Iron overload leading to cirrhosis in a patient with hereditary spherocytosis and heterozygosity for H63D mutation in the HFE gene

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Abstract

Hereditary spherocytosis (HS) refers to a group of autosomal dominantly inherited heterogeneous hereditary haemolytic anaemias (HHA). Significant iron overload in HS is uncommon. Iron overload has been described as a complication of HS when there is co-inheritance of hereditary haemochromatosis (HH). H63D mutation accounts for a minority of hereditary hemochromatosis cases and does not cause iron overload in an otherwise healthy heterozygous carrier state. We present a 64-year-old man, diagnosed with HS presenting with cirrhosis without significant on-going haemolysis. He had a markedly high serum ferritin and transferrin saturation. Magnetic Resonance Imaging for liver iron concentration revealed haemochromatosis of the liver. HFE genotyping showed heterozygosity for the H63D mutant allele. Haemolysis in HS does not usually result in clinically significant iron excess leading to haemochromatosis and the presence of H63D heterozygous mutation will increase the risk of clinically significant iron overload which can lead to hepatic iron deposition and fibrosis. Therefore, if a patient with H63D mutation demonstrates clinically significant iron overload, clinicians should search for other factors that increase iron excess such as on-going haemolysis, alcohol abuse and presence of metabolic syndrome.

Key words: Hereditary spherocytosis, Haemochromatosis, Cirrhosis, H63D mutation

Introduction

Hereditary spherocytosis (HS) refers to a group of autosomal dominantly inherited heterogeneous hereditary haemolytic anaemias (HHA). Clinical severity of HS is variable. Patients with a mild phenotype are often asymptomatic due to having a compensated haemolysis with mild anaemia. On the other end of the spectrum, patients with severe disease can have transfusion-dependent anaemia.

Iron overload in HHAs has been extensively studied in β-thalassemia.(1) However, data on the prevalence of iron overload in HS is limited.(1) Iron overload in patients in HHAs are usually due to recurrent blood transfusions and/or inappropriately high dietary iron absorption as a result of ineffective and increased erythropoiesis. Iron overload has been described as a complication of HS mostly when there is co-inheritance of hereditary haemochromatosis (HH). (2,3)

HH is an autosomal recessive condition and homozygosity for the C282Y variant in HFE is present in about 80% of individuals of European origin with the disease. A smaller proportion (5%) with
compound heterozygosity for the C282Y/H63D mutations is observed. H63D mutation accounts for a minority of hereditary hemochromatosis cases. Patients who are homozygous or heterozygous for the H63D mutation are not at increased risk of developing clinical iron overload compared to those without this mutation, though they may still present with an elevation in transferrin saturation and serum ferritin levels.(4)

Here we present a 64-year-old patient with HS without significant haemolysis presenting with clinically significant iron overload. He was found to have H63D heterozygous haemochromatosis mutation.

Case presentation

A 64-year-old man, diagnosed with hereditary spherocytosis in 2008, presented to the National Hospital of Sri Lanka in October 2022, with progressively worsening lower limb and abdominal swelling associated with increased skin pigmentation for 4 months.

A month prior to presentation, he had also developed yellowish discoloration of the eyes without steatorrhoea, pruritus, or passage of tea-coloured urine. He did not have exertional dyspnoea, orthopnoea or paroxysmal dyspnoea. He denied loss of libido and erectile dysfunction, or joint pains. He had been a teetotaler with no history of alternative medicine use or long-term medications.

He was diagnosed with hereditary spherocytosis during family screening in 2008 when his daughter was diagnosed with the same disease. Since diagnosis, he had been followed up in the haematology clinic, and had maintained his haemoglobin levels between 9-10g/dL and a reticulocyte count between 6-7%. He had received only 4 units of red cell transfusions to date since the diagnosis. Five years ago, he underwent a laparoscopic cholecystectomy for symptomatic gallstones. Although a splenectomy was planned due to massive splenomegaly, it was deferred due to personal preference.

On general examination, his body mass index was 17 kg/m2, waist circumference was 76 cm and he had conjunctival pallor, icterus and generalised hyperpigmentation of skin. He had leukonychia, beau’s lines and peripheral stigmata of cirrhosis such as spider naevi, loss of axillary and body hair and palmar erythema. There was pitting oedema up to the mid-calf level. Abdominal examination revealed a distended abdomen with a massive splenomegaly, spanning 9 cm from the left costal margin, and tense ascites. He had mild bilateral pleural effusions. Cardiovascular and neurology examinations were unremarkable.

Full blood count revealed mild neutrophilia (11.84x10⁹/L; neutrophils 79%), normocytic normochromic anaemia (haemoglobin 8.8 g/dL) with normal mean cell volume (87 fL) and increased mean cell haemoglobin concentration (37 g/dL) and thrombocytopenia (platelets – 101x10⁹/L). Reticulocyte count was 6.5%. His erythrocyte sedimentation rate (ESR) was 24mm/ 1ʰ hour and C-reactive protein (CRP) was 9.5 mg/dL.

Liver profile revealed, aspartate transaminase (AST) of 65 U/L, alanine transaminase (ALT) of 34 U/L, low albumin (2.5 g/dL) and globulin (2.8 g/dL), with a reversed albumin to globulin ratio, mild direct hyperbilirubinaemia (total 2.6 mg/dL; direct 1.2 mg/dL) and slightly elevated alkaline phosphatase (ALP) of 189 U/L and gamma-glutamyl transferase (GGT) of 80 U/L. Clotting profile revealed prolonged international normalised ratio (INR) 1.45, activated partial thromboplastin time (APTT) of 38s. Abdominal ultrasonography confirmed chronic liver cell disease with portal hypertension, massive splenomegaly (21cm) with gross ascites.

His serum ferritin was markedly high (1303 ng/mL), with elevated transferrin saturation (87.51%). Liver Magnetic Resonance Imaging (MRI) for liver iron concentration (LIC) via Signal intensity ratios (SIR) method based on T2*-weighted imaging revealed low signal of T2*Gradient echo (GRE) compared to the erector spinae muscle (Liver/ Muscle ratio less than 0.9) confirming evidence of haemochromatosis of the liver (Figure 1). (5)

There were no other contributing factors for the iron overload such as long-term iron supplementation, or concomitant alcohol consumption. Serological tests for Hepatitis B and C viral infections, as well as inflammatory aetiologies such as primary biliary cholangitis, and autoimmune hepatitis were negative. HFE genotyping showed heterozygosity for the p.H63D mutant allele.

His upper gastrointestinal endoscopy (UGIE) showed grade 1 oesophageal varices. Diagnostic paracentesis revealed evidence of portal hypertension (Serum to ascitic albumin gradient; SAAG 1.5 g/dL; ascitic protein 1.2 g/dL) without spontaneous bacterial peritonitis.
Fasting plasma glucose was normal (87 mg/dL), lipid profile was normal (Total cholesterol 128mg/dL; LDL cholesterol 87 mg/dL; Triglycerides 98 mg/dL) with normal levels of follicular stimulating hormone (FSH), luteinizing hormone (LH) and testosterone.

Echocardiogram showed normal biventricular function and normal chamber sizes. Cardiac MRI facility was not available.

Iron chelation therapy was initiated as the patient would benefit from prevention of further deposition of iron. Phlebotomy was not considered in view of baseline moderate anaemia.

**Figure 1** - T2* gradient axial echo slice of liver MRI - This demonstrates an abnormal low signal intensity of the liver compared to erector spinae muscle (L/M ratio <0.9).

**Discussion**

Index patient despite not having significant haemolysis ended with iron overload with organ dysfunction. Iron overload in patients with HS has mainly been reported with co-inheritance of HFE mutations. (6) This prompted us to look for coexistence of factors that would increase iron overload.

Most of the HFE-related hemochromatosis is associated with homozygosity for C282Y. The association of homozygosity for H63D with iron overload is debated. The H63D genotype might be considered a genetic variant that predisposes to slight alterations in iron parameters but not a disease-causing variant. (7)

However, other risk factors or other genetic causes of iron overload should be sought when patients with this genotype demonstrate iron excess. In combination with other acquired risk factors such as alcohol, metabolic syndrome, H63D is associated with a higher risk of mild iron overload. (8) In our patient, who is a teetotaler, risk factors for metabolic syndrome such as hypertension, diabetes, hyperlipidaemia and obesity were excluded. Hence, we can postulate that in our patient the presence of H63D mutation and concurrent haemolysis may have led to the profound iron excess.

C282Y/H63D compound heterozygosity may be a risk factor predisposing to mild or moderate forms of iron overload when in association with comorbidity factors, for example, alcohol or metabolic syndrome. (8,9) It is very rare for compound heterozygosity for C282Y/ H63D to be associated with a severe iron overload phenotype in the absence of acquired causes. (10)

We postulate that the following mechanisms might have contributed to the clinically significant iron overload in our patient.

1. Ineffective erythropoiesis and chronic haemolysis within the reticulo-endothelial system and the resultant erythropoietic drive may promote iron absorption via downregulation of hepcidin.
2. Heterozygous H63D mutation related increased risk of iron overload.

Our patient had clinically significant iron overload in the liver, he did not have clinical or echocardiographic evidence of myocardial iron overload or heart failure. We could not find literature supporting the preponderance of iron overload in the liver over myocardium in HS, in patients with non-transfusion dependent beta thalassemia. However, it has been observed that iron overload differentially affects the liver rather than the myocardium. (11)

It is also worth noting that this patient has a massive splenomegaly (21cm) which is not usually expected to be observed in HS. This may be due to a combination of chronic haemolysis induced extramedullary haemopoiesis, cirrhosis induced portal hypertension and iron deposition.

In patients without homozygosity for p.C282Y as in the index case, in the presence of additional risk factors for hepatic iron overload, such as the metabolic syndrome and chronic alcohol excess, non-invasive quantification of liver, spleen, pancreas and cardiac iron can guide diagnosis and management.
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Conclusion

This case illustrates that although haemolysis in HS does not usually result in clinically significant iron excess leading to haemochromatosis, the presence of H63D heterozygous mutation will increase the risk of clinically significant iron overload which can lead to hepatic iron deposition and fibrosis. If a patient with H63D mutation demonstrates clinically significant iron overload, clinicians should search for other factors that increase iron excess such as on-going haemolysis, alcohol abuse and presence of metabolic syndrome.

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