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Abstract Form

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Project Title:	A Rare Case of Co-Existing Polycythemia Vera and Chronic Myelogenous Leukemia

Research Category (please check one):

☐	**Original Research**	☒	**Clinical Vignette**	☐	**Quality Improvement**	☐	**Medical Education Innovation**

Abstract

Introduction: Polycythemia vera (PV) is the most common myeloproliferative neoplasm (MPN). MPNs are characterized by overproduction of clonal cells in the myeloid lineage and can cause life-threatening complications such as bleeding and thrombosis. PV in particular can also transform to myelofibrosis and to a more aggressive acute myeloid leukemia, with the risk of transformation increasing over time; however, post-PV chronic myeloid leukemia (CML) is a rare phenomenon. We describe a rare case of PV and CML co-occurrence to increase the awareness and to describe the mechanisms.

Case Presentation: We present a 50-year-old Egyptian male with a history of homozygous factor V Leiden mutation diagnosed in 2013 in Egypt, complicated by recurrent deep venous thrombosis in the bilateral lower extremities on warfarin. He presented with new abdominal pain and generalized pruritus and was found to have a hemoglobin (Hgb) level of 19 g/dL. Further workup revealed *JAK2*^{V617F}-positive, BCR-ABL1-negative PV. His PV was managed conservatively with regular phlebotomies every four to six months without pharmacologic intervention due to concerns for side effects of systemic therapy on reproductive health. In 2020, the patient presented to our facility to establish care, at which time laboratory values showed white blood cells (WBC) of 7.6 K/μL, Hgb of 16.9 g/dL, hematocrit (Hct) of 52.9%, mean corpuscular volume (MCV) of 74 fL, and platelet (PLT) of 486 K/μL. Iron studies showed iron of 47 mcg/dL, total iron-binding capacity of 475 mcg/dL, iron saturation of 9.9%, and ferritin of 14 ng/mL. CT scan of the abdomen revealed splenomegaly of 18.7-cm but no evidence of thrombosis in the bilateral lower extremities on ultrasound. JAK2 cascading panel on peripheral blood (PB) was also performed showing *JAK2*^{V617F}-positive exon 14 missense mutation. Patient was continued on regular phlebotomies every two to three months, with Hct goal less than 45%. In 2022, patient presented to a routine clinic visit; he was asymptomatic but was noted to have WBC of 30 K/μL with left shift, Hgb of 11.4 g/dL, Hct of 34.1%, and PLT of 199 K/μL. He underwent an infectious workup, which was unremarkable. PB smear showed leucoerythroblastosis with basophilia, absolute neutrophilia, concurrent left shift of granulocytes with increased marked myelocytes and rare blasts. There was an increased suspicion for CML in chronic phase. BCR-ABL1 PCR revealed positive P210 fusion transcript frequency of 84% in the PB. Bone marrow (BM) biopsy was performed and its core revealed hypercellular BM (>95%) with right-shifted myelopoiesis and erythroid hypoplasia. There were also megakaryocytic atypia and pleomorphism, with rare, small hypolobated forms and with disjointed nuclei. Patchy mild reticulin fibrosis (MF-0-1) was present. Myeloid:Erythroid (M:E) ratio of 8:1 was noted without increased blasts, with approximately 1% by manual count. Overall, BM findings were consistent with mixed features of PV and CML in chronic phase. FISH analysis of BM aspirate confirmed BCR-ABL1 fusion t(9;22) with concurrent ASS gene deletion in 85% of examined nuclei. MPN next generation sequencing on the marrow showed concurrent JAK2 V617F mutation present with a variant frequency of 6.1.

The patient was initiated on imatinib 400 mg daily but was subsequently trialed on other BCR-ABL1 tyrosine-kinase inhibitors (TKIs) due to intolerability; nevertheless, patient has had an adequate reduction in the BCR-ABL mutation burden. Patient is currently on nilotinib 150 mg twice daily. Pre- and post-treatment BCR-ABL1 transcript levels after nine months were 77% and 0.23%, respectively. Hct and PLT were also rising post-treatment to 46.3% and 439 K/μL, respectively.

Discussion: This is a rare case of PV and chronic phase CML co-occurrence. The mechanisms of this phenomenon are poorly understood but thought to involve many theories. At the cellular level, there are two widely accepted theoretical mechanisms: 1) the Darwinian concept of co-occurrence and survival of the fittest (i.e. treatment of phenotypic CML would result in eradication of CML-expressing cells and lead to phenotypic expression of next predominant cells (PV)); 2) transformation with sequential mutations (i.e. JAK2 mutation followed by BCR-ABL1 mutation). The former mechanism is consistent with the presented case, given the co-existence of PV and CML in the BM and subsequent treatment of CML led to increase in Hct and PLT, which is suggestive of increasing predominance of PV cells. The latter theory can be further expanded at the molecular level, where the mechanisms involve a crosstalk between JAK2 and BCR-ABL1 molecular pathways, through indirect activating interaction via STAT5 and direct interaction involving a downstream induction of c-myc. Prognosis of these patients remains unclear due to the rarity of this phenomenon. Better understanding of appropriate treatment pathways and outcomes will likely depend on ongoing reporting of these cases in the literature.