A photo-distributed papulopustular eruption and multiple squamous cell carcinomas in a patient on ruxolitinib

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INTRODUCTION

The use of Janus kinase (JAK) inhibitors in dermatology is rapidly increasing to treat various diseases such as psoriasis, alopecia areata, vitiligo, and a variety of other inflammatory skin disorders.[1,2] Ruxolitinib is a JAK inhibitor that is approved by the US Food and Drug Administration for the treatment of myelofibrosis and polycythemia vera (PCV).[3] In dermatology, ruxolitinib has been tried as a topical cream for treating psoriasis and vitiligo, and has been used both topically and orally for the treatment of alopecia areata.[2,4] Here we report a photo-distributed papulopustular skin rash in a patient on ruxolitinib for PCV.

Abbreviations used:

JAK: Janus kinase
PCV: polycythemia vera

CASE REPORT

A white man in his 80s with PCV was referred to the integrated care clinic for evaluation of a pruritic eruption on the upper chest, neck, and face. He was being treated with concurrent ruxolitinib and hydroxyurea for his PCV, and the rash developed 1 month after ruxolitinib was introduced. On cutaneous examination, there was an unusual photo-distributed eruption composed of papules and pustules on the face, V area of the neck, and chest (Fig 1). The patient had received topical steroids from his oncologist without improvement. Serologic workup was within normal limits including low creatine kinase levels (40 U/L), a normal antinuclear antibody titer (1:80) and negative anti SS-A/B antibodies. Two skin biopsies were performed, and empiric therapy with doxycycline, 100 mg twice daily, was started. This treatment was quickly discontinued because of severe headache and stomach upset. The skin biopsies found a folliculocentric neutrophilic infiltrate with small foci of suprabasal acantholysis (Fig 2, *A*). The patient did not respond to oral antibiotics or multiple topical treatments including various steroids, pimecrolimus cream, chlorhexidine washes, ivermectin cream, and clindamycin gel and a

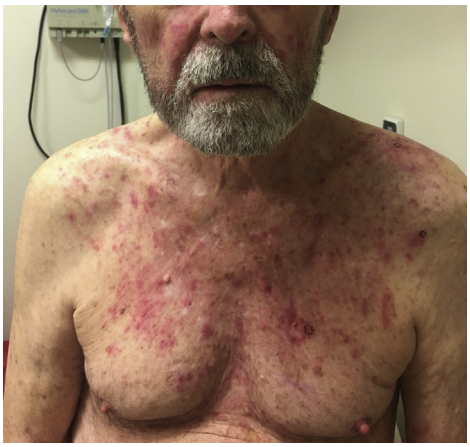

Fig 1. Cutaneous eruption. Papules and pustules with background erythema are seen over the centro-facial area, neck, and upper chest, with distinct sparing of the upper arms and the lower chest.

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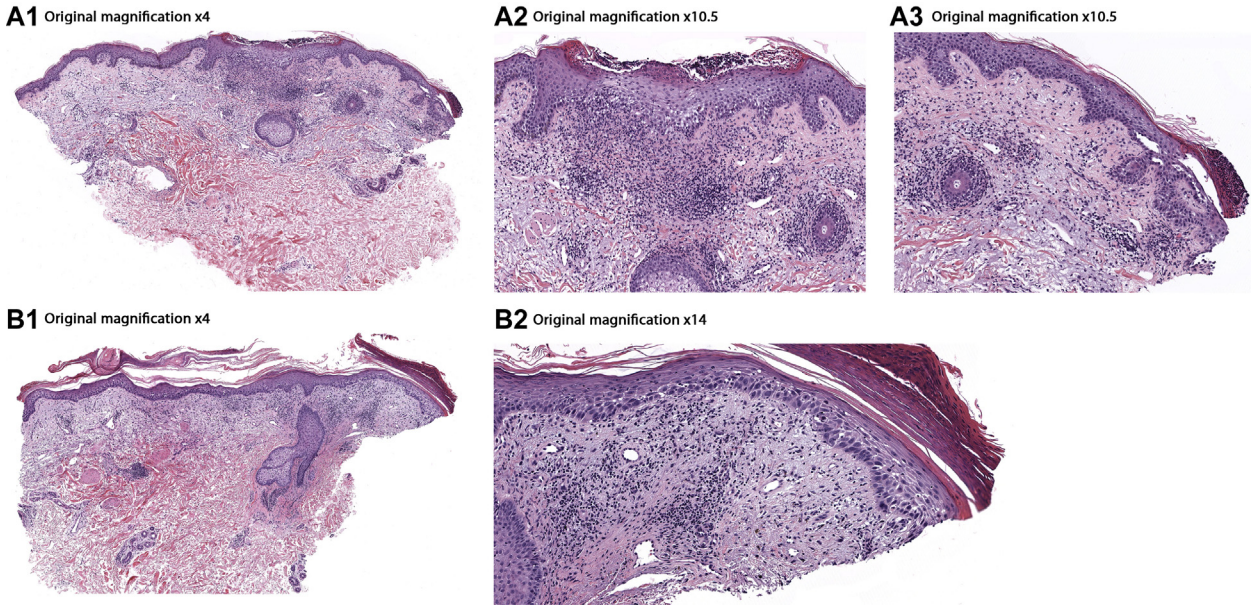

Fig 2. Histopathologic findings. Hematoxylin-eosin stains of the initial biopsy showed prominent folliculocentric inflammation **(A1)** composed of lymphocytes, histiocytes, and numerous neutrophils **(A2)**. The epidermis was eroded and surmounted by neutrophilic serum crust. Focal suprabasal acantholysis was present **(A3)**. Additional biopsies found parakeratosis overlying an atrophic epidermis **(B1)** and lymphohistiocytic inflammation at the dermoepidermal junction with associated dyskeratosis **(B2)**.

brief course of oral prednisone. Additional biopsies were performed because of the recalcitrant nature of his eruption. Results showed interface dermatitis with lymphocytes at the dermoepidermal junction (Fig 2, *B*). During this 2- to 3-month period, 5 new squamous cell carcinomas developed. Because of PCV stability and his recalcitrant rash, the patient had his ruxolitinib discontinued, and in about 3 weeks, significant clinical improvement was noted. The rash has not returned in 6 months since cessation of ruxolitinib, although he continues to have additional new keratinocytic carcinomas.

DISCUSSION

Several inflammatory dermatoses are driven by molecular pathways that converge on the common JAK signal transducer and activator of transcription (STAT) signaling pathway. Thus, inhibition of this proinflammatory pathway using the JAK inhibitors is a promising new addition to the existing treatment options for several dermatologic conditions including psoriasis, atopic dermatitis, vitiligo, alopecia areata, dermatomyositis, and graft-versus-host disease.[1,2] Broadly, there are 2 generations of JAK inhibitors. The first generation of JAK inhibitors includes tofacitinib, ruxolitinib, baricitinib, and oclacitinib. The second generation of JAK inhibitors includes peficitinib, filgotinib, fedratinib, momelotinib, lestaurtinib, and decernotinib and is mostly still under development.[5] JAK inhibitors can result in various cutaneous and noncutaneous side effects. The former includes herpes zoster, reactivation of herpes simplex, disseminated molluscum contagiosum, eruptive squamous cell carcinoma, and drug eruptions including drug rash with eosinophilia and systemic symptoms (DRESS) syndrome.[2,6] The US Food and Drug Administration–approved dose of ruxolitinib for myelofibrosis and polycythemia vera ranges from 5 mg to 25 mg twice daily.[3] Our patient had received 10 mg/d.

There could be a few explanations for the photodistributed nature of the rash. The patient was also receiving hydroxyurea apart from the ruxolitinib, and there is a possibility that the hydroxyurea-induced photosensitivity may have contributed to the distribution of the rash. Alternatively, it could be caused by a ultraviolet recall–type reaction or because the affected areas are sites of previously damaged skin (ie, locus minoris resistentiae). However, the clinical course of the eruption suggests that it was primarily caused by the JAK inhibitor. Our patient experienced his eruption shortly after the addition of ruxolitinib to his regimen. The eruption remained treatment resistant throughout his ruxolitinib course and resolved on discontinuation of the ruxolitinib without any recurrence at follow-up. The development of numerous squamous cell carcinomas while on treatment in this patient is consistent

with prior reports of eruptive squamous cell carcinomas in the setting of JAK inhibitor therapy, which is thought to promote tumorigenesis by inhibiting the antineoplastic effects of interferons as well as natural killer and T cells.[7]

The use of JAK inhibitors is growing, and dermatologists will need to be aware of the cutaneous side effects of this class of medications. To the best of our knowledge, a case of ruxolitinib-associated photodistributed rash, with overlapping interface dermatitis and neutrophilic inflammation, has not been previously reported.

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