Hemophagocytic Syndrome Associated with Fatal Veno-Occlusive Disease in the Liver

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Abstract

A 47-year-old man presented with hemophagocytic syndrome (HPS) without any obvious underlying diseases. On computed tomography, his liver was occupied by multiple ill-defined low intensity lesions. Liver biopsy revealed diffuse infiltration of numerous histiocytes without cytologic atypism and prominent fibrotic changes. These histiocytes showed S100(+) CD68(+), CD1a(-), and lysozyme(+) and Langerhans cell granules were not observed by electron microscopic examination. He failed to respond to immunosuppressive and chemotherapeutic treatments and progressed to severe liver failure. At autopsy, his liver exhibited veno-occlusive disease (VOD). Since VOD is regarded as a rare complication of HPS, the presence of VOD associated with HPS may be easily overlooked.

Key words: hemophagocytic syndrome, macrophage, veno-occlusive disease, liver failure

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Case Report

A 47-year-old man was admitted to a community hospital with a two-week history of upper abdominal pain. By endoscopic examination, a duodenal ulcer was found and medications including famotidine were started. The symptom disappeared and was followed by an increase in serum lactic dehydrogenase (LDH) and neutropenia. His physician suspected drug allergy and discontinued all medications. After 4 months, the increased LDH level and neutropenia appeared again and they were accompanied by new symptoms: a deterioration of liver function, thrombocytopenia, fever spikes and purpura on bilateral lower legs, auriculae and eyelids. Therefore, he was referred for further examination and treatment. On examination, hemorrhagic purpura was observed on his face and limbs. His temperature was 39.0 °C, blood pressure 110/76 mmHg, and pulse 96/min. No lymphadenopathy was found. Laboratory studies revealed a white cell count of 2600/mm³ with 29% segmented neutrophils, 31% band forms and 26% eosinophils, a hemoglobin level of 13.7 g/dL, and a platelet count of 68,000/mm³. Serum albumin was 31.6 g/L (39-49), aspartate aminotransferase level was 535 U/L (11-32), serum alanine aminotransferase 581 U/L (6-39), γ-glutamyl transpeptidase 76 U/L (3-40), LDH level 1,846 U/L (236-455), and total bilirubin level 0.50 mg/dL (0.33-1.28). The serum level of electrolytes, creatinine, and blood urea nitrogen were normal and prothrombin time (PT)-INR was 1.03 (0.8-1.2). C-reactive protein (CRP) was 7.6 mg/dL. Serum complement level was normal and anti-nuclear antibody was negative. Notably, the serum soluble interleukin-2 receptor (sIL2R) level was 3,122 U/mL (190-650), serum ferritin level 2,360 μg/L (39.9-465.0) and interleukin-6 32,800 pg/mL (<4). Urinalysis showed no abnormalities.

On the first hospital day, bone marrow aspiration smear and clot section revealed typical hemophagocytic macrophages with ingested erythrocytes; however they demonstrated normocellular marrow and no malignant cells. Computed tomography (CT) showed multiple ill-defined low density lesions in the right and left lobes of his liver. Notably, the lesions neither showed apparent enhancement by contrast medium nor had mass effects on hepatic arteries and veins (Fig. 1). The lesions were demonstrated as hyperechoic areas on ultrasound examination, while high intensity areas on T1-weighted image and low intensity areas on...
Figure 1. CT scans of the abdomen. CT scan showed low density lesions at the hepatic right lobe at the time of admission to community hospital (Panel A), and multiple ill-defined low intensity lesions appeared on referral (Panel B). The lesions neither showed apparent enhancement by contrast medium and nor had mass effects on hepatic arteries and veins (Panel C). One year after admission, low-density areas occupied the entire liver without a mass effect (Panel D).

T2-weighted image were visualized by magnetic resonance imaging. CT of the neck, chest, abdomen and pelvis showed no solid malignancies and lymphadenopathy. We made a diagnosis of hemophagocytic syndrome (HPS) according to the Diagnostic Guidelines of the Histiocyte Society (1). On the second hospital day, prednisolone (PSL) 40 mg per day was initiated since the platelet count became 18,000/mm³. High-grade fever, liver function abnormalities and thrombocytopenia were ameliorated; however the symptoms recurred during a tapering of PSL. He received three courses of bi-weekly intravenous methylprednisolone pulse therapy and maintenance of oral PSL 20-40 mg per day was continued. As for the cause of HPS, virus-associated HPS was unlikely, since the results of serologic tests for Epstein–Barr virus (EBV), cytomegalovirus (CMV), parvovirus B19, hepatitis A, B and C were all negative for acute infection; serum polymerase chain reaction (PCR) assays for EBV and CMV were also negative. On the eighth hospital day, liver biopsy was performed and the specimen revealed diffuse infiltration of numerous histiocytes. Immunohistochemical staining showed S100(+), CD68(+), CD1a(-), lysozyme(+) and negative findings favoring lymphoid lineage, i.e. negative for cell surface antigens of T and B lymphocytes. Infiltrated histiocytes without cytologic atypism did not form a solid mass and Langerhans cell (Birbeck) granules were not observed by electron microscope. Multinucleated giant cells (Langerhans cells) showing similar phenotype, S100(+), CD68(+), CD1a(-), and lysozyme(+), were also observed in his liver (Fig. 2). Additionally, fibrotic and necrotic changes were prominent surrounding the central veins and histiocytes located at the periphery of the fibrotic areas (Fig. 2).

Prednisolone was not effective to control disease activity completely; the combination therapy with etoposide (VP-16) was initiated. Furthermore, from 4 months after admission, 4 courses of CHOP (cyclophosphamide, doxorubicin, vincristine, and PSL) with VP-16 therapy were performed and maintenance therapy with PSL and cyclosporine A (CyA) was initiated. His symptoms subsided for a few months. At 9 months after admission, he again presented high-grade fever and deterioration of liver function, and ascites and pleural effusion gradually increased. Serum (24.5 g/L) to ascetic (5.6 g/L) albumin gradient indicated that ascitic fluid was transudative. Since his poor performance status did not allow CHOP therapy, we substituted tacrolimus for CyA as a calcineurin inhibitor since they do not share receptors, i.e. cyclophilin and FK binding protein. At this point, bone marrow aspiration showed normocellular marrow without the picture of hemophagocytic cells and abdominal CT indicated that low-density areas occupied entire his liver without a mass effect. Gastrointestinal fiberscopy revealed esophageal varices, which indicated the presence of portal hypertension. At 15 months after admission, rituximab 60 mg per day, which is reported to be effective for Rosai-Dorfman sinus histiocytosis with similar cell surface markers of CD1a(-), S
Figure 2. Liver biopsy specimens. Irregular-shaped necrotic foci were observed around a central vein, which were associated with histiocytic cells including multinucleated cells (inset) and lymphocyte infiltration and fibrosis (Panel A, hematoxylin & eosin). The histiocytic cells were positive for periodic acid-Schiff reaction (Panel B, periodic acid-Schiff). Immunohistological examination revealed that most of histiocytic cells including multinucleated giant cells were positive for S100 protein (Panel C), CD68 (Panel D), and lysozyme (Panel F), whereas negative for CD1a (Panel E). (Bar=50 μm).

100(+)(2), was administrated. However, no remarkable improvement was obtained. At 18 months, massive pleural effusion and ascites progressively deteriorated, and he finally died of bacterial pneumonia and progressive hepatic decompensation.

The autopsy revealed that there was no macro- or microscopically identifiable malignancy in any organ or lymph nodes. His bone marrow was hypocellular and erythrophagocytosis was found and his spleen showed extramedullary hematopoiesis. His liver weighed 1000 g and was macroscopically moderately sclerotic and atrophic. Microscopically, his liver showed reversed lobulation pattern, i.e. fibrosis bridging central veins. Central veins were occluded and narrowed by surrounding fibrosis, the so-called veno-occlusive disease (VOD) (Fig. 3). The numbers of hepatocytes and Kupffer cells were considerably reduced and replaced by fibrotic tissues. In the liver, there was no apparent accumulation of abnormal histiocytes, which were observed at the time of liver
biopsy. There was no evidence of viral antigens, such as EBV and CMV, in his liver as revealed by immunoperoxidase staining. Although fibrous-capsulated abscess containing necrotic tissues and bacteria was observed in the upper lobe of his right lung, hepatic decompensation due to veno-occlusive disease was the primary cause of death.

**Discussion**

HPS is a reactive disorder of the mononuclear phagocytic system, characterized by benign, generalized histiocytic proliferation (3). The classification of disorders associated with histiocytosis (International Histiocyte Society) was modified in 1997; these disorders were divided into subgroups depending upon ontogeny, i.e. dendritic cell-related disorders, macrophage-related disorders, and malignant disorders of histiocytes (4). Usually, adult cases of HPS are accompanied with underlying disorders, especially viral infections (e.g. EBV, herpes simplex virus (HSV)-1, HSV-2, varicella zoster virus, adenovirus type 11, measles, Coxsacki virus A9, rubella and influenza A and human herpesvirus-6), malignancies including lymphoma and autoimmune diseases (3, 5, 6).

Here, we performed liver biopsy to rule out diffuse type of lymphoma, intravascular lymphoma, sarcoidosis, and other rare malignancies, and did not find such underlying diseases. A positive stain of S100 indicated that the pathognomonic histiocytes were likely to be either Langerhans cells, indeterminate cells, or interdigitating dendritic cells. However, the absence of Langerhans cell (Birbeck) granules and negativity for CD1a excluded the possibility of Langerhans cell histiocytosis (LCH). His hepatic lesion mimicked extranodal lesions of Rosai-Dorfman disease, in which histiocytes and activated macrophage are S100(+), CD68(+) and lysozyme (+), but the characteristic cellular features were lacking (7).

The hepatic manifestation in the present case was unusual for HPS. Hepatic lesions without mass effects were compatible with focal fatty infiltration due to the lipid-rich nature of histiocytes (8). Activated Kupffer cells, that is hepatic macrophages, enhance the production of reactive oxygen species, cytolysyl proteinases and proinflammatory cytokines and chemokines, and interact with the stellate cells, endothelial cells, sinusoidal lymphocytes, and hepatocytes (9). Endothelial injury at the central veins induces obstruction of the central veins and subsequent necrosis of the zone 3 hepatocytes susceptible to the effects of ischemia, which result in VOD (10). VOD is usually described as a complication of chemotherapy and radiation therapy (10, 11). In the present case, the initial liver biopsy already showed hepatic fibrosis surrounding the central veins prior to the administration of cytotoxic agents and he did not receive any radiation therapy. Thus, we would explain his disease process as follows;

**Figure 3.** Liver tissue specimens obtained at autopsy from the patient. Prominent hepatic-cell destruction with fibrosis (blue) resulted in bridging and the residual hepatocytes showed a lobulation pattern (Panel A, Masson Trichrome). Central veins were narrowed (Panel B) and occluded (Panel C) by the surrounding fibrosis, resembling the so-called veno-occlusive disease. In an area of zone 3, the hepatocyte cords were damaged and penetrated by fibrous tissue (Panel D). (Bars=1 mm in A, 100 μm in B, 50 μm in C, and 20 μm in D).
primarily the activation of macrophages was induced by an unknown cause, following by an enhanced cytokine storm inducing endothelial injury. Sustained activation of both histiocytes and local Kupffer cells enhanced endothelial damage, which resulted in zone 3 lesions damage and VOD. Subsequently, he presented severe portal hypertension and died. At the time of autopsy hemophagocytic syndrome was thought to have subsided, however the following sustained endothelial damage induced VOD progression. In the literature, VOD-associated HPS was reported in only one child case, particularly within the lungs and other organs such as liver, spleen, pancreas and kidneys. Small venules demonstrated vascular injury and various stages of destruction; vessels were surrounded by extravasation of fibrin, fresh and degenerated erythrocytes and necrotic materials (12). Similar pathological processes were observed in the zone 3 lesions surrounding the central veins. We were overlooking the association of such vascular injuries and subsequent VOD with HPS.

As for therapy, there is a helpful treatment protocol, the HLH-94 protocol proposed by the Histiocyte Society, consisting of VP-16, dexamethasone, CyA followed by stem cell transplantation or bone marrow transplantation (13). Histological examinations would assist the diagnosis of rare but fatal complication of the HPS. Here, we presented an HPS case associated with fatal VOD in the liver. The vascular injuries of hepatic central veins resulted in zone 3 lesions damage presenting the necrosis of hepatocytes, fibrosis, and the appearance of S100 (+), CD68(+), CD1a(-), lysozyme(+) cells, i.e. activated macrophages. Since VOD is regarded as a rare complication of HPS, we may overlook the presence of VOD associated with HPS. The characteristic CT findings and histological examinations would assist the diagnosis of rare but fatal complication of the HPS.

References