Aggressive squamous cell carcinoma in a patient on the Janus kinase inhibitor ruxolitinib

Nader Aboul-Fettouh, BS, and Rajiv I. Nijhawan, MD
Dallas, Texas

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INTRODUCTION

Ruxolitinib, an orally administered inhibitor of Janus kinase (JAK) 1 and 2, which are intracellular nonreceptor tyrosine kinases, is used to treat patients with myelofibrosis[1] and is found to have significant clinical benefits including reductions in splenomegaly and total symptom score.[2] Ruxolitinib is also found to be superior to standard single-agent therapy in controlling hematocrit, reducing the spleen volume, and improving symptoms associated with polycythemia vera.[3] The most common adverse events associated with ruxolitinib is anemia and thrombocytopenia, which rarely lead to drug discontinuation.[2] Of note, 5-year efficacy data on ruxolitinib showed 17.1% of patients on ruxolitinib went on to have basal cell carcinomas (BCCs) or squamous cell carcinomas (SCCs) compared with only 2.7% of patients on best-available therapy.[4] Current ruxolitinib prescriber information labels warn of the risk of nonmelanoma skin cancers, and performing periodic skin examinations is recommended.[5] Skin cancers occurring in patients treated with ruxolitinib have been reported in the dermatology literature to display more aggressive biological behavior and metastatic potential.[6,7] We present another case of a patient having aggressive cutaneous malignancy after ruxolitinib initiation and urge physicians to be aware of this associated risk.

Abbreviations used:

BCC: basal cell carcinoma
JAK: Janus kinase
SCC: squamous cell carcinoma

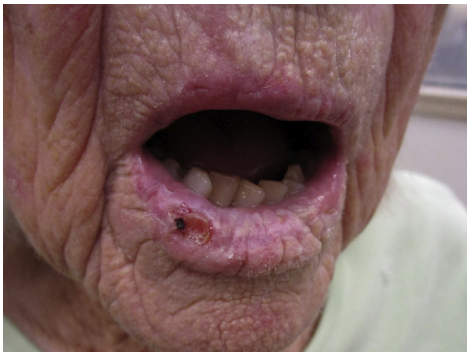

Fig 1. Clinical lesion 0.7 × 1.0 cm.

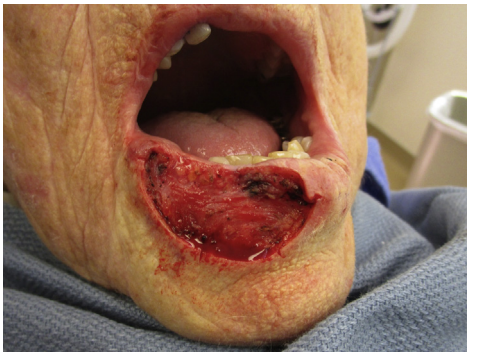

Fig 2. Intraoperative photo of Mohs section. Moderate to poorly differentiated SCC into muscularis, perineural invasion (<0.1 mm) requiring 4 stages of Mohs micrographic surgery for clearance results in defect measuring 2 × 3.5 cm.

CASE REPORT

A 70-year-old white woman, who denied a history of extensive sun exposure, had polycythemia vera

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Correspondence to: Rajiv I. Nijhawan, MD, Department of Dermatology, The University of Texas Southwestern Medical Center, 5939 Harry Hines Blvd, Suite 400, Dallas, TX, 75390-9191. E-mail: Rajiv.Nijhawan@UTSouthwestern.edu.

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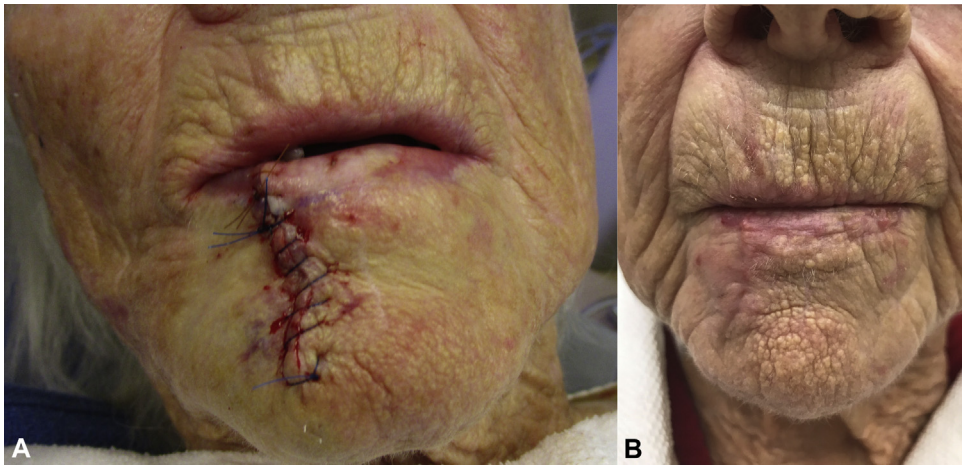

Fig 3. **A**, Wedge repair. **B**, Well-healed scar 3 months postoperatively.

with JAK-2^{+} myelofibrosis about 15 years before presentation. She was initially treated with phlebotomy for 6 years, followed by hydroxyurea for 5 years. Eleven years after diagnosis, ruxolitinib was initiated at 10 mg twice daily for about 2 years, at which point the dose was slowly tapered down over 3 years to 10 mg once daily. The patient reported a history of actinic keratosis 20 years prior along with one BCC on the nose diagnosed and treated 5 years before the myelofibrosis diagnosis.

After one year of ruxolitinib therapy, the patient reported "dozens" of SCCs, all of which had been treated by a dermatologist before the patient relocated to Texas. About 3 years after initiation of ruxolitinib, the patient's BCC on her nose recurred and was treated by radiation therapy. Five years after initiation of ruxolitinib, the patient presented to our clinic with a few-month history of a 0.7- x 1.0-cm lesion on the right lower vermilion border (Fig 1). The lesion proved to be an aggressive squamous cell carcinoma with moderate to poor differentiation extending into the muscularis with extensive nerve twig perineural invasion (<0.1 mm in nerve caliber) that required 4 stages of Mohs micrographic surgery for tumor clearance revealing a defect measuring 2 × 3.5 cm (Fig 2) and repaired with a wedge repair (Fig 3, *A* and *B*). Head and neck imaging found no evidence of lymph node involvement, and the patient declined adjuvant radiation. Over the subsequent 3 months, the patient had 4 additional SCCs treated with Mohs micrographic surgery.

DISCUSSION

Development of cutaneous malignancy in patients treated with immunosuppressive agents is well reported.[8] Although this patient was on hydroxyurea for several years, the patient only had a history of precancerous lesions and BCC before initiation of ruxolitinib. The JAK/STAT molecular pathway is involved in the signaling of various cytokines, which are important for regulating inflammatory and immune responses.[9] With new reports of aggressive skin cancers developing in patients on ruxolitinib therapy,[6,7] appropriate surveillance of cutaneous malignancies is warranted in these patients. Current prescribing information for ruxolitinib recommends routine skin examination.[5] Typically, patients with a history of nonmelanoma skin cancers are recommended to have full body skin checks at least every 6 months for the first few years and annually afterwards if there is no evidence of additional skin cancers. Patients on immunosuppressive agents are also typically followed up every 3 to 12 months given their higher risk for skin cancer.[8] Although further research is needed on the role of ruxolitinib and other JAK kinase inhibitors in the development of cutaneous malignancies, patients on these medications, especially those with a history of skin cancer, should have comprehensive routine skin examinations. In addition, dermatologists should be aware the association of ruxolitinib with aggressive nonmelanoma skin cancers and anticipate the potential for extensive subclinical tumor extension.

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