Merkel cell carcinoma associated with tofacitinib therapy

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INTRODUCTION

Merkel cell carcinoma (MCC) is a highly aggressive neuroendocrine neoplasm and the second most common cause of skin cancer-related death.[1] It is thought to be derived from Merkel cells which reside in the basement layer of the skin and function to provide somatosensory input to the body. A higher incidence of these aggressive malignancies has been seen in patients with B cell neoplasms, solid organ transplants, HIV infections as well as in countries with higher levels of UV radiation.[2]

Tofacitinib is an orally administered selective inhibitor of Janus-associated kinases (JAK) 1 and 3 exerting its antiinflammatory activity through suppression of the JAK signal transducer and activator of transcription (STAT) signaling pathway.[3] It is used primarily in the management rheumatoid and psoriatic arthritis as well as ulcerative colitis in cases who failed to respond to traditional disease-modifying antirheumatic drugs or biologic agents. Herein, we report a case of MCC developing in a 60-year-old woman with rheumatoid arthritis after 8 months of therapy with tofacitinib. This case, along with 2 previously published reports, underscores the possibility of JAK-STAT inhibitor-induced immunosuppression contributing to the development of MCC.[1,3,4]

Abbreviations used:

IFN:	interferon
IL:	interleukin
JAK:	Janus-associated kinases
MCC:	Merkel cell carcinoma
MCPyV:	Merkel cell polyomavirus
STAT:	signal transducer and activator of transcription

CASE REPORT

A 60-year-old female with a 10-year history of mild rheumatoid arthritis received monotherapy with tofacitinib (11 mg daily) beginning in July 2019. For almost 10 years prior, she received symptomatic control with only occasional nonsteroidal antiinflammatory drug use. Before being transitioned to tofacitinib, she received methotrexate for 3 months, which was discontinued due to methotrexate-induced nodulosis. After initiation of tofacitinib, the patient reported improvement in her symptoms with no adverse effects. Eight months into therapy, an indurated, nontender, pink, dome-shaped plaque appeared on the left volar forearm (Fig 1), exhibiting rapid growth over next 2 months and measuring 2.5 cm × 2.5 cm upon presentation. Biopsy results showed a dermal proliferation of small blue epithelioid cells with "salt-and-pepper" chromatin with scant cytoplasm and frequent mitoses (Fig 2, *A* and *B*). The tumor cells were negative for thyroid transcription factor-1 and positive for pancytokeratin AE1/3, cytokeratin 20 (Fig 2, *C*) with perinuclear "dot" staining, and neuron-specific enolase as well as the Merkel cell polyomavirus (MCPyV) (Fig 2, *D*) consistent with the diagnosis of MCC. Tofacitinib was discontinued immediately, the tumor was removed with 5-cm margins, and the defect repaired with an

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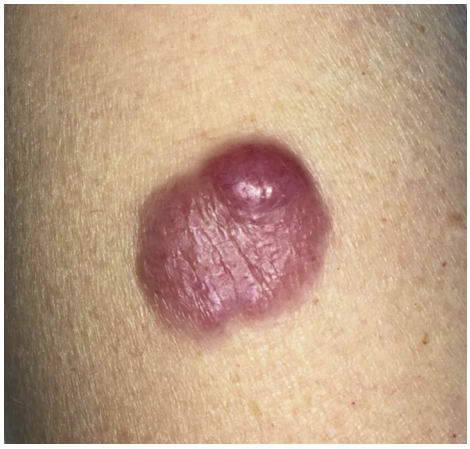

Fig 1. Onset of Merkel cell carcinoma of the left volar forearm measuring 2.5 cm × 2.5 cm during therapy with the oral Janus-associated kinases inhibitor, tofacitinib.

advancement flap. Sentinel lymph nodes were negative, and computed tomography scans of the chest, abdomen, and pelvis as well as brain magnetic resonance imaging revealed no evidence of distant disease. Despite the lack of nodal involvement, at follow up, adjuvant radiation and pembrolizumab immunotherapy was initiated. At the patient's 6- and 12-month postoperative encounter, no signs of local recurrence or metastasis were noted. She will be followed closely every 6 months.

DISCUSSION

MCCs, also known as cutaneous neuroendocrine carcinomas, demonstrate both neuroendocrine and epithelial differentiation.[2] Most frequently, they present on the head and neck as asymptomatic indurated papules or nodules with aggressive growth.[2] They are rare, occurring at an incidence rate of 0.7 per 100,000 person-years in the United States.[5] MCC is twice as common in men and typically arises in immunosuppressed individuals with 4 out of 5 new cases in patients over 70 years old.[2,5,6] Systemic immunosuppression is present in approximately 10% of MCC patients and predicts diminished survival, independent of stage.[3] MCCs are linked with the clonal integration of MCPyV DNA into the host genome.[2] While the majority of people are naturally exposed to MCPyV, very few go on to develop MCC highlighting the importance of immunosuppression in its pathogenesis.[3] Another factor contributing to MCPyV's neoplastic potential is ultraviolet radiation as MCCs tend to occur on sun-exposed areas.

Tofacitinib is an oral small-molecule compound exerting its antiinflammatory effects by suppression of the JAK-STAT signaling pathway.[7] This signaling cascade is an important second messenger for many cytokines important for both innate and adaptive immune responses, such as interferons (IFN-α, IFN-β, IFN-γ) and interleukins (IL-6, IL-7, IL-10, IL-12, IL-15, IL-21 and IL-23) also involved in proinflammatory activity in the synovial membrane in patients with rheumatoid arthritis.[7] Tofacitinib administration leads to rapid inhibition of the JAK-STAT signaling in keratinocytes within 24 hours.[8] The subsequent inhibition of the following (1) adequate recruitment of dendritic antigen-presenting cells, (2) effector T cells, and (3) IFN-γ signaling could have contributed to possible MCPyV immune escape, its proliferation, and genomic integration.[7,9]

Epidemiologic evidence suggests that MCC development in tofacitinib-treated patients is rare[4]; however, it may be difficult to capture these rare occurrences in clinical trials. Recent publications (Table I) of patients developing MCC while on long-term therapy with JAK inhibitors, including our patient as a fourth, suggest that this may not be coincidental. While typical patients with MCC are men and older than 70 years old, all reported cases (Table I) occurring while on tofacitinib occurred in women less than 70 years old.[6] It is difficult to confirm a causative relationship between JAK inhibitors and MCC given the rarity of this cancer, the limited size of long-term tofacitinib extension studies, and the relatively small population of patients using these newer agents.[4] Until larger studies are performed, increases in rare malignancies such as MCC may not be captured in study data. The main factors we believe contributed to the development of MCC in our patient are as follows: (1) the degree of immunosuppression (high dose for extended periods of time), (2) previously altered immune system due to underlying rheumatoid arthritis, (3) lighter skin type and location on sun-exposed area. Continued surveillance of patients treated with this category of medications may shed more light on long-term risks of such profound immunosuppression involving the JAK-STAT signaling pathway.

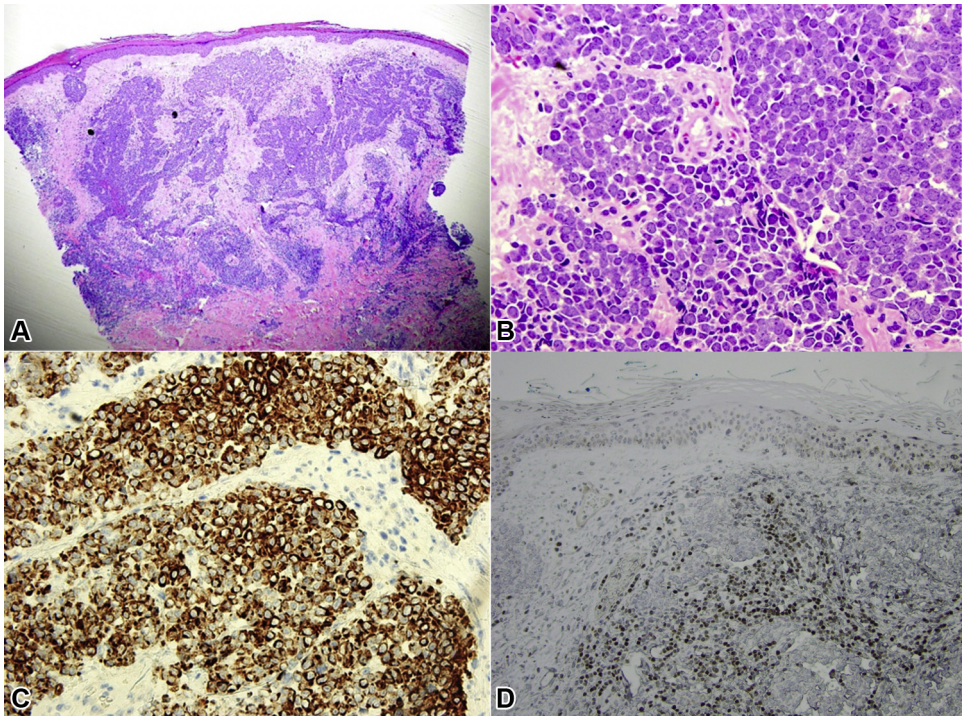

Fig 2. Histopathology of the Merkel cell carcinoma. **A**, Dense proliferation of neoplastic cells within the dermis extending into the subcutaneous tissue corneum. (Hematoxylin-eosin stain; original magnification: ×40.) **B**, Small, round basophilic cells packed tightly in sheets with numerous mitoses. (Hematoxylin-eosin stain; original magnification: ×40.) **C**, Immunohistochemistry with cytokeratin-20 staining in a paranuclear pattern. (Original magnification: ×20.) **D**, Immunohistochemistry with Merkel cell polyomavirus antigen. (Original magnification: ×20.)

Table I. Summary of cases involving Merkel cell carcinoma in patients on Janus-associated kinases-signal transducer and activator of transcription inhibitor drugs

Report	Age/sex	Location	Medication	Course (months)	Dose (mg)
Rastrelli et al[1]	47/F	Right elbow	Ruxolitinib	84	20, twice a day*
Koike et al[3]	66/F	Left posterior aspect of the thigh	Tofacitinib	40	5, once a day
Curtis et al[4]	NS	NS	Tofacitinib	NS	NS
Current case	60/F	Left volar forearm	Tofacitinib	8	11, once a day

F, Female; *NS*, not specified.
*This patient was started on 10 mg twice daily.

Conflicts of interest

None disclosed.

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