Scholars Journal of Medical Case Reports
Abbreviated Key Title: Sch J Med Case Rep
ISSN 2347-9507 (Print) | ISSN 2347-6559 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Gastroenterology

Anemia as an Unusual Presenting Manifestation of Hereditary Hemochromatosis: A Case Report

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DOI: https://doi.org/10.36347/sjmcr.2026.v14i11.054 | **Received:** 19.08.2026 | **Accepted:** 27.10.2026 | **Published:** 16.11.2026

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Abstract **Case Report**

Hereditary hemochromatosis is a genetic disorder characterized by excessive intestinal iron absorption, leading to progressive iron overload affecting multiple organs, particularly the liver, heart, and pancreas. The present case illustrates an atypical presentation revealed by progressive anemia in the absence of digestive or extra-digestive manifestations, highlighting the importance of a thorough diagnostic evaluation. Treatment is based on individualized therapeutic phlebotomy, which effectively prevents organ damage, while regular biological monitoring is essential to optimize patient management. Hereditary hemochromatosis is an inherited disorder characterized by excessive intestinal iron absorption resulting in progressive iron deposition in several organs, particularly the liver, heart, and pancreas. Its clinical presentation is highly variable and often nonspecific. Anemia, however, is an uncommon presenting feature. We report the case of a 75-year-old man who presented with an anemic syndrome that had progressed over several months, associated with marked asthenia but without digestive or extra-digestive symptoms suggestive of iron overload. Laboratory investigations revealed moderate anemia associated with marked hyperferritinemia and an elevated transferrin saturation, raising suspicion of iron overload. Imaging demonstrated homogeneous hepatomegaly, prompting hepatic magnetic resonance imaging (MRI) for quantitative assessment of hepatic iron deposition. This case highlights the importance of considering hereditary hemochromatosis in the differential diagnosis of abnormalities in iron metabolism, even in the setting of an atypical clinical presentation.

Keywords: Hereditary hemochromatosis; anemia; iron overload; atypical diagnosis; inherited iron metabolism disorders.

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INTRODUCTION

Hereditary hemochromatosis is an inherited disorder of iron metabolism characterized by excessive intestinal iron absorption, resulting in progressive iron deposition in several vital organs, including the liver, heart, joints, and pancreas. This iron overload may lead to severe complications such as cirrhosis, diabetes mellitus, and heart failure. [1,2] Nevertheless, hereditary hemochromatosis remains underdiagnosed because its clinical manifestations are often subtle, nonspecific, and highly variable. [3]

The present case describes a patient in whom hereditary hemochromatosis was revealed by an anemic syndrome, an uncommon presenting feature of the disease. Although anemia is a frequent manifestation of numerous clinical conditions, this case highlights the importance of investigating iron overload in patients presenting with progressively worsening anemia in the absence of obvious gastrointestinal or extraintestinal manifestations. It also emphasizes the need for a comprehensive diagnostic approach to identify hereditary hemochromatosis, even in atypical clinical settings.

CASE PRESENTATION

We report the case of a 75-year-old man with a medical history of chronic tobacco use (30 pack-years), who had quit smoking 20 years earlier, and occasional alcohol consumption, also discontinued. His past medical history included SAPHO syndrome diagnosed in 2008 (previously treated, although treatment records were unavailable), inflammatory clavicular rheumatism diagnosed in 2006 and treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol for four months, and IgA nephropathy diagnosed in March 2025

during the etiological work-up of an edematous syndrome. Since then, he had been receiving dapagliflozin 10 mg/day and furosemide 120 mg/day. There was no history of hematological disorders, malignancy, or peptic ulcer disease.

The patient presented with an anemic syndrome that had progressively evolved over approximately five months in the setting of profound asthenia. He reported palpitations, dizziness, and trophic changes involving the skin appendages, without associated gastrointestinal symptoms. He denied upper or lower gastrointestinal bleeding, vomiting, jaundice, or bowel habit disturbances. The clinical course occurred in an afebrile context with marked fatigue.

On physical examination, the patient was hemodynamically stable, with normal vital signs: blood pressure of 130/80 mmHg, heart rate of 82 beats/min, body temperature of 37.2°C, and respiratory rate of 20 breaths/min. He exhibited marked cutaneous and conjunctival pallor, associated with signs of malnutrition characterized by loss of subcutaneous fat and muscle mass. Bilateral pitting edema of the lower limbs extending to the mid-calf was also noted, consistent with an edematous syndrome.

Abdominal examination revealed a soft, non-tender abdomen that moved normally with respiration, without guarding or rebound tenderness. No hepatomegaly or splenomegaly was detected. Cardiovascular examination demonstrated a regular heart rhythm with a normally located apical impulse, no cardiac murmurs or additional heart sounds, and symmetrical peripheral pulses. Pulmonary examination was unremarkable, with normal breath sounds and no crackles on auscultation. Dermatological examination revealed no specific skin lesions.

Laboratory investigations showed moderate macrocytic anemia, with a hemoglobin level of 8.4 g/dL and a mean corpuscular volume (MCV) of 103 fL. Iron studies demonstrated marked hyperferritinemia (serum ferritin: 1,606 ng/mL) and a markedly elevated transferrin saturation of 89%, strongly suggesting systemic iron overload. The serum transferrin concentration was reduced (1.93 g/L), further supporting iron excess. Serum vitamin B9 (folate) and vitamin B12 levels were within the normal range, thereby excluding vitamin deficiency as the cause of the macrocytic anemia

An immunological work-up and viral serological testing were performed and showed no significant abnormalities, with negative anti-double-stranded DNA antibodies, negative rheumatoid factor, and negative viral serologies.

Contrast-enhanced thoracoabdominal computed tomography (CT) revealed several abnormalities, including homogeneous hepatomegaly associated with mild intrahepatic bile duct dilatation, findings that may be consistent with hepatic iron overload. The examination also demonstrated apical pulmonary micronodules associated with subpleural ground-glass opacities, warranting radiological follow-up to exclude an infectious etiology. In addition, mild periportal and celiomesenteric fat infiltration was observed, which may also be related to hepatic iron deposition.

Liver magnetic resonance imaging (MRI) was subsequently requested to accurately assess and quantify hepatic iron overload and to further characterize the hepatic abnormalities identified on CT.

DISCUSSION

Hereditary hemochromatosis is an inherited disorder of iron metabolism characterized by excessive intestinal iron absorption, leading to progressive iron accumulation in multiple organs, particularly the liver, heart, and pancreas. If left untreated, iron overload may result in irreversible organ damage, including cirrhosis, cardiomyopathy, and endocrine dysfunction. [4]

The most common pathogenic variants of the HFE gene, C282Y and H63D, are responsible for the autosomal recessive form of hereditary hemochromatosis. Less frequently, the disease may result from pathogenic variants in other genes involved in iron homeostasis, including HAMP, HJV, TFR2, and SLC40A1. [5]

Furthermore, recent studies have shown that the autosomal dominant form of hereditary hemochromatosis, also known as ferroportin disease, is associated with pathogenic variants in the SLC40A1 gene, which encodes ferroportin, the principal cellular iron export protein and a key regulator of systemic iron homeostasis. [6]

Anemia represents an unusual manifestation of hereditary hemochromatosis. Indeed, hereditary hemochromatosis is more commonly associated with normal or even increased hemoglobin levels because of enhanced iron availability, making anemia an uncommon presenting feature. When anemia occurs, it is usually attributable to concomitant conditions such as vitamin B12 or folate deficiency, gastrointestinal bleeding, chronic inflammation, chronic kidney disease, or other causes of anemia, thereby masking the classical presentation of the disease and potentially delaying diagnosis. This atypical presentation underscores the importance of considering hereditary hemochromatosis even in anemic patients, particularly when laboratory findings suggest iron overload. [7]

Therapeutic phlebotomy remains the cornerstone of treatment for hereditary hemochromatosis. It effectively reduces body iron stores

by mobilizing excess iron, thereby preventing hepatic, cardiac, and metabolic complications. Management generally consists of an induction phase involving regular phlebotomies until serum ferritin reaches the target range, followed by an individualized maintenance phase based on the patient's iron status and clinical tolerance.

In patients presenting with anemia, as in the present case, the frequency and volume of therapeutic phlebotomies should be carefully individualized to avoid exacerbating anemia. Therefore, any concomitant cause of anemia should be thoroughly investigated and appropriately managed before or alongside iron depletion therapy. In patients with contraindications to or intolerance of phlebotomy, iron chelation therapy may be considered. Long-term follow-up relies on regular biological monitoring, including serum ferritin, transferrin saturation, and complete blood count, allowing treatment to be tailored according to the patient's clinical and biochemical response. [8,9]

CONCLUSION

Although hereditary hemochromatosis is one of the most common inherited disorders among individuals of European ancestry, it remains underrecognized in clinical practice. This underdiagnosis is largely attributable to the nonspecific and highly variable nature of its clinical manifestations, which frequently results in delayed diagnosis. Nevertheless, early recognition and prompt initiation of therapeutic phlebotomy can effectively prevent progressive iron accumulation and substantially reduce the risk of irreversible organ damage.

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