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Aggressive Skin Cancers Occurring in Patients Treated With the Janus Kinase Inhibitor Ruxolitinib

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ABSTRACT

The Food and Drug Administration approved Ruxolitinib in 2011 for the treatment of primary myelofibrosis. Five-year safety data showed a higher incidence of skin cancer in patients treated with Ruxolitinib compared to best available therapy for myelofibrosis. This report presents a series of five patients with history of myelofibrosis treated with Ruxolitinib who subsequently developed numerous skin cancers with aggressive biological behavior. Each patient in this report was treated by a Mohs surgeon affiliated with an academic institution. All patients had a history of myelofibrosis and were exposed to Ruxolitinib. Some patients were exposed to other immunomodulatory medications such as Hydroxyurea and Rituximab. The total number of skin cancers and skin cancers with particularly aggressive behavior were noted. All five patients in this series developed numerous skin cancers with aggressive biological behavior during or after therapy with Ruxolitinib. Also, one patient developed lentigo maligna melanoma and another developed metastatic undifferentiated pleomorphic sarcoma. The repeat observation of skin cancers with aggressive features during JAK inhibitor treatment suggests that these medications may promote cutaneous malignant transformation in at risk patients. Further surveillance and testing of JAK kinases regarding the risk of skin cancers is indicated.

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INTRODUCTION

Ruxolitinib selectively inhibits JAK1 and JAK2, two molecules of the Janus kinase (JAK) family.[1] JAKs are tyrosine kinases connected in pairs to intracellular domains of transmembrane receptors. Many patients with myeloproliferative disorders have gain of function V617F mutations in JAK2. These patients have longer disease duration and increased chance of fibrosis.[2] The Food and Drug Administration approved Ruxolitinib in 2011 for the treatment of primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.[1]

Five-year efficacy data on Ruxolitinib showed it improves quality of life and overall survival in patients with myelofibrosis compared with best available therapy. Among the side effects, 17.1% of patients on Ruxolitinib developed basal cell carcinomas (BCCs) or squamous cell carcinomas (SCCs) compared with only 2.7% of patients on best available therapy.[1] We report a series of five patients with history of myelofibrosis treated with Ruxolitinib who developed multiple skin cancers with particularly aggressive features.

REPORT OF CASES

Case 1

A 60-year-old male was diagnosed with polycythemia vera (PCV) with Jak-2+ myelofibrosis. The patient was treated with Hydroxyurea 500 mg three times a week up to 2 grams daily and phlebotomy for ten years until he developed fatigue. Approximately two years later the patient was started on PO Ruxolitinib 10 mg BID, which after a few months was increased to 20 mg BID. He continued this dose for four years without any other immunomodulatory medications.

The patient had a Fitzpatrick skin type II and endorsed an active outdoor lifestyle with extensive sun exposure. The patient had no known history of skin cancer prior to the diagnosis of PCV with myelofibrosis. He developed his first skin cancers, two squamous cell carcinoma in situ (SCCISs), approximately ten years after PCV diagnosis and commencing Hydroxyurea. Over the following seven years, he developed three new SCCIS, one BCC, three SCCs and one undifferentiated pleomorphic sarcoma of the scalp, the majority of which were diagnosed during the last four years of patient's life, while he was being treated with Ruxolitinib and off Hydroxyurea.

The pleomorphic sarcoma was treated with Mohs surgery and radiation therapy. CT of the neck, chest, abdomen and pelvis did not show any metastases. One year later repeat imaging showed multiple pulmonary nodules consistent with metastatic disease. The patient passed away at age 77 from intracerebral hemorrhage following surgery at an outside facility for metastatic sarcoma to the brain.

Case 2

A 73-year-old male with history of chronic lymphocytic leukemia was diagnosed with Jak-2+ myelofibrosis. Six months later the patient was treated with four doses of IV Rituximab. One year after diagnosis he was started on PO Ruxolitinib 5 mg BID. Two years later, the dose was increased to 10 mg BID for four months and then stopped. Patient was not treated with any other immunomodulatory medications.

The patient had a Fitzpatrick skin type II and noted a few sunburns as a child. Patient did not report any history of skin cancer prior to the diagnosis of myelofibrosis. Two years after patient was started on Ruxolitinib he developed several skin cancers including a poorly differentiated SCC on the left earlobe. The SCC was treated with Mohs surgery but one year later, he was diagnosed with a recurrent SCC at the same location. Also, a poorly differentiated SCC was diagnosed on the right preauricular area, excised and then recurred four months later demonstrating perineural invasion which after repeat excision still showed positive margins. Three subcutaneous lymph nodes were positive for metastatic SCC. The patient was diagnosed with at least three more SCCs over the same time period. Patient was also diagnosed with a 0.45 mm deep lentigo maligna melanoma on the left neck.

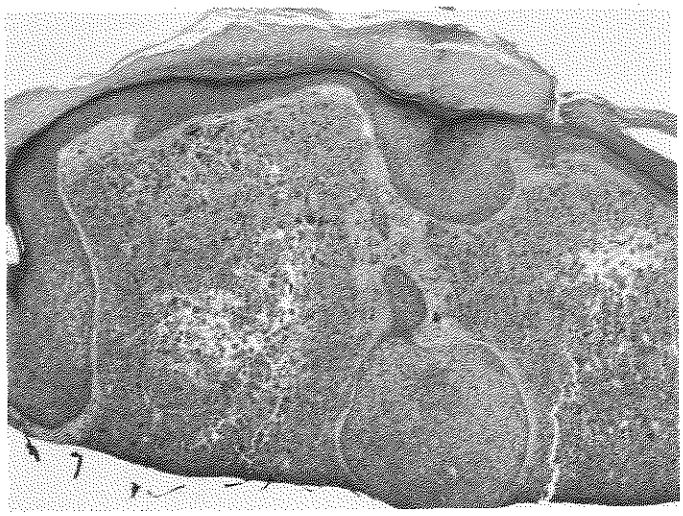
A PET CT scan was performed as a staging procedure, which demonstrated multifocal areas of uptake located on the face, scalp and neck. Ruxolitinib was discontinued and the patient was referred for radiation therapy.

Case 3

A 69-year-old male was diagnosed with myelofibrosis. Three years later he was started on Ruxolitinib 20 mg BID, which he continued for three years. Patient was not treated with any other immunomodulatory medications.

The patient had a Fitzpatrick skin type II and worked in construction outdoors. Patient noted a history of BCC of the scalp twelve years before starting Ruxolitinib. Beginning one and a half years after starting Ruxolitinib, he was diagnosed with a BCC of the right neck and several SCCs of the right mid cheek, left preauricular, right temple, right parietal scalp, left eyebrow and left frontal scalp. On examination of the right frontal scalp, he had several four millimeter flesh colored firm papules which were biopsied and showed metastatic poorly differentiated SCC with acantholytic features and perineural invasion (Figure 1).

FIGURE 1. Histologic findings from papule on right frontal scalp biopsied in Case 3. Histology shows metastatic poorly differentiated SCC with acantholytic features. The biopsy also showed perineural invasion.



Patient was referred to head and neck oncology. CT scan showed multiple nodular lesions in the frontal and parietal scalp concerning for metastases. Patient was referred back to his medical oncologist with a plan to discuss chemotherapy options.

Cases 4 and 5

See Table 1 for summary of all cases, including cases 4 and 5.

DISCUSSION

Eruption of SCCs in patients treated with Ruxolitinib has been reported.[1,3] This is the first article to report a series of patients with history of myelofibrosis treated with Ruxolitinib who subsequently developed numerous skin cancers with aggressive biological behavior. Also, one patient developed lentigo maligna melanoma and another developed metastatic undifferentiated pleomorphic sarcoma.

The increased risk of cutaneous malignancies in patients treated with immunomodulatory agents is well reported.[4,5] JAK kinases regulate signaling of various cytokines and growth factors making them involved in both innate and adaptive immunity.[6] Therefore, JAK inhibitors might similarly lead to impaired skin immunosurveillance. Alternatively, inhibition of the JAK pathway might lead to dysregulation of the cell cycle in skin cells. JAK2 gain of function mutations result in cytokine-independent proliferation of hematopoietic cells and are associated with myeloproliferative disease.[2,7] Although JAK inhibition is comparable to a loss of function mutation, paradoxical pathway activation is possible similar to the eruption of SCCs observed in patients with melanoma treated with BRAF inhibitors.[8]

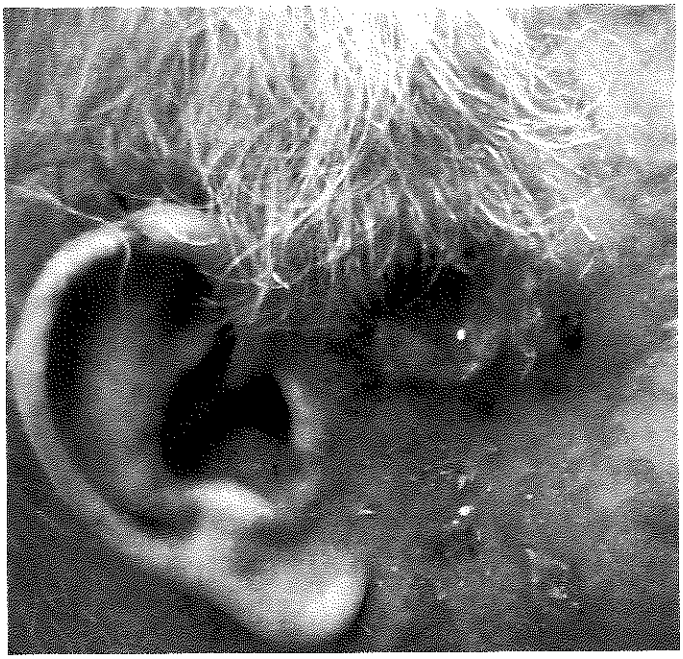
TABLE 1.

Summary of Skin Cancers in Each Case Occurring Before and After Ruxolitinib Treatment

Sex	Skin Type	Sun Exposure	Age at Diagnosis of Myelofibrosis	Treatments Prior to Ruxolitinib	Ruxolitinib Dose	Skin cancers prior to Myelofibrosis	Skin cancers while on Ruxolitinib	Most Aggressive Skin Cancers on Ruxolitinib	Patient's Treatment Plan & Prognosis
M	II	Active outdoor lifestyle	60	PO Hydroxyurea 500 mgTID up to 2 g daily	10 mg BID for few months then 20 mg BID for four years	None known	SCC - right lower leg, right lateral canthus, left shoulder; UPS - vertex scalp	UPS metastatic to lungs and brain.	Passed away from intracerebral hemorrhage following surgery for metastatic sarcoma to the brain
M	II	Few sunburns	73	Four doses of IV Rituximab	5 mg BID for two years then increased to 10 mg BID for four months	None	SCC - left earlobe, right preauricular, right ear, mid forehead, left antihelix; LMM - left neck	Recurrent poorly differentiated SCC of left earlobe, recurrent poorly differentiated SCC of right preauricular with perineural invasion, metastatic SCC and 0.45 mm deep LMM	Ruxolitinib discontinued, plan for radiation therapy to both sides of face
M	II	Works in outdoor construction.	69	None	20 mg BID for three years	BCC on scalp 12 years before starting Ruxolitinib	BCC - right neck; SCC - right mid cheek, left preauricular, right temple, right parietal scalp, left eyebrow, left frontal scalp	Metastatic poorly differentiated SCC of the scalp	Plan for chemotherapy, patient elected for hospice
M	I	Golf enthusiast	50	PO Hydroxyurea 500 mg BID	5 mg BID for 18 months	Several SCCs on face, arm, dorsal hands.	SCC - cutaneous lip, right temple	Aggressive SCC of right temple treated with Mohs surgery but required deep margin resection in OR. Tumor recurred 6 months later and after resection in OR still had positive margin.	Patient treated with radiation and placed on systemic retinoid. Ruxolitinib decreased to 2 mg daily.
M	II	Grew up on farm, worked in construction	59	PO Hydroxyurea	15-25 mg BID for 26 months	None	BCC - nose, right forearm, back of neck; SCC - left cheek, left lower lip	SCCs of left cheek and left lower lip both of which had perineural invasion and metastases to the neck.	Mohs surgery for left lower lip SCC. Excision with superficial parotidectomy in OR for left cheek SCC. Plan for radiation therapy.

BCC, Basal cell carcinoma; SCC, Squamous cell carcinoma; LMM, Lentigo maligna melanoma; UPS - Undifferentiated pleomorphic sarcoma.

FIGURE 2. Clinical image of squamous cell carcinoma with aggressive behavior on right temple from Case 4. Image of aggressive SCC on right temple that required deep margin resection in the operating room and then recurred 6 month later.



All five patients in this series have a history of myeloproliferative disease, which is a risk factor for skin cancer.[9] Also, three patients in this series were treated with Hydroxyurea, which is associated with aggressive skin cancers.[10] Though, the patient from case one was on Hydroxyurea for ten years and only developed two SCCISs during that time. It was during the last four years of his life while he was on Ruxolitinib and off Hydroxyurea that he developed numerous invasive SCCs and an undifferentiated pleomorphic sarcoma.

Recent reports of another JAK kinase inhibitor, Tofacitinib, show promise in the treatment of several relatively common dermatoses such as psoriasis, vitiligo, alopecia areata and dermatomyositis.[7,11-14] Increased indications for JAK inhibitors will lead to more patients treated with these medications making further studies even more important.

CONCLUSION

The repeat observation of skin cancers with aggressive features during JAK inhibitor treatment suggests that these medications may promote cutaneous malignant transformation in at risk patients. The carcinogenic potential is likely additive to other risk factors in patients commonly treated with JAK inhibitors such as history of myeloproliferative disease and history of treatment with other immunomodulatory agents. Further surveillance and testing of JAK kinases regarding the risk of skin cancers is indicated.

DISCLOSURES

The authors have no conflicts.

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