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Case Report

Rapid development of multiple nonmelanoma skin cancers secondary to ruxolitinib: a case report

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ABSTRACT

Janus kinase (JAK) inhibitors are immunosuppressive medications that function by deactivating the JAK-STAT pathway causing inhibition of cellular growth. Ruxolitinib is a JAK inhibitor that is commonly used to treat disease processes such as myelofibrosis, polycythemia vera and graft versus host disease, with some evidence of benefit with prostate cancer as well. Side effects of ruxolitinib include increased risk of infection, pancytopenia, cardiovascular disease and malignancy relating to the medication's immunosuppressive effects. Here we reported a 69-year-old male with prostate cancer being treated with ruxolitinib who developed multiple nonmelanoma skin cancers over a 13-month period.

Keywords: Janus kinase inhibitor, Ruxolitinib, Squamous cell carcinoma, Basal cell carcinoma, Nonmelanoma skin cancer, Prostate adenocarcinoma

INTRODUCTION

Ruxolitinib is an oral JAK inhibitor used to treat myelofibrosis, polycythemia vera, acute graft versus host disease and solid organ malignancies such as prostate cancer.[1,2] JAK inhibition, both topically and orally, has emerged in recent years as a leading therapeutic option in the treatment of numerous dermatologic conditions including psoriasis and atopic dermatitis. JAK inhibitors function by reducing cytokine signaling involved in hematopoiesis and immune function, thereby diminishing the inflammatory response.[3] While inhibition of the JAK-STAT pathway is an effective strategy on a biochemical level for the treatment of such inflammatory conditions and malignancies, JAK inhibition notably reduces the body's innate immune function. Some research suggests that there is an increased risk of nonmelanoma skin cancer (NMSC) in patients taking JAK inhibitors and recommends that providers advise patients to monitor new or changing skin lesions, but there are minimal reports in the literature.[2] Here we presented a 69-year-old patient taking ruxolitinib for the treatment of prostate adenocarcinoma who developed nine malignant skin lesions after the initiation of therapy. The significance of this case lies in its high number and rate of NMSCs associated with the medication.

CASE REPORT

A 69-year-old Caucasian male presented to the dermatology clinic with two skin lesions that have been growing in size over the past three months. The lesions were erythematous nodules with telangiectasias located on the left medial inferior chest and xiphoid region. The

patient had a history of adenocarcinoma of the prostate and was being treated with ruxolitinib at the time, which was started several months prior according to the patient, in addition to adjunctive radiation therapy. Other medications included low dose aspirin, losartan, rosuvastatin and atenolol. He was diagnosed clinically and confirmed via biopsy with two basal cell carcinoma lesions. Over the next year, several different malignant skin lesions located on the face, head, back, chest and shoulders were biopsied and excised. Figure 1 shows the patient's latest NMSC lesions, including two basal cell carcinomas and one squamous cell carcinoma.

In total, the patient was diagnosed and treated for nine NMSCs, most of which were nodular basal cell carcinomas as well as multiple infiltrative basal cell carcinomas, superficial basal cell carcinomas and one invasive squamous cell carcinoma. The NMSCs were treated by means of electrodesiccation and curettage, surgical local excision and Mohs micrographic surgery. The patient was recommended to follow up with total body skin examinations every three months to monitor for skin cancer recurrence.

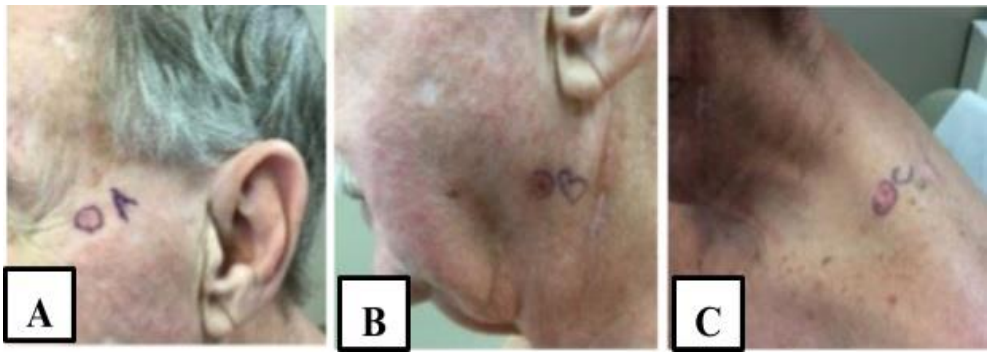

Figure 1: Physical examination findings of the most recent skin malignancies; (A) Invasive squamous cell carcinoma located on the left central zygoma; (B) Infiltrating basal cell carcinoma on the left lateral mandibular region; (C) Ulcerated superficial basal cell carcinoma on the left clavicular neck region.

DISCUSSION

Ruxolitinib, a JAK1 and JAK2 specific inhibitor, functions by halting cellular growth and immune response, which in this case, aids in the termination of prostate tumor growth. Cancerous cells commonly depend on activated signal transduction and activation of transcription 3 (STAT3) for survival and growth.[4] Upstream tyrosine kinases such as JAK1 or JAK2 are responsible for the activation of STAT3.[4] JAK inhibitors prevent proliferation and differentiation of malignant cells that express abnormal activation of the JAK-STAT signaling pathway.[4]

While this anti-carcinogenic effect is beneficial, there are many adverse effects of the medication, including increased risk of infection, pancytopenia, cardiovascular disease and secondary malignancy.[5] The proposed mechanism of secondary malignancy development involves inhibition of T cell and NK cell dysfunction in immunosurveillance, in addition to suppression of the antineoplastic interferons.[5]

This case was significant due to its abundance of NMSCs in such a short period of time. NMSCs are known potential sequelae after the implementation of immunosuppressive treatment regimens.[6] One study, a 5 year safety and efficacy review of ruxolitinib for the treatment of myelofibrosis, reported that 17.1% of patients using ruxolitinib developed newly diagnosed NMSC while this occurred in only 2.7% of patients in the control arm.[7] While the development of NMSCs secondary to JAK inhibition use is a known adverse effect, this is generally a chronic development over years. With this case, nine different NMSCs within a 13 month time period highlighted the risk of NMSC development and showed a degree of progression not previously reported. Of note, the patient did report significant sun exposure throughout his life, suggesting a predisposition to NMSC development.

In patients taking JAK inhibitors, emphasis should be placed on the importance of increased skin monitoring and periodic dermatologic examinations to biopsy and excise cutaneous pre-cancerous and malignant lesions early before significant growth occurs. Current literature recommends that patients taking immunosuppressive therapy should follow up with their physician every 3-12 months due to the increased chance for cutaneous malignancy development.[6] Evidence suggests that physicians who prescribe ruxolitinib may consider dermatology referral of these patients. Close monitoring can prevent late detection, metastatic spread and invasive surgical procedures, ultimately reducing morbidity and mortality.

Patient education is of vital importance when starting a patient on an immunosuppressant such as ruxolitinib. Patients should be counseled about routinely monitoring their skin for new lesions. It is essential to advise patients to schedule follow-up appointments with a physician if any new skin lesions arise. In addition, it is important to educate patients about ultraviolet light avoidance to reduce exposure that contributes to the pathogenesis of skin cancer.

CONCLUSION

This case demonstrates an association between the usage of ruxolitinib with the development of non-melanoma skin cancers. While there might be confounding factors such as age, sun exposure and immune status, it is important to make patients aware of this adverse effect. Providers who prescribe this medication long-term may consider performing periodic skin examinations or referring these patients to a dermatologist.

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