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A JAK2-positive essential thrombocythemia revealed by a brainstem ischemic stroke: A case report

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Abstract
Essential thrombocythemia (ET) is a rare yet notable risk factor for ischemic stroke. Early detection and effective management of ET play pivotal roles in preventing stroke recurrence. Antithrombotic therapy is based on low-dose aspirin for ET patients with higher risk, and those with Janus Kinase 2 (JAK2) mutation. The present case reports a 68-year-old man presenting with ataxia, acute vertigo and dysphagia consistent with Wallenberg syndrome due to brainstem ischemic stroke. Laboratory analysis revealed elevated platelet and leukocyte counts. A positive JAK2 mutation examination and bone marrow biopsy confirmed the diagnosis of ET. Notably, these cerebrovascular events were the first manifestations of ET. This case underscores the need for careful screening of complete blood counts in patients with ischemic stroke, as early recognition and management of the underlying ET can significantly impact patient outcomes.

Keywords: Ischemic stroke, Wallenberg syndrome, Essential thrombocythemia, Janus Kinase 2, Brainstem infarction, Myeloproliferative Neoplasm.

Introduction
Essential Thrombocythemia (ET) is an underrecognized cause of ischemic stroke. ET is a chronic Philadelphia-negative Myeloproliferative Neoplasm (MPN), characterized by marked thrombocytosis, thrombotic and hemorrhagic risk and constitutional symptoms [1]. Abnormal megakaryopoiesis and platelet dysfunction in ET contribute to thrombus formation, particularly in the cerebrovascular system, leading to ischemic stroke and other thrombotic events [2].
Early detection and timely treatment of ET are crucial role in preventing stroke recurrence and mitigating neurological deficits. This case report discusses a brainstem ischemic stroke, emphasizing the importance of screening for ET in strokes of unknown cause through comprehensive patient history, clinical examination, and systematic blood count analysis.

Case presentation
A 68-year-old male was admitted to the emergency department with a 12-hour history of gait ataxia with sudden-onset vertigo, vomiting, nausea, hiccups, and swallowing difficulties. There was no loss of consciousness or seizure. His medical history included hypertension and type 2 diabetes. He had quit smoking 20 years ago, and denied any current alcohol or illicit drug use.
Upon examination, the patient was found to be conscious and well-oriented, with stable vital signs. Neurological examination revealed severe ataxia, rendering walking and standing impossible, while the muscle strength and tone were intact in all limbs. Deep tendon reflexes were normal, and there was no Babinski sign. Impaired pain and thermal sensations were noted on the left trunk and limbs, sparing the left half of the face, with preserved tactile, arthrokinetic, and vibratory sensations. Cranial nerve examination revealed impaired pain and thermal sensation in the right half of the face, gaze-evoked horizontal nystagmus without ophthalmoplegia, absence of gag reflex, severe dysphagia, dysphonia, and uvula deviation to the left. These findings are indicative of Wallenberg syndrome.
An urgent non-enhanced brain scan revealed multiple chronic lacunar lesions located in the internal capsule and lenticular nucleus bilaterally, and in the left centrum semiovale; however no recent ischemic lesions were identified (Figure 1). Brain magnetic resonance imaging (MRI) revealed an acute infarct involving the right lateral part of the medulla (Figure 2).

The MRI also showed hyperintense T_2 and Fluid-attenuated inversion recovery (FLAIR) periventricular signals related to leukoaraiosis. The patient was not a candidate for a revascularization intervention. He was started on aspirin 160mg daily and transferred to the stroke department.

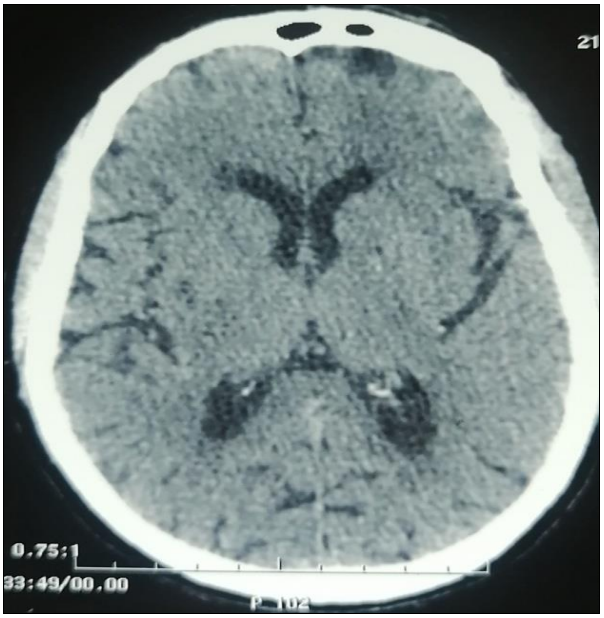

Fig 1: Non-enhanced brain scan demonstrating multiple chronic lacunar lesions in the internal capsule and the lenticular nucleus bilaterally and in the left centrum semiovale.

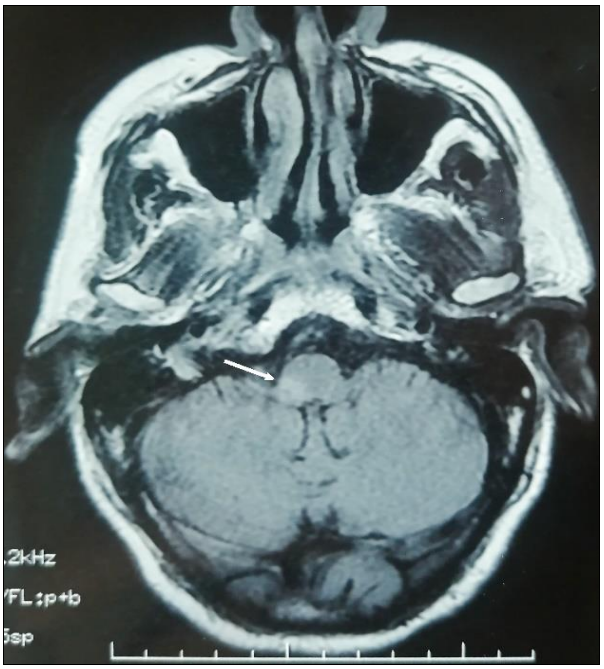

Fig 2: Axial FLAIR sequence of cerebral MRI showing acute infarct involving the right lateral part of medulla (white arrow).

Routine admission blood tests revealed abnormal blood counts, with a platelet count of 1,165x10^9/L total leukocyte count of 22,1x10^9/L, and hemoglobin level of 17 g/dl. Platelet and leukocyte count elevations persisted in subsequent blood tests, while a peripheral blood smear revealed thrombocytosis. Full cardiac work-up, including Holter monitoring, transthoracic echocardiogram and Doppler ultrasound of the supra-aortic trunks, revealed no abnormalities. A comprehensive metabolic panel and sepsis work up were negative.

Following a hematologist consultation, markers of clonal thrombocytosis were studied. A JAK2 mutation was found, with no detection of mutations in BCR-ABL1, calreticulin and myeloproliferative leukemia virus. Other causes of reactive thrombocytosis were ruled out. Bone marrow biopsy found hypercellular marrow with a significant increase of large mature megakaryocytes. Based on these findings, the patient was diagnosed with ET.

The patient underwent regular functional and balance rehabilitation sessions during hospitalization, which resulted in a noticeable improvement of balance. He was discharged on day 12 with prescriptions for aspirin 160mg and atorvastatin 20mg daily. He was also referred to the hematology department for further evaluation and management. Antithrombotic therapy was subsequently optimized with the addition of hydroxyurea. At the six-month follow-up, the patient remained stable and exhibited no new symptoms.

Discussion

Essential Thrombocythemia (ET) is a myeloproliferative neoplasm (MPN) associated with elevated platelet counts, increased risks of thrombosis and hemorrhage, and a range of constitutional symptoms [1]. Accurate diagnosis of ET involves the exclusion of other causes of thrombocytosis, such as infections, blood loss, iron deficiency, inflammation, malignancy and post-splenectomy state [2]. The World Health Organization (WHO) has established a classification system incorporating major and minor criteria to distinguish ET from other MPNs [3]. A diagnosis of ET requires meeting all four major criteria or the first three major criteria along with one minor criterion (Table 1).

Table 1: World Health Organization criteria for Essential Thrombocythemia [3]

Major criteria
Platelet count ≥450 ×10*9/L
Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers.
Not meeting WHO criteria for BCR-ABL1 + CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms
Presence of JAK2, CALR, or MPL mutation
Minor criterion
Presence of a clonal marker or absence of evidence for reactive thrombocytosis
ET: Essential Thrombocythemia; PMF: Primary Myelofibrosis; PV: Polycythemia Vera; CML: Chronic Myeloid Leukemia

Thrombotic complications are common in patients with MPNs. According to a study by Frederiksen *et al*., the 5-year risk of vascular disease in patients with MPNs ranges from 0.5% to 7.7%, significantly higher than in the general population [4]. Additionally, multiple or recurrent territorial infarcts are among the indicators suggesting MPNs as a cause of stroke [5]. In recent years, the development and validation of a scoring system known as IPSET-thrombosis has allowed clinicians to identify ET patients with high risk of thrombosis [6, 7]. It incorporates age > 60 years, cardiovascular risk factors, previous thrombotic events, and the presence of JAK2 mutation. A score of 3 and higher indicates a high risk for recurrent thrombosis.

Currently, no specific recommendations exist for the management of acute ischemic stroke in patients with ET concerning thrombolysis or endovascular thrombectomy [8]. The treatment algorithm for ET patients emphasizes a thorough evaluation of cardiovascular risk factors and the administration of low-dose aspirin, provided there are no contraindications [9]. For those with high-risk disease, a combination of low-dose aspirin and cytoreductive therapy is recommended [10].

In our case, the patient presented with a lateral medullary syndrome, also known as Wallenberg syndrome. Neuroimaging in our patient revealed multiple chronic lacunar lesions and leukoaraiosis, in addition to an acute infarct involving the right medulla, suggesting the occurrence of several cerebrovascular events. The patient was at high risk for recurrent stroke event with an IPSET-thrombosis score of 6. Thus, he received once-daily aspirin and cytoreductive therapy (hydroxyurea).

Our case highlights a patient presenting with Wallenberg syndrome due to brainstem ischemic stroke, leading to the diagnosis of ET. In patients with ischemic stroke, complete blood counts should be performed upon admission, with careful screening for elevated platelet counts or leukocytosis. Confirmation of an ET diagnosis should involve a hematologist to initiate appropriate treatment.

Conclusion

Essential thrombocythemia is a seldom-recognized etiology for ischemic stroke. Blood counts in patients with ischemic stroke should be carefully evaluated to detect elevated platelet counts. Genetic screening and bone marrow biopsy are necessary to establish a definitive diagnosis of ET, and low-dose aspirin remains the cornerstone of antithrombotic therapy.

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Conflict of Interest

None declared.

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Informed consent

Written consent was obtained from the patient for publication.

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