WHEN SMOKING IS NOT THE WHOLE STORY: DIAGNOSING POLYCYTHEMIA VERA WITH A RARE JAK2 EXON 12 VARIANT COMPLICATED BY HYDROXYUREA-INDUCED VASCULOPATHIC DERMATOSIS

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INTRODUCTION

Polycythemia vera (PV) is a clonal myeloproliferative neoplasm driven by constitutive JAK2 activation. Approximately 95% of patients harbor the canonical JAK2 V617F mutation, whereas JAK2 exon 12 mutations account for only approximately 2-3% of PV cases and define a distinct, erythrocytosis-predominant molecular subset. JAK2 exon 12 alterations comprise a heterogeneous and uncommon group of in-frame deletions, insertions and substitutions clustered within the region encoding amino acids 537-547 of JAK2. The specific c.1627_1632del, p.(Glu543_Asp544del) variant is an uncommon JAK2 exon 12 deletion. It has been reported in V617F-negative PV and may occur at a low variant allele burden, making sensitive molecular testing particularly relevant.

The diagnosis may be challenging when concomitant causes of secondary erythrocytosis are present, such as heavy tobacco exposure and chronic pulmonary disease.

We present a case of PV harboring this rare JAK2 exon 12 variant in a heavy smoker with apparent potential secondary causes of erythrocytosis, further complicated by a painful vasculopathic dermatosis associated with hydroxyurea (HU).

RESULTS

CASE PRESENTATION: A 62-year-old man with 73 pack-years of smoking, mild restrictive ventilatory disease, hypertension, dyslipidaemia and severe peripheral arterial disease was referred for persistent erythrocytosis. Initial haemoglobin/haematocrit values reached 18.5 g/dL / 51.5%, with persistent leukocytosis. Although smoking and pulmonary disease represented plausible secondary contributors, EPO was repeatedly suppressed (3.7 to 2.7 IU/L).

MOLECULAR & MARROW FINDINGS:
JAK2 V617F: negative;
BCR::ABL1: negative;
JAK2 exon 12: positive. Variant: c.1627_1632del, p.(Glu543_Asp544del). Variant allele frequency: 5.8%.
Bone marrow biopsy demonstrated panmyelosis with MF-0, supporting the diagnosis of PV.
Although a hereditary cause of erythrocytosis, including an EPOR mutation, was considered less likely given the patient's age, previous laboratory records showed normal haemoglobin levels; therefore, EPOR mutation analysis was not performed.

DIAGNOSIS: This combination of erythrocytosis, suppressed EPO, *JAK2* exon 12 mutation and characteristic marrow morphology is consistent with current diagnostic frameworks for PV.

THERAPEUTIC COURSE: Given high-risk PV by age (>60 years), with significant cardiovascular comorbidity also informing treatment intensity, therapeutic phlebotomy targeting Hct <45% and cytoreduction with HU 500 mg/day were initiated.
Approximately three weeks after HU initiation, the patient developed a severe painful bilateral palmar dermatosis, initially raising concern for infection or neutrophilic dermatosis. Skin biopsy showed moderate superficial and deep perivascular and interstitial inflammatory infiltrate with lymphocytes, histiocytes and plasma cells, associated with vascular wall lymphocytic permeation, mild erythrocyte extravasation and focal mild necrosis. The findings were considered compatible with vasculopathic dermatosis.
HU was discontinued and systemic corticosteroids were initiated, with marked clinical improvement. Rechallenge with HU resulted in recurrence of the skin lesions, followed by improvement after withdrawal, strongly supporting a drug-related mechanism.

MANAGEMENT ADAPTATION:
During HU interruption, haematocrit was maintained with therapeutic phlebotomy. Following dermatological improvement, a cautious HU rechallenge at 500 mg three times weekly was attempted. Recurrence of the dermatological syndrome led to definitive consideration of HU intolerance.
Ropeginterferon alfa-2b was initiated as an alternative cytoreductive strategy following hydroxyurea intolerance, with subsequent achievement of the target hematocrit <45%.

CONCLUSION

This case highlights the diagnostic value of extended molecular testing in JAK2 V617F-negative erythrocytosis, particularly when erythropoietin is suppressed, even in the presence of plausible secondary contributors such as heavy smoking and chronic pulmonary disease.

The identification of the uncommon JAK2 exon 12 c.1627_1632del, p.(Glu543_Asp544del) variant, together with characteristic bone marrow panmyelosis, established the diagnosis of polycythemia vera and illustrates the importance of looking beyond the most prevalent JAK2 V617F mutation.

The development of a painful vasculopathic dermatosis shortly after hydroxyurea initiation, its improvement after drug withdrawal and recurrence upon rechallenge strongly supported hydroxyurea-associated cutaneous toxicity and significantly influenced subsequent treatment decisions.

Interferon-based therapy is recommended as an alternative when HU intolerance or treatment change is required, and randomized data support its efficacy in PV.

Overall, this case underscores the importance of integrating clinical phenotype, erythropoietin levels, sensitive molecular profiling, bone marrow morphology and treatment-related adverse events to achieve an accurate diagnosis and individualized management of PV.

KEY MESSAGE: Rare molecular findings can be decisive in PV diagnosis, while early recognition of treatment-limiting toxicity is essential for individualized management.

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