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Ruxolitinib-associated squamous cell carcinoma

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A 62-year-old Caucasian female with Fitzpatrick III phototype presented to our Dermatology consult due to an ulcerated nodule on the dorsum of her right hand which had been steadily growing over the last year. The patient had been under primary treatment with ruxolitinib 20 mg bid for four years due to primary myelofibrosis with unbalanced t(1;19) translocation, without V617F *JAK2* mutation. No other relevant medical conditions were reported, and the patient was not under any other concomitant medication. She denied significant exposure to ultraviolet radiation during her lifetime, either on a daily basis or during holidays. On physical exam, we observed a nodule with a 3 cm diameter, with central keratinization and ulceration, on the dorsum of the right hand (Figure 1A). The patient bore no stigmata of significant actinic damage either locally or on the remaining tegument. No premalignant lesions were detected. We conducted a punch biopsy that revealed a squamous cell carcinoma with moderate differentiation, but rather infiltrative, reaching the dermohypodermal junction (Figure 1B). Ruxolitinib was withdrawn, and the lesion was surgically removed.

Ruxolitinib is a Janus kinase (JAK) inhibitor which selectively targets JAK1 and JAK2. This drug is approved for treatment of high-risk myelofibrosis, polycythemia vera refractory or with intolerance to hydroxyurea and steroid-refractory acute graft-versus-host disease. Despite these indications, ruxolitinib, along with other JAK inhibitors, has been suggested to be useful in multiple dermatological conditions such as alopecia areata [1, 2], vitiligo [3], psoriasis [4] and atopic dermatitis [5] and rheumatological diseases such as rheumatoid arthritis or psoriatic arthritis. Long-term follow-up of patients enrolled in phase III trials for ruxolitinib has identified an increased risk for developing aggressive non-melanoma skin cancer (NMSC) [6], but other studies have failed to do so.

The case we report is highly suggestive to be related to ruxolitinib treatment, because this patient reported no significant exposure to ultraviolet radiation, had no signs of actinic damage, and had never been under other immunosuppressive treatments linked with NMSC risk. Recently, risk for NMSC under ruxolitinib has been shown to be particularly high in patients without *JAK2* mutation, as in this case [7].

The JAK-STAT pathway is an intracellular signaling pathway which is implicated in signal transduction for a wide range of extra-cellular stimuli, and its inhibition has gathered interest as a potent anti-inflammatory strategy for a number of hematological, rheumatological and dermatological conditions. The pro-oncogenic potential of ruxolitinib has been proposed to immune dysregulation with cytotoxic response dampening, thus facilitating neoplastic proliferation, but the mechanisms are far from clear [8, 9].

While this risk has been identified for ruxolitinib, tofacitinib, a specific JAK1 inhibitor, seems not to carry such an increased risk for NMSC [10]. Baricitinib, another JAK2 and JAK3 inhibitor, has been approved for the treatment of rheumatoid arthritis and atopic dermatitis. While sharing a common mechanism with ruxolitinib, to date no reports of increased risk for NMSC have emerged, but long-term data for this drug is still relatively scarce.

While JAK inhibitors are being proposed for the treatment of multiple conditions, caution is needed regarding the potential adverse effects. The analysis of pharmacovigilance data on long-term use of these drugs is warranted, and *in vitro* studies should be conducted to clarify the mechanisms underlying the apparent predisposition to NMSC in patients under some JAK inhibitors. Patients under these treatments should undergo regular skin inspection to detect potential malignant neoplasms early on.

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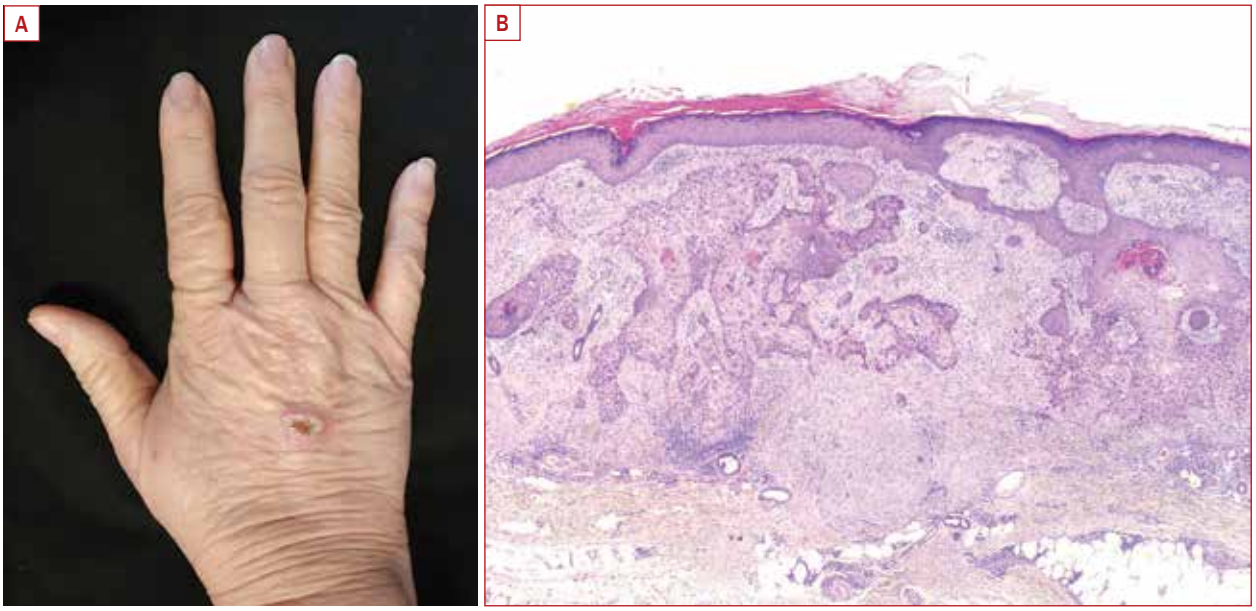

Figure 1A. Clinical picture of lesion; **B.** Histopathology of lesion [hematoxylin and eosin (H&E) stain, 25× magnification]

Hematologists, rheumatologists and other physicians prescribing these drugs should become acquainted with the clinical image of NMSC and conduct regular full body checks, even in patients without evident sun damage. Referral to a dermatologist should be considered as a preventive measure.

Authors' contributions

All authors contributed equally to the manuscript.

Conflict of interests

None.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to biomedical journals.

References

1. de Oliveira AB, Alpalhão M, Filipe P, et al. The role of Janus kinase inhibitors in the treatment of alopecia areata: a systematic review. Dermatol Ther. 2019; 32(5): e13053, doi: 10.1111/dth.13053, indexed in Pubmed: 31381252.
2. Peterson DM, Vesely MD. Successful treatment of alopecia totalis with ruxolitinib in a preadolescent patient. JAAD Case Rep. 2020; 6(4): 257–259, doi: 10.1016/j.jdcr.2020.02.007, indexed in Pubmed: 32258291.
3. Harris JE, Rashighi M, Nguyen N, et al. Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA). J Am Acad Dermatol. 2016; 74(2): 370–371, doi: 10.1016/j.jaad.2015.09.073, indexed in Pubmed: 26685721.
4. Kvist-Hansen A, Hansen PR, Skov L. Systemic treatment of psoriasis with JAK inhibitors: a review. Dermatol Ther (Heidelb). 2020; 10(1): 29–42, doi: 10.1007/s13555-019-00347-w, indexed in Pubmed: 31893355.
5. Rodrigues MA, Torres T. JAK/STAT inhibitors for the treatment of atopic dermatitis. J Dermatolog Treat. 2020; 31(1): 33–40, doi: 10.1080/09546634.2019.1577549, indexed in Pubmed: 30703333.
6. Harrison CN, Vannucchi AM, Kiladjian JJ, et al. Long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs best available therapy for myelofibrosis. Leukemia. 2016; 30(8): 1701–1707, doi: 10.1038/leu.2016.148, indexed in Pubmed: 27211272.
7. Lin JQ, Li SQ, Li S, et al. A 10-year retrospective cohort study of ruxolitinib and association with nonmelanoma skin cancer in patients with polycythemia vera and myelofibrosis. J Am Acad Dermatol. 2022; 86(2): 339–344, doi: 10.1016/j.jaad.2021.10.004, indexed in Pubmed: 34648874.
8. Barbui T, Ghirardi A, Masciulli A, et al. Second cancer in Philadelphia negative myeloproliferative neoplasms (MPN-K). A nested case-control study. Leukemia. 2019; 33(8): 1996–2005, doi: 10.1038/s41375-019-0487-8, indexed in Pubmed: 31142846.
9. Polverelli N, Elli EM, Abruzzese E, et al. Second primary malignancy in myelofibrosis patients treated with ruxolitinib. Br J Haematol. 2021; 193(2): 356–368, doi: 10.1111/bjh.17192, indexed in Pubmed: 33222197.
10. Curtis JR, Lee EB, Kaplan IV, et al. Tofacitinib, an oral Janus kinase inhibitor: analysis of malignancies across the rheumatoid arthritis clinical development programme. Ann Rheum Dis. 2016; 75(5): 831–841, doi: 10.1136/annrheumdis-2014-205847, indexed in Pubmed: 25902789.