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Cystic Fibrosis-related cirrhosis

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Abstract

While liver involvement is common in cystic fibrosis, the major liver disorder with impact on the clinical outcome of individuals with CF is the development of multilobular cirrhosis with progression to portal hypertension. Interestingly, this is a disorder primarily of children and adolescents. We review the proposed pathogenesis, clinical presentation, diagnostic work-up, medical and surgical management, and complications of CF cirrhosis.
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Keywords: Liver disease; Cirrhosis; Portal hypertension

1. Background

Liver involvement in cystic fibrosis is common. The spectrum of liver involvement and the reported prevalence ranges is shown in Table 1. In the liver, CFTR is localized to the apical surface of bile duct epithelium and not found in hepatocytes [1]. CFTR in biliary epithelium increases apical biliary chloride secretion primarily increasing bile acid independent bile flow. The most commonly espoused theory for the development of liver disease in CF is abnormal biliary chloride transport leading to lack of alkalinization and dehydration of bile [2]. This in turn may lead to inspissated bile in the small bile ducts with plugging, inflammation and subsequent fibrosis. This is consistent with the histopathologic lesions of biliary fibrosis in CF (Fig. 1A).

While liver involvement is common, the major liver disorder with impact on the clinical outcome of individuals with CF is the development of multilobular cirrhosis (Figs. 1B, C, and 2) with progression to portal hypertension [3,4]. Interestingly, this is a disorder of children and adolescents. In the largest series of 561 individuals with CF and cirrhosis and portal hypertension, 90% presented by 18 years of age with a mean age of diagnosis of 10 years [5]. This suggests that this is a disorder that presents early in the disease course of CF. The reason so few adults with CF are newly diagnosed with multilobular cirrhosis is unclear. In contrast, there is increasing recognition of hepatolithiasis, often associated with stricturing biliary disease and sclerosing cholangitis in adults with CF which require multiple procedures to clear stones from the liver [6].

CF associated liver disease is generally not the determinant of outcome in CF. However, multilobular cirrhosis with portal hypertension does impact outcome [7]. The main complications associated with cirrhosis are GI bleeding (10–40% in 5–10 years after diagnosis of cirrhosis), malnutrition and ascites, which are all related to portal hypertension [3,8]. Although synthetic dysfunction is rare in CF liver disease, liver disease remains the third leading cause of death but only accounts for 2–3% of deaths annually. Close to 300 individuals with CF have undergone liver transplantation in the US with about 75% occurring in children [9].

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Table 1
Spectrum CF liver involvement with reported prevalence.

Abnormality	Prevalence and/or frequency
Elevated AST and ALT	Persistent abnormalities >1.5 × ULN at well visits (>6 months apart), 30% by 20 years of age [23] 2/100 person months [16]
Elevated GGT	Persistent abnormalities >1.5 × ULN at well visits (>6 months apart), 20% by 20 years of age [23] 0.8/100 person months [16]
Hepatic Steatosis	Imaging US: 5% [12] Liver Biopsy: 23–75% [24]
Imaging abnormalities on US	18% [12]
Focal biliary cirrhosis	11–50% (autopsy studies) [33,34]
Multilobular cirrhosis	7% [13]
Neonatal cholestasis	<1%, usually associated with meconium ileus
Cholangiopathy	Increasingly recognized in adults with CF [6]

2. Clinical presentation and differential diagnosis

As mentioned above, the term cystic fibrosis related liver disease (CFLD) has been used to describe a wide spectrum of manifestations ranging from neonatal cholestasis, elevation of liver transaminases, steatosis (Fig. 1D), and gallbladder abnormalities to the development of biliary cirrhosis with or without portal hypertension [10]. Biliary cirrhosis secondary to CF (referred to as CF cirrhosis from this point forward) with portal hypertension is the most clinically important manifestation of CFLD. The most common physical exam findings of CF cirrhosis are an enlarged firm liver with or without splenomegaly. While persistent elevations greater than two times the upper limit of normal for aspartate aminotransferase (AST), alanine transaminase (ALT), or gamma-glutamyl transpeptidase (GGTP) should prompt further evaluation for subclinical CF cirrhosis, these biochemical parameters may be normal in patients with cirrhosis [11] and the specificity of these abnormalities for CF cirrhosis is poor. In patients with CF, a relative and consistent drop in platelet count over a finite period of time may also be concerning even if limits for thrombocytopenia are not met. An ultrasound revealing an abnormal heterogeneous pattern of increased echogenicity or nodularity should spur further investigation, but its prognostic value remains to be validated in a multi-center fashion [12]. Interestingly, the clinical hallmarks of advanced liver disease such as ascites, thrombocytopenia, splenomegaly, and caput medusa are often subtle, asymptomatic, or do not present until very late into the disease course in patients with CF cirrhosis, when it is irreversible and liver transplantation is indicated. While CF cirrhosis is understood to have a hepatobiliary etiology, patients rarely present with jaundice or icterus until end-stage liver disease has developed. Unfortunately, unexpected hematemesis from an esophageal variceal bleed or gastropathy secondary to advanced hepatic fibrosis and subsequent portal hypertension is often both a sentinel event and a declaration of CF cirrhosis [8]. Nearly all patients with CF cirrhosis will suffer from significant malnutrition due to a combination of anorexia and increased catabolism from chronic liver disease, early satiety due to organomegaly, and chronic liver disease. Noteworthy organomegaly and physical deconditioning also predisposes to constipation, though interestingly in CF, cirrhosis is often not characterized by hard or painful bowel movements. Rather, stools may remain soft but infrequent,

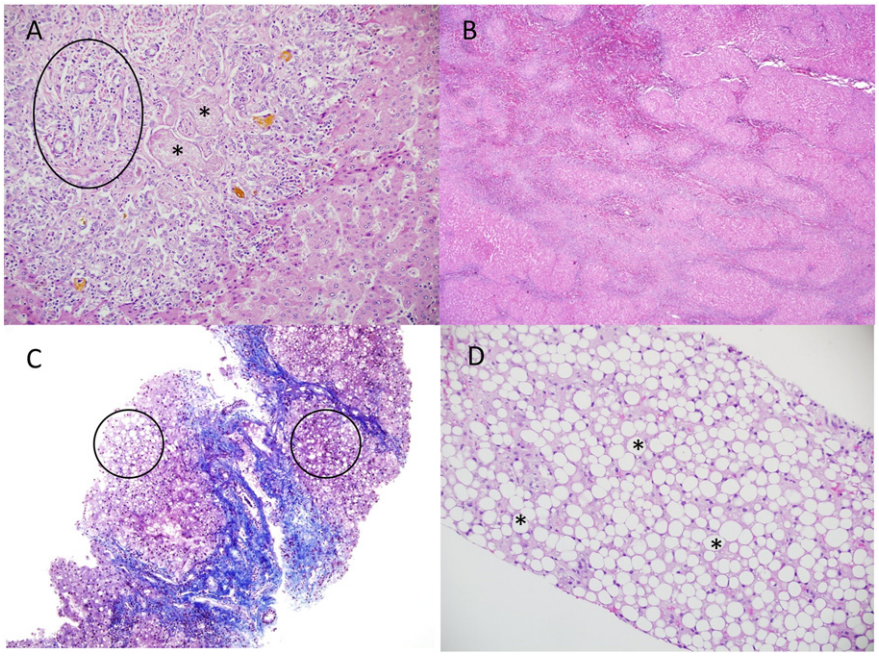

Fig. 1. Histopathology of cystic fibrosis liver disease. A-Portal fibrosis (outlined), eosinophilic concretions (*), and bile plugs (brown) adjacent to relatively unremarkable hepatic parenchyma, 20×. B-Micronodular pattern on H&E with replacement of hepatocytes with fibrosis, 20×. C-Trichrome stain highlighting thick bands of fibrosis (blue) representing cirrhosis as well as patchy steatosis (outlined), 10×. D-Liver parenchyma with diffuse macrovesicular steatosis (*) with microvesicular steatosis, 20× Images courtesy of Dr. Deborah Schady and Dr. Kelley Capocelli.

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