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JAK2 exon 12 mutation-positive myeloproliferative neoplasm associated with recurrent thromboembolism

TO THE EDITOR: Detailed analysis of Philadelphia (Ph) chromosome-negative myeloproliferative neoplasms, essential thrombocythemia (ET), and polycythemia vera (PV) paved the way for the recognition of Janus kinase 2 (JAK2) as a potential genetic factor [1]. While most cases of these diseases are related to JAK2 V617F, some are associated with JAK2 exon 12 mutation. JAK2 exon 12 mutation is a rare phenomenon that is not yet well studied. Although, the presence of JAK2 exon 12 mutation is linked to PV and ET, its phenotypic features are not clear, especially in cases without ET and PV. The JAK2 exon 12 G571S variant has also not been studied well, and its phenotypic features are unknown. We present a case of recurrent deep vein thrombosis (DVT) and pulmonary embolism that had a negative coagulation workup, but was positive for JAK2 exon 12 (G571S) mutation. The presented case suggests a possible relationship between JAK2 exon 12 mutation and recurrent thrombosis. While JAK2 V617F is inherently related to thrombotic events, irrespective of the platelet level, JAK2 exon 12 might have similar procoagulant effects. It is hypothesized that further molecular studies can reveal the underlying factors that cause this co-occurrence.

CASE
A 38-year-old Hispanic woman with a past medical history of pulmonary embolism, DVT, and asthma was seen for an evaluation of her recurrent episodes of thrombosis. She had experienced three episodes of DVT and one episode of pulmonary embolism. The first episode of DVT occurred 5 years ago, and the second episode happened 3 years ago. The pulmonary embolism occurred 1 year ago, following her third episode of DVT. Each DVT episode presented with lower leg edema and pain, and was confirmed by lower extremity ultrasound. The pulmonary embolism episodes presented as shortness of breath and low oxygen saturation.

She was given the following medications to take at home: Ipratropium-Albuterol (Duoneb Neb), 3 mL by inhalation every 4 hours as needed, and warfarin sodium (Coumadin), 12 mg orally once daily. However, she was non-adherent to the use of warfarin. The notable aspects of her family history were that her mother had diabetes mellitus and hypertension, while her father had colon cancer at age of 42. She was a current smoker and had been smoking 2 packs of cigarettes daily for 20 years. She denied alcohol and drug use. A review of systems was non-contributory.

A recent complete blood cell count revealed the following: white blood count 11.1×10^9/L, hemoglobin level 14.9 g/dL,
from 350×10⁹/L to 800×10⁹/L, during the last 5 years. Some articles have mentioned that, in order to diagnose ET, it is necessary to have two platelet counts above 600×10⁹/L. However, some patients with JAK2 exon 12 mutation have elevated numbers of megakaryocytes [2]. JAK2 V617F has been associated with thrombotic events, such as Budd-Chiari syndrome. Interestingly, in JAK2 V617F-positive patients, thrombotic events can occur even in the absence of increased red blood cells or platelets [3]. It has been shown that, in comparison with platelet quantity, platelet dysfunction is more important in thrombosis formation. To date, no association has been observed between JAK2 exon 12-positive status (without erythrocytosis or essential thrombosis) and recurrent thrombus events. Limited number of studies regarding JAK2 exon 12 have shown that mutations are more predominantly related to PV, with fewer cases of thrombosis [2].

ET is mainly caused by mutations in exon 9 of CALR, exon 10 of MPL, or JAK2 V617F in more than 90% of cases. The remaining cases are known as “triple negative.” In a recent study, Milosevic Feenstra et al. [4] performed whole-exome sequencing (WES) on samples from eight triple-negative patients. The authors were able to identify somatic mutations in three of the eight patients. For the three patients with clonal hematopoiesis, the analysis showed S204F and V285E mutations in MPL, and G571S mutation in JAK2 exon12. However, Milosevic Feenstra et al. [4] did not describe any thrombotic event in the three patients (including the G571S mutation). Additionally, our case does not satisfy the criteria for ET despite having high-normal platelet levels.

To date, the phenotypic features of the individual mutations of JAK2 exon 12 are understudied and unknown. One study has described five cases of the abovementioned G571S variant [5]. Here, we have reported a case of recurrent DVT and pulmonary embolism in which the patient had a negative coagulation workup, but was positive for JAK2 exon 12 (G571S) mutation. The presented case did not satisfy the criteria for PV and ET, even though our patient had a higher than normal platelet count over several years.

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Letters to the Editor

Is N-acetylcysteine infusion an effective treatment option in L-asparaginase associated hepatotoxicity?

TO THE EDITOR: L-asparaginase is an enzyme whose therapeutic effect has been well documented in children with acute lymphoblastic leukemia (ALL). The drug induces a relative asparagine deficiency that leads to the death of human lymphoblasts [1]. However, the mechanism of L-asparaginase-associated hepatotoxicity is not clear. There are few reports on the treatment of L-asparaginase-associated hepatotoxicity [2-4]. An experimental study conducted by Roesmann et al. [2] reported that when L-carnitine is administered in combination with L-asparaginase for steatosis, carnitine reduces the toxicity associated with L-asparaginase. Alshiekh-Nasany and Douer [3] reported that polyethylene glycol (PEG)-asparaginase related high-grade liver toxicity in adult patients could be rapidly and permanently reversed using the amino acid derivative L-carnitine. Al-Nawalki et al. [4] reported that histopathological macrovesicular steatosis was detected in 3 adult patients who developed L-asparaginase toxicity, and that the hepatotoxicity resolved after administration of carnitine and a vitamin B complex.

L-asparaginase is enzymatically active against glutamine, but with a significantly lower affinity against glutamine than L-asparagine [5]. L-glutaminase activity results in a reduction in the plasma glutamine level [6]. N-acetylcysteine (NAC) increases glutathione and antioxidant pools in hepatic cells, and thus increases the resistance of hepatic cell membranes [7]. Here, we describe a pediatric patient who developed severe hepatotoxicity accompanied by hyperamylasemia, hyperlipidemia, and elevated transaminase and bilirubin levels following the administration of 5 doses of L-asparaginase, and the parameters that were resolved following NAC infusion.

In the 2.5-year-old patient who was being followed-up after a diagnosis of pre-B ALL, induction therapy was initiated with a combination chemotherapy regimen comprising 60 mg/m² prednisolone (oral) (days 1–33), 1.5 mg/m² vincristine and 30 mg/m² daunorubicin (days 7, 15, 22, and 29), and 5,000 μm² L-asparaginase (E. Coli-Asp) (8 doses) (days 12, 15, 18, 21, 24, 27, 30, and 33). After the fifth L-asparaginase administration, the patient’s laboratory results were as follows: alanine transaminase (ALT) 501 IU/L, aspartate transaminase (AST) 664 IU/L, gamma-glutamyl transferase (GGT) 1,297 IU/L, alkaline phosphatase (ALP) 246 IU/L, total/direct bilirubin 7/6.09 mg/dL, total cholesterol 272 mg/dL, triglyceride 571 mg/dL, and amylase 146 IU/L. The patient’s clinical findings rapidly deteriorated, and abdominal distention and hepatomegaly were observed. Oral feeding was discontinued, and antibiotic (carbapenem and teicoplanin) and antifungal therapy (liposomal amphotericin B) was initiated. Tests for hepatitis A, B, and C, cytomegalovirus, Epstein Barr virus, parvovirus, and human immunodeficiency virus serology returned negative results. There was no growth in blood cultures. Abdominal computerized tomography revealed an increased liver size and density due to hepatosteatosis (Fig. 1). Drug-related toxic hepatitis was considered because of the progressively increased serum transaminase, bilirubin, amylase, and triglyceride levels. Liver biopsy could not be performed. The sixth dose of L-asparaginase was omitted. The NAC was started at a dose of 150 mg/kg for the first hour, 50 mg/kg for a subsequent 4 hours, and 100 mg/kg for the remaining 16 hours. Our patient received NAC infusion at a dose of 100 mg/kg/day over 4 days. The seventh administered dose of L-asparaginase was reduced by 50%. However, on day 2 of therapy, serum ALT was 689 IU/L, AST was 397 IU/L, and ALP was 302 IU/L. NAC therapy was re-started at an oral dose of 10 mg/kg daily and after the sixth day of NAC therapy, serum transaminase levels decreased to

Fig. 1. Abdominal computed tomography showed a hepatomegaly and hepatosteatosis.