CASE REPORT

Delayed granulomatous eruption of the nose associated with ruxolitinib

Margaret Brown, MD,a Katherine Smith, BS,b and Sandra Osswald, MDa
San Antonio, Texas

Key words: drug eruption; granulomatous; granulomatous drug eruption; Janus kinase inhibitor; nose; ruxolitinib.

INTRODUCTION

The Janus kinase (JAK) signal transducer and activator of transcription pathway is a signaling mechanism that mediates cellular responses involved in inflammation.1 Ruxolitinib is a JAK1/2 inhibitor with US Food and Drug Administration approval for the treatment of myelofibrosis, polycythemia vera, and steroid-refractory graft-versus-host disease.2 JAK inhibitors are emerging as therapeutic agents in dermatology, with evidence of their efficacy shown in psoriasis, alopecia areata, vitiligo, and atopic dermatitis.3,4 Promising results have also been reported in connective tissue diseases and granulomatous diseases.3,5 Here we report a case of a delayed granulomatous eruption of the nose associated with ruxolitinib. This case is relevant as the use of JAK inhibitors becomes more prevalent in dermatology.

CASE REPORT

A 77-year-old woman with a history of JAK2V617F-positive post–essential thrombocythemia myelofibrosis on ruxolitinib for 5 years, Hashimoto thyroiditis, hypertension, depression, and osteoarthritis presented to our dermatology clinic with redness and swelling of her nose. Physical examination found an erythematous papule on the nasal dorsum. Shave biopsy of the papule found a moderate-to-dense dermal infiltrate of lymphocytes, histiocytes, and few plasma cells extending from the reticular dermis to the deepest aspect of the biopsy with one focal area of caseation necrosis (Fig 1, A and B). Periodic acid–Schiff stain was negative for organisms. Approximately 6 months later, more pink papules appeared on the nose and began to coalesce into a plaque. A second shave biopsy from the nasal dorsum found a dermal lymphohistiocytic infiltrate surrounding a ruptured hair follicle (Fig 2). Gomori methenamine-silver nitrate and Fite stains were negative for organisms. Paraffin immunoperoxidase studies found small-to-medium-sized lymphocytes, predominantly CD3+ T cells, with approximately 75% CD4+ and 25% CD8+. The T cells expressed CD2 and CD5 with mildly decreased expression of CD7. Bcl-6 stained some of the histiocytic component and scattered small lymphocytes. CXCL-13 and PD-1 highlighted only rare scattered cells. Immunophenotyping did not favor a primary lymphoproliferative disorder.

A working diagnosis of granulomatous rosacea was made, and the patient was treated with oral doxycycline, 100 mg twice daily, and a sulfur-containing cleanser for 3 months. Despite this therapy, the nasal lesions developed into a disfiguring red-brown crusted plaque encompassing the entire nose (Fig 3, A and B). A third shave biopsy found light growth of coagulase-negative staphylococci, likely representing normal skin flora. Acid-fast bacterial and fungal stains and culture were negative. Laboratory workup was positive for mild anemia and mildly elevated inflammatory markers. Pertinent

From the Division of Dermatology and Cutaneous Surgery, Department of Medicinea and the Long School of Medicine,b UT Health San Antonio.
Funding sources: None.
Conflicts of interest: None disclosed.
Correspondence to: Margaret Brown, MD, Division of Dermatology and Cutaneous Surgery, Department of Medicine, UT Health San Antonio, 7979 Wurzbach Rd. MC 7876, San Antonio, TX 78229. E-mail: BrownME@UTHSCSA.edu.

Abbreviations used:
GDEs: Granulomatous drug eruptions
JAK: Janus kinase

JAAD Case Reports 2020;6:646-9.
2352-5126
© 2020 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
https://doi.org/10.1016/j.jdcr.2020.04.040
negative workup included white blood cell count, platelet count, complete metabolic panel, serum calcium, serum protein electrophoresis, urine protein electrophoresis, serum immunofixation, lactate dehydrogenase, antinuclear antibodies, anti-Ro antibodies, anti-La antibodies, antineutrophil cytoplasmic antibodies, and Quantiferon-TB Gold test within normal limits. A chest radiograph was normal. During the course of the workup, formal evaluation by the rheumatology and ophthalmology departments found no evidence of inflammatory arthritis, connective tissue disease, or ocular signs of sarcoidosis.

**Fig 1.** Shave biopsy from the nasal dorsum shows a moderate-to-dense dermal infiltrate of lymphocytes, histiocytes, and few plasma cells extending from the reticular dermis to the deepest aspect of the biopsy with a focal area of caseation necrosis. (A and B, Hematoxylin-eosin stain; original magnifications: A, ×40; B, ×100.)

**Fig 2.** Shave biopsy from the nasal dorsum shows a dermal lymphohistiocytic infiltrate surrounding a ruptured hair follicle. (Hematoxylin-eosin stain; original magnification: ×40.)
Over the next 6 months, various treatments were tried and failed including topical ivermectin 1% cream, adapalene 0.1% gel, intralesional triamcinolone injections (10 mg/mL), oral minocycline 100 mg twice daily, oral prednisone (max dose of 20 mg/d), oral isotretinoin (20 mg/d), and a Jessner’s-trichloroacetic acid (35%) peel on one occasion. Eventually, all treatments were discontinued due to lack of efficacy, and a drug eruption was considered. On review of her medications, all were unchanged for several years and included ruxolitinib (15 mg twice daily), levothyroxine, gabapentin, hydrochlorothiazide, duloxetine, and aspirin. Although she had been taking ruxolitinib continuously for 5 years, the decision was made to trial off of it. Within the first week of stopping ruxolitinib, the patient reported improvement, and within 6 months, her granulomatous dermatitis resolved (Fig 4, A and B). At follow-up with the dermatology department 12 months later, she maintained clinical remission without specific therapy. Her myelofibrosis is now managed with routine monitoring and active nonintervention by the hematology department.

DISCUSSION
Granulomatous drug eruptions (GDEs) are uncommon drug eruptions defined by histiocytic inflammation of the skin, with or without systemic involvement. Various subtypes of GDEs have been described, but realistically, not all GDEs fit neatly into these categories. A further diagnostic challenge is posed by the potentially extended lag time, ranging from weeks to years, between initiation of the drug and presentation of the GDE.6

In our patient, we observed a delayed temporal relationship between the development of a granulomatous dermatitis of the nose and ruxolitinib, with complete resolution of the dermatitis shortly after withdrawal of the drug. Our patient’s presentation was clinically similar to lupus pernio, raising concern for sarcoidosis or a drug-induced sarcoidosis-like reaction; however, the histology findings did not
demonstrate sarcoidal granulomas, and she demonstrated no signs or symptoms of systemic sarcoidosis. The differential diagnosis also included a granulomatous infection that resolved with discontinuation of immunosuppression; however, no organisms were identified on tissue stains or culture.

Because of the increasing use of JAK inhibitors in dermatology, thorough documentation of the potential side effects of this drug class are warranted. Commonly reported systemic side effects include infections, cytopenias, and lipid elevations.2,3 Reported cutaneous side effects include reactivation of herpes simplex virus, herpes zoster, disseminated molluscum contagiosum, and squamous cell carcinoma.4 Of note, there have been reports of acneiform eruptions with tofacitinib, which may be relevant to this case, as the granulomatous inflammation seen in our patient’s second biopsy was oriented around a ruptured follicle.7 Regarding ruxolitinib specifically, only a few inflammatory drug eruptions have been reported, including 1 morbilliform eruption, 1 photodistributed papulopustular eruption, and 1 case of necrotic leg lesions.8-10 Despite the clinical variability between these cases, each demonstrated some degree of lymphohistiocytic inflammation histologically.8-10 This paradox is interesting, as recent reports suggest that JAK inhibitors may be effective in treating granulomatous disorders, including sarcoidosis.5

We report a case of a granulomatous eruption of the nose associated with ruxolitinib. Dermatologists should be aware of the potential association between JAK inhibitors and granulomatous eruptions.

REFERENCES
1. Singer JW, Al-Fayoumi S, Taylor J, Velichko S, O’Mahony A. Comparative phenotypic profiling of the JAK2 inhibitors ruxolitinib, fedratinib, momelotinib, and pacritinib reveals distinct mechanistic signatures. PLoS One. 2019;14(9):e0222944.
2. JAKAFI® (ruxolitinib) tablets. Incyte Corporation. Available at: https://www.jakafi.com; 2020. Accessed February 1, 2020.
3. Damsky W, King BA. JAK inhibitors in dermatology: the promise of a new drug class. J Am Acad Dermatol. 2017; 76(4):736-744.
4. Shreberk-Hassidim R, Ramot Y, Zlotogorski A. Janus kinase inhibitors in dermatology: a systematic review. J Am Acad Dermatol. 2017;76(4):745-753.e19.
5. Rosenbach M. Jak-inhibitors offer promise for a new era of targeted treatment for granulomatous disorders. J Am Acad Dermatol. 2019;82(3):e91-e92.
6. Dodik-Gad RP, Shear NH. Granulomatous drug eruptions. Dermatol Clin. 2015;33(3):525-539.
7. Montilla AM, Gómez-García F, Gómez-Arias PJ, et al. Scoping review on the use of drugs targeting JAK/STAT pathway in atopic dermatitis, vitiligo, and alopecia areata. Dermatol Ther (Heidelb). 2019;9:655-683.
8. Fournier JB, Cummings F, Cannella J, Breen C, Zhou L, Iwamoto S. Drug-associated skin lesions in a patient with myelofibrosis receiving ruxolitinib. Dermatol Online J. 2014; 20(10), 13030/qt2jg3q02x.
9. Khanna U, Richardson V, Hexner E, Nguyen CV, Elenitsas R, Rosenbach M. A photodistributed pustular eruption and multiple squamous cell carcinomas in a patient on ruxolitinib. JAAD Case Rep. 2019;5(10):895-897.
10. Dasanu CA. Erythematous skin lesions with necrotic centers on lower extremities due to the use of ruxolitinib for primary myelofibrosis. J Oncol Pharm Pract. 2019;25(4):990-992.