Published in final edited form as:

Surg Pathol Clin. 2017 June ; 10(2): 399–408. doi:10.1016/j.path.2017.01.013.

Merkel Cell Carcinoma

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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.

Keywords

Neuroendocrine; Merkel cell; Polyomavirus; UV

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, 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 1A). 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 1B], or basal cell carcinoma [BCC]),⁶ epithelial involvement (within epidermis [see Fig 1C] or adnexal epithelium [see Fig 1D]),^{7,8} architectural arrangement (infiltrative periphery vs smooth nodular borders [see Fig 1E]),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 1F).

A majority of MCC express cytokeratins, most characteristically CK20 in 95% of cases (Fig 2A) 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 2B). 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 markers¹⁷ 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 3A), 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 3B).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 nucleoli, coarse chromatin, and more abundant cytoplasm than seen in MCC (see Fig 3C). Immunohistochemistry favoring metastatic disease includes TTF-1 (eg, lung or thyroid [up to 85%]),²⁴ CK7 (73% of metastatic NEC),^{14,25–27} and CDX-2.²⁸ MCV is negative in metastatic NEC.²⁹

Metastatic Well-Differentiated Neuroendocrine Tumor

Histologic lack of high-grade neuroendocrine features can exclude metastatic NEC but may be seen in metastatic well-differentiated neuroendocrine tumor (WDNET) (see Fig 3D). Although these tumors are often positive for synaptophysin, chromogranin, and CD56, they are negative for CK20.

Ewing Sarcoma

Ewing sarcoma (EWS) and MCC are both small round blue cell tumors that may show strong membranous labeling for CD99 and nuclear labeling for FLI-1. Most cutaneous EWS

show EWS rearrangements, for example, t (11; 22), by fluorescence in situ hybridization (FISH) or reverse transcription–polymerase chain reaction (RT-PCR). All cases are immunohistochemically negative for MCV.³⁰

Lymphoma

Peripheral lymphomas may mimic small cell MCC morphologically and immunohistochemically; PAX-5, Terminal deoxynucleotidyl Transferase (TdT), CD56, and CD99 may be positive in MCC.^{15,19} A small panel of immunohistochemistry, including CD43 and/or CD45, CK20, and MCV, typically resolves the diagnosis.

Sebaceous Carcinoma

Rippled architecture, sebaceous mantle involvement, and pagetoid intraepidermal spread can make sebaceous carcinoma a suspect entity in the differential diagnosis of superficial MCC (see Fig 3E). Occasional EMA, p53, and p63 positivity in MCC confounds. A helpful feature is that sebaceous carcinoma is CK20³¹ and MCV negative.

Squamous Cell Carcinoma

SCC with robust neuroendocrine differentiation may be impossible to tease apart from MCC (see Fig 3F). If CK20 is positive or there is abundant NF and/or neuroendocrine granule positivity, these tumors are traditionally categorized as MCC. Evidence builds, however, that MCC with squamous differentiation is clinically different and harbors histologic and molecular signatures, similar to CK20-negative MCC,³² of UV-related squamous epithelial tumors.^{4,16,17} Such tumors show less CK20 and NF positivity and more p53 and follicular stem cell markers^{16–18} and are always negative for MCV. Well-differentiated SCC is easily diagnosed.

Diagnosis

As many as half of all MCCs are unsuspected at the time of biopsy; therefore, the most important aspects of diagnosis are an open mind to pattern recognition, knowledge of MCC as a diagnostic possibility in solitary cutaneous growths, and attention to the clinical description of a nodular lesion in the context of superficial biopsies. Although the most common diagnostic pitfall is probably misdiagnosis of MCC as BCC, a significant runner-up is the failure to diagnose MCC in a too-superficial biopsy. As with all superficial biopsies, if the histopathologic findings do not match the clinical suspicion, deeper levels and a recommendation to the clinician to perform a deeper or excisional biopsy are strongly encouraged.

Cytomorphologic neuroendocrine features, when recognized in a skin tumor, require evaluation by CK20 for any type of staining (membranous, cytoplasmic, or Golgi, although dot-like perinuclear pattern is common) as well as limited markers of extracutaneous NEC, including TTF-1 and CDX-2.²¹ CK20 labeling may require higher-power microscopic assessment to identify occasional sparse and/or faint dot-like staining. Along with CK20, assessment of at least 1 marker of neuroendocrine differentiation (eg, synaptophysin) can be helpful to confirm the neuroendocrine nature of the tumor and to prevent missed diagnoses

in the occasional CK20-negative MCC. In such a case, positive evidence of neuroendocrine granules should prompt evaluation of another low-molecular-weight cytokeratin, in particular, Cam5.2, which labels many of the CK20-negative MCCs. Immunohistochemistry for MCV is specific but not sensitive and is not available in all laboratories. If a truly undifferentiated small round blue cell tumor is encountered in a routine biopsy sample, it may be reasonable to request a limited immunohistochemical panel to rule out melanoma and lymphoma (S100 or SOX10 and CD43). If there is distinct dermoepidermal junction nesting, then a second melanocytic differentiation marker, such as Melan-A, may be assessed (Fig. 4).

Pathologic reporting should include, at a minimum, tumor size, peripheral and deep margin status, lymphovascular invasion, and the presence/absence of bone/muscle/fascia or cartilage involvement.³³ The authors encourage the reporting of second tumor phenotypes, for example, SCC or BCC. Additional reporting considerations include thickness, mitotic rate, growth pattern,⁹ tumor infiltrating lymphocytes,³⁴ and MCV immunohistochemistry.

Sentinel lymph node evaluation is commonly requested. For tumors that do not show diffuse involvement or large clusters of metastatic tumor, immunohistochemistry may be needed to identify scattered intranodal tumor cells. Most commonly, if the nodal tumor volume is low, cells present in a peripheral intraparenchymal pattern of single cells, most easily found with CK20 (and/or Cam5.2 as appropriate).³⁵ The American Joint Committee on Cancer recommendation for lymph node reporting includes tumor burden, size, and the presence/absence of extracapsular invasion.⁵

Prognosis

DSS in MCC is difficult to measure, given the overwhelming occurrence of this disease in an older population.³⁶ Between 50% and 76% of MCCs present as localized skin disease.^{2,36,37} Most people with a diagnosis of local, cutaneous-only disease have the same life expectancy as those without the disease,³⁸ keeping in mind that MCC presents predominantly in the seventh to eighth decades. Recurrences of all MCCs are common and only partly related to the adequacy of excision, with recurrence occurring even in patients with greater than 2.5-cm surgical margins.^{39–41} Nodal metastases to local regional lymph nodes occur early, and patients may have disease progression to distant sites, such as liver, bones, lung, brain, and distant lymph nodes. When the disease involves noncutaneous sites, more than half of MCC patients seem to succumb.³⁸ MCC survival analyses that control for the impact of deaths due to other causes are drawn from small groups but confirm a significant impact of the disease at all stages, with a reported 5-year relative percent survival of 69 in stage I disease and 64 in all local disease, 39 in regional nodal disease, and 18 in patients with distant metastases, indicating a broad and highly stage-dependent prognostic range for a diagnosis with this cancer.³⁶ Recent analyses failed to control for the effect of death due to other causes in this population³³ but have higher statistical power due to greater numbers of patients in tumor registries. In these studies, pathologically node-negative skin-limited disease (without involvement of deep structures) is associated with a 5-year overall survival rate of 54% to 63.8%, whereas involvement of deep cutaneous structures (fascia, muscle, cartilage, or bone) and/or lymph node positivity by either clinical or sentinel lymph

node evaluation correlates with decreased overall survival rates of 26% to 40.3%.³³ Primary tumor size cutoff of 2 cm is still considered a significant break point in prognosis.³⁷ Microscopic lymph node analysis allows for a more clear-cut prognostic stratification of 5-year overall survival rates in stage I (<2 cm) and stage II or above.⁵ Nodal tumors of unknown primary skin site seem to have a better prognosis and are considered separately.⁵

Additional features that may affect prognosis of patients with MCC include other disease states that associate with MCC, including immunodeficiencies, such as chronic lymphocytic leukemia/lymphoma, HIV, and post-transplant–related immunosuppression. In future algorithms, the impact of immunosuppression, polyomavirus positivity, and molecular/morphologic-based stratification may be useful.

Regarding pathologically prognostic features, on multivariate as well as univariate analysis, the presence of lymphovascular invasion has been repeatedly shown to risk-stratify patients.^{42,43} Univariate analysis of pathologic features, such as tumor size,⁴⁴ cell size,^{11,44} inflammatory reaction,⁴⁵ number of mitoses/high-power field,⁴⁴ and p63,^{11,46} and a few other features have occasionally suggested slight associations with outcomes but require additional validation.

Acknowledgments

Sources of Support: This research was funded in part through the NIH/NCI Cancer Center Support Grant P30CA008748.

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Table 1
Pathologic Key Features, for Merkel Cell
Carcinoma

Clinical^{4,47}

- Nonspecific dome-shaped firm nodule or tumor
- Flesh-colored to erythematous to violaceous
- +/- overlying scale and telangiectasia (more in UV areas)

Dermoscopic^{4,48,49}

- Polymorphic vascular pattern
- Milky-white structureless areas

Histologic^{9,50}

- Small round blue cell tumor in dermis/subcutis ± epidermal/adnexal involvement
- +/- overlying/intermingled atypical epidermis or intratumoral squamous islands/eddies
- Circumscribed or infiltrative borders
- Sometimes extensive surrounding lymphovascular tumor emboli
- Sometimes islands of tumor necrosis
- Numerous mitotic figures
- Cell types include
 - Small: hyperchromatic nuclei, fragile chromatin, molding, crush artifact
 - Medium: cleared out nuclei, salt-and-pepper chromatin, defined nuclear borders, inconspicuous cytoplasm
 - Large: large size, pleomorphic, irregular chromatin, abundant cytoplasm, +/- nucleoli

Table 2
Differential Diagnosis, Of Merkel Cell Carcinoma

Differential Diagnostic Consideration	Helpful Distinguishing Features	Helpful Immunohistochemical Findings
BCC	Abundant peripheral palisading, low cuboidal to columnar cells, budding off of the epidermis, mucin, single-cell necrosis	BEREP4 ⁺ MCV ⁻
Melanoma	Predominance of irregular intraepidermal nests, cytologic pleomorphism, irregular nuclear borders, prominent nucleoli, melanin pigment, +/- regressive dermal changes	MelanA ⁺ , HMB-45 ⁺ , MART-1 ⁺ , SOX10 ⁺ , NKI-C3 ⁺
Metastatic NEC	Large, pleomorphic cytology	TTF-1 ⁺ , CDX-2 ⁺ CK20 ⁻ , MCV ⁻
Metastatic WDNET	Lobulated islands/trabeculae of cells, pooling of hemorrhage, uniform cytology	TTF-1 ⁺ , CDX-2 ⁺ CK20 ⁻ , MCV ⁻
EWS	EWS rearrangements for example, t(11;22), by FISH or RT-PCR	MCV ⁻
Lymphoma	Vesicular, cerebriform, reniform or wreath-shaped nuclei, scant cytoplasm	CD3 ⁺ or CD20 ⁺ CD43 ⁻ , CD45 ⁻ , CK20 ⁻ , MCV ⁻
Sebaceous carcinoma	Crenulated nuclei, vacuolated cytoplasm, often extensive intraepidermal or intra-adnexal involvement	CK20 ⁻ , MCV ⁻
SCC	Preponderance of squamous differentiation, in situ SCC component, clear transition between well differentiated and less well differentiated areas	CK20 ⁻ , MCV ⁻

Table 3
Pitfalls, in Diagnosis of Merkel, Cell Carcinoma

! Mucin, stromal-tumor clefts, and focal palisading may lead to an erroneous diagnosis of BCC. Remember that Ber-EP4 can be positive in MCC as well as BCC.

! Superficial biopsies showing SCC with basaloid cells at the base — consider CK20!

! CK20 negativity does not exclude MCC; Cam5.2 and/or synaptophysin should allow correct diagnosis.

! Large nucleoli do not exclude MCC, although extracutaneous NEC should be considered.

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.

Fig. 1.

(A). Cytomorphology of MCC showing round nuclei, scant cytoplasm, salt-and-pepper chromatin, indistinct nucleoli [Hematoxylin-eosin, original magnification $\times 200$]. (B) Combined MCC; a small cell component demonstrates small round nuclei with crush artifact whereas a second more epitheloid population is punctuated by large keratinizing squamous cells [Hematoxylin-eosin, original magnification $\times 400$]. (C) Intraepidermal pagetoid extension of MCC overlying a dermal tumor nodule (focally seen in left lower corner) [Hematoxylin-eosin, original magnification $\times 400$]. (D) MCC in situ arising within severely dysplastic squamous epithelium/SCC in situ of epithelium, associated with invasive NEC in adjacent dermis [Hematoxylin-eosin, original magnification $\times 400$]. (E) Low-power photomicrograph showing nodular circumscription of a dermal tumor [Hematoxylin-eosin, original magnification $\times 40$]. (F) Intralymphatic tumor emboli of MCC within ectatic deep dermal lymphatics [Hematoxylin-eosin, original magnification $\times 400$].

Fig. 2.

(A) CK20 stain in a combined tumor shows a varied pattern of labeling, including patchy but diffuse perinuclear dots as well as areas of membranous accentuation [Hematoxylin-eosin, original magnification $\times 400$]. Squamous cell shows strong cytoplasmic labeling as well [Hematoxylin-eosin, original magnification $\times 200$]. (B) Polyomavirus immunohistochemical stain diffusely labels tumor nuclei [Hematoxylin-eosin, original magnification $\times 400$].

Fig. 3.

Differential diagnostic considerations of MCC. (A) Islands of small round blue cells with mucinous tumor-stroma retraction in MCC mimicking BCC [Hematoxylin-eosin, original magnification $\times 400$]. (B) Extensive intraepidermal and pagetoid spread in MCC mimicking melanoma in situ [Hematoxylin-eosin, original magnification $\times 200$]. (C) Pleomorphism (architecturally and cytologically) characteristic of a metastatic NEC, in a tumor derived from the lung [Hematoxylin-eosin, original magnification $\times 400$]. (D) WDNET/carcinoid metastatic to the skin shows organized, organoid architecture and lacks high grade nuclear features [Hematoxylin-eosin, original magnification $\times 400$]. (E) In situ component of MCC; some intraepidermal tumor cells appear to have bubbly cytoplasm and an intrafollicular localization reminiscent of sebaceous carcinoma [Hematoxylin-eosin, original magnification $\times 400$]. (F) Combined MCC/SCC; immunohistochemistry would be needed to distinguish from poorly differentiated SCC [Hematoxylin-eosin, original magnification $\times 100$].

Fig. 4.
Diagnostic algorithm for MCC. H&E, hematoxylin-eosin stain.