Myeloproliferative Neoplasms with Subsequent Development of Chronic Myelogenous Leukemia: A Case Series

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Abstract

Background: Myeloproliferative neoplasms (MPN) are broadly divided by the presence or absence of the Philadelphia chromosome (Ph), with its presence considered a major marker of chronic myelogenous leukemia (CML). The co-occurence of a *Ph*-negative and *Ph*-positive MPN is a rare phenomenon with potentially significant prognostic and treatment implications, but there is a paucity of literature with regard to this co-occurrence and its subsequent management. Additionally, these unusual cases provide a lens through which one can better understand hematopoietic clonal dynamics. With progressive adoption of next-generation sequencing, the discovery of this co-occurrence will likely become more common with time.

Case presentation: Herein, we present three separate cases of concomitant Ph-positive and *Ph*-negative MPN, their implications with respect to clonality, and discuss potential therapeutic approaches.

Conclusions: Though the co-occurence of a *Ph*-negative and *Ph*-positive MPN is a rare phenomenon, it is most prevalent with JAK2 + MPN, seen in 0.4% of cases. This co-occurrence will likely become more prevalent over time with the progressive adoption of next-generation sequencing techniques and detection of subclinical clones. Cases of monoclonality and polyclonality have been shown to be responsible for the development of MPN co-occurrence. The development of unexplained new marrow fibrosis, leukocytosis, or thrombocytosis in previously well-controlled MPN should prompt evaluation for concomitant CML or other *Ph*-negative MPN, including systemic mastocytosis. Treatment resistance to TKI in CML, particularly in the absence of an identifiable resistance mutation, may be suggestive of developing *JAK2*-positivity.

Abbreviations

MPN: Myeloproliferative Neoplasm; CML: Chronic Myelogenous Leukemia; PMF: Primary Myelofibrosis; Ph: Philadelphia Chromosome; JAK2: Janus-kinase 2; CALR: Calreticulin; MPL: Proto-Oncogene for the Thrombopoietin Receptor; PNH: Paroxysmal Nocturnal Hemoglobinuria; SM: Systemic Mastocytosis; MMR: Major Molecular Response; NGS: Next-Generation Sequencing

Background

Myeloproliferative neoplasms (MPN) are broadly divided by the presence or absence of the Philadelphia chromosome (Ph), with its presence considered a major marker of chronic myelogenous leukemia (CML) [1]. *Ph*-negative MPN, such as polycythemia vera (PV), essential thrombocytosis (ET), and primary myelofibrosis (PMF), typically possess other driver mutations, most commonly *JAK*-2, *MPL,* and *CALR* [2]. *JAK*-2 mutations render hematopoietic stem cells more sensitive to growth and overproliferation, while *MPL* mutations lead to constitutive *TPO* receptor stimulation. *CALR* is involved with

apoptosis, cell proliferation and immune mediated cell death [2]. As a result of increased *JAK/STAT* pathway signaling, mar-

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row fibrosis can complicate the course both *Ph*-negative and *Ph*-positive MPN [3].

The mutations that belie each MPN have long been considered to be fairly exclusive for each disorder. The presence of concomitant MPN within an individual is a rare phenomenon, with very few case reports published to date [4,5], and whether or not there is an underlying genetic predisposition for this phenomenon remains unclear. With respect to individual cases, the prevalence of familial MPN cases is estimated to be around 7.6-11% [6]. A Swedish population-based study demonstrated that first-degree relatives of MPN patients have a 5 to 7-fold increased risk of developing MPN, suggestive that certain susceptibility may genes play a role in the development of MPN [6,7].

The development of CML after a previous diagnosis of a *Ph*-negative MPN is a rare phenomenon. *JAK2*-positive MPN appears to have the most frequent co-occurrence, in up to 0.4% of cases. Owing to this, the presence of a *JAK2* mutation has been described as a potential risk factor for the subsequent development of CML [8]. Conversely, *CALR*- and *MPL*-positive MPN very seldomly develop CML, with only six and one case reports to date, respectively. The true incidence of this co-occurrence is unclear, as a result, as to whether either *CALR* or *MPL* predisposes to CML is unknown [5].

The question as to whether the two disorders arise from the same or independent myeloid clones also remains unclear. Previous reports have provided evidence for both theories, with concomitant *Ph*-positive and *Ph*-negative MPN arising from the same [7] or independent clones [8]. Within individuals found to have concomitant MPN, the presence of driver mutations may have a further role in determining whether these are two separate events or clonally derived. Identifying the presence of coincident MPN is critically important, for clinical, therapeutic, and histopathological features may depend on the interactions between mutant proteins [3]. In order to highlight the potential overlapping genetic spectrum of MPNs and features leading to the development of CML, we herein report three patients with *Ph*-negative MPN - one with *CALR*-positive ET, one with *MPL*-positive ET, and one with both *JAK2*-positive PV and systemic mastocytosis (SM) - who subsequently developed CML [4].

Case 1

A 59-year-old man was diagnosed with ET in 1994 on the basis of marked thrombocytosis of 1.1 million in the absence of any underlying cause. Treatment with hydroxyurea maintained stable disease for many years.

In December of 2015, there was a marked increase in his platelet count to 2.01 million with an accompanying new leukocytosis of 16,400 and accompanying few blast forms on peripheral smear. Bone marrow biopsy demonstrated hypercellular marrow with trilineage proliferation, mild-to-moderate fibrosis, panmyelosis, dysmorphic features, but no evidence of acute leukemia. JAK2 returned negative. However, *BCR-ABL1* on PCR and the Philadelphia chromosome present on FISH were positive, suggesting either newly diagnosed CML or CML in the background of ET.

He was placed on imatinib in January 2016 with normalization of his WBC count and decrease in platelet count to 1.42 million, with a decrease in the amount of detectable *BCR-ABL1* via PCR. In February 2016, platelet count increased to 3.26 million and so was also placed on Ruxolitinib 20 mg with improvement to less than 1 million. Maculopapular rash development led to a change to dasatinib in February 2016. *BCR-ABL1* PCR further decreased to < 1%.

In May 2016, platelet count again increased to 1.2 million. Testing for mutation in *CALR* was performed and found to be positive for a type 1 mutation of the *CALR* gene. PCR for *BCR-ABL1* remained undetectable. Despite major molecular response (MMR) to dasatinib therapy, as well as continued control of the white blood cell count, platelet count remained above one million.

The suppression of *BCR-ABL1* while on targeted therapy, the presence of *CALR* mutation, and continued marked thrombocytosis suggested the presence of independent clones and a diagnosis of CML arising in a patient with a long-standing concurrent diagnosis of *JAK-2*-negative/*CALR*-positive ET.

Next generation sequencing (NGS) was performed in January 2017, only re-demonstrating a type 1 *CALR* mutation. He has remained in major molecular remission (MMR) since starting dasatinib and has done well clinically.

Case 2

A 79-year-old man was diagnosed with ET in 1994 and was treated with radioactive phosphorus, the standard of care at that time. Nine years later, he developed unexplained leukocytosis and was diagnosed with CML. He was started on imatinib, later changed to dasatinib, and had good disease control until 2010. Bone marrow biopsy at that time demonstrated emergence of an abnormal clone of cells at the b3a2 locus and so was changed to nilotinib with subsequent attainment of MMR. In February 2012, he had an unexplained decline in hemoglobin to 9.8, initially felt to be secondary to nilotinib. His dose was decreased from 400 mg to 200 mg without improvement and hemoglobin declined further, necessitating intermittent blood transfusion. Darbopoetin was added for hematopoietic support. Workup revealed a positive PNH FLAER so was started on eculizumab in August 2012. He was unable to become transfusion independent and so darbepoetin was stopped in March 2013. He was started on biweekly IVIG and danazol but remained transfusion-dependent. Bone marrow biopsy in October 2013 demonstrated hypercellular marrow with myeloid predominance and marked 3 +/4 fibrosis, consistent with progression of CML and/or ET into the spent stage. Megakaryocytes were increased in number, with many hypolobated, hyperchromic nuclei, consistent with ET. There was no increase in blasts. Scattered erythroid islands were seen with marked myeloid predominance. Monocytes showed loss of CD14, consistent with PNH. Repeat PNH FLAER revealed a large granulocyte and monocyte clone of > 97%. BCR/ABL remained undetectable. NGS panel demonstrated an *MPL* mutation.

He was started on dasatinib with prompt MMR. In January 2014, development of cutaneous vasculitis of the hands

led to change back to nilotinib. Eculizumab was discontinued in September 2014. He remained transfusion dependent and required deferoxamine and deferasirox for control of his iron stores. He was lost to follow-up thereafter.

Case 3

68-year-old man was diagnosed with polycythemia vera in 2008 after presenting with both erythrocytosis and thrombocytosis. *JAK2 V617F* mutation was positive and hydroxyurea was initiated with good control for several years. Hemoglobin and platelet count began decreasing, necessitating a decrease and then discontinuation in 2012. Curiously, *JAK2* was rechecked and was found to be negative. He developed unexplained weight loss and repeat CBC in early 2013 demonstrated a WBC count greater than 100,000. *BCR-ABL1* PCR was positive and bone marrow biopsy in May 2013 features were consistent with CML in chronic phase. Initiation of dasatinib led to CMR.

He thereafter developed hives on his abdomen and back and biopsy was consistent with systemic mastocytosis. Tryptase level was 489. He started on cetirizine and fexofenadine with good control. Repeat bone marrow biopsy in May 2015 demonstrated systemic mastocytosis with associated clonal hematologic non-mast cell lineage disease. Repeat *JAK2* V617F was positive. PET/CT was negative for any other organ infiltration.

In February 2016, his serum tryptase levels continue to rise. Myeloid molecular panel demonstrated that *JAK2 V617F* was present within 75% of his cells in his peripheral blood, along with a TP53 mutation (30%), and KIT D618V, consistent with systemic mastocytosis. Cladribine was offered but he declined wishing to pursue systemic chemotherapy. Given the coexistence of mastocytosis with antecedent PV, he was started on ruxolitinib with good response in his symptoms. He was subsequently lost to follow up.

Discussion

In the past twenty years, several driver mutations have been found to belie the development of MPN. In PV and ET, the *JAK2 V617F* mutation is most common, found in approximately 95% and 50% of individuals, respectively. In *JAK2 V617F* mutation-negative individuals, mutations in *CALR* are found in 50-80% of those with ET or PMF, accounting for approximately 25-33% of all patients diagnosed with ET. Mutations of *MPL* at exon 10 are less common and are identified in 3-5% and 5-8% of *JAK2*-negative cases of ET and PMF, respectively. These mutations in signaling proteins involved in MPN have long been considered to be largely mutually exclusive.

The co-occurrence of a *Ph*-positive and *Ph*-negative MPN is a fairly rare phenomenon [1]. In the largest case serie to date by Soderquist, et al., the incidence of concomitant *Ph*-negative MPN and CML appears to be greatest with the *JAK2 V617F* mutation, seen in approximately 0.4% of cases of PV [9,10]. *JAK2* mutations have been shown to predispose to abnormalities in DNA repair and stability, potentially leading to an increased risk in the development of CML as compared to other MPN. Additionally, both *JAK2 and BCR-ABL1,* but not *CALR or MPL*, inhibit apoptosis in response to DNA damage

and so may partially explain the increased coincidence of *JAK2*-positive and *Ph*-positive MPN . With CML, the degree of *JAK/STAT* pathway activity and risk of progression to acute leukemia or marrow fibrosis is variable depending upon the *BCR/ABL1* isoform present, most prevalent with the P190 isoform [3].

However, it remains unclear as to whether this disorders a rise from single or separate clones [5]. Literature demonstrates incidences of both monoclonality and polyclonality being responsible for the development of both disorders [3]. All three of our cases are suggestive of polyclonality. The third case is suggestive of the two disorders occurring in independent clones, for the disappearance of detectable *JAK2 V617F* mutation at the time of CML diagnosis may have been explained by suppression by the dominant CML clone, only later to reappear after MMR of the CML clone was attained. To the best of our knowledge, only 30 cases of coincident *JAK2*-positive and *Ph*-positive MPN have been reported [5].

The co-occurrence of a *BCR-ABL1* translocation with a *CALR* mutation appears to be much less common, with only six case reports to date [7]. As was seen in the first case, a patient diagnosed with *JAK2*-negative ET, who twenty-one years from initial diagnosis was found to have detectable *BCR-ABL1* and upon further testing was found to carry a mutation in *CALR.* Some case reports have suggested that there is true co-occurrence of driver mutations within a dominant clone, leading to an atypical phenotype of both disorders [11-14]. This was suggested in the first case, for the development of both a *CALR* mutation and *BCR-ABL1* led to sudden, profound thrombocytosis despite prolonged stability of the platelet count for over twenty years on hydroxyurea and anagrelide.

However, *CALR* and *BCR-ABL1* clones may arise separately. Interestingly, low-level *BCR-ABL* circulating transcripts have been found in some patients with ET, though the clinical significance of this is uncertain [11]. It is possible that they may suggest smaller, clinically less significant clones that are phenotypically overshadowed by a dominant *CALR* clone [15]. Conversely, in some cases of well-controlled CML, the loss of perceived treatment control with sudden, uncontrolled thrombocytosis has led to the discovery of a *CALR*-positive clone [16,17]. Genetic analysis in some cases has shown that the *CALR*-clone predates the development of CML, suggesting that clonal heterogeneity appears to play a strong role in the phenotypic variability of MPN [15-19].

The co-occurrence of *MPL*-positive MPN with subsequent CML development is extremely rare, with only one case report to date [20]. Despite its rarity, leukemic long-term hematopoietic stem cells (LTHSC) have been shown in mouse models to have increased expression of *MPL* on their surface, compared to non-leukemic LTHSC. This has shown increased *JAK/STAT* signaling and proliferation both *in vitro* and *in vivo*. Interestingly, patients with high *MPL* expression have reduced sensitivity to TKIs but appear to have increased sensitivity to *JAK* inhibitors. This mirrors what was seen in our third case, for the addition of ruxolitinib led to significant improvement in disease control. Further research is being performed with high *MPL*-expressing CML stem cells as a potential target for therapies.

Unlike other *Ph*-negative MPN, the association of systemic mastocytosis with other non-mast cell lineage diseases has been well established. Systemic mastocytosis with associated clonal hematologic non-mast cell lineage disease (SM-AHN-MD) is a fairly common subclass of SM and is most commonly seen with CMML, AML, or other *Ph*-negative MPN. However, it is still rare in association with CML, with only six cases to date. Interestingly, though the initiation of a TKI such as imatinib or dasatinib has been shown to help control both diseases simultaneously in SM-AHNMD, systemic mastocytosis was only uncovered after the initiation of dasatinib in our third case, potentially suggesting that the two diseases may have arisen from distinct clones and/or that suppression of a CML-dominant subclone allowed for the progression of pre-existing mastocytosis [19].

Conclusions

In summary, the co-occurence of a *Ph*-negative and *Ph*-positive MPN is a rare phenomenon. However, with progressive greater adoption of next-generation sequencing, this phenomenon will likely become more common than 0.4%, as the detection of co-occurring driver mutations and subclinical clones will also likely increase over time [20]. Our patients had a lead time of 4, 9, and 21 years, all having different driver mutations. We plan to retrieve archival tissue to perform serial genetic analyses to assess for clonality. We encourage physicians to perform a thorough evaluation of patients with *Ph*-negative MPN who develop unexplained leukocytosis or thrombocytosis for the concomitant presence of CML or other *Ph*-negative MPN. Treatment resistance to TKI in CML may be suggestive of developing *JAK2*-positivity. Also, unexplained marrow fibrosis in a *Ph*-negative or *Ph*-positive MPN, particularly in the presence of adequate disease control, should prompt consideration for evaluation for an underlying different MPN. Further work is required to determine whether these events are stochastic or represent clonal evolution on a case-by-case basis.

Declarations

Ethics approval and consent to participate

As this is a case series, no ethics approval was required prior to the drafting of this manuscript.

Consent for publication

No identifying patient information is listed within this manuscript. These are historical case reports and the patients were subsequently lost to follow up.

Availability of data and material

N/A.

Competing interests

No competing interests to declare.

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Authors' contributions

All authors contributed equally to this body of work. Dr. Reap was involved with case review, manuscript drafting, editing, and submission. Drs. Patel and Kim were both involved in the drafting and editing of the manuscript. Drs. Shammo and Terebelo were involved in oversight of the manuscript, responsible for final editing and revisions.

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