

## Case Report

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# Unmasking hereditary hemochromatosis with CFTR modulator therapy

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## Abstract

Cystic Fibrosis (CF) is a genetic condition affecting the ability to excrete chloride, resulting in multi-system organ damage. Liver disease is one co-morbidity that affects 20-40% of people with CF. This case describes a 16-year-old male with CF (F508Del and Q493X mutations) who was started on one lexacaftor/tezacaftor/ivacaftor triple CF Transmembrane Regulator (CFTR) modulator therapy. Prior to starting treatment, it was noted that he had transaminitis (AST 69, ALT 120, Total bilirubin 0.4). His liver enzymes continued to increase with therapy and at week 8 of treatment he complained of abdominal pain, body aches, and fatigue warranting further evaluation. At that time, AST and ALT were elevated at 5- and 13-times the Upper Limits of Normal (ULN) and creatinine kinase was elevated at 12-times ULN. A dose reduction led to a decrease in AST and ALT to 2 and 4-times ULN, but total and direct bilirubin increased to 2.2 mg/dl and 0.5 mg/dl, warranting a liver ultrasound and biopsy. Pathology showed fatty liver and hepatocyte iron deposition, but no indications of cirrhosis. Iron studies and genetic testing confirmed a diagnosis of HH (Homozygous H63AS gene mutation). After stopping triple CFTR modulator therapy, AST and ALT continued to rise, prompting further evaluation by hepatology and hematology. Upon discontinuation of drug therapy, his lung function dropped significantly back to baseline values and respiratory symptoms returned.

**Discussion:** Hereditary hemochromatosis gene mutations have been shown to have a gene modulating impact on CFTR gene mutations that can affect CF disease phenotype, which negatively affects pulmonary function and gastrointestinal disease. In this case, the introduction of a new medication instigated further work-up leading to the discovery of a potential alternative cause of hepatic dysfunction while attempting to optimize medications to sustain improvements in pulmonary function. Although elevated hepatic transaminases can be expected from CF and CFTR modulator therapy, further investigation may be indicated in patients with persistent elevations despite medication adjustments. This workup may lead to important considerations in balancing liver function with lung function.

**Abbreviations:** CAP: Controlled Attenuation Parameter; CF: Cystic Fibrosis; CFTR: Cystic Fibrosis Transmembrane Regulator; ETI: Elexacaftor/Tezacaftor/Ivacaftor; FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; HH: hereditary hemochromatosis; HFE: Homeostatic Iron Regulator.

**Keywords:** cystic fibrosis; elexacaftor; tezacaftor; ivacaftor; liver transaminases; hereditary hemochromatosis.

## Introduction

Cystic Fibrosis (CF) is a genetic condition affecting the excretion of chloride, resulting in multi-system organ damage. Triple CF Transmembrane Regulator (CFTR) modulator therapy (Elexacaftor/Tezacaftor/Ivacaftor - ETI) represents a promising option for many patients with CF. Pre-marketing trials reported about a 10% incidence of elevations in liver transaminases, warranting close monitoring. This report reviews a case in which the workup of unusually elevated liver enzymes uncovered an underlying disease process, altering the management of CF in this patient.

## Case presentation

This patient was born with F508Del and Q493X CF mutations and adopted by his nonbiological foster parents at 4 months of age. Shortly after birth, he developed liver failure and was put on the liver transplant list, but his liver function promptly recovered. In addition to CF associated hepatic disease, his medical history required numerous hepatically metabolized medications such as treatments for *Mycobacterium avium* intracellulare. Now, at 16 years old, he was started on Triple CFTR Modulator Therapy (ETI) in an attempt to improve his pulmonary function. Prior to starting treatment, his lung function as measured by Forced Expiratory Volume in 1 second (FEV1) was 58% and it was noted that he had mild transaminitis with AST 69, ALT 120, Total bilirubin 0.4. At Week 8 of therapy, he complained of abdominal pain, body aches, and fatigue with AST 170, ALT 416 and creatinine kinase elevated at 12-times previous. His FEV1 had improved to 98%, but with the new initiation of ETI and the known interactions of this medication with liver function, it was determined that he undergo a trial dose reduction to determine if the ETI was the underlying cause of these changes. At Week 12, his labs indicated AST 68, ALT 128, but showed a persistently elevated total bilirubin of 2.2 mg/dl and direct bilirubin 0.5 mg/dl. Improvement of the transaminitis could have been a result of the decreased ETI dosage, but the new findings of increased bilirubin warranted further workup. Hepatitis, Epstein-Barr Virus, Cytomegalovirus, and Alpha-Fetoprotein labs were unremarkable. The patient then underwent a liver ultrasound and biopsy to investigate for other underlying causes of elevated liver enzymes and hyperbilirubinemia. Imaging confirmed the patient had mild hepatomegaly with liver span of 15.8 cm and liver biopsy showed fatty liver and hepatocyte iron deposition, with no indications of cirrhosis. Iron studies at that time indicated abnormalities in Iron 161, Ferritin 1524, Iron Sat 51.2%, Transferrin 211, TIBC 314 and genetic testing confirmed a diagnosis of Hereditary Hemochromatosis (HH), Homozygous H1S63ASP (H63D) gene mutation.

After stopping triple CFTR modulator therapy, AST and ALT continued to rise and his lung function dropped significantly back to pre-intervention baseline. Persistent transaminitis prompted evaluation with hematology who determined that his elevated ferritin was due to chronic inflammation and hepatology. Thus, ruling out hematologic etiologies of elevated transaminases and confirming HH diagnosis. At his hepatologist, he underwent a Fibroscan® and Controlled Attenuation Parameter (CAP) score assessment was consistent with steatosis and fibrosis in patients with CF. Recommendation was for the patient to

restart therapy at a modified dose to help improve his diminished lung function and titrate up as tolerated by his liver with serial laboratory testing and maintaining Child-Pugh scores below level C.

## Discussion

HH is an autosomal recessive genetic disease mainly involving the Homeostatic Iron Regulator (HFE) gene on chromosome 6. A dysfunctional regulatory signal due to genetic malformations results in an excessive amount of iron absorption through the gastrointestinal tract due to decreased expression of the regulatory hormone hepcidin or its receptor, leading to potential iron overload. Dysfunctional iron utilization and dysregulation results in iron deposition within organs, commonly the liver, contributing to oxidative stress, damage, and fibrosis [1,2].

Like CF, HH can be attributed to multiple genetic mutations resulting in different polymorphisms and degree of penetrance. Because there are many genetic variants of HH, this disease has been calculated to be 10-fold more prevalent than a genetic mutation that causes CF. While the common C282Y polymorphism has been associated with northern European descent, our patient's mutation H63D has no geographic associations [3].

HH gene mutations may modulate CFTR gene mutations, affecting the CF disease phenotype and negatively affecting pulmonary function and gastrointestinal disease. Some studies indicate that having a carrier of 1 HFE gene compared to a non-carrier of HFE among the CF population is associated with worse lung function with more substantial lung function decline over time at almost 3 times the difference in FEV1 % predicted and 10 times the difference in Forced Vital Capacity (FVC) % predicted [3]. Although C282Y variants of HH with CF can result in declines in FEV1 and FVC relative to CF patients with normal genotype, CF patients with H63D, like our patient, will have a more notable decline in FVC compared to normal genotypes. Other correlations between H63D and CF include a higher incidence of meconium ileus [4].

Our patient has many comorbidities requiring a regimen of medications. HH diagnosis in this patient emphasized the importance of individualized medicine as many of his medications are hepatically metabolized. To mitigate hepatotoxic stress on his liver, one of his newer medications, ETI, was titrated downwards as his liver function was monitored. Had this newer medication not been started, this patient's diagnosis of HH would have not been made. In his medical management, there continues to be a balance of pulmonary function versus drug-induced hepatotoxicity given his new diagnosis. Shortly after initiation, his ETI therapy provided significant improvements in pulmonary function with over 40% improvement in FEV1. However, his Child Pugh scores increased due to potential effects of medication with underlying HH. As ETI medication was titrated because of hepatotoxicity concerns, his pulmonary function had a reflective decrease back down to pre-intervention baseline.

Newer CFTR modulator medications provide renewed hope within the CF patient population with significant gains in pulmonary function. However, this patient's medical management will require more strict medication dosing due to his HH diagnosis in order to optimize pulmonary function. Given the preva-

lence and genetic relationship of HH within a similar population that affects patients with CF, patients need to be assessed for underlying liver disease when newer therapies that promote improved lung function are implemented into their medication regimen.

### Conclusion

In this case, the introduction of a new medication instigated further work-up of unusually elevated liver enzymes, leading to the discovery of a critical underlying genetic disorder in this patient. Although elevated hepatic transaminases can be expected from basic CF liver involvement and CFTR modulator therapy, further investigation may be indicated in patients with persistent elevations despite medication adjustments. This workup led to discovery of underlying liver disorder and further important considerations relating to the balance of liver function with lung function.

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