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Letter to the Editor

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Unexpected insights in the aetiology and management of abdominal vein thrombosis

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Abstract

Myeloproliferative neoplasms (MPN) – polycythaemia vera (PV) and essential thrombocythaemia (ET) are common causes of abdominal vein thrombosis (portal and hepatic veins). The JAK2 mutation is found in 50% of ET and 95% of cases of PV and should be a standard investigation for all cases of abdominal vein thrombosis. Two cases are presented of portal vein thrombosis due to underlying ET with normal or near normal platelet counts. There was a long delay in diagnosing the MPN in these two cases when relying on the current diagnostic criteria. These diagnostic classifications tend to miss cases of early or latent cases of ET, particularly those that are JAK2 negative. In JAK2 negative cases, diagnosis depends on marrow histology which is often unreliable. Moreover, the thrombotic risk is independent of the platelet count in ET and can occur even in ET with normal or mildly elevated platelets. Awareness of these possible scenarios can avoid debilitating thrombosis by the early institution of antiplatelet therapy.

Keywords: abdominal vein thrombosis; myeloproliferative disease; essential thrombocythaemia

The diagnosis of MPNs is based on criteria set out by the Polycythaemia Vera Study Group (PVSG) and the WHO. These diagnostic criteria of essential thrombocythaemia (ET) are directed primarily at the exclusion of other myeloproliferative neoplasms (MPN) and of reactive thrombocytosis. For the diagnosis of ET, a platelet count of 600 × 10^9/l is considered to be the absolute requirement [1]. This in effect rules out the diagnosis of early stage ET, thereby excluding from specific therapy a subset of patients who are prone to certain ET-related thrombotic complications. To address this lacuna, subsequent classifications have lowered the cut off value for platelets. In the WHO classification, the major criteria is a platelet count > 550 × 10^9/l [2]. In the revised WHO classification, the limit was lowered further to a platelet count of > 450 × 10^9/l [3]. No reactive cause for thrombocytosis and normal iron stores is another criteria that must be met for diagnosing the MPN. These modifications reduce but still do not eliminate the possibility of missing latent or early cases of ET. This is illustrated by the following two cases.

Case#1: A 51-year-old lady who presented with portal vein thrombosis. The blood count was WBC 15.3 × 10^9/l, Hb 11.5 g/dl, MCV 66 fl, platelets 678 × 10^9/l. A marrow investigation revealed absent iron stores and the thrombocytosis was attributed to iron deficiency anaemia. Anticoagulation was commenced together with replacement iron therapy and the platelet count normalized after two weeks. The thrombophilia screen was normal. The Philadelphia chromosome was not detected and paroxysmal nocturnal haemoglobinuria was excluded by flow cytometry. One year later, the platelet count was elevated at 672 × 10^9/l and a repeat marrow investigation was consistent with MPN and the JAK2 mutation was detected. Cytoreduction with hydroxyurea was commenced.

Case#2: A 43-year-old man presented with portal vein thrombosis. The blood count was WBC 4.4 × 10^9/l, Hb 8.9 g/l, MCV 90 fl, platelets 324 × 10^9/l. The marrow aspirate showed low iron stores. Iron deficiency anaemia was diagnosed. Anticoagulation and iron supplementation were commenced. One year later, the blood count was WBC 10.7 × 10^9/l, Hb 15.4 g/l, Hct 50.4, platelets 527 × 10^9/l. The marrow investigation was now considered to be consistent with MPN and the JAK2 mutation was detected. Hydroxyurea therapy was commenced.

Discussion

In both cases, the platelet count was only marginally elevated and the clinical and haematological features were attributed to iron deficiency anaemia. Had the JAK2

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mutation been detected at the outset, the delay in the diagnosis of ET would have been avoided even though the platelet count did not fulfill the standard criteria for a diagnosis of ET.

Patients with MPD have an unusually high rate of intra-abdominal vein thrombosis. The JAK2 V617F mutation was detected in 58% of subjects with Budd-Chiari Syndrome [4]. Young patients appear to be particularly vulnerable to this complication [5]. Moreover, the platelet count per se is not correlated with thrombotic risk and abdominal vein thrombosis can commonly occur in patients with slight thrombocytosis or even with platelet counts in the upper normal range. The presence of leucocytosis and a raised haematocrit increases the thrombotic risk of the thrombocytosis. JAK2 positive ET patients also have a higher risk of thrombosis [6].

Patients with ET are normally managed according to a risk-stratified regimen based on age, platelet count and previous history of thrombosis. The use of myelosuppressive agents is advocated in cases where the platelet count exceeds 1,000 x 10^9/l in order to avoid overtreatment of cases with a mild course of ET. Aspirin is used in low risk cases if the platelet count exceeds 600 x 10^9/l and if the patient is less than forty years of age. This arbitrary approach however, in the case of abdominal vein thrombosis is inadequate and unlikely to prevent thrombosis in some cases of early stage ET. The JAK2 mutation analysis should be included in the routine investigation of abdominal vein thrombosis.

With the identification of the JAK2 and MPL mutations, the biology of ET is now better understood. However, 50% of cases of ET are JAK2 negative [7] and the diagnostic approach in these cases remains problematic as it continues to rely on poorly standardized techniques. Emphasis on bone marrow histology in the WHO classification is controversial as the interpretation is subjective and not reproducible. A group of four experienced pathologists asked to reclassify 115 patients with PVSG – defined ET in a blinded fashion misdiagnosed 70% of these cases [8]. An important breakthrough has been the identification of the CALR mutation which is present in 70% of JAK2 negative ET. Patients with this mutation have a milder disease course with fewer thrombotic episodes and better survival than those with the JAK2 mutation [9].

Even in the JAK2 era, heightened clinical awareness of the potentially serious thrombotic effects of mild thrombocytosis is mandatory. It will contribute to the early introduction of antiplatelet therapy long before the platelet count rises to the trigger level established by current criteria for therapy.

Key points

1. Myeloproliferative neoplasms (MPN) account for a significant proportion of abdominal vein thrombosis. 2. Abdominal vein thrombosis can occur in MPNs with a normal or near normal platelet count. 3. JAK2 positivity is documented in 50% of ET and 95% of PV. 4. JAK2 detection by PCR on peripheral blood samples should be performed in all cases of unexplained abdominal vein thrombosis. 5. The risk of thrombosis in ET is independent of the severity of the thrombocytosis. 6. The current diagnostic criteria for diagnosing ET may miss latent or early cases of the MPNs especially in JAK 2 negative cases when histology can be unreliable. 7. Identification of JAK2, MPL and CALR mutations can diagnose 90% of cases of ET. 8. Early diagnosis of the underlying MPN is important as the introduction of aspirin can prevent devastating thrombotic episodes and may even obviate the need for lifelong prophylactic anticoagulation.

Conflicts of interest

Author declares no conflicts of interest.

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