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Case Report

A rare case report of decompensated cirrhosis from hereditary hemochromatosis following lung transplant in a person with cystic fibrosis

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ABSTRACT

A 33-year-old woman with cystic fibrosis following bilateral sequential cadaveric lung transplantation experienced prolonged intermittent liver enzyme elevation. An abdominal ultrasound revealed increased hepatic echogenicity and cirrhotic features, warranting further investigation with iron studies and liver biopsy, which confirmed hereditary hemochromatosis. This rare case underscores the importance of considering hereditary hemochromatosis post lung transplantation irrespective of not receiving multiple blood products or iron replacement.

1. Introduction

CF-Hepatobiliary Involvement (CFHBI) is the primary consideration in patients with cystic fibrosis (CF). It presents with a wide range of clinical manifestations, ranging from asymptomatic elevations of transaminase to advanced CFHBI with portal hypertension. CF patients, irrespective of receiving lung transplantation, should undergo a thorough evaluation to determine disease severity and determine the cause of liver disease. Etiologies can include alpha-1 antitrypsin deficiency, viral hepatitis, Wilson's disease, and even hereditary hemochromatosis (HH). Here, we present the first case of a HH in a lung transplantation recipient with cystic fibrosis who subsequently developed end-stage liver disease from under-recognized HH.

2. Case presentation

A 33-year-old woman with CF [$\Delta F508/N1303K$ mutations] underwent bilateral lung transplantation at age 24 due to progressive respiratory failure. Her co-morbidities included chronic sinusitis, pancreatic insufficiency, malabsorption, and CF-related diabetes mellitus (CFRD), but no hepatobiliary disease. Her triple drug immunosuppression regimen included prednisone, tacrolimus, and mycophenolate mofetil. Several years after her transplant, she exhibited intermittent mild transaminase elevation. Potential offending agents were either dose reduced or discontinued, and abdominal ultrasound evaluations were unrevealing. Ursodeoxycholic acid was prescribed for concerns of CFHBI without any benefit and was discontinued. Unfortunately, her liver function tests worsened with a mixed hepatocellular and cholestatic pattern. Viral serologies, autoimmune markers, immunoglobulin profiling, ceruloplasmin, and

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alpha-1 antitrypsin testing were negative. There was no family history of hemochromatosis. An abdominal ultrasound demonstrated progressive hepatic steatosis with increased echogenicity with mild hepatosplenomegaly. Iron studies indicated iron overload (ferritin >4000 ng/mL, saturation at 91%). A liver biopsy was performed and revealed cirrhosis with 4+ iron deposition in hepatocytes and biliary epithelium. Although bile duct proliferation and fibrosis suggested CFHBI, the absence of steatosis and the presence of extensive iron deposition were atypical. A HFE gene test confirmed C282Y homozygosity, diagnostic of Type 1 HH. She had no prior exposure to iron infusions or significant blood transfusions.

Following the diagnosis of HH, therapeutic phlebotomy was initiated, totaling 66 phlebotomy sessions performed over four years. Ferritin levels decreased from >4000 ng/mL to 145 ng/mL, though the therapeutic goal of <50 ng/mL was not achieved due to treatment-limiting anemia. Elexacaftor 100mg/tezacaftor 50 mg/ivacaftor 75 mg was started in hopes of helping confounding issues of her CF-related diabetes mellitus and sinus disease. It did not help with her hepatic function as it continued to decline and developed decompensated cirrhosis within six months, presenting with ascites and esophageal varices requiring banding. Although she was listed for liver transplant, she unfortunately unexpectedly passed away at home in her sleep. Autopsy was declined by the family to conclude the cause of death. Written informed consent had been obtained by the patient prior to her passing.

3. Discussion

The vast majority of morbidity in people with cystic fibrosis are lung related, but a standardized approach for monitoring of cystic fibrosis-hepatobiliary involvement is now recommended by the Cystic Fibrosis Foundation [1]. When CFHBI is suspected, due diligence is recommended to assess for alternative causes. Several case reports and cohort studies have identified coexisting disease-modifying genes, including alpha-1 antitrypsin deficiency and HH, as culprits of severe hepatic outcomes in CF patients [2]. These findings underscore the importance of considering overlapping liver pathologies, particularly in patients with atypical clinical features. End-stage liver disease in CF is not always attributable to CFHBI alone. In our case, the C282Y/C282Y genotype of HFE likely contributed significantly to hepatic injury, and its recognition was delayed due to overlapping CF pathology. Key clinical, genetic, and prognostic distinctions between CFHBI and HH are summarized to highlight their overlapping yet distinct hepatic manifestations (Table 1).

When diagnosed early, HH generally carries a favorable prognosis due to the efficacy of iron-reduction therapy [7]. Current guidelines recommend regular phlebotomy as first-line therapy for HH, with goal of maintaining serum ferritin below 50 ng/mL and transferrin saturation below 50% [7]. In patient's intolerant to phlebotomy, iron chelation may be considered [7]. HFE gene mutations, particularly C282Y, have been shown to worsen CF outcomes, including increased risk of intestinal obstruction and CFHBI [8]. Lung function in the non-lung transplant cystic fibrosis patients with the C282Y mutation had FEV1 54% predicted versus 66% predicted in cystic fibrosis patients without the mutation [9]. Additionally, having the C282Y mutation resulted in higher number of pulmonary exacerbations in the pediatric population compared to those without the mutation (8.5 ± 4.6 vs. 5.4 ± 4.4) [10]. Emerging evidence suggests that CFTR modulators may stabilize liver enzyme levels in some patients, although long-term impact on fibrosis progression remains unclear [3]. For patients who progress to end-stage liver disease, liver transplantation remains the definitive therapy [11]. The limitation of this case report is that this is the first case following lung transplantation and it is unclear whether there are any confounding issues that can produce HH in the post-transplant phase.

4. Conclusions

We report the first documented case of HH in a person with CF following lung transplantation. In our patient, the coexistence of HH in a post-transplant setting contributed to a delayed diagnosis and led to accelerated hepatic deterioration and eventual hepatic decompensation despite appropriate medical management. Among people with CF, particularly those on immunosuppressive therapy following lung transplantation, abnormal liver enzymes are frequently attributed to CFHBI or medication toxicity, which may delay the recognition of coexisting genetic liver disorders. This case highlights the limitations of phlebotomy in advanced HH and the uncertain benefit of CFTR modulators in reversing established hepatic injury, ultimately leading to decompensated liver disease.

CRediT authorship contribution statement

Eunjeong Joo: Writing – review & editing, Writing – original draft, Data curation. **Rebecca Golts:** Writing – review & editing. **Harim Kang:** Writing – review & editing. **Ajmera Veeral:** Writing – review & editing. **Reice Robinson:** Writing – review & editing. **Aiden Walters:** Writing – review & editing. **Eugene Golts:** Writing – review & editing. **Christine M. Lin:** Writing – review & editing. **Gordon Yung:** Writing – review & editing. **Kamyar Afshar:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing financial interests or personal relationships that could have affected the work reported.

Table 1
Comparison of liver disease in cystic fibrosis and hereditary hemochromatosis [1,3,4–6].

	Cystic Fibrosis Hepatobiliary Involvement	Hereditary Hemochromatosis
Prevalence	1 in 3000 worldwide	1 in 200–300 among White individuals
Etiology	CFTR gene mutation	Type 1: HFE gene mutation (M/C) Type 2A: HJV gene mutation Type 2B: HAMP gene mutation Type 3: TFR2 gene mutation Type 4: SLC40A1 gene mutation
Typical Age of Onset	CFLD: 0–25 years old	Type 1: 40–50 years old Type 2: 15–20 years old (Juvenile) Type 3: 30–40 years old Type 4: 10–80 years old
Gender Predilection	No strong predilection in CF overall, mild male predominance in liver involvement.	Type 1: Male predominance (More common and severe in males) Type 2, 3 and 4: No Preference
Pathogenesis	Multifactorial with combined defects in the bile secretion, immune dysregulation, gut–liver axis interactions, and obliterative portal venopathy and non-cirrhotic portal hypertension	Systemic iron overload → hepatic iron deposition → oxidative stress and hepatocellular injury
Clinical manifestations	Cholelithiasis, steatosis, multilobular cirrhosis, portal hypertension	Fatigue, skin pigmentation, diabetes, hepatomegaly
Lab abnormalities	Elevated AST/ALT, GGT, conjugated bilirubin, or alkaline phosphatase	Increased ferritin, transferrin saturation, elevated serum iron
Diagnostic approach	Imaging (US, Liver elastography, MRI elastography), Liver enzyme panels, AST-to-Platelet Ratio Index, GGT-to-Platelet Ratio. Liver biopsy to rule out other causes in select cases	Iron studies, Genetic test, Liver biopsy
Prognosis	Incidence rate of cirrhosis: 2.28%–4%. Incidence of advanced liver disease requiring LT in cirrhotic: 5.9%–26.3%.	Incidence rate of cirrhosis: 4.4–11.8% in male, 2.7% in female patients. Incidence of advanced liver disease requiring liver transplant is unknown
Treatment Strategies	Supportive care CFTR modulators Portosystemic Shunts Liver transplantation	Phlebotomy Iron chelation Liver transplantation

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmcr.2026.102382>.

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