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Single Case

An Unusual Presentation of Merkel Cell Carcinoma in the Setting of Immunosuppression on TNF-Alpha Inhibitor Therapy

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Keywords
Merkel cell carcinoma · Immunosuppression · Skin cancer · TNF-alpha inhibitor · Malignancy

Abstract
Merkel cell carcinoma (MCC) is a rare but deadly skin cancer, observed classically in the sun-damaged skin of older, white males. The cancer is characterized by rapid growth as well as high morbidity and mortality. In this article, we detail an atypical presentation of MCC in an African-American patient being treated with prednisone, methotrexate, and adalimumab for rheumatoid arthritis. Initially presenting as a subcutaneous nodule, the tumor in our patient was misdiagnosed first as an abscess and treated accordingly. Only after the subcutaneous mass failed to resolve with antibiotics as well as repeated incision and drainage was a biopsy performed, which yielded the final diagnosis. In the text, we detail the patient's symptomatology as well as steps that eventually lead to diagnostic confirmation. Our case demonstrates the importance of heightened clinical suspicion for MCC in immunosuppressed patients with unexplained subcutaneous nodules. Prompt diagnosis is crucial for positive outcomes; therefore, we aim to provide information that may aid in identification of MCC tumors in future patients. With the increasing use of biologic agents such as adalimumab to treat rheumatic disease, the literature is demonstrating an increasing incidence of previously "rare" malignancies such as MCC. It is crucial for physicians to convey these risks when initiating a patient on chronic immunosuppressive therapy and to provide routine surveillance for MCC and other complications.

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Introduction

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine malignancy that typically affects the head and neck or other sun-exposed areas of elderly, light-skinned individuals with a long history of ultraviolet ray exposure [1, 2]. While most cases are observed in elderly white males, MCC is also being diagnosed more frequently in immunosuppressed individuals who do not fit this "typical" patient description [3]. These immunosuppressed patients have increased mortality compared to immunocompetent patients, emphasizing the need for improved medical management and increased surveillance of this population [2–4].

In this article, we present a 67-year-old African-American female with a history of rheumatoid arthritis who was diagnosed with MCC of the left elbow in the setting of chronic immunosuppressive treatment with prednisone, methotrexate, and adalimumab. This case demonstrates that, in the setting of chronic immunosuppression, it is important to consider MCC in the differential diagnosis of a spontaneously arising soft tissue mass.

Case Report

A 67-year-old African-American female with a medical history significant for rheumatoid arthritis and sclerosing keratitis initially presented to the outpatient rheumatology clinic (day 0, initial presentation) with a 1-month history of a painless enlarging mass on the left elbow and subjective intermittent fever. Physical examination revealed a 2-cm indurated and erythematous mass over the left elbow with mild tenderness to palpation. Bloodwork was notable only for a mildly elevated white blood cell count of 13×10^3. At the time, the patient's medications included prednisone 10 mg daily, methotrexate 25 mg once weekly, and adalimumab 40-mg subcutaneous injection once weekly. Due to concerns for a possible infection/abscess, the patient was advised to discontinue adalimumab and was referred to acute general surgery (AGS).

The patient then presented to our outpatient primary care clinic on day 5 with similar symptoms. Physical examination was unchanged except for enlargement of the mass to an area of 3-cm × 4-cm (Fig. 1a). History, physical examination, and workup were consistent with an abscess; a 7-day course of Cephalexin 500 mg every 6 h was prescribed. On day 6, our patient was seen by AGS and again diagnosed with an abscess. An incision and drainage (I&D) procedure was performed (Fig. 1b depicts the lesion after drainage). Purulent discharge was expressed from the wound and sent for evaluation. Gram stain results revealed moderate white blood cells but no microorganisms. The final culture report was negative. Approximately 2 weeks later (day 20), the patient followed up with AGS complaining of a painless, enlarging mass beneath the previous I&D site. AGS cleared the patient, stating the mass was consistent with a hematoma with no concerns for abscess recurrence.

Our patient followed up at our outpatient primary care clinic once again on day 27 with continued complaints of left elbow mass growth, now associated with erythema and tenderness. Physical exam was notable for a 3-cm by 3-cm erythematous, superficial mass that was firm, mobile, and mildly tender to palpation. There was concern that the abscess capsule was not entirely resected after I&D procedure, so the patient was again prescribed a 7-day course of Cephalexin 500 mg every 6 hours. In addition, a complete blood count and left elbow radiograph (XR) were ordered. The CBC was unremarkable, but the XR findings were suspicious for a soft tissue lesion (Fig. 2). Ultrasound of the left elbow was performed 1 week later, revealing a hypervascular subcutaneous soft tissue mass concerning for malignancy (Fig. 3).

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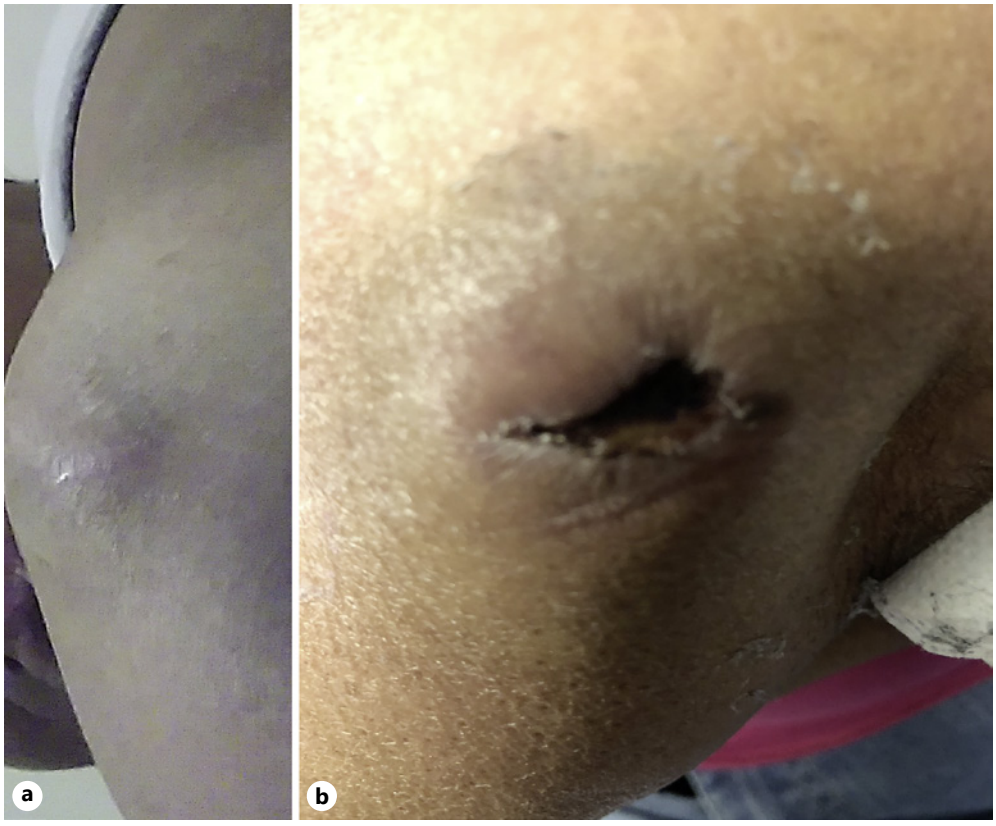

Fig. 1. a Image of initial presentation of left elbow mass. **b** Status-post I&D.

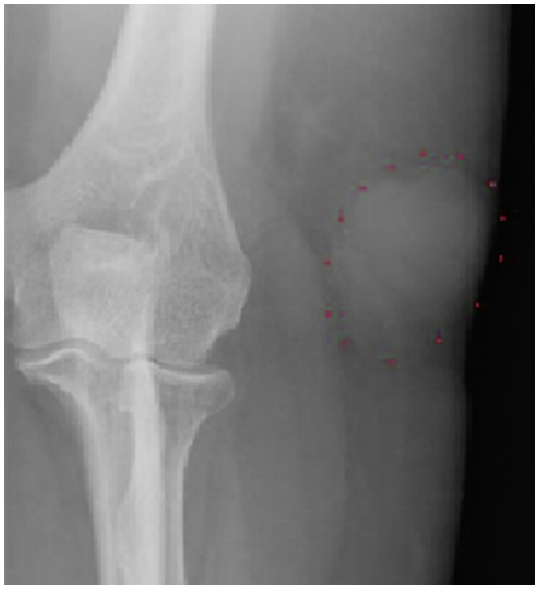

Fig. 2. Plain radiograph of the left elbow revealing slightly lobulated soft tissue mass along the lateral aspect of the elbow, measuring approximately 4 cm in diameter. Findings show no specific internal features other than a tiny circular calcification at the margin of the mass. XR is concerning for a variety of soft tissue lesions, including cysts or soft tissue neoplasm.

On day 41, our patient followed up with AGS for an incisional tissue biopsy. Histological examination revealed dermal and subcutaneous tissue sections with lesional cell proliferation, mitotic figures, and apoptosis (Fig. 4a). Immunohistochemistry revealed positive cytokeratin

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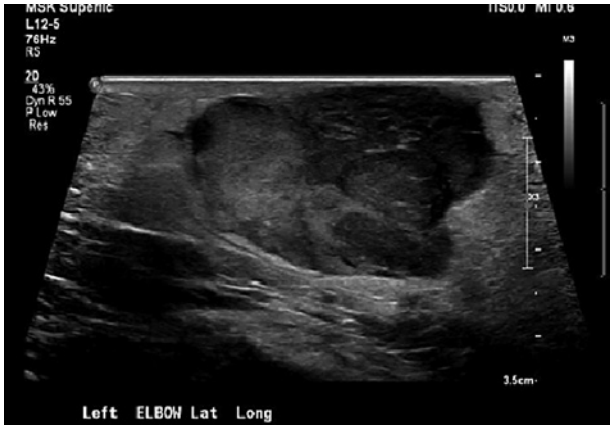

Fig. 3. Ultrasound of the left elbow revealing hypervascular soft tissue mass, measuring up to 3.7 cm located in the subcutaneous tissues over the lateral aspect of the left elbow, concerning for malignancy.

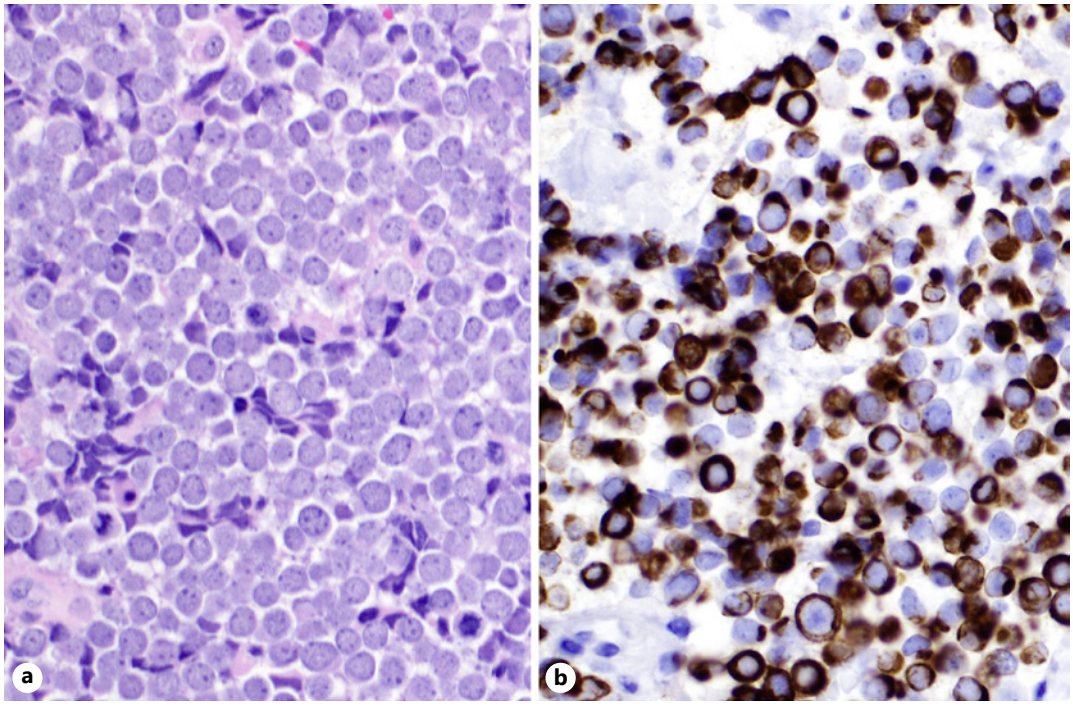

Fig. 4. a Histological examination of tissue sections revealed dermal and subcutaneous proliferation of basophilic cells with nodular and diffuse growth, scant cytoplasm, and large nuclei with finely stippled chromatin. **b** Abundant mitotic figures and apoptosis are noted. Immunohistochemistry staining revealed cells positive for CK20 (with perinuclear accentuation) and negative for TTF-1. TTF-1, thyroid transcription factor 1.

20 (CK20) and negative thyroid transcription factor 1 staining, consistent with MCC (Fig. 4b). Our patient was referred to surgical oncology, and the tumor was resected with wide local excision (2-cm margins) 71 days after initial presentation. Sentinel lymph node biopsy of three axillary lymph nodes revealed two lymph nodes positive for metastatic disease with positive immunohistochemical staining for CK20 and CK-AE1/3, leading to classification of the patient's MCC as stage IIIA (pT2 N1a M0). Computed tomography of the chest, abdomen, and pelvis; computed tomography of the left upper arm; magnetic resonance imaging of the

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brain; and a whole-body positron emission tomography scan were ordered for prognosis, staging, and diagnosis of any distant metastatic disease. All scans were negative.

The next step in management for our patient was adjuvant radiation therapy to the left elbow, managed by radiation oncology. Once monthly radiation therapy was completed, for a total of 4 months of treatment, her recovery from surgery was largely uncomplicated, and her current management plan includes regular follow-up to assess for systemic disease.

Discussion

MCC is a rapidly growing malignancy of the mechanoreceptor unit of the skin with a variable clinical presentation; most commonly, patients present with a violaceous, indurated nodule on sun-exposed skin [1]. The diagnosis is often missed at first presentation due to the benign appearance of subcutaneous nodules, which rarely ulcerate and are often <2-cm in size [5].

The role of immunosuppressive therapy in MCC pathogenesis has been suggested previously by reports of partial spontaneous regression of metastatic MCC after treatment discontinuation [6]. A large proportion of available evidence has suggested no association between TNF-alpha inhibitor therapy (such as adalimumab) and overall cancer risk [7]. However, post-marketing reporting and meta-analyses of clinical trials have suggested a potentially increased risk of lymphoma and some dermatologic malignancies, including MCC, in patients with RA [8–10].

Our case demonstrates that an increased clinical suspicion should be present when evaluating persistent soft tissue masses in immunosuppressed patients, even if they do not fit the "typical" patient profile. Although darker pigmentation plays a protective role against MCC, the disease is not limited to fair-skinned individuals. Physicians who routinely prescribe TNF-alpha inhibitors, including adalimumab, should receive increased education on MCC and maintain a low threshold to diagnostic workup of suspicious soft tissue masses. Lesions thought to be chronic abscesses which do not respond to oral antibiotics should be promptly biopsied, as delayed diagnosis contributes to a significantly worse prognosis for affected patients.

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines. The material in this publication has not been published previously, nor is it under consideration for publication elsewhere.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Kristen Delans produced the abstract, case report, and much of the discussion portion of the manuscript. Dr. Rachel Semus participated in the initial patient's evaluation and care, gathered diagnostic results and imaging studies, and wrote a significant portion of the case report section of the manuscript. Dr. Nasiffa Hossain participated in the initial patient's evaluation and care, gathered diagnostic results and imaging studies, and provided valuable feedback and modifications of the initial manuscript. Dr. Jack Ledford provided pharmacologic background information, reviewed the manuscript, provided valuable feedback and modifications, and contributed a portion of the discussion section.

Data Availability Statement

All data that support the findings of this study are included in this article. Further inquiries may be directed to the corresponding author.

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