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Coexisting Hemochromatosis and Autoimmune Hepatitis: Diagnostic Dilemmas in the Context of Iron Overload

Orivaldo Alves Barbosa M.D[1], Dower Frota Barroso[2], João Paulo Uchoa Fontenele[3], Talita Guimarães Andrade MD[4], Danilo Alencar Martins MD[5]

[1]*General Hospital Dr. César Cals, Master in Health Education, Hospital César Cals, Avenida do Imperador, 545, Centro, Fortaleza /Ceará, Brazil*

[2]*Radiologist, São Carlos Imagem, Rua Otoni Façanha de Sá, 69, Dionísio Torres, Fortaleza/Ceará, Brazil*

[3]*Pathologist, Hospital César Cals, Avenida do Imperador, 545, Centro, Fortaleza /Ceará, Brazil*

[4,5]*Internal Medicine Resident at General Hospital Dr. César Cals, Brazil*

Corresponding Author:** ***Orivaldo Alves Barbosa M.D, *General Hospital Dr. César Cals, Master in Health Education, Hospital César Cals, Avenida do Imperador, 545, Centro, Fortaleza /Ceará, Brazil*

Abstract

This case report presents a rare occurrence of concurrent autoimmune hepatitis (AIH) and hereditary hemochromatosis (HH) in a 50-year-old male patient. The patient, with a history of hypertension, exhibited symptoms of jaundice, dark urine, abdominal enlargement, and weight loss. Laboratory evaluations indicated elevated liver enzymes, iron overload, and heterozygosity for the H63D mutation associated with HH. Liver biopsy confirmed chronic hepatitis with marked hepatocellular siderosis. The therapeutic regimen included prednisone, azathioprine, and weekly phlebotomies, which led to significant clinical improvement. This case underscores the diagnostic and therapeutic challenges posed by the coexistence of AIH and HH, and explores the potential contribution of iron-induced ferroptosis to the pathogenesis of AIH, suggesting avenues for future research into innovative treatment strategies

Keywords: *Autoimmune hepatitis, Hereditary hemochromatosis, Iron overload*

Learning Points:

1. Diagnostic Challenge: *Coexisting autoimmune hepatitis (AIH) and hereditary hemochromatosis (HH) require a thorough diagnostic approach, including genetic testing and liver biopsy, to distinguish and manage these overlapping conditions.*

2. Iron Overload in AIH: *The case suggests that iron-induced ferroptosis may play a role in AIH pathogenesis, highlighting the importance of managing iron levels to prevent liver damage.*

3. Tailored Treatment: *The successful use of corticosteroids, azathioprine, and phlebotomies underscores the need for a multidisciplinary approach in treating concurrent AIH and HH.*

1. Introduction

Autoimmune hepatitis (AIH) and hereditary hemochromatosis (HH) are distinct clinical conditions affecting the liver, each with specific etiological, pathophysiological, and clinical characteristics. AIH is a chronic inflammatory liver disease characterized by autoimmune-mediated destruction of hepatocytes(1), whereas HH is a genetic condition marked by increased iron absorption in the intestine, leading to excessive iron accumulation in tissues, particularly the liver(2). Although both are relatively uncommon, the coexistence of these conditions in a single patient is extremely rare and poorly documented in the medical literature. This case report provides a detailed account of a patient with autoimmune hepatitis and hereditary hemochromatosis, addressing their clinical presentation, diagnosis, treatment, and progression.

2. Objective

To document and analyze a rare case of the coexistence of autoimmune hepatitis and hereditary hemochromatosis, highlighting the clinical, laboratory, radiological, histopathological, therapeutic, and evolutionary aspects of this complex condition. Following the guidelines established by Resolution 196/1996

of the Brazilian Unified Health System for studies involving human subjects, the Research Ethics Committee evaluated and authorized the publication of this case. The patient voluntarily consented to the study.

3. Case Report

A 50-year-old male patient, a fisherman from Beberibe, Ceará, with a history of hypertension, presented with jaundice, dark urine, abdominal enlargement, and weight loss in December 2022. Following laboratory abnormalities indicative of liver disease, he was transferred to a tertiary hospital in Fortaleza. Admitted on 01/05/2024, he exhibited jaundice and was hemodynamically stable. Tests revealed normocytic and normochromic anemia, hypoalbuminemia, hyperbilirubinemia, and elevated transaminases (Table 1). Abdominal ultrasound showed signs of non-homogeneous hepatic deposition disease. Protein electrophoresis indicated hypoalbuminemia and a polyclonal peak in the gamma fraction. Tests for autoimmune hepatitis antibodies were requested.

Table 1. *Key Laboratory Findings*

	Result	Reference
Hemoglobin	10,1g/dL	13,5-18 g/dL
MCV	97,5 fL	80-96 fL
MCHC	32,7 g/dL	31,8-35,4 g/dL
Platelets	304.000	150.000-450.000
Albumin	2,49 mg/dL	3,5-4,8 mg/dl
AST	922 U/L	13-38 U/L
ATL	784 U/L	7-41 U/L
ALP	108 U/L	65-300 U/L (20-60 anos)
GGT	140 U/L	11-50 U/L (homens)
Total Bilirubin	14 mg/dl	< 1,2mg/dl
Direct Bilirubin	9,71 mg/dl	< 0,4 mg/dl
Indirect Bilirubin	4,29 mg/dl	< 4,29 mg/dl
Ferritin	>1500 ng/ml	28-365 ng/ml (homens)
Transferrin Saturation Index	98,1%	20-50% (homens)
Serum Iron	242,2 mg/dL	65-175 mg/ml (homens)
Total Iron-Binding Capacity	273,1 ug/dL	155-355 ug/dL
Total Testosterone	21,77 ng/dL	175-781 ng/dL
Free Testosterone	0,436 ng/dL	1,67-18,3 ng/dL

Anemia investigation revealed a positive monospecific Coombs test and elevated levels of ferritin and transferrin saturation (Table 1). Corticosteroid therapy was initiated for suspected autoimmune hemolytic anemia. Additional tests included HFE gene mutation testing, hepatic MRI, and hormone and immunoglobulin assays.

During hospitalization, there was progressive improvement in jaundice and laboratory parameters. Autoimmune hepatitis antibodies were non-reactive, and HFE gene mutation showed heterozygosity for H63D (Table 2). The patient also had reduced testosterone levels (Table 1) and complained of decreased libido and testicular volume.

Table 2. *Autoantibody Profile and HFE Mutation Status*

	Result Non-reactive Non-reactive	Reference Value
Anti-Smooth Muscle Antibody (ASMA)	Non-reactive	Non-reactive
Anti-LKM1 Antibody	Non-reactive	Non-reactive
Anti-Mitochondrial Antibodies (AMA)	Non-reactive	Non-reactive
C282Y Mutation	Negative - Wild-type Homozygous	Negative - Wild-type Homozygous
H63D Mutation	Heterozygous	Negative - Wild-type Homozygous

After improvement and initiation of corticosteroid tapering, hepatic MRI indicated iron deposition in the liver (Figures 1). Liver biopsy confirmed chronic hepatitis with intense interface activity and hepatocellular siderosis (Figures 2 and 3). Prednisone, azathioprine, and weekly phlebotomies were started.

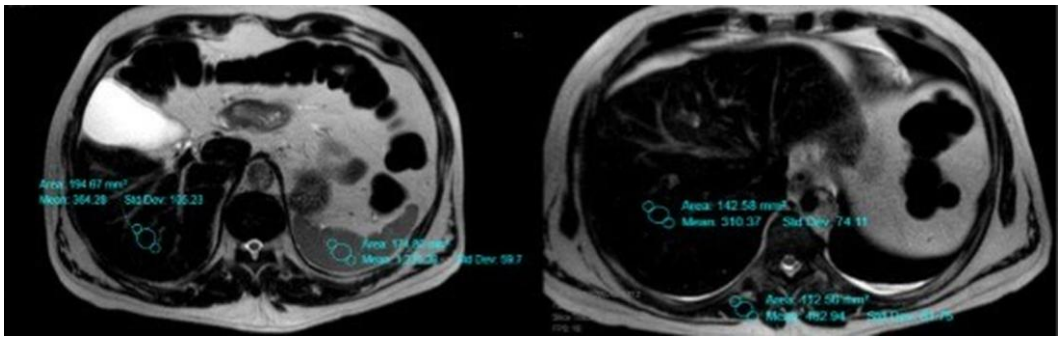

Figure 1. *T2-weighted imaging (T2WI) reveals a hypointensesignal in theliverparenchyma, indicativeof iron deposition*

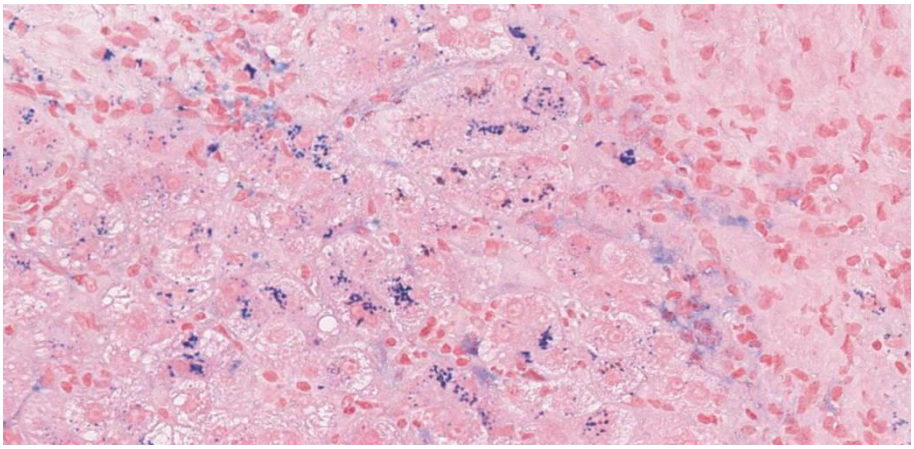

Figure 2. *Hemossiderin granules are observed in the cytoplasm of hepatocytes in zone 1 of the hepaticacinus. Stained with Perls' technique, magnification 400x.*

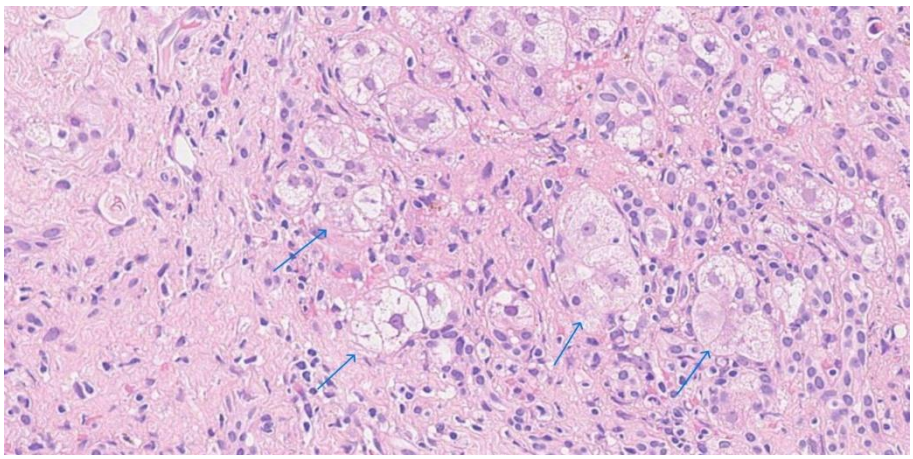

Figure 3. *Interface activity is observed, with mild lymphoplasmacytic in filtrate and the presence of hepatocyte rosettes (indicated by arrows). Stained with Hematoxylin and Eosin (HE), magnification 400x.*

4. DISCUSSION

Iron regulation disorders have been described in various chronic liver diseases beyond hereditary hemochromatosis(3). Elevated serum ferritin levels are common in non-alcoholic fatty liver disease (NAFLD), chronic alcoholic liver disease, chronic hepatitis B, chronic hepatitis C, alpha-1 antitrypsin deficiency, and autoimmune hepatitis(4). Disturbances in iron homeostasis in chronic liver diseases can be a collateral manifestation of active inflammation and parenchymal damage or a mechanism by which iron toxicity worsens liver injury.

In autoimmune hepatitis, serum ferritin is elevated in 65% of untreated patients, and serum iron and transferrin saturation levels are abnormally elevated in 58% and 48%, respectively (5). Ferritin is an acute phase reactant, and its serum level correlates with serum CRP and the pro-inflammatory cytokine IL-6. Alternatively, hyperferritinemia and increased transferrin saturation in some patients with autoimmune hepatitis may reflect inadequate hepcidin suppression and increased intestinal absorption and tissue mobilization of iron by unrestricted ferroportin activity.

Our reported case is atypical because, in addition to clinical and histological evidence of autoimmune hepatitis, the patient has a transferrin saturation index > 90%, prompting further investigation with hepatic MRI, genetic testing, and liver biopsy, confirming the concomitant diagnosis of Hereditary Hemochromatosis and iron overload syndrome. We question whether the presence of iron overload, through apoptosis mechanisms, could precipitate autoimmune hepatitis.

Ferroptosis is a type of programmed cell death distinct from traditional apoptosis, characterized by iron accumulation and lipid peroxidation, leading to cell death. Ferroptosis is induced by intracellular iron accumulation that catalyzes the formation of reactive oxygen species (ROS) through the Fenton reaction, causing oxidative damage to cellular membrane lipids, resulting in cell death (6). Excess iron can promote oxidative stress and cellular damage, exacerbating hepatic inflammation. Ferroptosis may contribute to liver damage in AIH, as excess iron can induce cell death through lipid peroxidation. The resulting cell death may release danger signals that attract and activate more immune system cells, perpetuating the inflammatory cycle characteristic of AIH (7).

HFE-related hereditary hemochromatosis is an autosomal recessive disease, with most patients being homozygous for the C282Y mutation (2). However, heterozygous C282Y mutation has also been associated with increased hepatic iron concentration in patients with chronic liver diseases, such as AIH. In a German study, 17.2% of patients diagnosed with AIH had the heterozygous C282Y mutation (3). On the other hand, heterozygosity for the H63D gene mutation causing iron overload in patients with AIH has rarely been reported in the literature.

As far as we know, there are very few reported cases of this association (4, 5, 8, 9). The exact pathophysiology behind elevated transferrin saturation in patients with AIH remains unclear. Possible mechanisms include dysregulation of iron absorption in enterocytes and the release of iron from hepatocytes following necroinflammatory cellular damage,linking a potential pathophysiological link between iron overload, iron-induced apoptosis, and autoimmune diseases, including autoimmune hepatitis.

5. Conclusion

The detailed description of this clinical case can provide a broader understanding of the clinical presentation and therapeutic management of patients with autoimmune hepatitis and hereditary hemochromatosis. It also highlights the importance of a multidisciplinary approach in diagnosing and treating these complex conditions, emphasizing the need for a comprehensive and integrated evaluation to ensure the best patient outcome. Understanding ferroptosis in AIH may open pathways for new therapeutic approaches. For example, the use of iron chelators or lipid peroxidation inhibitors could be investigated as ways to reduce liver damage in patients with AIH (10).

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