CASE REPORT

Development of sebaceous carcinoma in a patient on ruxolitinib therapy

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INTRODUCTION

The first Janus kinase (JAK) inhibitor, ruxolitinib, was approved as a treatment for primary myelofibrosis in 2011. Recently, evidence has emerged suggesting an association between the use of JAK inhibitors, such as ruxolitinib, and nonmelanoma skin cancers (NMSCs), including basal cell carcinoma, squamous cell carcinoma (SCC), and Merkel cell carcinoma.1,2 To our knowledge, sebaceous carcinoma (SC), a rare and aggressive cutaneous malignancy, has not previously been reported in a patient taking ruxolitinib or any other JAK inhibitor. We describe a case of SC development in a patient after 2.5 years of ruxolitinib therapy.

CASE REPORT

A 75-year-old woman with a history of JAK2-positive myeloproliferative neoplasm/myelodysplastic syndrome with ringed sideroblasts and thrombocytosis treated with ruxolitinib monotherapy for 30 months presented in October 2020 for the assessment of a tumor on her right flank that had been growing rapidly for 3 months (Fig 1). In 2009, she initially had a diagnosis of essential thrombocytosis and was treated with hydroxyurea. However, mild, persistent leukopenia and anemia prompted a repeat bone marrow biopsy in 2018, leading to the diagnosis of myeloproliferative neoplasm/myelodysplastic syndrome with ringed sideroblasts and thrombocytosis. Hydroxyurea was discontinued in February 2018, and she was transitioned to ruxolitinib in March 2018, titrating from 10 mg daily to 30 mg daily in divided doses. She lacked a history of marked immunosuppression, opportunistic infections, and significant lymphocytopenia. She reported no personal or family history of skin cancer. Except for a history of hypothyroidism, which was treated with levothyroxine, the patient’s additional medical history and medication use were not relevant.

The asymptomatic, nonpigmented, focally eroded, exophytic lesion on her right flank was pedunculated and 2 cm in the largest dimension. No lymphadenopathy was palpable. A shave biopsy was performed, and histopathologic examination

Abbreviations used:
JAK: Janus kinase
NMSC: nonmelanoma skin cancer
SC: sebaceous carcinoma
SCC: squamous cell carcinoma

Fig 1. A 2-cm sebaceous carcinoma on the right flank of a patient taking ruxolitinib for the last 2.5 years.

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showed dermal proliferation of atypical basaloid cells with focal sebaceous differentiation, patchy necrosis, and numerous mitotic figures. These findings, which were consistent with SC, can be visualized in Fig 2, A and B. Immunohistochemistry of the sample was obtained and showed intact expression of MLH1 and PMS2 but no nuclear expression of MSH2 or MSH6 in the tumor cells (Fig 3). Because the patient’s SC was not located on the head or neck region and demonstrated mismatch repair protein loss, she was referred for genetic testing to rule out Lynch and Muir Torre syndromes. Germline DNA was collected, and a 47 cancer–gene panel did not identify any genetic variants. A virtual colonoscopy that was performed in September 2019 showed no significant findings, and the patient had no history of gynecological cancers, although her uterus and both ovaries were removed at the age of 29 years because of endometriosis.

The remainder of the lesion on her flank was excised with clear surgical margins using Mohs surgery. At a follow-up visit in September 2021, the patient remained free of skin neoplasms.

**DISCUSSION**

Orally administered ruxolitinib is a JAK 1 and 2 inhibitor that is approved for the treatment of myelofibrosis, polycythemia vera, and graft-versus-host disease. Long-term efficacy data have shown that ruxolitinib has significant clinical benefits in patients with myelofibrosis, including reductions in spleen volume, improvement in core symptoms, and potential survival benefits. Reports documenting aggressive NMSCs (basal cell carcinoma, SCC, and Merkel cell carcinoma) in patients taking JAK inhibitors have recently emerged in the literature. A 10-year retrospective study found that in patients with myelofibrosis or polycythemia vera, ruxolitinib use is associated with increased risk of SCC. To our knowledge, a case of SC occurring in a patient taking JAK inhibitor therapy is yet to be reported.

The annual incidence rate of SC is 1 or 2 cases per 1 million individuals, and the median age of onset is 72 years. SC is usually confined to the head and neck, often the periocular region. Only a few hundred cases of extraocular SC have been reported in the literature. Sebaceous neoplasms, including SC, below the neck, are often associated with Muir-Torre syndrome. Muir Torre Syndrome should also be considered in patients with sebaceous neoplasms who show absence of nuclear staining for mismatch repair gene products. Although molecular testing was not indicated by appropriate use criteria in this 75-year-old patient, her gene sequencing was negative for Muir-Torre syndrome.

JAK inhibitor use appears to be the primary risk factor for aggressive NMSC formation in our patient. Although SC has been reported in patients with non-Hodgkin lymphoma, myelodysplastic syndrome is
not strongly associated with the risk of SC or NMSC. Patients taking long-term hydroxyurea have also been reported to form NMSCs\(^8\); however, our patient had been off hydroxyurea for 2.5 years. The immunosuppression caused by JAK inhibitors, such as ruxolitinib, is believed to be the primary factor hastening the development of NMSCs. The prescribing information for ruxolitinib recommends that patients on this medication be periodically examined for NMSCs, including basal cell carcinoma, SCC, and Merkel cell carcinoma.\(^3\) The present case suggests that there may also be an increased risk of SC associated with JAK inhibitor use. Dermatologists should be aware that rare and aggressive skin cancers, including SC, have been reported in patients taking JAK inhibitors. JAK inhibitors will continue to have broad applications in the future. Consequently, clinical attention to cutaneous adverse effects is warranted.

**Conflicts of interest**

None disclosed.

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