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## Case Presentation

### Drug-associated skin lesions in a patient with myelofibrosis receiving ruxolitinib

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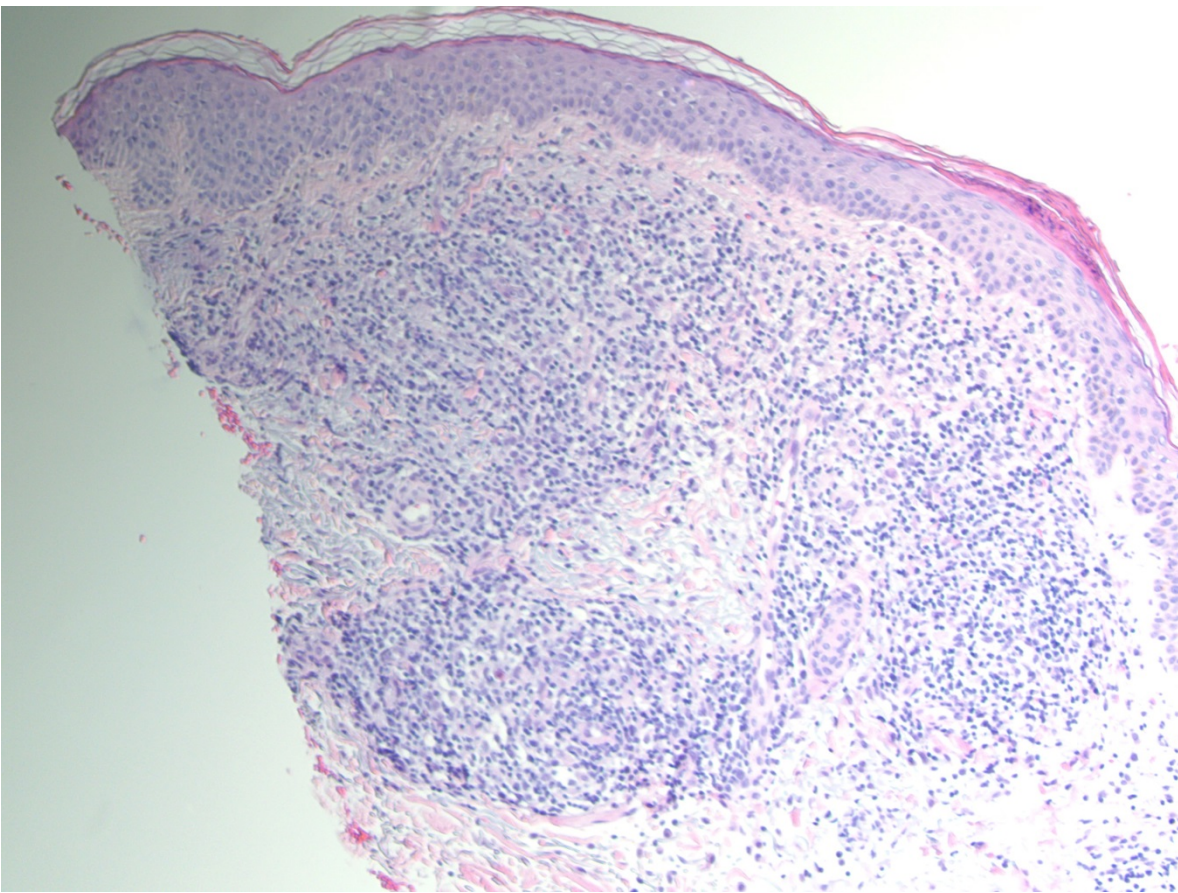
## Abstract

Ruxolitinib, a small molecule JAK-1/2 inhibitor, was approved by the U.S. Food and Drug Administration (FDA) in November 2011, as the first therapeutic for the treatment of intermediate and high-risk myelofibrosis. The Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway is one of the most well-studied intracellular signaling networks. Recent advances in our understanding of the complexities of signal activation and regulation of gene expression has provided opportunities for targeted therapeutic interventions. Although numerous inhibitors of the JAK/STAT pathway are currently being evaluated in clinical trials, ruxolitinib represents the first FDA approved in-class JAK inhibitor. We report a drug eruption associated with ruxolitinib.

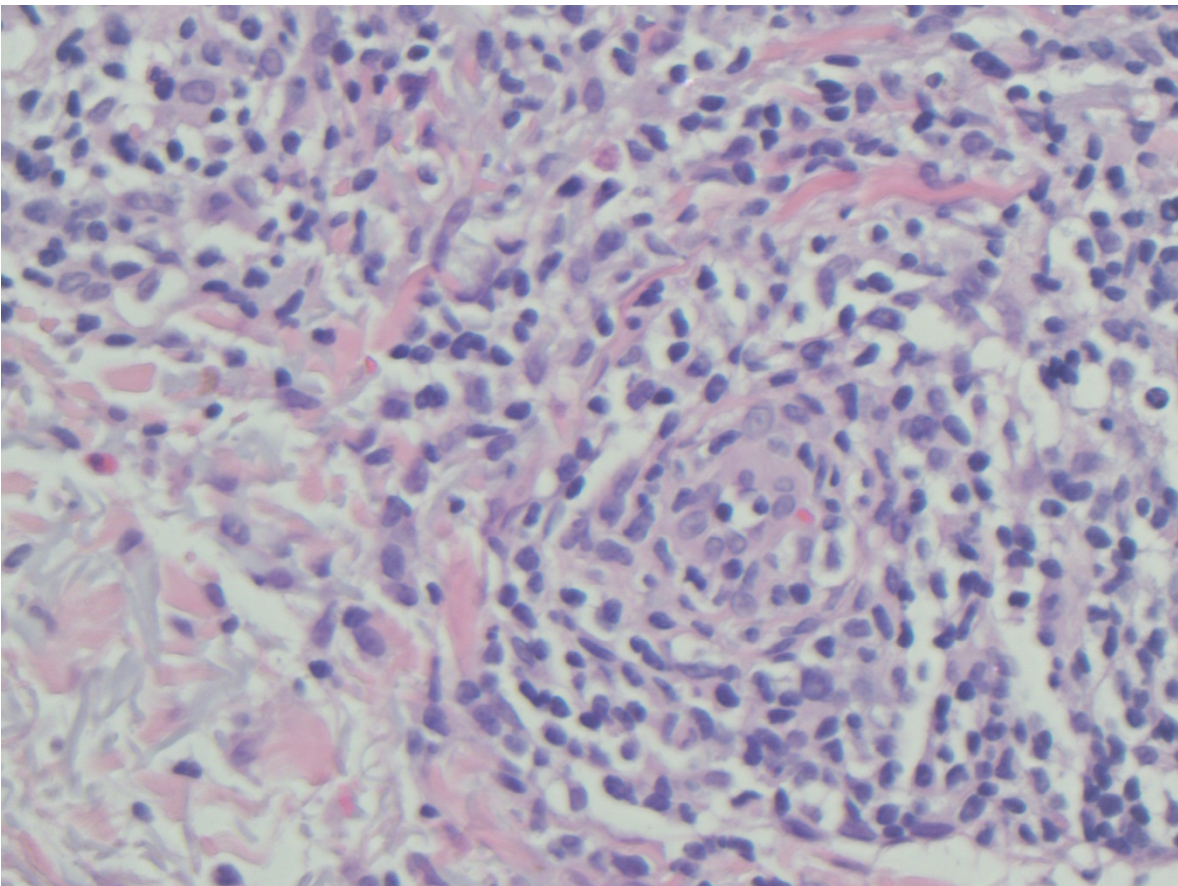
## Case Synopsis

A 61-year-old man presented with a 2-week history of pruritic erythematous macules and papules on the trunk and extremities. On physical examination, confluent erythematous macules and papules in a symmetric distribution were seen on the chest, back, and upper and lower extremities, sparing the palms and soles. The patient also reported a new history of lower leg swelling within the previous two weeks, and 2+ pitting edema of the legs and arms was present on examination. The patient had a fifteen year history of polycythemia vera, that converted to myelofibrosis several years prior to presentation. He also had a history of diabetes mellitus, hypertension, and renal insufficiency. He had no prior dermatologic history. The patient began ruxolitinib (a JAK 1/2 inhibitor) 20mg twice daily, three weeks prior to the appearance of the morbilliform eruption. The only medication change within the prior 6 months was a switch to linagliptin from sitagliptin, both glipizides, with identical mechanisms of actions.

A skin biopsy of the left arm revealed superficial and deep perivascular granulomatous inflammation, composed of lymphocytes, histiocytes, rare foreign body giant cells, and scattered eosinophils. (Figure 1). PAS, Fite, and AFB stains were negative for fungal and mycobacterial organisms. Alcian Blue with and without hyaluronidase digestion demonstrated no increase in mucin. The patient's clinical presentation was consistent with a drug eruption, and the histopathologic findings in this clinical setting suggested a diagnosis of a granulomatous drug reaction. The patient began a slow taper of ruxolitinib (tapered off over 5 weeks), and started triamcinolone 0.1% cream, applied twice daily. The patient presented in follow-up one week later, with persistence of the morbilliform eruption on the trunk (now with more confluent macules and papules and with fine scale), and an exfoliative dermatitis on the extremities, with widespread scaling and confluent erythema (Figure 2). Oral steroids and emollients were started at this time, and he continued with the ruxolitinib taper.



**Figure 1a.** Histological Image 10x. Examination reveals a superficial and deep granulomatous perivascular infiltrate (hematoxylin-eosin, original magnification x 4)



**Figure 1b.** Histological Image 40x. The infiltrate is composed of lymphocytes, histiocytes, rare foreign body giant cells, and scattered eosinophils (hematoxylin-eosin, original magnification x 40)



**Figure 2.** Confluent erythematous macules and papules in a symmetric distribution were seen on the chest and back, with fine scale present. Widespread confluent erythema and scale were present on the arms and legs

Two weeks later (the patient was still receiving ruxolitinib, as the taper of the medication continued), his skin condition had markedly improved, but the erythema did not resolve completely, and similar lesions reappeared following the withdrawal of steroids. A second skin biopsy was performed on the right arm and also revealed superficial and deep perivascular granulomatous inflammation, and the infiltrate was also primarily lymphohistiocytic. No clonal T cell population was identified by T-cell receptor gene rearrangement studies. Given these findings, the second skin biopsy was consistent with a reactive hypersensitivity process, including drug eruption. One month after discontinuing ruxolitinib, the patient developed systemic inflammatory response syndrome (SIRS) and disseminated intravascular coagulation (DIC). Autopsy revealed multi-organ failure.

## Comment

Cytokines act through the JAK/STAT intracellular pathway to affect cell growth and differentiation [1]. More than half of patients with primary myelofibrosis have an activating mutation in JAK2V617F. Ruxolitinib, an orally bioavailable selective inhibitor of JAK1/JAK2, inhibits STAT3 phosphorylation, leading to attenuation of cytokine signaling. Ruxolitinib has demonstrated clinical benefits in patients with myelofibrosis by reducing spleen size and by alleviating debilitating disease-related symptoms [2-3].

We report a drug eruption associated with ruxolitinib, with morbilliform lesions on the trunk and extremities, and the subsequent development of an exfoliative dermatitis limited to the extremities (possibly occurring secondary to edema). The skin biopsies revealed granulomatous inflammation, yet this finding differs from an interstitial granulomatous drug reaction (IGDR), as the infiltrates are primarily perivascular rather than interstitial. Interstitial granulomatous drug reactions are a recently described drug-induced eruption that can present with erythroderma [4]. While most patients who develop an IGDR present with asymptomatic erythematous to violaceous plaques mainly involving the intertriginous areas, one patient developed mildly pruritic erythema on the chest and abdomen (2 years after starting enalapril maleate), which progressed to widespread erythroderma covering his entire body [4]. In that patient, the cutaneous lesions resolved within 2 months of discontinuing the enalapril maleate [4].

Although ruxolitinib has not previously been reported to be associated with a drug eruption, a withdrawal syndrome following discontinuation of ruxolitinib has been reported, often with associated accelerated splenomegaly and worsening of cytopenias, but also including instances with systemic inflammatory response syndrome (SIRS) and disseminated intravascular coagulation (DIC)

[5]. The pathogenesis of the withdrawal syndrome remains unclear, but may involve changes in inflammatory cytokine activity [5]. While the vast majority of patients benefit from ruxolitinib's favorable side effect profile, clinicians should be alerted to the possibility of a morbilliform eruption and exfoliative dermatitis occurring in patients treated with ruxolitinib, in addition to the reported adverse hematologic effects and the potential for a serious ruxolitinib withdrawal syndrome.

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