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Case report

Hereditary hemochromatosis caused by a C282Y/H63D mutation in the HFE gene: A case report

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ABSTRACT

Hereditary hemochromatosis (HH) is a disease characterized by disordered iron metabolism. It often involves mutations of the *HFE* gene, which encodes the homeostatic iron regulator protein (HFE), as well as mutations affecting hepcidin antimicrobial peptide, hemojuvelin, or transferrin receptor 2. Historically, HH has been observed primarily in European and European diaspora populations, while classical HH is rare in Asian populations, including in China. In this article, we report a rare case of HH in a Chinese man that could be attributed to a heterozygous C282Y/H63D HFE mutation. Based on clinical examination, liver biopsy, and genetic testing results, the patient was diagnosed with HH. Clinical signs and symptoms and serum iron-related test results were recorded for a period of two years after the patient began treatment. Over this observation period, the patient was subjected to 25 phlebotomies (accounting for a total blood loss of 10.2 L). His serum ferritin levels decreased from 1550 μg/L to 454 μg/L, his serum iron concentration decreased from 40 μmol/L to 24.6 μmol/L, and his transferrin saturation decreased from 97.5% to 55.1%. Early diagnosis is essential for patients with HH to obtain good outcomes. Regular phlebotomy after diagnosis can improve HH symptoms and delay HH disease progression.

1. Background

Hereditary hemochromatosis (HH) is a genetic disease characterized by excessive absorption of iron from the diet, leading to the accumulation of iron in various organs throughout the body [1]. There is a close association between the HFE gene and HH. The HFE gene plays a key role in regulating iron metabolism by interacting with transferrin, a protein responsible for transporting iron ions. Transferrin binds to transferrin receptor 1 (TFR1) on the cell surface to transport iron ions into the cells. The HFE protein could bind to TFR1 and inhibit transferrin uptake, reducing cellular iron demand and balancing intestinal iron absorption and hepatic iron storage [2]. However, mutations in the HFE gene disrupt this regulatory mechanism, leading to excessive iron absorption. Two common mutations associated with HH are C282Y and H63D. The C282Y mutation involves the substitution of a cysteine residue with a tyrosine residue at position 282 of the HFE protein. This mutation interferes with the normal interaction between the HFE protein and the TFR, which is responsible for controlling the uptake of iron ions by cells. As a result, the C282Y mutation disrupts the ability to perceive and

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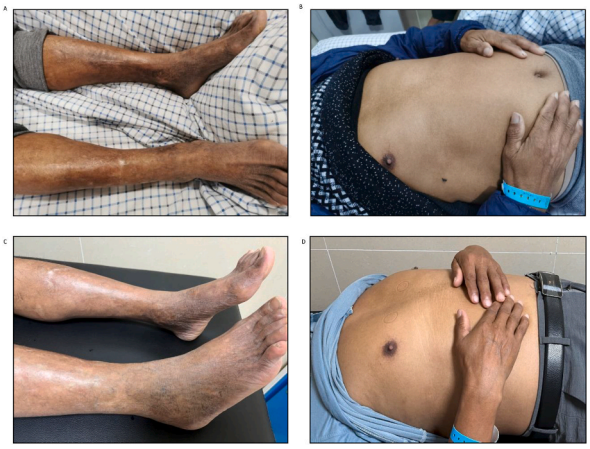

Fig. 1. Bronze pigmentation of the trunk and limbs (A and B) improved after treatment (C and D).

regulate the levels of iron ions, leading to an excessive accumulation of iron in tissues. On the other hand, the H63D mutation involves the substitution of a histidine residue with an aspartic acid residue at position 63 of the HFE protein. While the exact mechanism is not fully understood, it is believed that the H63D mutation similarly disrupts the interaction between the HFE protein and the TFR, resulting in impaired regulation of iron ions and an increased uptake of iron [3]. The risk of developing HH is associated with inheriting either two C282Y mutation genes (C282Y/C282Y) or one C282Y mutation gene and one H63D mutation gene (C282Y/H63D). The presence of these mutations leads to abnormal iron metabolism, which ultimately causes an excessive deposition of iron in various organs such as the liver, heart, pancreas, and joints [4].Whereas there is a 0.3–0.5% prevalence of HH in northwestern Europe [5], HH is a very rare disease in China. The first Chinese case of HH was reported in 1935 [6], and the Chinese National Knowledge Infrastructure has records of only 150 cases of HH from 1975 to 2022.

HH has been classified into four types based on genotype. The most common type, known as type 1, is associated with mutations of the gene *HFE*, which encodes the homeostatic iron regulator protein (HFE). Type 1 HH has three subtypes with characteristic HFE mutations: type 1a, C282Y homozygote [7,8]; type 1b, C282Y/H63D heterozygote [9]; and type 1c, presence of the S65C allele [10,11]. Type 2 HH, also known as juvenile hemochromatosis, is associated with mutations in non-HFE genes. It includes subtypes 2a (hemojuvelin gene) and 2b (hepcidin antimicrobial peptide gene) [12]. Type 3 HH is associated with mutations in the transferrin receptor 2 gene [13,14]. Finally, type 4 HH, which is also known as ferroportin disease, is associated with autosomal dominant mutations in SLC40A1 [15,16], the gene that encodes ferroportin 1. Asymptomatic type 4 HH is referred to as type 4a, whereas symptomatic type 4 HH is termed type 4b. In either case, excessive iron levels are attributed to resistance of ferroportin 1 [17].

The diverse phenotypic expressions of HH can make HH diagnosis difficult. Up to 18% of men and 5% of women may have some level of hepatic iron overload without any apparent clinical symptoms[[18]]. Common early symptoms of HH include fatigue and arthralgia [19,20]. HH-associated fatigue ranges in severity from mild to debilitating and can be ameliorated with treatment [21]. Hyperpigmentation is another early manifestation of HH. Iron deposition in the skin leads to increased melanin production and deposition, which produces the characteristic metallic or slate gray skin tones commonly referred to as bronzing. This alteration in skin pigmentation is typically generalized, but is most frequently observed on the skin of the face, neck, extensor aspects of the forearms, backs of the hands, lower legs, and genital areas [22]. Patients experiencing HH disease progression may develop severe skin pigmentation changes, arrhythmias, and impotence [23].

The liver is the most commonly affected organ in type 1 HH, wherein liver damage may manifest as asymptomatic elevations in serum aminotransferase levels, nonspecific pain in the right upper quadrant, or complications of end-stage liver disease [24,25]. Although cardiac manifestations of excess iron deposition are relatively uncommon in patients with type 1 HH, cardiomyopathy remains the second leading cause of death in HH patients [26]. Iron deposition in the heart leads to cardiac disease, including restrictive and dilated cardiomyopathy, cardiac arrhythmias (e.g., sick sinus syndrome and ventricular fibrillation), and heart failure [27]. Osteoporosis has also been reported in HH patients [28,29].

In this article, we report a rare case of HH caused by C282Y/H63D heterozygous HFE mutation. After regular phlebotomy, serum ferritin (SF), serum iron (SI), and transferrin saturation (TSAT) decreased, transferrin (TF) and liver function returned to normal, and the patient's clinical symptoms improved.

2. Case presentation

A 68-year-old man was admitted to the hospital on December 15, 2020, due to elevated bilirubin that had persisted for more than 3 months. He had a 40-year history of smoking 10 cigarettes/day and drinking 100 g of alcohol/day. The patient also denied oral iron intake and blood transfusions. Physical examination revealed bronzed skin throughout the body surface, hyperpigmentation in the skin folds of the extremities (Fig. 1A and B), and slight jaundice of the sclera, but no other significant abnormalities.

Laboratory evaluation identified elevated bilirubin levels, predominantly indirect bilirubin (Table 1). His serum iron level was

Table 1
Baseline and post-treatment characteristics of the case study patient.

Auxiliary examination	Baseline	Posttreatment
Routine blood panel		
WBC ($\times 10^9$/L)	7.72	8.78
NE ($\times 10^9$/L)	4.85	5.79
RBC ($\times 10^{12}$/L)	4.05	3.87
HGB (g/L)	138	126
Routine biochemical tests		
ALT (U/L)	41	12
AST (U/L)	46	19
TB (μmol/L)	73.3	15.6
DB (μmol/L)	10.7	7.2
IB (μmol/L)	62.6	8.4
TP (g/L)	71.4	75.1
ALB (g/L)	45.6	42.4
GLB (g/L)	25.8	32.9
GLU (mmol/L)	3.94	4.25
CHOL (mmol/L)	1.91	2.35
TG (mmol/L)	0.71	1.05
UA (μmol/L)	167	188
Serum iron index		
SI (μmol/L)	40	24.6
SF (μg/L)	1550	454
TF (mg/dL)	136	226
TSAT (%)	97.5	55.1

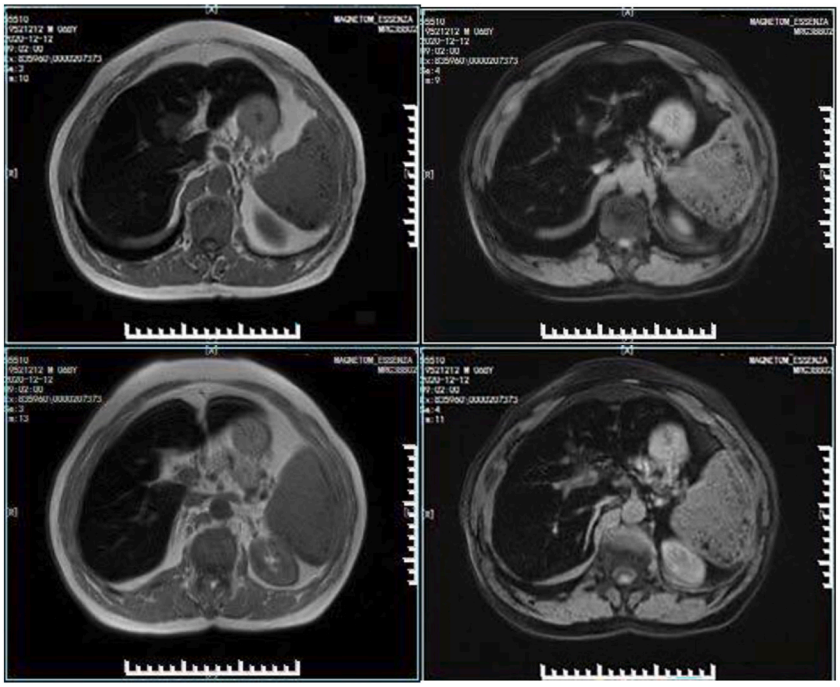

Fig. 2. Black liver in HH. MRI of the liver showing reduced T1W1 and T2W2 signal intensities throughout the liver.

slightly elevated, while his SF was substantially elevated, and his TSAT was abnormal. Laboratory tests for viral hepatitis, autoimmune hepatitis, coagulation function, tumors, Ham test, and Coombs test were all negative. An electrocardiogram showed sinus tachycardia, a complete right bundle branch block, and suspected right heart hypertrophy. Echocardiography showed enlargement of the left heart. Color Doppler ultrasound of the liver, gallbladder, pancreas, and spleen showed normal liver shape, smooth capsule, uneven echo, gallstones, and splenomegaly. A color Doppler ultrasound examination did not reveal any signs of Budd-Chiari syndrome in the hepatic vein, portal vein, or inferior vena cava. MRI showed low signal intensity of the liver parenchyma, and the possibility of hepatic hemochromatosis and splenomegaly were considered (Fig. 2). Magnetic resonance cholangiopancreatography showed no obvious abnormalities.

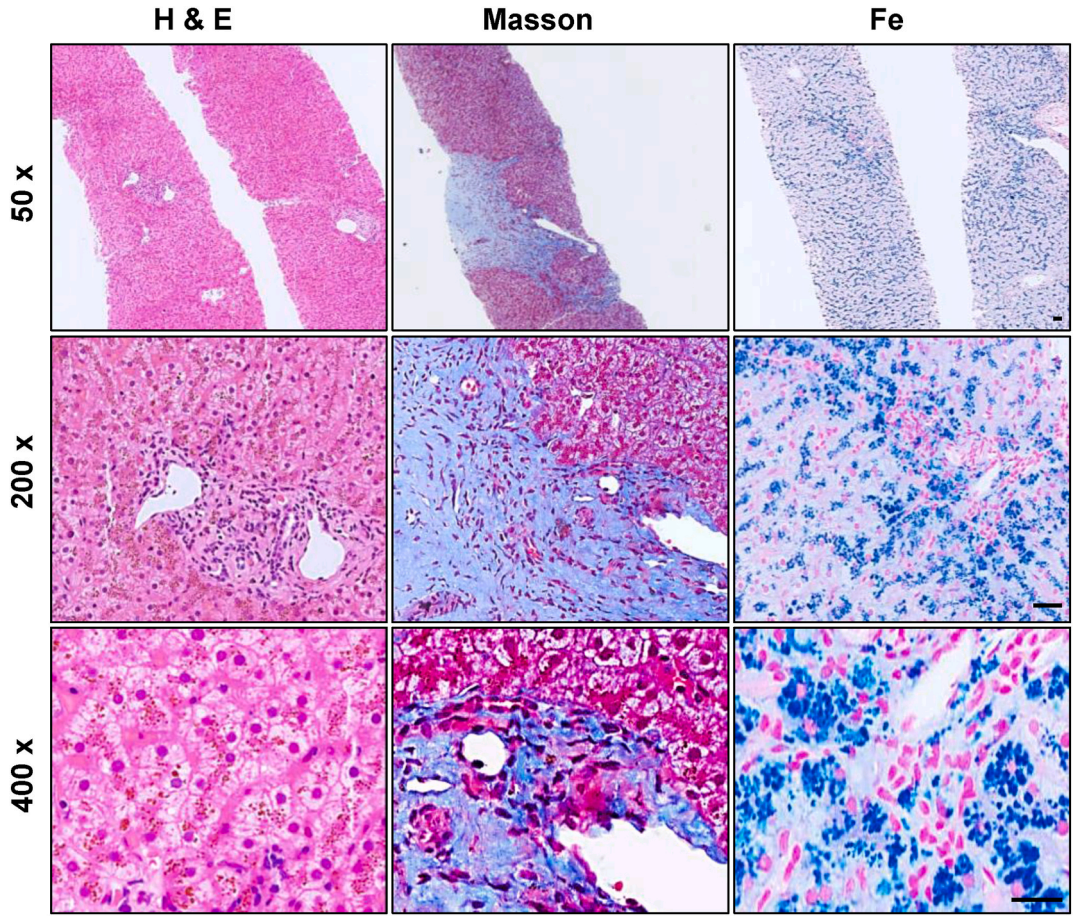

Fig. 3. Liver biopsy histopathology revealing signs of HH. H&E-stained sections (left column) showing preservation of the hepatic lobular structure and many tan pigment granules in the cytoplasm. Masson-stained sections (center column) showing subcutaneous fibrosis in the central vein and occasional bridging fibrosis. Prussian blue-stained sections (right column) showing 4^{+} grade iron particle deposition in hepatocytes, and sparse iron particles in Kupffer cells and plasma cells. Scale bars: 50 × , 5 μm; 200 × , 20 μm; 400 × , 40 μm.

Liver biopsy and genetic testing were conducted to evaluate these abnormalities. Histological examination of the patient's liver biopsy specimen confirmed the diagnosis of hemochromatosis. As shown in Fig. 3, examination of hematoxylin-eosin (H&E) stained sections of the patient's liver demonstrated preservation of the hepatic lobular structure with numerous tan-colored pigment granules in the hepatocyte cytoplasm. Masson staining revealed subcutaneous fibrosis in the central vein with occasional bridging fibrosis. Prussian blue staining revealed pervasive deposition of iron particles (grade 4^{+}) [30] in hepatocytes, as well as a small amount of iron particles deposited in Kupffer cells and plasma cells. The patient's modified Scheuer score was G2S2. To further confirm the diagnosis of hemochromatosis, immunohistochemistry was performed (Fig. 4). Elevated numbers of CK19-immunopositve (+) cholangiocytes and $IgG4^{+}$ hepatocytes (≥3 per high power field) were observed, consistent with inflammation and fibrosis caused by iron deposition in hepatocytes. There were numerous lymphocytes and plasma cells present in the lesion area, and IgG4-secreting plasma cells were found in the inflamed area. Elevated levels of CD68 were observed in Kupffer cells.

Genetic testing revealed a missense mutation (c.187C > G, His63Asp) in *HFE*. Because the patient's parents had died, genetic testing could not be performed to determine whether either of them had the same mutation. The patient's wife and children were advised to undergo genetic testing in the future.

Therapeutic phlebotomy was performed according to the 2019 clinical practice guidelines of the American College of Gastroenterology. After ruling out any contraindications for the therapy, the patient received his first phlebotomy on January 14, 2021. He had poor compliance in the early stages of treatment, and initial increases in the patient's TSAT were hypothesized to be due to that poor compliance.

In September 2022, the patient was readmitted due to heart palpitations and chest discomfort. After admission, electrocardiography showed that the patient had cardiac arrhythmia, including atrial fibrillation, tachycardia, and an apparent complete right bundle branch block. The patient was educated again about the serious consequences of insufficient treatment, and his compliance with the recommended treatment plan improved thereafter. After 2 years of treatment, the patient had stopped drinking alcohol, and his overall skin pigmentation abnormalities in the skin folds of his extremities was no longer worsening and appeared to be improving

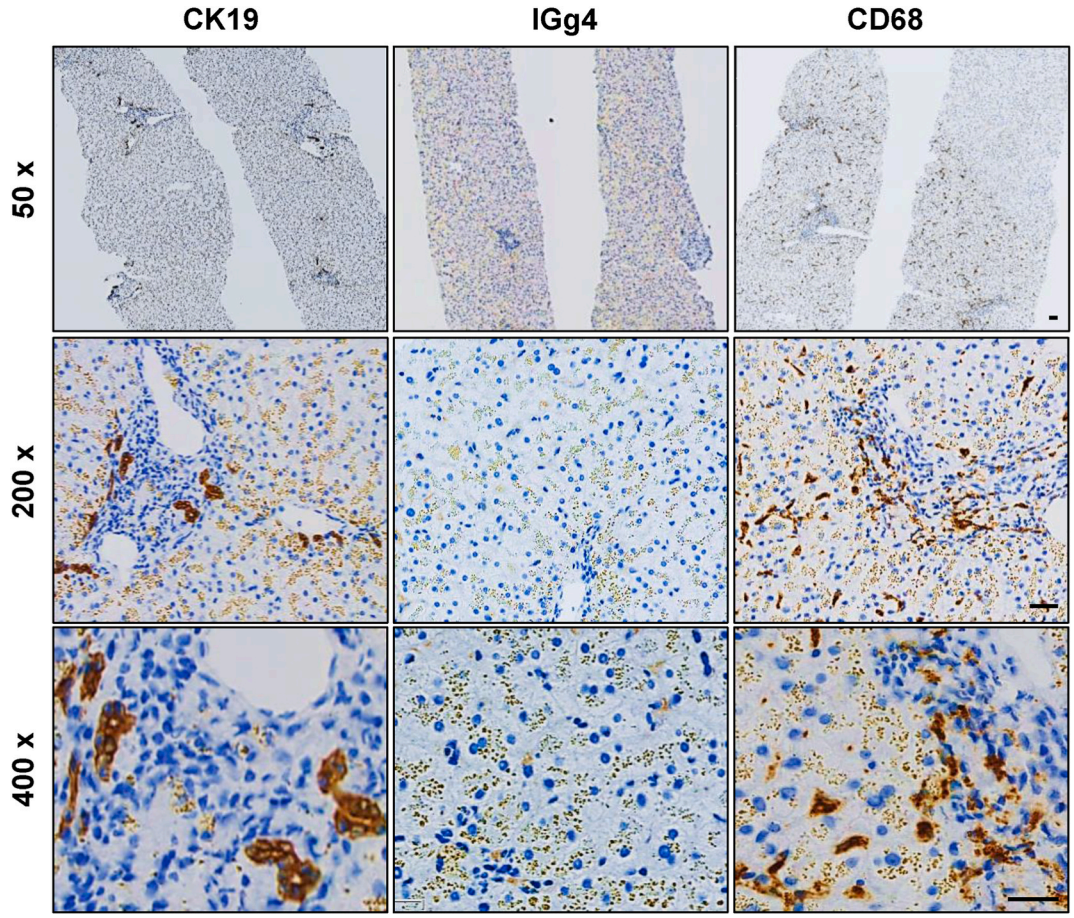

Fig. 4. Immunohistochemistry of liver biopsy sections in patient with HH. $CK19^{+}$ cholangiocytes and $IgG4^{+}$ cells indicative of inflammation and fibrosis due to iron deposition in hepatocytes can be seen. Lymphocytes and plasma cells, IgG4-secreting plasma cells, and activated Kupffer cells were observed in liver tissue. Scale bars: 50 × , 5 μm; 200 × , 20 μm; 400 × , 40 μm.

(Fig. 1C and D). Meanwhile, the patient's serum iron, SF, and TSAT levels were also trending downward (Fig. 5A–D). By December 2022, the patient's TSAT had decreased to 55.1% (Table 1) and his blood laboratory indicators had returned to normal.

3. Discussion

In the presently reported case, our patient's HH presented with asymptomatic, slightly elevated aspartate aminotransferase and bilirubin levels, arrhythmia (sinus tachycardia and atrial fibrillation), osteoporosis, abnormal skin pigmentation (back of hands and legs), and fatigue. His condition improved after two years of therapeutic phlebotomy.

For evaluation of suspected hemochromatosis, MRI is preferred over CT [31,32] because the paramagnetic effect of hemosiderin can dampen liver tissue signals and shorten the T2 relaxation time, producing the so-called black liver sign [33]. In the present case in which the patient did not present with obvious clinical symptoms of HH, the possibility of HH was considered only after MRI examination revealed hypo-intense signals within the liver parenchyma. The gold standard for hemochromatosis diagnosis is the confirmation of hemosiderin deposition within liver cells in a hepatic biopsy. Fortunately, the patient agreed to undergo a liver biopsy, thus enabling histopathological examination consistent with hemochromatosis.

The American College of Gastroenterology guidelines for HH recommend iron-removal therapy when (1) a biopsy shows elevated iron deposition and (2) genetic testing shows that the patient has a genetic indicator of HH, including C282Y HFE homozygosity or compound C282Y/H63D HFE heterozygosity. The goal of HH treatment is to remove excess iron from the body as expeditiously as possible. Adjunctive symptom-targeting treatments should be carried out as needed. This patient was a C282Y/H63D compound HFE heterozygote with elevated iron deposition in the liver. Based on these findings, the patient was started immediately on a therapeutic phlebotomy regimen. After two years of treatment, his TSAT and other iron-related measures had normalized, his abnormal skin pigmentation had not worsened, and his fatigue symptoms had improved. In the early months of treatment, the patient's SF levels remained outside the target range of 50–100 ng/ml, likely due to poor treatment adherence. Efforts are ongoing to improve patient compliance to more reliably achieve SF levels around 50 ng/ml.

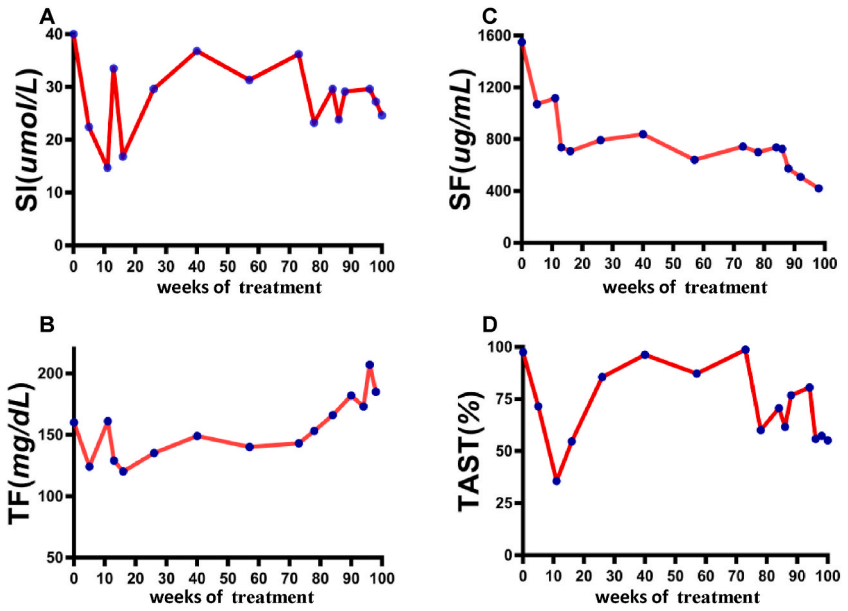

Fig. 5. Iron-related measures tracked over a 2-year course of therapeutic phlebotomy. By the end of the treatment period, (A) serum iron (SI) had decreased, (B) serum ferritin (SF) had decreased, (C) transferrin (TF) levels had increased, and (D) transferrin saturation (TAST) had decreased.

A key determinant of prognosis in patients with HH is the presence or absence of cirrhosis at the time of diagnosis. Remarkably, in a retrospective study, Strohmeyer and colleagues found that the cumulative survival of HH patients without cirrhosis was similar to that of the general population, whereas patients with HH and cirrhosis had significantly lower survival [34]. Liver biopsy results were not suggestive of cirrhosis in the present case, and the patient was started on a therapeutic phlebotomy treatment regimen promptly after the diagnosis. The findings of evaluations conducted throughout the patient's course of treatment were suggestive of a good prognosis, at least in the short term. In addition, the patient quit smoking and drinking, which should improve his overall health and recovery expectations. This article describes the case evolution over a period of only two years during ongoing treatment. Follow-up examinations will be conducted to monitor this patient's long-term prognosis.

4. Conclusion

HH is rare in the Chinese population, and cases caused by C282Y/H63D HFE heterozygosity are rarer still. Once diagnosed, regular phlebotomy should be performed to help alleviate clinical symptoms and delay progression of the disease. Many physicians have an insufficient understanding of HH, which may lead to missed or mistaken diagnoses. Importantly, HH is a progressive disease that will lead to multiple organ damage if left untreated. Furthermore, clinicians should take precautions to prevent poor patient treatment compliance. More HH research should be conducted in China to improve physicians' understanding of this disease and its early detection and diagnosis.

Data availability statement

This is a review paper and datasets under review were public and their sources were included in the paper.

Ethics statement

This study was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College, with ethics number 2022KY080. Written informed consent has been obtained from the participant.

CRediT authorship contribution statement

Dongdong Li: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jinfeng Li:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Hongkun Zhang:** Software, Resources, Investigation. **Qiuyu Zhu:** Supervision, Software. **Teng Wang:** Software, Investigation, Data curation, Conceptualization. **Wen Zhao:** Validation, Methodology, Formal analysis. **Shousong Zhao:** Methodology, Funding acquisition. **Wei**

Li: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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