

Case Report

Interleukin 18 and Hepatocyte Growth Factor in Fulminant Hepatic Failure of Adult Onset Still's Disease

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ABSTRACT. Adult onset Still's disease (AOSD) is a rheumatoid disorder characterized by polyarthritis, intermittent high fever, and salmon colored rashes. Liver dysfunction is usually mild and fulminant liver failure is rare. We describe a 20-year-old woman with AOSD and severe hepatic necrosis leading to hepatic failure requiring liver transplant. This severe liver disorder developed after decreases in fever, arthritis, and C-reactive protein. Interleukin 18 (IL-18), but not ferritin, increased in association with liver dysfunction. Hepatocyte growth factor (HGF) increased at the time of hepatic failure. IL-18 and HGF elevation may have contributed to this rare severe liver injury in AOSD. (J Rheumatol 2003;30:1093-6)

Key Indexing Terms:

ADULT ONSET STILL'S DISEASE
LIVER TRANSPLANT INTERLEUKIN 18

FULMINANT HEPATIC FAILURE
HEPATOCTYTE GROWTH FACTOR

Adult onset Still's disease (AOSD) is an uncommon disorder first described by Bywaters in 1971¹. Diagnosis is based on a constellation of clinical and laboratory features as proposed by the Adult Still's Disease Research Committee of Japan in 1992². Clinical findings include intermittent high fevers, polyarthritis, salmon colored rashes, sore throat, lymphadenopathy, splenomegaly, and liver dysfunction. Laboratory results represent nonspecific evidence of inflammation, such as C-reactive protein (CRP) elevation, leukocytosis, and anemia. Recently, serum ferritin and interleukin 18 (IL-18) concentrations have been measured as sensitive indicators of disease activity in AOSD^{3,4}. However, the specific pathogenic roles of ferritin and IL-18 are unclear.

Liver dysfunction in AOSD usually is mild; severe hepatic failure requiring liver transplant is extremely rare⁵⁻⁷. We describe a patient who received a transplant after severe hepatic necrosis had led to liver failure. Profiles of IL-18 and hepatocyte growth factor (HGF) concentrations during this patient's course suggest pathogenic importance.

CASE REPORT

A 20-year-old woman was admitted to our hospital in September 2000 because of an exacerbation of AOSD. Based on the presence of intermittent high fevers, polyarthritis, salmon colored rashes, elevated concentrations of CRP, hyperferritinemia, and mild liver dysfunction, she had been diagnosed with AOSD in December 1997. Symptoms improved with daily oral administration of 60 mg of prednisolone (PSL). A second exacerbation developed in August 1998 after PSL tapering. Symptoms did not improve with oral PSL (30 mg/day) and pulse steroid therapy (3 days of methyl-PSL at 1 g), but responded to intermittent low dose methotrexate (MTX) therapy (7.5 mg/wk). After discontinuation of MTX because of amenorrhea, a third exacerbation developed in April 1999, still unaccompanied at first by liver dysfunction. After symptoms responded to a resumption of MTX together with oral PSL (40 mg/day), liver dysfunction appeared. Liver function improved after the discontinuation of MTX and initiation of pulse steroid therapy. Addition of cyclosporine A (CSA) therapy (100 mg/day) was effective in stabilizing the disease activity. Steroid therapy was discontinued in April 2000.

In September 2000, a fourth exacerbation developed after tapering of CSA (100 to 50 mg/day). Again, liver dysfunction was not present at the beginning of the episode. After symptoms improved with increased CSA, pulse steroid therapy, and oral PSL (40 mg/day), liver dysfunction developed. No antibodies against hepatitis A, B, C, or Epstein-Barr virus were detected. Antinuclear antibody (ANA), rheumatoid factor (RF), and anti-mitochondrial antibody were absent. Liver function improved upon discontinuing CSA while continuing oral PSL therapy (40 mg/day). Based on this improvement, PSL then was tapered to 15 mg/day, but severe liver dysfunction developed, with jaundice becoming evident by December 8. No inflammatory markers or signs were present, including elevated CRP,

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Submitted April 8, 2002; revision accepted October 31, 2002.

arthritis, fever, or rash at that time. Polymerase chain reactions did not detect hepatitis viruses, including hepatitis B virus DNA, or hepatitis C virus RNA, GB virus C/hepatitis G virus (GBV-C/HGV) RNA, and TT virus DNA. Pulse steroid therapy and plasma exchange failed to improve liver function. Hepatic coma and convulsions occurred. An emergency liver transplant was performed on December 16. Examination of the native liver showed massive hepatic necrosis. The patient became conscious and attained full neurologic recovery. Acute rejection 2 weeks after transplant was controlled by pulse steroid therapy. Moderate liver dysfunction developed. No exacerbation of AOSD complicated the therapy for rejection (15 mg of PSL and 3.0 mg of FK506). However, the patient later had a fifth exacerbation of AOSD in February 2002, after the tapering of PSL to 10 mg/day and FK506 to 2.0 mg/day. The cause of the moderate liver dysfunction in April 2001 was stenosis of the grafted liver artery, confirmed by angiography. The patient underwent percutaneous transluminal angioplasty⁸. The stenosis was successfully dilated and the liver dysfunction improved.

Serum concentrations of IL-18 and HGF were measured during the fourth exacerbation (Figure 1). IL-18 increased, correlating with the liver

dysfunction (aspartate aminotransferase or AST vs IL-18, $R^2 = 0.787$; alanine aminotransferase or ALT vs IL-18, $R^2 = 0.925$). Serum concentrations of HGF were increased during the severe hepatic failure in December 2000 but not during the liver dysfunction in October 2000. CRP was increased only in September 2000 (Figure 1). Ferritin was not increased in November and December 2000 (data not shown). These AOSD activity markers did not correlate with the liver dysfunction (AST vs CRP, $R^2 = 0.046$; AST vs ferritin, $R^2 = 0.000$). We also measured serum concentrations of IL-6 and interferon- γ (IFN- γ) during the fourth exacerbation. IFN- γ was not detectable and serum concentrations of IL-6 showed no significant changes. These cytokines may not play significant roles in this case.

DISCUSSION

Liver involvement frequently occurs in AOSD, but is usually mild. Severe hepatitis and fulminant hepatic failure leading to death or liver transplant are rare^{5,6}. Some cases of fulminant hepatic failure have been attributed to drugs, viral infection, hemophagocytic syndrome, or AOSD itself.

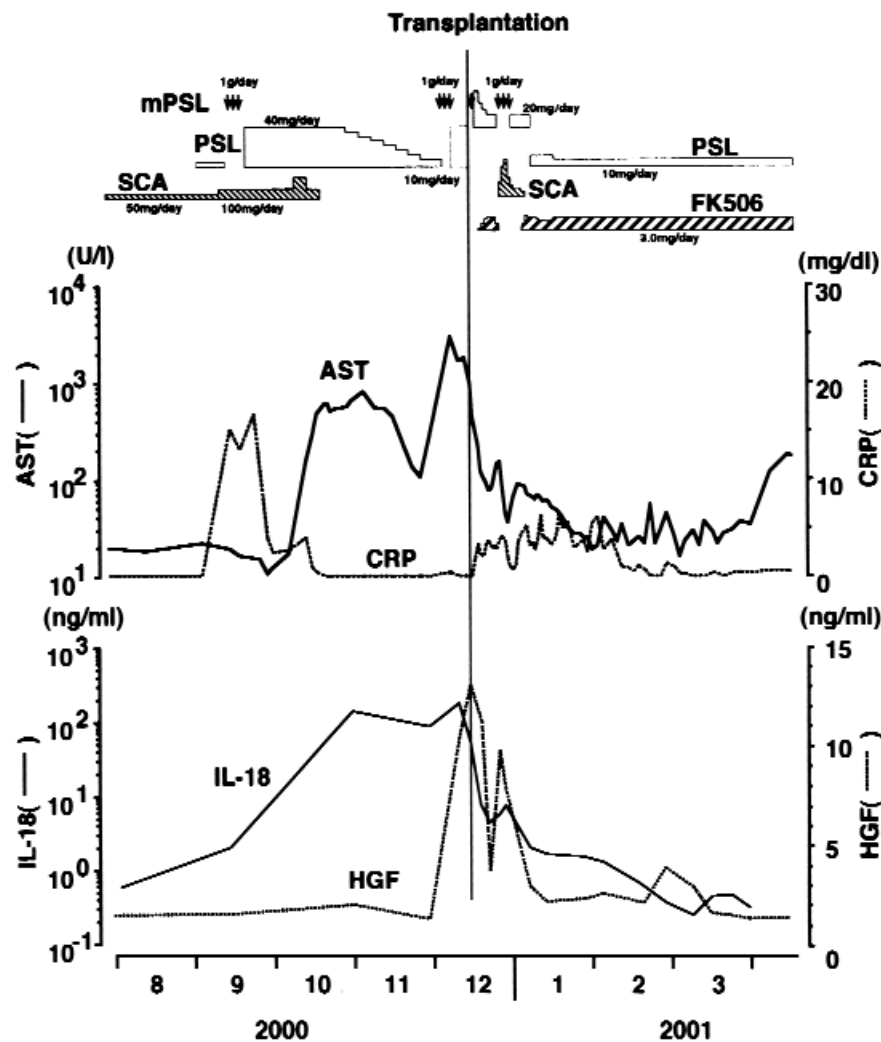


Figure 1. Time course of CRP, IL-18, hepatocyte growth factor (HGF), and AST before and after liver transplantation (August 2000 to April 2001). CRP increased during inflammatory states without liver dysfunction, but not during liver dysfunction. IL-18 correlated with liver dysfunction; HGF increased in hepatic failure but not liver dysfunction. Prednisolone (PSL), methyl-PSL (mPSL), and cyclosporine A (CSA) and FK506 therapy were given. Arrows show pulse steroid therapy. Liver transplant was performed on December 16.

Drug induced liver injury is a common cause of fulminant liver failure in AOSD⁹⁻¹². However, only PSL and CSA were started before liver dysfunction in our patient. CSA had been started uneventfully 10 months before liver dysfunction, and PSL had been used even earlier. MTX, also a possible cause of liver injury, was discontinued more than 1 year before liver failure. Further, neither CSA nor other drugs were in use just prior to the exacerbation of liver dysfunction in December 2000. Thus fulminant hepatic failure in this woman was probably not drug induced. Another cause of hepatic failure we considered was viral infection¹³⁻¹⁵. In some patients, hepatitis or other viral infection can mimic the symptoms of AOSD. Further, fulminant liver failure induced by virally associated hemophagocytic syndrome (VAHS) has been reported in AOSD¹⁶. Since our patient lacked fever, pancytopenia, disseminated intravascular coagulation, and the signs of multiple organ failure at the time of liver failure, the possibility of VAHS was ruled out.

Fulminant hepatic failure can result from AOSD itself¹⁷. The latter seems most likely in this case, i.e., liver dysfunction was triggered by the tapering of immunosuppressive therapy, and possibly mediated by IL-18, which increased.

Interestingly, our patient showed 2 patterns of liver dysfunction (Table 1). The first pattern was mild liver dysfunction occurring together with inflammatory symptoms (high fever and polyarthritis) in December 1997 and August 1998. The second type of liver dysfunction was severe and developed after improvement of inflammatory symptoms, as seen in April 1999 and September 2000. Since liver dysfunction developed after treatment for inflammatory symptoms of AOSD, possible drug induced liver dysfunction and delayed liver dysfunction due to AOSD need to be differentiated. Delayed-type liver dysfunction in this case did not improve with drug discontinuation alone, and indeed rapid tapering of the immunosuppressive therapy might have aggravated liver dysfunction. Some cases previously reported as drug induced liver failure might represent a delayed-type liver dysfunction in AOSD.

Cytokine profiles in the period of liver dysfunction suggested pathogenetic roles of IL-18 and HGF. The serum concentration of IL-18 in AOSD is far greater than that seen in healthy controls (1 to 180 ng/ml vs less than 100 pg/ml)⁴.

IL-18 is usually produced to a lesser extent in the patients with fulminant liver failure from other diseases (0.7 to 1.6 ng/ml)¹⁸. Extremely high concentrations of IL-18 in our patient (maximum 159.95 ng/ml) suggested that IL-18 production occurred in relation to AOSD activity rather than simply secondarily to liver damage. The mechanism of AOSD related liver injury may involve upregulation of the cytotoxic activities of NK cells and CD8+ T cells by IL-18¹⁹. The pivotal role of IL-18 in liver injury has been demonstrated using an IL-18-deficient mouse model²⁰. Most AOSD patients have only mild liver dysfunction, but in our patient, dysfunction progressed to irreversible liver failure because of impaired protective and reparative mechanisms of liver cells. Production of HGF, a hepatic regeneration factor, was not demonstrable until severe liver destruction had occurred, which suggests the possibility of such impairment. The pathogenic role of HGF in mild liver dysfunction is not clear. HGF may prevent liver damage in mild liver dysfunction of AOSD, or mild liver dysfunction of AOSD may be insufficient to induce HGF. More analysis is needed to clarify the pathogenic role of HGF. On the other hand, HGF was induced during acute rejection of the transplanted liver, at which time CRP was increased. Mechanisms of liver injury in AOSD and in liver transplant rejection may differ.

Serum IL-18 concentrations were particularly increased in the period of severe liver damage without obvious general disease activity such as arthritis, fever, or elevated CRP. This suggests that AOSD activity had not lessened in this period. Ferritin and CRP produced by the liver and spleen are not reliable clinical markers in AOSD with severe liver dysfunction. Further analysis of other cases is needed to clarify the pathogenetic roles of IL-18 and HGF in liver dysfunction occurring in AOSD.

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Table 1. Liver dysfunction at each exacerbation of AOSD.

	December 1997	August 1998	April 1999	September 2000
Delay, days*	0	0	44	41
Peak AST, U/l	127	177	2040	848
Peak ALT, U/l	239	180	3990	2587
Peak CRP, ng/dl	26.0	21.1	13.0	16.8
Peak ferritin, ng/ml	10,000	1910	583.1	354.0

*Indicates interval from maximum CRP to maximum liver dysfunction. AOSD: adult-onset still's disease; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRP: C-reactive protein.

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