A case of aggressive squamous cell carcinoma with lymphovascular invasion during treatment with the Janus kinase inhibitor tofacitinib

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INTRODUCTION

Tofacitinib is an oral immunomodulator approved for the treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. It has commonly been used off label to manage other inflammatory conditions, such as psoriasis, atopic dermatitis, vitiligo, and alopecia areata.[1,2] This drug exerts its potent anti-inflammatory effects by blocking the activity of Janus kinase 1/3, thereby interfering with the downstream signal transduction cascade involving cytokines and growth factors essential for hematopoiesis and immune cell function.

Tofacitinib use is associated with an increased susceptibility to infections, malignancies, and, as of recently, thromboembolic events in high-risk patients.[3] The long-term data in rheumatoid arthritis patients have noted that patients receiving tofacitinib have a risk of developing nonmelanoma skin cancers comparable to that of patients receiving tumor necrosis factor α inhibitors, with basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) comprising 98% of all cases.[4,5] This risk appears to be highest in patients with additional skin cancer risk factors, including a history of nonmelanoma skin cancers, actinic damage, older than 65 years, and concomitant use of other immunosuppressive medications.[5]

Several case reports have demonstrated the association of aggressive nonmelanoma skin cancers with the Janus kinase inhibitor ruxolitinib.[6-8] In 1 report, a patient with a remote history of 1 BCC developed numerous SCCs after initiation of ruxolitinib, including an aggressive SCC located on the lower lip vermilion border, which was poorly

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Abbreviations used:

BCC: basal cell carcinoma
SCC: squamous cell carcinoma

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differentiated, with extension into the orbicularis oris muscle and extensive perineural invasion.[6] After 1 year of treatment, another patient received a diagnosis of a highly aggressive SCC on the cheek, with extension into the parotid gland and extensive perineural invasion. It recurred despite extensive surgery into the parotid gland and facial nerve.[7] The rare Merkel cell carcinoma was also reported with the long-term use of ruxolitinib. After having received ruxolitinib for 7 years, 1 patient developed this highly aggressive tumor on her elbow, with lymphovascular invasion and nodal involvement.[8] However, although this correlation has been described for ruxolitinib, a literature search of the English language, using the term "tofacitinib AND skin cancer," revealed no similar reports for tofacitinib. Here we present the case of a highly aggressive SCC with the extremely rare feature of lymphovascular invasion in a patient receiving tofacitinib therapy.

CASE REPORT

This case concerns a 77-year-old white man with a history of rheumatoid arthritis. He never smoked and was a former tennis player. He had previously received a diagnosis of actinic keratoses, 1 BCC, and no other skin cancers before initiating tofacitinib. Since 2001, his rheumatoid arthritis had been

managed with methotrexate and multiple tumor necrosis factor α inhibitors. In November 2013, his treatment regimen was switched to tofacitinib at 5 mg twice daily with concurrent methotrexate, leading to improvement of his joint disease.

Since then, 6 BCCs and 23 SCCs occurred on the head and neck. They were managed with several treatment modalities, including curettage, cryosurgery, topical chemotherapy, and Mohs micrographic surgery. Many of his nonmelanoma skin cancers exhibited aggressive growth. He has had numerous infiltrative BCCs. Several SCCs have had high-risk features, including acantholysis, moderate or poor differentiation, rapid growth, large tumor size greater than 2 cm in diameter despite frequent surveillance, perineural invasion, and significant subclinical spread requiring multiple Mohs micrographic surgery stages.

In 2016, our patient's methotrexate dose was tapered from 12.5 to 5 mg weekly without a significant change in his nonmelanoma skin cancer incidence, and methotrexate was discontinued in April 2019 to minimize his immunosuppression. Three months later, he presented with a 2-cm indurated plaque on the right temple (Fig 1), and a biopsy confirmed the diagnosis of invasive acantholytic SCC. Mohs micrographic surgery was performed and required 4 stages to achieve clear margins. Lymphovascular invasion was noted in the frozen section and confirmed by our dermatopathologists (Fig 2, *A* and *B*). The resultant 5 × 3.2-cm defect was closed with a tripolar flap (Fig 3, *A* and *B*). Subsequent computed tomographic scan of the head and neck did not demonstrate intracranial or nodal involvement. Because of the high risk for local recurrence and metastasis, our patient agreed to proceed with adjuvant radiation therapy.

On his 3-month follow-up visit, he received a diagnosis of another invasive SCC on the left parietal aspect of the scalp and a large SCC in situ on the right parietal aspect of the scalp. The former lesion was managed with Mohs micrographic surgery, whereas topical 5-fluorouracil was used to treat the latter. On his 9-month follow-up visit, there was no evidence of recurrence of the right-sided temporal SCC (Fig 4). There was no temporal nerve deficit and no facial asymmetry, and the patient was satisfied with the cosmetic outcome.

DISCUSSION

As a potent immunomodulator, tofacitinib has been associated with an increased risk of nonmelanoma skin cancer development. This risk is amplified by the presence of additional skin cancer risk factors, especially high degrees of ultraviolet
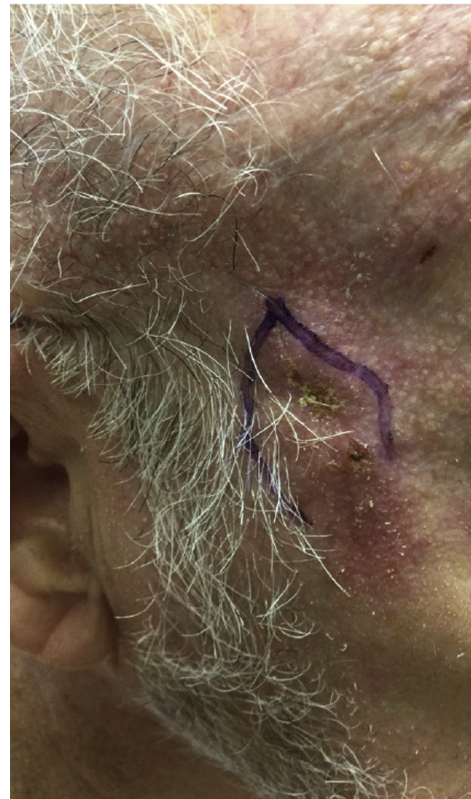

Fig 1. Right temple with a 2-cm indurated erythematous plaque with erosion and scales.

radiation exposure.[4,5] This association is consistent with the strong evidence linking immunosuppression to the development of cutaneous malignancies.

Our patient exhibited numerous risk factors for developing nonmelanoma skin cancers, including advanced age, actinic damage, and long-term immunosuppressive therapy. Although studies have demonstrated that there is a propensity to develop nonmelanoma skin cancers when methotrexate and tumor necrosis factor α inhibitor combination therapy is used, the role of these medications in this patient's course remains unclear.[9] This is highlighted by the temporal relationship between tofacitinib initiation and the development of numerous tumors with high-risk features. Specifically, although our patient experienced only 1 BCC throughout greater than 10 years of immunosuppressive therapy, he developed extensive, aggressive cancers only after he began receiving tofacitinib. However, the effects of these other medications cannot be entirely discounted. Regardless, skin cancers in immunocompromised patients tend to behave aggressively and metastasize more frequently, thereby warranting aggressive treatment.[10]

High-risk features of SCCs include tumor diameter greater than 2 cm, recurrence, poor differentiation,
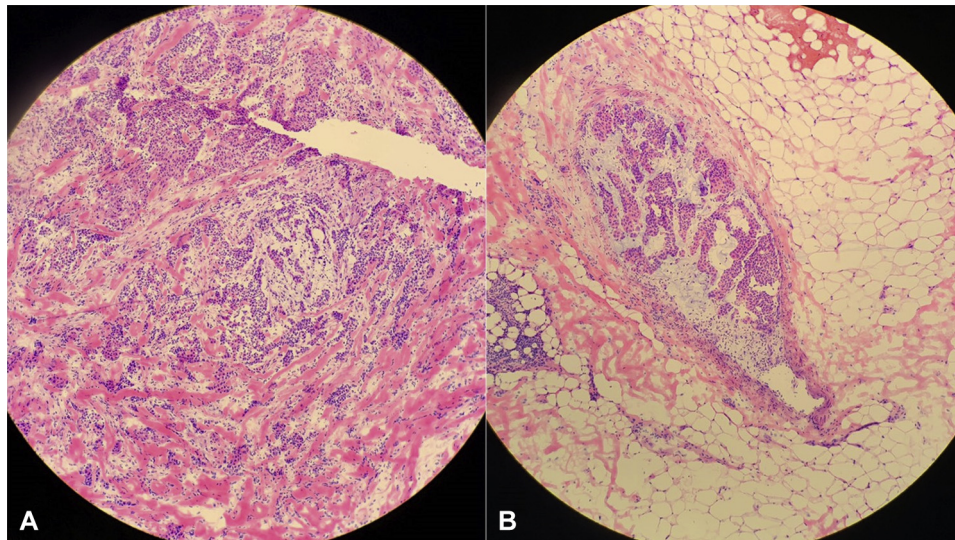
Fig 2. Frozen section demonstrating aggressive squamous cell carcinoma (**A**) with lympho-vascular invasion (**B**).
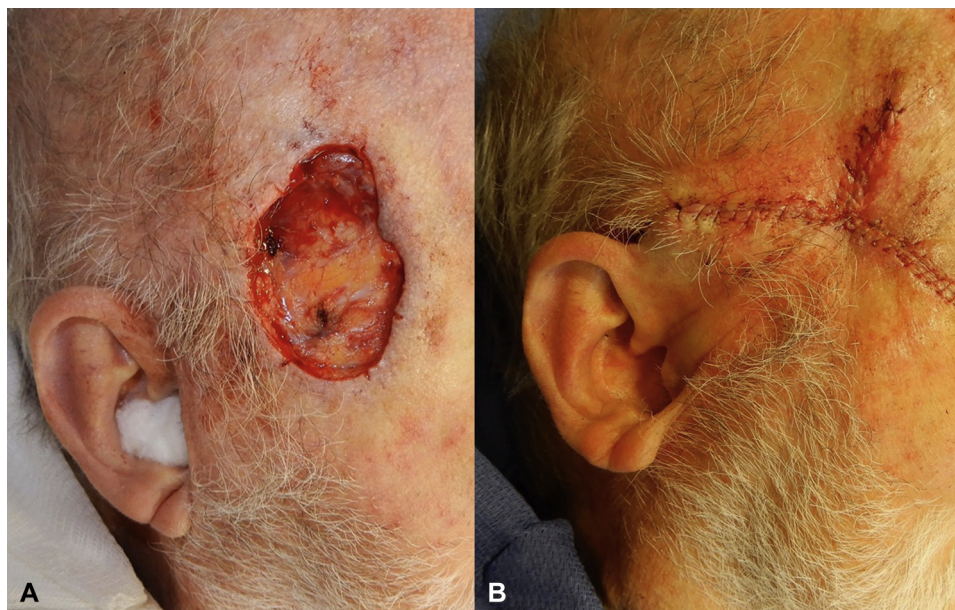
Fig 3. A, Final 5 × 3.2-cm defect with negative margin results after 4 stages of Mohs micrographic surgery. **B**, Tripolar flap reconstruction.

acantholytic histologic subtype, extension past subcutaneous fat, and perineural or lymphovascular invasion.[11] Lymphovascular invasion is an extremely rare feature and associated with a high risk of metastasis and death.

With the increased use of tofacitinib as a favorable treatment option in rheumatology and dermatology, providers should be aware of the increased risk of cutaneous malignancies. The prescriber information label currently recommends periodic surveillance for nonmelanoma skin cancers. However, in patients with additional risk factors for skin cancer, this practice should be emphasized because of the enhanced risk of developing nonmelanoma skin cancers. In addition, aggressive nonmelanoma skin cancers with extensive subclinical disease may exist in this patient population, and this should be considered throughout patient counseling and treatment.

Fig 4. Right temple with a well-healed scar and no signs of recurrence 9 months postoperatively.

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