Chapter 18

Hepatic Complications

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Introduction

Hepatic involvement in dyskeratosis congenita (DC) and related Telomere Biology Disorders (TBDs) may vary from mildly abnormal liver tests to advanced cirrhosis, portal hypertension and hepatocellular carcinoma. The time of onset of liver involvement also varies and depends on the mutated gene, the type of pathogenic variant, length of telomeres, genetic anticipation, and interaction with environmental factors.

Overview

As indicated in Chapter 4, The Genetics of Dyskeratosis Congenita and Telomere Biology Disorders, many patients with hepatic involvement are older and carry mutations in the *TERT* or *TERC* genes [1-3]. In fact, in patients with *TERT* or *TERC* mutations, who may not have the usual skin, mucosal and nail abnormalities that characterize DC, liver disease may be the only clinical manifestation of a TBD [4]. In other cases, liver disease can accompany aplastic anemia or be found in relatives of patients with aplastic anemia who are otherwise silent carriers of a TBD.

However, individuals with DC/TBD are at high risk of developing liver disease in their youth. Children with DC who undergo hematopoietic cell transplantation (HCT) for marrow failure in the first decade of life may be particularly prone to the HCT complication of veno-occlusive disease, and should be monitored carefully for cirrhosis after transplant [5]. Modern reduced intensity conditioning regimens may reduce the risk of liver toxicity [6].

Additionally, cryptogenic cirrhosis is found in a small proportion of patients with idiopathic pulmonary fibrosis, implicating telomere erosion in both fibrotic processes [7]. It is important to note that the same telomerase mutation may manifest differently in different individuals of the same family; whereas some may develop liver disease, others may be diagnosed with aplastic anemia or idiopathic pulmonary fibrosis [8].

The pattern of hepatic involvement is variable. The most common liver pathologies associated with telomere disorders are described below.

Cirrhosis

Cirrhosis is a late stage of progressive liver fibrosis and is characterized histologically by distortion of hepatic architecture and formation of regenerative nodules [9]. Although historically histology had been used to confirm the diagnosis of cirrhosis, liver biopsy

has now been successfully replaced by noninvasive fibrosis assessment tools, such as transient elastography or magnetic resonance elastography, in patients with early compensated disease.

In early stages, individuals are often asymptomatic and the diagnosis of cirrhosis may be suspected on the basis of abnormal liver chemistries or imaging.

In late presentation, individuals may complain of chronic fatigue, jaundice (yellowing of the eyes and skin), hematemesis (vomiting blood), ascites (fluid distension in the abdomen), peripheral edema (swelling of legs and feet), and in more advanced cases, symptoms of hepatic encephalopathy, including sleep-wake cycle reversal, disorientation, confusion, and even coma. Physical examination may reveal signs of hepatic insufficiency, such as jaundice, spider telangieactasias (small dilated blood vessels visible in the chest), palmar erythema (redness of the palms), gynecomastia (breast enlargement), and/or signs of portal hypertension, including splenomegaly (enlarged spleen), ascites, or asterixis (flapping tremor). Laboratory tests frequently show elevated hepatocellular enzymes and alkaline phosphatase.

At late stages, synthetic liver function may become impaired, resulting in low serum albumin (largest circulating protein in the blood), and prolonged prothrombin time (reflection of decreased hepatic production of clotting proteins).

Finally, imaging of the liver reveals a nodular hepatic surface with increased echogenicity as well as signs of portal hypertension, including splenomegaly and portosystemic collaterals, such as gastroesophageal varices.

Although the pathogenesis of cirrhosis is not completely understood, it appears that telomere attrition plays an important role. Chronic liver injury stimulates hepatocellular proliferation, cell turnover and progressive telomere loss, which in turn promotes cell proliferation arrest and apoptosis [10]. In fact, telomere shortening by itself is associated with cirrhosis formation [11].

Therefore, cirrhosis is not only a direct consequence of TBD, but *TERT* mutations also are risk factors for cirrhosis development in patients with chronic hepatitis C infection or alcohol-associated liver disease [10]. *TERT* mutations are more prevalent in patients with these conditions than in the normal population. However, it is not clear whether disease may be more severe when a *TERT* mutation is present.

Non-Cirrhotic Portal Hypertension

Although cirrhosis is the most common cause of portal hypertension, approximately 10-15% of individuals with clinically significant portal hypertension do not have advanced liver fibrosis. A variety of morphologic changes in the liver tissue may result in an increase in portal pressure, such as nodular regenerative hyperplasia (NRH) [12].

The association of NRH and TBD-related mutations has been described in several families, with or without the presence of bone marrow failure and/or pulmonary fibrosis [13, 14].

Like cirrhosis, patients with NRH are often asymptomatic in early stages of disease, but a large proportion go on to develop complications of portal hypertension, including ascites and gastroesophageal varices. As opposed to cirrhosis, however, synthetic liver function is typically preserved in NRH due to absence of fibrosis.

Pathology

When liver biopsy is performed, histology may reveal distortion of the hepatic architecture, with bridging fibrosis (fibrosis connecting portal areas) or perisinusoidal fibrosis. Inflammatory infiltrate is another common feature, and macrovesicular steatosis and Mallory bodies may be noted. Additionally, sinusoidal endothelial cells around the portal areas and central veins may stain positive for CD34, which suggests abnormal arterial blood flow to the sinuses. Mild iron accumulation in hepatocytes is also usually noted. On the other hand, nodular regenerative hyperplasia (NRH) is

histologically characterized by small regenerative hepatic nodules in the absence of significant fibrosis [15]. CD34 may be positive in sinusoidal endothelial cells, which is consistent with portal hypertension.

Hepatopulmonary Syndrome

Although pulmonary fibrosis and emphysema are the most common respiratory complications of TBD, patients with portal hypertension (cirrhosis- or NRH-related) are at increased risk for hepatopulmonary syndrome (HPS). HPS is a vascular complication of liver disease characterized by low pulmonary vascular resistance secondary to intrapulmonary vasodilatation and shunting [16]. The prevalence of HPS in noncirrhotic portal hypertension is estimated to be around 10% [17], and patients with TBD may be at a higher risk [18]. HPS is manifested by progressive shortness of breath, worse in upright position, and hypoxemia (low oxygen levels in the blood). No directed therapy for HPS currently exists, and treatment is limited to liver transplantation with an expectation of resolution of hypoxia in patients post-transplant.

Hepatocellular Carcinoma

Development of hepatocellular carcinoma in patients with telomerase mutations has been reported [10, 19]. However, the number of cases reported so far is too small to determine whether the clinical behavior or tumor aggressiveness differs in patients with TBD compared to the general population. It appears that the pattern of liver damage is similar to the involvement seen in hematopoietic tissue, in which telomere dysfunction results in organ failure and subsequent malignant transformation.

Other Manifestations

Hepatic veno-occlusive disease may be a complication following HCT for aplastic anemia in patients with DC [5]. Some patients with telomerase mutations have also

been found to have hepatic steatosis (fatty liver) in the absence of risk factors, such as excessive alcohol use or metabolic syndrome [3].

Monitoring Liver Involvement in TBD

Individuals with TBD, including dyskeratosis congenita, should be screened for liver involvement at diagnosis and monitored approximately once a year, depending on the patient's specific clinical manifestations. Complete liver chemistries (aminotransferases, alkaline phosphatase and total bilirubin), as well as markers of synthetic liver function (prothrombin time and albumin) should be performed.

Abnormal liver tests or physical examination findings suggestive of advanced liver disease (as outlined above) should prompt for additional testing, including abdominal ultrasound and/or noninvasive fibrosis assessment (with liver and spleen stiffness measurement). Similarly, MR elastography or transient elastography should be obtained in the presence of additional risk factors for advanced liver fibrosis, including metabolic syndrome, alcohol misuse and/or chronic hepatitis C. Transjugular liver biopsy with hepatic venous pressure gradient measurement may be needed if other tests are inconclusive.

The liver is also of major concern for side effects of polypharmacy. Patients should always inform their medical team of all prescribed medications. Patients taking androgens are particularly susceptible to developing liver complications, although more recent work has not found an increased rate of abnormal liver tests in these patients (see also Chapter 10, Medical Management of Bone Marrow Failure in Telomere Biology Disorders) [20].

Surveillance of hepatocellular carcinoma, in the form of abdominal imaging (ultrasound, CT or MRI) should be obtained every 6 months in those with established cirrhosis. Screening for hepatopulmonary syndrome is not indicated, except in the presence of respiratory symptoms or complaints. The diagnosis of HPS should be suspected in the

presence of hypoxia or hypoxemia with elevated alveolar-arterial gradient. Contrast-enhanced echocardiogram should be used to confirm the presence of intrapulmonary right-to-left shunting.

As in other complex multi-organ diseases, several subspecialties should be involved in the care of patients of TBD, and referral to an expert hepatologist is recommended for all individuals with TBD.

Treatment Options

There is no specific treatment for liver disease in TBD. Although androgens can be used to improve cytopenias in patients with TBD, studies remain inconclusive about their liver-specific benefits [21], and patients receiving androgens should be carefully monitored for liver toxicity. In more severe cases of liver disease or the development of hepatocellular carcinoma, liver transplant may be an option, which is increasingly described in the literature [3, 19, 22-26].

Cirrhosis and portal hypertension are managed as they are for other etiologies, with a focus on prevention and treatment of additional liver and other organ injury, and management of symptoms. Hepatic veno-occlusive disease following HCT is also managed in patients with TBD as it is in patients undergoing HCT for other indications. Progression of liver disease may lead to gastroesophageal varices and bleeding, portal hypertensive gastropathy, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatocellular carcinoma, and/or hepatopulmonary syndrome.

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