A case report of macrophage activation syndrome associated with adult-onset Still's disease

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Introduction

Macrophage activation syndrome (MAS) is a rare but potentially fatal systemic inflammatory abnormality. It can be idiopathic (primary) or secondary to infections, malignancies, autoimmune diseases (such as systemic juvenile idiopathic arthritis (sJIA), adult-onset Still's disease (AOSD), and systemic lupus erythematosus (SLE)), or drugs. (1) The inflammation is caused by the uncontrolled activation of macrophages and T cells. (1) Mortality has been reported to be 20-53%. (1) The characteristic presentations of MAS are persistent high fever, hepatosplenomegaly, coagulopathy, thrombocytopenia, hepatopathy, hyperferritinemia, and hemophagocytosis, which are similar to the manifestations in patients with AOSD and other conditions, such as systemic infection and malignancy. Therefore, recognizing the early-stage MAS is challenging and many of them are underdiagnosed. (2,3) The diagnosis is usually suspected on clinical and biochemical grounds and supported by the findings of well-differentiated macrophages phagocytosing hematopoietic cells in the bone marrow. (4) We would like to report a case of MAS in patients with AOSD, who presented with unremarkable bone marrow aspiration but a diagnostic liver biopsy.

Case presentation

The patient was a 31 years old lady with good past health, admitted for pyrexia of unknown origin for 3 weeks. She presented with sudden onset on and off high fever up to 39.6 degrees Celsius accompanied by chills and rigors. Pain over bilateral knees and lower thigh with swelling was reported. Respiratory, gastrointestinal, or urinary symptoms were absent. The fever persisted despite multiple trials of antibiotics. Physical examination showed stable vital signs, bilateral knee, and low thigh swelling with mild erythema and tenderness. The initial blood test revealed a mildly deranged liver function test. Other blood tests were unremarkable. Septic workups including blood culture, sputum culture, bone marrow culture, stool culture, and echocardiogram were negative. Computer tomography of the bilateral thigh showed diffuse deep subcutaneous edema or nodular opacities, suggestive of cellulitis. A skin biopsy was then taken and showed no pathological diagnosis. Bone marrow aspirations were performed twice and showed normocellular marrow with no abnormal infiltrations. Subsequent blood tests revealed deteriorating liver function test (ALT up to 486 U/L, ALP up to 1070 U/L), pancytopenia, elevated LDH (3616 U/L), and sky-high ferritin (35856 pmol/L). Viral hepatitis serology was negative. The anti-SM antibody was weakly positive but other autoimmune markers were negative. Serial computer tomography of the abdomen showed a slightly enlarged liver. Adult-onset Still's disease was clinically suspected and the patient was treated with steroids. The inflammatory markers and ferritin level trended down with steroids but liver function progressively worsen. A liver biopsy was performed and revealed haemophagocytic syndrome (HS) (synonymous with macrophage activation syndrome). Tacrolimus was added on top of the steroid and the liver function improved.

Microscopy

The liver biopsy showed a core of liver parenchymal tissue with up to 2 well-visualized portal tracts. The architecture was intact. The most striking feature was marked Kupffer cell hyperplasia with haemophagocytosis of erythrocytes and leucocytes (Figure 1a-1c). The portal tracts were infiltrated by some monocytes, without interface hepatitis. Patchy and mild macrovesicular steatosis, accompanied by a moderate degree of spotty liver cell necrosis, and mononuclear infiltrate were seen. (Figure 1d) Mallory hyaline or pericellular fibrosis was not found. The bile ducts were unremarkable and cholestasis was absent. Mild endothelial cell and Kupffer cell siderosis were noted. No epithelioid granuloma or specific microorganism was detected.

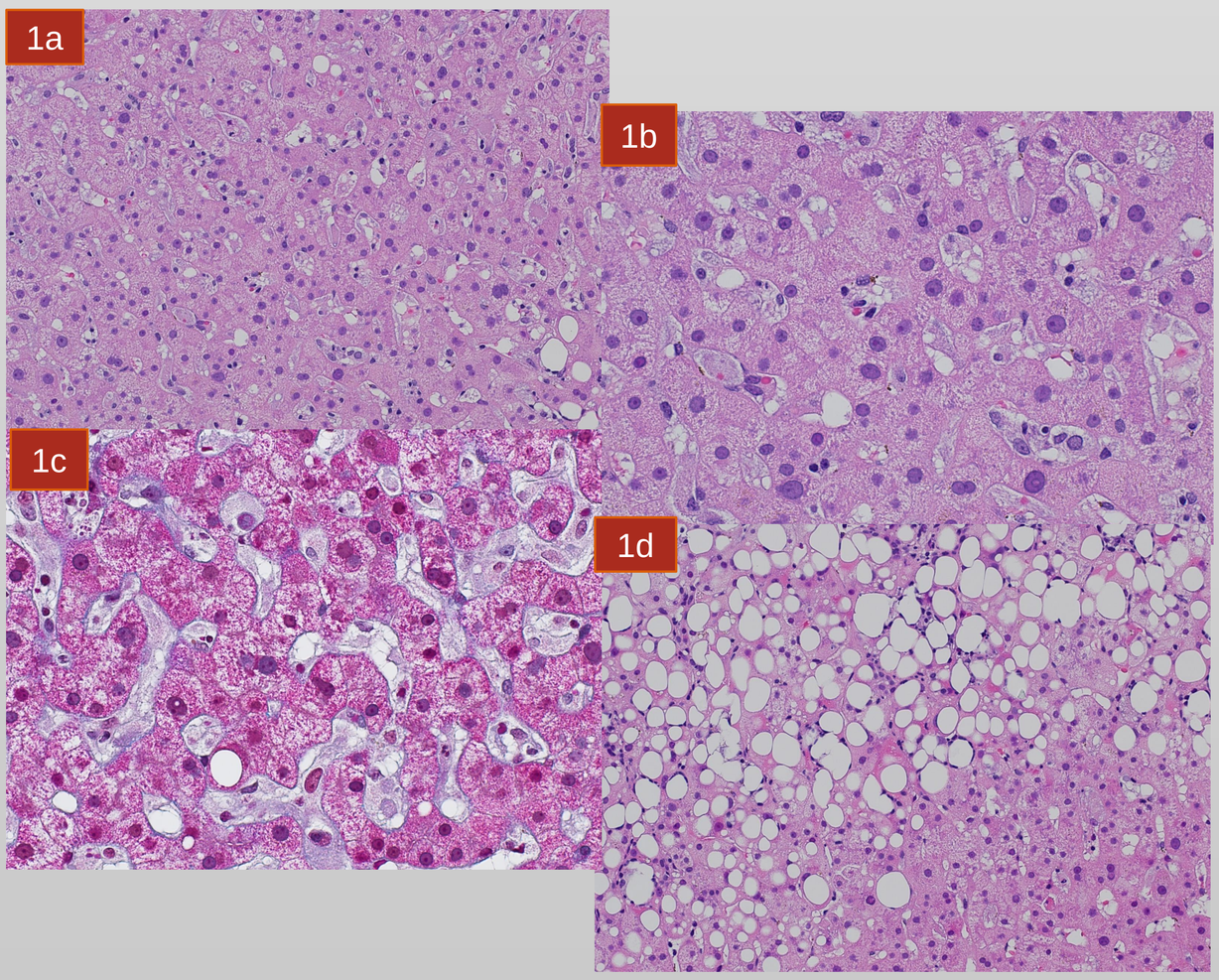
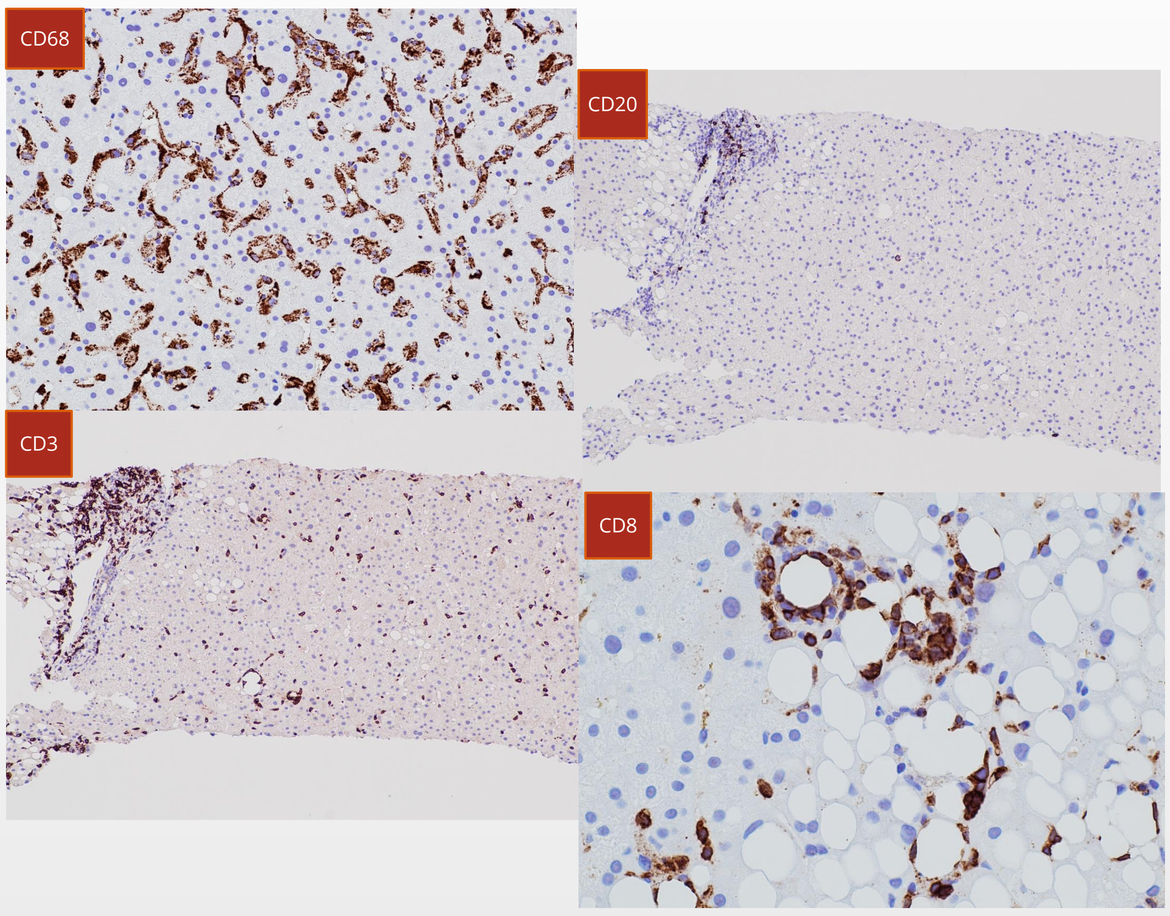


Figure 1a-1c: Kupffer cell hyperplasia with hemophagocytosis of erythrocytes and leucocytes. (1a-1b H&E; 1c Trichrome) 1d: Macrosteatosis with spotty necrosis. (1c H&E)

Immunohistochemical studies revealed a marked proliferation of CD68-positive macrophages. There was a predominance of CD3-positive T cells in the portal tracts and lobules, especially clustering around necrotic foci. Some CD20-positive B cells are present in portal tracts, but are almost entirely absent in the lobular parenchyma.

The features were those of haemophagocytic syndrome/macrophage activation syndrome. Lobular inflammation and steatosis can be part of the disease.



Discussion

The terminology of MAS is inconsistent in the literature. Many authors considered MAS equivalent to hemophagocytic syndromes, which are characterized by proliferation and accumulation of macrophages and dendritic cells, that can be primary or secondary, benign or malignant. (1) MAS has been reported in association with autoimmune diseases (such as sJIA, AOSD, SLE), Hodgkin's and non-Hodgkin lymphoma, leukemia, infection (such as herpes virus hepatitis, tuberculosis, and CMV infection), and drugs. (1, 5) It is widely accepted that MAS results from uncontrolled activation and proliferation of T cells and excessive activation of macrophages. (4) The prevailing pathogenesis of MAS is the involvement of activated IFN-γ-producing CD8+ lymphocytes, and TNF-α and IL-6-producing macrophages. (4) Our case also demonstrated the presence of predominantly CD8-positive T cells in the liver biopsy.

MAS is the major cause of death in AOSD patients. (6) The estimated prevalence of MAS in AOSD patients is 10-19% and the associated mortality rate is 10-20%. (2) MAS shows similar manifestations to patients with AOSD and other conditions, such as systemic infection and malignancy. Therefore, early recognition of MAS is challenging, leading to late diagnosis and death. Currently, there are several diagnostic or classification criteria for MAS based on clinical and biochemical findings to aid in early diagnosis, including hemophagocytic lymphohistiocytosis (HLH)-2004 and HLH-2009 diagnostic criteria, HScore for secondary MAS, and EULAR/ACR/PRINTO classification criteria for sJIA-associated MAS. (2) Notable liver dysfunction, splenomegaly, low number of platelets or neutrophils, high levels of serum ferritin, and reduced levels of fibrinogen are risk factors for poor outcomes. (6)

MAS has been defined as the combination of a proliferation of cytologically benign, actively phagocytic macrophages in bone marrow, spleen, or lymph nodes in association with fever, cytopenia, splenomegaly, and hypertriglyceridemia in some studies. (7,8) The hepatic manifestation in liver biopsy is not fully characterized. Kupffer cell hyperplasia and sinusoidal dilatation are the most reliable features. Hemophagocytosis, erythrophagocytosis, macrophages containing pigments, hepatocellular necrosis, fatty change, siderosis, lobular granuloma, and portal infiltrate are reported in some patients. (3,7,8) The number of CD8-positive lymphocytes is reported to be greater than that of CD4-positive lymphocytes. (8)

In summary, MAS should be suspected in patients with persistent high fever, hepatosplenomegaly, coagulopathy, thrombocytopenia, hepatopathy, and hyperferritinemia. Hepatic manifestations are characterized by sinusoidal dilatation and Kupffer cell hyperplasia with hemophagocytosis. Early diagnosis is vital to prevent mortality and underlying conditions should be actively looked for in cases of MAS.

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