

Aggressive Merkel Cell Carcinoma in a Liver Transplant Recipient

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PRACTICE POINTS

- Organ transplant recipients are at an increased risk for Merkel cell carcinoma (MCC).
- Early recognition and diagnosis of MCC is important to improve morbidity and mortality.

Merkel cell carcinoma (MCC) is a rare aggressive cutaneous tumor that commonly occurs in sun-exposed sites. It has a tendency for rapid growth, local recurrence, lymph node invasion, and distant metastases. Risk factors include immunosuppression, advanced age, exposure to UV radiation, and infection with the Merkel cell polyomavirus. We report a case of a 67-year-old woman with rapidly aggressive MCC 6 years after liver transplantation.

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Merkel cell carcinoma (MCC) is a rare cutaneous neuroendocrine tumor derived from the nerve-associated Merkel cell touch receptors.¹ It typically presents as a solitary, rapidly growing, red to violaceous, asymptomatic nodule, though ulcerated, acneiform, and cystic lesions also have been described.² Merkel cell carcinoma follows an aggressive clinical course with a tendency for rapid growth, local recurrence (26%–60% of cases), lymph node invasion, and distant metastases (18%–52% of cases).³

Several risk factors contribute to the development of MCC, including chronic immunosuppression, exposure to UV radiation, and infection with the Merkel cell polyomavirus. Immunosuppression has been shown to increase the risk for MCC and is associated with a worse prognosis independent of stage at diagnosis.⁴ Organ transplant recipients represent a subset of immunosuppressed patients who are at increased risk for the development of

MCC. We report a case of metastatic MCC in a 67-year-old woman 6 years after liver transplantation.

Case Report

A 67-year-old woman presented to our clinic with 2 masses—1 on the left buttock and 1 on the left hip—of 4 months' duration. The patient's medical history was remarkable for autoimmune hepatitis requiring liver transplantation 6 years prior as well as hypertension and thyroid disorder. Her posttransplantation course was unremarkable, and she was maintained on chronic immunosuppression with tacrolimus and mycophenolate mofetil. Six years after transplantation, the patient was observed to have a 4-cm, red-violaceous, painless, dome-shaped tumor on the left buttock (Figure 1). She also was noted to have pink-red papulonodules forming a painless 8-cm plaque on the left hip that was present for 2 weeks prior to presentation (Figure 1). Both lesions were subsequently biopsied.

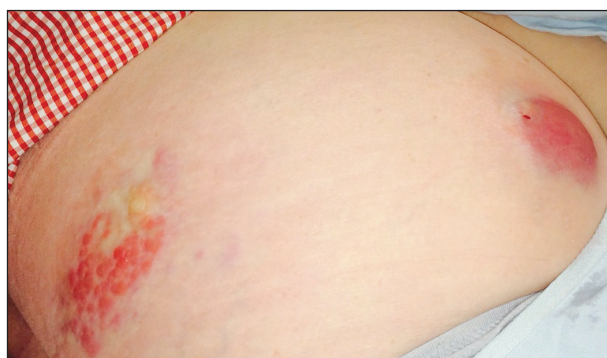


FIGURE 1. Clinical appearance of Merkel cell carcinoma lesions on the left buttock and left hip on initial presentation.

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Microscopic examination of both lesions was consistent with the diagnosis of MCC. On histopathology, both samples exhibited a dense cellular dermis composed of atypical basophilic tumor cells with extension into superficial dilated lymphatic channels indicating lymphovascular invasion (Figure 2). Tumor cells were positive for the immunohistochemical markers pankeratin AE1/AE3, CAM 5.2, cytokeratin 20, synaptophysin, chromogranin A, and Merkel cell polyomavirus.

Total-body computed tomography and positron emission tomography revealed a hypermetabolic lobular density in the left gluteal region measuring 3.9×1.1 cm. The mass was associated with avid disease involving the left inguinal, bilateral iliac chain, and retroperitoneal lymph nodes. The patient was determined to have stage IV MCC based on the presence of distant lymph node metastases. The mass on the left hip was identified as an in-transit metastasis from the primary tumor on the left buttock.

The patient was referred to surgical and medical oncology. The decision was made to start palliative chemotherapy without surgical intervention given the extent of metastases not amenable for resection. The patient was subsequently initiated on chemotherapy with etoposide and carboplatin. After one cycle of chemotherapy, both tumors initially decreased in size; however, 4 months later, despite multiple cycles of chemotherapy, the patient was noted to have growth of existing tumors and interval development of a new 7×5-cm erythematous plaque in the left groin (Figure 3A) and a 1.1×1.0-cm smooth nodule on the right upper back (Figure 3B), both also found to be consistent with distant skin metastases of MCC upon microscopic examination after biopsy. Despite chemotherapy, the patient's tumor continued to spread and the patient died within 8 months of diagnosis.

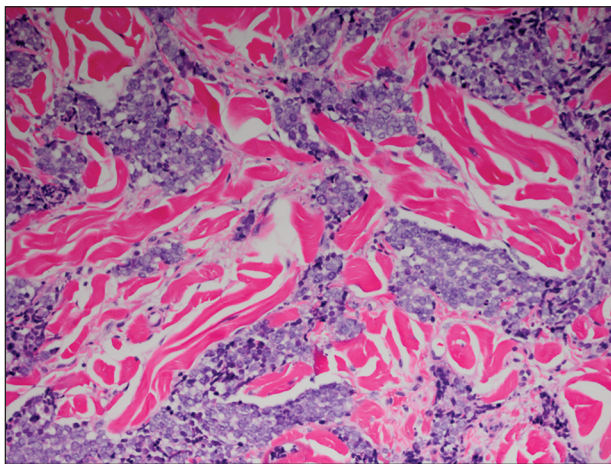


FIGURE 2. Merkel cell carcinoma tumor consisted of dense cellular dermis composed of atypical basophilic tumor cells with extension into superficial dilated lymphatic channels indicating lymphovascular invasion (H&E, original magnification ×20).



FIGURE 3. Metastatic Merkel cell carcinoma on the left groin (A) and on the right upper back (B) 4 months after initial presentation.

Comment

Transplant recipients represent a well-described cohort of immunosuppressed patients prone to the development of MCC. Merkel cell carcinoma in organ transplant recipients has been most frequently documented to occur after kidney transplantation and less frequently after heart and liver transplantations.^{5,6} However, the role of organ type and immunosuppressive regimen is not well characterized in the literature. Clarke et al⁷ investigated the risk for MCC in a large cohort of solid organ transplant recipients based on specific immunosuppression medications. They found a higher risk for MCC in patients who were maintained on cyclosporine, azathioprine, and mTOR (mechanistic target of rapamycin) inhibitors rather than tacrolimus, mycophenolate mofetil, and corticosteroids. In comparison to combination tacrolimus-mycophenolate mofetil, cyclosporine-azathioprine was associated with an increased incidence of MCC; this risk

CONTINUED ON PAGE 124

CONTINUED FROM PAGE 104

rose remarkably in patients who resided in geographic locations with a higher average of UV exposure. The authors suggested that UV radiation and immunosuppression-induced DNA damage may be synergistic in the development of MCC.⁷

Merkel cell carcinoma most frequently occurs on sun-exposed sites, including the face, head, and neck (55%); upper and lower extremities (40%); and truncal regions (5%).⁸ However, case reports highlight MCC arising in atypical locations such as the buttocks and gluteal region in organ transplant recipients.^{7,9} In the general population, MCC predominantly arises in elderly patients (ie, >70 years), but it is more likely to present at an earlier age in transplant recipients.^{6,10} In a retrospective analysis of 41 solid organ transplant recipients, 12 were diagnosed before the age of 50 years.⁶ Data from the US Scientific Registry of Transplant Recipients showed a median age at diagnosis of 62 years, with the highest incidence occurring 10 or more years after transplantation.⁷

Merkel cell carcinoma behaves aggressively and is the most common cause of skin cancer death after melanoma.¹¹ Organ transplant recipients with MCC have a worse prognosis than MCC patients who are not transplant recipients. In a retrospective registry analysis of 45 de novo cases, Buell et al⁵ found a 60% mortality rate in transplant recipients, almost double the 33% mortality rate of the general population. Furthermore, Arron et al¹⁰ revealed substantially increased rates of disease progression and decreased rates of disease-specific and overall survival in solid organ transplant recipients on immunosuppression compared to immunocompetent controls. The most important factor for poor prognosis is the presence of lymph node invasion, which lowers survival rate.¹²

Conclusion

Merkel cell carcinoma following liver transplantation is not well described in the literature. We highlight a

case of an aggressive MCC arising in a sun-protected site with rapid metastasis 6 years after liver transplantation. This case emphasizes the importance of surveillance for cutaneous malignancy in solid organ transplant recipients.

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