Merkel cell carcinoma (MCC) is a rare neuroendocrine carcinoma of the skin. It is highly aggressive and represents the second most common cause of skin cancer-related death. Ruxolitinib is an orally administered selective inhibitor of Janus-associated kinases 1 and 2, which is used in the management of patients with symptomatic myelofibrosis and polycythemia vera who are non-responders or intolerant to hydroxyurea. Herein, we report the case of a 47-year-old woman with a 14-year history of chronic myeloproliferative syndrome initially treated with hydroxyurea for 4 years. She was then enrolled in the Response trial and treated for 7 years with ruxolitinib subsequently developing an MCC. This report shows the possibility of development of MCC in patients treated with ruxolitinib. Periodic skin examination is indicated in patients who undergo ruxolitinib therapy, especially if they have a history of skin cancer; dermatologists and oncohematologists should be aware of this possibility in order to introduce appropriate preventive strategies.

Merkel cell carcinoma (MCC) is a rare neuroendocrine carcinoma of the skin. It is highly aggressive and is the second most common cause of skin cancer-related death (1). MCC is usually asymptomatic, but has rapid growth. It frequently occurs on the head, neck and arms in skin exposed to sunlight (1, 2).

The immune system has an essential role in preventing the development of MCC and in countering its progression and 10% of patients affected by MCC are immune suppressed (3).

Ruxolitinib is an orally administered selective inhibitor of Janus-associated kinases (JAK) 1 and 2 used in the management of patients with symptomatic myelofibrosis and polycythemia vera (PV) who are non-responders or intolerant to hydroxyurea. Clinical trials with ruxolitinib have demonstrated significant benefits in terms of reductions of splenomegaly and increased control of disease-related symptoms with improving quality of life in patient with myeloproliferative disease compared with best available therapy (BAT) (4-7). Most common adverse events of ruxolitinib therapy are correlated with hematological toxicity, in particular anemia and thrombocytopenia; it is also associated with a potentially increased risk of opportunistic infections. In general, ruxolitinib is well tolerated and discontinuation due to adverse events is rare.

In the 5-year analysis of the COMFORT-II trial, a phase III study comparing ruxolitinib to BAT in patients with myelofibrosis, 17.1% of patients in the ruxolitinib-treated arm had newly diagnosed non-melanoma skin cancer, compared to 2.7% in BAT-treated arm. In the RESPONSE trial, a phase III study comparing ruxolitinib to BAT in patients with PV, the rates of non-melanoma skin cancer per 100 patient-years of exposure were 4.4 and 2.7, respectively. In this article, we describe a case of MCC in a patient with myeloproliferative syndrome treated with ruxolitinib.

Case Report

A 47-year-old woman with a 14-year history of chronic myeloproliferative syndrome treated firstly with hydroxyurea for 4 years and then for 7 years with ruxolitinib presented with a rapidly expanding, solitary, red-to-violet nodule on her right elbow which had appeared 5 months previously. The patient
had familial history of hypertension and cardiovascular diseases but not with cancer. She had been under treatment with atenolol since 2002. This patient had metabolic comorbidities such as hyperlipidemia and hypertriglyceridemia, and her body mass index (BMI) had increased from 29 to 37 during the previous 10 years. In 2004, the patient was diagnosed with JAK2 V617F+ PV and started phlebotomy and once-daily aspirin. Three years later, an increase in white blood cell count and platelet level was observed, consequently therapy was switched to oral hydroxyurea. In 2011, due to the worsening of splenomegaly and poor control of blood cell count, the patient was enrolled in the RESPONSE trial, a randomized, open label, multicenter phase IIIb study evaluating the efficacy and safety of ruxolitinib compared with BAT in patients with PV resistant or intolerant to hydroxyurea.

Firstly, our patient received 10 mg twice daily and then 20 mg twice daily for 7 years (from December 2011 to February 2018). Control of her hematocrit level was good and there was a reduction of spleen volume >35%. In March 2018, she presented with a rapidly expanding, solitary, red-to-violet nodule on her right elbow which had appeared 5 months previously. The tumor stained positively with CAM5.2 for cytokeratin 7 and 8, and for cytokeratin 20 and synaptophysin, and proved to be MCC with lymph node involvement. A tru-cut biopsy and then core-needle biopsy were performed in the diagnostic process. The right axillary lymph nodes appeared clinically, radiologically and histologically involved. In July 2018, the patient underwent wide excision of the lesion and complete lymph node dissection. The pathological examination revealed clear margins, nodal involvement (6+/38) and lymphovascular invasion. After multidisciplinary discussion, in August 2018, the patient underwent local radiation therapy (54 Gy dose radiation in 27 sessions). At the check up at 1 year after surgery, there was no evidence of disease.

Discussion

Immune suppression is one of the main risk factors for the development of MCC, as suggested by its high incidence in patients with hematological malignancies, HIV infection, organ transplantation and in those treated with immune-suppressive drugs (3). Moreover, when a patient is affected by MCC when receiving immunomodulatory drugs for the treatment of other comorbidities, this is associated with impaired disease-specific and disease-free survival (8). Failure of immune surveillance of cancer due to iatrogenic immune suppression caused by immunomodulatory drugs may explain the impaired survival of such patients.

The administration of oral ruxolitinib to patients markedly reduced splenomegaly and circulating levels of proinflammatory cytokines and eliminated neoplastic cells with mutated JAK2 (9). JAK1/2 inhibitors reduce the signaling of pathogenic cytokines such as interleukin-6 and -23, and as a result they can inhibit the production of an array of additional proinflammatory cytokines, chemokines, and adhesion molecules produced by other cell types, leading to interruption of the cytokine cascade (10, 11).

Our patient developed MCC during long treatment with ruxolitinib and had been treated in the past with hydroxyurea, an anti-metabolite also associated with many cutaneous adverse effects ranging in severity from ichthyosis to aggressive non-melanoma skin cancer (12, 13). Therefore, iatrogenic immune suppression due to the pharmacological treatment received by our patient might have been the cause of MCC development (14-16).

Periodic skin examination should be offered to patients who receive ruxolitinib therapy, especially if they have a history of skin cancer; dermatologists and oncohematologists should be aware of this possibility in order to undertake appropriate preventive measures.

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Availability of Data and Materials

The dataset used and/or analyzed during the current study is available from the corresponding Author on reasonable request.

Ethics Approval and Consent to Participate

No. 4/2018 on 23 July 2018.

Consent for Publication

The patient gave her approval for publication.

Conflicts of Interest

The Authors declare no conflict of interest.

Authors’ Contributions

Conceptualization: Mauro Alaibac, Marco Rastrelli; Collection of medical follow up data: Paolo Del Fiore, Beatrice Ferrazzi; Collection of surgical follow up: Saveria Tropea; Data Collection: Beatrice Ferrazzi, Paolo Del Fiore, Alessandra Costa; Writing-Original Draft Preparation: Beatrice Ferrazzi, Silvia Finotto; All Authors read and approved the final article.

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