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Merkel Cell Carcinoma: Update and Review

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Merkel cell carcinoma (MCC) is a rare, aggressive, and often fatal cutaneous malignancy that is not usually suspected at the time of biopsy. Because of its increasing incidence and the discovery of a possible viral association, interest in MCC has escalated. Recent effort has broadened our breadth of knowledge regarding MCC and developed instruments to improve data collection and future study. This article provides an update on current thinking about the Merkel cell and MCC.
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Merkel cell carcinoma (MCC) is a rare, aggressive, and often fatal cutaneous malignancy. It usually presents as a banal-appearing lesion and the diagnosis is rarely suspected at the time of biopsy. Because of increasing incidence and the discovery of a possible viral association, interest in MCC has escalated rapidly.

From 1986 to 2001, the incidence of MCC in the United States has tripled, and approximately 1500 new cases are diagnosed each year.[1,2] MCC occurs most frequently among elderly white patients and perhaps slightly more commonly in men. MCCs tend to occur on sun-exposed areas, with nearly 80% presenting on the head, neck, and extremities.[3] Immunosuppression increases the relative risk of MCC with an approximately 13-fold increase in patients with HIV and a 10-fold increase in solid-organ transplant patients.[4,5] Patients with chronic lymphocytic leukemia (CLL) have an increased risk of MCC as well.[6] MCC is particularly aggressive with a relative mortality of approximately 30% at 2 years after diagnosis and 50% at 5 years after diagnosis.[7] Many patients present with metastatic disease, and there is a high risk of local, regional, and distant recurrence despite treatment.

Recent research has broadened our breadth of knowledge on the subject of MCC. This article provides an update on current thinking, including novel insights into the Merkel cell; a review of the 2010 National Comprehensive Cancer Network (NCCN) therapeutic guidelines and new American Joint Committee on Cancer (AJCC) staging system; recommendations for pathologic reporting and new diagnostic codes; and the recently described Merkel cell polyoma virus (MCPyV).

History

Merkel cells (MCs) were first described by Friedrich Merkel in 1875 as clear cells associated with nerve fibers.[8] Merkel assumed that MCs were involved in sensation, and called them *tastzellen* or touch cells. MCC was first described by Toker in 1972.[9] Termed "trabecular cell" carcinoma, reports of its pathogenesis, course, and treatment were relatively sparse and mostly limited to case reports or small series. Efforts to advance knowledge in the disease were confounded by its rarity, lack of reliable specific markers for diagnosis, and varied staging systems. Because of their similar histologic characteristics, MCC is generally believed to derive from cutaneous MCs or a common precursor.

Clinical Presentation

The primary lesion of MCC is distinguished by its absence of distinctive clinical characteristics. Rarely suspected at the time of biopsy, the clinical differential diagnosis includes more common lesions, such as basal cell carcinoma (BCC), epidermoid cyst, or even amelanotic melanoma. MCC often presents as a rapidly growing, asymptomatic, reddish-blue dermal papule or nodule that develops over the course of weeks to months (Fig. 1). The mnemonic AEIOU has been used to describe its clinical appearance and demographic characteristics: asymptomatic, expanding rapidly, immune

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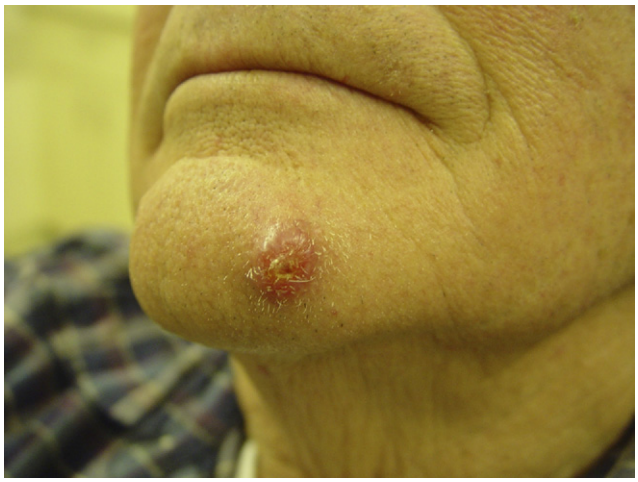


Figure 1 Primary MCC, chin.

suppression, older than 50 years, ultraviolet-exposed/fair skin.[10] However, most of these tumors are likely diagnosed through a combination of vigilance, a low threshold for biopsy, and microscopic evaluation, rather than by clinical findings.

Histology

The Merkel Cell

MCs are clear oval cells measuring 10-15 μm in diameter. They are found most commonly in the basal layer of the epidermis in specialized groupings called *haarscheiben*, in the outer root sheath of hair follicles and in the skin of the palms and soles. They are also found in oral mucosa and are rarely distributed singly in interfollicular skin.[11] MCs in *haarscheiben*, palms and soles, and interfollicular skin are usually associated with a sensory axon forming a Merkel cell-neurite complex. However, in hair follicles and mucosa, MCs are often not associated with a nerve.[11]

Haarscheiben are specialized structures of epidermis containing multiple MCs and associated nerve fibers. They were originally described in animals, where they are associated with whisker and sinus hairs and thought to signal directional movement. In humans, however, they are not consistently associated with hairs and are more commonly found on the neck and abdomen. In animals, they are sometimes visible to the naked eye on depilated skin, but in humans they are not. Other names for *haarscheiben* include touch domes, hair disks and *tastflecke*.[12]

In hair follicles MCs are found in 2 distinct bands, one near the bulge and the other close to the skin surface in the upper infundibulum. In the palms and soles, they are found at the base of epidermal ridges and are especially numerous on the fingertips. On the basis of studies of structural proteins, distinct populations of MCs have been shown to exist at various locations in the body.[13]

Whether MCs arise from epidermal or neural crest progenitors has been a matter of controversy for many years. Recent evidence suggests that MCs arise from epidermal progenitors during embryonic development; in adults, they mature and are then replaced from an epidermal stem cell source-not from the proliferation of differentiated MCs.[14]

MCs have long been considered important in the response to touch. Nerve fibers associated with MCs are slowly-adapting type 1 fibers, important in light touch and discrimination of fine detail. Mice genetically deficient in MCs demonstrated an absence of slowly-adapting type 1 mechanoreceptor responses, lending support to the Merkel cell's presumed role in light touch.[15]

MCs are difficult to see on light microscopy. Merkel himself used special techniques to visualize these cells and even today, without immunohistochemical stains, they are nearly impossible to detect. Their morphologic description has been gleaned principally by use of electron microscopy. Their hallmarks include lobulated nuclei; a loose cytoskeletal network of intermediate filaments; electron-dense (dense-core) membrane-bound cytoplasmic granules; and spine-like microvilli protruding from the cell surface into invaginations in surrounding keratinocytes. These projections may play a role in "connecting" the Merkel cell to its surrounding cells, thereby enhancing mechanical sensation.[13] In different tissues and even within similar tissues, their spine-like protrusions are highly variable in length.

Immunohistochemically, MCs demonstrate both epithelial and neuroendocrine markers. The loosely arranged intermediate filaments stain positively for low molecular weight cytokeratins (CK) 8, 18, 19, and 20.[16] CK20 in particular has been shown to be a highly specific marker for MCs in normal skin.[17] In normal MCs, CK20 stains in a diffuse manner, rather than in the paranuclear pattern seen in MCC. The dense-core granules stain positively for the neuroendocrine markers chromgranin A, neuron-specific enolase, and synaptophysin, and immunohistochemistry for these markers may be useful as diagnostic adjuncts. Vasoactive intestinal polypeptide, serotonin and substance P show variable positivity.

Merkel Cell Carcinoma

MCCs are dermally based tumors composed of small uniform round blue cells arranged in anastomosing cords, bands and clusters. Their cells commonly possess ill-defined, scanty cytoplasm, and round vesicular nuclei with "salt and pepper" chromatin and frequent mitotic figures (Fig. 2A). Up to 10% of MCCs contain pagetoid intraepidermal involvement and apoptotic bodies are often seen.[18] MCCs sometimes contain areas of squamotization and can occur in combination with other epithelial tumors. Nearly 40% are associated with adjacent or overlying Bowen's disease or squamous cell carcinoma.[19] Less frequently, MCCs are found in association with BCC or eccrine tumors.

Many terms have been used to describe the architecture of MCCs, including the trabecular pattern as originally described by Toker, which is thought to account for approximately 10% of MCCs.[20] Other recognized patterns include organoid, ribbon-like, diffuse, intermediate, and mixed and small types. Whether these subtypes prove to be of prognostic significance is yet undetermined. The most recent recom-

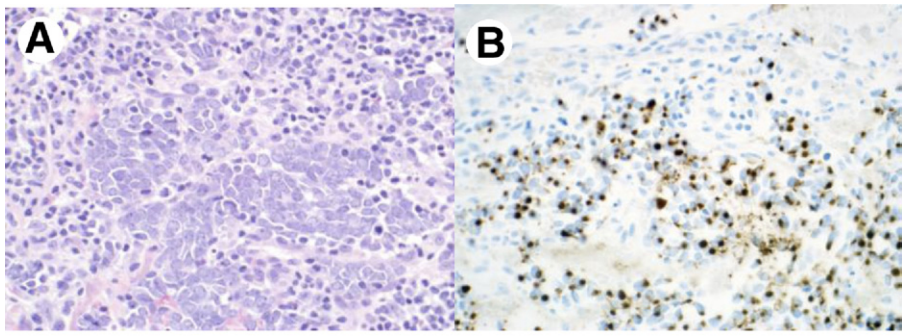


Figure 2 Microscopic appearance of MCC. (A) H&E (original magnification, 200×) B. CK20 (original magnification, 200×).

mendations by the College of American Pathologists suggest that a growth pattern of nodular or infiltrative be specifically recorded.

The histopathologic differential diagnosis for MCC includes other small round blue cell tumors, such as metastatic small cell carcinoma of the lung, small cell cutaneous lymphoma, melanoma, Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, and BCC.

Immunohistochemistry is often used to secure the diagnosis of MCC and, when used appropriately, is usually definitive. CK20 is the predominant tool used by pathologists, and stains approximately 80%-90% of all MCCs in a distinctive paranuclear dot-like pattern.[21] (The terms peri- and paranuclear have been used throughout the literature to describe the same phenomenon.) The characteristic paranuclear staining is due to clumping of intermediate filaments (Fig. 2B)

Neurofilament immunostains are also positive in a paranuclear dot pattern in up to 95% of MCCs (greater than CK20) and may be useful as a primary stain and/or in CK20-negative MCCs.[22] Positive thyroid transcription factor-1 staining is useful in differentiating small cell carcinoma of the lung from MCC. As in normal MCs, MCCs frequently stain positively with neuroendocrine markers, ie, chromgranin A, neuron-specific enolase, and synaptophysin. CM2B4 is an antibody that recognizes the Large T (LT) antigen of the MCPyV and has been demonstrated in approximately 70% of MCC.[5] Table 1 lists the immunostains that are generally useful for making the diagnosis of MCC.

Table 1 Immunostains for MCC

Stain	MCC	Small Cell Lung Cancer	Lymphoma	Melanoma
CK 20	+	−	−	−
CK 7	−	+	−	−
TTF-1	−	+	−	−
LCA	−	−	+	−
S100	−	−	−	+

CK, cytokeratin; TTF-1, thyroid transcription factor-1; LCA, leukocyte common antigen.

New Pathology Reporting Recommendations

The College of American Pathologists develops protocols to assist pathologists in reporting relevant pathologic information to clinicians. In 2010, they released recommendations for reporting MCC of the skin.[23] The protocol consists of a checklist of required and suggested elements for the pathologic reporting of cutaneous MCC and not only includes elements found in the most recent AJCC staging system but also suggests reporting additional characteristics that may prove to be valuable. Thus, in addition to required elements of tumor site, size, margins, etc., suggested elements include tumor thickness, lymph-vascular invasion, mitotic index/mm^2, tumor-infiltrating lymphocytes, tumor growth pattern and pathologic staging (Table 2). Explanatory notes and diagrams are included to assist the pathologist and clinician in understanding and interpreting these characteristics. Clini-

Table 2 Checklist for Reporting MCC

Required elements
Type of procedure (excision, re-excision, SLN etc)
Macroscopic tumor (presence or absence)
Tumor site
Tumor size (mm)
Margins (peripheral and deep)
Lymphovascular invasion (presence or absence)
Invasion of bone, muscle, fascia or cartilage
Lymph nodes (total number and number positive, presence or absence of macroscopic tumor)
Pathologic staging (pTNM)
Suggested elements
Tumor thickness (mm)
Mitotic index (per mm^2)
Tumor-Infiltrating lymphocytes (presence: brisk or nonbrisk or absence)
Tumor growth pattern (nodular or infiltrative)
Presence of second malignancy
Lymph nodes (size of largest metastatic focus and presence or absence of extra-nodal extension)

Adapted from Rao et al.[23]

Table 3 TNM Criteria and Stage Groupings of New American Joint Committee on Cancer Staging System for Merkel Cell Carcinoma

Stage	T	N	M
	Tx, Primary tumor cannot be assessed	Nx, Regional nodes cannot be assessed	Mx, Distant metastasis cannot be assessed
		N0, No regional node metastasis*	
	T0, No primary tumor	cN0, Nodes not clinically detectable*	M0, No distant metastasis
	Tis, In situ primary tumor	cN1, nodes clinically detectable*	M1, distant metastasis†
	T1, Primary tumor ≤2 cm	pN0, nodes negative by pathologic examination	M1a, distant skin, distant subcutaneous tissues, or distant lymph nodes
	T2, Primary tumor >2 but ≤5 cm		
	T3, Primary tumor >5 cm	pNx, nodes not examined pathologically	
	T4, Primary tumor invades bone, muscle, fascia, or cartilage	N1a, micrometastasis‡	M1b, Lung
		N1b, macrometastasis§	M1c, all other visceral sites
		N2, In-transit metastasis¶	

Stage	Stage Grouping		
0	Tis	N0	M0
IA	T1	pN0	M0
IB	T1	cN0	M0
IIA	T2/T3	pN0	M0
IIB	T2/T3	cN0	M0
IIC	T4	N0	M0
IIIA	Any T	N1a	M0
IIIB	Any T	N1b/N2	M0
IV	Any T	Any N	M1

From Lemos et al.[7]

*"N0" denotes negative nodes by clinical, pathologic, or both types of examination. Clinical detection of nodal disease may be via inspection, palpation, and/or imaging; cN0 is used only for patients who did not undergo pathologic node staging.

†Because there are no data to suggest significant effect of M categories on survival in Merkel cell carcinoma, M1a-c are included in same stage grouping.

‡Micrometastases are diagnosed after sentinel or elective lymphadenectomy.

§Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically by biopsy or therapeutic lympadenectomy.

¶In-transit metastasis is tumor distinct from primary lesion and located either: (1) between primary lesion and draining regional lymph nodes; or (2) distal to primary lesion.

cians should familiarize themselves with these recommendations and request them from pathologists reporting MCC.

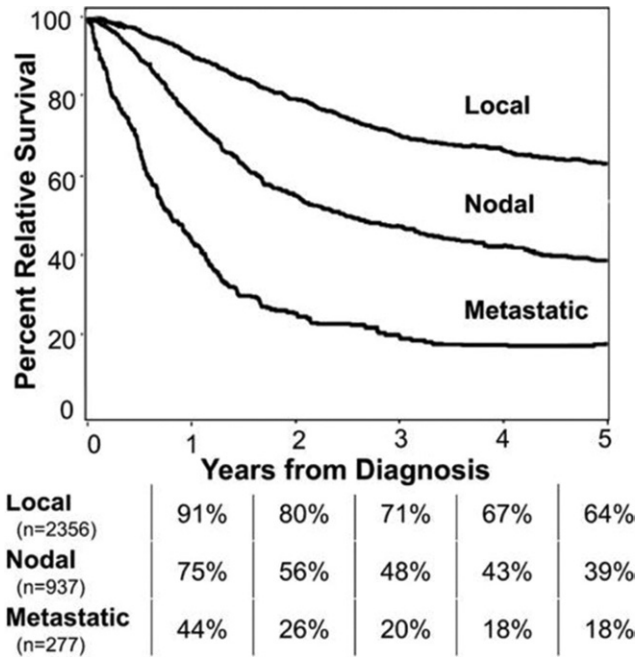
Staging

In the recent past, 5 staging systems have been proposed for MCC.[7] MCC is a rare malignancy and these systems were often based on single-institution experience with relatively few patients and short follow-up. In 2010, the AJCC released its first-ever consensus staging system for MCC. Their proposed tumor-nodes-metastases (TNM) criteria and stage groupings are based on analysis of national Cancer DataBase data from more than 4000 MCC patients with at least 5 years' follow-up and thus represent a significant advancement in the study of MCC. The proposed system adopts many definitions used in the classification of melanoma and other malignancies and maintains the architecture of other AJCC staging systems. It will likely lead to better standardization of patient data and prognostic information and aid the clinician in counseling patients with MCC (Table 3).

The following is a brief review of the AJCC findings which form the basis for their proposed TNM criteria and stage groupings. As noted in previous studies, significant differences have been found between patients presenting with local, regional and distant metastatic disease (Figs 3 and 4).

Primary Tumor (T Category)

The characteristics used in defining the T category are the size of the primary tumor and/or invasion of deep tissues, such as bone, muscle, fascia or cartilage. Consistent with previous studies, the size of the primary tumor was found to be an important factor in survival. In patients with local disease only, primary tumor size of <2 cm appears to be a natural prognostic break-point; patients with primary tumors ≤2 cm in diameter (T1) fared better than those with tumors >2 cm (T2 and T3). No difference in survival was found in patients with primary tumors >2 cm in diameter, and the T2 and T3 categories were both therefore included in the same stage grouping, II. The T4 category was added specifically to represent deeply invasive tumors, ie, those invading bone, muscle, fascia or cartilage, as in other AJCC staging systems. For all patients (presenting with local, regional or distant disease), the size of the primary tumor had a significant impact



Local (n=2356)	91%	80%	71%	67%	64%
Nodal (n=937)	75%	56%	48%	43%	39%
Metastatic (n=277)	44%	26%	20%	18%	18%

Figure 3 Relative survival by extent of MCC. From Lemos et al.[7]

on survival when the primary tumor was ≤4 cm. No impact on survival was noted for tumors >4 cm.

Regional Lymph Nodes (N Category)

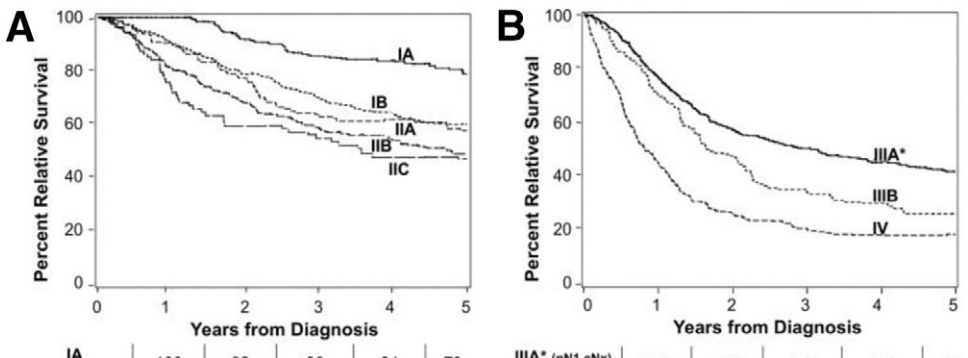
The N classification is determined by whether the patient's regional lymph nodes have been clinically or pathologically staged and in patients with nodal disease whether their disease is palpable (macroscopic) or not (microscopic). The N2 category was added solely to denote in-transit disease.

Upon analysis of the data, patients categorized as node negative by clinical examination only were found to do more poorly than those who were classified as node negative after histopathologic examination of clinically negative lymph nodes. Thus, clinically node-negative (cN0) and pathologically node-negative (pN0) criteria have been incorporated into the proposed staging system. The distinction between clinical and pathologic staging is important, as fully one-third of patients presenting with local disease harbor occult metastases.[24] Pathologic staging of clinically negative lymph nodes (such as by sentinel lymph node [SLN] biopsy) has been shown to improve prognostic accuracy.[7]

In patients with confirmed nodal disease, those with clinically palpable (macroscopic) nodal disease (N1b) did worse than those with microscopic (clinically negative but found to be positive on pathologic examination, such as by SLN biopsy) disease (N1a). Thus, N1a and N1b are categorized in sub-stages IIIA and IIIB, respectively. In-transit cutaneous disease (either between the primary site and the primary nodal basin or distal to the primary site) is classified as N2.

Distant Metastasis (M Category)

The prognosis for patients presenting with stage IV disease is grave, with an approximately 44% 1-year survival.[7] The M classification is divided into the absence or presence of distant metastatic disease (M0 and M1, respectively). Although there is no evidence of survival differences based on the site of metastasis, the M1 category is subdivided into M1a—distant



IA (n=266)	100	92	86	84	79
IB (n=754)	90	79	70	64	60
IIA (n=124)	90	77	64	62	58
IIB (n=414)	81	68	58	54	49
IIC (n=84)	72	59	55	48	47

IIIA* (pN1,cNx) (n=794)	76*	57*	50*	45*	42*
IIIB (n=143)	70	47	34	30	26
IV (n=277)	44	26	20	18	18

Figure 4 Relative survival for MCC by stage at presentation in 2856 patients. Relative survival for MCC by stage at presentation in 2856 patients. Sufficient local, nodal, and distant data were available for stage classification of 2856 patients with MCC as summarized in Fig. 2. Cases presenting with local (A) or regional nodal/distant metastatic (B) disease are shown by substages with annual percent relative survival below each panel. Stages are as indicated directly on survival curves except for stage IIIA (microscopic node positive, clinical node negative), which could not be derived using National Cancer DataBase as described in the "Discussion" section. Curve *IIIA** represents pathologically node-positive patients whose clinical node status was unknown (*pN1, cNx*). It is anticipated that patients at true stage IIIA with known clinically negative node status (pN1, cN0) may have better survival than line marked IIIA* (pN1, cNx). From Lemos et al.[7]

Table 4 New ICD Codes for Merkel Cell Carcinoma

- **209.31—Merkel cell carcinoma of the face**
- **209.32 – . . . Scalp and neck**
- **209.33 – . . . Upper limb**
- **209.34 – . . . Lower limb**
- **209.35 – . . . Trunk**
- **209.36 – . . . Other sites.**
- **209.75—Merkel cell carcinoma, unknown primary site, nodal presentation, secondary (any site), visceral metastatic presentation.**

V10.9 (unspecified personal history of malignant neoplasm) expanded to:

- **V10.90—Personal history of unspecified type of malignant neoplasm**
- **V10.91—Personal history of malignant neuroendocrine tumor.**

From Beebe et al.[26]

skin, subcutaneous tissue or distant lymph node involvement, M1b—lung, and M1c—all other visceral sites. These subdivisions were devised to mirror the staging system used in melanoma, where survival differences between these sites have been demonstrated.[25]

Stage Groupings

Patients with local disease only are categorized as stage I or II, stage I for patients with primary tumors ≤2 cm and stage II for those >2 cm. Subdivisions of stages I and II are based on size of the primary tumor and whether the absence of nodal disease is based on clinical findings or pathologic evaluation of a clinically negative lymph node (such as by SLN biopsy). Stage IIC was added to distinguish node negative patients (either clinically or pathologically) with tumors involving bone, muscle, fascia or cartilage (deeply invasive). Patients with regional disease—stage III, are subdivided into those with micrometastases (discovered on pathologic examination only) vs. macrometastases (determined either clinically or on imaging) or in-transit disease. There are no subdivisions of stage IV disease.

New Diagnostic Codes

In 2009, 7 new International Classification of Diseases (ICD) codes for MCC were developed and adopted (Table 4).[26] The new MCC codes describe primary cutaneous MCCs at specific sites (209.3x) and metastatic MCC (209.75) with unknown primary site, nodal presentation, secondary (any site), or visceral metastatic presentation.

Before the adoption of these codes, MCC was coded in the ICD system as 173.x, which includes BCC and SCC, tumors that rarely require aggressive therapy. As a result, for patients with MCC classified as 173.x, obtaining insurance approval for treatment was sometimes difficult.

For follow-up after treatment, the V10.9 code: "Unspecified personal history of malignant neoplasm" has been expanded to include V10.91: "Personal history of malignant neuroendocrine tumor." These new codes should facilitate more accurate classification of patients with MCC for research and insurance purposes.

Treatment

The main components of MCC therapy are surgery and radiotherapy. MCC has been demonstrated to be radiosensitive and radiotherapy is now used mainly as an adjuvant to surgery. Ultimately, aggressive surgery may prove to be overused and radiotherapy underused in MCC. At present, much controversy exists and the specific roles of these therapeutic modalities are still being elucidated. The National Comprehensive Cancer Network annually updates consensus recommendations for the treatment of MCC. The following is a summary of their recommendations and discussions with panel members and experts in the field.[27] A multidisciplinary approach to treatment of MCC is vital to optimize outcomes.[28]

Surgery

The mainstay of therapy for patients newly diagnosed with primary MCC remains surgical. Current recommendations are based on the clinical size of the primary tumor, and call for tumor excision with 1 cm margins for tumors <2 cm in size and 2 cm margins for those >2 cm in size.[27] Radiotherapy has been used as monotherapy for primary tumors with reported success, but until more data become available, surgery remains the mainstay of therapy for primary MCC tumors.[29,30]

Because nearly one-third of clinically node-negative patients harbor microscopic nodal disease, SLN biopsy is currently recommended for all untreated primary tumors at the time of wide local excision.[24] SLN biopsy has been shown to be important in the staging and prognosis of MCC, and SLN status is included in the most recent AJCC staging guidelines.[7] SLN biopsies should be examined by both hematoxylin and eosin (H&E) and immunoperoxidase staining, including CK20.

If sentinel nodes are positive, completion lymph node dissection (CLND) of the nodal basin followed by radiotherapy of the basin is recommended. In cases where SLN positivity is found on immunostaining but not H&E staining of the lymph node, radiotherapy without CLND may be considered as sole regional therapy.

SLN biopsy on the head and neck can be technically challenging but may have prognostic value and is therefore recommended. As in other cancers, the predictive value of SLN biopsy relies on intact lymphatic drainage patterns at the site of the primary tumor, and SLN biopsy should be performed at the time of wide local excision. Although it has been suggested that SLN may not be indicated for primary MCC <1 cm, SLN positivity has been shown sometimes to be independent of primary tumor size.[31,32]

Radiation Therapy

MCC is considered a radiosensitive neoplasm and radiotherapy plays an important role in its management. Although its

role in MCC treatment may ultimately increase, radiotherapy is currently used as an adjunct to surgery, and as primary therapy only in inoperable cases or when the patient refuses surgery. Areas for consideration of radiotherapy include the primary site, the draining nodal basin and intervening in-transit lymphatics.

After wide local excision, adjuvant radiotherapy to the primary site is recommended in nearly all cases of MCC. Radiotherapy to the primary tumor site has been shown to decrease the incidence of local recurrence 3.7-fold.[33] Radiotherapy to the primary site may be considered optional in patients deemed at lowest risk for local recurrence, including immunocompetent patients whose primary tumor measured <1 cm and possessed no adverse histologic features, whose wide local excisions showed unequivocally clear margins, and whose SLN biopsy was negative by both H&E and immunohistochemical staining.

Recommendation for adjuvant radiation to the draining nodal basin is dictated by SLN status and confidence in the predictive value of the SLN biopsy. There is evidence that surgery plus adjuvant radiotherapy to the regional nodal basin significantly decreases the rate of regional recurrence and improves survival.[33,34] If the SLN is positive, radiotherapy after CLND to the nodal basin is recommended. Patients at greatest risk for regional recurrence include those with macroscopic nodal disease, multiple node involvement or extracapsular extension. Although the use of radiotherapy alone for regionally metastatic MCC has been described, thoughtful commentary highlights the difficulties involved with study design in this patient population.[35,36]

In cases in which SLN biopsy was not performed or when the predictive value of the SLN biopsy may be questioned (eg, altered draining lymphatics or lack of immunohistochemical staining), radiotherapy to the draining basin should be considered. Because of the complexity of SLN biopsy in the head and neck, adjuvant radiation should be considered even in the setting of a negative SLN in this region. For lesions on the trunk or extremities where SLN biopsy is felt to be reliable, radiation may not be indicated when the SLN is negative on both H&E and immunohistochemistry.

In light of MCC's relative radiosensitivity, adjuvant radiotherapy is generally recommended in all patients except for those at lowest risk. Risk assessment is based on patient factors (such as immune status, overall health), tumor and nodal characteristics (including size of the primary tumor, lymphovascular invasion, depth of invasion, and extracapsular extension) and technical aspects of therapy (altered lymphatics, challenging location, compromised margins, lack of SLN biopsy or immunohistochemical staining). The morbidity of adjuvant radiotherapy, especially after CLND, must always be weighed against the risk of recurrence.

Chemotherapy

The role of chemotherapy in the treatment of MCC remains unclear. Although a majority of patients with locally advanced or distant disease may initially respond to treatment with chemotherapy, no survival benefit has been demonstrated in these patients.[37] The most commonly used agents combine platinum containing agents with etoposide and are associated with significant morbidity and, in some cases, mortality.[38] Chemotherapy is therefore currently considered as palliative treatment in cases of disseminated disease, but not as an adjuvant or primary therapy unless clinically warranted.

Merkel Cell Polyoma Virus

In 2008, Feng et al characterized a novel polyomavirus, the MCPyV, and inferred an association between it and the pathogenesis of MCC. This seminal work has sparked great interest in MCC and has opened a new pathway in the study of viral tumorigenesis.[39,40]

Feng's group detected MCPyV DNA in 80% of MCC tumors but in only 16% of normal tissue samples. Viral DNA was found to be clonally integrated within an individual tumor's genome, suggesting that viral infection and integration occurred before clonal expansion of the tumor cells. In one patient, an identical integration pattern was found in the primary tumor and a metastatic lymph node, supporting the notion that viral integration and clonal expansion preceded metastasis. In different MCC tumors, MCPyV DNA sequences were found to be integrated at different sites within the genome.

Further work by this group described mutations within the LT antigen coding region of the MCPyV. These mutations were found in MCPyV positive MCC tissue samples but not in MCPyV-positive control (non-MCC) samples, allowing at least an association to be drawn between these mutations and MCC tumors. The MCPyV found in control samples was thus felt to be epigenomic, wild-type MCPyV. The authors propose that MCPyV-associated transformation of MCs into MCC is a 2-step process: (1) integration of MCPyV DNA into the genome and (2) LT antigen mutation.

Polyoma viruses are small double-stranded DNA viruses. Although known to be capable of producing multiple tumors in animal models (hence the term poly+oma), none has been proven to cause tumors in humans. To date, 14 have been identified and 6 (including the MCPyV) infect humans. They are BK, JC, KI, WU, and MCPy viruses and the very recently discovered TS virus. All polyoma viruses encode T antigen proteins which are important in viral DNA replication, virion assembly and cellular transformation, and capsid proteins VP1, 2, and 3, which are structural-coating proteins. T-antigen proteins are subdivided into Large, Small, and sometimes Middle T-antigen proteins. T-antigen genes are expressed early and genes that encode capsid proteins are expressed late.

Shuda et al[40] described multiple distinct LT antigen mutations in the MCPyV of MCC tumors. Normal LT antigen protein contains binding sites for retinoblastoma tumor suppressor protein and heat shock protein—tumor suppressor and cell cycle regulatory proteins and a helicase domain—necessary for autonomous viral replication. The mutations found by Shuda et al resulted in stop codons within the LT antigen transcript and subsequent truncation (shortening) of

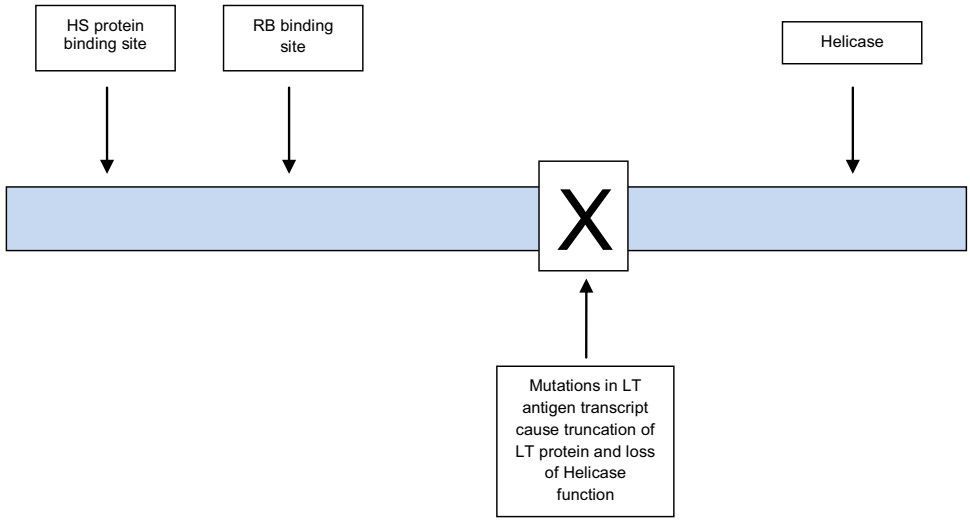


Figure 5 LT antigen protein. LT, large T antigen; HS, heat shock; RB, retinoblastoma tumor suppressor protein.

the LT antigen protein. Truncation of the LT antigen protein leads to loss of the virus's ability to replicate epigenomically, implying integration before clonal expansion. In this study, while multiple distinct mutations in the LT antigen transcript were found, all mutations led to loss of helicase function but preservation of retinoblastoma tumor suppressor protein and heat shock protein binding sites (Fig. 5). It is interesting to note that no CC → TT signature mutations for ultraviolet-induced changes were found among the LT antigen mutations.

Since its discovery, MCPyV has been found in normal skin samples from both immune competent and immunocompromised patients and in a minority of BCC, invasive SCC, and SCC in situ. However, no connection between MCPyV and these tumors has yet been drawn.[41–43]

Other investigators have shown that nearly 90% of healthy non-MCC adults possess antibodies to the MCPyVs. As with other polyoma viruses, exposure to MCPyV likely occurs in childhood.[44,45] Although patients with MCC have higher titers of antibodies to MCPyV VP1 capsid proteins compared with control subjects, these titers have not been shown to correlate with clinical course and appear to offer no protection against MCC. Recently, titers of antibodies recognizing MCPyV T antigens were found to fall in treated MCC patients and to rise preceding the detection of metastases.[46]

Since the discovery of the MCC polyoma virus, additional studies have substantiated that approximately 80% of MCC tumors contain MCPyV. In one Australian study, however, MCPyV was found in a significantly lower percentage of MCC tumors.[47] These results may imply MCPyV's association in only a subset of MCCs. It is interesting to note that MCC cell lines that have monoclonally integrated MCPyV genomes form loose suspensions in culture, whereas MCC cell lines without MCPyV grow as tightly adherent spindle shaped cells.[48]

Recently, MCPyV has been found in highly purified leukemic cells of approximately one-quarter of CLL patients studied. A novel LT antigen mutation was found in a subset of these MCPyV-positive CLL patients that was not seen in the MCPyV of normal controls. This discovery may argue for a potential role for MCPyV in a subset of CLL cases.[49]

Discovery of alterations in the LT antigen in the MCPyV has led to development of a monoclonal antibody against it, CM2B4. This antibody has been demonstrated to be useful in both formalin-fixed paraffin embedded and fresh, frozen specimens and has been used to investigate the presence of MCPyV in these samples. It stains positively in approximately 70% of MCCs and may prove to be a useful adjunct to CK20 in the identification of MCC tumor cells.[5]

Conclusions

MCC is an aggressive cutaneous malignancy whose diagnosis is often overlooked at the time of clinical presentation. The incidence of MCC is on the rise, and increasing awareness along with advances in immunohistopathologic staining have greatly aided in diagnosis. New staging recommendations, practice guidelines, and diagnostic coding are of considerable benefit to patient care, and a multidisciplinary approach is vital to optimize outcomes. The emerging role of MCPyV in MCC provides exciting insights into the etiology of this rare tumor.

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