Case Report

Acute Severe Hepatitis and Hemophagocytosis in Adult Onset Still's Disease

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Abstract

We report a 44-year-old male Turkish patient with adult onset Still's disease (AOSD) complicated by acute severe hepatitis and hemophagocytosis. Initial investigations for fever and rapidly progressive elevation of liver function tests were not diagnostic. Routine evaluations of liver and bone marrow biopsies missed the fundamental pathology. Extremely elevated ferritin levels led to a more detailed search, and immunohistochemical staining with CD68 for macrophages revealed extensive hemophagocytosis in both the first and second bone marrow biopsies, as well as in the liver biopsy. Treatment with steroid and cyclosporine A induced complete remission.

Keywords: CD68, ferritin, hemophagocytosis, hepatitis, Still's disease

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Introduction

Adult onset Still's disease (AOSD) is a systemic disease characterized by fever, arthritis/arthralgia, sore throat, evanescent rash and neutrophilic leukocytosis. The clinical spectrum ranges from mild to severe, with extensive involvement of almost every organ systems. Although it has been increasingly recognized and several diagnostic criteria have been proposed since its initial description by Eric Bywaters in 1971, the diagnosis can still be challenging due to the lack of specific diagnostic markers and its nature as a diagnosis of exclusion.[1–3] Anemia, thrombocytosis and liver dysfunction are common, while hemophagocytosis, severe hepatitis, and adult respiratory distress syndrome are rarely encountered.[4,5] We present a patient with AOSD complicated by acute severe hepatitis (ASH) and reactive hemophagocytic syndrome (RHS) and a brief review of the literature.

Case Report

A previously healthy 44-year-old male presented to the outpatient clinic with fever, fatigue, weight loss, jaundice, and itching. His complaints started about 2 months ago, and he was treated sequentially with amoxicillin/klavulonate, ebastine, flurbiprofen, clindamycin, pheniramin, meloxicam, levofloxacin, hydroxyzine and fexofenadine without any improvement. Initial laboratory tests revealed only a mild increase in transaminases (Tables 1 and 2).

He was an active smoker, and used to drink alcohol equivalent to 160 g/day, 4 days a week for the last 15 years; otherwise he was previously healthy. His mother had diabetes and hypertension, his father had colorectal cancer and died of myocardial infarction, and his brother had coronary artery disease.

On physical exam, he appeared ill and had jaundice. Axillary temperature was 40ºC. There were pinkish red colored, nonpalpable, blenching macular lesions throughout the trunk and extremities, and these lesions had a tendency to erupt with fever. Blood pressure was 110/70 mmHg, and the pulse was 100/minute. Painless 1-cm lymphadenomegalies were palpable in supraclavicular, axillary, and inguinal regions. The liver was painless and palpable 2 cm below the costal arch. Traube's space was dull on percussion, but the spleen was not palpable. The rest of the physical exam was normal. The patient was admitted to the inpatient service for further investigation.

Multiple blood and urine cultures were sterile. Empiric ceftriaxone and doxycyline were started. Thoracoabdominal CT scans showed hepatomegaly, splenomegaly and generalized lymphadenomegalies with the largest one measuring 1.5 × 2 cm. Repeated laboratory tests showed even higher levels of liver enzymes, prolonged prothrombin time and a remarkably high level of ferritin (Table 1). Peripheral blood smear was normal. Liver biopsy was performed following fresh frozen plasma transfusion, and revealed severe zone 3 necrosis, diffuse lymphocyte/macrophage and scarce neutrophil/eosinophil infiltration. Thrombocytopenia and anemia occurred within one week of admission. Bone marrow aspiration and biopsy were performed and revealed nonspecific changes and no features of hemophagocytosis despite a detailed examination (Figure 1). Intravenous methylprednisolone 40 mg/day was started. On the fifth day of steroid treatment, a second bone marrow biopsy revealed scarce erythro- and leukophagocytosis on Giemsa staining and extensive infiltration of hemophagocytic macrophages were identified when the specimen was stained with anti-CD68 (Figure 2). The liver and the first bone marrow biopsies were re-examined with anti-CD68 immunohistochemical staining and extensive infiltration of hemophagocytic macrophages were also seen in both biopsies (Figure 3). Additional serological tests to identify a possible etiology were all negative (Table 3). The patient's clinical and laboratory abnormalities, including extreme levels of ferritin, returned to near normal levels within two weeks of steroid treatment, and a diagnosis of acute

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Table 1. Laboratory tests results before and after admission.

	One month before admission	3 days before admission	On admission	One week after admission	10 days after admission
White blood cell count (per μL)	9300	5700	5300	5000	2100
Neutrophils (per μL)			3180		
Lymphocyte (per μL)	1500	1600	1180	600	300
Platelets (per μL)	245000	203000	275000	97000	35000
Hemoglobin (gram/dL)	13,2	11,6	10,5	7,6	8
Mean corpuscular volume (fL)			83	82	
Prothrombin time (seconds)			15,8	23,4	40
International normalised ratio			1,42		
D-dimer (μg/L)				2429	
Fibrinogen (mg/dL)				220	
Lactate dehydrogenase (U/L)	1904	1563	1152	2200	1820
Aspartate transaminase (U/L)	111	1196	1009	987	376
Alanin transaminase (U/L)	61	885	793	402	333
Alkaline phosphatase (U/L)	89	905	1116	260	
Gamma glutamyl transferase (U/L)	95	543	624	504	752
Total bilirubin (mg/dL)			15,4	19,4	16,1
Direct bilirubin (mg/dL)			15,2	18,1	15,2
Erythrocyte sedimentation rate (mm/hour)	51	41	22	35	10
C-reactive protein (mg/dL)	82		17	34,2	18,4
Ferritin (ng/mL)		33962	21781	165200	62818
Iron (μg/dL)			74		
Total Iron Binding Capacity (μg/dL)			262		
Albumin (gram/dL)			3,1	1,7	2,37
Trigliceride (mg/dL)			335		
Glucose (mg/dL)			87	83	
Creatinine (mg/dL)			0,8	0,06	0,1
Urea (mg/dl)			25,2	14	13,7
Sodium (mEq/L)			134	117	133,4
Potassium (mEq/L)			4,1	3,04	3,3
Phosphate (mg/dL)			3,7		
Calcium (total) (mg/dL)			8,1		
Uric acid (mg/dL)			3,2		
Magnesium (mg/dL)					

Table 2. Initial serologic tests.

Anti-HCV IgM	Negative
HBsAg	Negative
Anti-HBc IgM	Negative
Anti-HBs	Negative
Anti-HAV IgM	Negative
Anti-Nuclear Antibody	Negative
Anti-HIV	Negative
Anti-Smooth Muscle Antigen	Negative
Anti-Soluble Liver Antigen	Negative
Anti-Liver Kidney Microsomal Antigen	Negative

severe hepatitis and reactive hemophagocytic syndrome (RHS) associated with adult onset Still's disease was made. He was discharged with steroid taper and oral cyclosporine A. He has been under cyclosporine A for the last 2.9 years of follow up without any relapse or adverse effects, and the treatment is planned to be discontinued soon.

Discussion

The incidence of AOSD is low and it is included in the differential diagnosis of fever of unknown origin.[6,7] Although various factors, such as MHC class I and II proteins, viral and bacterial infections, have been implicated in its etiology, the cause of AOSD is still unknown.[8,9] The diagnosis is clinical and depends mainly on

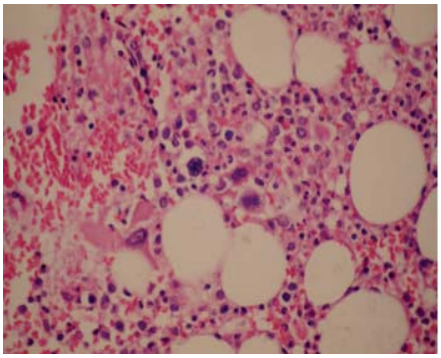

Figure 1. First bone marrow biopsy shows minor nonspecific alterations. (Hematoxylin and eosin stain, 400x)

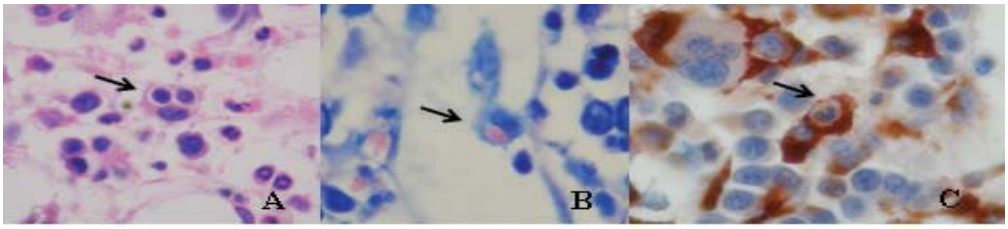

Figure 2. Second bone marrow biopsy. **A)** phagocytosis of two leukocytes by a histiocyte (arrow) (Hematoxylin and Eosin, 400x). **B)** erythrophagocytosis (arrow) (Giemsa, 400x). **C)** phagocytosis of a leukocyte by a histiocyte (arrow) (anti-CD68 immunostaining, 400x).

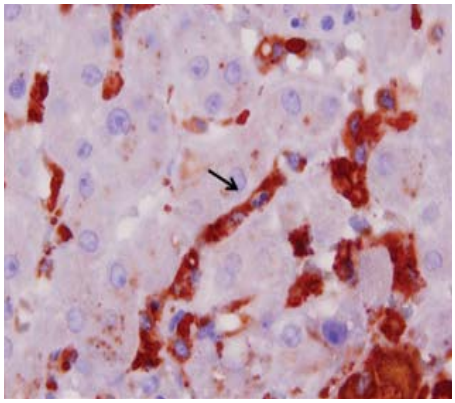

Figure 3. The liver biopsy shows diffuse macrophage infiltrations with phagocytosis of a leukocyte (arrow) (anti-CD68 immunohistochemical staining, 400x).

Table 3. Additional serologic tests.

HCV-RNA	Negative
Anti-EBV-VCA IgM	Negative
Anti-CMV IgM	Negative
RF	Negative
Anti-HIV	Negative
Anti-nuclear cytoplasmic antibodies	Negative
Wright's test	Negative
Gruber-Widal	Negative
Anti-HSV typ1 IgM	Negative
Anti-HSV typ2 IgM	Negative
Anti-VZV IgM	Negative
HIV-RNA PCR	Negative
Anti-Toxoplasma IgM	Negative
Anti-Rubella IgM	Negative
Anti-Measles IgM	Negative
Anti-Parvovirus B19	Negative
Anti-Borrelia Burgdorferi IgM	Negative
Anti-Chlamydia IgM	Negative
Anti-Mycoplasma IgM	Negative

exclusion of infectious, neoplastic and autoimmune disorders that can cause similar symptoms and findings. Therefore, the treatment can be delayed in cases with late presentation or rapid progression. Several sets of classification criteria have been developed; the most sensitive ones are those of the Yamaguchi's criteria.[10] However, lack of combined sensitivity and specificity is the major handicap of these criteria, but they can still be helpful in guiding diagnostic workup and identifying patients with higher likelihood of having AOSD.

Typical hematological manifestations of AOSD are characterized by neutrophil predominant leukocytosis (often > 15,000 cells/μL), normocytic, normochromic anemia and reactive thrombocytosis. Microangiopathic hemolytic anemia associated with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome and disseminated intravascular coagulation have been rarely reported in severe cases.[5,11] In one report of pathological review of 12 patients, the most frequent findings in bone marrow examination were granulocytic hyperplasia and hypercellularity with 25% and 16.7% of histiocytosis and RHS, respectively.[12] The actual prevalence of RHS is not known, because the diagnosis is based on identifying extensive infiltration of the reticuloendothelial system with well differentiated macrophages that are actively engulfing hemopoietic elements and routine bone marrow biopsy is not performed unless leukopenia and/or thrombocytopenia occur [13]. Moreover, identification of hemophagocytic macrophages with routine hematoxylin /eosin or Giemsa stains can also be challenging, even to an experienced eye. This can cause a challenge in everyday clinical practice; for instance in our case, we actually informed the pathologists that we were considering RHS for our patient, but hemophagocytic macrophages could not be identified under H/E and Giemsa stains despite careful examinations by senior pathologists. Hence, in suspicious cases, routine immunohistochemical staining with anti-CD68, a specific macrophage marker, can provide a better diagnostic performance, as in our case.[14]

Increased serum levels of HO-1, soluble CD163 and soluble IL2Rα levels have been suggested as specific biomarkers of RHS, but they are not widely accessible for clinical use.[13,15–17] However, serum ferritin levels are easily tested in daily practice and the degree of hyperferritinemia has been shown to be particularly important, as the levels exceeding 10.000 ng/mL are strongly suggestive of hemophagocytosis.[18,19] Lower levels of ferritin can also be compatible with RHS, but the specificity decreases. The lower percentage of glycosylated ferritin has been proposed to differentiate AOSD from other rheumatic diseases, but it is not widely available and its value in clinical practice has not been validated yet.[20] Other than being a diagnostic clue, levels of ferritin have been shown to correlate with disease activity and they are proposed to be used to monitor the disease activity in AOSD.[21] In our case, very high levels of ferritin mandated us to re-examine the biopsy specimens more vigorously to find hemophagocytic histiocytes, and we observed a gradual decline in ferritin levels that correlated with clinical improvement.

Hepatic involvement is commonly seen in AOSD, and typically characterized with hepatomegaly and mildly elevated liver enzymes; but severe liver disease is rare. There are no studies that systematically examined the liver biopsy findings in AOSD, but infiltration of the portal tracts and sinusoids with CD3+, CD8+, granzyme B+ lymphocytes admixed with CD68+, CD1a- histiocytes that exhibited hemophagocytosis, endothelialitis of portal and central veins and lymphocyte mediated bile duct injury were reported in an article dedicated to the pathological assessment of the liver in patients with familial hemophagocytic lymphohistiocytosis.[22] The degree of portal and sinusoidal lymphohistiocytic infiltrate and endothelialitis varied from mild to marked and correlated with clinical severity. In addition to routine stains, immunohistochemical stains were done for all cases in that study.[22] In our case, despite careful examination, we could identify characteristic infiltration of the liver by hemophagocytic histiocytes only after staining the specimens with anti-CD68. Another aspect of the liver involvement in AOSD is its possible association with concurrent NSAIDs ingestion. In a case series of 62 patients with AOSD, 2 deaths were attributed to severe liver failure and it was stated that severe liver failure always occurred in conjunction with either aspirin or NSAID therapy.[23] Interestingly, our patient also took two different NSAIDs before the development of severe hepatic disease. Whether there is a causal association between NSAIDs and severe hepatitis is unknown yet, but it would probably be judicial to abstain from NSAIDs.

Treatment of AOSD aims to induce clinical and laboratory remission, prevent severe complications and minimize the adverse effects of therapy. There are no randomized clinical trials to compare different therapeutic strategies yet, thus the treatment options are mainly based on clinical experience and case report series. Mild and moderately severe disease can be treated with low dose corticosteroids with or without disease modifying drugs, whereas severe disease is treated with high dose corticosteroids with disease modifying drugs. Guidelines for the treatment of hemophagocytosis suggest a combination of immunosuppressive and chemotherapeutic agents, such as steroids, etoposide and cyclosporine A.[13] However, cyclosporine A plus high dose corticosteroids can also successfully cure reactive hemophagocytosis associated with severe AOSD, and this option was successful in our case.[24,25]

Finally, prompt diagnosis of AOSD and its severe complications can be lifesaving. As specific laboratory markers are still lacking, we believe that attention to markedly elevated ferritin levels and routine staining of biopsy specimens with anti-CD68 can save time in the process of diagnosis. Although there is no evidence, a possible association between NSAIDs and severe hepatic disease should be kept in mind. High dose corticosteroids plus cyclosporine A could be the initial treatment in severe cases.

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