Merkel cell carcinoma (MCC) is a rare aggressive neuroendocrine tumor that manifests as an asymptomatic enlarging lesion often in the setting of immunosuppression, advanced age, or UV exposure. Immunosuppression has been associated with melanoma, lymphoma, and nonmelanoma skin cancer (NMSC). We present a case of a patient with a long-standing history of rheumatoid arthritis treated with adalimumab, methotrexate, and prednisone who developed a painless, rapidly enlarging lesion that was found to be MCC with lymph node involvement. As the use of tumor necrosis factor (TNF) α inhibitors becomes more popular, it is important to identify the potential long-term risks associated with chronic immune modulation. Systemic immunosuppression may be a risk factor for the development of advanced-stage MCC. Treatment with the TNF-α inhibitor adalimumab may enhance this risk.

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Merkel cell carcinoma (MCC) is a rare aggressive cutaneous malignancy that is thought to arise from the neuroendocrine Merkel cells in the basal layer of the epidermis and hair follicles. Immunosuppression has been reported as a risk factor for developing MCC, particularly in the setting of human immunodeficiency virus infection, chronic lymphocytic leukemia, and organ transplant. In the last 10 years, immune modulating medications, such as tumor necrosis factor (TNF) α inhibitors, have become widely used to treat inflammatory conditions such as rheumatoid arthritis and psoriasis. These biologic agents have been safe and highly effective. However, the long-term consequences of immune modulation with TNF-α inhibitors are not known. Specifically, it is unclear if the risk for malignancy known to occur with long-term immunosuppression applies to immune modulation with biologic agents.

Case Report

A 51-year-old woman with a history of rheumatoid arthritis, osteoporosis, hiatal hernia, gastroesophageal reflux disease, steroid-induced diabetes, fibromyalgia, congestive heart failure, hypertension, and steroid-induced Cushing syndrome presented with a painful red nodule of the upper left arm that had been growing over the previous 4 weeks. The patient’s family history was remarkable for an uncle and brother with rheumatoid arthritis and a mother and father with nonmelanoma skin cancer (NMSC) (basal cell carcinoma and squamous cell carcinoma, respectively). The patient had no history of malignancy. She denied alcohol use and smoking. The patient’s medications included adalimumab 40 mg every other week, methotrexate, prednisone 10 mg daily, metformin, glyburide, celecoxib, omeprazole, atorvastatin, methocarbamol, furosemide, spironolactone, temazepam, folic acid, and tramadol.

On physical examination, the patient had a firm, pink, 2-cm subcutaneous nodule of the left upper arm with surrounding erythema. She was given cephalexin 500 mg 4 times daily for 10 days for a presumed inflamed cyst with surrounding cellulitis. When she returned for an excisional biopsy of the lesion, the surrounding erythema had resolved, but the lesion had become exophytic and had doubled in size in 4 weeks (Figure 1). Histopathologic analysis revealed a nodular and diffuse proliferation of atypical small basoloid cells arranged in sheets and fascicles that splayed between collagen bundles and extended deeply into the subcutaneous tissue (Figure 2). There were highly pleomorphic tumor cells that stained strongly and diffusely with synaptophysin.
Merkel Cell Carcinoma

and also showed a perinuclear dot pattern of cytokeratin 20 (Figure 3). These findings were diagnostic for MCC.

Subsequent whole body positron emission tomography/computed tomography scan showed no hypermetabolic tumor. The tumor was widely excised and sentinel lymph node mapping revealed 1 positive lymph node in the left axilla. As a result, radical axillary dissection was performed with removal of 21 additional lymph nodes; 2 were positive for MCC. The patient underwent subsequent systemic chemotherapy and conventional fractionated radiation therapy. On latest follow-up 4 years later, the patient was doing well with no recurrence of disease.

Comment
The clinical characteristics, risk factors, and pathogenesis of MCC are not well-defined. A review by Heath et al\textsuperscript{10} revealed that although the incidence of MCC is on the rise, clinicians almost always misdiagnose MCC, usually as an inflamed cyst. The authors confirmed that immunosuppression, advanced age, and UV exposure are important risk factors for developing MCC. They described that MCC most

Figure 1. Clinical lesion on the left upper arm.

Figure 2. Excisional biopsy from the upper arm revealed a diffuse proliferation of atypical and pleomorphic cells (H&E, original magnification ×40).
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commonly presents as a rapidly growing, painless, bluish red, intracutaneous nodule. 10

Histopathologically, MCC appears in the dermis and extends to the subcutis. It appears as a poorly differentiated small blue cell tumor and on light microscopy often appears similar to lymphoma, melanoma, and basal cell carcinoma. Immunohistochemical staining, however, shows a characteristic perinuclear dot and is positive for cytokeratin 20, neuron-specific enolase, and neurofilament protein, and negative for cytokeratin 7, S-100, and leukocyte common antigen. 11

First-line treatment of localized MCC is wide surgical excision. Postoperative radiotherapy to the primary site and possible involved lymph nodes also is recommended, and although controversial, patients with distant disease can benefit from chemotherapy. Unlike other small blue cell tumors such as lymphoma, chemotherapy is not well-established for the primary treatment of MCC.

Immunosuppression has been shown in many studies to increase the risk for melanoma; lymphoma; and NMSC, specifically squamous cell carcinoma. 12-14 However, these studies do not specifically delineate the role of TNF-α inhibitors in the etiology of such malignancies, and this relationship has been controversial. Setoguchi et al15 suggested that patients with rheumatoid arthritis treated with an anti–TNF-α agent do not have an increased risk for lymphoma and solid tumors, including melanoma and NMSC, when compared to patients treated with methotrexate. A meta-analysis of patients with rheumatoid arthritis specifically taking TNF-α inhibitors did not show a significant aggregate increased risk for NMSC. Melanoma was not examined. 16 Registry studies of the incidence of NMSC in patients with rheumatoid arthritis showed that the use of any TNF-α inhibitor was associated with a slight, statistically insignificant, elevated risk for NMSC; however, concomitant use of methotrexate considerably increased this risk (hazard ratio of 1.24 for TNF-α inhibitors without concomitant methotrexate; hazard ratio of 1.97 for TNF-α inhibitors in combination with methotrexate), which suggests that there is an increased risk for NMSC with increased immunosuppressive medications. 17

The relationship of TNF-α inhibitors with lymphoma also has been controversial. An initial report to the US Food and Drug Administration from 2002 stated that the rate of lymphoma in patients with rheumatoid arthritis was similar to the general population. 18 Interestingly, 14 of 26 patients (54%) who developed lymphoma were diagnosed within 8 weeks after initiation of TNF-α antagonist treatment. In 2 of these patients the lymphoma remitted after cessation of TNF-α antagonist treatment. Asling et al 19 evaluated the risk for lymphoma in patients with rheumatoid arthritis treated with TNF-α antagonist therapy versus TNF-α antagonist–naïve patients. Their results suggested that rheumatoid arthritis patients treated with TNF-α antagonists were at a slight but nonsignificant increased risk as compared to rheumatoid arthritis patients not treated with such therapy. They further concluded that anti–TNF-α therapy does not markedly increase lymphoma risk per se in contemporary patients with rheumatoid arthritis, but the inherent lymphoma risk in rheumatoid arthritis patients starting TNF-α antagonist therapy may have changed over time. 19

The notion that immunosuppression is a risk factor for developing malignancies such as MCC, lymphoma, melanoma, and NMSC is a growing body of research, particularly in the context of our expanding armamentarium of immunosuppressive medications, such as TNF-α inhibitors. In a study of MCC in organ transplant recipients, Buell et al 20 reported that disseminated disease was the principal mode of presentation, which suggests that immunosuppressed patients with MCC present earlier and with more aggressive disease.

Conclusion
We present a case of a patient with rheumatoid arthritis on multiple immunosuppressive drugs, particularly adalimumab, who developed MCC with nodal involvement.

REFERENCES