Merkel cell carcinoma in a young female on infliximab

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INTRODUCTION
Merkel cell carcinoma (MCC) is a highly aggressive neuroendocrine skin cancer that presents most frequently on the head and neck of elderly Caucasian males. Its morphology can be variable, but it most commonly appears as a rapidly growing, erythematous to violaceous cutaneous nodule. This condition is associated with a number of risk factors, including chronic ultraviolet exposure, advanced age, immunosuppression, and Merkel cell polyomavirus (MCPyV). Although rare, MCC has been increasing in frequency over the last few decades, with an estimated incidence in the United States of 3 per million per year. It is therefore important to include MCC in a differential diagnosis for a nonspecific dermal nodule, even for a patient who does not fit the typical demographic. This is especially true for immunosuppressed patients. Here, we present a case of MCC on the lower limb of a young female taking infliximab, a tumor necrosis factor-α (TNF-α) inhibitor.

CASE REPORT
A 31-year-old Caucasian female presented to the dermatology office for a nodule increasing in size on her left posterior calf that had been present for approximately 1 year. Her past medical history was significant for ulcerative colitis, which was controlled with infliximab for 17 years. Physical examination demonstrated a violaceous firm nodule that was tender to palpation (Fig 1). A 6 mm punch biopsy was performed. Histological evaluation demonstrated a dermal tumor with infiltrative growth pattern composed of cords and aggregates of cells with scant cytoplasm and enlarged, overlapping round to ovoid nuclei with stippled chromatin and prominent nucleoli (Fig 2, A). There was frequent mitotic activity. Immunohistochemistry showed positive paranuclear dot-like staining with cytokeratin 20 (Fig 2, B) and positive staining for chromogranin and synaptophysin. It was negative for thyroid transcription factor-1. This confirmed the diagnosis of MCC. She was referred to oncology, and a whole-body positron emission tomography-computed tomography revealed no suspicious foci. A wide local excision with 1.6 cm margins was performed with complete tumor clearance. Histological review of the excision specimen revealed the greatest diameter of the tumor was 1.3 cm with a depth of 7 mm. The patient had adjuvant...
intensity-modulated radiation therapy to the left posterior calf and draining lymph node basin. Her infliximab regimen was adjusted to every 12 weeks instead of every 8 weeks, and she had no evidence of recurrence at her 5-months follow-up.

**DISCUSSION**

MCC is an aggressive neuroendocrine tumor that predominantly affects sun-exposed skin of elderly Caucasian males. The average age at presentation is 69 years, with only 5% of MCC cases occurring before age 50. Within this 5%, the majority of cases are thought to be due to immunosuppression, as was the case with our patient. Immunosuppression can be due to a number of reasons, including iatrogenic, inherited, or acquired.

Similar to our case, Davenport et al describe a case of MCC arising in a 51-year-old woman on long-term infliximab therapy for Crohn's disease. The patient's treatment regimen consisted of infliximab, mercaptopurine, and sulfasalazine for many years. The tumor presented as a 1.5 cm subcutaneous nodule without surface change, growing slowly over 6 months. After negative sentinel node biopsy and whole-body positron emission tomography-computed tomography, the patient was treated successfully with definitive radiation therapy. The patient continued taking infliximab with no recurrence of the tumor at a 6-month follow-up. Due to concurrent mercaptopurine use, a causal relationship between infliximab and MCC could not be established. In addition to this case, a few cases of MCC arising during therapy with other TNF-α inhibitors have been reported. Many of these patients were also taking additional immunosuppressive medications for the treatment of rheumatoid arthritis. Our case helps support infliximab's association with MCC development since our patient was not receiving simultaneous immunosuppressive therapy. Notably, MCC was often mistaken for a benign mimicker such as an inflamed cyst or lipoma leading to a delayed diagnosis. It is vital to retain a low index of suspicion for new lesions on immunosuppressed patients, including those on TNF-α inhibitor therapy.

TNF-α inhibitors have long been documented to show carcinogenic potential. The exact mechanism by which inhibition of TNF-α predisposes patients to MCC is unclear; however, it is hypothesized that TNF-α inhibitors can encourage malignant growth by blocking the anti-tumor mechanisms of TNF-α. The name “tumor necrosis factor” reflects an inherent tumor-fighting mechanism. The antitumor effects of TNF-α have been harnessed to successfully treat MCC in both intralesional and limb perfusion formulations. Therefore, it is reasonable to postulate that inhibition of these mechanisms with anti-TNF-α therapy produces a setting conducive to tumor growth. Additionally, MCPyV, a ubiquitous human virus, is implicated in the development of most MCCs. MCPyV viral oncogenic elements have been found integrated in human DNA prior to clonal expansion, highly suggestive of a pathogenic role in MCC development. Immunosuppression may facilitate the genomic integration of MCPyV. This, combined with impaired immune recognition of aberrant cells, leads to unrestricted cellular replication and could explain the role of anti-TNF-α therapy in MCC development.

Our case describes an incidence of MCC arising in a young, immunosuppressed patient. Given that
TNF-α therapy was the only identifiable risk factor in our patient; our case supports that long-term TNF-α inhibitor therapy in the setting of ulcerative colitis can promote a microenvironment suitable for MCC tumorigenesis. With the increasing incidence of MCC overall, it is essential to keep this diagnosis in mind when evaluating immunosuppressed patients with a suspicious clinical picture, even when outside of the usual demographic. While more research is needed to prove a specific causation between TNF-α inhibitors and MCC, we believe that providers should be aware of this potential predisposition when prescribing these medications.

Conflicts of interest
None disclosed.

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Fig 2. Merkel cell carcinoma punch biopsy. A, Hematoxylin and eosin, ×20, sheets of tumor cells with scant cytoplasm and enlarged nuclei with finely dispersed (“salt and pepper”) chromatin and frequent mitotic activity. B, Cytokeratin 20, 20×, positive paranuclear dot-like cytoplasmic staining in tumor cells.