Implications of Janus Kinase 2 Mutation in Embolic Stroke of Unknown Source

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The role of genetic mutations in cerebral ischemia is not completely understood. Among these genetic variations, Philadelphia-negative gain-of-function mutation in the janus kinase 2 (JAK2) protein leads to overexpression of the genes involved in cell growth and proliferation, and has been linked to development of hematological malignancies, specifically, myeloproliferative neoplasms (MPNs; essential thrombocythemia [ET], polycythemia vera [PV], and primary myelofibrosis). Overt ET and PV are known to induce a prothrombotic state that leads to development of vascular complications, including cerebral arterial or venous thrombosis. Thromboembolism can precede overt presentation of an MPN by 2-3 years. As such, for the selected cases of embolic stroke or cerebrovascular sinus thrombosis with otherwise undetermined source and persistent thrombocytosis or polycythemia, in the absence of a confirmed MPN diagnosis, screening for JAK2 mutation may be reasonable, as early diagnosis and appropriate treatment can influence outcome by preventing recurrent thrombotic events. In this article, we review the literature on the genetics, pathogenesis, clinical manifestations, and treatment of JAK2-associated thrombosis, and present 2 cases of JAK2-associated cerebral arterial infarction and cerebral and systemic venous thromboembolism with otherwise negative etiology workup for stroke.

Key Words: JAK2 mutation—stroke—cerebral sinus thrombosis—myeloproliferative neoplasms

Introduction

Stroke is the leading cause of disability and the fifth leading cause of death in the United States.[1] Hypertension, diabetes, tobacco use and other traditional vascular risk factors are known to increase the risk of stroke. The role of genetic mutations in cerebral ischemia, however, is less clearly established. In recent years, a genetic mutation of the Janus kinase 2 (JAK2) protein has been associated with arterial and/or venous thrombosis.[2] The role of JAK2 mutations in cerebral ischemia of unknown origin has not been well described. Here we present 2 cases of JAK2 gene mutation-associated cerebral and systemic arterial and venous occlusions, and review the pathogenesis and treatment of JAK2-associated thrombosis.

Case 1

An 81-year-old woman presented to an outside hospital for evaluation of 2-week duration of left-sided periorbital pain and swelling. Her prior medical history was significant for hypertension, diabetes, and hyperlipidemia but had no previous history of thrombosis, known cancer, or recurrent miscarriages. The original evaluation included laboratory analyses, which revealed persistent thrombocytosis above 500,000/mm^3 throughout hospital stay (max value 573,000/mm^3), mild anemia with averaged hemoglobin levels of 10.5 g/dL and normal ranges for iron (40 μg/dL) and ferritin (102 ng/mL) levels; few schistocytes were present on peripheral smear. Erythrocyte sedimentation rate was slightly increased, 34 mm/hr, and the patient had a normal C-reactive protein level (0.59 mg/dL). Initial contrast enhanced computed tomography (CT) and magnetic resonance imaging (MRI) of the brain and orbits revealed significant edema of the intra- and extraconal fat, enlargement and enhancement of the extraocular muscles,

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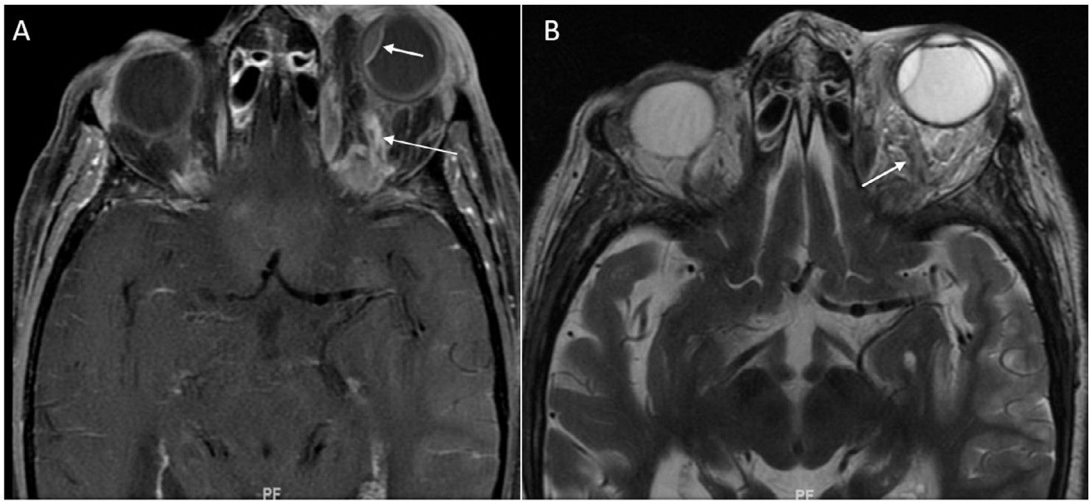

Figure 1. *Contrast enhanced magnetic resonance imaging. (A) Axial T1-weighted image of the orbits showing the presence of a thrombus in the left superior ophthalmic vein (white long arrow) and choroidal detachment with underlying hemorrhage (short white arrow). (B) Axial T2-weighted image of the orbits showing significant edema of the intra- and extraconal fat and periorbital edema with proptosis of the left eye. The superior ophthalmic vein is enlarged and thrombosed (white arrow).*

choroidal detachment with underlying hemorrhage, and thrombosis of the left superior ophthalmic vein and left cavernous venous sinus (Fig 1). In addition, her initial MRI revealed a left ischemic cerebellar stroke. Patient underwent digital subtraction cerebral angiogram (DSA) that revealed a left-sided carotid-cavernous fistula with retrograde flow into the thrombosed superior ophthalmic vein (Fig 2). Within the next 24 hours, the patient developed a new right hemiplegia. A new MRI brain revealed scattered areas of ischemia in both cerebellar and cerebral hemispheres and acute thrombosis of the left middle cerebral artery (Fig 3), which was treated with mechanical thrombectomy. Due to the presence of arterial and venous thromboses, the patient underwent additional workup with CT of the chest, abdomen, and pelvis, hypercoagulable and rheumatologic assessments, transthoracic echocardiography, and lower extremity Doppler. These studies were negative for cardiac sources of embolism, occult malignancy, or procoagulability. The patient was eventually transferred to our tertiary center for higher level of care. The general exam was significant for left-sided periorbital edema and lagophthalmos. The neurologic exam on admission was pertinent for partial global aphasia and right hemiplegia. Repeat blood work was significant for persistent thrombocytosis and mild anemia. Antiphospholipid antibody titers and protein C, protein S, and antithrombin III levels were normal. Genetic

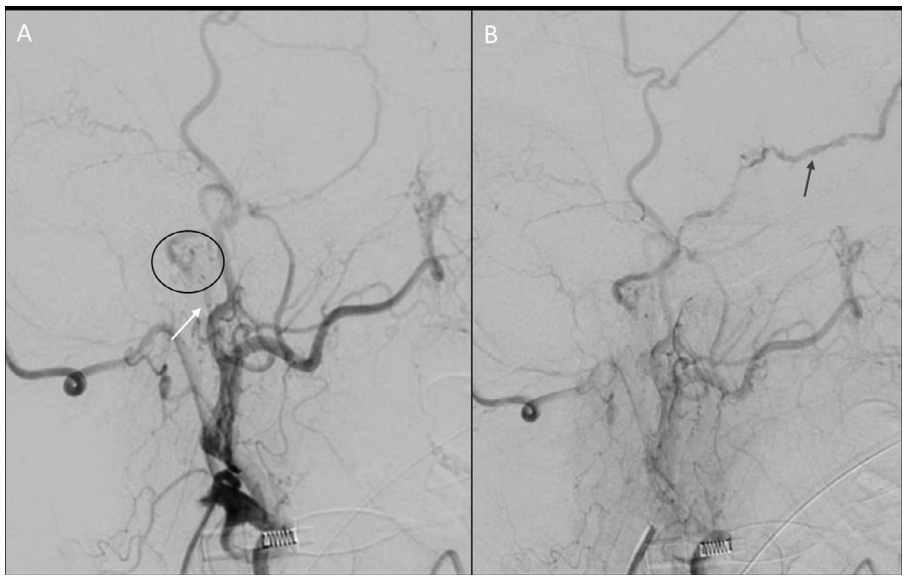

Figure 2. *Digital subtraction angiography. Time elapsed anteroposterior views of the arterial (A) and venous phases (B) after left external carotid artery injection, showing a carotid-cavernous fistula fed by the ascending pharyngeal branches (white arrow) into the inferior petrosal sinus (black circle) and ultimately with venous reflux to superior ophthalmic vein (black arrow).*