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LEUKOCYTOCLASTIC VASCULITIS IN JAK2-POSITIVE ESSENTIAL THROMBOCYTHEMIA: A CASE OF CYTOKINE-DRIVEN URTICARIAL RASH RESPONSIVE TO RUXOLITINIB

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ABSTRACT

Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm characterised by sustained thrombocytosis and frequently associated with JAK2 V617F mutations. It is primarily known for its thrombotic and haemorrhagic complications, which dominate its clinical presentation. However, inflammatory and dermatologic manifestations are uncommon and less well recognised. Among these, cutaneous vasculitis – particularly leukocytoclastic vasculitis (LCV) – is a rare and underreported feature. We present the case of a 54-year-old woman with JAK2-positive ET who developed a persistent urticarial rash that coincided with worsening thrombocytosis. Bone marrow biopsy revealed megakaryocytic hyperplasia, confirming the diagnosis of ET. Initially, the patient responded to hydroxyurea, but her disease eventually became refractory, and anagrelide failed to control either her platelet count or symptoms. Her skin rash progressed in parallel with uncontrolled thrombocytosis, and biopsy confirmed LCV. Initiation of ruxolitinib, a JAK1/2 inhibitor, led to haematologic improvement and complete resolution of the vasculitis. This case highlights a rare but clinically significant association between ET and cutaneous vasculitis and suggests a potential role for JAK inhibition in managing such refractory inflammatory manifestations.

KEYWORDS

Essential thrombocythaemia, leukocytoclastic vasculitis (LCV), JAK2 mutation, ruxolitinib, urticarial rash

LEARNING POINTS

- Cutaneous vasculitis is a rare but significant manifestation of essential thrombocythemia.
- Leukocytoclastic vasculitis may present with urticarial lesions resistant to standard therapy.
- Janus kinase (JAK) inhibition with ruxolitinib can achieve both haematologic and dermatologic remission in refractory cases.

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INTRODUCTION

Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm marked by clonal proliferation of megakaryocytes and persistent elevation in platelet counts. JAK2 V617F mutations are identified in approximately 50–60% of cases, activating the JAK-STAT pathway and contributing to both thrombocytosis and systemic inflammation. While vasomotor symptoms such as erythromelalgia are common in ET, cutaneous vasculitis is rarely reported. Leukocytoclastic vasculitis (LCV), an immune-complex mediated small-vessel vasculitis, can manifest as urticarial or purpuric skin lesions, and may indicate underlying systemic or neoplastic processes. We describe a case of JAK2-positive ET complicated by LCV that was resistant to first-line therapies, but resolved completely with ruxolitinib.

CASE DESCRIPTION

A 54-year-old Hispanic woman with a history of gastroesophageal reflux disease who presented to the clinic with fatigue of 6 months duration. Initial laboratory work showed white blood cell count of 4.5, haemoglobin 17.7 g/dL, haematocrit 50.1% and platelets 700 $\times 10^3$/µl. Additional testing included erythropoietin which was within normal limits and a bone marrow biopsy which revealed hypercellular marrow (~70–80%) with prominent megakaryocytic hyperplasia, increased large, mature megakaryocytes with hyperlobulated nuclei, and no significant erythroid or granulocytic abnormalities. Reticulin staining showed no significant fibrosis (MF-0). These findings were consistent with ET, and JAK2 V617F came back positive. Her initial treatment plan included hydroxyurea, which initially controlled her platelets. On later follow-up, she had developed a five-month history of recurrent, pruritic, non-blanchable urticarial rash affecting her trunk and extremities *(Fig. 1)*. The rash appeared as erythematous wheals and worsened with warm showers. Individual hives would last more than 24 hours. The onset of the rash was concurrent with lack of efficacy of hydroxyurea, which had effectively controlled her platelet count for the first year after diagnosis.

Over time, the patient reported increased frequency and severity of the rash coinciding with progressive thrombocytosis. At presentation, her platelet count had risen to 765 $\times 10^3$/µl.

Initial workup for systemic autoimmune or allergic disease, including anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, complement components C3 and C4, total complement activity (CH50), erythrocyte sedimentation rate, C-reactive protein, tryptase and total immunoglobulin E was negative. Serologic testing for hepatitis B, hepatitis C and HIV was non-reactive.

Despite titration of hydroxyurea to maximal tolerated dose, the patient's platelet count remained uncontrolled, and her rash intensified. She was transitioned to anagrelide, but within weeks developed worsening symptoms including fatigue and persistent urticarial flares. A dermatologic skin biopsy demonstrated perivascular neutrophilic infiltration with leukocytoclasia and fibrinoid necrosis – consistent with LCV *(Fig. 2)*.

Given her ongoing symptom burden and cytorefractoriness, a shared decision was made to initiate ruxolitinib and within four weeks, her platelet count decreased to <400 $\times 10^3$/µl, and her urticarial vasculitis resolved entirely. She remained in remission at six-month follow-up, with no recurrence of skin lesions or systemic symptoms.

DISCUSSION

Essential thrombocythemia (ET) is a myeloproliferative neoplasm characterised by sustained thrombocytosis and frequent mutations in JAK2, CALR or MPL genes. It is primarily associated with thrombotic complications, haemorrhagic events and vasomotor symptoms[1]. Cutaneous manifestations are well documented but are often underrecognised, particularly when they reflect inflammatory or immune-mediated processes rather than microvascular ischaemia.

Classically, ET-related skin findings are attributed



Figure 1. Raised urticarial lesions on the legs and abdomen, respectively.

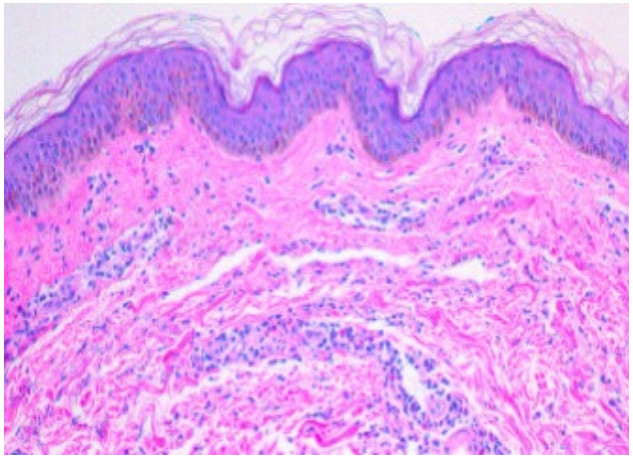


Figure 2. Skin with superficial perivascular neutrophilic infiltrate.

to microvascular occlusion and platelet-mediated thrombosis. These include livedo reticularis, acrocyanosis, erythromelalgia and painful digital ischaemia. Erythromelalgia, a hallmark vasomotor symptom, manifests as episodic burning pain and erythema in the extremities and is relieved by aspirin – suggesting a platelet aggregation–mediated mechanism. Petechiae and purpura may also occur, especially in cases of extreme thrombocytosis or when platelet dysfunction impairs haemostasis. However, true vasculitic lesions, especially histologically confirmed LCV, are rare.

LCV is a small-vessel vasculitis resulting from immune-complex deposition and subsequent complement activation. It typically presents with palpable purpura or urticarial lesions that last longer than 24 hours and often leave residual pigmentation. In the context of haematologic malignancies, particularly myelodysplastic syndromes or chronic lymphocytic leukaemia, LCV has been described as a paraneoplastic manifestation. However, in ET, reports are exceedingly rare. A limited number of case series and isolated reports have identified vasculitis, often urticarial or ulcerative in nature, as a potential but poorly understood manifestation. For instance, Itin and Winkelmann (1991) reported non-specific skin lesions in ET patients but did not confirm vasculitis histologically[2]. Similarly, Velasco et al. (1991) described ulceronecrotic lesions in ET but without specific pathologic correlation[3].

The novelty of this case lies in the convergence of histologically confirmed LCV with uncontrolled thrombocytosis and the failure of conventional therapies such as hydroxyurea and anagrelide. The patient's rash was urticarial, non-blanchable and persistent, and worsened in parallel with rising platelet counts, suggesting a cytokine-driven inflammatory mechanism. Notably, the skin lesions were unresponsive to antihistamines or steroids, further supporting a non-allergic aetiology.

What distinguishes this report is the patient's robust response to ruxolitinib, a JAK1/2 inhibitor with dual action on clonal haematopoiesis and cytokine modulation. Ruxolitinib is approved for myelofibrosis and polycythaemia vera, and while its use in ET is off-label in some regions, emerging evidence supports its benefit in hydroxyurea-refractory or intolerant cases[4]. The resolution of LCV with ruxolitinib strongly implicates JAK-STAT pathway activation and downstream cytokine release as key mediators of the inflammatory process.

This case underscores a few critical clinical insights. First, cutaneous symptoms in ET – particularly when atypical or treatment-refractory – should prompt consideration of vasculitis and trigger skin biopsy[5]. Second, the temporal association between disease activity and inflammatory skin lesions supports a mechanistic link between clonal haematopoiesis and immune dysregulation. Finally, targeted JAK inhibition may serve not only as cytoreductive therapy but also as an immunomodulatory strategy for ET patients with systemic inflammatory complications.

In conclusion, while thrombotic and haemorrhagic risks dominate the clinical landscape of ET, inflammatory and immune-mediated phenomena such as LCV represent underappreciated facets of disease burden. This case provides evidence that ruxolitinib may offer therapeutic value beyond cytoreduction, particularly in patients with inflammatory complications refractory to standard agents. Greater awareness of these manifestations may facilitate earlier recognition, appropriate biopsy and tailored therapy, ultimately improving patient outcomes.

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