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LETTER TO THE EDITOR

The *JAK2* V617F Allele Burden in Latent Myeloproliferative Neoplasms Presenting with Splanchnic Vein Thrombosis

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To the Editor:

Myeloproliferative neoplasms (MPN) are a recognised underlying cause of splanchnic vein thrombosis (SVT) and by strict definition, have abnormal peripheral full blood counts (FBC) and morphological features [1, 2]. The most commonly observed acquired mutation in MPN is the *JAK2* V617F, detected in the majority of polycythemia vera patients and 50–60 % of patients with essential thrombocythemia and primary myelofibrosis. Assessment of the *JAK2* V617F allele burden by quantitative PCR (qPCR) in MPN has been shown to be of value in measuring response to certain therapies [3], and can be predictive of thrombotic risk and myelofibrotic or leukemic transformation. A significant proportion of patients with otherwise unexplained SVT are found to have evidence of the *JAK2* V617F mutation in the presence of a normal FBC: a latent MPN [4]. Despite this well documented phenomenon, data on the impact of the *JAK2* V617F and its allele burden on subsequent disease evolution in those patients with a latent MPN are scarce [5–7]. In order to investigate this issue, the incidence of *JAK2* V617F-positive patients presenting with an SVT from a single-centre was identified, the *JAK2* V617F allele burden of those patients with both a latent and overt MPN were determined at this time, with subsequent follow up of FBC indices.

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Of 171 *JAK2* V617F-positive patients identified in a single-centre between March 2006 and October 2013, 17 (10 %) had a history of SVT comprising portal vein thrombosis (n = 3), hepatic vein thrombosis (n = 6), splenic vein thrombosis (n = 1), combined portal and superior mesenteric vein thrombosis (n = 3), combined portal and splenic vein thrombosis (n = 2), and combined portal superior mesenteric and splenic vein thrombosis (n = 2). The median age of SVT presentation was 37 years (range 14–61 years) and of which ten patients were male and seven were female. One patient had known essential thrombocythaemia and of the remaining 16, seven (44 %) had a normal and nine (56 %) an abnormal FBC (thrombocytosis: n = 5; leukocytosis: n = 2; polycythemia: n = 1; cytopenias: n = 1). The *JAK2* V617F allele burden was retrospectively assessed by qPCR [8] in archival peripheral blood DNA from the time of SVT. No statistically significant difference was observed in the *JAK2* V617F allele burden between those patients with a latent MPN (median 9.6 %, range 6.8–55.5 %) and those with an overt MPN (median 19.8 %, range 3.1–62.1 %) (P = 0.475). Intriguingly, and despite the further finding of a morphologically evident MPN on bone marrow biopsy in two of these patients, all seven *JAK2* V617F-positive patients with an SVT who had a normal FBC continue to do so at a median follow-up of 54 months (range 34–90), with none receiving any cytoreductive therapy.

The *JAK2* V617F mutation provides a diagnostic marker of clonal disease, in the majority of patients with classical MPN with determination of the mutant allele burden kinetics by qPCR able to provide information on disease progression and risk of thrombosis. However, there remains considerable uncertainty regarding the prognostic significance of the *JAK2* V617F

mutation in those patients without overt signs of an MPN. The data in this brief but informative study is generally in agreement with that previously described in which a minority of SVT patients were identified who subsequently acquired the *JAK2* V617F without an overt MPN and who displayed superior disease-free and thrombosis-free survival to those with a noted MPN [7]. Screening and re-evaluation of *JAK2* V617F-positive individuals in the general population has demonstrated that the development and progression rate of MPN, as evidenced by an increasing *JAK2* V617F allele burden, is slow but almost inevitable [9]. Somewhat conversely to the findings described herein in which latent MPN patients had a median *JAK2* V617F allele burden of 9.6 %, this latter study established a *JAK2* V617F mutation burden cut-off point of 2 % indicative of disease versus no disease [9]. A further study has shown that the clinical outcomes for patients with low levels (0.1–2 %) of *JAK2* V617F at diagnosis are variable and are dependent upon the clinical and hematological scenario in which they arise [10].

In conclusion, we have identified a small but distinguishable subset of patients presenting with an SVT and a latent *JAK2* V617F-positive MPN and who did not display disease expansion or progression evidenced by hematological indices. Further longitudinal studies are warranted with longer follow up and repeated *JAK2* V617F quantitation in order to understand the disease course and to define the best clinical intervention for an MPN other than anticoagulation, if any, is indicated in such patients.

Conflict of Interest The authors declare that there are no conflicts of interest.

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