Update on Merkel Cell Carcinoma

Paul W. Harms, MD, PhD[a,b,*]

KEYWORDS

• Merkel cell carcinoma • Merkel cell polyomavirus • T antigen
• Neuroendocrine carcinoma • Immunotherapy

KEY POINTS

- Merkel cell carcinoma (MCC) is a rare, highly aggressive cutaneous neuroendocrine malignancy.
- Most MCC tumors are associated with Merkel cell polyomavirus (MCPyV), which expresses viral oncoproteins including large T and small T antigens.
- A panel of immunohistochemical markers is necessary for the diagnosis of MCC and distinction from morphologically similar tumors involving the skin.
- MCCs do not consistently display activation of cellular oncogenes for which clinical inhibitors are available, therefore implementing targeted therapies for these tumors has been challenging.
- Viral antigens expressed by MCPyV-positive MCC, and mutation-associated neoantigens expressed by MCPyV-negative MCC, may render these tumors sensitive to immunotherapy.

INTRODUCTION

Primary cutaneous neuroendocrine carcinoma, or Merkel cell carcinoma (MCC), is a highly aggressive malignancy. Although rare, MCC represents the second most common cause of skin cancer death after melanoma.[1,2] MCC was originally described as "trabecular carcinoma" in 1972 by Toker.[3] Ultrastructural studies established similarity to Merkel cells (a type of cutaneous mechanoreceptor cell),[4] prompting the tumor to be renamed Merkel cell carcinoma. Most cases harbor the tumorigenic DNA virus Merkel cell polyomavirus (MCPyV) that expresses

No relevant conflicts of interest to disclose.

[a] Department of Pathology, University of Michigan Medical School, 3261 Medical Science I, 1301 Catherine Street, Ann Arbor, MI 48109-5602, USA; [b] Department of Dermatology, University of Michigan Medical School, 3261 Medical Science I, 1301 Catherine Street, Ann Arbor, MI 48109-5602, USA
* Department of Pathology, University of Michigan Medical School, 3261 Medical Science I, 1301 Catherine Street, Ann Arbor, MI 48109-5602.
E-mail address: paulharm@med.umich.edu

Clin Lab Med ■ (2017) ■–■
http://dx.doi.org/10.1016/j.cll.2017.05.004 labmed.theclinics.com

oncogenic viral proteins including large T antigen (LTAg) and small T antigen (sTAg).[5] In contrast, MCC tumors lacking MCPyV demonstrate evidence of UV-associated genomic damage,[6–9] suggesting tumors may arise via viral-mediated or photodamage-mediated pathways.

EPIDEMIOLOGY

As of 2011, the annual incidence of MCC in the United States was 0.79 per 100,000, with slightly lower incidence in Europe and higher incidence in Australia.[1,10] There is higher incidence in fair-skinned populations.[1] The incidence of MCC has displayed a greater than three-fold increase in the past three decades, accompanied by increased mortality.[10]

MCC risk is influenced by patient factors including ethnicity, age, sex, and medical history. Greater than 95% of individuals with MCC are white.[11,12] There is male predominance.[11] The median age of incidence is approximately 76 years[11]; most patients are older than 50, and childhood cases are exceedingly rare.[12] UV exposure is a risk factor.[1] There is increased risk among patients with impaired immune function, including chronic lymphocytic leukemia, organ transplant, immunosuppressant medications, and human immunodeficiency virus.[1,12] Patients with MCC are at increased risk for a second malignancy, such as melanoma or hematologic malignancy.

CLINICAL PRESENTATION

MCC classically presents as a rapidly growing, firm, red or violaceous nodule on sun-exposed skin.[12] Clinical findings have been described by the AEIOU acronym (*a*symptomatic/lack of tenderness, *e*xpanding rapidly, *i*mmune suppression, *o*lder than 50 years, *u*ltraviolet-exposed site on fair skin).[12] The clinical differential diagnosis often includes cyst, lipoma, or nonmelanoma skin cancer.[12,13]

PATHOLOGIC EVALUATION

Scanning Magnification Features

A basic approach for histopathologic evaluation of MCC is shown in **Box 1**. At low power, MCC typically forms a large nodule with infiltrative borders in the dermis or subcutis (**Fig. 1**A).[14] Circumscribed nodules or entirely infiltrative patterns (see **Fig. 1**B) may also be seen. Areas of cordlike or trabecular growth through thickened collagen are often present (see **Fig. 1**C). Some tumors display organoid patterning (see **Fig. 1**D, E). Tumor necrosis is common. Stromal changes may include mucin (see **Fig. 1**F), inflammation, and increased vascularity.[15]

High Magnification Features

At high magnification, tumors consist of small round cells with minimal cytoplasm and pale, finely stippled (salt and pepper) neuroendocrine chromatin (**Fig. 2**A). Hyperchromasia, molding, and crush artifact are often present (see **Fig. 2**B). Larger cells may form cords or trabeculae (see **Fig. 2**C). In some cases, small cells with hyperchromatic nuclei and minimal cytoplasm comprise part or all of the tumor (see **Fig. 2**D). Mitotic figures and apoptotic cells are usually numerous. Epidermal involvement with pagetoid scatter is present in a minority of cases (see **Fig. 2**E, F): entirely intraepidermal cases are rare.[15] Angiolymphatic invasion may be extensive. Rosettes may be observed (see **Fig. 2**G).[16] Rare morphologies include plasmacytoid, clear cell, or anaplastic.[16]