Chapter 3
Celiac Disease and the Liver

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Case Presentation

A 58-year-old male presented to the emergency department with jaundice, ascites, and hepatic encephalopathy, which have been worsening over the previous 3 months. He was diagnosed with CeD at the age of 25 after developing abdominal cramping, diarrhea, and weight loss. At the time of diagnosis, the patient was noted to have a positive EMA and tTG. Upper endoscopy findings were confirmatory of CeD with Marsh 3a lesions on duodenal biopsies. He was also noted to have a mild elevation in transaminases. The patient's aspartate aminotransferase (AST) ranged from 85 to 201 IU and alanine aminotransferase (ALT) ranged from 48 to 108 IU. He was managed with a strict GFD with improvement in symptoms, however, without resolution of his hepatic abnormalities. Work-up also included viral hepatitis (hepatitis A, B, and C) serology, cytomegalovirus

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(CMV) PCR, Epstein-Barr virus (EBV) PCR, and herpes simplex virus (HSV) PCR, all of which returned negative. Liver ultrasound showed only evidence of hepatic steatosis. His hepatic function tests continued to worsen with transaminases increasing, with an AST peak of 520 IU, an ALT peak of 800 IU, and a total bilirubin of 8.5 mg/dL. Additional work-up also included a positive antinuclear antibody (ANA) with a titer of 1:160 and a positive anti-smooth muscle antibody (ASMA) with a titer of 1:80. A liver biopsy was subsequently performed, showing lymphocyte infiltration, increased plasma cells, and interface hepatitis, consistent with autoimmune hepatitis (AIH) (Fig. 3.1). The patient was started on oral prednisone 60 mg daily with initial normalization of the liver tests, followed by a corticosteroid taper with initiation of oral azathioprine 50 mg daily. His GI symptoms improved; however, he did have intermittent recurrences. Repeat celiac serology was positive, and a repeat upper endoscopy after a year with duodenal biopsies showed regression from Marsh 3c to Marsh 2.

At the age of 43, his abdominal pain, cramping, and diarrhea recurred despite being on a strict GFD and adherent to azathioprine. A repeat upper endoscopy with duodenal biopsies showed active CeD with Marsh 3c lesions, compatible with refractory CeD (RCD), without T-cell aberrancy on immunohistochemistry. His transaminases started increasing shortly after the recurrence of his abdominal symptoms. A repeat corticosteroid taper and mycophenolate mofetil (MMF) followed by the addition of tacrolimus were tried as second- and third-line agents for AIH with underlying type I RCD, unfortunately without benefit.

At the age of 58, he presented to the emergency department with decompensated liver cirrhosis and portal hypertension-associated ascites and hepatic encephalopathy. His Model for End-Stage Liver Disease (MELD) score on admission was 35. He was admitted to the liver floor for liver transplant evaluation and listing.

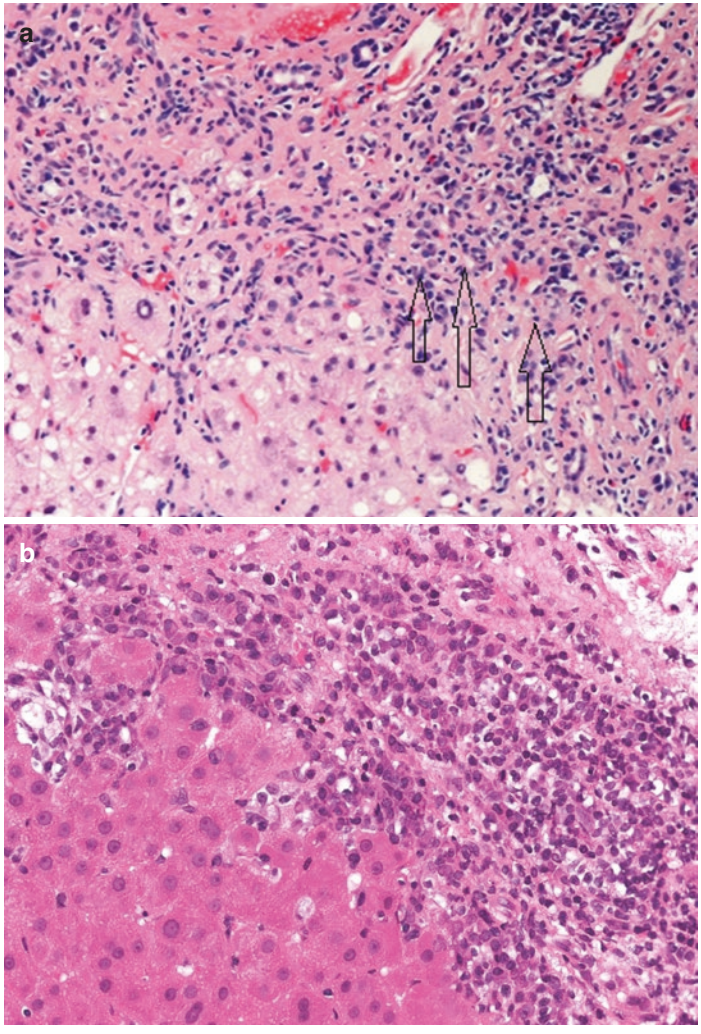

FIGURE 3.1 Liver biopsy suggesting AIH (at 100× magnification). (**a**) highlights interface hepatitis (long arrows), abundance of lymphocytes (white arrows), and rosette formation. (**b**) highlights the inflammatory cells of AIH including multiple plasma cells and lymphocyte infiltration

Diagnosis and Management

Our patient developed cirrhosis secondary to AIH in the setting of secondary type I RCD. This is not an uncommon scenario, as 6–9% of patients with CeD will develop elevated transaminases [1, 2]. In most cases, the transaminases normalize with a GFD. However, up to 2% of these patients will be diagnosed with AIH. The first report of the association between CeD and liver inflammation was made in 1977 by Hagander and colleagues, who reported that 30 out of 74 adults with known CeD developed elevated transaminases that would then normalize on a GFD within 6–12 months [3]. The following year, Lindberg and colleagues confirmed diet-dependent liver damage in patients with CeD in childhood by showing improvement in transaminases and histology via liver biopsy after maintaining a GFD [4]. Subsequently, an Italian study showed that 57% of children with active CeD had elevated transaminases [5]. With time, reports on the hepatic involvement in CeD have increased. Current U.S. data shows a rate of 40% of gluten-dependent elevated transaminases in patients with CeD, resonating Hagander's findings [6].

Two major categories of CeD-associated liver disorders have been described, cryptogenic and autoimmune. While both subcategories share some similar laboratory findings, from mild to severe elevations in transaminases, through mild to severe liver dysfunction, and up to decompensated cirrhosis with portal hypertension, they differ in histological findings and clinical response to a GFD [7–9]. In CeD-associated hepatitis, biopsies show preserved liver architecture with a mild mononuclear infiltrate of the portal tract and/or the lobular tract [7–9] and slight hyperplasia of the Kupffer cells [7–9]. After 12 months of a GFD, the above-mentioned histological findings usually normalize [7–9]. In cases of AIH in patients with CeD, along with elevated transaminases, laboratory findings include elevated ANA, ASMA, anti-liver kidney microsomal antibody (LKM), and/or anti-liver cytosol type 1 antibody [8, 9]. Liver biopsies for

the latter disorder often show both mononuclear and eosinophilic infiltration of the portal tract [8, 9]. Patients with AIH generally do not improve with gluten avoidance alone and will require additional immunosuppressive therapy [7–11]. Although these clinical differences exist between cryptogenic hepatitis and AIH in CeD, it is unknown if they are truly two separate diseases with a different pathogenesis or if they are varied expressions of the same disease [12–14]. It is hypothesized that patient factors, such as genetic predisposition, immunological factors such as F-actin antibody positivity, and cumulative exposure to gluten, can help determine the type and reversibility of the liver involvement CeD patients encounter [12–14]. Furthermore, patients with AIH tend to have a more pronounced hepatitis and are more likely to progress to cirrhosis despite a GFD and immunosuppression. While patients who are diagnosed with cryptogenic turned CeD-associated hepatitis usually improve with a GFD, the longer the gluten exposure, the more resistant the hepatitis becomes.

It is hypothesized that in the pathogenesis of AIH and CeD, a genetic link exists [15]. Both diseases tend to express specific combinations of genes located on chromosome 6 for class II HLA [15]. These findings are seen in both pediatric and adult populations [9, 18, 19].

AIH is further categorized as AIH-type 1 and AIH-type 2, based on the autoantibodies detected in the bloodstream [20]. AIH-type 1 is represented by a positive ANA and/or ASMA and in some cases elevation of the IgG levels [20]. In AIH-type 2, positive anti-LKM1 is seen [21]. It is often difficult to diagnose AIH in patients with active CeD, partly due to the fact that the positivity of ASMA is shared in both conditions. Thus, the discrimination between AIH and cryptogenic or CeD-associated hepatitis is a diagnostic challenge, often mitigated by a liver biopsy. Accordingly, a patient with CeD and severe villous atrophy but no apparent liver damage may have elevated ASMA of unclear significance. In such cases, treatment can be a difficult clinical decision between a GFD alone and additional immunosup-

pressive therapy. Currently the clinical impact of a GFD in patients with AIH is not well established [8, 9]. Interestingly, patients with AIH and diet-treated CeD have fewer hepatic relapses off immunosuppression, compared to patients with AIH without CeD [24]. Table 3.1 lists the liver diseases associated with CeD. The mechanism of liver injury in CeD is poorly understood; however, several theories have been proposed (Table 3.1).

Case Outcome

Management of decompensated cirrhosis was initiated on hospital admission. A paracentesis did not show evidence of spontaneous bacterial peritonitis. Blood cultures, urine culture, and chest x-ray were unremarkable. Abdominal ultrasound with Doppler showed patent vasculature without hepatic malignancy. The patient was symptomatically treated with lactulose, rifaximin, furosemide, and spironolactone. His immunosuppression regimen was discontinued given his decompensated cirrhosis. Due to the high MELD score on admission, an expedited liver transplant evaluation was initiated and completed during the same hospitalization, and he was listed for liver transplantation. During his admission, he developed hematemesis and was diagnosed with esophageal variceal bleeding, requiring endoscopic band ligation. A successful orthotopic liver transplant was completed approximately 2 weeks later.

Post-liver transplant, the patient recovered well and was discharged home 10 days later. He continues a strict GFD. His current chronic immunosuppression regimen includes tacrolimus and MMF. Currently, 5 years post-transplant, the patient is doing well and remains asymptomatic. His liver tests continue to be normal, and he has not experienced any bouts of rejection since the liver transplant.

Table 3.1 Prevalence, Mechanism of Liver Injury, and Outcomes of CeD-associated Hepatic Disorders

Liver disorder	Prevalence[a]	Proposed mechanism(s) of liver injury	Outcome	References
Cryptogenic or CeD-associated Hepatitis (transaminitis of unclear etiology)	4–24%	– Increased intestinal permeability causing an inflammatory reaction with cytokines traveling to the liver through the portal circulation – SIBO and development of endotoxemia – Chronic inflammation and tTG IgA deposits in the hepatocytes – Activated T-cells may home the liver	80–90% of patients have resolution of the elevated transaminases and histologic findings after 1 year on GFD	[2, 9, 25]
Autoimmune Hepatitis (AIH)	1.6%	– Association of HLA II gene on chromosome 6 in both CeD and AIH – F-actin antibody positivity in both diseases	– Unclear benefit of GFD – Relapse after withdrawal of immunosuppressive therapy often happens – Increased risk of progression to end-stage liver disease	[8, 9, 15–24]
Primary Sclerosing Cholangitis (PSC)	1.6%	Unknown	Increased progression to end-stage liver disease	[26–29]

(continued)

Table 3.1 (continued)

Liver disorder	Prevalence[a]	Proposed mechanism(s) of liver injury	Outcome	References
Primary Biliary Cholangitis (PBC)	3–6%	Unknown	– Increased progression to end-stage liver disease – Early detection and diagnosis may improve outcome	[9, 30–34]
NAFLD/NASH	Likely higher than in the general population (>25%)	Cytokine production and malabsorption	– Improvement with a combination of GFD and weight loss – Non-adherence is associated with increased risk for disease progression and end-stage liver disease	[35–45]
End-stage Liver Disease	Unknown	tTG and EMA levels decrease on immunosuppression post-liver transplantation	– Most require liver transplantation – CeD often remits with the high-dose immunosuppressive therapy used post-liver transplant	[46–70]

[a]Prevalence of liver disease in patients with CeD and not vice versa. CeD has a much higher prevalence in patients with primary liver disease like AIH and cryptogenic hepatitis

Clinical Pearls/Pitfalls

1. The presence of elevated transaminases is not an uncommon phenomenon in CeD.
2. Prompt evaluation by hepatology is warranted if the liver tests do not improve despite a GFD to assess for AIH, viral hepatitis, NAFLD, PBC, PSC, and cryptogenic liver disease.
3. Persistent transaminitis despite a negative hepatic serological work-up in a GFD-compliant patient with resolved GI symptoms may require a liver biopsy.
4. Persistent transaminitis after 1 year on a GFD with serology suggestive AIH warrants a trial of immunosuppressive therapy.
5. Early detection of reversible liver disorders is key in preventing progression to end-stage liver disease and transplantation.

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