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The JAK2^{V617F} Mutation Seen in Myeloproliferative Neoplasms (MPNs) Occurs in Patients with Inflammatory Bowel Disease: Implications of a Pilot Study

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ABSTRACT

Patients with IBD frequently have hematologic abnormalities suggestive of JAK2 mutated MPNs, but are traditionally classified as reactive processes. Haplotype 46/1 is a well-characterized genetic predisposition, common to both inflammatory bowel disease (IBD) and myeloproliferative neoplasms (MPN). In view of this shared genetic predisposition, we measured the frequency of the JAK2^{V617F} mutation in IBD patients with thrombocytosis or erythrocytosis, in order to ascertain whether a higher than expected proportion of these patients may in fact have underlying MPNs. 1121 patients were identified with an active diagnosis of Crohn's disease or ulcerative colitis, of which 474 had either thrombocytosis or erythrocytosis. Patients with abnormal counts were tested for the JAK2^{V617F} mutation during routine follow-up visits. Interim analysis of first 23 patients tested was performed to assess whether the JAK2^{V617F} positivity rate was statistically significant compared with known expected frequencies in a comparable control population. Of 23 patients, 13 patients had thrombocytosis and 10 had erythrocytosis. Three patients with thrombocytosis (23%), and 1 patient with erythrocytosis (10%), tested positive for JAK2^{V617F}, exceeding the expected thresholds for statistical significance. In patients with IBD and thrombocytosis or erythrocytosis, a meaningful proportion may harbor an undiagnosed MPN, as indicated by clonal abnormalities such as JAK2^{V617F}. These findings imply the need for increased testing of these patients for clonal hematologic abnormalities, and importantly, if found, suggest the need for therapeutic strategies with drugs, such as JAK2 inhibitors, in patients with both MPN and IBD.

Keywords: JAK2^{V617F}; Myeloproliferative Neoplasms; Inflammatory Bowel Disease; Thrombocythemia; Polycythemia

1. Introduction

Thrombocytosis is a common finding in patients with inflammatory bowel disease (IBD), as well as other autoimmune diseases and connective tissue disorders [1-3]. Traditionally defined as reactive or secondary thrombocytosis, the increased platelet count in these settings is attributed to various causes, including chronic inflammation, bleeding, iron deficiency, and abnormally elevated serum inflammatory cytokines (e.g. IL6) and growth factors such as thrombopoietin [3-5]. In contrast, clonal thrombocytosis as seen in the myeloproliferative neoplasms (MPN), including essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF), carries a significantly higher risk of thromboembolic disease and evolution of the underlying MPN to acute leukemia, making it important, and challenging, to clinically distinguish between these two categories in patients with thrombocytosis [3,5].

Clonal thrombocytosis and erythrocytosis are characterized by identifiable cytogenetic or molecular abnor-

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malities in the hematopoietic stem cells, progenitor cells, and/or circulating mature leukocytes [5,6]. In the MPNs, the most common such abnormality is the JAK2^{V617F} mutation, seen in more than 95% of patients with PV, and 50% of patients with ET and PMF [7,8]. Since secondary thrombocytosis occurs more commonly than the clonal thrombocytosis of the MPNs [4,5], patients with thrombocytosis in the setting of IBD are commonly and appropriately diagnosed as having reactive thrombocytosis. However, an important and therapeutically relevant question that remains unanswered is whether or not a significant proportion of these patients might have unrecognized clonal thrombocytosis.

Large population-based studies have shown that patients with autoimmune diseases including IBD are more predisposed to developing MPNs [8]. Patients with a history of Crohn's disease (CD) and other autoimmune disorders are 2 to 3 times more likely to develop MPN compared to normal controls, translating into a 20% increased lifetime risk [9,10]. Several independently conducted genome-wide association studies (GWAS) in patients with IBD and MPNs have revealed shared genetic predisposition factors between these two seemingly disparate diseases [11-15]. GWAS studies in patients with CD identified predisposition variants in the genes coding for IL23R, IL12B, JAK2, and STAT3 [11,12]. That JAK2 and STAT3 are downstream components of IL23 signaling by TH1 and TH17 cells involved in the pathogenesis of IBD, serves as a possible mechanistic link among these associations [16].

Intriguingly, the same haplotype 46/1 within the JAK2 gene predisposes to IBD and substantially increases the risk of acquiring the JAK2^{V617F} mutation and MPNs [13-15]. The 46/1 haplotype occurs with a frequency as high as 56% in patients with JAK2 mutated MPNs, compared with 24% in the general population [13]. Importantly, this haplotype confers an increased predisposition not only to acquiring the JAK2^{V617F} mutation, but also to mutations in JAK2 exon 12, MPL, and JAK2 non-mutated MPNs [13].

Although the mechanisms underlying these shared predispositions are poorly understood, these findings collectively suggest a plausible and largely unexplored pathophysiologic link between IBD and MPNs that may have important diagnostic and therapeutic implications for both diseases.

To examine such a potential link, we performed a pilot study where patients with IBD and thrombocytosis or erythrocytosis were screened for the JAK2^{V617F} mutation. We found that a higher than expected proportion of patients with IBD has JAK2 mutated clonal rather than secondary hematologic abnormalities, indicating a heretofore unrecognized subset of patients with IBD who carry the JAK2 mutation. In addition to providing clinical confirmation of a known genetic association between two seemingly distinct diseases, our findings may lend credence to the notion of using JAK2 inhibitors to treat not only MPNs, but also IBD.

2. Patients and Methods

First, after obtaining approval by the Institutional Review Board (IRB) at Weill Cornell Medical College, we identified all patients actively being followed at the Center for Inflammatory Bowel Disease using diagnosis codes for Crohn's disease (CD) or ulcerative colitis (UC) in the electronic medical record (EMR) system. Patients with IBD and thrombocytosis or erythrocytosis were then identified by setting appropriate search filters within the EMR. Thrombocytosis was divided into 3 categories: patients with platelet counts of 450 to 600 ($\times 10^3/\mu L$), 600 to 1000 ($\times 10^3/\mu L$), and greater than 1000 ($\times 10^3/\mu L$). Erythrocytosis was similarly categorized into patients with hemoglobin (Hb) of 16 to 18 g/dL, and more than 18 g/dL. In order to be included in the screen, patients required elevated platelet or hemoglobin values in the defined category on at least two separate occasions, no less than 8 weeks apart. Care was taken to ensure that none of the patients were receiving medications known to increase Hb or platelet counts. JAK2^{V617F} mutation testing on peripheral blood was performed when patients identified in the screen came for routine follow-up visits to the IBD Center at Weill Cornell. Informed consent for JAK2^{V617F} mutational testing was obtained prior to collecting peripheral blood. JAK2^{V617F} allele burdens were determined by pyrosequencing, which quantifies mutant alleles more than 5% [14]. If negative by pyrosequencing, we used an ARMS-PCR assay with a sensitivity of 0.1% [14].

Interim analysis of the first 23 patients tested for JAK2^{V617F} (13 with thrombocytosis, 10 with erythrocytosis) was performed as a pilot study, with the intent of expanding testing to a larger patient cohort only if the number of positive results met thresholds for statistical significance, derived using JAK2^{V617F} mutation frequencies in a comparable control population. Given that ET accounts for approximately 10% of all patients with thrombocytosis [3,5], of which only half carry the JAK2^{V617F} mutation [8], a 5% positivity rate would be predicted in a control population. Based on our sample size of 13 patients with thrombocytosis, 1 positive result or an 8% positivity rate was set as the threshold to meet statistical significance ($p < 0.05$) using the one-tailed Chi^2 test for categorical variables. Since JAK2 mutated PV accounts for an even lower proportion of all-comers with erythrocytosis (<5%) [17], the same threshold level for statistical significance was set for the 10 patients in

our study who had erythrocytosis.

3. Results

A screen of the EMR at Weill Cornell Medical College identified 1121 patients with an active diagnosis of CD or UC. The median age of this cohort was 39 years (range: 18 - 103 years). Of these, 345 (30.7%) had thrombocytosis (platelet count > 450 × 10^3/μL) and 129 (11.5%) had erythrocytosis (Hb > 16 g/dL) (**Figure 1**). Of patients with thrombocytosis, 60.5% had platelet counts between 450 - 600 (×10^3/μL) and the remainder had counts more than 600 × 10^3/μL, with 10 patients having platelet counts more than 1000 × 10^3/μL (**Figure 1**).

Of the 474 patients with abnormal counts, we were able to test 23 (13 with thrombocytosis and 10 with erythrocytosis) for JAK2^{V617F} over a period of 6 months. Median age of this group was 36 years (range: 18 - 69 years) (**Table 1**). The median platelet count in the thrombocytosis group was 941 × 10^3/μL (range: 478 - 1677 × 10^3/μL); median Hb in the erythrocytosis group was 16.9 g/dL (range: 15.8 - 21.2 g/dL). Other patient characteristics are outlined in **Table 1**.

The median duration of IBD in the 23 patients was 10 years (range: 3 - 52 years). Disease activity, as defined by the Crohn's Disease Activity Index (CDAI), was low in 11, moderate in 5, and severe in 7 patients at the time of JAK2 mutation testing. All patients had received an average of at least 4 treatments (range 1 - 12) during their disease course, including systemic steroids, bowel specific anti-inflammatory drugs (mesalamine), cytotoxic drugs (6-MP, methotrexate), and monoclonal antibodies(infliximab, adalimumab, ustekinumab).

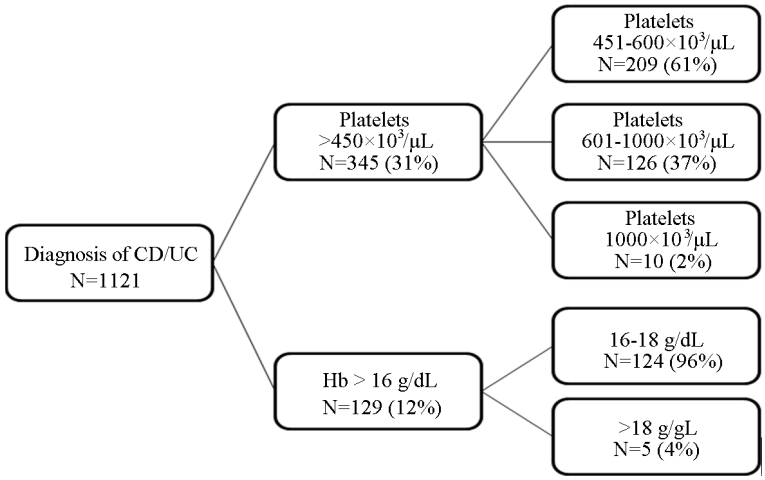

Figure 1. Results of the EMR screen.

Table 1. Patient demographics.

Variable	Number (%)
Median age (yr)	36 (rang: 18 - 69)
Male	16 (70%)
Female	7 (30%)
Crohn's disease	15 (65%)
Ulcerative colitis	8 (35%)
Erythrocytosis (Hb > 16)	10 (43.5%)
Median (range)	16.9 (15.8 - 21.2)
Thrombocytosis (Plts > 600)	13 (56.5%)
Median (range)	941 (478 - 1677)
Number of patoents found to have MPN	5 (21.7%)
JAK2^{V617F} positive*	4 (17.4%)
JAK2^{V617F} negative**	1 (4%)

*3 with thrombocytosis (ET). 1 with erythrocytosis (undiagnosed MPN); **PMF with thrombocytosis.

Three patients in the thrombocytosis group (23%), and one patient in the erythrocytosis group (10%) tested positive for the JAK2^{V617F} mutation, exceeding our threshold positivity level for statistical significance based on the one-tailed Chi^2 test for categorical variables ($p < 0.05$). The platelet counts of the 3 thrombocythemic patients with the JAK2 mutation were 748, 1492, and 734 ($\times 10^3/\mu L$). All 3 had essential thrombocytosis (ET) and were on antiplatelet therapy with ASA. One was on systemic anticoagulation for deep vein thrombosis (DVT). One patient with thrombocytosis who tested negative for JAK2^{V617F}, had a diagnosis of primary myelofibrosis (PMF). The patient with erythrocytosis who tested positive for JAK2^{V617F} had a Hb of 16.7 g/dL and had no prior history of phlebotomy or known diagnosis of MPN.

4. Discussion

In light of substantial data from GWAS, studies supporting a shared genetic predisposition for both MPN and IBD in the form of the 46/1 haplotype, JAK2^{V617F} testing in IBD patients would be a step towards validation of these findings, particularly in patients with hematologic abnormalities suggestive of MPNs. Our results indicate that clonal hematologic abnormalities may occur at a greater frequency in this patient cohort than traditionally thought.

Of our 13 patients with thrombocytosis, 23% had the JAK2^{V617F} mutation, significantly exceeding the expected frequency of clonal causes in all-comers with thrombocytosis. Since only 50% of patients with ET and PMF carry the JAK2 mutation [7,8], the actual proportion of IBD patients with clonal thrombocytosis may potentially be twice that observed in this study, since we only screened for those carrying the mutation. Indeed, our pilot study revealed one patient with JAK2 wild-type PMF. As testing is expanded to the larger cohort of patients, identifying those patients with JAK2 wild-type ET or PMF will entail further diagnostic tests for MPNs as recently outlined [18,19]. Our findings imply that a non-trivial proportion (at least 20%) of patients with IBD and thrombocytosis may have an underlying MPN. Whether or not this is true within the entire spectrum of autoimmune diseases with thrombocytosis is unknown, and warrants further study.

As with thrombocytosis, erythrocytosis occurs more commonly from secondary causes than clonal JAK2 mutated PV [17]. Most patients with IBD have low Hb owing to anemia of chronic disease and/or iron deficiency anemia [20], but experience significant fluctuations in Hb over time from episodic volume depletion and hemoconcentration or blood transfusions. Taken together, one would predict a low likelihood of identifying true clonal erythrocytosis in IBD patients using only Hb as a screening tool. Therefore, the finding of JAK2^{V617F} in even 1 of our 10 patients is especially striking. As 10% in our entire cohort of more than a thousand IBD patients had erythrocytosis, the expansion phase of the study may approximate the actual incidence of clonal erythrocytosis (PV) in these patients.

Patients with IBD are at the increased risk of both arterial and venous thrombosis, as high as a 40% frequency of thromboembolic disease [2-5], and at a 3.6 fold increased risk of thrombosis compared with normals [3]. Since thromboembolic disease is one of the most frequently observed manifestations of MPNs, particularly in those carrying JAK2 mutations [5,21], coexisting IBD and MPN would arguably increase the baseline risk of thrombosis by several fold in these patients. A small study in which 48 patients with IBD and thrombotic events were tested for the JAK2^{V617F} mutation was negative, although none of the patients had overt hematologic abnormalities [22]. Since only a small minority of patients with JAK2 mutated MPNs have normal peripheral counts by definition [19], testing for JAK2 mutations in IBD patients with hematologic abnormalities has a higher likelihood of identifying those at the increased risk of thrombosis. Indeed, in our pilot study of selected patients with hematologic abnormalities, one of 13 patients with thrombocytosis had a thrombotic event in the setting of IBD and JAK2 mutation. That 46/1 is one among several haplotypes within various genes involved in the IL23 and JAK2 signaling pathway, suggests increased JAK2 signaling in IBD, even in the absence of somatically acquired mutations [16]. Since it is known that 46/1 increases the chance of acquiring the JAK2^{V617F} and other mutations in the JAK2 gene, the important question arises from whether JAK2 mutations may contribute to the pathophysiology of IBD, independent of any effect on the hematopoietic compartment.

Since several JAK2 inhibitors are now available and show efficacy in treating both JAK2 mutated and non-mutated MPNs [23,24], the finding of a higher than expected JAK2 mutation rate in IBDs poses the therapeutic question about whether these drugs might improve symptoms of IBD in refractory patients. This question has been explored with the JAK1 and JAK3 inhibitor tofacitinib in ulcerative colitis [25], but JAK2 specific inhibitors have yet to undergo large-scale testing in this disease setting. Our findings support a common link between MPNs and IBDs warrant therapeutic trials of JAK2 inhibitors in IBD patients, whether hematologic abnormalities are present or not.

In conclusion, the results of this pilot study indicate that the actual incidence of clonal thrombocytosis or erythrocytosis in patients with IBD may be more substantial than traditionally thought. Our findings may rep-

resent the clinical manifestation of a shared genetic predisposition for IBD and MPN in the form of the 46/1 haplotype, and therefore, warrant not only large scale testing for MPNs in patients with IBD, but therapeutic trials of drugs with potential to simultaneously improve outcomes for both diseases.

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