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Case Report

Extremely high serum ferritin level in a patient with Hemophagocytic Syndrome and Adult-Onset Still's disease

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ABSTRACT
Hemophagocytic syndrome (HS) and Adult-onset Still's disease (AOSD) are both rarely systemic inflammatory disorders. It may be difficult to differentiate these inflammatory disorders from each other. There are some signs that may help clinicians in the diagnosis such as high ferritin levels for AOSD, and leukopenia, thrombocytopenia, hypertriglyceridemia for HS. Hemophagocytic syndrome secondary to Adult-onset Still's disease was reported rarely in literature. In this article, we aimed to report a patient of 65-year old female diagnosed with HS and AOSD with extremely high serum ferritin levels.

Keywords: Adult-Onset Still's disease, Hemophagocytic Syndrome, ferritin

INTRODUCTION

Adult-onset Still's disease (AOSD) generally affects children or young adults, and also was described up to 83 years (1). The etiology of AOSD remains unknown. Genetic (HLA-B17, HLA-B18, HLA-DR2 etc.) and environmental factors such as infections (Epstein-Barr virus, hepatitis B and C virus, human immunodeficiency virus, yersinia enterocolitica etc.) have been suspected in the pathogenesis (1). Hemophagocytic syndrome (HS) is also a rare disorder. It may be primary, or secondary to infections, malignancies, juvenile idiopathic arthritis and AOSD (1). Serum ferritin may be useful marker for AOSD disease activity, but has limited value for the diagnosis of AOSD (1,2). Although elevated serum ferritin levels are associated with leukaemia, lymphomas, haemochromatosis; levels up to 10.000 µg/L was described in patients with multiple blood transfusion and hemophagocytic syndrome (2,3).

CASE REPORT

A 65-year-old female patient was admitted to our clinic with recurrent episodes of fever of unknown origin for 4 weeks duration, and also fatigue, diarrhea, and non-pruritic rash. The rash was generally associated with fever. She had a history of receiving leflunamide (20 mg/day) and sulfasalazine (1000 mg/day) for probably rheumatoid arthritis since five years. There was no medical history about alcohol consumption, surgical procedure or blood transfusion.

General condition was moderate with pale appearance. Her blood pressure was 110/70 mmHg, pulse 103/minute (regular), respiratory rate 16/minute and fever 39,5 ^{o}C. Increase in body temperature continued during follow-up in the hospital. Her physical examination revealed hepatosplenomegaly, enlarged axillary lymph nodes in the left and right axillary region (mobile, palpable, and non-tender). The blood parameters were as follows: hemoglobin 8,8 g/dl, mean corpuscular volume 77,9 fL, leukocyte 15.070/mkrL, neutrophil 12.090/mkrL, lymphocyte 1.360/mkrL, platelet 171.000/mkrL, fibrinogen 193,1 mg/dl. The erythrocyte sedimentation rate (ESR) was 91 mm/hour, C-reactive protein (CRP) 161.89 mg/L, and procalcitonin was within normal range. The other laboratory findings were as follows: urea: 24 mg/dl, creatinine 0.5 mg/dl, alanine transaminase: 34 U/L, alkaline phosphatase: 227 U/L, gamma-glutamyl transpeptidase: 66 U/L, total bilirubine: 0,6 mg/dL, albumin: 2,6 g/dl, globulin: 3,2 g/dl, lactate dehydrogenase: 455 U/L, fasting trigliseride: 285 mg/dl, and hyperferritinemia (126.486, 31.123, 17.609 and 5.654 ng/mL, at the time of diagnosis and during follow up, respectively). Serum protein electrophoresis revealed polyclonal gammopathy. Bacterial, viral, fungal, mycobacterial, and parasitic studies of blood, urine, stool, and sputum revealed no evidence for specific agents. Serological and viral markers were negative, and also the empiric antimicrobial therapy was ineffective.

Thoracic computed tomography revealed left lower paratracheal, subcarinal lymph nodes (with a short-axis diameter of 17 mm) without any infiltration or lesion of the pulmonary parenchyma. The abdominal ultrasound revealed hepatomegaly (168 cm). There was no lesion, pathological microcalcification or significant structural deterioration in mammography except for left (24x11 mm in diameter) and right (30x12 mm in diameter) axillary lymphadenopathy. Bone marrow biopsy and axillary lymph node biopsy demonstrated hemophagocytosis (Figure 1). And, accumulation of macrophages with erythroid cells and lymphocytes (in the sinuses than cortex) were observed.

Based on clinical, laboratory and histopathological findings, the case was diagnosed as Adult-Onset Still's Disease and Hemophagocytic Syndrome. Hemophagocytic Syndrome was confirmed by bone marrow biopsy and lymph node biopsy. Methylprednisolone was started 1000 mg daily for 3 days intravenously, followed by 1 mg/kg/day. After stopping the sulfasalazine, methotrexate at dose of 10 mg/week was added as steroid sparing treatment. ESR, CRP, the level of ferritin, leukocyte, and neutrophil showed significant regression. Also, liver function tests and fever were normalized. The patient is still on follow-up in our clinic.

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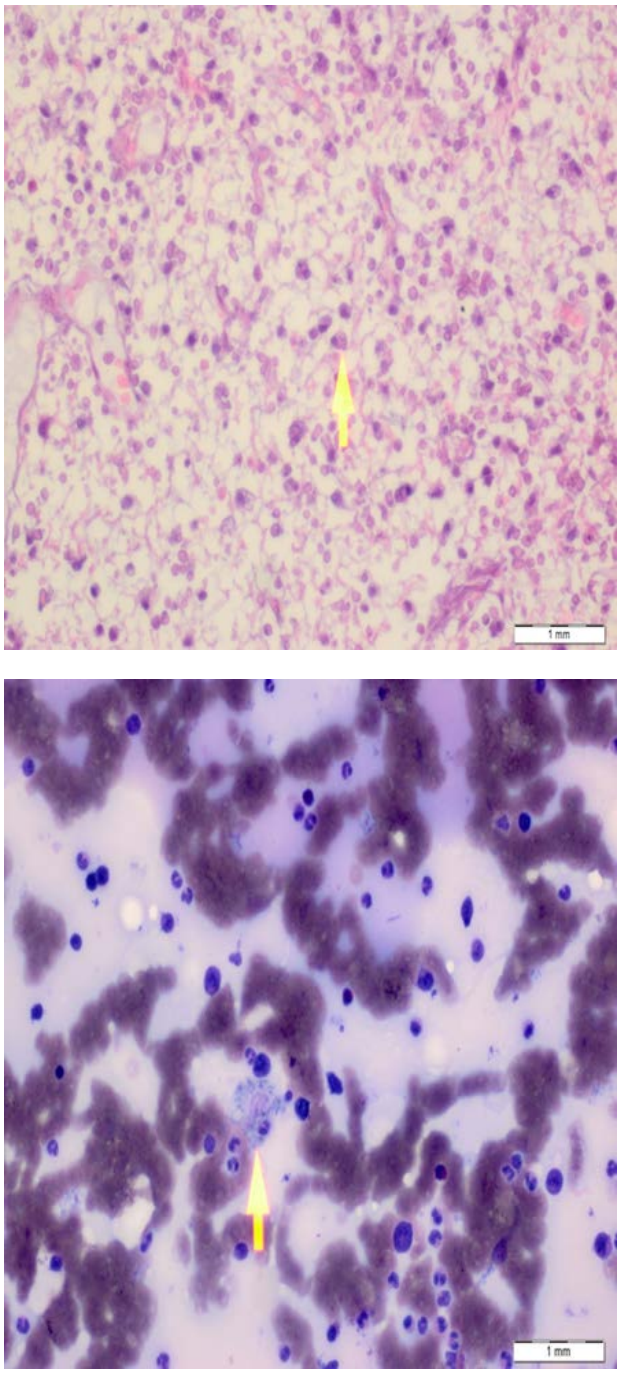

Figure 1: *(a) Hemophagocytosis (yellow arrow) on lymph node biopsy and (b) bone marrow biopsy*

DISCUSSION

Our case was considered as HS due to fever, splenomegaly, hypertrigliseridemia, hyperferritinemia and hemophagocytosis in both bone marrow and lymph node biopsies, and AOSD due to fever, leukocytosis with neutrophil predominance, lymphadenopathy, hepatosplenomegaly, abnormal liver function tests and negative results for antinuclear antibody (ANA) and rheumatoid factor (Rf).

Still disease was used to describe juvenile inflammatory arthritis, and Adult-onset Still's disease was used to describe the adult patients without all the criterias of rheumatoid artritis, but similar criterias of systemic onset juvenile rheumatoid artritis (1). The clinical signs that enable us to suspect about this disease are follows: Episodic-recurrent high fever, transient maculopapular, salmon-colored rash of trunk or extremities and arthralgia or arthritis. Lymphadenopathy, hepatosplenomegaly, and serositis (pericarditis, pleuritis) may be accompanied with this systemic inflammatory disorder. Other systemic conditions such as infections and malignancies must be excluded before the diagnosis of AOSD (1). There was no evidence for malignancy and infections in our patient. HS is characterized by fever, hepatosplenomegaly, cytopenias (at least 2 cell lines), high ferritin levels (>500 µg/L) of, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in bone marrow or lymph nodes without evidence of malignancy. Also, there is an absent or decreased natural killer cell activity in HS (4).

Non-specific laboratuary markers such as high ESR, neutrophilia, elevated liver enzymes and negative results for Rf and ANA are important for AOSD (1). Serum ferritin is a non-specific positive acute-phase reactant high molecular weight. It plays an important role in malign diseases and inflammatory disorders such as sepsis, macrophage activation syndrome (MAS), and systemic inflammatory response syndrome (5). Although proinflammatory cytokines induce expression of ferritin, ferritin also may induce these proinflammatory cytokines. Ferritin leads to phosphatidylinositol 3-kinase, protein kinase C and NF-KB activation through TIMP-2 independent pathways. Proinflammatory mediators such as IL-1β, iNOS etc. are synthesized with NF-KB activation (5). Also, inflammatory cytokines (IL-1, IL-6, TNF-α) lead ferritin synthesis, liver necrosis and stimulate haeme oxygenase-1 that cause to hyperferritinemia. (6, 7). Namas et al. (6) reported a case of AOSD with HS, necrotic leukoencephalopathy and disseminated intravascular coagulation with elevated ferritin levels of 7.000 ng/mL which increased to 22.000 ng/mL. Hamidou et al. (7) reported 2 cases of AOSD with elevated ferritin levels of 80.000 mg/L and 120.000 mg/L. Our patient's ferritin level was extremely high at the time of diagnosis (126.486 ng/mL). The ferritin level of our patient decreased to 5.654 ng/mL with corticosteroid therapy. Elevated serum ferritin levels (>10.000 mg/L) was reported as more suggestive of HS complicating AOSD, and associated with hemophagocytosis syndrome (8). MAS, AOSD, septic shock and catastrophic antiphospholipid syndrome are associated with very high ferritin levels. It was proposed these four disorders under a single nomenclature as 'The Hyperferritinemic Syndrome' due to similar pathogenic mechanisms, clinical, laboratory presentations and treatment modalities (5). HS secondary to AOSD was reported rarely (8-11). IL-18 may play an important role for both AOSD and HS. In literature, it was reported HS in AOSD after sulfasalazine (9). Our patient had also a history of receiving sulfasalazine.

Episodic-recurrent fever, hepatosplenomegaly, hyperferritinemia are similar clinical findings for both HS and AOSD. It may be difficult to establish these two systemic inflammatory disorder from each other or the other inflammatory disease. It may be difficult to differentiate these inflammatory disorders from each other and other diagnoses. There are some signs that may help clinicians in the diagnosis such as high ferritin levels for AOSD, and leukopenia, thrombocytopenia, hypertriglyceridemia for HS (1, 4). Non-steroidal anti-inflammatory drugs, corticosteroids, methotrexate, TNF-α blocking agents, anakinra, and IL-6 antagonists have been recommended for the treatment of AOSD (1). We have received clinical response with corticosteroid. And, the patient is still on follow-up without any clinical problems.

In conclusion, HS secondary to AOSD is rarely systemic clinical disorders. Very high ferritin levels may be helpful diagnostically. Althought serum ferritin levels are not included in the diagnostic criteria of these orders, we need to be careful for HS when extremly serum ferritin levels in the patients with AOSD.

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