Case Report

# Hepatitis A-Associated Macrophage Activation Syndrome in Children with Systemic Juvenile Idiopathic Arthritis: Report of 2 Cases

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***ABSTRACT.*** We describe two 3-year-old patients with systemic juvenile idiopathic arthritis (SJIA) who developed hepatitis A-associated macrophage activation syndrome (MAS). One patient showed MAS as the presenting manifestation of SJIA, while MAS complicated SJIA during the second year of the disease course in the other child. Both girls presented with fever, jaundice, hepatosplenomegaly, neurological involvement, mucosal hemorrhage, and purpura. Cytopenias, hypofibrinogenemia, and hemophagocytosis confirmed the diagnosis. After aggressive treatment with high-dose corticosteroids and immunosuppressants one patient entered remission while the other one died. Hepatitis A virus may induce severe MAS in SJIA. (First Release Nov 15 2007; J Rheumatol 2008;35:166–8)

*Key Indexing Terms:*
MACROPHAGE ACTIVATION SYNDROME
HEPATITIS A
JUVENILE IDIOPATHIC ARTHRITIS
HEMOPHAGOCYTOSIS

Macrophage activation syndrome (MAS) is a clinical condition caused by the excessive activation and proliferation of lymphocytes and macrophages[1]. It is considered a form of secondary hemophagocytic lymphohistiocytosis occurring in a patient with a rheumatic condition, predominantly systemic juvenile idiopathic arthritis (SJIA)[2]. Infectious (especially herpes viruses) and pharmacological agents have been identified as the most common triggers for this association[3]. Hepatitis A virus (HAV)-associated reactive lymphohystiocytosis and MAS have been reported in adults[4,5].

We describe 2 cases of HAV-associated MAS complicating SJIA in young children.

## CASE REPORT

*Case 1*. In July 1998, a previously healthy 3-year-old girl presented at a peripheral hospital with a 3-day history of fever, jaundice, and somnolence alternating with irritability, oral mucosal bleeding, and diffuse edema on lower limbs. A clinical diagnosis of acute hepatitis was made. Despite supportive treatment with vitamin K, plasma infusions, and lactulose, she showed progressive worsening and was transferred to our center with a diagnosis of fulminant hepatic failure for emergency liver transplantation. Clinical and laboratory findings at admission are shown in Table 1. ELISA was positive for immunoglobulin M (IgM) anti-HAV antibody. Serological tests for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and parvovirus B19 were negative; polymerase chain reaction (PCR) assay for EBV in plasma was negative. Blood and cerebrospinal fluid (CSF) cultures were negative. CSF analysis disclosed 2 mononuclear cells/mm$^3$ (normal 0–5), proteins 120 mg/dl (normal 15–40), sterile. Tests for antinuclear antibodies, rheumatoid factor, and anti-DNA antibodies were negative. Virus-associated hemophagocytic syndrome was suspected and bone marrow aspirate and biopsy were performed: aspirate smear showed severe hypoplasia of all series and abundance of plasma cells, while biopsy evidenced hemophagocytosis. Bone marrow bacteriologic cultures were negative. She was treated according to the HLH-94 protocol for hemophagocytic lymphohistiocytosis[6], which consisted of dexamethasone 10 mg/m$^2$/day for 2 weeks with progressive tapering, plus etoposide 150 mg/m$^2$ twice weekly for 2 weeks and weekly thereafter for 3 months. Additionally, she received 4 weekly doses of intrathecal methotrexate (MTX; 12 mg) and dexamethasone (4 mg). Fever resolved immediately, while other clinical and biochemical disturbances improved progressively and finally normalized after 4 weeks. She was subsequently discharged in good condition. During the next year she remained symptom-free. Twelve months after treatment had finished, she was admitted with an evanescent salmon-colored rash on trunk and proximal limbs, intermittent fever (quotidian for the previous 10 days), and limb pains. Signs of arthritis on elbows, wrists, knees, ankles, and hips were evident. Laboratory examinations showed leukocytosis and elevated erythrocyte sedimentation rate. A diagnosis of SJIA was made and she was treated with daily naproxen plus weekly MTX at 10 mg/m$^2$. She entered remission after 6 months, and she is currently symptom-free and off all medications.

*Case 2*. In March 2006, a 3-year-old girl with a 2-year history of SJIA presented at the Emergency Department with malaise, jaundice, and continuous high-grade fever that had begun 2 days prior to admission. On her previous visit to the Rheumatology Clinic (1 month before admission) she had been well, with no systemic symptoms; her joint examination had been remarkable only for arthritis in both ankles. At that time, white blood cell count was 30.7 × 10$^9$/l, hemoglobin 11.0 g/dl, and platelet count 436 × 10$^9$/l. She was receiving MTX 15 mg/m$^2$ weekly, folic acid 5 mg weekly, and naproxen 18 mg/kg/day. On admission she was acutely ill and lethargic. Initial clinical and laboratory findings are shown in Table 1. ELISA was positive for IgM anti-HAV antibody, while investigations for HBV, HCV, HIV, varicella-zoster

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*Table 1.* Clinical, biochemical, and immunological features of macrophage activation syndrome. Normal values given in parentheses.

| | Patient 1 | Patient 2 |
|---|---|---|
| Fever | + | + |
| Hepatosplenomegaly | + | + |
| Jaundice | + | + |
| Purpura | + | + |
| Lethargy | + | + |
| White cell count (5.0–11 × $10^9$/l) | 3.0 | 20.3 |
| Platelet count (150–400 × $10^9$/l) | 40 | 39 |
| Hemoglobin (11.5–14 g/dl) | 5.4 | 10.5 |
| ESR (1–15 mm/h) | 12 | 10 |
| ALT (7–61 U/l) | 1450 | 6300 |
| AST (7–67 U/l) | 3440 | 11,800 |
| Bilirubin (0.1–1 mg/dl) | 20 | 10.1 |
| Albumin (35–45 g/l) | 20 | 24 |
| Triglycerides (50–180 mg/dl) | 259 | 124 |
| Ferritin (7–142 ng/ml) | ND | 1100 |
| Prothrombin concentration (70–100% normal) | 14 | 15 |
| aPTT (35–45 s) | 92 | 62 |
| Fibrinogen (1.5–4.0 g/l) | 0.3 | 0.4 |
| Natremia (136–145 mEq/l) | 126 | 126 |
| Natural killer cell function (15–25% lysis) | 10 | 1 |
| Soluble interleukin 2 receptor (269–1,116 U/ml) | ND | 24,500 |
| Hemophagocytosis in bone marrow | + | + |

ND: not done; ESR: erythrocyte sedimentation rate; aPTT: activated partial thromboplastin time.

virus, herpes virus 1 and 2, CMV, EBV, and parvovirus B19 were negative. Blood and urine cultures were negative. No autoantibodies were detected. Bone marrow aspiration revealed hemophagocytosis of erythroid precursors, which confirmed MAS at this stage. She was treated with 3 daily pulses of intravenous methylprednisolone (30 mg/kg) and cyclosporine 3 mg/kg/day. However, she entered a comatose state and was admitted to the intensive care unit for mechanical ventilatory support. Over the following days plasma infusions and cardiovascular support were provided. Etanercept 0.4 mg/kg was added, while m-prednisolone was administered daily at 2 mg/kg. Despite therapy, renal insufficiency and progressive hemodynamic instability followed. She died 1 week after admission.

## DISCUSSION

Both a previously healthy young child and a girl with established SJIA developed acute hepatitis induced by HAV, characterized by hepatomegaly, jaundice, and continuous fever. Subsequent neurological involvement, hemorrhage, and sudden onset of absolute or relative cytopenia alerted us to the possibility of MAS. Hypertriglyceridemia, hypofibrinogenemia, elevated serum ferritin, defective natural killer (NK) cell activity, and hemophagocytosis supported the diagnosis and immunosuppressive therapy was begun, followed by remission in 1 patient (who later developed SJIA) and death in the other girl. The patients we describe appear to be the first reported cases of hepatitis A-associated MAS occurring in young children with a diagnosis of SJIA.

MAS is a well known, severe complication of SJIA[7]. The basic immunological abnormalities of MAS are defective natural killer cell activity, excessive proliferation of T cells and macrophages, and overproduction of cytokines[8]. Multiorgan involvement, including massive infiltration of lymphocytes and histiocytes into the liver[9], is common in MAS.

Hepatitis A is a highly prevalent disease in developing countries. While most pediatric infections are asymptomatic, 0.1% of patients undergo manifestations of fulminant hepatic failure leading to death, liver transplantation, or, more rarely, spontaneous remission[10]. Hepatitis A-induced hemophagocytic syndrome in previously healthy adults has been reported[4,11]. Virus-associated MAS has been described in patients with SJIA, with viruses of the herpes family being the most frequent triggers[3]. McPeake, *et al* described a 20-year-old patient with a diagnosis of SJIA since childhood who had EBV-induced MAS at age 8 and hepatitis A-associated MAS at age 20[5]. Although virus-associated hemophagocytic syndrome may have developed in a healthy child who later developed SJIA, we believe our first patient most likely had HAV-associated MAS as the first manifestation of SJIA. The use of immunosuppressive therapy for MAS may have delayed the onset of the typical clinical features of SJIA in Patient 1. MAS as the presenting manifestation of SJIA has been reported[12].

The presentation and course of MAS in our patients did not show any differential feature from MAS unrelated to HAV occurring in children with SJIA. Hepatic failure, observed in both cases, has been reported in patients with very severe forms of MAS. Since hepatomegaly, fever, jaundice, and other signs of liver failure are common to MAS and acute hepatitis, additional features may help differentiate both conditions. Splenomegaly, edema, rapidly evolving cytopenias — or a sharp drop in neutrophil or platelet count — hypofibrinogenemia, hyperferritinemia, and hypertriglyceridemia should alert the rheumatologist about the probability of MAS and prompt performance of a bone marrow biopsy to look for evidence of hemophagocytosis. Additionally, elevated circulating soluble interleukin 2 receptor (as shown in Patient 2) and soluble CD163, as well as defective natural killer cell function, are valuable markers of MAS[13]. To aid in the formulation of a diagnosis, preliminary diagnostic guidelines for MAS in SJIA have been recently proposed by Ravelli, *et al*[14].

MAS carries a somber prognosis, with mortality rates varying between 20% and 30%[3]. Our first patient received the current standard therapy for hemophagocytic lymphohistiocytosis, leading to complete remission of MAS. In the second patient, the usual initial therapy for SJIA-related MAS (high-dose corticosteroids and cyclosporine) was administered. However, it proved ineffective despite addition of the tumor necrosis factor blocking agent etanercept, which has been successfully used in MAS complicating SJIA[15]. A more aggressive approach including etoposide might be beneficial for very severe cases of MAS in SJIA as well.

HAV may trigger severe MAS, a potentially lethal complication of SJIA. Differentiation from an ordinary acute hepatitis, based on clinical and biochemical evidence, is vital to allow early recognition and intense therapy.

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