CALR-Positive Essential Thrombocytosis Presenting With Microvascular Neuropathy: A Case Report

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ABSTRACT
Essential thrombocytosis (ET) is a chronic myeloproliferative neoplasm characterized by sustained thrombocytosis and megakaryocytic proliferation in the bone marrow. Although vasomotor symptoms such as headaches and erythromelalgia are well recognized, peripheral neuropathy as an initial manifestation remains uncommon. We describe a 55-year-old woman who presented with progressive burning limb pain and distal sensory disturbances. Laboratory testing revealed marked thrombocytosis and moderate anemia, and molecular analysis confirmed a CALR mutation. Bone marrow examination demonstrated typical megakaryocytic hyperplasia with hyperlobulated forms and minimal reticulin fibrosis. Her symptoms were attributed to microvascular ischemic injury affecting the peripheral nerves. This case highlights the importance of recognizing atypical neurological manifestations in CALR-mutated ET and reinforces the diagnostic value of molecular testing in distinguishing ET subtypes.

Keywords: *Essential thrombocytosis, CALR mutation, Peripheral neuropathy, Microvascular complication, Thrombocytosis*
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INTRODUCTION

Essential thrombocytosis belongs to the group of Philadelphia chromosome–negative myeloproliferative neoplasms characterized by clonal platelet overproduction. It is defined by persistent elevation of platelet counts, characteristic megakaryocytic morphology, and the presence of driver mutations such as JAK2 V617F, CALR, or MPL. Most CALR mutations involve exon 9 insertions or deletions, resulting in an abnormal calreticulin protein that aberrantly activates the thrombopoietin receptor (MPL). Patients with CALR-mutated ET usually present at a younger age and tend to have a lower risk of arterial thrombosis when compared with JAK2-positive disease, despite harboring higher platelet counts.

Neurological manifestations in ET are usually related to microvascular disturbances. Vasomotor symptoms arise from abnormal platelet activation and transient occlusion of small vessels. Although headaches, visual aura, and erythromelalgia are frequently reported, ischemic neuropathy is less well documented. This case adds to the limited literature on peripheral neuropathy associated with CALR-positive ET and underscores the need for clinicians to consider myeloproliferative disorders in patients with unexplained neuropathic symptoms and thrombocytosis.

CASE PRESENTATION

A 55-year-old woman presented with a one-week history of worsening burning pain in her extremities, associated with tingling and distal numbness. She reported experiencing mild limb discomfort for nearly a year, but the symptoms had intensified significantly. There was no history of diabetes, alcohol use, nutritional deficiency, toxin exposure, or prior neurological illness. Her vital signs were stable, and general examination showed no hepatosplenomegaly.

Neurological evaluation revealed distal sensory impairment to pinprick and vibration, while motor strength and deep tendon reflexes were preserved. Peripheral pulses were intact bilaterally.

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Laboratory investigations demonstrated:

- Hemoglobin: 8 g/dL (moderate anemia)
- Platelet count: $9.27 \times 10^5/\mu L$ (severe thrombocytosis)
- White cell count: within normal limits
- Vitamin B12: within normal limits
- Renal and hepatic function: normal
- Peripheral smear showed marked thrombocytosis with large platelets

Nerve conduction studies indicated sensory-predominant axonal neuropathy. Molecular testing was positive for a CALR mutation, while tests for JAK2 V617F and MPL mutations were negative.

BONE MARROW BIOPSY FINDINGS

Bone marrow biopsy showed a normocellular marrow for age with marked megakaryocytic hyperplasia. Megakaryocytes appeared large with hyperlobulated, sometimes "staghorn-like" nuclei, a morphological pattern consistent with CALR-mutated ET. Erythroid and granulocytic lineages were unremarkable. Reticulin staining demonstrated minimal fibrosis (MF-0/1), effectively excluding prefibrotic myelofibrosis. No increase in blast forms was observed. These findings reinforced the diagnosis of essential thrombocytosis in conjunction with the patient's clinical and molecular profile.

The constellation of severe thrombocytosis, microvascular symptoms, sensory neuropathy, and CALR positivity supported a diagnosis of ET-associated microvascular neuropathy.

EXPANDED DISCUSSION

CALR mutations have reshaped the understanding of ET by identifying a biologically distinct subgroup with unique clinical features. The mutation results in a truncated calreticulin protein that aberrantly interacts with the MPL receptor, activating downstream JAK-STAT signalling and driving sustained megakaryocyte proliferation. Patients with CALR mutations typically exhibit higher platelet counts but a comparatively lower risk of thrombosis relative to JAK2-positive patients.

Microvascular symptoms in ET arise from platelet-rich microthrombi within small vessels. Vasomotor events such as erythromelalgia, livedo reticularis, or transient neurological episodes result from transient vascular obstruction and dysregulated platelet function. Peripheral neuropathy, although infrequent, is believed to develop through repeated ischemic insults to the vasa nervorum. Chronic ischemia compromises nerve perfusion, leading to axonal injury, as reflected in this patient's electrophysiological findings.

The differential diagnosis of sensory neuropathy is broad and includes diabetic neuropathy, nutritional deficiencies, autoimmune neuropathies, toxic exposures, and hereditary neuropathies. In this patient, the absence of common risk factors and the presence of marked thrombocytosis prompted evaluation for an underlying myeloproliferative neoplasm.

Bone marrow examination is critical for establishing the diagnosis and distinguishing ET from early myelofibrosis. The characteristic megakaryocytic morphology in CALR-mutated ET includes large, mature megakaryocytes with hyperlobulated nuclei, often described as "staghorn-like," which was evident in this case. The lack of significant reticulin fibrosis helps differentiate ET from prefibrotic myelofibrosis.

Management of ET is tailored based on risk stratification, symptom burden, and mutation profile. Low-dose aspirin is effective in alleviating microvascular symptoms, while cytoreductive therapy is indicated for high-risk patients or those with significant symptomatology. Hydroxyurea remains first-line therapy, though interferon-α is an alternative for younger individuals and those intolerant to hydroxyurea. Monitoring for potential progression to myelofibrosis or leukemic transformation is essential, although such evolution is less frequent in CALR-positive disease.

This case highlights the importance of considering ET as a cause of otherwise unexplained peripheral neuropathy, particularly when accompanied by hematological abnormalities. Early recognition and intervention can prevent further microvascular complications and improve quality of life.

CONCLUSION

CALR-positive essential thrombocytosis is a unique myeloproliferative neoplasm that may present with atypical neurological manifestations such as peripheral neuropathy. Microvascular ischemia caused by excessive platelet activation likely underlies this complication. Comprehensive evaluation—including molecular testing and bone marrow examination—is crucial for timely diagnosis. Early treatment aimed at reducing platelet activity and burden can mitigate microvascular symptoms and prevent progression.

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