



A case of Merkel cell carcinoma development under treatment with a Janus kinase inhibitor

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INTRODUCTION

Merkel cell carcinoma (MCC) is an aggressive neuroendocrine skin cancer thought to be derived from Merkel cells present in the cutaneous basement layer; these cells have synaptic contacts with somatosensory afferents. MCC is a rare malignant tumor, the development of which may be associated with immunosuppressive conditions.¹ Tofacitinib is a Janus kinase (JAK) inhibitor that exerts anti-inflammatory activity by inhibiting JAK enzymes, thereby interfering with the JAK signal transducers and activator of transcription (STAT) signaling pathway. Tofacitinib is recommended for individuals with active moderate-to-severe rheumatoid arthritis (RA) that show an inadequate response to traditional disease-modifying antirheumatic drugs or biologic agents.² Here we report a case of MCC in an RA patient thought to be caused by immunosuppression during treatment with tofacitinib.

CASE REPORT

A 66-year-old woman with refractory RA previously treated with disease-modifying antirheumatic drugs (methotrexate, d-penicillamine, and salazosulfapyridine) received monotherapy with tofacitinib (5 mg/d) from December 2009. In May 2012, she contracted herpes zoster, which was treated successfully with intravenous acyclovir. In April 2013, a reddish, elastic, hard, and dome-shaped nodule appeared on the posterior surface of the left thigh, which grew to the size of a walnut after 4 months (Fig 1). Histologic analysis found densely proliferating small round cells with numerous

Abbreviations used:

IL:	interleukin
JAK:	Janus kinase
MCC:	Merkel cell carcinoma
MCPyV:	Merkel cell polyomavirus
RA:	rheumatoid arthritis
STAT:	signal transducers and activator of transcription



Fig 1. Merkel cell carcinoma that developed on the posterior surface of the left thigh during treatment with the oral JAK inhibitor, tofacitinib.

mitoses that occupied the full thickness of the dermis (Fig 2, A and B). The tumor cells stained positive for cytokeratin 20, chromogranin A, and Merkel cell polyomavirus (MCPyV) large T antigen but were negative for thyroid transcription factor 1 (Fig 2, C and D). Thus, the cutaneous neoplasm was diagnosed as MCC. Treatment with tofacitinib was discontinued with no alternative antirheumatic drugs

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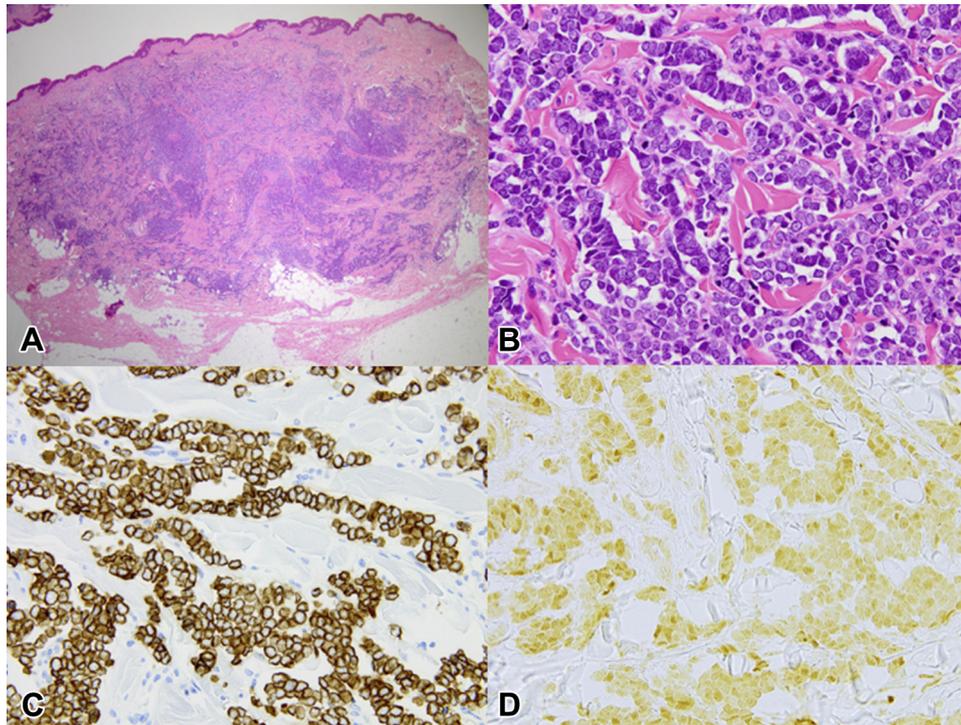


Fig 2. Histopathologic examination of the tumor. **A**, Hematoxylin-eosin staining found proliferation of tumor cells within the dermis. **B**, Small, round basophilic cells are arranged in cordlike structures. **C** and **D**, Immunohistochemical analysis found that the tumor was positive for **(C)** cytokeratin 20 and **(D)** MCPyV large T antigen. (Original magnifications: **A**, $\times 40$; **B**, $\times 400$.)

prescribed. Positron emission tomography found no metastasis to internal organs or lymph nodes. The tumor was surgically excised with a 2-cm margin. A sentinel lymph node biopsy found metastasis to 1 lymph node. Therefore, the left inguinal lymph nodes were dissected, which found no other metastasis in lymphoid tissue. Adjuvant therapy comprised irradiation (60 G) of the primary and left inguinal lesions. Four years after treatment, there are no signs of local recurrence or metastasis, even after resumption of tacrolimus treatment for recurrent arthritis. In addition, the patient had no other skin neoplasms before and during treatment with JAK inhibitor or tacrolimus.

DISCUSSION

MCCs are characterized according to the acronym AEIOU: asymptomatic/lack of tenderness, expanding rapidly (<3 months), immunosuppression, older than 50 years, and ultraviolet-exposed location.³ Among these, immunosuppressive conditions (including hematologic malignancies, acquired immune deficiency syndrome, solid organ transplants, and autoimmune disease) are associated with an increased risk of MCC development.¹ Indeed, immunosuppressed

individuals make up approximately 10% of MCC patients and show poorer MCC-specific survival.⁴

This patient was positive for MCPyV large T antigen, which is present in about 80% of MCCs and is thought to be a link between MCC and immunosuppression. Although most individuals are naturally exposed to MCPyV, very few go on to have MCC.⁵ Therefore, other factors such as an immunosuppressed state contribute to viral integration, mutagenesis, and carcinogenesis.⁶ Other tumors caused by viruses include Kaposi sarcoma and Burkitt lymphoma; both are more prevalent in immunodeficient patients.⁷ However, it is unclear whether MCPyV affects the proliferation of MCC or patient survival.

Tofacitinib is an oral synthetic small molecule drug used to treat RA. It acts by inhibiting JAK1 and JAK3, thereby interfering with the JAK-STAT signaling pathway and blocking production of interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, and IL-21. A previous study concluded that the age- and sex-adjusted standardized incidence ratio for all malignancies, excluding nonmelanoma skin cancer, among tofacitinib-treated RA patients was not elevated.⁸ However, we believe that this patient had MCC caused by tofacitinib-induced

immunosuppression because (1) she was treated with tofacitinib alone and (2) the back of the thigh is an unusual site for MCC, as it is usually shielded from ultraviolet irradiation. Additionally, It was found that phosphorylated-STAT3 signaling had an association with development of MCC and survival of patients.⁹ Previous studies report MCC associated with tumor necrosis factor inhibitors.^{10,11} JAK inhibitors and several biological agents are relatively new treatments, so it is unclear whether they have the potential to drive development of MCC; therefore, it is important to gather more MCC cases occurring in individuals treated with these immunosuppressive agents.

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