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Brief Clinical Observation

New-onset autoimmune hepatitis in young patients with preexisting liver disease

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ABSTRACT

Autoimmune hepatitis (AIH) is thought to be a primary liver disease, occurring in the absence of any known etiology. We present three unusual cases of new-onset AIH in young female patients with longstanding preexisting liver disease (Alagille's syndrome, cystic fibrosis liver disease and sickle cell hepatopathy). All patients developed an insidious onset of abdominal pain, fatigue, jaundice and hepatitis after many years of their primary diagnosis and had negative serology for hepatitis A, B, C, cytomegalovirus and Epstein–Barr virus. The occurrence of AIH in these patients may be due to a complex interaction between the underlying liver disease, chronic medication use and genetic predisposition resulting in altered immunoregulatory mechanisms.

Autoimmune hepatitis (AIH) is a chronic liver disease of unknown etiology, characterized by the presence of interface hepatitis, portal plasma cell infiltration, increased levels of immunoglobulin G (IgG) and positive autoantibodies [1,2]. The clinical presentation of AIH is either insidious or acute, often mimics viral hepatitis and is responsive to immunosuppressive agents [3]. The aim of this manuscript is to describe the onset of AIH in three young female patients with preexisting liver disease. The patients had negative serology for hepatitis A, B, C, cytomegalovirus, Epstein–Barr virus (EBV), negative hepatitis C RNA, and normal alpha-1-antitrypsin phenotype. Wilson disease was excluded.

1. Case reports

Patient 1 is a 15-year-old white female with Alagille syndrome presenting in the neonatal period with cholestasis, a ventricular septal defect and liver histology demonstrating bile duct paucity. She was in generally good health with the exception of pruritus until 15 years old when she developed intermittent right-sided abdominal pain, progressive jaundice, fatigue and low grade fever. Daily medications were vitamins A, D, E, and K and rifampin. On physical examination she was a thin, jaundiced female with Alagille facies (broad forehead, deep set eyes, pointed chin), mild alopecia and fever 38.2 °C. There were multiple spider telangiectasias on her extremities and tender hepatomegaly without splenomegaly or ascites. A consultant dermatologist diagnosed alopecia areata. Laboratory evaluation is listed in Table 1. Prothrombin time (PT) was 14.6 s (normal 11.5–13.5 s) and partial prothrombin time (PTT) 32.5 s (normal 20.0–31.6 s). Serum ammonia, amylase and lipase were normal. White count was 7300/μL, hematocrit 38.6% and platelet count 338,000/μL. Multiple bacterial blood cultures were negative. A percutaneous liver biopsy (PLB) showed ductopenia, chronic active hepatitis with lymphoplasmacytic infiltration, focal portal and septal fibrosis and increased hepatocyte turnover (Photo 1A). These findings suggested autoimmune hepatitis and serum autoantibodies were obtained (Table 1).

Treatment with prednisone 2 mg/kg of body weight was initiated and the fever and jaundice resolved gradually over the following 3 weeks. After 4 months, azathioprine 2 mg/kg daily was added and a month later serum ALT decreased to 49 IU/L. Ursodeoxycholic acid therapy was initiated due to persistent itching. Prednisone was discontinued over the next 3 months and azathioprine monotherapy sustained clinical and biochemical remission.

A follow-up PLB performed 1 year after diagnosis while on azathioprine monotherapy was improved with slight focal portal inflammation and fibrosis and decreased liver cell turnover and CD3+ T-lymphocytes (Photo 1B). At that time, serum ALT was 43 IU/L, alkaline phosphatase 239 IU/L and total bilirubin 1.5 mg/dL.

Patient 2 is a 19-year-old female with cystic fibrosis diagnosed at 4 months of age by a positive sweat chloride (130 mEq Na/L) and CFTR genotype Δ F 508. Chronic medications included: pancre-

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Table 1
Clinical characteristics at presentation in 3 patients with preexisting liver disease who developed autoimmune hepatitis.

Diagnosis	Patient 1 Alagille syndrome	Patient 2 Cystic fibrosis liver disease	Patient 3 Sickle cell disease
Age at diagnosis (years)	15	17	24
Aspartate aminotransferase [<32 IU/L]	357	409	50
Alanine aminotransferase [0–31 IU/L]	524	359	46
Alkaline phosphatase [100–320 IU/L]	385	391	59
Total serum bilirubin [0.1–1.2 mg/dL]	7.8	2.6	5.5
Direct serum bilirubin [0–0.4 mg/dL]	6.0	1.6	2.8
Total protein [6.0–8.2 g/dL]	7.7	8.5	8
Albumin [3.5–5.3 g/dL]	3.7	3.7	2.5
ESR [4–25 mm/h]	70	55	>100
Serum immunoglobulin G [690–1620 mg/dL]	1800	1950	3260
ANA titre [<1:40]	1:640	1:640	1:320
ASMA titre [<1:20]	Negative	1:40	1:320
Anti-LKM-1 [<1:20]	Negative	Negative	Negative
AMA [<1:20]	Negative	Negative	Negative
Anti-DNA titre [<1:10]	Negative	1:640	Negative

[ ], normal values; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; Anti-LKM, anti-liver kidney microsomal antibody; AMA, anti-mitochondrial antibody.

atic enzyme replacement therapy, vitamins A, D, E, K and albuterol inhalers. She was in good health until 11 years old, when she developed frequent pulmonary infections requiring intravenous antibiotics. At age 16 years, in a routine evaluation, ALT elevation (79 IU/L) was attributed to cystic fibrosis liver disease as physical examination was normal. A year later, she developed right upper quadrant abdominal pain without fever, vomiting, diarrhea or pruritus. Laboratory evaluation is listed in Table 1. PT was 14.9 s and PTT was normal. Her white count was 7150/μL, platelet count 341,000/μL and hematocrit 37.3%. Liver ultrasound showed a liver span of 12 cm with normal echogenicity, no intra- or extrahepatic bile duct dilatation, normal gallbladder and a small pancreas. Endoscopic retrograde cholangiopancreatography (ERCP) was normal and a concomitant PLB showed moderately severe panlobular hepatitis with numerous plasma cells and portal and early septate fibrosis. There were no changes suggestive of cystic fibrosis biliary tract disease (Photo 2A). Based on pathology, serum autoantibodies were sent (Table 1).

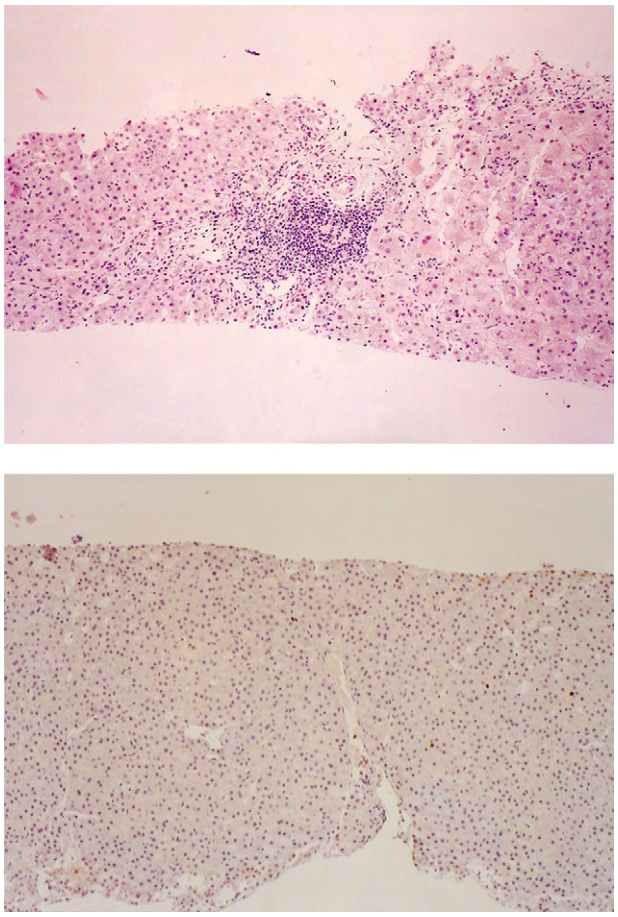

Photo 1. (A) Hematoxylin and eosin stain of baseline liver biopsy of patient 1 with Alagille's syndrome showing intense chronic active hepatitis with chronic portal inflammation and patchy lobular inflammation. (B) Ki67 S phase stain of follow-up liver biopsy of patient 1 while on azathioprine monotherapy indicating decreased hepatocyte cell necrosis and turnover, decreased lymphocyte infiltration.

She was treated with prednisone 2 mg/kg of body weight daily for 6 months with good response. Oral azathioprine 2 mg/kg/day was started 6 months after diagnosis and allowed discontinuation of prednisone. Azathioprine monotherapy was administered for 2 years overall achieving clinical and biochemical remission until sudden anorexia and jaundice developed. Serum total/direct bilirubin 4.3/3.3 mg/dL, ALT 510 IU/L, GGT 46 IU/L, albumin 3.3 g/dL, and erythrocyte sedimentation rate 100 mm/h. Liver ultrasound showed increased liver echogenicity, normal intra/extrahepatic bile ducts and gallbladder. A repeat PLB showed severe panlobular hepatitis with numerous plasma cells, fibroinflammatory bridging without biliary tract disease (Photo 2B). Methylprednisolone (1 mg/kg/day) was given for 3 days followed by equal dose oral prednisone. Upon hospital discharge, serum ALT decreased to 368 IU/L and total bilirubin to 2.4 mg/dL. Addition of azathioprine (100 mg daily) achieved remission.

Patient 3 is a 25-year-old female with sickle cell disease, mental retardation, cerebral palsy and blindness due to multiple cerebral vascular accidents. Hepatomegaly and jaundice (serum bilirubin ranging from 1.8 to 3.1 mg/dL) were noted for the last year. Presenting laboratory data are listed in Table 1. Daily medications were phenobarbital, carbamazepime and desferoxamine. She was diagnosed with cholecystitis by abdominal ultrasonography and underwent open cholecystectomy. Concurrent wedge liver biopsy showed sinusoidal hemophagocytosis of sickled red blood cells, moderate hemosiderin accumulation, portal fibrosis and increased lobular T-lymphocytes (Photo 3A). Autoimmune serology was sent (Table 1). She then developed clinical pancreatitis and worsening jaundice with a total bilirubin of 21 mg/dL. ERCP showed normal biliary and pancreatic ducts. Repeat PLB, a few months later, showed chronic sickle cell hepatopathy with progression to cirrhosis, lobular hepatitis with nests of plasma cells and lymphocytes (Photo 3B). However, the patient expired from sepsis complicating a jejunostomy procedure and AIH treatment was never initiated.