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Hyperferritinemia in Hereditary Spherocytosis: A Diagnostic Challenge

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Authors' contributions

This work was carried out in collaboration with both authors. Author GK designed the study, wrote the main protocol, managed the literature searches, drafted and revised the article. Author SP managed the literature searches, analyzed the patient's data and revised the article. Both authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: Hereditary spherocytosis is an autosomal dominant disorder characterized by increased red blood cell osmotic fragility and impaired deformability. Hereditary hemochromatosis is an autosomal recessive disorder of iron metabolism which results in damage to multiple organs.
Presentation of Case: This case describes a 42 year old Chinese male who presents with jaundice. He denies any fever, vomiting, anorexia or loss of weight. Urine and stool colour were normal. He had no history of blood transfusions or prolonged iron therapy. In addition, he had a past history of open cholecystectomy for recurrent acute cholecystitis. He had a family history of jaundice in which his father underwent a cholecystectomy and had multiple blood transfusions. On physical examination, he was jaundiced. His spleen was enlarged 6 cms from the left costal margin. The peripheral blood film showed mild anemia with increased reticulocyte response and spherocytosis suggestive of hereditary spherocytosis. Direct Coombs test was negative and there was an increase in red blood cell osmotic fragility. Iron studies revealed hyperferritinemia. Genetic

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testing showed homozygosity for the (hemochromatosis gene) *HFE* mutation C282Y. Ultrasonography of the abdomen revealed splenomegaly with no evidence of liver cirrhosis. He underwent regular venesections and his serum ferritin improved subsequently.

Conclusion: Iron overload in a patient with non transfusional hereditary spherocytosis should prompt screening for *HFE* mutations and warrant early screening of family members to prevent serious complications.

Keywords: Hereditary spherocytosis; hereditary hemochromatosis; hyperferritinemia; cholecystectomy; transfusions.

1. INTRODUCTION

Hereditary spherocytosis is a common hereditary disorder characterized by corpuscular hemolytic anemia of varying severity with increased red blood cell osmotic fragility and impaired deformability [1]. It is an autosomal dominant disorder. Chronic symptoms include anemia, increased blood viscosity and splenomegaly [2]. The severity of this disorder significantly varies between individuals due to the incomplete penetrance in its expression.

Hereditary hemochromatosis is characterized by progressive iron accumulation in the parenchymal tissues because of a defect in the regulation of duodenal iron absorption [3]. It is an autosomal recessive disorder of iron metabolism which results in damage to multiple organs causing bronze diabetes, cardiac failure, hypogonadism, arthropathy, chronic liver disease and skin hyperpigmentation. In 1996, a group of United States researchers identified the hemochromatosis gene; it belongs to the major histocompatibility complex and is found on the short arm of chromosome 6 [4]. This gene was initially called HLA-H (Human Leucocyte Antigen - hemochromatosis) and later the *HFE* gene (classical hereditary hemochromatosis) [5]. The HFE gene has two common mutations which are the C282Y and H63D. The C282Y allele is a transition point mutation from guanine to adenine at nucleotide 845 in the *HFE* gene, resulting in a missense mutation that replaces the cysteine residue at position 282 with a tyrosine amino acid [6]. In H63D subtype, the aspartate is substituted for histidine at the 63rd position.

Here, we report a challenging case of hyperferritinemia in hereditary spherocytosis.

2. PRESENTATION OF CASE

This case describes a 42 year old Chinese male who was referred from a health clinic for jaundice. He complained of yellow discoloration of both scleras. There was no history of fever, nausea, vomiting or abdominal pain. He had no change in weight, appetite or bowel habit. His stool and urine were normal in color with no obvious skin pruritus. He had a history of open cholecystectomy a year ago for recurrent episodes of acute cholecystitis. He was noted to have black pigment gallstones during surgery. He had a family history of jaundice in which his father underwent a similar cholecystectomy with multiple visits to the hospital for blood transfusions. He was a non-smoker and a teetotaler.

On physical examination, he had jaundiced sclera. His blood pressure was 130/80 mmHg with a heart rate of 88 beats per minute. Cardiovascular examination revealed normal heart sounds with no audible murmurs. Lungs were clear on auscultation. Abdominal examination revealed a Kocher's scar and an enlarged spleen measuring 6 cms from the left costal margin. The liver was not palpable. He had no ascites. There was no pitting pedal edema.

The complete blood count, renal profile, liver function tests and iron studies are as shown in Table 1. The peripheral blood film showed mild anemia with increased reticulocyte response, dimorphic red blood cells and spherocytosis which were highly suggestive of hereditary spherocytosis. His direct and indirect Coombs test was negative with indirect hyperbilirubinemia. There was increased red blood cell osmotic fragility. His folate, B12 and thyroid hormone levels were within normal ranges. Viral hepatitis screening was non-reactive. The iron studies were abnormal with an obvious hyperferritinemia of 1256 ng/ml. Ultrasonography of the abdomen showed homogenous splenomegaly measuring 18cms. No focal splenic lesion seen. Liver was of normal echotexture. On further genetic testing using Polymerase Chain Reaction (PCR) analysis, he showed homozygosity for the *HFE* mutation C282Y.

Table 1. Laboratory values

Serum (international units)	Values (normal range)
Hemoglobin (g/dL)	11.0 (11.5-18)
Hematocrit (%)	32.1 (37-54)
Reticulocyte count (/nl)	341 (18-80)
Mean cell volume (fL)	101 (80-100)
Total white cell count (10^9/L)	8.7 (4.0-11.0)
Platelet (10^9/L)	250 (150-400)
Urea (mmol/L)	3.6 (2.5-7.3)
Creatinine (umol/L)	73 (40-80)
Total bilirubin (umol/L)	80.2 (0-21)
Indirect bilirubin (umol/L)	69.0 (3.0-23.0)
Albumin (g/L)	21 (35-52)
Alanine transaminase (U/L)	12.1 (0-41)
Aspartate transaminase (U/L)	6.9 (0-35)
Alkaline phosphatase (U/L)	240 (40-129)
Lactate dehydrogenase (U/L)	720 (240-480)
Iron (umol/L)	28 (3-23)
Ferritin (ng/ml)	1256 (30-400)
Transferrin saturation (%)	72 (15-50)

He never required any blood transfusion. He was not on prolonged iron therapy or supplementation. He underwent regular venesections with the aim of maintaining serum ferritin below 50 ng/ml. With regular venesections, his serum ferritin improved. The patient was monitored with regular follow ups at the specialist clinic.

3. DISCUSSION

This case highlights an individual who presents with chronic hemolytic anemia due to hereditary spherocytosis. The finding of non transfusional iron overload with no past history of iron therapy or alcoholism in hereditary spherocytosis remains a diagnostic challenge to many physicians. The first who described hemo-chromatosis in combination with spherocytosis was Lawrence in 1949 [7].

Hereditary spherocytosis is caused by a variety of molecular defects in the genes that code for the red blood cell proteins spectrin (alpha and beta), ankyrin, band 3 protein, protein 4.2 and other red blood cell membrane proteins [8]. These proteins are essential to maintain the biconcave disk shape of red blood cells. The defects of these proteins hence contribute to the abnormality of membrane surface area resulting in the formation of spherocytes with reduced deformability. These spherocytes undergo extravascular hemolysis by the spleen. This patient had obvious splenomegaly but he was not splenectomised as he did not exhibit any signs of severe hemolytic anemia.

Common secondary causes for iron overload include multiple blood transfusions, excess iron supplements, dietary iron intake, malignancy, inflammatory disorders, septicaemia, porphyrias, alcoholism, prolonged hemodialysis, acaerulo-plasminemia and congenital atransferrinaemia.

There are a few mechanisms which may account for the iron overload in this patient. The dominant effect of the erythropoetic demand for iron over the inhibitory signals of excessive iron stores mediated by hepcidin, which is the principal regulator of iron metabolism in humans could contribute to the inappropriate stimulation of iron absorption in hemolytic anemia [9]. The other mechanism which explains this iron overload is the HFE mutation C282Y which is commonly seen in hereditary hemochromatosis. It has been demonstrated that mice and humans with homozygous *HFE*-related hemochromatosis display inappropriately low hepatic expression and serum levels of hepcidin [10]. Hepcidin is a human antimicrobial peptide synthesized in the liver that plays a key role in the downregulation of iron release by enterocytes and macrophages (inhibits iron absorption in the gut and iron mobilization from the hepatic stores) [11]. The degradation of cellular iron exporter (ferroportin) caused by hepcidin is the mechanism of cellular iron efflux inhibition [12]. The absence of hepcidin results in more severe iron overload phenotype. It is also inappropriately low in adult-onset *HFE* -related disease [12].

4. CONCLUSION

Iron overload in a patient with non transfusional hereditary spherocytosis should prompt screening for *HFE* mutations and warrant early screening of family members to prevent serious complications.

CONSENT

Both authors declare that 'written informed consent was obtained from the patient for publication of this case report and accompanying images'.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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