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Concomitant chromosome 5q-deletion and JAK2^{V617F} mutation present with myelodysplastic and myeloproliferative overlap features

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Introduction

Myelodysplastic Syndrome (MDS) with an isolated deletion of chromosome 5q [del(5q)] is a relatively rare MDS variant (5%) characterized by a moderate to severe anemia and normal or elevated platelet count with modest neutropenia [1-3]. These latter features, in addition to its excellent response to lenalidomide, are likely what contribute for its favorable prognosis [3-5]. The somatic gain of function mutation in *JAK2* ^{V617F} is a driving mutation in Myeloproliferative Neoplasms (MPN), occurring in 97% of polycythemia vera (PV), 50-60% of essential thrombocytosis (ET) and primary myelofibrosis (PMF) [6]. This mutation results in constitutive activation of the JAK-STAT signaling pathway leading to increased proliferation and hypersensitivity to cytokines erythropoietin, IL-3, thrombopoietin, and GCSF. An allelic burden of *JAK2* ^{V617F} mutation correlates with an increased risk of thrombosis and hemorrhage, as well as secondary fibrosis in MPN patients [7]. Compared to MPNs, *JAK2* mutations are infrequent in MDS, occurring in less than 5% of the cases. This frequency is mirrored in the del(5q) subtype [8,9]. Concomitant presence of *JAK2* ^{V617F} and del(5q) has been reported in the literature, although not much is known about how the prognosis of this combination differs from an isolated del(5q); and in particular with the risk of transformation to Acute Myeloid Leukemia (AML) and response to lenalidomide therapy. While classified as an MDS subset, patients with this combination exhibit specific clinical and pathologic features characteristic of both MDS and MPN. There have been reports that these patients present with a more proliferative bone marrow and retain morphologic features of MPN even after transformation to AML [10,11]. Here we describe two patients with a concomitant *JAK2* ^{V617F} mutation and del5(q), both presenting with severe macrocytic anemia, marked thrombocytosis and characteristic bone marrow morphology.

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Case description

The first patient is a 49-year-old woman who presented with exertional shortness of breath and exercise intolerance. Complete Blood Count (CBC) showed severe anemia, hemoglobin of 76 g/L and marked thrombocytosis, platelet count of 673 X 10^9/L (Table 1). Physical exam revelated marked pallor without lymphadenopathy or splenomegaly. Marrow biopsy was hypercellular (Figure 1A) with a myeloid predominance, no increase in myeloblasts and prominent clustering of atypical hypolobated megakaryocytes with hyperchromatic nuclei (Figure 1B). Reticulin stain showed mild to focally moderate reticulin fibrosis, MF grade 1-2/3 (Figure 1C), without any collagen fibrosis. Myeloid mutation panel by Next-Generation Sequencing (NGS) revealed one tier 1 mutation, *JAK2* ^{V617F}, with a variant frequency of 33%. Marrow karyotype showed del5(q13q33) in 20/20 cells. Based on the presence of del5(q), she was treated with lenalidomide 10 mg daily and was transfused with red cells. After approximately six weeks of treatment, she developed severe pancytopenia and a delayed hemolytic transfusion reaction mediated by anti-E and anti-Lu9(a) antibodies. Subsequently, she was unable to tolerate lenalidomide, despite a dose reduction, due to grade 3- 4 neutropenia. She elected to discontinue lenalidomide and was later switched to intravenous azacitidine 75 mg/m^2 for five consecutive days, every 28 days. To date, patient received 6 cycles of azacitidine with no hemoglobin response and continues to require red cell transfusions.

The second patient, a 72- year-old woman, presented with severe fatigue, 25lbs of unintentional weight loss over one year and aquagenic pruritus. CBC at initial presentation showed similar findings to Patient 1 with a normal white blood cell count, severe anemia, and marked thrombocytosis (Table 1). Physical exam was notable for splenomegaly measuring 8 cm from the left costal margin in the midclavicular line. Marrow examination revealed hypercellular marrow with increased myeloblasts (10-15%) and atypical hypolobated megakaryocytes in clusters (Figure 1D). Karyotype showed an isolated del5(q31q35) in 18/20 (90%) cells. The myeloid NGS panel showed multiple tier 1 mutations in *JAK2*, *GATA2*, *DNMT3A*, *ASXL1*, *BCOR*, and *KRAS* (Table 1). Based on increased blast percentage, treatment with azacitidine was recommended but the patient declined intravenous therapy. Oral lenalidomide was recommended for the treatment of anemia. After three months of oral lenalidomide treatment, hemoglobin and platelet counts normalized and marrow examination after 6 months of lenalidomide treatment showed del5(q) in 3/20 (15%) cells. Anemia response was maintained for approximately one year, at which point patient developed progressive anemia and thrombocytopenia. Marrow examination continued to show clusters of atypical megakaryocytes (Figure 1E) and 60% myeloblasts on CD34 immunostaining indicating progression to AML (Figure 1F). No substantial changes in *JAK2*^{V617F} allele burden was observed on treatment with lenalidomide or at progression to AML (Table 1). She received remission induction with liposomal daunorubicin and cytarabine [12]. A complete response was observed on follow up marrow examination and she subsequently received consolidation therapy with liposomal formulation of cytarabine and daunorubicin (Vyxeos). An allogenic stem cell transplant was recommended to the patient; however, she declined and remains in remission after one year since achieving a CR.

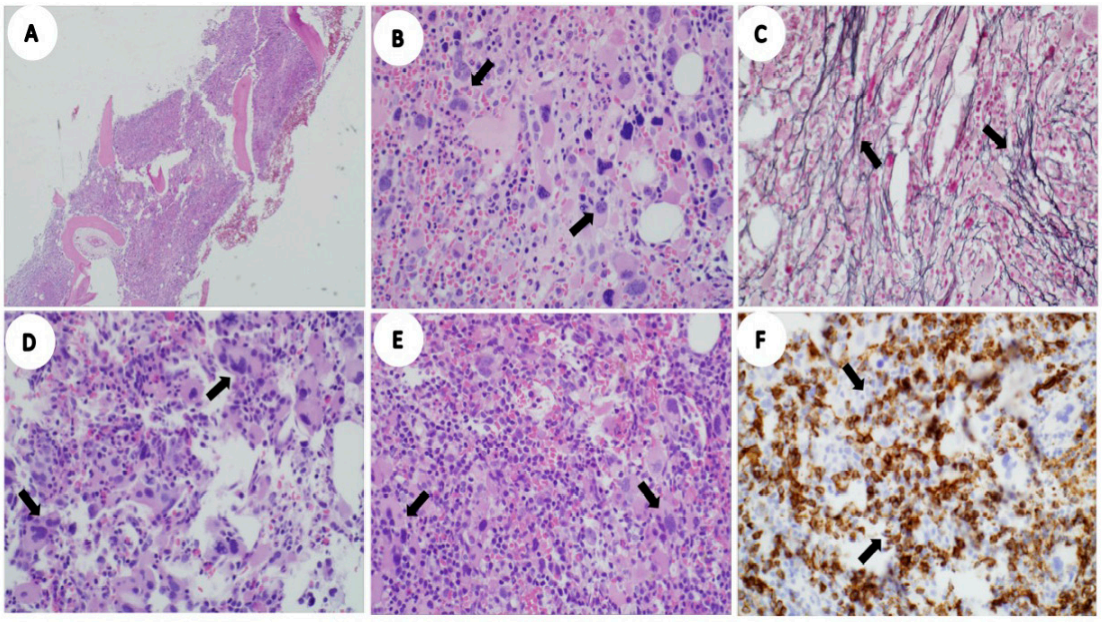

Figure 1: **(A)** Marrow examination of Patient 1 at diagnosis showing markedly hypercellular marrow (4X); **(B)** Marrow examination of Patient 1 showing clusters of atypical hypolobated megakaryocytes (arrows) with hyperchromatic nuclei (10X). **(C)** Reticulin stain of Patient 1 marrow biopsy showing mild to focally moderate reticulin fibrosis (arrows) (10X); **(D)** Marrow examination of Patient 2 at diagnosis showing hypercellular marrow with clusters of atypical hypolobated megakaryocytes (arrows) (10X); **(E)** Marrow of Patient 2 at the time of progression to AML showing sheets of immature cells along atypical megakaryocytes in clusters (arrows); **(F)** CD34 immunohistochemical stain in marrow of Patient 2 showing 60% myeloblasts at time of progression.

Table 1: Summary of pertinent laboratory studies.

	Patient 1	Patient 2 (at the time of diagnosis)	Patient 2 (at progression to AML)
WBC count	6.8X10^9/L	5.1X10^9/L	2.5X10^9/L
Hemoglobin	76 g/L	81g/L	89g/L
Platelet	673X10^9/L	887X10^9/L	262X10^9/L
Peripheral blood blasts%	None	None	14%
Bone marrow cellularity	90%	60%	80%
Bone marrow blasts % on morphology	2.5%	<1%	65%
Karyotype	46,XX,del(5)(q13q33)[20]	46,XX,del(5)(q31q35)[18]/46,XX[2]	46,XX,del(5)(q31q35)[18]/48,sl,+8[1]/46,XX[1]
Somatic mutations on myeloid NGS panel (VAF%)	1. JAK2 c.1849G>T, p.Val617Phe (NM_004972.3) Variant Frequency: 33.0%	1. JAK2 c.1849G>T, p.Val617Phe (NM_004972.3) Variant Frequency: 35.9% 2. DNMT3A c.2579G>A, p.Trp860* (NM_175629.2) Variant Frequency: 3.6% 3. ASXL1 c.1720-1G>A, p.? (NM_015338.5) Variant Frequency: 1.2% 4. BCOR c.3254dup, p.Asn1086fs (NM_001123385.1) Variant Frequency: 1.1% 5. KRAS c.351A>T, p.Lys117Asn (NM_004985.4) Variant Frequency: 1.5% 6. GATA2 c.1075T>G, p.Leu359Val (NM_001145661.1) Variant Frequency: 29.2%	1. JAK2 c.1849G>T, p.Val617Phe (NM_004972.3) Variant Frequency: 32.4% 2. DNMT3A c.2579G>A, p.Trp860* (NM_175629.2) Variant Frequency: 3.9% 3. ASXL1 c.1720-1G>A, p.? (NM_015338.5) Variant Frequency: 4.7% 4. BCOR c.3254dup, p.Asn1086fs (NM_001123385.1) Variant Frequency: 11.3% 5. KRAS c.351A>T, p.Lys117Asn (NM_004985.4) Variant Frequency: 13.8% 6. GATA2 c.1075T>G, p.Leu359Val (NM_001145661.1) Variant Frequency: 29.2% 7. ETV6 c.428_429dup, p.Pro144fs (NM_001987.4) Variant Frequency: 1.7%

Discussion

As previously reported in patients with a concomitant del(5q) and *JAK2* ^{V617F} mutation, the hallmark of our patients' presentations include anemia and marked thrombocytosis [10]. A majority of patients are also transfusion dependent [10,13,14]. While this appears similar to MPNs, the transfusion-dependent anemia and thrombocytosis does not typically respond to erythropoietin and hydroxyurea respectively [14-16]. In some cases with a del (5q) and *JAK2*^{V617F} mutation, platelet and leukocyte counts did normalize with a regimen of interferon-alpha, aspirin and hydroxyurea, but this did not improve the anemia [10,13]. This behavior, as well as the response to lenalidomide, is more similar to an MDS-type clinical course. In most case reports, treatment with lenalidomide obliterates all cellular clones with del(5q) and in some cases reduction in *JAK2* ^{V617F} positive clone was observed [13-16]. For example, a complete molecular response occurred in one patient with undetectable *JAK2*^{V617F} mutation by quantitative real time polymerase reaction after 9 months of lenalidomide treatment compared to baseline *JAK2*^{V617F} allele burden of 26.28% [14]. In another case report, *JAK2*^{V617F} allele burden reduced from 18.472% from baseline to 0.018% after 6 months of lenalidomide treatment [15]. Transient clinical response to single agent lenalidomide was also reported in one patient who presented with transformation to AML with history of previously untreated MDS with del(5q) and *JAK2*^{V617F} mutation [17]. Interestingly, this patient was *JAK2*^{V617F} positive at transformation to AML similar to our patient 2 [17]. As previously reported grade 3/4 neutropenia is common with lenalidomide treatment, as experienced in patient 1 [18]. The marrow of our patients did not demonstrate overt morphologic features of dysplasia, but showed numerous hypolobated megakaryocytes more consistent with MPN. These MPN-like features were preserved in transformation to AML in patient 2, similar to prior reports [11]. A recent analysis of 5q deletion patients showed that the additional somatic mutations with highest frequency of were *SF3B1*, *DNMT3A*, *TP53*, *TET2, CSNK1A1* and *ASXL1,* as well as *JAK2* genes. Mutations occurred commonly as singular mutations (43%) or with one additional somatic mutation (23%) and it was rare to have three or more somatic mutations such as in patient 2. *CSNK1A1* and *SF3B1* were the only two mutations found to be significantly associated with each other. The presence of an *SF3B1, TP53,* or *RUNX1* mutation were each suggestive of a higher likelihood of transformation to AML and worse prognosis [9]. Whether the prognosis and transformation to AML differs in patients with concomitant 5q deletion and *JAK2* mutation is unknown. Less than 10% of patients with an isolated deletion 5q transform to AML, although this occurred in one of our two patients. However, there is a paucity of literature describing the concomitant presence of these two hematological entities. Significant focal

myelofibrosis (2/3) was demonstrated in patient 1 as well (Figure 1B), which is rarely seen in 5q syndrome but has been reported before in 5q syndrome with a *JAK2* mutation [19]. This indicates the need for longer follow-up data and greater study numbers to assess more accurately leukemic transformation rates and predict prognosis in this population. Based on the mixed clinical picture, response to treatment and possibly distinct rates of transformation to AML, perhaps del(5q) patients with concomitant *JAK2*V617F mutation should be categorized as myelodysplastic/myeloproliferative neoplasms (MDS/MPN).

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