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## Steroid Therapy in Fulminant Hepatic Failure Secondary to Autoimmune Hepatitis

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**ABSTRACT.** Autoimmune hepatitis is a chronic inflammatory liver disorder of unknown etiology associated with serum autoantibodies and hypergammaglobulinemia. This disease has a broad spectrum of presentations ranging from asymptomatic to fulminant hepatic failure. A 36 year old female with past history of hypothyroidism developed jaundice 2 months prior to admission. Outpatient evaluation revealed ANA and anti-SMA antibodies in high titers, negative viral markers for hepatitis, and hypergammaglobulinemia. A presumptive diagnosis of autoimmune hepatitis was made; steroids were recommended but the patient did not take them. She was admitted to the University Hospital due to

increased jaundice, general malaise and ascites 5 weeks later. She deteriorated developing coagulopathy, encephalopathy and increasing hyperbilirubinemia. Intravenous corticosteroids were started. The patient improved and was discharged 3 weeks after admission. Fulminant hepatic failure has a high mortality and may require liver transplant. Our patient survived fulminant hepatic failure that resolved after corticosteroid therapy. It is important to identify and distinguish autoimmune hepatitis from other forms of liver disease because of the high percentage of response to immuno-suppressive therapy. Early diagnosis and treatment of this condition could improve survival, quality of life, and defer liver transplantation.

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**A**utoimmune hepatitis is a chronic inflammatory liver disorder of unknown etiology associated with serum autoantibodies and hypergammaglobulinemia. This disease has a broad spectrum of presentations ranging from asymptomatic to fulminant hepatic failure. We report and discuss the case of a patient that developed fulminant hepatic failure secondary to autoimmune hepatitis and had a dramatic response to steroid therapy. This case illustrates how early diagnosis and therapy for autoimmune hepatitis improves survival, even in critically ill patients.

### Case Report

A 36 year-old female was referred to the University Hospital for evaluation of jaundice. She had a history of hypothyroidism and received synthroid for seven years. She was using no medications at the moment of her initial evaluation and denied any history of allergies, blood transfusions, smoking, alcohol use, or intravenous drugs use. The patient had been asymptomatic until 2 months prior to admission when she developed diffuse abdominal pain, general malaise, anorexia, nausea and occasional unquantified fever. In addition to these symptoms the patient developed jaundice and dark colored urine. She denied any hematemesis, melena, hemochezia, night sweats, chills, myalgia, arthralgia, past history of hepatitis or family history of liver disease. Initial laboratory tests results are shown in Table 1. An abdominal sonogram showed mild hepatomegaly, normal common hepatic duct, normal gallbladder and no intrahepatic duct dilatation. The diagnosis of autoimmune hepatitis was made and steroids were prescribed but the patient did

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**Table 1. Initial Laboratories**

WBC: 5,700/mm <sup>3</sup>	PT: 13/15 sec	total bilirubin 13.6 mg/dl
Hgb: 11.1 gm/dl	PTT: 31/45 sec	direct bilirubin 7.0 mg/dl
Hct: 32.2%	AST: 1059 U/L	LDH: 286 U/L
plt: 215,000	ALT: 856 U/L	142 U/L Alkaline phosphatase
SPEP: gamma globulin fraction = 48.25 (nl=11.9-16.3)		
HAV, HBV, HCV: Negative		
ANA: (+) > 1320	SMA: (+) > 1320	
ceruloplasmin: 16 AMA: negative		
alpha - 1 antitrypsin: 153		
anti LKM1: negative		
TSH = 1.25		

not take them. Five weeks later she noticed progressive jaundice, increase in her abdominal girth and complained general malaise. She was admitted to the University Hospital for further evaluation and management. Upon admission, the temperature was 36.2°C, the pulse was 90 per minute, and the respirations were 20 per minute. The blood pressure was 130/80. Physical examination showed an alert, active, oriented female, acutely ill, in no respiratory distress. The skin and sclerae were jaundiced, the lungs were clear to auscultation. Abdominal examination showed mild ascites, tenderness to palpation of the right upper quadrant and palpable liver. There was bilateral grade 2 edema of the lower extremities, the neurologic examination revealed no focal deficits and asterixis was absent. The results of laboratory tests upon admission are shown in Table 2.

**Table 2. Admission Laboratories**

WBC: 34,900/mm <sup>3</sup>	PT: 11/24 sec	total bilirubin: 24.0 mg/dl
Hgb: 10.2 gm/dl	PTT: 30/77 sec	INR: 3.79
HCT: 27.8%	AST: 113 U/L	
plt: 260,000	ALT: 122 U/L	

The patient was started on prednisone 60 mg p.o. daily, vitamin K 10 mg s/q daily, furosemide 20mg p.o. daily and cimetidine 400 mg po b.i.d. Two days later spironolactone 50 mg p.o. daily was added due to increasing leg edema. Leukocytosis increased to 58,600, (neut: 85%, bands: 4%). The patient was afebrile and blood, urine and sputum cultures were negative. Chest X-ray was negative, a diagnostic abdominal paracentesis showed normal cellularity and peritoneal fluid cultures were negative. Five days after admission the patient developed somnolence, asterixis and hypotension. Lactulose 30cc p.o. t.i.d., intravenous fluids and inotropics were prescribed. Ceftazidime 2 gr I.V. q 8h and

clindamycin 900 mg I.V. q 8 hours were started because of progressive leukocytosis (81,300/mm<sup>3</sup>). Oral prednisone was discontinued and the intravenous hydrocortisone was started. Inotropics were discontinued 24 hours later and the episodes of hypoglycemia were treated with 10% dextrose solution intravenously. Six days after admission, the coagulation parameters and bilirubin levels started to decrease (PT: 11/20, PTT: 30/50, INR: 2.65, total bilirubin: 17.3mg/dl) although significant leukocytosis persisted (WBC: 79,900, neut: 82%). A bone marrow aspiration was performed which showed spur cells, target cells, and toxic granulations, without other abnormalities. These findings were considered as compatible with liver disease and a possible leukemoid reaction. In an effort to exclude a concealed infectious process, an abdominopelvic CT scan was obtained showing ascites, bilateral pleural effusions, no fluid collections, adenopathies or visceromegaly. A 2-D echocardiogram showed no vegetations, normal heart chambers and normal functional parameters (EF 70%). Ten days after admission asterixis and somnolence disappeared. The coagulation parameters and bilirubin continued improving and leukocytosis was also decreasing (WBC: 47,500, neut: 85%). The patient's clinical condition improved markedly, antibiotics were discontinued and she was discharged 20 days after admission. Laboratories upon discharge are reported in Table 3. She is followed at the outpatient clinics and two years after her admission she is asymptomatic, without medications and with normal coagulation and liver function tests.

**Table 3. Discharge Laboratories**

WBC: 47,800/mm <sup>3</sup>	PT: 11/17 sec	total bilirubin: 13.3 mg/dl
Hgb: 9.8 gm/dl	PTT: 31/37 sec	INR: 1.92
Hct: 27.0%	plt: 140,000	

## Discussion

Autoimmune hepatitis is a chronic inflammatory liver disorder of unknown etiology associated with serum autoantibodies and hypergammaglobulinemia and the presence of at least periportal hepatitis on histological examination (1). This disease was first described by Waldenstrom in 1950 as "lupoid hepatitis". Since then it has been known by a variety of terms, most commonly, autoimmune chronic active hepatitis. In 1992 the International Autoimmune Hepatitis Group developed criteria for the probable or definitive diagnosis of this disease (Table 4) and also recommended the term

**Table 4. Recommended Scoring System for Diagnosis of Autoimmune Hepatitis**

Clinical features	Autoantibodies ANA, SMA or LKM1 titers		
Gender			
Male	0	>1:80	+3
Female	+2	1:80	+2
Immunological disease(s)	+1	1:40	+1
Epidemiologic features		<1:40	0
Blood transfusions/drugs		Other markers	+2
Yes	-2	AMA	
No	+1	Present	-2
Alcohol consumption (adjusted by amount)	0	Absent	0
	-1	Histological features	
	-2	Piecemeal necrosis	+3
	+2	lobular hepatitis and bridging necrosis	
IgM anti-HAV	-3	Bridging necrosis	+2
HBsAg or IgM anti-HBc	-3	Rosettes	+1
HCV RNA	-3	Plasma cells (marked)	+1
Anti-HCV and/or RIBA	-2	Bile duct changes	
Other viral markers	-3	Mild	-1
No viral markers	+3	Severe	
		Incompatible changes	-3
Laboratory features		Treatment response	
HLA B8-DR3 or DR4	+1	Complete response	+2
Globulin, IgG or GG		Partial response	0
x2 normal	+3	No response	-2
x1.5-2 normal	+2	Relapse	+3
x1-1.5 normal	+1	Treatment Failure	0
<1 normal	0		
Alk phosphatase:ALT			
x<3 normal	+2		
x≥3 normal	-2		
Aggregate scores			
Before treatment			
Definite diagnosis	>15		
Probable diagnosis	10 to 15		
After treatment			
Definite diagnosis	>17		
Probable diagnosis	12 to 17		

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autoimmune hepatitis as the most appropriate for this disease (2).

Confirming the autoimmune nature of this condition has been difficult as several studies have implicated viruses and drugs as etiologic agents. Advances in molecular biology and the development of sensitive and specific diagnostic assays for viral infection have given support to the concept of autoimmune hepatitis (3,4).

It is important to differentiate autoimmune hepatitis

from other forms of liver disease because a high percentage of cases respond to antiinflammatory and immuno-suppressive treatment (5). Early diagnosis and treatment of this condition can improve survival quality of life, and defer liver transplantation (6). Autoimmune hepatitis has a broad spectrum of presentations ranging from asymptomatic to fulminant hepatic failure. Several types of autoimmune hepatitis have been established based on clinical, laboratory and epidemiologic findings (1). (Table 5)

The distinction between autoimmune hepatitis and other autoimmune liver diseases such as primary biliary cirrhosis and primary sclerosing cholangitis is sometimes difficult due to the existence of overlapping syndromes in which features of more than one disease are present (7). Similarly, the presence of hypergammaglobulinemia or autoantibodies in chronic viral hepatitis (8) can make the distinction between these entities and autoimmune hepatitis difficult (5,7).

Corticosteroids are the standard therapy for patients with severe autoimmune hepatitis with a remission rate of approximately 80% induced by initial therapy (1,6). Although corticosteroid therapy remains the mainstay of therapy, a reduction in corticosteroid dose can be accomplished by concomitant administration of azathioprine, thus reducing the side effects of prolonged steroid therapy. Several promising treatments for autoimmune hepatitis have been described and are under investigation including cyclosporine, and tacrolimus. Treatment failure occurs in about 20 percent of patients with autoimmune hepatitis, and is more frequent in patients in whom disease develops at a young age, those with established cirrhosis, long duration of disease before therapy, and in patients with the HLA-B8 or DR3 phenotype (6).

Fulminant hepatic failure is defined as the rapid onset of hepatic dysfunction, manifested by coagulopathy and jaundice, encephalopathy and no prior history of liver disease. Fulminant hepatic failure is considered to be present if the interval between the onset of the illness and the appearance of encephalopathy is 8 weeks or less, but there is marked heterogeneity among patients with respect to temporal progression of disease (9). Fulminant hepatic failure is the result of diverse etiologies. The most common causes are viral hepatitis, drugs and toxins. Rare causes include Budd Chiari syndrome, autoimmune liver disease, Wilson's disease, heat stroke, Reye's syndrome and vascular ischemia of the liver (9,10).

Although improvement in supportive care has resulted in increased survival in patients with fulminant hepatic failure, acute hepatic failure from all causes still has a mortality rate over 50%(10). Orthotopic liver

**Table 5.** Proposed Subtypes of Autoimmune Hepatitis Based on Autoantibodies

Features	Type 1	Type 2	Type 3
Signature autoantibodies	ANA, SMA, anti-F actin	Anti-LKMI, anti-P450 IID6, anti-core motif (254-271), anti-liver cytosol 1	Anti-SLA, eliminate anti liver-pancreas
Putative autoantigen	Unknown	P-450 IID6	Cytokeratins 8 and 18
HCV infection (%)	11	44-86	0
Age (years)	10-20 45-70	2-14 (adults, 4%)	30-50
Women (%)	70	Uncertain	90
Immunological disease (%)	17	34	58
Hypergammaglobulinemia	+	+++	+
Low IgA	-	+	-
ANA ≥ 1:160 (%)	67	2	29
SMA ≥ 1:160 (%)	62	0	74
Anti-PDH-E2 (%)	5	0	14
Parietal cell antibodies (%)	4	30	Uncertain
Develop cirrhosis (%)	45	82	75
Steroid response	+++	++	+++

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transplantation is performed in cases of fulminant hepatic failure in which hepatic function is markedly impaired and recovery with conventional therapy is doubtful. Survival rates following liver transplantation average nearly 70% (10).

Several adverse prognostic indicators have been associated with fulminant hepatic failure. These are cryptogenic or drug associated disease, age under 10 years old or over 40 years old, duration of jaundice more than one week prior to encephalopathy, serum bilirubin concentration over 10 mg/dl and prothrombin time over 50 seconds (11). In patients with causes other than acetaminophen toxicity, the presence of a single adverse factor is associated with a mortality of 80%; the presence of three adverse factors is associated with a mortality of over 95%(11). Aggressive search for the cause of fulminant hepatic failure can identify autoimmune hepatitis allowing specific treatment and improved survival.

Our patient presented jaundice and symptoms suggestive of liver disease. Upon evaluation she had the majority of clinical and laboratory features needed to make the definite diagnosis of autoimmune hepatitis. She developed fulminant hepatic failure secondary to autoimmune hepatitis. The patient presented 4 of the previously mentioned adverse prognostic factors. In spite of an expected mortality of over 95%, she survived, showing a dramatic response to corticosteroid therapy.

The patient had complete resolution of symptoms and laboratory abnormalities after treatment and has been free of disease for 2 years following her initial episode.

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