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IM - CASE RECORD

Progressive splenomegaly and mild thrombocytosis in beta-thalassaemia trait and coexisting hereditary hemochromatosis: possible confounders for a subsequent hematological diagnosis

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Case presentation

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A 63-year-old woman regularly followed in our outpatient clinic and affected by hereditary hemochromatosis (HH), presented with sudden acute pain in the upper left abdominal quadrant.

The woman had been referred to our outpatient clinic several years before, at the age of 34, for the finding of elevated ferritin and circulating iron levels during hospitalization for acute hepatitis A. Elevation in iron parameters persisted even after hepatitis resolution.

Her previous medical history included a diagnosis of beta-thalassemia trait (hemoglobin levels 10–11 g/dl) and hysterectomy for menorrhagia at the age of 29. She had two full-term pregnancies, and had received iron therapy during those periods.

The family history was negative for hyperferritinemia. She reported 20 g ethanol consumption per day.

Her blood tests at first observation showed high levels in ferritin and transferrin saturation, lower end of normal platelet count, and the already known beta-thalassemia trait, as shown in Table 1.

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Suspecting a primary iron overload disease, like hereditary hemochromatosis (HH), the patient underwent a multidisciplinary work up. At presentation, abdominal ultrasound (US) found the liver to be of normal size, with regular margins and homogeneous structure; portal vein diameter of 12 mm, normal hepatic veins, and an upper end of normal range of spleen (longitudinal diameter 12 cm). Furthermore, echocardiography showed an initial impaired diastolic compliance, while an esophagogastroduodenoscopy (EGDS) revealed gastroduodenitis. She had normal bone densitometry and no arthropathy. To confirm the diagnosis of HH, a liver biopsy was performed that demonstrated severe parenchymal siderosis (Scheuer grade IV) with predominant parenchymal iron deposition and no significant fibrosis (Fig. 1).

Analysis of the HFE genotype, determined several years later when the genetic test became available, showed homozygosity for the C282Y mutation.

The patient was started on weekly phlebotomy, well tolerated despite thalassemia, until iron depletion (about 50 sessions of 300 ml each corresponding to the removal of 7.5 g of iron) followed by maintenance phlebotomies, every 4 months for several years, with clinical stability of hematological and iron parameters, but with progressive increase in spleen volume in subsequent controls along the years (longitudinal diameter 12 → 13 → 14.5 cm).

Some months before the episode of acute abdominal pain, a larger increase in spleen volume (longitudinal diameter 14.5 → 17 cm) with a maintained stability in blood parameters (Hb 11.5 g/dl, MCV 60 fl, WBC 6800/mm^3, and PLT 377,000/mm^3) had been observed. LDH and β2-microglobulin were in the normal range. To rule out the presence of a hematological disease, a hematology consultation was obtained, but the hematology specialist suggested only follow-up. For

Table 1 Blood tests and abdominal ultrasound (US) findings at diagnosis of hemochromatosis and at last observation

	Presentation	Last observation
Hb (g/dl)	11	11.1
MCV (fl)	62	66
WBC (/mm^3)	4900	5610
PLT (/mm^3)	180,000	410,000
Serum iron (µg/dl)	216	160
Transferrin (mg/dl)	212	175
Ferritin (ng/ml)	800	76
Transferrin saturation (%)	85	30
GOT/GPT (UI/l)	14/37	25/12
Spleen longitudinal diameter (cm)	12	14.5

Hb hemoglobin, *MCV* mean corpuscular volume, *WBC* white blood cells, *PLT* platelets, *GPT* glutamic–pyruvic transaminase, *GOT* glutamic–oxaloacetic transaminase

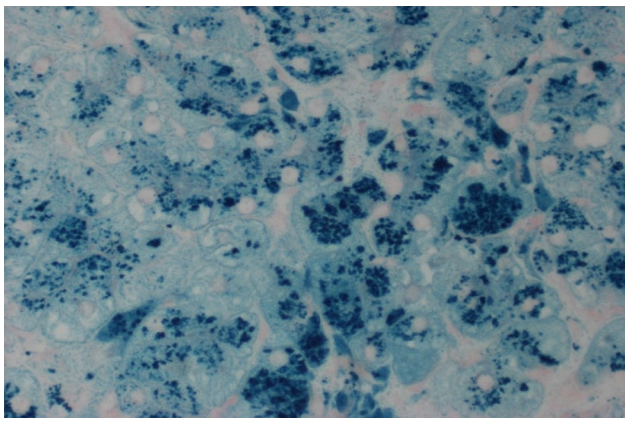

Fig. 1 Liver biopsy. Perls' stain, iron deposition in haemosiderin is shown in blue (color figure online)

a progressive increase in spleen size, a fluorodeoxyglucose positron emission tomography (FDG PET) was performed that showed mild not specific bone-marrow uptake.

An ultrasound study, performed for the acute abdominal pain in the upper left quadrant, revealed splenic infarction (Fig. 2). She promptly underwent abdominal CT that showed an enlarged spleen with multiple subcapsular splenic infarctions. At routine blood tests, mild anemia, mild leucocytosis (neutrophils count 6570/mm^3), platelet count at the upper limits of normal (PLT 380,000/mm^3), LDH, and β2-microglobulin within normal range, although at the upper limits, were observed.

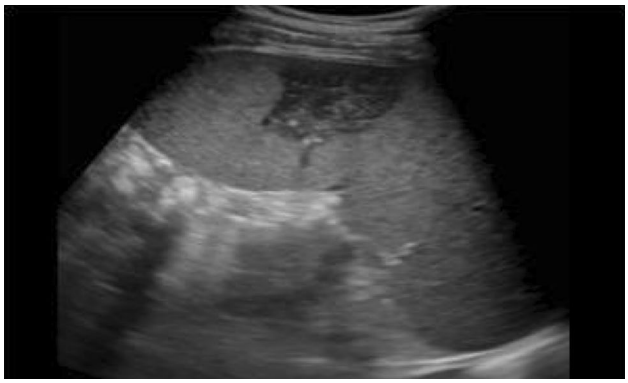

Fig. 2 Liver ultrasound showing enlarged spleen and splenic infarction

Further investigations, diagnosis, and treatment

Prof. Fracanzani, Prof. Gianelli

In the hypothesis of a myeloproliferative neoplasm, thrombophilia screening and Bcr-abl p210 mutation analysis were performed, which were negative, while the V617 mutation in Jak-2 gene was present.

FDG PET scan performed 1 year after the previous one and showed irregular splenic hyperaccumulation, non-specific diffuse bone-marrow accumulation, and non-specific FDG uptake in retroperitoneal lympho-nodal elements.

Bone-marrow biopsy showed increased overall bone-marrow cellularity (accounting for about 70% of the nucleated population), with hyperplasia of erythroid progenitors and left-shifting, well-represented granulocytic precursor cells and increased number of megakaryocytes with mature forms, a large-to giant element with hyperlobulated nuclei; CD34$^+$ blasts accounted for about 1–2% and loose network of reticulin fibers with many intersections (MF-1) could be identified. Altogether, bone-marrow morphology was consistent with a diagnosis of myeloproliferative neoplasm, unclassifiable according to the WHO classification (Fig. 3).

The patient, consequently, started hydroxyurea 500 mg/day, and was eventually included in a trial with a JAK2 inhibitor for symptomatic splenomegaly.

Follow-up revealed reduced spleen volume (longitudinal diameter 14.5 cm at abdomen US) and symptoms improvement without major side effects of the JAK2 inhibitor. The patient's blood tests at the last observation are shown in Table 1.

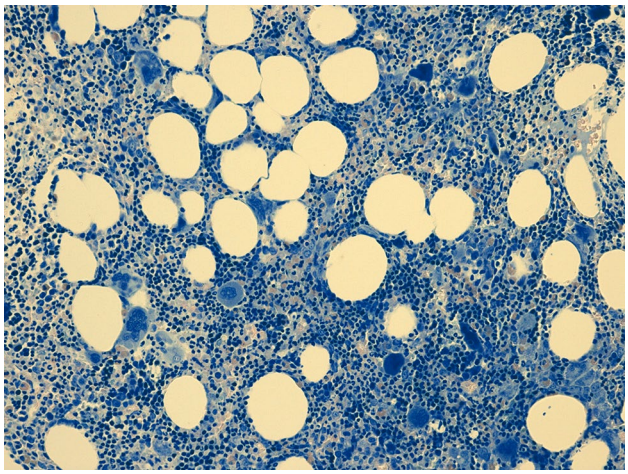

Fig. 3 Bone-marrow biopsy showing increased overall bone-marrow cellularity (70% of the nucleated population), hyperplasia of erythroid progenitors and left-shifting, well-represented granulocytic precursor cells and increased number of megakaryocytes with mature forms, $CD34^+$ blasts accounting for about 1–2% and loose network of reticulin fibers with many intersections (MF-1)

Discussion

Dr. Pelusi, Prof. Fracanzani, and Prof. Fargion

We illustrate a case of hereditary hemochromatosis in a patient carrier of beta-thalassemia trait who developed a myeloproliferative disorder after years of phlebotomy.

Hereditary hemochromatosis (HH) is a recessive genetic disorder, with a prevalence of 3–4/1000 in Caucasian populations, leading to severe iron overload for increased iron absorption and deposition in the liver and parenchymal organs, in the large majority of the cases related to mutations in the HFE gene. The most common mutation in the HFE gene is a single-nucleotide substitution leading to a cysteine-to-tyrosine substitution in position 282 (C282Y), the other mutation, much more frequent and less important in causing iron overload, involves a histidine to aspartate substitution in position 63 (H63D), that very likely interferes with the capacity of the HFE protein to bind to transferrin receptor 1 (TFR-1) [1].

The penetrance of the disease depends on age, gender, environmental factors and on the role of modifier genes. For example, iron overload and phenotype are usually more severe in patients carrying the beta-thalassemia trait [2]. These subjects present a mild impairment in globin chain synthesis leading to defective erythrocytes and consequent mild anemia. It has been speculated that the coexistence of the beta-thalassaemia trait increases the rate of intestinal iron absorption beyond that induced by the lack of HFE in C282Y homozygous patients, possibly through a mild ineffective erythropoiesis [3].

It is also unknown whether the mild ineffective erythropoiesis of beta-thalassemia trait may predispose to myeloproliferative diseases.

The combination of myeloproliferative diseases and thalassemia is unusual, but some cases have already been reported in literature.

Martinez-Lopez et al. [4] describe the case of a 19-year-old female, diagnosed with delta-beta minor thalassemia and 11.5 g/dl basal hemoglobin levels, referred to the hematology service to be evaluated for leukocytosis, thrombocytosis, and painful splenomegaly. Another case was reported by Lopes da Silva [5]; the patient was a 75-year-old Caucasian female with a previous medical history of bilateral chronic venous insufficiency and beta-thalassemia trait referred because of abnormal blood count (erythrocytosis with a red cell count of 9.0×10^{12}/l, slightly elevated hemoglobin for an adult female, 15.4 g/dl, elevated hematocrit, 51.8%, microcytosis with a mean corpuscular volume of 59.2 fl, white blood cell count of 13.5×10^9/l, and total platelet count of 500×10^9/l). Mild splenomegaly was also present (3 cm below left costal margin). A further case reported in literature involves a 71-year-old white woman referred for hematological evaluation because of abnormal results obtained on a complete blood count, performed as part of an evaluation for coronary artery disease. Her previous medical history included hypertension, beta-thalassemia minor, hyperlipidemia, and three spontaneous abortions [6]

In each of these cases, a diagnosis of polycythemia vera, a clonal disorder of hematopoietic stem cells characterized by an absolute elevation in total body erythrocyte volume, was made. Polycythemia vera is classified in a group of diseases called myeloproliferative syndromes along with essential thrombocytosis, myelofibrosis, and chronic myelocytic leukemia. Leukocytosis or thrombocytosis often accompany erythrocytosis.

Approximately 95% patients affected by polycythemia vera harbour the JAK2 p.V617F mutation, which leads to constitutively activated, intracellular JAK-STAT signalling resulting in increased production of red and white blood cells and platelets in hematopoietic stem cells [7].

The authors emphasize that the diagnosis of a myeloproliferative disease in a patient with beta-thalassemia can be challenging because of the presence of antagonizing hematological effects, masking one another (the higher red cell mass and increased hematocrit value associated with polycythemia can be prevented by microcytosis and hemolysis associated with thalassemia), and because of some overlapping clinical features between the two pathological entities.

For example, the initial mild splenomegaly has been justified for a long time in our patient because of the presence of beta-thalassemia trait and consequent extramedullary hematopoiesis. Thus, the identification of a myeloproliferative disease can be delayed (Lopes da Silva) as occurred in

our patient. However, in "a posteriori" evaluation, the mild increase in platelet count we registered during the years of follow-up, although still in the range of normality, in the presence of a progressively increasing spleen, probably represented a warning sign that was underestimated.

Moreover, as shown by a recent paper published in this Journal, platelet counts over time and their dynamism has been described as a possible predictor of the risk of developing thrombotic/hemorrhagic events in low-risk patients with essential thrombocythemia [8].

The second main issue discussed in this case is the hypothesis that a longstanding abnormal erythropoiesis driven by beta-thalassemia trait associated with external stimuli such as phlebotomy in the presence of hemochromatosis linked to C282Y homozygosity might have predisposed our patient to a myeloproliferative disorder.

Literature is scarce in this respect, and the role of HFE genotypes as risk factors for development of myeloproliferative disorders or the possible stimulus given by phlebotomy to stress hematopoiesis remains confounding [9, 10].

Barton et al. evaluated 100 consecutive unrelated Caucasian adults with malignancy in a community medical oncology practice, including 7 patients with myeloproliferative disease (6 of whom had polycythemia vera). C282Y and H63D genotype frequency was elevated in patients (21.4% and 28.6%, respectively), compared with controls (8.9% and 14.5%). C282Y and H63D were reported to be risk factors for malignancy on the basis of OR above 2.0 (2.8 and 2.4, respectively), although *P* values were not significant due to the low case numbers [9].

On the other hand, Andrikovics et al. find that HFE C282Y might play a protective role against myeloproliferative diseases contrasting the effect of chronic iron deficiency and latent anemia in triggering disease susceptibility for myeloproliferative disorders [10].

Nevertheless, in one epidemiological study involving 842 patients affected by polycythemia vera, a surprising excess of former blood donors was observed (20.7% in patients with polycythemia compared to 8% in the population of reference), possibly supporting the role of stress erythropoiesis in the development of such hematological disorders [11].

Conclusion

Prof. Fargion

Our case emphasizes the difficulty in diagnosis a myeloproliferative disease in a subject carrier of beta thalassemia trait, and hints at the possibility that frequent phlebotomies in a patient with increased, although ineffective, erythropoiesis may favour the development of a myeloproliferative disorder.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with human and animals performed by any of the authors.

Informed consent Informed consent by the patient was obtained by the authors.

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