Merkel Cell Carcinoma

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KEYWORDS

• Neuroendocrine • Merkel cell • Polyomavirus • UV

Key Points

- Merkel cell carcinoma (MCC) is an aggressive neoplasm with a high risk of metastasis, relapse, and disease-related mortality.
- The presence of lymphovascular invasion and the pattern of involvement of MCC in lymph nodes may have bearing on prognosis.
- An evolving paradigm suggests 2 distinct types of MCC, most easily stratified by Merkel cell polyomavirus (MCV) presence but also exhibited by morphologic, immunophenotypic, molecular, and clinical features.

ABSTRACT

Merkel cell carcinoma (MCC) encompasses neuroendocrine carcinomas primary to skin and occurs most commonly in association with clonally integrated Merkel cell polyomavirus with related retinoblastoma protein sequestration or in association with UV radiation–induced alterations involving the TP53 gene and mutations, heterozygous deletion, and hypermethylation of the *Retinoblastoma* gene. Molecular genetic signatures may provide therapeutic guidance. Morphologic features, although patterned, are associated with predictable diagnostic pitfalls, usually resolvable by immunohistochemistry. Therapeutic options for MCC, traditionally limited to surgical intervention and later chemotherapy and radiation, are growing, given promising early results of immunotherapeutic regimens.

OVERVIEW

Diagnosis of stage IV MCC is associated with an approximate 11% survival and a median survival of 6 months. Overall, the 5-year disease-specific survival (DSS) rate for MCC is estimated to be between 30% and 64%,[1] with a DSS rate greater than 90% for those with local disease.[2] It is thus clear that the timely and accurate diagnosis of this aggressive primary cutaneous neuroendocrine carcinoma (NEC) is critical, yet as many as 56% of MCCs are thought to be clinically benign at biopsy.[3] The thoughtful evaluation of poorly differentiated/basaloid infiltrates in the skin, subcutaneous tissues, salivary glands, and lymph nodes can allow for earlier recognition, correct diagnosis, and clinically useful pathologic characterization of MCC. Pathologic pitfalls in the diagnosis of MCC derive from lack of exposure to these rare tumors, lack of adequate sectioning of nondiagnostic tissue, hasty interpretation of small round blue cell tumors in the skin, inadequate provision of clinical history, and underutilization of immunohistochemistry in the diagnostic work-up. A basic understanding of the lymphovascular nature of tumor spread as well as the two major and apparently distinct pathways of MCC pathogenesis can serve as a reminder of the most salient reportable features of these tumors to enable the best prognostic and therapeutic algorithms for individual patients with this disease.

GROSS FEATURES

MCC most often presents in an older white population with a male predominance. The median age of presentation falls within the late seventh decade, despite a broad age range (fourth to tenth decades). Sun-exposed sites, including the head/neck and limbs, are the most common sites of presentation. There seem to be 2 patterns of clinical presentation that align with either MCV-positive,

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morphologically monophenotypic, and/or cytokeratin 20 (CK20)-positive tumors versus MCV-negative, often morphologically heterogeneous, tumors. The first, more prevalent group (80% of cases) arises in a slightly younger population and is equally present on the limbs and head/neck, sometimes found on the buttock or other non–sun-exposed sites. These tumors are often (>45%) indeterminate to clinically benign flesh-colored to violaceous dome-shaped nodules with chief differential diagnoses of cysts, pimples, dermatofibromas, lipomas, and lymphomas; 10% are suspected to be nonmelanoma skin cancer. The second group of patients more commonly presents with tumors in sun-damaged skin of the head and neck, in a background of other nonmelanoma skin cancers, and are clinically more likely to be diagnosed as a new nonmelanoma skin cancer (58%), with only 15% suspected to be benign.[4] Clinical features, such as overlying scale and nearby actinic keratoses, solar lentigines, and telangiectasia, are common. A third, smaller group of patients presents with nodal adenopathy, eventuating in a biopsy-diagnosis of apparently metastatic MCC of unknown primary skin site.[5]

MICROSCOPIC FEATURES

The quintessential small round blue cell tumor with salt-and-pepper chromatin, MCC practically defines pattern recognition. Most often, the tumor cells are uniform, with round to oval nuclei, finely dispersed chromatin, inconspicuous nucleoli, distinct nuclear membranes, scant cytoplasm, and numerous mitoses with nuclear fragmentation (**Fig 1**A). Small cell variants also show nuclear molding and crush artifact. Morphologic subtypes have been suggested evaluating the presence/absence of second tumor-types (eg, squamous cell carcinoma [SCC], in up to 15% of cases [see **Fig 1**B], or basal cell carcinoma [BCC]),[6] epithelial involvement (within epidermis [see **Fig 1**C] or adnexal epithelium [see **Fig 1**D]),[7,8] architectural arrangement (infiltrative periphery vs smooth nodular borders [see **Fig 1**E]),[9] cell size (small, medium, or large), and cell shape.[10] Regardless of pattern, tumors localize predominantly to the dermis as 1 or multiple nodules and may invade deeply into the subcutis. Tumor microemboli are frequently found within peritumoral lymphatic spaces (see **Fig 1**F).

A majority of MCC express cytokeratins, most characteristically CK20 in 95% of cases (**Fig 2**A) or Cam5.2 in a paranuclear dot-like and/or cytoplasmic pattern, neuroendocrine markers (most commonly synaptophysin, chromogranin, and CD56), and neurofilament (NF). Thyroid transcription factor-1 (TTF-1) and CDX-2 are negative. P63 is reported present in 60% of MCC and may be associated with a poorer overall and disease specific survival rates.[11–13] CK7 is generally negative, but occasional reported cases are positive.[14,15]

MCV is present in 55% to 90% of MCC by immunohistochemistry (see **Fig 2**B). NF is more frequently negative in MCV-negative cases with combined morphology.[16] These cases are more highly represented among the CK20-negative MCC population and have been shown to uniquely express follicular stem cell markers[17] and higher labeling with p53.[16,18]

DIFFERENTIAL DIAGNOSIS

BASAL CELL CARCINOMA

Distinguishing MCC from BCC requires attention to cytologic and stromal detail. Specifically, MCC lacks palisading peripheral cells and displays characteristic neuroendocrine cytology. MCC may be seen within the epidermis/adnexal epithelium, but does not bud from the base of the epidermis. Other confounders in MCC include mucinous stroma, stroma-tumor clefts, mucinous intratumoral glandular spaces (see **Fig 3**A), and focal peripheral palisading,[15] but these are limited. Ber-EP4 and epithelial membrane antigen (EMA) may be positive in MCC.[19] BCC can show neuroendocrine-type chromatin and immunolabeling, for example, with chromogranin.[20] Cam5.2 can be seen in BCC.[15] Strong dot-like labeling by CK20 strongly favors MCC,[21] and MCV is negative in BCC.

MELANOMA

Small cell melanoma occasionally enters the differential diagnosis of MCC. Both tumors may exhibit irregular nesting at the dermoepidermal junction,[15] and pagetoid/bowenoid extension in the epidermis (see **Fig 3**B).[22] Large irregular nuclei and prominent cherry-red nucleoli are unusual in MCC and favor melanoma, although in one study 20% of MCCs showed intranuclear inclusions.[15] Pigment granules favor melanoma, although melanophages may be noted in MCC. Immunohistochemistry resolves the diagnosis in most cases. Occasional MCCs are S100 positive but HMB-45 negative and NKI/C3 negative.[23] MCV is negative in melanoma.

METASTATIC NEUROENDOCRINE CARCINOMA

Clinical evaluation is paramount to diagnose metastatic neuroendocrine carcinoma (NEC) to skin. A few pathologic features may be helpful. Architectural and cytologic features of concern include extensive lymphovascular involvement, adenoidal patterns of growth, anisocytosis, large irregular