Merkel cell carcinoma in organ transplant recipients: Case reports and review of the literature

Giorgia L. Garrett, MD,[a] Hanieh Zargham,[b] Joshua M. Schulman, MD,[a] Fatemeh Jafarian, MD,[c] Siegrid S. Yu, MD,[a] and Sarah T. Arron, MD, PhD[a]
San Francisco, California and Montreal, Quebec, Canada

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INTRODUCTION

Merkel cell carcinoma (MCC) is an aggressive tumor of the skin and mucous membranes that typically occurs in elderly white men and in immunosuppressed individuals. The reported incidence of MCC has tripled over the last 20 years in the United States[1] from 0.15 to 0.44 cases per 100 000 between 1986 and 2001.[2] In light of the poor prognosis and high risk for recurrence, metastasis, and death associated with MCC, this increasing trend is of concern. The risk factors for MCC are similar to those for other skin cancers, mainly ultraviolet light exposure, older age, T-cell immunosuppression, fair skin, and male sex.[3,4] Although a rare tumor, MCC is seen more frequently in the immunosuppressed population, and immunosuppressed MCC patients tend to be younger at diagnosis and have less favorable disease outcomes. Specifically, HIV positivity,[1] lymphocytic leukemia,[2] and iatrogenic immunosuppression after organ transplantation[3] confer an increased risk of MCC.

Here we report 2 cases of MCC occurring in organ transplant recipients (OTRs), illustrating how iatrogenic immunosuppression in the setting of organ transplantation can impact tumor progression and potentially decrease survival. We summarize current evidence regarding the pathogenesis, staging, and treatment of MCC and bring forth our recommendation to monitor high-risk OTR with frequent skin examinations. MCC has a poor prognosis and its management remains a challenge. Early recognition can improve clinical outcomes and disease-specific and overall survival in the transplant population.

Abbreviations used:

MCC: Merkel cell carcinoma
OTRs: organ transplant recipients

CASE REPORTS

Patient 1

A 64-year-old male kidney transplant recipient with Fitzpatrick skin type II received a kidney transplant in 2007 because of diabetic nephropathy and was maintained on tacrolimus and mycophenolate mofetil. He was treated with Mohs surgery for a basal cell carcinoma and a squamous cell carcinoma in situ of the face in 2012. He presented again in 2013 for the evaluation of a lesion on the dorsal surface of his left forearm (Fig 1, *A*).

On examination, a 2- × 1.5-cm erythematous nodule was noted. Histologic analysis of a biopsy specimen found sheets of small round blue cells with numerous mitotic figures infiltrating the dermis and extending into the subcutaneous tissue (Fig 1, *B*). Immunohistochemistry analysis found characteristic MCC features, including paranuclear dotlike staining for CK20.

Fluorodeoxyglucose-positron emission tomography scan did not find any abnormal focal uptake in the left upper extremity or any evidence of axillary adenopathy. Sentinel lymph node biopsy of the left axilla did not find any evidence of metastasis. Management consisted of wide local excision with 2.5-cm margins and 25 sessions of local (55 Gy) and axillary (45 Gy) external beam radiation over 5 weeks. Three months after completing radiation,

From the Department of Dermatology, University of California, San Francisco[a] and the Faculty of Medicine[b] and Division of Dermatology,[c] McGill University.

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Correspondence to: Sarah T. Arron, MD, Department of Dermatology, 1701 Divisadero St, San Francisco, CA 94115. E-mail: arrons@derm.ucsf.edu.

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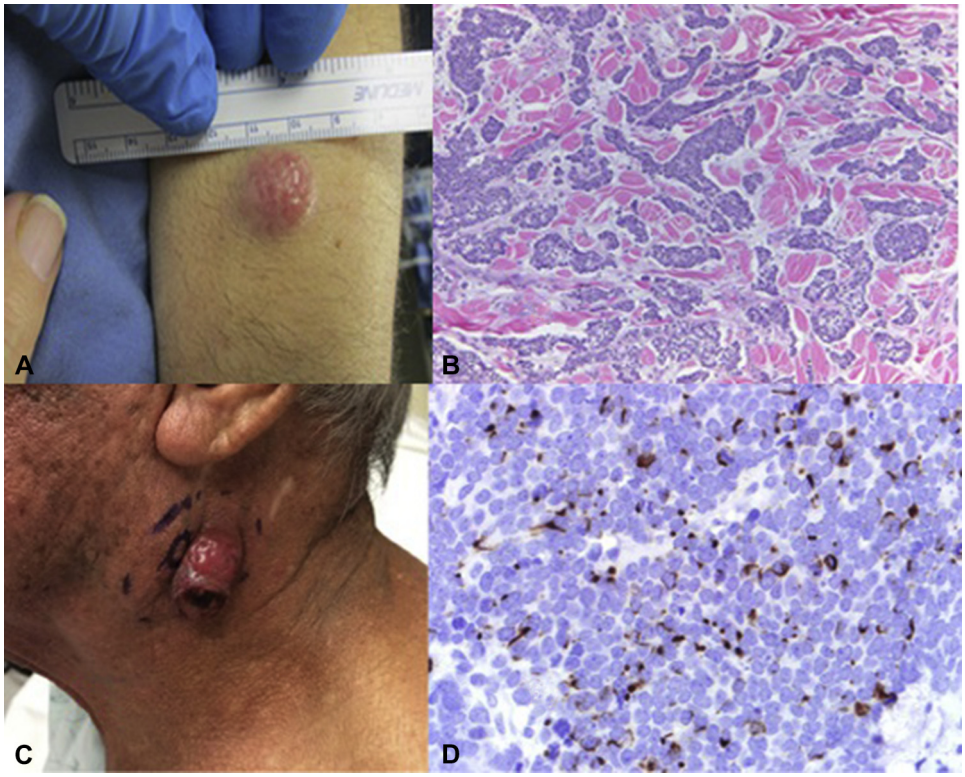

Fig 1. **A**, Rapidly growing 2- × 1.5-cm erythematous nodule on dorsal left arm of patient 1. **B**, Sheets of small round uniformed blue cells infiltrating the dermis in patient 1. **C**, Rapidly growing 2- x 3-cm exophytic erythematous nodule on the left side of the neck inpatient 2. **D**, Immunostaining for neurofilament demonstrating pathognomonic paranuclear dotlike expression in patient 2.

the patient presented with a rapidly growing 1- × 1-cm erythematous nodule on the ventral surface of left forearm, outside of the radiation field. Biopsy results of the lesion showed pathology consistent with MCC. He is currently scheduled to have complementary radiologic imaging for adequate staging and therapeutic guidance.

Patient 2

A 68-year-old Hispanic man with Fitzpatrick skin type IV received a lung transplant in 2001 for silicosis and was maintained on an immunosuppressive regime of prednisone and mycophenolate mofetil before being switched to sirolimus in 2013. He was followed closely by the dermatology department for multiple posttransplant cutaneous SCCs, despite chemoprophylaxis with acitretin, photodynamic therapy, and topical 5-fluorouracil.

Twelve years after the transplant, the patient presented with a rapidly growing 2- × 3-cm exophytic erythematous nodule with an underlying firm mass on the left side of the neck (Fig 1, *C*). A biopsy found sheets of basaloid cells with finely stippled chromatin, nuclear molding, and numerous mitotic figures. Immunostaining for neurofilament showed paranuclear dotlike positivity, consistent with MCC, and D2-40 immunostaining confirmed lymphovascular invasion (Fig 1, *D*).

Positron emission tomography/computed tomography found intraparotid and level II-VA and VB cervical lymphadenopathy, consistent with nodal metastasis. His case was presented at the multidisciplinary tumor board, and he was deemed to be a poor surgical candidate, given the rapidity of growth and poor chance for surgical control. The patient received 66 Gy external beam radiation over 6 weeks and is currently in follow-up with guarded prognosis. He has had no evidence of MCC disease for 4 months.

DISCUSSION

These cases illustrate the aggressive nature of MCC in the setting of organ transplantation. The patients had the additional risk factors of male sex and age over 60.[4] In a study examining 8 solid OTRs with MCC and 89 immunocompetent control subjects, Arron et al[5] reported that OTR with MCC

had a 4-fold increased hazard for progression (95% confidence interval [CI], 1.57-10.95), a 10-fold increased hazard for overall mortality (95% CI, 3.06-35.98), and a 12-fold increased hazard for MCC-specific mortality (95% CI, 2.67-53.08), adjusted for sex, age, and stage at presentation. OTRs also had a significantly lower 1-year overall survival rate (47% vs 89%) and a significantly lower 1-year MCC-specific survival rate (56% vs 95%).[5] Although the approach to MCC in OTR follows general management guidelines, dermatologists should act quickly to coordinate multidisciplinary care.

The evaluation of OTRs with MCC includes a complete physical examination and a low threshold for radiologic imaging to screen for nodal and metastatic spread. Histopathology and immunohistochemistry of the primary lesion can be used to confirm the diagnosis of MCC, and sentinel lymph node biopsy can identify microscopic nodal invasion in patients with negative node status on clinical examination and radiologic imaging.[6] Although the efficacy and cost effectiveness of sentinel lymph node biopsy needs further evaluation, patients with negative node status determined by pathology have a better outcome (75% at 5 years) than those who only undergo clinical nodal evaluation (59%; $P < .0001$).[7] The presence of nodal disease can provide information about prognosis and help identify the draining nodal basin for additional treatment via completion lymph node dissection or adjuvant radiation therapy.

The American Joint Committee on Cancer published a new international consensus MCC staging system, which can be used to determine prognosis and guide treatment decisions in our patients.[7] The decision to defer surgery in patient 2 was primarily influenced by the rapid growth rate, size larger than 2 cm, and presence of vascular and lymphatic invasion, which are high-risk features of MCC associated with higher rates of regional and distant metastasis and postsurgical local recurrence. The reported 5-year survival rates for local, nodal, and metastatic disease are 64%, 39%, and 18%, respectively.[7] In this unfortunate setting, surgical control was deemed unlikely. In contrast, patient 1 was considered a good candidate for wide local excision and postoperative adjuvant radiation therapy for his primary tumor. Despite these measures, a local recurrence developed outside of the radiation field.

The optimal treatment of patients with MCC is a subject of debate. Ongoing investigational studies are using molecular-targeted therapies and immunotherapy in select patient populations. Surgical excision with negative margins remains the preferred treatment for local disease, and radiation therapy is recommended for both regional and local tumors with high-risk features. Despite aggressive management with wide local excision and radiation therapy, local recurrence, distant metastasis, and in-transit metastasis are common. Most recurrences occur within 2 years of the primary tumor, with local recurrence, nodal metastasis, and distant metastasis usually noted at 4 months, 8 months, and 18 months after excision of the primary lesion, respectively.[8] Patient 1 had a second lesion 3 months after completing radiotherapy. Considering the anatomic location of his second tumor compared with the first, it is likely that the second tumor is a local recurrence or an in-transit metastasis. There is no evidence supporting the use of adjuvant chemotherapy in regional MCC disease,[9] which can actually worsen the prognosis because of the associated increase of immunosuppression and systemic side effects.[10,11] Palliative chemotherapy has a high response rate but a limited duration of response in metastatic disease.[12,13] In OTR with very aggressive MCC, a reduction or revision of immunosuppression can be considered, carefully balancing the benefits of this intervention against the risk of graft failure. However, the chances of reversing advanced disease are slim, and quality of life is an important consideration.

MCC is a late complication of transplantation. Arron et al[5] found that the time from transplantation to diagnosis ranged from 1.6 to 24.8 years (median, 5.0; interquartile range, 4.6-7.4). The risk of MCC recurrence can be minimized by aggressive and careful management, where a multidisciplinary approach based on prevention, collaboration, and early intervention can improve outcomes in high-risk patients. Most MCCs recur within 3 years of diagnosis,[10] so a full skin and regional lymph node examination is recommended, at least every 3 months in the first year, every 6 months in the second year, and annually thereafter. Dermatologists are an essential resource to the transplant team in the care of transplanted patients with advanced-stage tumors. Dermatologists should have an increased level of vigilance in their evaluation of OTR, especially in the presence of additional risk factors for MCC.

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