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CLONAL COMPETITION BETWEEN JAK2 AND BCR-ABL IN MYELOPROLIFERATIVE NEOPLASM

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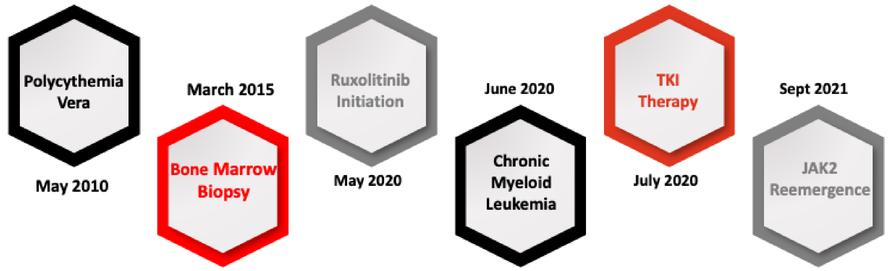
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INTRODUCTION

- Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm (MPN) classified under the *BCR-ABL*–positive subgroup
- *BCR-ABL1* is positive in 95% of CML as translocation t(9;22)
- a small percentage is negative for this translocation
- Other common mutations in MPN are *JAK2* V617F, *CALR*, and *MPL*
- *JAK2* V617F is present in nearly all patients with polycythemia vera (PV)
- *BCR-ABL1* and *JAK2* V617F mutations are generally considered mutually exclusive

CASE DESCRIPTION

- 67-year-old male initially diagnosed with *JAK2* V617F-positive PV
- Initiated treatment with therapeutic phlebotomy, cytoreduction with hydroxyurea
- After 10 years therapy was changed to ruxolitinib due to hydroxyurea failure
- One month late he was found to have hyperleukocytosis with WBC 600 x10^9/L
- Molecular studies revealed t(9;22) *BCR-ABL1* break point p210 consistent with chronic myeloid leukemia
- *JAK2* V617F was undetectable hence ruxolitinib was tapered and discontinued
- CML-directed therapy was started with Tyrosine Kinase Inhibitor (TKI) nilotinib 9/2020 and then switched to bosutinib 11/2021 due to inadequate response.
- Subsequent monitoring revealed reemergence of *JAK2* V617F
- Transitioned to asciminib which he remains on with therapeutic phlebotomy for PV



Timeline of clinical course. PV diagnosed 5/2010 treated with therapeutic phlebotomy and hydroxyurea. Bone marrow biopsy 3/2015 revealed Chronic MPN not requiring treatment. Due to hydroxyurea failure PV therapy changed to ruxolitinib 5/2020. CML diagnosed via bone marrow biopsy 6/2020. Nilotinib therapy started 9/2020 switched to bosutinib 11/2021 due to inadequate response. JAK2 reemerged on bone marrow biopsy 11/2021, therapy switched to asciminib and therapeutic phlebotomy.

CONCLUSIONS

This report presents a rare case of coexisting *JAK2* V617F and *BCR-ABL1* manifesting as severe leukocytosis and erythrocytosis that required simultaneous treatment for both CML and PV. The biological basis for the coexistence of these mutations remains unclear. Studies suggest TKI therapy may unmask pre-existing clones. The appearance of CML has been noted in patients treated with hydroxyurea. Alternatively, these concurrent MPNs might arise independently from different susceptible polyclonal stem cells. One study of patients with MPN found coexistence of these mutations in 0.4% of the cohort. Currently, asciminib is being evaluated as first-line therapy for CML. Additional investigation is necessary to manage the coexistence of these mutations.

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