A Rare Case of Severe Acute Hepatitis Associated with Adult-Onset Still Disease Dramatically Improved by High-Dose Steroid Therapy

Tiffany Hogan, MD\textsuperscript{1}  
Kevin T. Kao, MD\textsuperscript{2}  
Jim Tung, MD\textsuperscript{2}

\textsuperscript{1}Department of Internal Medicine,  
\textsuperscript{2}Department of Gastroenterology and Hepatology, Kaiser Permanente, Los Angeles Medical Center, Los Angeles, California

A dult-onset Still disease (AOSD) is a rare systemic inflammatory disorder with an unknown etiology. It is characterized by daily fevers of at least 39°C, arthralgias or arthritis, evanescent rash, and leukocytosis ($\geq 10,000$ cells/mm$^3$) with at least 80% neutrophils.\textsuperscript{1} Hyperferritinemia is frequently seen in AOSD; however, this sign is not pathognomonic. Other common symptoms associated with AOSD include sore throat, myalgia, lymphadenopathy, pleuritis or pericarditis, splenomegaly, and abdominal pain secondary to deep lymphadenitis.\textsuperscript{1} AOSD can be associated with liver dysfunction. Rarely, AOSD can lead to fulminant liver failure. This case describes a patient who presented with severe hepatitis and worsening coagulopathy; the patient was diagnosed with AOSD-associated severe hepatitis and successfully treated with high-dose steroid therapy.

AOSD is diagnosed using the Yamaguchi criteria.\textsuperscript{2} The 4 major criteria proposed by Yamaguchi include: 1) fever of at least 39°C lasting at least 1 week; 2) arthralgias or arthritis lasting 2 weeks or longer; 3) nonpruritic macular or maculopapular skin rash that is salmon-colored in appearance and usually found over the trunk or extremities during febrile episodes; and 4) leukocytosis ($\geq 10,000$ cells/mm$^3$) with at least 80% granulocytes.\textsuperscript{2} Minor criteria include sore throat, lymphadenopathy, hepatomegaly and/or splenomegaly, abnormal liver function, and negative test results for antinuclear antibody and rheumatoid factor.\textsuperscript{2} Rarely, acute liver failure can be associated with AOSD, but only 11 such cases have been documented in the literature since September 2009.

Case Report

History of the Present Illness

The patient was a 35-year-old Japanese-American woman with a history of hypertension who was transferred to our institution for suspected impending liver failure associated with a febrile illness. Her symptoms started 3 months prior to presentation with multiple joint arthralgias and rash that initially started in the lower extremities. During her initial visit to her primary care physician, she was found to have palpable cervical lymphadenopathy.

She was evaluated by physicians in the rheumatology and dermatology departments, but neither evaluation led to a definite diagnosis. A trial of prednisone was then started but did not yield any notable clinical improvement. A second rheumatologist, who felt the patient had rheumatoid factor–negative rheumatoid arthritis (RA), subsequently started her on sulfasalazine.

During routine evaluation, the patient was noted to have elevated levels of liver function enzymes. Given her recent diagnosis of RA, this finding was thought to be due to a related autoimmune liver disease.

Unfortunately, the patient’s symptoms did not improve, and she presented to the emergency room with a fever of 105°F, rash, and diffuse joint pain. She denied any history of alcohol or recreational drug abuse. She also reported no travel history or use of herbal supplements. Within 48 hours, she was found to have rapidly rising levels of liver function enzymes: Her alanine aminotransferase (ALT) level increased from...
165 U/L to 889 U/L, her aspartate aminotransferase (AST) level increased from 241 U/L to 1,696 U/L, and her bilirubin level was 4 mg/dL. Her international normalized ratio (INR) was 1.9 (normal, 0.9–1.1). Given her deteriorating condition, she was urgently transferred to our facility for tertiary care.

**Physical Examination**
On presentation to our facility, the patient’s vital signs were significant for a fever of 103.3°F. She was alert and oriented, and she did not show signs of encephalopathy. Her examination was significant for cervical lymphadenopathy and a diffuse, salmon-colored maculopapular rash located on her trunk, proximal limbs, and face (Figure 1). She also had swollen hands (Figure 2). She was notably jaundiced, and icteric sclerae were observed. Her abdominal examination showed midepigastrium and right upper quadrant tenderness without rebound tenderness.

**Laboratory Findings**
The patient’s white blood cell count was 16,100 cells/mL (normal, 4,000–11,000 cells/mL) with a differential of 83% neutrophils. Her ALT level was 1,148 U/L (normal, 14–54 U/L), her AST level was 1,908 U/L (normal, <31 U/L), her bilirubin level was 4.7 mg/dL (normal, 0.1–1.0 mg/dL), and her INR was 2.9 (normal, 0.9–1.1). Her creatinine level was 1.5 mg/dL (normal, 0.6–1.1 mg/dL). Tests for antinuclear antibody, anti-mitochondrial antibody, anti-smooth muscle antibody, anti-liver/kidney microsomal antibody, immunoglobulins, ceruloplasmin, and α1 antitrypsin were all negative.

Infectious studies—including tests for viral hepatitis A, viral hepatitis B, viral hepatitis C, viral hepatitis E, Epstein-Barr virus, cytomegalovirus, HIV, and West Nile virus; Rickettsial serology; Leptospira serology; Borrelia serology; and blood and urine cultures—were also negative. Likewise, her hemostatic work-up—including testing for double-stranded DNA, anti-JO-1 antibodies, and rheumatoid factors—were negative. Her ferritin level was 31,425 ng/mL (normal, 13–150 ng/mL).

**Imaging**
Ultrasound imaging of the abdomen showed thickening of the gallbladder wall with some pericholecystic fluid but no biliary ductal dilation. Computed tomography imaging of the thorax, abdomen, and pelvis showed enlarged lymph nodes in the neck, small right pleural effusion, and small pericardial effusion.

**Pathology Findings**
A liver biopsy showed cholestatic chronic necroinflammatory disease with mild portal and lobular inflammation. Regenerative changes were also seen, including hepatocyte pleomorphism, increased numbers of binucleated hepatocytes, and cholestatic acinar transformation. Periodic acid–Schiff–positive macrophages were prominent, which is consistent with relevant liver cell necrosis. Features of autoimmune hepatitis were not seen.

**Clinical Course**
The patient was diagnosed with AOSD based on the fact that she fulfilled all of the Yamaguchi diagnostic criteria. She was promptly started on intravenous methylprednisolone at a dose of 80 mg every 8 hours. Unfortunately, her INR continued to rise despite aggressive treatment. Given her Model for End-Stage Liver Disease score of 28, she was transferred to an affiliated hospital for urgent listing for liver transplantation. After 2 days of methylprednisolone treatment, however, the patient’s liver enzyme levels began to trend down dramatically. She was transferred back to our facility and switched to an oral prednisone taper. After 24 days in the hospital, she showed normal liver function test results and was discharged in good condition.

**Discussion**
AOSD is an uncommon inflammatory disease that was first described by Eric George Bywaters in 1971.3 Bywaters...
described a set of adult patients who presented with symptoms of juvenile inflammatory arthritis, or Still disease, which had been previously described by George Still in 1896. By definition, AOSD affects individuals older than 16 years of age; it can occur either de novo or in patients with a history of systemic juvenile inflammatory arthritis. AOSD is a rare disease. Based on an epidemiologic survey in Japan, Wakai and colleagues estimated the crude prevalence of AOSD among adults 16 years or older to be 0.73 per 100,000 men and 1.47 per 100,000 women, with corresponding crude incidence rates of 0.22 and 0.34. The sex ratio of the reported patients was 2.1. In a retrospective study of 62 patients from western France, AOSD was found to have a bimodal distribution with peaks at ages 15–25 years and 36–46 years.

AOSD is mainly a clinical diagnosis. The diagnostic criteria were formulated by Yamaguchi and coauthors through a multicenter survey of 90 Japanese patients with AOSD and 267 control patients. The criteria consist of both major criteria (such as fever, arthralgias, macular or maculopapular nonpruritic salmon-colored rash, and leukocytosis) and minor criteria (including sore throat, lymphadenopathy and/or splenomegaly, liver dysfunction, and the absence of rheumatoid factor and antinuclear antibody). A diagnosis is made when 5 or more criteria, including 2 or more major criteria, are present. The sensitivity and specificity of these criteria were shown to be 96.2% and 92.1%, respectively.

AOSD can be divided into 3 distinct clinical courses: 1) a self-limited monophasic pattern that usually lasts less than 1 year with complete resolution of symptoms; 2) an intermittent or polycyclic systemic pattern in which patients have 1 or more flares of AOSD with complete remission between each episode; and 3) a chronic pattern in which patients have persistently active disease that is most commonly associated with destructive arthritis. Approximately one third of patients fall into each of these 3 categories. Patients with chronic articular disease generally have more disability and worse prognoses than patients with systemic symptoms. In contrast, patients with systemic disease have more favorable prognoses with only rare complications from the disease, such as pericarditis, pericardial tamponade, hepatic disease, respiratory failure, or treatment complications (such as infections and gastrointestinal bleeding).

As with other rheumatic diseases, the pathogenesis of AOSD is unknown; however, a few theories have been proposed that may explain the disease process. The most widely researched theory is the immunologic model of AOSD. According to this theory, AOSD is thought to occur when environmental factors such as bacteria, parasites, or chemical/toxic agents activate macrophages and cause cytokine hyperproduction. Elevated interleukin (IL)-6 and/or IL-18 levels have been associated with systemic symptoms such as fever, rash, and hepatic dysfunction; elevations in IL-6 and/or IL-18 levels also correlate with elevated levels of serum C-reactive protein. Moreover, overproduction of IL-18 has been related to high serum ferritin levels, a finding that is highly suggestive of AOSD. This finding is considered to be the main factor in causing hepatitis.

A nonsteroidal anti-inflammatory drug (NSAID) or aspirin is recommended as the initial treatment in AOSD, but the reported response rate is only 20–25%. For patients who lack an initial response to NSAIDs, steroids are generally used, with reported efficacy rates as high as 95%. Prednisolone should be used for patients suffering from persistent anemia, pericarditis, serositis, or hepatitis. Other treatments such as methotrexate, azathioprine, cyclosporine, and infliximab (Remicade, Janssen) have also been reported to be effective treatments for AOSD.

Rarely, AOSD has been associated with liver failure, which often affects young people and carries a very high mortality. Although acute liver failure is a rare complication in AOSD, 8 reported cases of fulminant liver failure in association with AOSD have been reported, including 4 fatalities. All 4 patients had been treated with NSAIDs.8–10

Our patient suffered from rapid deterioration of liver function without a history of hepatotoxic drug use. This observation suggests that AOSD can cause severe liver injury in the absence of other concomitant factors. This case also demonstrates that patients suffering from AOSD can present with severe hepatitis; in addition, it shows that prompt diagnosis and initiation of the right therapy are keys to successful management. This case also suggests that use of
steroids rather than NSAIDs may be a safer first-line therapy in AOSD patients with concurrent liver dysfunction.

References

Review
Still Disease and the Liver—
An Underappreciated Association
Kieron B. L. Lim, MBBS, MRCP, FAMS1,2
Thomas D. Schiano, MD1
1Division of Liver Diseases, Mount Sinai Medical Center, New York, New York;
2Department of Gastroenterology & Hepatology, National University Hospital Singapore, Singapore, Singapore

Liver dysfunction is common in adult-onset Still disease (AOSD); indeed, liver dysfunction is one of the diagnostic criteria described by Yamaguchi and colleagues. Among the collagen vascular diseases, AOSD is associated with the highest incidence of liver dysfunction, with a reported range of 35–85%.2 Liver involvement in AOSD can vary from asymptomatic aminotransferase elevations to life-threatening fulminant hepatic failure (FHF) requiring liver transplantation (LT). Liver dysfunction and FHF may occur at the time of AOSD diagnosis, during the corticosteroid taper, or many years after diagnosis when symptoms are well controlled.3,4 In the case by Hogan and colleagues, the authors describe a case of AOSD with severe hepatic dysfunction that was successfully treated with parenteral corticosteroid therapy; had this therapy not been successful, this patient could have developed FHF and had a poor outcome.5 This case highlights some pertinent issues for clinicians who manage these complex and potentially fatal cases.

Symptoms of AOSD can be easily overlooked or attributed to another diagnosis, as these symptoms can be nonspecific and may overlap with other diseases. Indeed, the patient described by Hogan and colleagues was evaluated by 3 physicians (a primary care physician, a rheumatologist, and a dermatologist) without a definitive diagnosis being made; the patient was then given a trial of prednisone and subsequently commenced on sulfasalazine by a second rheumatologist but did not show much improvement.

Liver toxicity secondary to sulfasalazine has been reported in patients with AOSD. Caspi and colleagues reported 2 young adults with juvenile rheumatoid arthritis who developed abnormal liver chemistry test results following treatment with sulfasalazine at doses of 1.5 g and 2 g daily; these abnormalities resolved with discontinuation of the drug.6 Liver dysfunction is known to occur at even lower doses of sulfasalazine (500 mg twice daily).7 As sulfasalazine is commonly prescribed for rheumatologic disorders, clinicians should be cognizant of the fact that it can cause liver dysfunction, even at low doses, in patients with AOSD.

Address correspondence to:
Dr. Thomas D. Schiano, Division of Liver Diseases, Mount Sinai Medical Center, One Gustave Levy Place, Box 1104, New York, NY 10029; Tel: 212-659-8502; Fax: 212-261-2138; E-mail: thomas.schiano@mountsinai.org
Clinicians should not attribute liver dysfunction in AOSD patients to an associated autoimmune liver disease or autoimmune hepatitis (AIH) until a thorough evaluation has been completed. A positive antinuclear antibody (ANA) test result is not sufficient to diagnose AIH, as ANA is positive in up to 10% of AOSD patients and the general population; hypergammaglobulinemia is also common in AOSD.8

Liver biopsy findings are important when establishing a diagnosis of AIH in patients with AOSD. Histologic features of AOSD patients with liver dysfunction include periportal mononuclear infiltrates, Kupffer-cell hyperplasia, lobular inflammation, focal hepatic cellular degeneration, periportal fibrosis, and massive or submassive hepatic necrosis. Ground glass–like cytoplasmic inclusions typically seen in chronic hepatitis B infection and sinusoidal dilatation typically associated with venous outflow impairment have also been described in AOSD patients with elevated liver enzyme levels.9,10 The utility of a liver biopsy in patients with AOSD and liver dysfunction is debatable.11 Although its direct role in establishing the diagnosis of AOSD is limited, liver histology may provide valuable information regarding previously undiagnosed concomitant liver pathology, which may influence the therapeutic strategy and eventual outcome of liver dysfunction in patients with AOSD.

A thorough search for previously undiagnosed hepatitis B virus (HBV) infection is also vital (including assessment of hepatitis B core antibody and hepatitis B surface antibody status if hepatitis B surface antigen testing is negative), as FHF secondary to HBV reactivation is well reported in patients on steroid therapy, chemotherapy, and anti–tumor necrosis factor (anti-TNF) agents.12-15 Antiviral drugs must be commenced if HBV infection is confirmed. Michel and colleagues described a patient with AOSD and inactive chronic HBV infection who developed FHF requiring LT after the second dose of infliximab (Remicade, Janssen). Interestingly, there was no evidence (either serologic or histologic) for HBV reactivation as the cause of hepatic failure; the authors concluded that infliximab per se was the primary cause of the fulminant hepatitis.16 Infliximab-induced AIH is well described and has also been reported to cause FHF requiring LT.17-19 Overall, causes of liver dysfunction in patients with collagen vascular diseases include drug-induced liver injury (26.1%), primary biliary cirrhosis (15.9%), fatty liver (7.6%), AIH (4.2%), viral hepatitis (1.3%), and the collagen vascular disease itself (15.5%). Collagen vascular disease itself is reported to be the most common cause of liver dysfunction in patients with AOSD.5

Portal vein thrombosis in the setting of AOSD with mildly elevated liver enzyme levels has been described and reinforces the importance of liver imaging in these patients.20 Hemophagocytic syndrome (HPS) is associated with AOSD in up to 12% of cases and may induce FHF.21 HPS, also known as macrophage activation syndrome, is a severe and potentially life-threatening condition that can be induced by chronic rheumatic diseases, including AOSD.22 This condition is characterized by fever, hepatosplenomegaly, lymphadenopathy, skin rash, lung infiltration, and liver dysfunction. Coagulopathy, hyperferritinemia, and hypertriglyceridemia are common. A conclusive diagnosis is established by histology demonstrating phagocytosis of hematopoietic precursor cells in the bone marrow, lymph nodes, liver, or spleen. Current therapy for HPS includes treatment of the underlying disease, intensification of immunosuppression, chemotherapy, plasmapheresis, whole blood exchange, and bone marrow or stem cell transplantation.17

As Hogan and colleagues mention in their report, the immunologic pathways involved in the pathogenesis of AOSD are of increasing and significant interest.3 Several cytokines have been well characterized in the pathogenesis of AOSD, including interleukin (IL)-1, IL-6, IL-18, and TNF-α.23 IL-18, in particular, is thought to play a pivotal role in the inflammatory cascade by orchestrating the T helper 1 cell response and inducing other cytokines, such as IL-1B, IL-8, and interferon-γ. IL-18 is thought to mediate the hepatotoxic manifestations of AOSD and has been found to correlate significantly with serum amino-transferase levels.24 Levels of circulating IL-18 are markedly increased in patients with FHF and acute hepatitis compared to patients with chronic liver diseases, suggesting that a substantial increase in IL-18 level is specific for and plays an important role in acute liver injury in humans.25 Extremely high serum IL-18 levels have been reported in patients with FHF associated with AOSD. Priori and colleagues demonstrated a marked increase in IL-18 expression by activated macrophages and Kupffer cells within the liver parenchyma of a patient with AOSD and hepatic involvement who was resistant to corticosteroids but not in a control liver with drug-induced hepatitis; this increase in IL-18 expression was accompanied by an associated increase in IL-18 serum concentration.26 Serum levels of IL-18 are now thought to correlate with disease activity and disease severity, and serum levels of IL-18 appear to serve as an early predictor of liver dysfunction. Insights into immunologic pathways and cytokine hyperproduction explain the rationale for employing anti-TNF agents (infliximab, etanercept [Enbrel, Immunex], adalimumab [Humira, Abbott]), anti–IL-1 (anakinra [Kineret, Biovitrum AB]), and anti–IL-6 (tocilizumab [Actemra, Genentech]) in the therapeutic strategy of AOSD.27-28 These agents are used in addition to the conventional treatment regimens of nonsteroidal anti-inflammatory drugs, corticosteroids, and disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, cyclosporine,
Hydroxychloroquine, gold, penicillamine, azathioprine, leflunomide, and cyclophosphamide. Liver enzyme levels must be monitored in patients taking nonsteroidal anti-inflammatory drugs and DMARDs. Methotrexate is known to cause steatosis, hepatic fibrosis, and FHF; azathioprine is associated with nodular regenerative hyperplasia (a cause of noncirrhotic portal hypertension) and deranged liver enzyme levels. Hydroxychloroquine and leflunomide have both been reported to cause severe hepatitis and FHF.

Some authors have suggested that the degree of liver dysfunction reflects the activity of the original disease, as liver enzyme levels improve in parallel with recovery of the collagen disease following steroid therapy, as in the case described by Hogan and coauthors. In a series of 104 AOSD patients in which over 60% of patients developed liver dysfunction at the onset of AOSD, 72% of patients achieved a complete response after 4 weeks of corticosteroid therapy; however, relapse rates up to 46.9% were noted. Leukocytosis above 3 × 10³ cells/μL, a ferritin level greater than 1,500 ng/mL, an erythrocyte sedimentation rate above 100 mm/h, and a starting steroid dose below 40 mg/d of prednisone are all risk factors for disease relapse. Steroid-refractory AOSD cases have been successfully treated with anakinra, tocilizumab, and cyclosporine. Occasionally, FHF ensues despite high-dose corticosteroid treatment and salvage therapies, with potentially fatal outcomes. Urgent transfer of the patient to a tertiary center and evaluation for LT is warranted under these circumstances. The timely diagnosis and treatment of AOSD, exhaustive exclusion of other liver pathology, recognition of potentially fatal hepatic failure, and expeditious evaluation for LT as described by Hogan and colleagues are key steps in managing patients with AOSD and liver dysfunction.

References