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Case Report

Hemophagocytic syndrome secondary to adult-onset still's disease but very similar to lymphoma

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Abstract: Hemophagocytic syndrome (HPS) is a clinicopathologic entity characterized by increased proliferation and activation of benign macrophages with hemophagocytosis throughout the reticuloendothelial system. HPS may be primary, or secondary to malignancy, infections, auto-immune diseases and pharmacotherapy. In patients with adult-onset Still's disease (AOSD), HPS is a rare but life-threatening complication. Herein, we described a female patient with HPS secondary to AOSD. During the therapy, giant gastric ulcer similar to lymphoma developed after treatment with corticosteroid and nonsteroidal anti-inflammatory drugs.

Keywords: Adult-onset Still's disease, hemophagocytic syndrome, giant gastric ulcer

Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder characterized by prolonged spiking fever, evanescent salmon-colored rashes, polyarthralgia or arthritis, leukocytosis and other manifestations involving multiple organs [1, 2]. Generally, AOSD has a good prognosis. Hemophagocytic syndrome (HPS) is a rare but life-threatening complication of AOSD. Herein, we reported a case of HPS secondary to AOSD in which giant gastric ulcer developed after treatment with high-dose steroids and nonsteroidal anti-inflammatory drugs.

Case report

A previously healthy 23-year-old woman with hyperpyrexia and skin rashes was admitted to our hospital in April 2006. Two weeks ago, she developed high spiking fever (up to 40°C), which was accompanied by skin rashes all over the body. Subsequently, she felt sore in the throat, polyarthralgia and myalgia. She denied having photosensitivity, oral ulcers and Raynaud phenomenon. She had been referred to a local hospital where she was treated with antibiotics for three days, but the symptoms were not improved. On admission, the vital signs were as follows: body temperature: 38°C, pulse rate: 96 beats/min, respiratory rate: 19 breaths/min, blood pressure: 97 mmHg /66 mmHg. Physical examination revealed skin rashes on the trunk and face, tenderness in elbows, wrists and knees, and right cervical lymphadenopathy (0.5-1 cm). Laboratory examinations on admission indicated white blood cell count (WBC) was 21.6×10^9/L (neutrophil: 87.9%; normal range: $4.0\text{-}10.0\times10^9$/L). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated to 69 mm/h and 51 mg/L, respectively (normal range: 1-20 mm/h and 0-8 mg/L, respectively). The serum ferritin level was increased to 13235.7 ng/ml (normal range: 13-150 ng/ml). Anti-nuclear antibodies (ANA) and rheumatoid factor (RF) were all negative. Repeated blood cultures showed negative and antibiotic therapy (cefuroxime and levofloxacin) was not beneficial for the fever. Based on Yamaguchi criteria [3], the patient was diagnosed as having AOSD. Following treatment with methylprednisolone (40 mg/d) and loxoprofen sodium (60 mg, every 8 h), the clinical symptoms significantly alleviated. On the 7th day after steroid therapy, the laboratory results were as follows: WBC, 13.9×10^9/L (neutrophil: 77.4%); glutamate-pyruvate transaminase (ALT), 1210 U/L; aspartate aminotransferase (AST), 488 U/L;

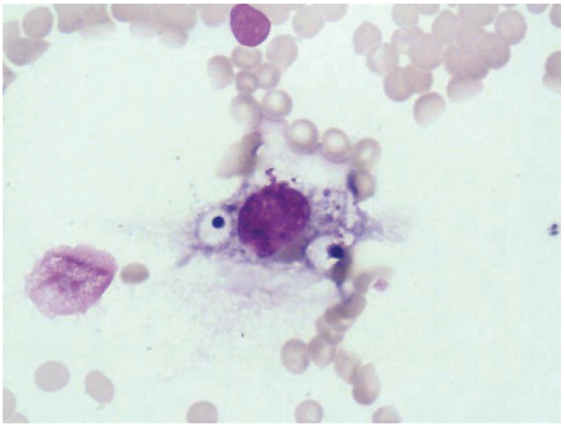

Figure 1. The phagocytic reticular cells accounted for 2%, and the phagocytosis of mature red blood cells and platelets by phagocytic reticular cells was also present.

ESR, 13 mm/h; CRP, 2.15 mg/L; ferritin, 24353.6 mg/ml.

On the 12th day after steroid therapy, the fever recurred and elevation of serum ferritin level (>40000.0 ng/ml) was observed again. At the same time, leukopenia, neutropenia and thrombocytopenia were present: WBC, 1.3×10^9/L (neutrophil: 3%); hemoglobin (HGB), 116 g/L; platelet (PLT), 52×10^9/L. The ALT and AST levels decreased to 491 U/L and 320 U/L respectively after 5 days of diammonium glycyrrhizinate (0.15g/d) treatment. In addition, ESR was decreased to 5 mm/h. Serological examinations showed negative for Epstein–Barr virus (EBV), cytomegalovirus (CMV). Bone marrow aspiration and subsequent examination showed that the phagocytic reticular cells accounted for 2%, and the phagocytosis of mature red blood cells and platelets by phagocytic reticular cells was also present (**Figure 1**). The pathological examination of bone marrow (HE staining) revealed hemopoietic tissues with active proliferation in which infiltrated lymphocytes and hemophagocytes were found (**Figure 2**). Immunohistochemistry indicated the CD3 positive cells increased and diffusely distributed, the nuclei of some cells were enlarged and irregular (**Figure 3**). Based on these findings, HPS secondary to AOSD or lymphoma was suspected. Then, the patient was treated with methylprednisolone (40 mg, twice daily) and immunoglobulin (20 g/d) for 5 days. However, fever was persistent and the patient complained of upper abdominal pain. WBC count decreased progressively to

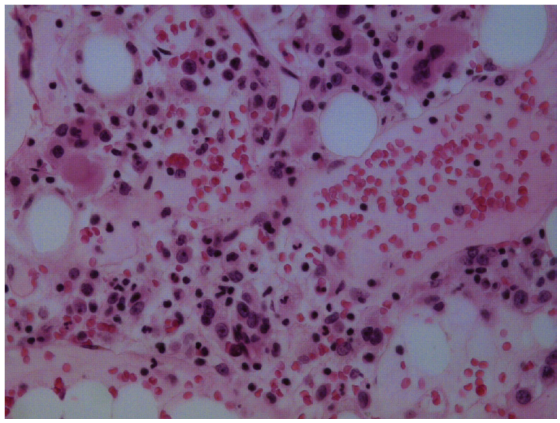

Figure 2. HE staining: hemopoietic tissues with active proliferation was present in which infiltrated lymphocytes and hemophagocytes were observed.

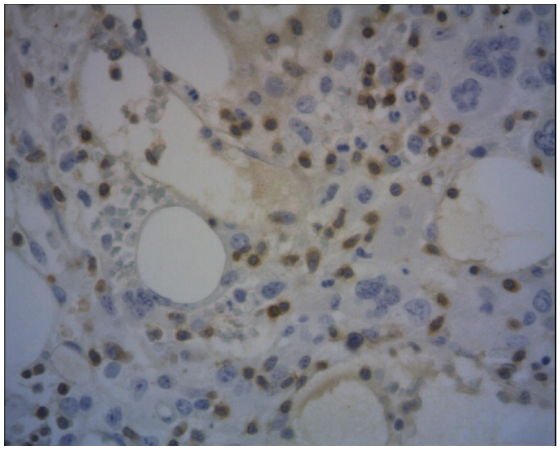

Figure 3. Immunohistochemistry: The CD3+ cells increased and diffusely distributed, the nuclei of some cells were enlarged and irregular.

0.5×10^9/L without neutrophils. Fever subsided after 3 days of methylprednisolone (80 mg, twice daily) treatment. The blood cell counts improved (WBC, 2.3×10^9/L; neutrophil: 50%; HGB, 103 g/L; PLT, 198×10^9/L). The lymphoma was diagnosed according to the clinical manifestations. However, this patient complained of upper abdominal pain and poor appetite. The gastroduodenoscopy showed giant ulcer at sinus ventriculi similar to a malignancy (**Figure 4**). The pathological examination of the biopsies demonstrated mild to moderate chronic active superficial inflammation of the gastric antrum mucosa in the absence of *Helicobacter pylori* infection. The symptoms improved greatly after

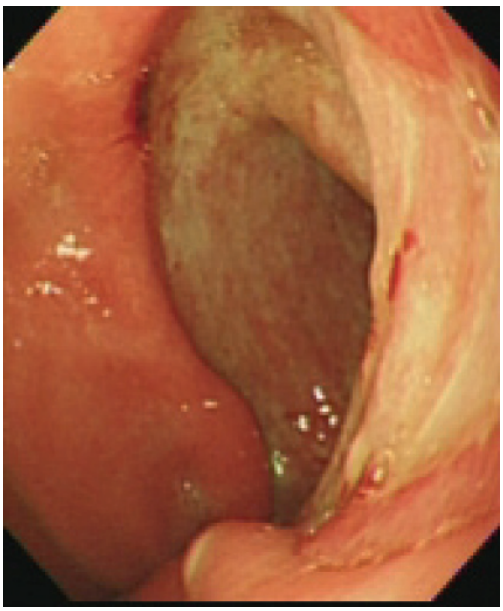

Figure 4. Gastroduodenoscopy showed a giant ulcer at the sinus ventriculi.

treatment with omeprazole and the decrement of methylprednisolone. The patient recovered after a total of 102 days of hospitalization, and the hyperferritinemia and blood cell count returned to normal. On her 5-year follow-up visit, she was asymptomatic on prednisone with tapering dose. She is currently well and off all medications and symptom-free.

Discussion

AOSD is a type of polyarthritis and has systemic manifestations such as a spiking fever and sore throat [2]. Diagnosis requires exclusion of infectious, malignant and other autoimmune diseases. In most studies, the serum ferritin level of 1000 ng/ml, 5 times higher the upper limit of normal [40-200 ng/ml], has been regarded as an indicator of AOSD [4]. In addition, hyperferritinemia serves as a marker of disease activity in AOSD [5]. The exact etiology of AOSD is still unknown, but considerable evidence has shown that the activation of macrophages appears to be one of the important clinicopathological findings in AOSD [6]. Activated macrophages may release ferritin, and the elevated serum ferritin level reflects the activation of macrophages to a certain extent [6].

HPS, also known as hemophagocytic lymphohistiocytosis, is a clinicopathological syndrome characterized by hyperpyrexia, hepatosplenomegaly, cytopenias, elevated serum ferritin level, and increased proliferation and activation of benign macrophages with hemophagocytosis throughout the reticuloendothelial system. HPS may be primary, or secondary to several diseases, such as malignancies, infections and autoimmune diseases [7]. It has been demonstrated that HPS may occur in patients with autoimmune systemic inflammatory diseases such as systemic lupus erythematosus (SLE), AOSD, and juvenile idiopathic arthritis [8]. Macrophage activation syndrome [MAS] is now recognized as a form of HPS associated with autoimmune diseases [9]. The development of HPS in AOSD might be attributed to increased IL-18 level, because IL-18 plays a critical role in AOSD by triggering macrophage activation [10].

The clinical features of the present patient illustrated a few interesting point. The patient was treated with corticosteroid based on the diagnosis of AOSD achieving response. Nevertheless, during the treatment, HPS developed. The HPS was considered to be due to AOSD itself initially. Then, the steroid dose was increased. However, the pathological examination of the bone marrow showed hemopoietic tissues with active proliferation was present in which infiltrated lymphocytes and hemophagocytes were observed. At the same time, the gastroduodenoscopy showed giant gastric ulcer similar to lymphoma. Thus, we speculated that the HPS might be due to lymphoma. However, the pathological examination of the gastroduodenoscopic biopsies demonstrated inflammation of gastric antrum mucosa alone. The patient recovered after treatment with omeprazole and the decrement of corticosteroid. Ultimately, the 5-year follow-up visit further confirmed the diagnosis of HPS secondary to AOSD.

HPS is an uncommon complication of AOSD, and it shares many clinical features with underlying AOSD, such as hyperpyrexia, hepatosplenomegaly, liver dysfunction and hyperferritinemia. Thus, the recognition of incipient HPS in AOSD patients requires a high index of suspicion. The presence of cytopenia is a most important indicator of HPS. In addition, similar to our case, Grom [11] and others [12-15] have suggested that the characteristically low ESR in MAS may act as a valuable signal to distinguish the MAS from worsening of inflammation in other disorders. In the patients with HPS, ESR

falls despite worsening of inflammation, but the aggravation of inflammation in other disorders manifests the increase in ESR.

The activated macrophages engulf erythrocytes, leukocytes, platelets and their precursor cells into the bone marrow, liver or lymph nodes, which is an important finding in HPS patients. In our patient, the examination of bone marrow demonstrated increased macrophages and hemophagocytosis.

Giant gastric ulcers refer to gastric ulcers with the maximum diameter exceeding 3 cm. It is thought that ulcers larger than 5 cm in diameter are more likely to be malignant [16]. Based on the findings in endoscopy and clinical manifestations, the *Helicobacter pylori*-negative patients presenting a giant gastric ulcer are usually considered as having lymphoma. However, the pathological examination of the biopsies excluded the diagnosis of malignancy in this patient. The patient recovered after the treatment with omeprazole and the decrement of methylprednisolone. Thus, we postulated that the giant gastric ulcer was attributed to the treatment with corticosteroids and nonsteroidal anti-inflammatory drugs [NSAIDs]. Whether glucocorticoids induce gastric mucosal injury remains controversial. However, it has been suggested that combined use of NSAIDs and steroids will increase the risk for peptic ulcer [17, 18].

In conclusion, HPS is an uncommon complication of AOSD. Although some triggering factors, such as EBV or CMV infections, and usage of gold, methotrexate, and tumor necrosis factor blockers have been defined for MAS [11, 19, 20], we could not detect any triggering factors or warning signs in the patients. Thus, we should pay enough attention to HPS secondary to AOSD.

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