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Distinguishing Autoimmune Hepatitis From Steatohepatitis in Adolescents With Obesity and Positive Screening Alanine Aminotransferase

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Abstract: Screening children with obesity for nonalcoholic fatty liver disease leads to identification of elevated alanine aminotransferase (ALT) and is a common cause for referral to pediatric gastroenterology. Guidelines recommend that children with positive screening ALT be evaluated for causes of ALT elevation beyond nonalcoholic fatty liver disease. One clinical challenge is that autoantibodies can be present in patients with obesity and thus may or may not represent autoimmune hepatitis. This case series highlights the importance of a comprehensive evaluation to reach an accurate diagnosis.

Key Words: nonalcoholic fatty liver disease, liver histology, ultrasound

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in children [1] and is routinely encountered by both primary care physicians and pediatric gastroenterologists. Autoimmune hepatitis (AIH), in contrast, is a less prevalent yet important cause of liver-related morbidity and mortality in children [2,3]. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines recommend excluding additional causes of liver disease in patients with suspected NAFLD if alanine aminotransferase (ALT) is persistently more than 2 times upper limit of normal. Specifically, guidelines recommend obtaining antinuclear (ANA), anti-smooth muscle, and anti-liver-kidney-microsomal antibodies as well as total IgG to evaluate for autoimmune liver disease [4]. Autoantibodies are more common in children with obesity compared with the general population [5], thus, their presence alone is insufficient to diagnose AIH and therefore the diagnosis in children requires liver histology. In addition, children often present with advanced stages of liver disease such that cirrhosis is present in one-third of cases at the time of diagnosis of AIH [6]. When NAFLD is diagnosed based on the presence of obesity and an abdominal ultrasound finding of steatosis without further evaluation, the diagnosis of AIH may be missed. We present a case series of 3 adolescent females with obesity, elevated ALT and abdominal ultrasound findings of steatosis, in whom thorough evaluation resulted in 3 different diagnoses.

PATIENT REPORTS

Table 1 shows data for 3 adolescent females with obesity and elevated ALT detected through screening in primary care referred to pediatric gastroenterology for evaluation of suspected NAFLD (patients A, B, and C). Each patient had abdominal ultrasonography performed as a part of the evaluation with findings of increased echogenicity suggestive of steatosis (Fig. 1). Each patient had normal

TABLE 1. Patient characteristics

	Patient A (NAFLD)	Patient B (AIH + NAFLD)	Patient C (AIH)
Age, y	15	15	15
Height, cm	156.7	159.6	160.0
Weight, kg	79.3	76.4	78.2
Body mass index, kg/m^2 (percentile)	32.3 (99)	30.0 (99)	30.5 (99)
ALT, U/L	187	74	179
AST, U/L	89	52	152
GGT, U/L	55	20	77
WBC, TH/μL	9.4	5.8	8.3
Hemoglobin, g/dL	12.8	12.5	13.6
Platelets, TH/μL	268	273	259
Triglycerides, mg/dL	169	111	131
HDL cholesterol, mg/dL	33	48	43
Hemoglobin A1c	5.7	6.2	5.3
Total protein, g/dL	8.0	8.4	8.2
Albumin, g/dL	4.0	4.4	3.6
ANA titer	1:80	1:1280	1:640
Anti-smooth muscle antibody	1:40	1:320	<1:20
Anti-liver-kidney-microsomal antibody	<1:20	<1:20	<1:20
IgG, mg/dL	1306	2015	3067

AIH = autoimmune hepatitis; ALT = alanine aminotransferase; ANA = antinuclear; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; HDL = high-density lipoprotein; NAFLD = nonalcoholic fatty liver disease; TH = thousand; WBC = white blood cell count

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hepatic synthetic function and was tested for liver diseases other than NAFLD. Test results were negative for viral hepatitis, Wilson's disease, and alpha-1 antitrypsin deficiency, but notable for positive ANA. Each patient had diagnostic liver biopsy. Informed patient consent was obtained for publication of case details.

Patient A had an ALT of 187 U/L and ANA of 1:80. Liver histology demonstrated predominantly macrovesicular steatosis with mild chronic inflammation of the portal tracts and stage 2 fibrosis. Plasma cells and interface hepatitis were absent (Fig. 2). These findings resulted in a diagnosis of nonalcoholic steatohepatitis. Patient B had an ALT of 74 U/L and ANA 1:1280 and elevated IgG of 2015 mg/dL. Liver histology demonstrated a portal-based plasma-cell rich infiltrate with interface hepatitis as well as moderate macrovesicular steatosis with stage 1 fibrosis (Fig. 2). These findings resulted in a diagnosis of AIH and NAFLD. Patient C had an ALT of 179 U/L, ANA 1:640, and total IgG 3067 mg/dL. Liver histology demonstrated a portal-based plasma cell-rich infiltrate with interface hepatitis, without evidence of steatosis. Stage 3–4 fibrosis with early developing cirrhosis was present (Fig. 2). These findings resulted in a diagnosis of AIH.

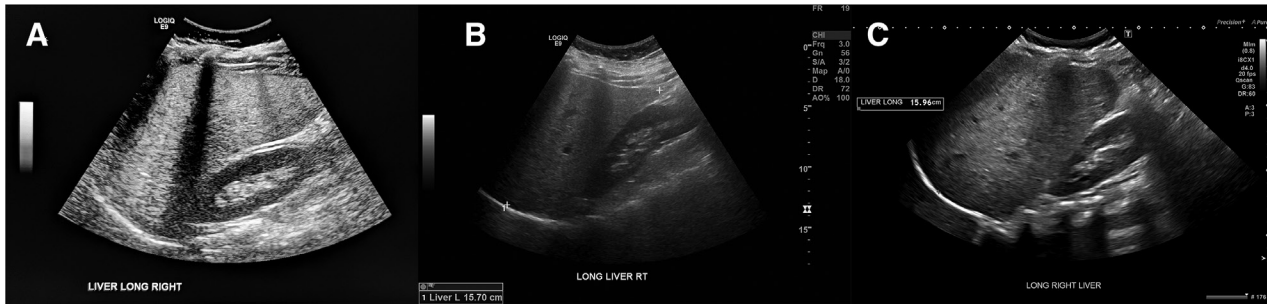

FIGURE 1. Ultrasound images for patients A, B, and C. Patient A: (A) Sagittal ultrasound image demonstrating increased echogenicity related to the kidney. There is decreased delineation of the vasculature. There is good penetration of the transducer with visualization of the diaphragm. Rib artifact present. Patient B: (B) Sagittal ultrasound image demonstrating increased echogenicity of the liver relative to the kidney. There is good delineation of the vasculature. There is good penetration of the transducer with visualization of the diaphragm and posterior structures. Patient C: (C) Sagittal ultrasound image demonstrating increased echogenicity of the liver relative to the kidney. There is decreased delineation of the vasculature. There is good penetration of the transducer with visualization of the diaphragm and posterior structures.

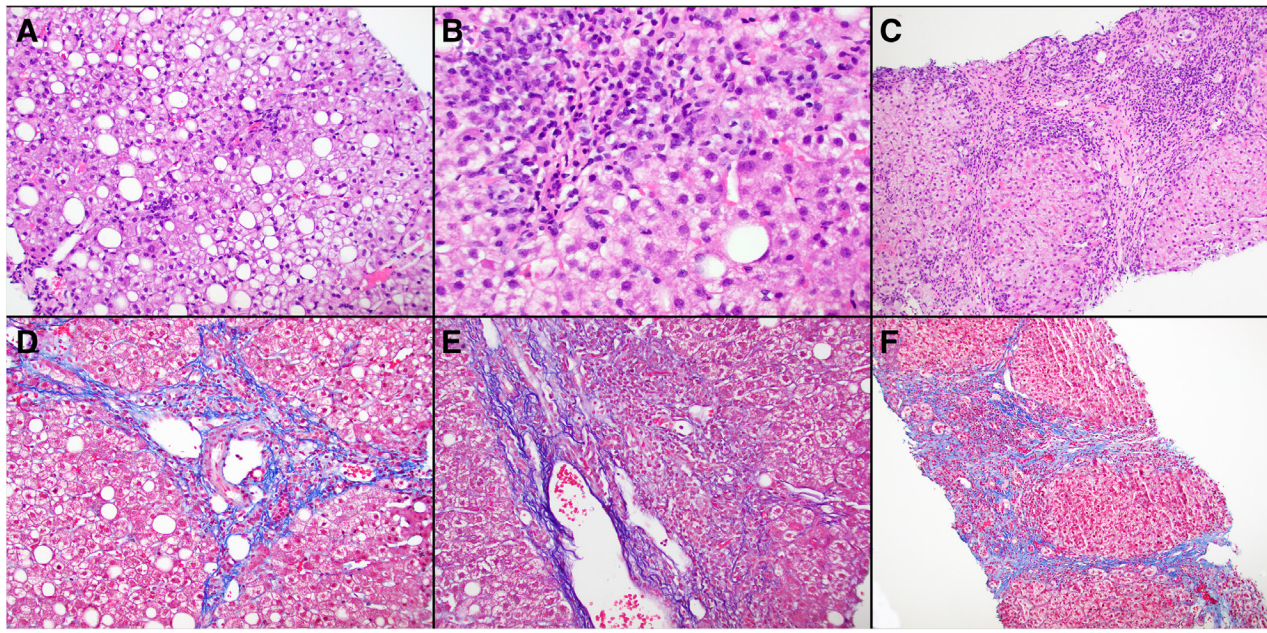

FIGURE 2. Liver histology for patients A, B, and C. Patient A: Steatohepatitis: (A)—H&E at 20× objective, histologic sections demonstrate a predominantly macrovesicular steatosis with scattered lobular inflammatory foci seen. There is no significant increase in plasma cells noted. D) Trichrome at 20× objective highlights central venular perisinusoidal/pericellular fibrosis and periportal fibrosis. Patient B: NAFLD and autoimmune hepatitis: (B) H&E at 40× objective, histologic sections demonstrate a portal-based plasma cell-rich inflammatory infiltrate with an associated moderate interface activity. There is moderate macrovesicular steatosis. E) Trichrome at 20× objective shows mild (stage 1) fibrosis. Patient C: autoimmune hepatitis: (C) H&E at 10× objective, histologic sections demonstrate a portal-based plasma cell-rich inflammatory infiltrate with an associated marked interface activity. No steatosis is present. F) Trichrome at 10× objective demonstrates focal parenchymal collapse with bridging fibrosis bordering on early cirrhotic nodule formation. NAFLD = nonalcoholic fatty liver disease.

DISCUSSION

These cases highlight the importance of evaluating for AIH in children presenting with sustained elevation of ALT regardless of body habitus or ultrasound findings. Khayat and Vitola [5] recently suggested that a body mass index >98th percentile was a breakpoint at which autoimmune liver disease was less likely. However, both of our patients with AIH had a body mass index in the 99th percentile, thus the diagnosis would have been missed if they were not evaluated for additional etiologies of liver disease. It is of particular importance to consider coincident NAFLD and AIH. De Luca-Johnson et al [7] reported that adults with both AIH and NAFLD are more likely to develop cirrhosis and have greater morbidity and mortality compared with patients with AIH alone.

Because NAFLD is very common, it makes knowing when to consider an alternative diagnosis more challenging. Dalekos et al [8] addressed these difficulties, pointing out that physicians may not consider an alternate diagnosis noting that there is wide variation in the extent to which studies in NAFLD overtly evaluate for AIH. It is important to remember that the screening test for NAFLD, ALT, is not specific for NAFLD but can identify other liver diseases as well. Our group has previously shown in a study of 347 children referred to pediatric gastroenterology for suspected NAFLD, 18% had a diagnosis other than NAFLD. In this cohort, AIH was the most common alternative diagnosis [9]. Two other studies have reported outcomes of evaluations for suspected NAFLD. Yodoshi et al [10] reported combined data from Cincinnati Children's and Yale; they found that 19 of 900 (2.1%) children with suspected NAFLD had an alternate diagnosis with the limitation that only 347 (38.6%) children had NAFLD confirmed by liver histology. Al-Harthy et al [11] reported on 95 children with suspected NAFLD and found that 28.4% had abnormal laboratory studies that resulted in 11.6% having a diagnosis of chronic liver disease other than NAFLD.

Abdominal ultrasound is commonly obtained as part of the evaluation for NAFLD. Features that are assessed to indicate hepatic steatosis are: (1) liver echogenicity greater than the renal cortex and spleen, (2) poor delineation of the intrahepatic architecture, and (3) poor wave penetration (hard to see deeper structures such as the diaphragm) [12]. However, liver ultrasound has low specificity for NAFLD in children, limiting is value as a diagnostic test [13]. In addition to creating false-positive diagnoses of NAFLD, abdominal ultrasound is not able to assess the etiology of steatosis or evaluate for concurrent diagnoses. With the push by some to change the name NAFLD to metabolic associated fatty liver disease, the diagnosis would be affirmed solely with ultrasound findings of steatosis in the presence of overweight or obesity [14]. The debate over changing the name of the disease has introduced greater potential for missed diagnosis of liver diseases such as AIH as evidenced by our case series.

Deciding which children should have a liver biopsy remains a clinical challenge. Although clinical guidelines recommend testing for AIH, this is often not done. In recent studies of subspecialty evaluation of children with suspected NAFLD, 20%–40% of patients did not have autoantibodies tested [10,11]. Moreover, in pediatric clinical practice, the confirmation of hepatic steatosis most often relies on abdominal ultrasound [15]. The cases presented reiterate the need for autoantibody testing in the evaluation of elevated liver chemistry, the inherent limitations of ultrasound as a measure of steatosis, and the need for liver histology when more than one diagnosis remains in the differential diagnosis based on noninvasive testing. Notably, in the cases presented, liver histology was required to make the correct diagnosis.

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