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CASE IMAGE

Concomitant *JAK2* mutated myeloproliferative neoplasms and hereditary hemochromatosis

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Myeloproliferative neoplasms (MPN) are a group of haematopoietic stem cell neoplasms including polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) that share driver mutations in *JAK2*/*CALR*/*MPL*. Hereditary hemochromatosis (HH) is an autosomal recessive disease, mainly caused by C282Y and H63D *HFE* mutations, characterized by iron tissue accumulation. Here, we report two cases of concomitant *JAK2*V617F mutated MPN and HH.

In June 2017, a 68-year-old man Caucasian man with the previous unremarkable medical history was referred to our Institution for hyperferritinimemia: ferritin levels were 977 ng/mL (ranges 26–388), iron levels 180 μg/dL (ranges 65–175) with a transferrin saturation of 53% (ranges 15–50%). Physical examination revealed splenomegaly, with spleen palpable at 5 cm from the left costal margin (LCM). Laboratory tests showed normal blood count, a mild increase of total bilirubin (2.2 mg/dL; ranges 0.2–1) and serum lactate dehydrogenase (LDH, 388 U/L; ranges 84–246). After excluding causes of the secondary hyperferritinimemia, HH was suspected. Genetic screening revealed *HFE* compound heterozygous mutations (C282Y/H63D). Quantification of liver iron concentration (LIC) by magnetic resonance imaging (MRI) documented a moderate overload. The patient was treated with phlebotomies. In September 2021, a progressive increase in splenomegaly and an LDH level was documented. With the suspicion of an MPN, a diagnostic work-up was performed; bone marrow (BM) histopathology showed an increased cellularity with a marked proliferation of pleomorphic megakaryocytes and fibrosis grade-2, without hemosiderin deposits (Figure 1, A and B). A *JAK2* V617F mutation with a variant allele frequency (VAF) of 45% was documented; karyotype was normal, whereas next-generation sequencing (NGS) analysis revealed the presence of *NF1*G2262R variant (VAF 5%). According to the 2016-WHO classification, a diagnosis of overt-PMF was done and classified as intermediate-risk according to the Mutation-Enhanced International Prognostic Scoring System 70 (MIPSS70). The patient started ruxolitinib at 20 mg/BID for symptomatic splenomegaly.

In May 2021, a 49-year-old Caucasian man presented at our Institution for erythrocytosis, and thrombocytosis discovered in the past year; no previous thrombosis was reported, and physical examination was unremarkable. Platelets were 603×10^9/L, haemoglobin 18.3 g/dL, haematocrit 52.9%, and leukocytes 8.5×10^9/L, with a moderately increased ferritin level (641 ng/mL), iron levels (170 μg/dL) and a transferrin saturation of 50%. Serum erythropoietin was 2.2 mUI/mL (range 3.2–31.9). *JAK2*V617F mutation with a VAF of 16% was detected. BM biopsy revealed increased cellularity with prominent erythropoiesis and dispersed or loosely clustered megakaryocytes. Fibrosis was absent while numerous hemosiderin-laden

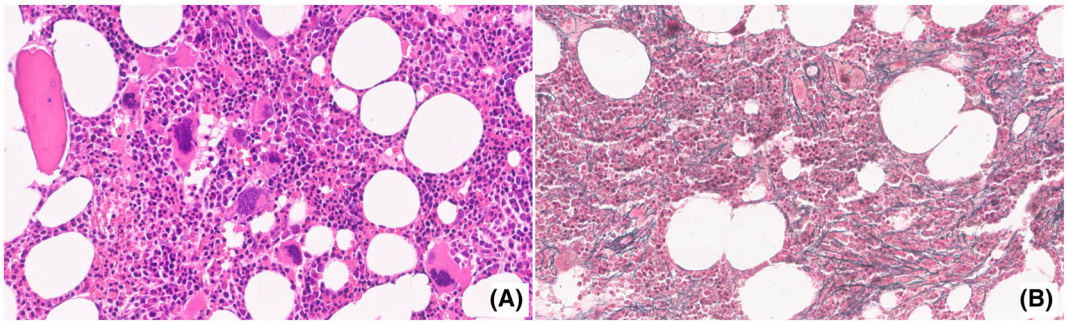

FIGURE 1 Hypercellular (>60%) bone marrow (BM) with trilinear proliferation pattern and numerous megakaryocytes with large to giants forms in addition to smaller ones. (A, H&E, x200). Diffuse increase in reticulin fibres with extensive intersections and focal bundles of collagen (MF-2) (B, Gomori stain, x200)

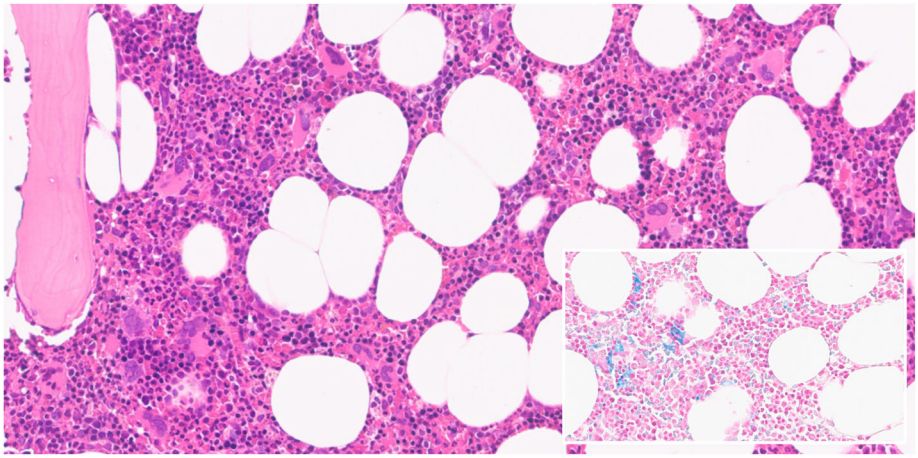

FIGURE 2 Age-adjusted bone marrow hypercellularity (50%) characterized by large islets of nucleated erythroid precursors with left-shifting and abundant pleomorphic megakaryocytes (H&E, x200). Iron stores were also evident (inset, Perls stain, x400)

macrophages were seen (Figure 2). Karyotype was normal and no additional mutation by NGS was detected; a diagnosis of PV was done. However, hyperferritinimemia along with hemosiderin deposition in the BM, which are usually absent in PV, led to investigate a possible cause of the primary iron overload. *HFE* gene mutation screening revealed the presence of a H63D homozygous mutation. The patient started aspirin at the dose of 100 mg/QD and phlebotomy to maintain the haematocrit below 45%. Quantification of LIC by MRI did not document a significant iron overload.

The co-existence of MPN and HH has been described in the previous two reports.[1,2] However, the role of C282Y and H63D *HFE* genotypes as risk factors for development of MPN remains largely unclear.[3] The cases reported above underline the importance of considering the possible co-occurrence of MPN and HH in the presence of clinical, laboratory and histopathological elements, such as splenomegaly in HH and hyperferritinemia along with tissue hemosiderin deposits in PV, that are not typical of these conditions.

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DATA AVAILABILITY STATEMENT

Available on request to corresponding author

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