Case Report

A Case of BCR-ABL-Negative Myeloproliferative Neoplasm Presenting with Basophilia

Abstract

The presence of basophilia on peripheral smear along with neutrophilic leukocytosis is the key differentiating point between chronic myeloid leukemia (CML) and all other myeloproliferative neoplasms (MPNs). However, this is not the case always. After getting negative results for the common transcripts (major, minor, and micro) of the BCR-ABL fusion gene in a case presenting with anemia, mild leukocytosis, basophilia, and eosinophilia; the patient was investigated thoroughly for other MPN-associated mutations. The results obtained were positive for the Jak2 V167 mutation. It is very unusual to find basophilia in BCR-ABL negative MPNs. This implies that any case presenting with basophilia and carrying a suspicion of MPN should be exhaustively tested for all possible mutations (JAK 2 exon 14, exon 12, CALR, MPL, CSF3R, PDGFRa, and FIPIL1) if the results for BCR-ABL are negative. Atypical CML should be the last diagnosis based on the exclusion of other MPNs.

Keywords: *Basophilia, chronic myeloid leukemia, eosinophilia, JAK-2, myelofibrosis*

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Introduction

Peripheral basophilia can be seen in any myeloproliferative neoplasm (MPN), but is commonly presenting feature of chronic myeloid leukemia (CML) which requires the presence of BCR-ABL fusion gene for confirmation.[1] Around 90%–95% cases of CML harbor the most common 210 kilodalton BCR-ABL transcript (p210, e13a2/e14a2) which is routinely tested by conventional PCR kits. This is called as the major (M) breakpoint. However, in 5%–10% of cases, BCR-ABL genes are coded by minor (m)-bcr, e1a2, and a micro (u)-bcr region, e14a2 transcripts which cannot be detected by routine PCR kits. These transcripts are known to have a different clinical course despite similar clinical and laboratory findings.[2] Here, we present an unusual case in a 79-year-old patient having anemia, mild leukocytosis, persistent basophilia, eosinophilia, and normal platelet counts. In view of basophilia and eosinophilia, the patient was thoroughly investigated for all possible transcripts of BCR-ABL. The results obtained were negative. On subsequent testing for other MPN-related mutations, a positive result for JAK 2 exon 14 mutation was obtained. This is the first case where basophilia is the presenting feature in a non-CML MPN. The differential diagnoses were polycythemia vera (PV) and primary myelofibrosis (PMF). It was on the basis of the morphological features on the bone marrow (BM) biopsy as highlighted by the WHO 2016 classification for MPN[3] along with the clinical features that helped in reaching the final diagnosis. We stress on the importance of histological features in conjunction with clinical symptoms in the diagnosis of MPNs.

Case Report

A 79-year-old male patient with chronic kidney disease undergoing treatment and dialysis in the nephrology department of our institute for the past 6 months was found to have mild leukocytosis, thrombocytosis, and anemia (hemoglobin: 5.1 g/dl, total leukocyte count: 14.4 × 10^3/ul, and platelets: 499 × 10^3/ul) refractory to treatment with antibiotics and supplementation with hematinics. Peripheral smear examination revealed neutrophilia, basophilia, and eosinophilia (neutrophils-84%, basophils-4%, eosinophils: 07%, and lymphocytes-05%) but no shift

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to the left [Figure 1b]. Anemia was a microcytic hypochromic with red blood cells (RBCs) showing moderate anisopoikilocytosis. Few polychromatic RBCs and elliptocytes were identified along with nucleated RBCs (3/100 white blood cells). Serum iron profile, Vitamin B12, and folic acid levels were within normal limits (ferritin: 30 ng/ml, Vitamin B12: 1268 pg/ml, and folate: 30 ng/ml). All other routine laboratory investigations (liver function test, lipid profile, coagulogram, and electrolytes) were unremarkable except for elevated serum urea (60 mg/dl), creatinine (2.5 mg/dl), and uric acid levels (8.2 mg/dl) owing to chronic kidney disease. Ultrasound of the abdomen showed an enlarged spleen. The patient also complained of weight loss and generalized weakness.-In view of the above findings, a BM examination was planned. The aspirate obtained was diluted and a particulate. However, the biopsy was hypercellular and showed increased myelopoiesis and normal erythropoiesis with normoblastic maturation [Figure 1a]. Megakaryocytes were increased in number and showed clustering of atypical hyperlobated and hypolobated bare nuclear forms at places [Figure 2a and b]. Reticulin stain for fibrosis revealed a Grade 1 pattern [Figure 3]. Based on these histological findings, a possibility of CML was suggested. For confirmation, molecular testing for BCR-ABL was ordered, but the results obtained were negative by both FISH and conventional PCR techniques. All major (p210), minor (190), and micro (230) transcripts of BCR-ABL were tested and found negative. Subsequently, a MPN reflex panel was ordered to rule out other MPN associated mutations. The result showed a V617 F mutation in exon 14 of the JAK 2 gene in the leukocytes of the patient. All other mutations (CALR, MPL, JAK2 exon 12, PDGFRa, PDGFRb, and FIPIL1) were negative. Hence, a diagnosis of JAK2V617F-positive MPN with an unusual presentation of peripheral basophilia and eosinophilia was rendered. A prefibrotic stage of PMF was then narrowed down as the final diagnosis. Table 1 highlights the unusual morphological features seen in this case.

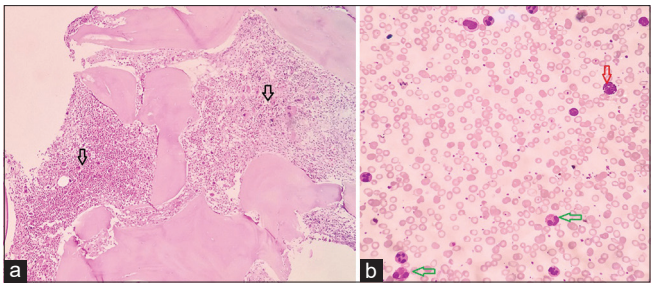

Figure 1: (a) Low-power view of a hypercellular bone marrow biopsy showing clustering of megakaryocytes (black arrow) which appear atypical as well (H and E, ×100). (b) High-power view of a peripheral smear showing eosinophils (green arrow) and a basophil (red arrow) along with neutrophils. Red blood cells show anisocytosis. However, no teardrop cells seen (H and E, ×400)

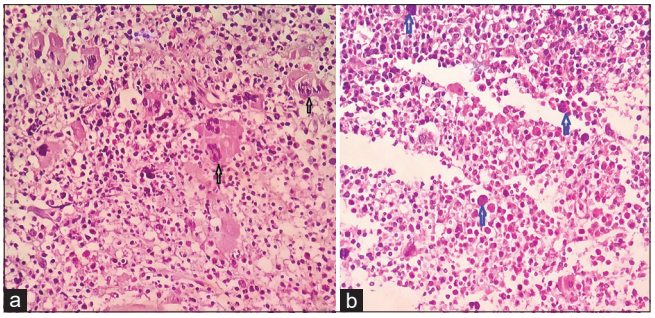

Figure 2: High-power view of the bone marrow biopsy showing atypical hyperlobulated megakaryocytes with ballooning (a, black arrow) and several hypolobulated bare nuclei of megakaryocytes (b, blue arrow) (H and E, ×400)

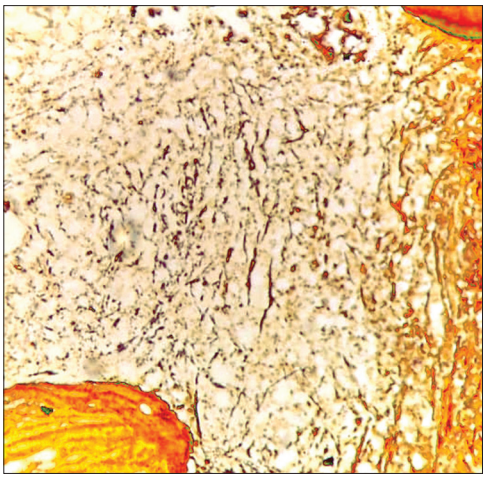

Figure 3: High-power view showing Grade 1 fibrosis (black-colored fibers) in bone marrow biopsy (Reticulin ×400)

Discussion

Peripheral blood basophilia is a rare hematological finding known to be associated with hypersensitivity disorders, iron deficiency, and chronic inflammation. These reactive causes are rare, and hence, basophilia is usually suggestive of an underlying MPN.[1] The 2016 WHO classification of MPN includes three major subcategories of JAK2/CALR/MPL mutation-related MPN which are PV, essential thrombocythemia (ET), and PMF, as well as four other clinicopathologic entities: CML, chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia-not otherwise specified (CEL-NOS), and MPN unclassifiable (MPN-U).[3] It has been observed that ET, PV, and PMF cannot be strictly discriminated by the BM morphology because of overlapping features and the ability to transform into each other. Hence, molecular genetics provide immense help in reaching a specific diagnosis.[4,5] There is a broad list of differential diagnoses for a BCR-ABL negative MPN presenting with findings similar to the index case. For example, CNL and CEL-NOS which show neutrophilia without a shift to the left and absolute eosinophilia, respectively. It is only by obtaining negative results for CSF3R, PDGFRA, PDGFRB, and FGFR1 mutations, that these can be excluded from the study. The patient in this study tested

Table 1: Morphological Features observed on peripheral smear and bone marrow

Features favoring CML	Features against CML/favoring pre-PMF
Basophilia and eosinophilia with mild leukocytosis on peripheral smea	Presence of predominantly mature neutrophils. No 'shift to left' seen (prominence of myeloid precursors)
Thrombocytosis and anemia.	Leukocytosis is not marked (<20 × 10 3 /ul)
Hypercellular marrow with myeloid hyperplasia	Megakaryocytic hyperplasia and clustering on marrow. No dwarf forms/hypolobated forms were seen and the myeloid precursor cells (myelocytes, metamyelocytes, band cells) were not increased
Grade 1 fibrosis (can be seen in PMF also)	

Fibrotic stage of PMF shows leukoerythoblastic picture on PS and teardrop cells. PMF: Primary myelofibrosis, CML: Chronic myeloid leukemia, PS: Peripheral smea

negative for other mutations and showed only JAK2V617 mutation positivity. This is a point mutation in exon 14 at residue 617 of JAK2 and has been reported in 90% cases of PV, 47% of ET, and 42.8% of PMF.[6] Since the patient had anemia, the possibility of JAK 2-positive PV was excluded from the study. This left us with PMF and ET as the possible differentials. ET was excluded on the basis of BM histology. As per the WHO 2008/2016 classification, there is an entity called pre-PMF which is characterized by megakaryocytic proliferation and atypia, with/without Grade 1 fibrosis and accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis. These features very closely mimic the criteria for ET. However, the differentiation between the two is crucial because of their different clinical behavior. ET is a more benign entity in terms of progression to blast crisis, overt fibrosis, and mortality in comparison to pre-PMF.[7] Laboratory data comprising the WHO minor criteria for the diagnosis of pre-PMF have been found to have an impact on the clinical outcome. The presence of least one minor criteria (anemia, leukocytosis, elevated lactate dehydrogenase levels, and splenomegaly) has been found to be highly prevalent and diagnostic (91%) in pre-PMF as compared to 48% in ET.[8] Apart from this, BM histology also plays a very important role. In ET, the proliferating megakaryocytes show large atypical forms with deeply lobulated or hyperlobulated nuclei (staghorn nuclear appearance) dispersed throughout the marrow with occasional loose clusters. Markedly dysplastic and small monolobulated megakaryocytes are not seen. Fibrosis is minimal, never more than Grade 1. Pre-PMF, on the other hand, shows large megakaryocytes arranged in clusters in paratrabecular and sinusoidal locations. They have aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous, and irregularly folded nuclei.[9] Bare megakaryocytic nuclei are commonly seen in PMF. There is accompanying granulocytic hyperplasia and fibrosis. The morphological features of megakaryocytes, in this case, were more in favor of PMF. Highly dysplastic large forms were not seen. Based on these features, a diagnosis of JAK2-positive pre-PMF was favored by the authors. There have been reports suggesting basophilia and monocytosis as markers of accelerated phase in PMF and later conversion into AML in CALR-positive PMF.[10] The association and outcome of basophilia in JAK2-positive MPN is not yet reported.

Conclusion

While morphology and laboratory investigations are essential components of MPN diagnosis, molecular analysis is becoming an integral part of the process providing both diagnostic and prognostic information. Given the high percentage of BCR-ABL1 identification in patients with basophilia, it is recommended that a stepwise analysis of BCR-ABL1, then JAK2 V617F, followed by CALR/MPL mutation analysis be implemented. Once CML is excluded, instead of attributing basophilia to reactive causes, molecular investigations for other MPNs should definitely be carried out so that any unusual association can be unmasked and its impact on the progression of disease be studied.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given his consent for the clinical information and related images to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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