, 17.5 mg/dL; alanine aspartate (AST), 468 IU/L; alanine aminotransferase (ALT), 1,301 IU/L; lactate dehydrogenase (LDH), 215 IU/L; alkaline phosphatase, 415 IU/L; γ-glutamyltranspeptidase, 30 IU/L; choline esterase, 168 IU/L; ferritin, 621 ng/mL; IgG, 835 mg/dL; IgM, 38 mg/dL; anti-glutamyltranspeptidase, 30 IU/L; IgG-EBV VCA Ab, 10 (+); IgM-cytomegalovirus (CMV) Ab, (-); IgG-CMV Ab, 2,000 (+); IgM-SHV Ab, (-); and human T-cell leukemia virus (HTLV)-1 Ab, (-). Based on these findings, the patient was diagnosed with acute hepatic failure without coma. Abdominal ultrasonography and a CT scan showed hepatosplenomegaly (Fig. 1); however, they did not demonstrate either dilatation of the common bile or intrahepatic bile ducts, indicating no obstructive jaundice. The images also did not reveal fatty liver. The patient was maintained under conditions of complete bed rest and received a drip infusion of glucose and coagulation factor.

Figure 1. Abdominal computed tomography (CT) performed on admission. Abdominal CT showed hepatosplenomegaly without fatty liver.

Figure 2. Histopathological findings of the needle biopsy. The specimen exhibited typical AIH findings, such as interface hepatitis (A) and histiocytic and lymphocytic infiltrates in the portal tracts extending into the lobule (B) with hepatic rosette formation (C, designated by arrows). (A) Periodic acid-Schiff (PAS) stain, original magnification ×200. (B, C) Hematoxylin and Eosin staining, original magnification ×200 (B) and ×300 (C).
moglobin (8.3 g/dL) and platelets (7.3×10^10/μL). A bone marrow test was performed, and hemophagocytosis by macrophages and normoblastic marrow were observed (Fig. 3). On day 24, combination therapy consisting of prednisolone (50 mg/day) and cyclosporine A (100 mg/day) was initiated (Fig. 4).

On day 103, the levels of hemoglobin and platelets had improved (12.6 g/dL and 20.4×10^10/μL, respectively). A bone marrow test was performed again, and no hemophagocytosis was detected. The levels of T-Bil, AST and ALT had also improved (1.1 mg/dL, 13 IU/L and 20 IU/L, respectively). A liver biopsy was performed again, and no significant findings of AIH were observed (Fig. 5). Subsequently, the doses of prednisolone and cyclosporine A were gradually tapered due to the lack of recurrence of either AIH or AAHS. In January 2013 (five years after the development of AIH and AAHS), the patient finally stopped taking any medications.

### Discussion

Many autoimmune disorders causative of AAHS have been reported. In 1991, Wong et al. reported patients with active SLE who demonstrated reactive HPS in the bone marrow (10). The occurrence of HPS was associated with the activity of SLE itself, and the authors proposed the disease entity of acute lupus HPS. In 1995, Kumakura et al. reported patients with reactive HPS associated with autoimmune diseases other than SLE and first proposed the disease entity of AAHS with diagnostic criteria (3). In this paper, we are the first to report a patient with AAHS originating from acute-onset AIH. The clinical features of acute-onset AIH include a higher serum ALT level, a lower serum IgG level and a lower AIH score in comparison with those observed in patients with classical AIH, as previously described (13).

The diagnosis of AAHS requires the presence of cytopenia affecting at least two lineages in the peripheral blood and the pathological finding of histiocytic hemophagocytosis in the bone marrow (8). Our patient exhibited two lineages of cytopenia (hemoglobin and platelets) in the peripheral blood and hemophagocytosis by macrophages in the bone marrow. In addition to these two factors, the diagnosis of AAHS requires confirmation that HPS occurs in the active phase of the underlying autoimmune disease, since the occurrence of AAHS is usually dependent on the disease activity (8). Our patient presented with severe acute hepatitis and subsequently developed HPS; therefore, the close correlation between the disease activity and the extent of HPS supports the possibility of AAHS. It is also necessary to ex-

![Figure 3](image-url)  
**Figure 3.** Hemophagocytosis in the bone marrow. The stimulated macrophages demonstrated marked phagocytosis of various hematopoietic cells, including mature erythrocytes (A) and platelets (B). May-Giemsa stain, original magnification x1,000.

![Figure 4](image-url)  
**Figure 4.** Clinical course with medications and the levels of blood biochemical parameters. On day 24, combination therapy consisting of prednisolone (50 mg/day) and cyclosporine A (100 mg/day) was initiated. Each medication was gradually tapered according to the amelioration of the blood biochemical data. A successful response to therapy was obtained following the administration of these drugs, and no disease recurrence was detected for a long period. CSA: cyclosporine A, PSL: prednisolone.
The other hand, patients with these findings have been re-
habited hematopoietic cells are recognized and phagocytosed by histiocytes via binding of the Fc portion of the antibodies and the Fc receptor on histiocytes (3, 4). On the other hand, patients with these findings have been re-
ported to have elevated levels of serum cytokines, such as interleukin (IL)-1β, IL-16 and macrophage-colony stimulating factor (M-CSF), without the presence of autoantibodies against hematopoietic cells (8). Although we were unable to examine the expression levels of these serum cytokines in the present case, it is thought that the differences in clinical features depend on the mechanism underlying hemophagocy-
tosis.

The treatment of AAHS is indicated in patients suffering from the active phase of the disease who exhibit severe cyto-
penia or progression of cytopenia. The treatment consists of therapy for the underlying disease. No standard treatment for AAHS has been established; however, most AAHS pa-
tients respond to immunosuppressive agents, such as corti-
costeroids. In severe cases or patients refractory to high-dose corticosteroid therapy, methylprednisolone pulse treatment is sometimes needed (8). In addition, a favorable effect of etoposide was reported in the treatment of a severe and re-
fractory case of AAHS (14). Treatment with granulocyte-colony stimulating factor (G-CSF) is a reliable alternative, which increases the neutrophil count in the majority of pa-
tients with neutropenia. The administration of G-CSF is beneficial in some AAHS patients with severe or life-
threatening neutropenia. Other therapies include cy-
closporine A, high-dose intravenous immunoglobulin G, plasma exchange and cytotoxic agents (15, 16). Our patient demonstrated severe anemia and thrombocytopenia in addition to life-threatening underlying disease; therefore, she was treated with both prednisolone and cyclosporine A. A suc-
cessful response was obtained following the administration of these drugs, and no disease recurrence was detected five years after treatment.

In conclusion, this is the first report of a case of AAHS originating from AIH with a successful response to therapy. The patient was followed up for a long period after treat-
ment, and no disease recurrence was detected.

The authors state that they have no Conflict of Interest (COI).

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References


Figure 5. Histopathological findings of the second needle bi-
opsy. A liver biopsy was performed again, and no significant findings of AIH, such as interface hepatitis, were observed (A). Ductular proliferation and fibrosis in the portal area were found, reflecting the remnant of the previous case of severe hepatitis (B). (A) PAS stain, original magnification ×200. (B) Hematoxylin and Eosin staining, original magnification ×200.

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