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The role of the Exon 13 G571S JAK2 mutation in myeloproliferative neoplasms

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ABSTRACT

The exon 14 JAK2 V617F mutation has been well established as a driver mutation in polycythemia vera (PV) and other myeloproliferative neoplasms. JAK2 exon 12 mutations have also been implicated in PV, although patients with these mutations may show isolated erythrocytosis. Recently additional JAK2 point mutations have been described—all in regions encoding the pseudokinase domain that regulates the tyrosine kinase activity of JAK2. We present a case of a patient with erythrocytosis and an exon 13 G571S mutation, and discuss the putative role of this mutation in myeloproliferative neoplasms.

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1. Report

A 49-year-old woman with past medical history of total thyroidectomy due to papillary thyroid carcinoma was found to have an elevated hemoglobin level. The patient reported to being in her usual health and denied any erythema, flushing, intolerance or irritation with hot showers, any shortness of breath or limitations in her daily activity. In addition, the patient denied any changes in her appetite, and reported no bowel or bladder dysfunction, and no change in weight. Patient noted isolated dyspnea 4–6 weeks ago during unusually strong exertion at work that ultimately resolved with rest. Physical examination of the patient was within normal limits. An abdominal ultrasound examination showed a spleen within normal limits in size.

At presentation, her complete blood count was as follows: hemoglobin 16.8 g/dL, hematocrit 49.8%, MCV 107.9 fL, MCH 36.4 pg, RDW 13%, leukocytes $7.6 \times 10^9/L$, platelets $171 \times 10^9/L$; with a differential showing granulocytes 72%, lymphocytes 17%, monocytes 9%, eosinophils 1%, basophils 1%. Other laboratory values were as follows: TSH 0.34 $\mu IU/mL$, fT_4 1.9 ng/dL, vitamin B₁₂ 294 pg/mL, folate 7.8 ng/mL, and erythropoietin 15.6 mIU/mL.

The bone marrow core biopsy was normocellular for age (50%). The aspirate smear showed trilineage hematopoiesis with progressive maturation of the myeloid and erythroid precursors. The myeloid to erythroid ratio was 3.2 to 1. Blasts were not increased (< 1%). There was no significant dyserythropoiesis. Occasional hypolobated megakaryocytes were present but most

megakaryocytes displayed normal morphology. Iron stain showed increased storage iron and decreased sideroblastic iron. Reticulin stain showed a very mild focal increase in reticulin fibers. Flow cytometric analysis performed on the bone marrow aspirate did not show a significant increase in the blast population. There was no evidence of a B-cell monoclonal population or a T-cell abnormality. Cytogenetic analysis showed a normal female karyotype. Molecular testing on the patient's plasma (RT-PCR amplification followed by sequencing, Quest Diagnostics) showed presence of at least one mutated JAK2 G571S allele in exon 13. The V617F mutation and exon 12 mutations were not detected. We were unable to perform a comprehensive genomic analysis on our patient to identify any additional mutations.

The patient's erythrocytosis has persisted for three years since the initial encounter, and has been treated with phlebotomy alone. Initially the patient received weekly phlebotomies. Currently, the patient receives phlebotomies as needed, with a target hematocrit of less than 45% [1].

2. Discussion

The exon 14 JAK2 V617F mutation is seen in 95% of all PV patients, and approximately 50% of patients with essential thrombocythemia (ET) and primary myelofibrosis (PMF) [2]. About 3% of the patients have JAK2 exon 12 mutations. Patients with exon 12 mutations often present with isolated erythrocytosis and may not meet the diagnostic criteria for polycythemia vera [3–5]. In addition to these mutations, Ma et al. discovered several mutations in the pseudokinase domain coding region of JAK2 including the

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G571S mutation in exon 13 [6].

The JAK2 G571S mutation is next to a tyrosine residue at position 570 (Y570). Y570 lies within the JH2 inhibitory domain and is thought to be the most important phosphorylation site for downregulation of JAK2 activity [7,8]. Biochemical studies show that autophosphorylation of Y570 rapidly downregulates kinase activity. The adjacent G571S mutation may cause a conformational change preventing Y570 phosphorylation, leading to constitutive JAK2 signaling. However, classical *in vitro* studies do not show activation of STAT5 [9] suggesting that the activating effect of the G571S mutation would be weak.

The G571S mutation is extremely rare. In the study by Ma et al. [6] approximately 20,000 blood samples from patients with suspected myeloproliferative neoplasms were analyzed for JAK2 mutations. The G571S mutation was found in only 3 samples, compared to the V617F mutation which was positive in 4280 samples. A recent report describes a family with germline G571S mutations [10], none of whom showed erythrocytosis. The G571S mutation was also found in two patients with “triple-negative” ET and PMF [9].

To our knowledge this is the first case description of a patient with erythrocytosis and a G571S JAK2 mutation. Based on the limited penetrance [10] and *in vitro* studies [9], it is unlikely that the G571S mutation is the sole driver of erythropoiesis. We hope that this report will facilitate additional studies of patients with the G571S and related exon 13 JAK2 mutations, so as to ascertain their role in the pathogenesis of myeloproliferative disorders.

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