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Case Report

Hemochromatosis: Revisiting an Old Disease – A Case Report

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Abstract

Introduction: Hemochromatosis is part of hereditary diseases that cause iron overload, aUecting the liver, pancreas, endocrine glands, and heart, leading to organ dysfunction.

Case presentation: A 51-year-old male with a history of insulin-dependent diabetes mellitus, hypogonadotropic hypogonadism, and seronegative arthritis presents with a condition of overall health deterioration, hematemesis, and melena lasting 24 hours. Laboratory tests compatible with diabetic ketoacidosis are requested, and treatment with fluid resuscitation and insulin is initiated, with good progress. To investigate the decompensating factor, a contrast-enhanced CT scan of the chest, abdomen, and pelvis is performed, revealing multifocal pneumonia, as well as Chronic Liver Disease (CLD) with esophageal varices and moderate splenomegaly. Following this incidental finding, a study for CLD was initiated, and ferritin levels were recorded as > 1200 ng/ml. given the high suspicion for hemochromatosis, an MRI of the liver for iron quantification, liver biopsy, and genetic testing are requested.

Discussion: The diagnosis of hereditary hemochromatosis requires a high level of suspicion, as it lacks specific symptoms or signs and usually presents asymptomatically. Transferrin saturation and ferritin tests are helpful, but the definitive diagnosis is made through iron concentration measurement via Magnetic Resonance Imaging (MRI) or liver biopsy. In this patient, the iron overload not only caused liver cirrhosis but is also inferred to be part of the origin of diabetes mellitus, hypogonadotropic hypogonadism, and joint involvement. The treatment is therapeutic phlebotomy, which improves symptoms and reduces morbidity and mortality if started early.

Introduction

Hemochromatosis is a condition that encompasses a group of hereditary disorders related to iron overload. Iron is primarily deposited in the joints and liver, which occurs due to a failure in hepcidin, a crucial protein in iron metabolism [1]. The diagnosis can be easily made through genetic testing and iron kinetics. The treatment remains phlebotomy, which is easily accessible worldwide. However, late diagnosis can severely compromise the quality of life of patients, as the symptoms are varied and can affect different organs. It is worth mentioning that the risk of hepatocellular carcinoma in these patients is approximately ten times higher compared to healthy individuals [2].

As mentioned previously, hemochromatosis is a disease caused by a genetic disorder that alters the regulatory function of hepcidin. 95% of cases result from the homozygous mutation of the HFE gene (iron homeostasis regulator), leading to a substitution of p.C282Y. This affects approximately 1 in every 150 to 220 people of Northern European descent. In the case of heterozygotes for p.C282Y, the incidence is 1 in every 7 individuals, and for the p.H63D variant, it is 1 in every 3 individuals of Northern European descent [1]. However, other genes related to iron metabolism have also been implicated in this pathology, such as the Transferrin Receptor 2 (TfR2), Hepcidin (HAMP), Hemojuvelin (HJV), and Ferroportin (FPN) [3]. Thus, the OMIM database classifies hemochromatosis

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into different types [4]. Type 1 is due to the mutation of the HFE gene; type 2 is divided into 2A (HMJ gene) and 2B (HAMP gene); type 3 (TfR2 gene); type 4 (SLC40A1 gene, which encodes ferroportin); and type 5, caused by a mutation in the FTH1 gene, first described in 2001 in 7 members of a Japanese family [5].

In Chile, there is limited data regarding the prevalence of this disease; however, a 2003 study estimated that the HFE gene mutation was present in 1 in 6250 patients, compared to the North American prevalence of 1 in every 270 individuals [6]. Given the scarcity of local studies on a pathology that severely impacts the quality of life of the patient and carries a high cancer risk, we would like to present the following clinical case.

Case presentation

A 51-year-old male patient with a history of insulin-dependent diabetes mellitus and hypogonadotropic hypogonadism, both diagnosed 12 years ago, and seronegative rheumatoid arthritis diagnosed 1 year ago. He uses NPH insulin 24 IU in the morning and 18 IU at night, metformin 850 mg, atorvastatin 40 mg, and aspirin 100 mg. His surgical history includes pleurostomy for pulmonary empyema in 1994 and right calcaneal fracture. He has no known allergies, denies significant family history, reports smoking 4 cigarettes per day, occasional alcohol consumption (which he stopped more than 20 years ago) and denies drug use.

The patient consulted at the emergency service of our center due to a condition of overall health deterioration, hematemesis, and melena lasting 24 hours. He presented with hypotension, with blood pressure of 96/52 mmHg, a respiratory rate of 18 breaths per minute, a heart rate of 95 beats per minute, afebrile, and 98% oxygen saturation in room air, with a high hemoglucotest. On physical examination, dehydrated mucous membranes were noted, capillary refill time of 3 seconds, regular rhythm with no murmurs auscultated, decreased breath sounds with no added noises, a soft, depressible, non-tender abdomen with splenomegaly, and diminished-sized gonads. Laboratory tests revealed hyperglycemia of 868 mg/dL, ketonemia of 6.3 mmol/L, venous gases showing metabolic acidosis with an elevated anion gap. Total bilirubin was 1.97 mg/dL, direct bilirubin 1.18 mg/dL, and transaminases were elevated with GOT 70 IU/L, GPT 89.9 IU/L, GGT 67.7 IU/L, and ALP 128 IU/L. The patient was hospitalized with Diabetic Ketoacidosis (DKA) and Upper Gastrointestinal Bleeding (UGIB). Treatment was initiated in the Intermediate Care Unit (ICU) with fluid resuscitation and insulin via Continuous Infusion Pump (CIP), with good progress. A contrast-enhanced CT scan of the Chest, abdomen, and pelvis (CT TAP) was ordered to investigate the cause of decompensation, revealing a mild left pleural effusion and pulmonary inflammatory foci consistent with multifocal pneumonia; hepatic morphological changes suggesting chronic damage with possible esophageal varices and moderate splenomegaly in the context of portal hypertension (Figures 1a,b). An upper gastrointestinal endoscopy was performed, showing grade B erosive esophagitis of Los Angeles, a small elevated lesion in the distal esophagus (biopsy), and diffuse

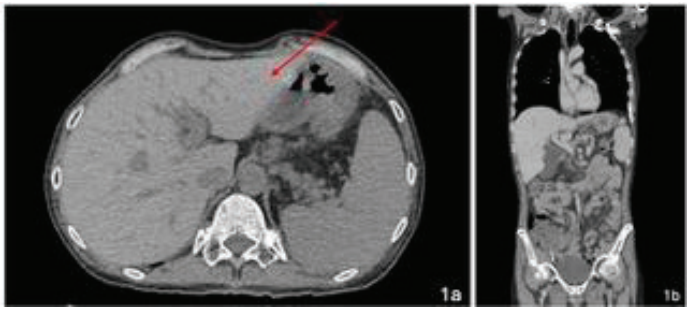

Figure 1a,b: CT TAP shows an increase in the size of the caudate lobe (1a; red arrow), irregularity of the liver borders (1b), and splenomegaly (1a).

hemorrhagic gastropathy associated with chronic congestive gastritis. No esophageal varices were founded.

Due to multilobar pneumonia, treatment was completed with ampicillin-sulbactam for 5 days, with a good response, and the patient progressed without further infectious complications.

The decision was made to transfer the patient to the internal medicine service for glycemic management and etiological investigation of Chronic Liver Disease (CLD). Given the patient's history, alcoholic etiology was ruled out. Among the requested tests, anti-centromere antibodies, anti-smooth muscle, Antinuclear Antibodies (ANA), anti-mitochondrial antibodies (AMA), anti-DNA, and anti-ENA were all negative. Hepatitis B and C virus tests were non-reactive. Iron kinetics showed transferrin 134 µg/dL , iron 166.5 µg/dL , and ferritin greater than 1200 ng/mL, with the latter interfering with the calculation of Total Iron-binding Capacity (TIBC) and transferrin saturation. Due to these findings, a liver MRI was requested for iron quantification, and liver biopsy and genetic testing were also planned. A liver biopsy was performed during hospitalization, revealing hepatic tissue with trabecular structure partially distorted by thick fibrous bands, collagen, and hepatocytic regeneration nodules . In the fibrous bands, there was a strong proliferation of bile ducts (Figures 2a,b). Hepatocytes and bile duct epithelium showed intense iron deposition (PERLS +++), compatible with hemochromatosis in cirrhotic phase (Figures 3a,b). The genetic study was negative for the HFE gene.

To assess the presence of cardiac involvement, a transthoracic echocardiogram was completed, which reported normal diameters and preserved systolic function of the left ventricle, with a Left Ventricular Ejection Fraction (LVEF) of 61%; a Global Longitudinal Strain (GLS) of 17%; preserved right-sided chambers, a Pulmonary Systolic Pressure (PSP) of 33 mmHg; and no significant valvulopathies.

The patient presented with difficult glycemic control and recurrent hypoglycemia, despite low insulin doses, suggesting, in this context, a likely diagnosis of pancreatogenic diabetes, probably due to iron deposits. The patient was discharged with insulin glargine (Lantus) 30 IU and outpatient follow-up with telemonitoring for subsequent insulin adjustments. It`s important to stand out that patient´s weight was normal (58.9 Kg) in relationship with his height (1.68 m) with a Body Mass Index (BMI) of 20.8, in other words, normal.

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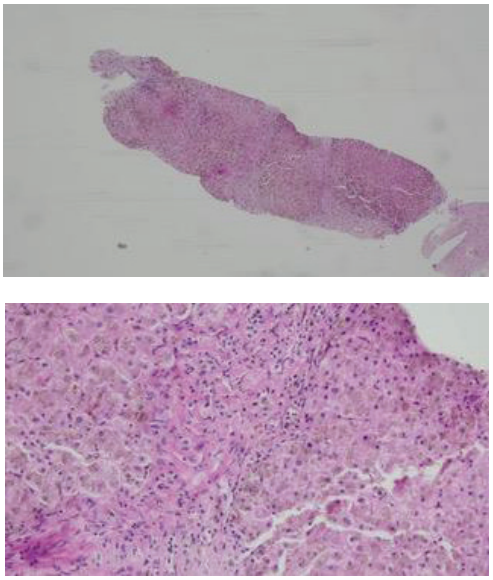

Figure 2a,b: Fragment of a hepatic parenchyma cylinder with histoarchitecture partially distorted by the presence of thick fibrous tissue bands, collagen, and regenerative hepatocytic nodules. Hepatocytes and biliary epithelium show intense deposition of brownish granular cytoplasmic pigment in a hematoxylin-eosin stain at 10x and 20x magnification.

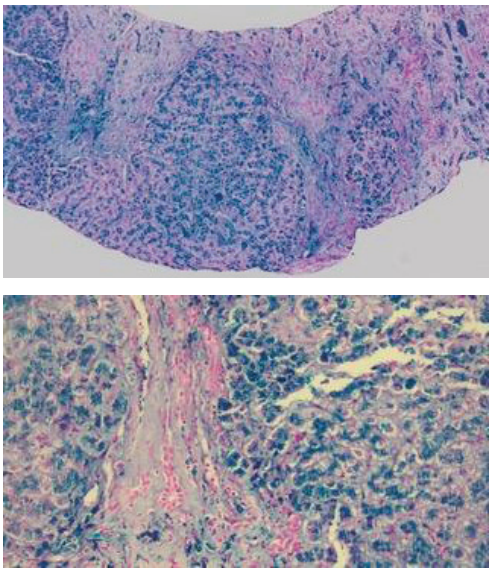

Figure 3a,b: Hepatocytes and biliary epithelium with cytoplasmic iron deposition demonstrated by intense positivity (+**/+++) of the PERLS histochemical technique at 10x and 20x magnification, respectively.

Upon hospital discharge, the patient is placed under gastroenterology follow-up with a diagnosis of hemochromatosis, involving hepatic, pancreatic, and gonadal impairment, for subsequent phlebotomy treatment and preventive monitoring for Hepatocellular Carcinoma (HCC). The remainder of the genetic study is pending due to cost considerations. Liver MRI was not possible due to previous calcaneal fracture with osteosynthesis element.

Discussion

The deficiency of hepcidin and the lack of ferroportin sensitivity to hepcidin are the two classic pathophysiological pathways that explain genetic iron overload syndromes, leading to increased ferritin, a characteristic finding of hemochromatosis. Hepcidin deficiency is caused by alterations in various genes, including HFE, TfR2, HJV, or HAMP. The absence of this hormone results in an increase in iron efflux from cells, primarily from macrophages and enterocytes, leading to elevated plasma iron levels and consequent transferrin saturation, along with circulating iron not bound to transferrin [7]. Ferroportin insensitivity to hepcidin is another cause, which is included in ferroportin disease. There are mainly two proposed functional mutations. A loss of ferroportin function results in increased iron in tissues (with elevated plasma ferritin) and a decrease in iron bound to transferrin (low transferrin saturation), and this phenotype is more prominent in the reticuloendothelial system [8,9]. A gain-of-function mutation in ferroportin, explained by the resistance of this protein to hepcidin, leads to an increase in iron absorption by enterocytes and an increased iron flow from macrophages, with a final consequence similar to what occurs in hepcidin deficiency [9]. Finally, free iron deposits primarily in hepatic, pancreatic, endocrine, and cardiac cells, causing organ failure and leading to the various symptoms [7].

Hereditary hemochromatosis does not have specific symptoms or signs and generally progresses asymptomatically; however, it is common to find elevated transaminases and ferritin levels in these patients. Fatigue, arthralgia, and decreased libido are classic, nonspecific early findings. The triad of diabetes mellitus, hepatic cirrhosis, and abnormal skin pigmentation is observed in the later stages [10]. Regarding the involvement of other organs, 15% of patients may develop cardiomyopathy, which will manifest asymptomatically in the early stages and progress to symptoms of heart failure. Echocardiographically, early evidence of left ventricular diastolic dysfunction is seen due to restrictive physiology, which will progress to dilated cardiomyopathy with reduced Left Ventricular Ejection Fraction (LVEF) [11].

Iron overload causes endocrine dysfunction, particularly in the pituitary axis, leading to Hypogonadotropic Hypogonadism (HH), with a reported frequency in the literature ranging from 10% to 100% of cases. In clinical practice, this is evidenced by loss of body hair and decreased testicular volume. Additionally, it impacts sexuality, causing reduced libido, erectile dysfunction, impaired ejaculation, and infertility. It is important to note that iron overload can affect fertility through various mechanisms such as HH, diabetes, and cirrhosis [12].

Joint involvement most commonly affects the metacarpophalangeal joints, leading to chronic, progressive, and symmetrical impairment [13].

A high level of suspicion is necessary to make the diagnosis. Elevated transferrin saturation levels (maintained above 45%) have a sensitivity of 94% in men and 73% in women. Ferritin values over 300 µg/L in men reach a sensitivity of 88%. Both findings should raise suspicion for hemochromatosis [1]. However, it is important to rule out infectious, inflammatory, or neoplastic conditions, as well as alcoholic liver disease or viral hepatitis, which can also elevate ferritin levels [13].

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In our patient's case, hemochromatosis was suspected as the cause of hepatic cirrhosis, and other etiologies were ruled out, given the concomitance with diabetes mellitus, hypogonadism, and joint involvement. The iron kinetics reinforced this clinical suspicion, and the liver biopsy confirmed it. Based on the literature, tissue iron concentration can be evaluated non-invasively using Magnetic Resonance Imaging (MRI) under T2 sequence [12]. However, this method is costly and has limited availability in our setting, so a liver biopsy was performed for etiological confirmation.

Patients with iron overload but without HFE mutations should be referred to a specialist for further genetic evaluation, as severe cases due to other mutations are uncommon. In many cases, other factors, such as alcoholic or metabolic liver disease, play a role. In this particular case there was not an alcholic habit, and the BMI was normal (valor of 20.8).

The first-line treatment for these patients is based on iron depletion through therapeutic phlebotomy, which consists of two phases: the induction phase, to deplete the body's iron stores, and the maintenance phase, to prevent iron re-accumulation . This treatment can reduce morbidity and mortality if initiated before the development of cirrhosis and/or diabetes. It also improves fatigue, arthralgia, and liver function tests [13].

There are alternative therapies when phlebotomy is not possible, such as iron chelators, including deferasirox, which effectively removes excess iron but comes with renal and hepatic side effects , as well as high costs [14]. Another therapeutic option is erythrocytapheresis, which is not widely available, is costly, and does not remove iron more quickly than blood extraction [7,13].

Finally, regular follow-up and screening for the development of Hepatocellular Carcinoma (HCC) should not be overlooked, through abdominal ultrasound and Alpha-fetoprotein (AFP) testing every 6 months [13]. Also routine follow-up in these patients involves iron level monitoring and screening for organ damage.

Conclusion

Hemochromatosis is a genetic condition that includes a group of hereditary disorders related to iron overload. This metal is primarily deposited in the joints and liver, but also in gonads, pancreas and heart. The diagnosis can be made through genetic testing and iron kinetics, but requires a high level of suspicions due to it´s not always compromise all the mentioned organs. The liver biopsy can be very useful to quantify iron deposition in liver tissue. The treatment remains phlebotomy. However, late diagnosis can severely compromise the quality of life of patients, as the disease can affect different organs. The risk of hepatocellular carcinoma in hemochromatosis patients is approximately ten times higher than in healthy individuals, making mandatory screening essential once cirrhosis develops.

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