Merkel Cell Carcinoma Arising in a Patient With a History of Multiple Malignancies

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Merkel cell carcinoma (MCC) is a rare and highly aggressive neuroendocrine carcinoma of the skin. Although the association between MCC and other primary malignancies has been documented, the mechanism of this association has not been elucidated. We report a case of MCC in a man with a history of multiple primary malignancies and treatment with immunomodulators. This case highlights the increased incidence of other malignancies in patients with MCC and is unique given the number and diversity of primary malignancies found in this patient.

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Merkel cell carcinoma (MCC) is a highly aggressive neuroendocrine carcinoma of the skin. The association of MCC with squamous cell carcinoma has given rise to the hypotheses of pluripotent stem cell origin or alternatively a shared response between 2 cellular lines to the same carcinogenic trigger.[1-3] The association between MCC and other primary malignancies has been documented in the literature.[3-5] Infection with the Merkel cell polyomavirus and immunosuppression also have been suggested as possible etiologic factors in the pathogenesis of MCC.[6-8]

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We report a case of MCC in a 67-year-old man who had a history of multiple primary malignancies and was undergoing treatment with immunomodulators. This case highlights the increased incidence of other malignancies in patients with MCC and is unique given the number of primary malignancies found in this patient.

Case Report

A 67-year-old man presented with an asymptomatic nodule on his left mid forearm of 2 weeks' duration. On physical examination the lesion was a firm, solitary, asymptomatic, pink to violaceous, dome-shaped nodule and was 3 cm in diameter (Figure 1). No axillary lymphadenopathy was noted. The patient denied

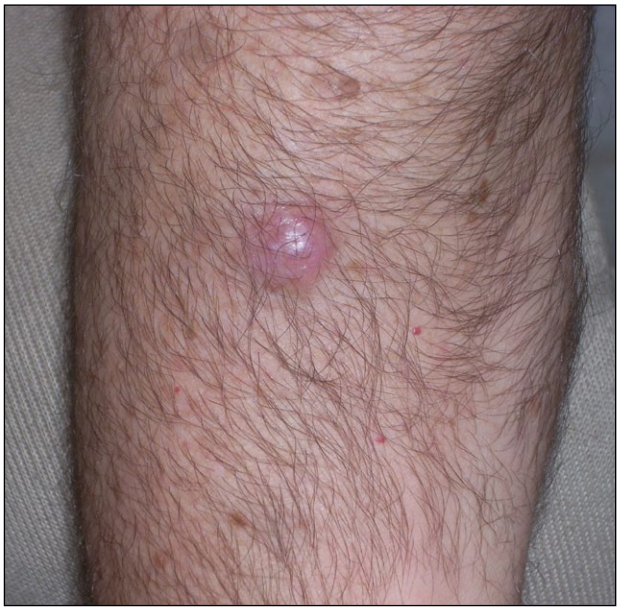

Figure 1. Merkel cell carcinoma on the left mid forearm.

symptoms of pain or pruritus at the site. A review of systems was negative for fever, weight loss, chills, and night sweats.

The patient's medical history was notable for hypertension, gout, chronic inflammatory demyelinating polyneuropathy, multiple basal cell carcinomas, bilateral renal cell carcinoma (with resection in 1992 and 2004), ductal carcinoma of the left breast (left mastectomy and negative sentinel lymph node biopsy in 2003), and non-Hodgkin lymphoma (diagnosed in 2004). At the time of presentation, the patient's medications included tamoxifen, rituximab (375 mg/m^2 for a dose of 960 mg every 2 months since February 2005), intravenous immunoglobulin infusions (50 g monthly since August 2009), atenolol, furosemide, lisinopril, colchicine, allopurinol, ranitidine, and sertraline. The patient denied a family history of skin cancer or other malignancies.

Microscopic examination of a biopsy specimen revealed a tumor composed of sheets and trabeculae of atypical cells with a stippled nuclear chromatin pattern and scant cytoplasm occupying the dermis (Figures 2A and 2B). Angiolymphatic invasion and numerous mitotic figures were identified. Immunohistochemistry was performed and the lesional cells showed staining for cytokeratin 20 in a paranuclear dotlike pattern (Figure 2C). There also was patchy positive staining for synaptophysin and chromogranin. Thyroid transcription factor 1 and cytokeratin 7 were negative. Wide local excision was performed with negative sentinel lymph node biopsy but positive margins of excision. The patient was treated with adjuvant radiation therapy and concurrently was being treated with rituximab and bendamustine for his non-Hodgkin lymphoma. Five months following excision, the patient had biopsy-proven recurrence of his MCC on the same arm but at a different site. Nine months following excision of the recurrent nodule, he had multiple recurrent MCC nodules with in-transit metastasis. The patient elected to undergo isolated limb perfusion with melphalan rather than amputation. The patient died 22 months after the initial biopsy.

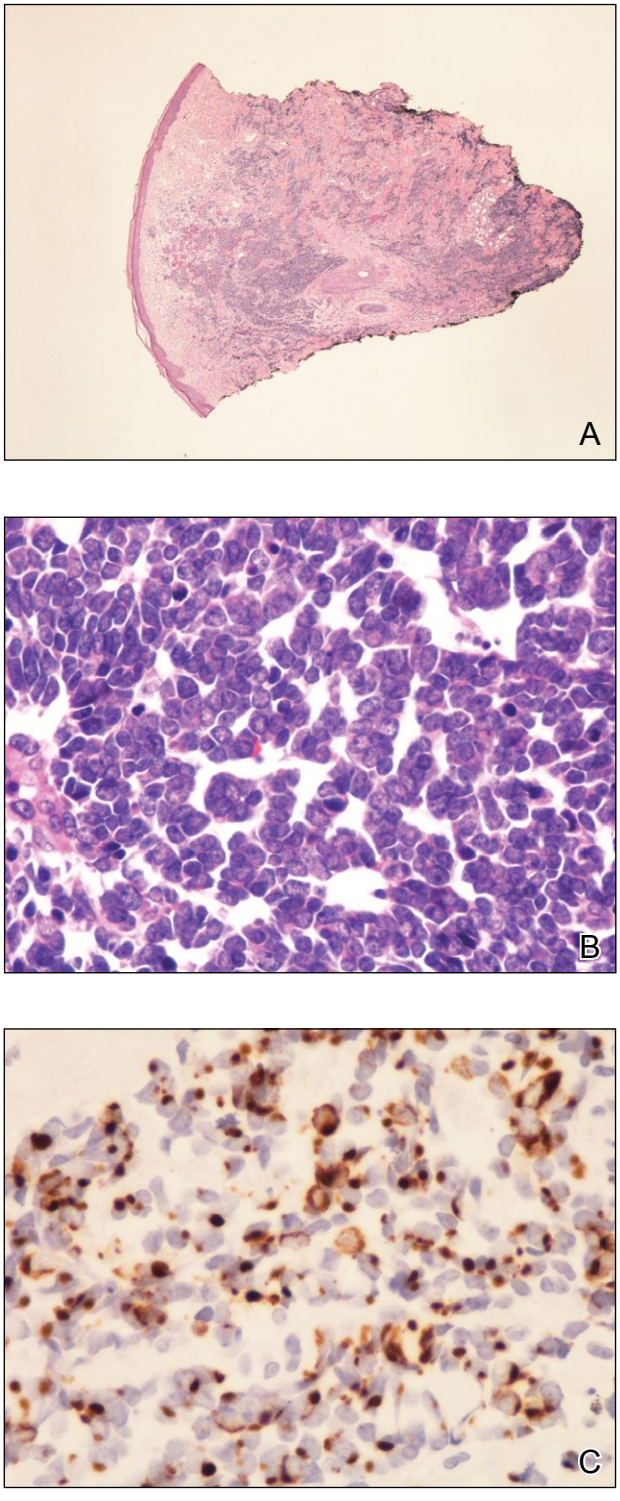

Figure 2. A punch biopsy showed an infiltrative tumor occupying the dermis (A)(H&E, original magnification ×2). High-power magnification demonstrated the stippled chromatin pattern of the lesional cells and scant cytoplasm, which are characteristic of neuroendocrine tumors. Mitotic figures were abundant (B)(H&E, original magnification ×60). An immunohistochemical stain for cytokeratin 20 was positive in a paranuclear dotlike pattern (C)(original magnification ×60).

Comment

First described by Toker[9] in 1972, MCC formerly was known as trabecular carcinoma and was defined by distinct anastomosing trabeculae and tumor cell nests within the dermis. Tang and Toker[10] later found these trabecular carcinomas to be of Merkel cell origin, given the neurosecretory granules observed via electron microscopy.

Merkel cell carcinoma is a rare tumor with approximately 1200 new cases reported in the United States each year or an annual incidence of 3 cases per

million individuals. The literature suggests an association between immunosuppression and MCC.[7,8] An increased incidence of MCC has been reported in AIDS patients, organ transplant recipients who use immunosuppressive therapies, and individuals with excessive sun exposure.[4,6,11-16] Additionally, the discovery of the Merkel cell polyomavirus, a *Polyomavirus* associated with roughly 80% of MCCs, has led to further questioning of the pathways involved in the development of MCC.[6] Of note, 3 reports have documented an association between rituximab and either development or rapid progression of MCC. In these cases, rapid growth of an existing or previously undetected MCC occurred soon after initiation of rituximab.[14-16]

Although the association between MCC and other malignancies has been reported, the etiology and pathogenesis of this connection are poorly elucidated. There is a high incidence of other cutaneous malignancies in patients with MCC, such as squamous cell carcinoma, basal cell carcinoma, and melanoma, all of them often presenting on sun-exposed areas of the skin.[3-5] Other studies also have suggested an increased association of MCC with B-cell and other hematologic malignancies, most notably chronic lymphocytic leukemia and multiple myeloma.[5,17-19]

Our patient presented with a history of malignancies that have been previously reported in association with MCC, such as breast cancer, non-Hodgkin lymphoma, and basal cell carcinoma, as well as renal cell carcinoma, which has not been reported. A shared etiologic trigger or mechanism that may play a role in the association between MCC and these other malignancies has yet to be established. Although increased surveillance, immunosuppression, and other factors may be related to the association between MCC and other malignancies, the exact molecular pathways still are undefined in the current literature. This patient represents an additional case of MCC in association with both numerous other primary malignancies as well as treatments with immunomodulatory effects. Increased recognition of the association between MCC and other specific primary malignancies may lead to greater clinical surveillance and subsequent improvements in patient outcomes due to earlier detection, diagnosis, and treatment in these patients.

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