ACTAS
Dermo-Sifiliográficas

Full English text available at
www.actasdermo.org

REVISIÓN

Update on Merkel Cell Carcinoma: Epidemiology, Etiopathogenesis, Clinical Features, Diagnosis, and Staging[☆]

B. Llombart,[a],* C. Requena,[a] J. Cruz[b]

[a] *Servicio de Dermatología, Instituto Valenciano de Oncología, Valencia, España*
[b] *Servicio de Anatomía Patológica, Instituto Valenciano de Oncología, Valencia, España*

Abstract   Merkel cell carcinoma (MCC) is a rare, highly aggressive tumor, and local or regional disease recurrence is common, as is metastasis. MCC usually develops in sun-exposed skin in patients of advanced age. Its incidence has risen 4-fold in recent decades as the population has aged and immunohistochemical techniques have led to more diagnoses. The pathogenesis of MCC remains unclear but UV radiation, immunosuppression, and the presence of Merkel cell polyomavirus in the tumor genome seem to play key roles. This review seeks to update our understanding of the epidemiology, etiology, pathogenesis, and clinical features of MCC. We also review histologic and immunohistochemical features required for diagnosis. MCC staging is discussed, given its great importance in establishing a prognosis for these patients.
© 2016 Elsevier España, S.L.U. and AEDV. All rights reserved.

Actualización en el carcinoma de células de Merkel: Epidemiología, etiopatogenia, clínica, diagnóstico y estadificación

Resumen   El carcinoma de células de Merkel (CCM) es un tumor poco frecuente, con un curso evolutivo muy agresivo, que con frecuencia origina recidivas locorregionales y metástasis. Asienta predominantemente en zonas fotoexpuestas en pacientes ancianos. Su incidencia se ha cuadriplicado en las últimas décadas debido al envejecimiento de la población y a un mayor diagnóstico gracias al uso de técnicas inmunohistoquímicas. La patogénesis del CCM no está clara, pero la radiación ultravioleta, la inmunosupresión y la presencia del poliomavirus MCPyV en el genoma del tumor parecen desempeñar un papel fundamental en el desarrollo de esta neoplasia.

El objetivo de este artículo es realizar una revisión actualizada sobre los diferentes aspectos de la epidemiología, la etiopatogenia y la clínica del CCM. A su vez, detallamos los aspectos histológicos e inmunohistoquímicos necesarios para su diagnóstico y revisamos la estadificación por su importante trascendencia en el pronóstico de estos pacientes.

Introduction

Merkel cell carcinoma (MCC), also known as primary cutaneous neuroendocrine carcinoma, is an rare skin tumor that affects patients of advanced age. MCC is highly aggressive, and local and regional spread and metastasis are very common. Because the incidence of MCC has risen and a virus has been implicated in its pathogenesis, interest has increased in recent years.

This review aims to update our understanding of the epidemiology, etiology, pathogenesis, and clinical features of MCC. We review the histologic and immunohistochemical findings that lead to diagnosis and discuss the current staging system of the American Joint Committee on Cancer.

History

The author of the first description of a MCC tumor, which appeared in 1972, was Toker,[1] who used the term trabecular carcinoma of the skin to suggest the possibility of an origin in glandular tissue. An ultrastructural study by Tang and Toker[2] that appeared 6 years later demonstrated the presence of electron-dense granules in the cytoplasm of tumor cells. They proposed a neuroendocrine origin similar to that of Merkel cells in the epidermis. In fact debate on the cellular origin of these tumors continues, accounting for the proliferation of nomenclature used over time: cutaneous APUdoma, primary small cell carcinoma of the skin, anaplastic carcinoma of the skin, endocrine carcinoma of the skin, Merkeloma, primary cutaneous neuroendocrine carcinoma, and MCC.[3–5] These terms reflect neuroendocrine cell differentiation, the cell morphology observed, and a histologic similarity to small cell lung cancer.

The term cutaneous neuroendocrine carcinoma is the one that perhaps best reflects the immunohistochemical and ultrastructural features of these tumors, but the most commonly used and universally accepted name in the literature is MCC.

Epidemiology

MCC is a rare but characteristically aggressive tumor whose mortality rate is twice that of melanoma.[6] Less than 1% of malignant skin tumors are MCCs,[7] but it is the third most frequent cause of death from skin cancer after melanoma and squamous cell carcinoma.[8]

The incidence of MCC in Spain is unknown at this time. However, it has risen 3-fold in recent decades in the United States, from 0.15 per 100 000 population in 1981 to 1.44 per 100 000 population in 2011.[9,10] The increase is attributable to greater awareness of the disease among dermatologists and pathologists; greater ease of diagnosis thanks to immunohistochemical techniques; and increased population risk due to UV light exposure, aging, and immunosuppression.[11]

MCC affects mainly white populations but also appears exceptionally in black persons. The prevalence is somewhat higher in men than women in some professions (1.4:1) but no differences between the sexes are seen in others.[7,12]

MCC is diagnosed more often in persons of advanced age, and the incidence peaks between the seventh and eighth decades of life.[13] The mean age at diagnosis is 75 years. Only 5% of patients are under the age of 50 years, when the tumor is usually associated with some form of immunosuppression.[12] Nonetheless, cases have been described even in children, the youngest being 7 years old.[14]

Etiopathogenesis and Populations at Risk

MCC affects light-skinned individuals (phototypes I-III) on sun-exposed parts of the body and is associated with other skin tumors. These associations point to an etiopathogenic role for UV light,[15,16] but MCC has also been seen in patients who have undergone radiation or psoralen-UV-A therapy, in individuals exposed to arsenic,[17] and in skin areas affected by erythema ab igne.[18] MCC patients also develop other skin tumors induced by UV radiation (e.g., basal cell or squamous cell carcinomas and melanoma) that may appear either before or after MCC. Patients with melanoma are at 3-fold higher risk of MCC than the general population.[19]

The frequency is higher in immunocompromised individuals,[12,20] especially after heart[21] or kidney[22] transplants; during immunosuppressant treatment with azathioprine, ciclosporin, cyclophosphamide, and mTOR (target of rapamycin) inhibitors[23]; and in persons living with human immunodeficiency virus (HIV) infection.[24] Therefore, immune compromise is a risk factor for MCC, which also develops at younger ages and follows a more aggressive course in this context. MCC appears about 10 years after a transplant on average, and the ratio of melanoma to MCC is 1:6 in transplanted patients and 1:65 in the general population.

Risk for MCC is 13-fold higher in HIV-infected individuals than in the general population. A study of 14 HIV-infected patients with MCC found that most were males and on average younger (49 years old) at diagnosis than patients with MCC and no HIV infection (70 years old).[25] Other differences between the behavior of MCC in HIV-infected and noninfected persons are that the tumor develops in unexposed areas in the presence of HIV (35% on the buttocks) and that

mean survival is shorter (less than 19 months after diagnosis).

Occasionally MCC has been described in association with blood diseases[26] (chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and multiple myeloma); with solid tumors[27] (of the lung, pancreas, prostate, breast, or colon); or with autoimmune diseases (rheumatoid arthritis, ankylosing spondylitis, Crohn disease, and inflammatory bowel disease).[28,29] Within these groups of diseases, chronic lymphocytic leukemia is the condition most often associated with MCC. There have been sporadic reports of a link between MCC and congenital ectodermal dysplasia and Cowden syndrome.[30]

The most important discovery related to pathogenesis came in 2008 with the description of the Merkel cell polyomavirus (MCPyV) in the genome of MCC tumor cells. Feng et al.[31] found MCPyV expression in 80% (8 of the 10 MCCs they analyzed) but in only 8% of control samples from various organs and in 16% of control samples of healthy skin. Later studies confirmed MCPyV expression in about 80% of MCCs. However, it has been suggested that variation in the incidence of expression may be related to geographic differences.

Clinical Features

MCC usually presents as a single firm, well-defined nodule that is erythematous, or violaceous in color, and mobile with respect to underlying tissue. The surface is soft, smooth and shiny, rarely ulcerated, and often marked by telangiectasis[32,33] (Fig. 1A). MCC may present as a single dermal or subcutaneous plaque or as a multinodular lesion (Fig. 1B). Less often a multifocal or disseminated lesion (Fig. 1C) might be found.[34–36] Pediculated tumors (Fig. 1D) have also been described.[37]

The tumor is asymptomatic and the patient usually consults a physician because of rapid growth over a period of weeks or months.[38] The average tumor size on diagnosis is 2 to 4 cm,[5,33,39–41] and large lesions sometimes have an erythematous inflammatory halo. Histology of the halo area does not show an inflammatory infiltrate, however, but does reveal vascular invasion. Therefore, a halo sign suggests a poor prognosis.

The tumor usually develops in a sun-exposed area but can grow in any skin or mucosal tissue. The head or neck is the most common site, accounting for around half; the next most common sites are the extremities (40%) and trunk and buttocks (10%).[32,35,42,43] A periorbital location is very frequent (10%) (Fig. 1A), and a tumor at this site may be confused with a benign cyst or lipid granuloma. MCC has very infrequently been described in unexposed areas, such as the genitals[44,45] or perianal and oropharyngeal[46] mucosal tissue.

MCC has been found in lymph nodes in the absence of a primary skin tumor.[47] Primary lymph node MCCs have been associated with a better prognosis than primary skin MCCs with affected lymph nodes.[48] Spontaneous partial or total regression of these tumors after biopsy has also been reported.[49,50]

In some cases, MCC in situ or a small incipient baby Merkel tumor is diagnosed while a patient is being followed for basal cell or squamous cell carcinoma.[51–54] This tumor may also

be an incidental finding on inspection of biopsy material. Prognosis in such cases is better.

If a lesion initially appears to be benign, treatment of MCC may be delayed, leading clinicians to use of the mnemonic AEIOU to recall relevant features: asymptomatic, expanding rapidly, immunosuppressed, older than 50 years, and UV exposed. The goal is to avoid delaying diagnosis. MCC is initially suspected in only about 1% of cases.[55]

Differential clinical diagnoses are highly varied, including both benign lesions (epidermal cyst, dermatofibroma, fibroma, angioma, and lipid granuloma) and malignant ones (squamous cell carcinoma, amelanotic melanoma, cutaneous metastasis of other tumors, lymphoma, basal cell carcinoma, keratoacanthoma, and adnexal tumors).[54]

Characteristic dermoscopic features of MCC have not been established, but there are published descriptions of the presence of unorganized milky-red areas and arborizing vessels, features that raise suspicion of malignancy in other lesions besides MCC.[56,57]

Histologic Features

Macroscopically, MCCs are well demarcated, unencapsulated, firm, and homogeneous. Microscopically, they are dermal lesions composed of 2 types of round, basophilic, monomorphic cells whose large vesicular nuclei have finely granular (salt-and-pepper) chromatin condensation[58] (Fig. 2). It is common to see necrotic areas, pyknotic nuclei, and an abundance of mitotic figures (Fig. 2D). Vascular invasion and an abundant inflammatory infiltrate of lymphocytes and plasma cells surrounding the tumor are other common findings. An infiltrate is sometimes also found inside the tumor.

An area separating the tumor from the epidermis (Fig. 3) is usually present; epidermal ulceration is found in only about 15% of cases, and less than 10% of MCCs show epidermal involvement (epidermotropism).[42,59] MCCs confined to the epidermis (MCC in situ)[53,60] or MCCs with only minimal dermal involvement[51] have been described. Aggregates may form in the epidermis or adopt a pagetoid pattern that can imitate other intraepidermal tumors such as melanoma as well as mycosis fungoides, Bowen disease, or Paget disease.[61]

Trabecular, nodular, and diffuse histologic patterns of no prognostic interest have been described.[62] The trabeculae reported by Toker[1] in 1972 are uncommon and, when found, are usually at the periphery of the tumor. In this pattern the cells are grouped in thick trabeculae separated by a fibrous stroma, appear compact, and mimic glands or rosettes. The nodular pattern, in which the cells form solid nodules, is the most frequent. A nodular MCC generally resembles a lymphoma. The diffuse pattern is characterized by an infiltrate of small cells arranged in sheets separated by abundant stroma. Mitotic activity is high and large necrotic areas are present. In such cases the tumor resembles small cell lung cancer. It is not unusual for a tumor to exhibit more than a single pattern.

Divergent histologic patterns have been described exceptionally (in 5% of cases).[63] Eccrine gland differentiation[64,65] is confirmed by a finding of immunohistochemical expression of cytokeratin (CK) 7 and carcinoembryonic antigen. Cases
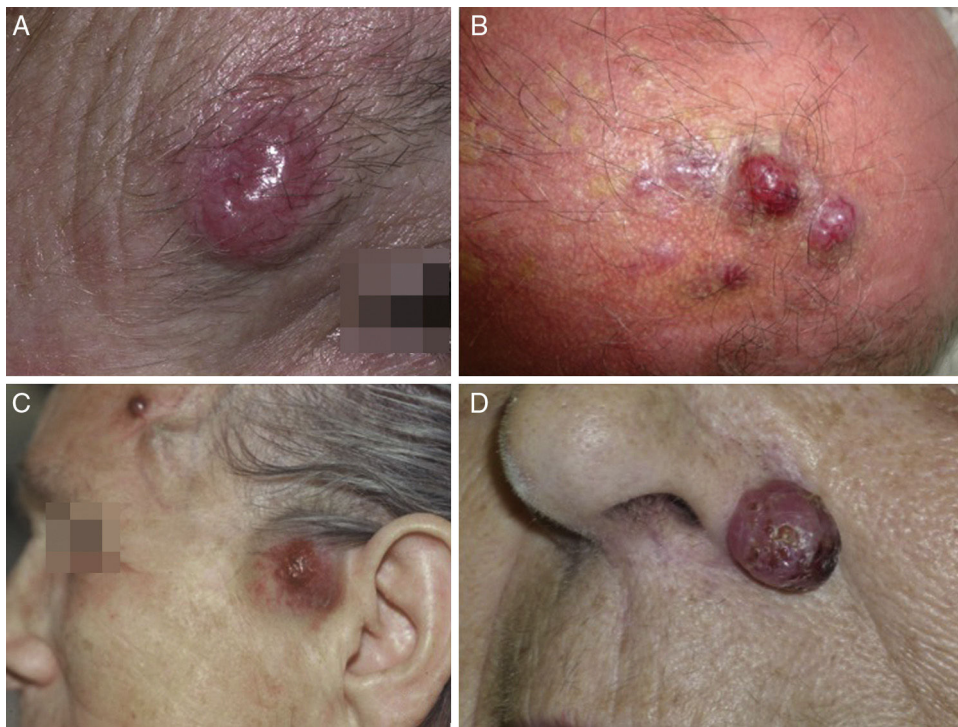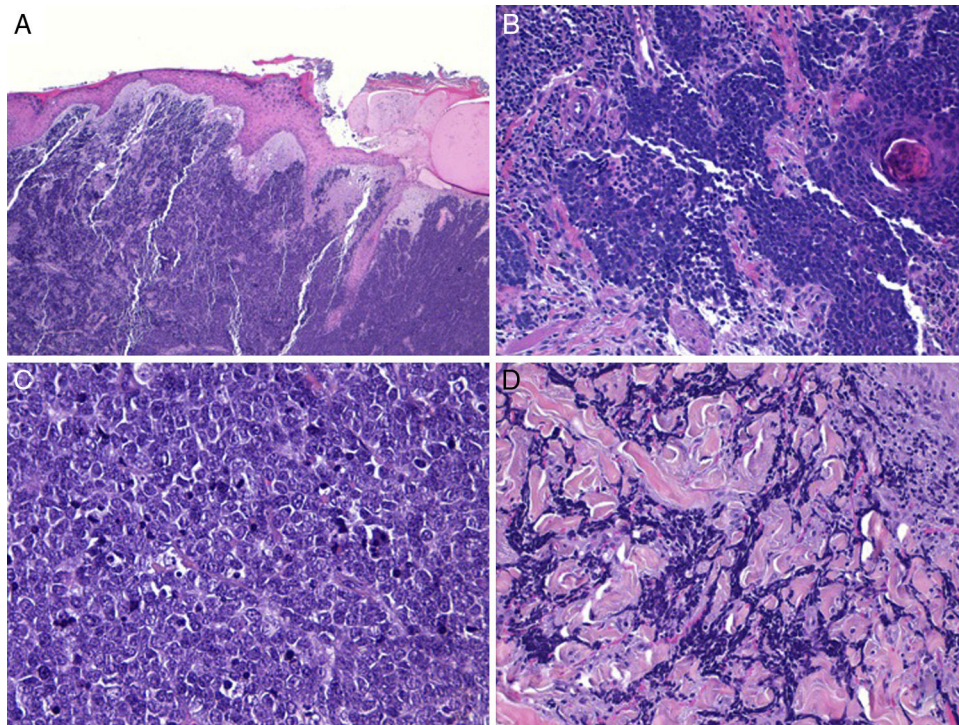
Figure 1   Merkel cell carcinoma tumors. A, Erythematous nodular lesion that is well defined, smooth, and shiny; telangiectases are evident on the surface. B, Poorly defined plaque with multiple nodules across its surface. C, Disseminated Merkel cell carcinoma. D, Small Merkel cell carcinoma.
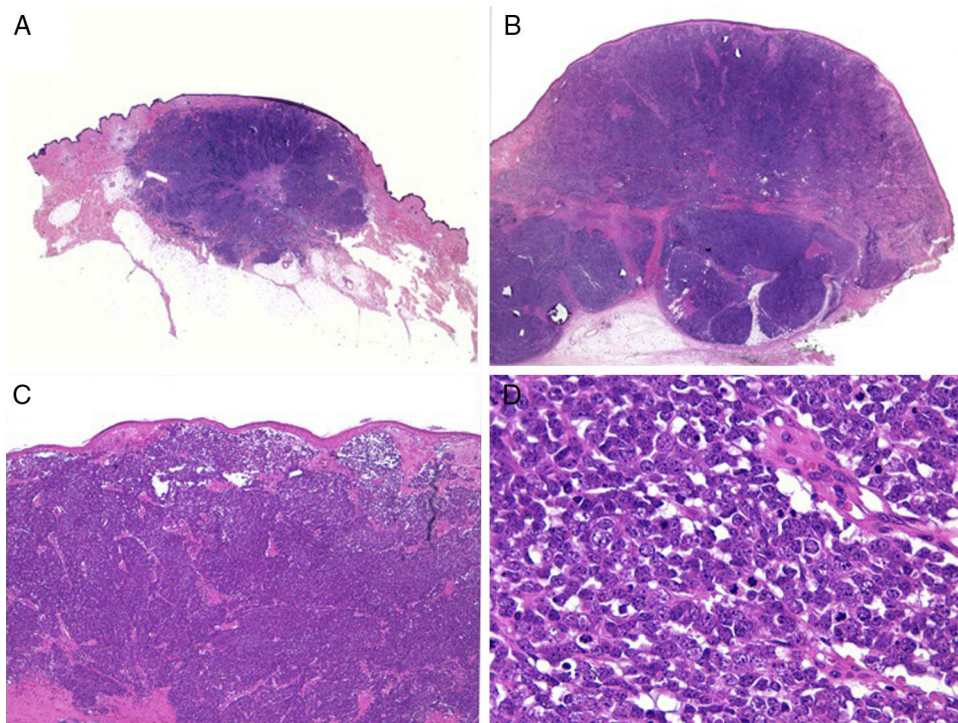
Figure 2   Histology. A and B, Panoramic view of a Merkel cell carcinoma. The tumor is well defined, unencapsulated, and nodular; hematoxylin-eosin, original magnification ×10. C, Localized tumor in the dermis. The cells are round, basophilic, and monomorphic; hematoxylin-eosin, original magnification ×100. D, Round, blue cells with scant cytoplasm, and finely granular chromatin condensation. Numerous mitotic figures are present; hematoxylin-eosin, original magnification ×400.

Figure 3 Merkel cell carcinoma with an infiltrative pattern. A, Tumor in the dermis, leaving the epidermis intact; hematoxylin-eosin, original magnification ×100. B, Tumor extensively infiltrating the dermis; hematoxylin-eosin, original magnification ×200. C, Atypical cells that are small, round, and basophilic; hematoxylin-eosin, original magnification ×400. D, Infiltrate and collagen bundles inside a tumor; hematoxylin-eosin, original magnification ×200.

of squamous,[66] melanocytic,[63] and muscular differentiation have been reported, as well as tumors with a so-called lymphoepithelioma pattern.[67] A lymphoid infiltrate has been linked to tumor regression. Squamous differentiation may be fibrosarcomatous,[68] leiomyosarcomatous,[69] or rhabdomyosarcomatous; multinucleated giant cells may also be present.[70] Cases with glandular, squamous, and melanocytic differentiation in the same tumor have been described.[63] The ability of MCCs to differentiate into other cell lines suggests an origin in pluripotential stem cells[71,72] rather than the traditional theory that they arise in the epidermis.

MCC presents as a collision tumor along with another lesion in 15% of cases.[42] The most common adjacency is with a squamous cell tumor,[53] but actinic keratosis, Bowen disease,[73] and basal cell carcinoma[70] have also been implicated. Other lesions that have been associated with MCC anecdotally are epidermal cysts, trichilemmal cysts, trichoblastoma, poroma,[74] and lentigo maligna.

Spontaneous regression of an MCC has sometimes been reported, but the mechanism involved is unknown. Takenaka et al.[75] suggested that regression might be an effect of immune system stimulation by the biopsy procedure. Histologic features in the area of regression include a perivascular lymphocytic infiltrate composed mainly of CD8+ cells and fibrosis. The host's immune defenses are thought to be determinants in the course of MCC tumors, opening the possibility of immunologic therapies in the future.

Histologic features that should be present in the pathology report to support a diagnosis of MCC are summarized in Table 1.[76–78]

Immunohistochemical Findings

Because MCCs are neuroendocrine carcinomas that express a set of CK and neuroendocrine markers, immunohistochemistry facilitates diagnosis. If optical microscopy alone is used, the risk of diagnostic error has been reported to be around 66%.[79]

Assays show positive findings for low-molecular-weight CKs (CK8, CK18, CK19, and CK20) in most MCCs. The high–molecular-weight CK7 is not expressed. Most studies conclude that a positive result for CK20 expression along with negative results for CK7 will be highly useful, providing an accurate diagnosis in 90% of cases.[80] CK20 presents a highly characteristic cytoplasmic paranuclear dot-like pattern (Fig. 4) and is considered one of the keys to diagnosis. However, the absence of CK20 expression does not rule out MCC. Cases of MCCs with CK7+ and CK20− cells have even been reported.[81]

Neuron-specific enolase is a very sensitive but fairly nonspecific neuroendocrine marker that also appears in other neoplasms (melanoma, other neuroendocrine tumors, and small cell lung cancer). The proteins chromogranin and synaptophysin are present in neurosecretory granules (Fig. 5). A typical cytoplasmic staining pattern shows globules that are 100% chromogranin B, 72% chromogranin A, and 50% synaptophysin.[42,82,83] Also worth mentioning is immunostaining for CD56, a glycoprotein present in neuroendocrine cells and whose expression has been described in around 94% of MCCs.[84]

The histologic differential diagnosis must include other round and small cell tumors, mainly those that metas-

Table 1 Features Required for a Histologic Diagnosis of MCC [a]

Tumor
  Procedure type (biopsy, exeresis, re-exeresis, other:_____)
  Macroscopic tumor (present or absent)
  Tumor location:_____
  Tumor size, cm:_____
  Tumor thickness, mm [b]:_____
  Margins (side, depth; involved structures or tumor free) (distance_____mm)
  Lymphovascular invasion (present or absent)
  Muscle, bone, fascia, or cartilage invasion
  Mitotic index, per mm^2 [b]:_____/mm^2
  Peritumoral lymphocytic infiltrate [b] (present or absent) (dense, not dense) (cell type: lymphocytic, plasmocytic, other:_____)
  Intratumoral lymphocytic infiltrate [b] (present or absent) (dense, not dense) (cell type: lymphocytic, plasmocytic, other:_____)
  Growth pattern [b] (nodular or infiltrative)
  Presence of differentiation [b]: squamous, eccrine, melanocytic, sarcomatous, other: _____)
  Presence of an adjacent tumor [b] (squamous cell carcinoma, basal cell carcinoma, actinic keratosis, other:_____)
  Immunohistochemical analyses:
    CK AE-1/AE-3) (positive [____%], negative)
    CK20 (positive [____%], negative)
    CK7 (positive [____%], negative)
    Chromogranin (positive [____%], negative)
    Synaptophysin (positive [____%], negative)
    CD56 (positive [____%], negative)
    TTF-1 (positive [____%], negative)

Lymph node
  Procedure type (sentinel lymph node biopsy, lymph node dissection:_____)
  Location
  Diagnostic hematoxylin staining: positive, negative, indeterminate
  Diagnostic immunohistochemistry: positive, negative, indeterminate
  Immunohistochemical technique used: _____
  No. of lymph nodes examined (total):_____; no. of involved nodes:____
  Tumor load (percentage of area affected and size of the largest focus of metastasis ____mm)
  Metastasis, location: subcapsular, parenchymal, germinal center
  Extranodal spread (present, absent, indeterminate)

*Pathological TNM stage:*_____

Abbreviations: CK, cytokeratin; MCC, Merkel cell carcinoma; TTF-1, thyroid transcription factor 1.
  [a] Adapted from the work of Rao et al.,[76] Wang et al.,,[77] and Bichakjian et al.[78]
  [b] Suggested features that are clinically important but not presently used to guide treatment.

Table 2 Immunohistochemical Differential Diagnosis in MCC

Tumor	CK	CK20	CK7	TTF-1/*Mash-1*	CD56/Cr	LCA	S-100	CD99
Merkel cell carcinoma	+	+	−	−	+	−	−	±
Small cell lung cancer	+	−	+	+	+	−	−	±
Lymphoma	−	−	−	−	−	+	−	−
Melanoma	−[a]	−	−	−	+	−	+	−
Ewing's sarcoma	−[a]	−	−	−	+	−	−	+

Abbreviations: ±, MCC and small cell lung cancer express CD99 in the cytoplasm but not in the membrane; CK, cytokeratin (AE1/AE3); Cr, chromogranin; LCA, leukocyte common antigen; *Mash-1*, mammalian achaete-scute homolog 1 gene; MCC, Merkel cell carcinoma; TTF-1, thyroid transcription factor 1.
  [a] CKs are sometimes expressed in melanoma and Ewing's sarcoma.

tasize to the skin such as small cell lung cancer, poorly differentiated squamous cell carcinoma, or lymphoma or anaplastic melanoma with round cells. The principal differential diagnoses and immunohistochemical techniques applied are listed in Table 2. A definitive diagnosis of MCC requires a negative finding for the S-100 protein, the leukocyte common antigen, and high molecular weight CKs.[85,86]

Immunohistochemical membrane staining for CD99 is a characteristic of Ewing sarcoma. However, between 40%
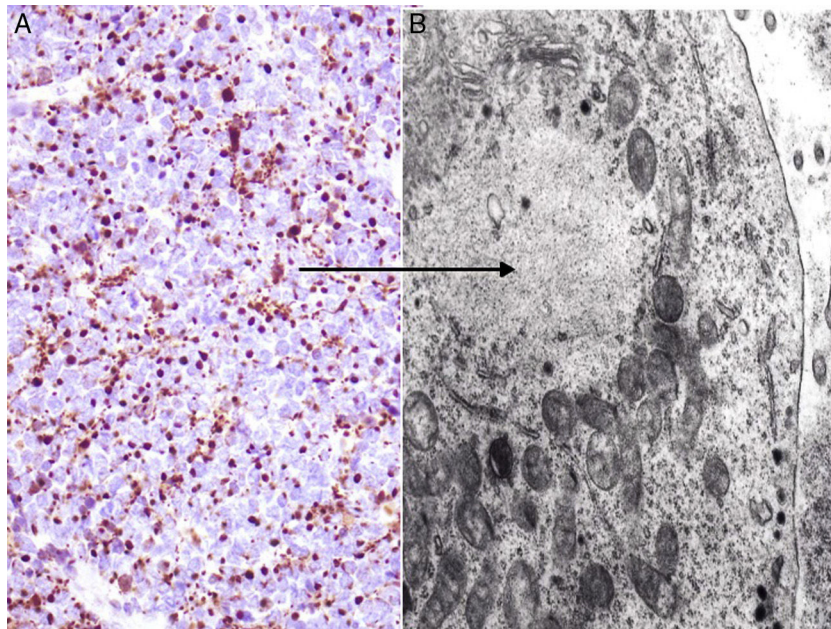
Figure 4 Immunohistochemistry of Merkel cell carcinoma. A, Positive cytoplasmic staining for cytokeratin 20 with the characteristic paranuclear (dot-like) pattern. B, Electron microscopic image of a tumor cell showing intermediate filaments grouped together.

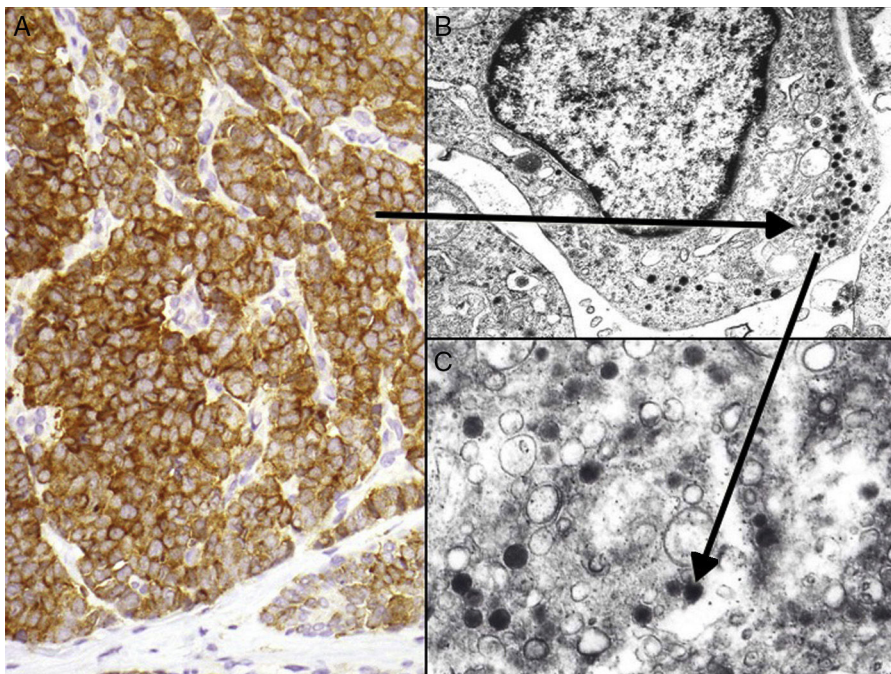**Figure 5** Immunohistochemistry of Merkel cell carcinoma. A, Immunohistochemical staining with chromogranin for neuroendocrine differentiation showing the characteristic granular pattern in the cytoplasm. B and C, Electron microscopic images showing electron-dense granules dispersed in the cytoplasm of cells from a Merkel cell tumor.

and 55% of MCCs have CD99+ cells, albeit only in the cytoplasm.[42,87]

Thyroid transcription factor 1 (TTF-1) is a nuclear protein involved in regulating transcriptional activity during embryonic development of the thyroid gland and respiratory epithelium.[88] This marker is typically positive in lung and thyroid cancers and negative in MCC, so a negative TTF-1 finding is considered more specific than a positive CK20 result, given that the latter can be negative in a considerable proportion (20%) of MCCs whereas TTF-1 is expressed in very few (3%).[89–91] Recent studies have found that the mammalian achaete-scute homolog 1 (*Mash-1*) gene, linked to embryonic development of brain and neuroendocrine cells, is useful in distinguishing between MCC and metastasis of

Table 3   TNM Classification of MCC According to the American Joint Committee on Cancer [a]

Tumor	Node	Metastasis
Tx, tumor cannot be assessed	Nx, lymph node involvement cannot be assessed	Mx, metastasis cannot be assessed
T0, no evidence of primary tumor	N0, no lymph node involvement	M0, no metastasis
Tis, primary tumor in situ	-cN0, no clinical signs of lymph node involvement (on inspection, palpation, and/or radiograph)	M1, distant metastasis
T1, primary tumor $\leq 2\,cm$	-pN0, no lymph node involvement detected by a pathologist	-M1a, metastasis to skin, subcutaneous cellular tissue, or distant lymph nodes
T2, primary tumor $> 2\,cm$ and $\leq 5\,cm$	-pNx, no histology of lymph nodes	-M1b, metastasis to the lung
T3, primary tumor $> 5\,cm$	N1a, micrometastasis[b]	-M1c, metastasis to other visceral organs
T4, primary tumor affecting bone, muscle, fascia, or cartilage	N1b, macrometastasis[c]	
	N2, in-transit metastasis[d]	

Abbreviation: MCC, Merkel cell carcinoma.
[a] Adapted from Lemos et al.[100]
[b] Micrometastasis refers to clinically undetectable lymph node involvement that is found in the sentinel lymph node on elective dissection.
[c] Macrometastasis refers to clinical evidence and pathologic confirmation of regional lymph node involvement on dissection or punch biopsy.
[d] In-transit metastasis refers to metastasis found between the primary tumor and the regional lymph nodes or distal to the primary tumor.

small cell lung cancer to the skin, especially in the rare cases when the tumor cells are TTF-1 positive. MCC does not express *Mash-1*, but 83% of small cell lung cancers do.[91,92] Thus, a combined finding of TTF-1, *Mash-1*, and CK20 expression should provide greater sensitivity and specificity for distinguishing between MCC and other small cell carcinomas.

In summary, immunohistochemical detection of intermediate filaments, essentially CK20[49] and neuroendocrine markers such as CD56, chromogranin or synaptophysin, and absence of expression of TTF-1, *Mash-1*, CK7, S-100 protein, and leukocyte common antigen offer useful information for distinguishing between MCC and other blue skin tumors with round cells (Table 2).[43]

Ultrastructural Features

Electron microscopy has played an important role in our understanding of MCC,[93] but this step is currently not ordered because the combined findings of optical microscopy and immunohistochemistry provides sufficient information for diagnosis. MCC tumor cells share the characteristics of Merkel cells themselves: a lobulated nucleus and multiple small nucleoli. The cytoplasm contains abundant ribosomes and a prominent Golgi apparatus.

MCC cells have 2 characteristic ultrastructural features: intermediate filaments (Fig. 4) and electron-dense granules[94] (Fig. 5). These granules in the cytoplasm typically measure between 100 and 250 nm in diameter. Small cell lung cancer and other carcinomas of the neuroendocrine system also present with electron-dense granules.

Paranuclear aggregates of intermediate filaments or fibrous bodies can also be observed in the cytoplasm of neoplastic cells. Paranuclear positioning is typical of these filaments in MCC, whereas they form a perinuclear pattern in small cell lung cancer.

Cytogenetic and Molecular Analysis

Certain cytogenetic changes affect 30% to 47% of MCCs; changes are usually on chromosome 1 but have also been found on chromosomes 3, 11, and 13.[95] Comparative genomic hybridization analyses have found gains and losses that are very similar to those seen in small cell lung cancer.

Studies have found alterations in the B-cell lymphoma 1 (*bcl-1*) oncogene[96] and mutations in the tumor protein (p53) gene[97] that might be related to progression and aggressiveness. The number of somatic mutations in the MCC tumor seems to be inversely related to the MCPyV load. MCPyV-positive samples show few mutations, whereas samples negative for the virus show many, especially mutations with a signature that corresponds to those observed in small cell lung cancer (i.e., the retinoblastoma protein and p53).[98,99]

Staging

Staging is of great importance for establishing prognosis and guiding proper treatment in MCC. The simple, traditional system described by Yiengpruksawan et al.[41] has 3 stages: stage I, localized skin lesion (IA, < 2 cm; IB, ≥ 2 cm); stage II, regional lymph node involvement; stage III, metastatic dis-

Table 4 Staging of MCC According to the American Joint Committee on Cancer [a]

Stage	Tumor	Lymph Nodes	Metastasis	5-Year Survival, %[a]
0	Tis	N0	M0	100
IA	T1	pN0	M0	79
IB	T1	cN0	M0	60
IIA	T2/T3	pN0	M0	58
IIB	T2/T3	cN0	M0	49
IIC	T4	N0	M0	47
IIIA	Any T	N1a	M0	42
IIIB	Any T	N1b/N2	M0	26
IV	Any T	Any N	M1	18

Abbreviation: MCC, Merkel cell carcinoma.
[a] Adapted from Lemos et al.[100]

ease. The American Joint Committee on Cancer proposed a new, more complete staging system in 2010 (Table 3) based on the analysis of over 4000 cases.[100] This new system highlights the importance of tumor size, regional lymph node status, and metastasis in relation to survival. Four clinical stages are possible at the moment of diagnosis (Table 4). The first two include localized disease that only affects the skin. The third includes cases with regional lymph node involvement while the fourth reflects metastatic dissemination. Five-year survival in truly localized disease (stages I and II) is about 50%, a percentage that drops to under 20% if there is metastasis (stage IV) (Table 4). Tumor size is the most important prognostic factor when the MCC is confined to the skin (stages I and II). Most studies have found that prognosis is worse when MCCs are larger than 2 cm ($\geq$ T2).[77] However, significant prognostic differences have not been found for tumors measuring between 2 and 5 cm (T2) as opposed to tumors larger than 5 cm (T3). Therefore, MCCs in both size categories are placed in stage II (Table 4). Lesions that invade the fascia, muscle, bone, or cartilage, however, are classified as stage IV (T4), indicating worse prognosis, regardless of their size.

The new staging system considers whether the absence of lymph node involvement is confirmed by a pathologist (pN0) rather than based only on clinical or radiologic criteria. This distinction between clinical and histologic staging is very important given that up to a third of patients with apparently local disease do in fact have undetected metastasis.[101] Nonetheless, micrometastasis (N1a) indicates a much better prognosis (5-year survival, 42%) than macrometastasis (N1b, 5-year survival, 26%) (Table 4).

One-year survival in patients who have metastasis at diagnosis is approximately 44%.[100] Although the new staging system gives different categories for metastasis to different locations, this aspect does not affect survival.

Ethical Disclosures

Protection of human and animal subjects.

The authors declare that no experiments were performed on humans or animals for this investigation.

Data confidentiality. The authors declare that they followed their hospitals' regulations regarding the publication of patient information and that written informed consent for voluntary participation was obtained for all patients.

Right to privacy and informed consent.

The authors declare that no private patient data are disclosed in this article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Toker C. Trabecular carcinoma of the skin. Arch Dermatol. 1972;105:107–10.
2. Tang CK, Toker C. Trabecular carcinoma of the skin: an ultrastructural study. Cancer. 1978;42:2311–21.
3. Silva EG, Ordonez NG, Lechago J. Immunohistochemical studies in endocrine carcinoma of the skin. Am J Clin Pathol. 1984;81:558–62.
4. Brousse C, Baumelou E, Moisson P, Epardeau B, Mignot L. [Merkel cell carcinoma: primary cutaneous neuroendocrine tumor]. Rev Med Interne. 1996;17:1025–8.
5. Cotlar AM, Gates JO, Gibbs FA Jr. Merkel cell carcinoma: Combined surgery and radiation therapy. Am Surg. 1986;52:159–64.
6. Lemos B, Nghiem P. Merkel cell carcinoma: More deaths but still no pathway to blame. J Invest Dermatol. 2007;127:2100–3.
7. Agelli M, Clegg LX. Epidemiology of primary Merkel cell carcinoma in the United States. J Am Acad Dermatol. 2003;49:832–41.
8. Garneski KM, Nghiem P. Merkel cell carcinoma adjuvant therapy: Current data support radiation but not chemotherapy. J Am Acad Dermatol. 2007;57:166–9.
9. Vilar-Coromina N, Perez Bueno F, Alsina Maqueda M, Vilardell Gil L, Izquierdo Font A, Marcos-Gragera R. [Merkel cell cancer of the skin: Population-based incidence and survival, 1995-2005]. Med Clin (Barc). 2009;132:701–3.
10. Guler-Nizam E, Leiter U, Metzler G, Breuninger H, Garbe C, Eigentler TK. Clinical course and prognostic factors of Merkel cell carcinoma of the skin. Br J Dermatol. 2009;161:90–4.
11. Albores-Saavedra J, Batich K, Chable-Montero F, Sagy N, Schwartz AM, Henson DE. Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: A population based study. J Cutan Pathol. 2010;37:20–7.
12. Medina-Franco H, Urist MM, Fiveash J, Heslin MJ, Bland KI, Beenken SW. Multimodality treatment of Merkel cell carcinoma: Case series and literature review of 1,024 cases. Ann Surg Oncol. 2001;8:204–8.
13. Eng TY, Boersma MG, Fuller CD, Goytia V, Jones WE 3rd, Joyner M, et al. A comprehensive review of the treatment of Merkel cell carcinoma. Am J Clin Oncol. 2007;30:624–36.
14. Schmid C, Beham A, Feichtinger J, Aubock L, Dietze O. Recurrent and subsequently metastasizing Merkel cell carcinoma in a 7-year-old girl. Histopathology. 1992;20:437–9.
15. Iacocca MV, Abernethy JL, Stefanato CM, Allan AE, Bhawan J. Mixed Merkel cell carcinoma and squamous cell carcinoma of the skin. J Am Acad Dermatol. 1998;39:882–7.
16. Popp S, Waltering S, Herbst C, Moll I, Boukamp P. UV-B-type mutations and chromosomal imbalances indicate common pathways for the development of Merkel and skin squamous cell carcinomas. Int J Cancer. 2002;99:352–60.

17. Lunder EJ, Stern RS. Merkel-cell carcinomas in patients treated with methoxsalen and ultraviolet A radiation. N Engl J Med. 1998;339:1247–8.

18. Hewitt JB, Sherif A, Kerr KM, Stankler L. Merkel cell and squamous cell carcinomas arising in erythema ab igne. Br J Dermatol. 1993;128:591–2.

19. Howard RA, Dores GM, Curtis RE, Anderson WF, Travis LB. Merkel cell carcinoma and multiple primary cancers. Cancer Epidemiol Biomarkers Prev. 2006;15:1545–9.

20. Penn I, First MR. Merkel's cell carcinoma in organ recipients: report of 41 cases. Transplantation. 1999;68:1717–21.

21. Maksymiuk B, Wygoda A, Zakliczynski M, Palen P. Primary undifferentiated small cell carcinoma (Merkel cell carcinoma) in a patient after heart transplantation-case report. Pol J Pathol. 2002;53:177–80.

22. Urbatsch A, Sams WM Jr, Urist MM, Sturdivant R. Merkel cell carcinoma occurring in renal transplant patients. J Am Acad Dermatol. 1999;41 2 Pt 2:289–91.

23. Gooptu C, Woollons A, Ross J, Price M, Wojnarowska F, Morris PJ, et al. Merkel cell carcinoma arising after therapeutic immunosuppression. Br J Dermatol. 1997;137: 637–41.

24. An KP, Ratner D. Merkel cell carcinoma in the setting of HIV infection. J Am Acad Dermatol. 2001;45:309–12.

25. Izikson L, Nornhold E, Iyer JG, Nghiem P, Zeitouni NC. Merkel cell carcinoma associated with HIV: Review of 14 patients. AIDS. 2011;25:119–21.

26. Ziprin P, Smith S, Salerno G, Rosin RD. Two cases of Merkel cell tumour arising in patients with chronic lymphocytic leukaemia. Br J Dermatol. 2000;142:525–8.

27. Akhtar S, Oza KK, Wright J. Merkel cell carcinoma: Report of 10 cases and review of the literature. J Am Acad Dermatol. 2000;43:755–67.

28. Sahi H, Koljonen V, Bohling T, Neuvonen PJ, Vainio H, Lamminpaa A, et al. Increased incidence of Merkel cell carcinoma among younger statin users. Cancer Epidemiol. 2012;36:421–4.

29. Ma JE, Brewer JD. Merkel cell carcinoma in immunosuppressed patients. Cancers (Basel). 2014;6:1328–50.

30. Van Gele M, Leonard JH, Van Roy N, Cook AL, de Paepe A, Speleman F. Frequent allelic loss at 10q23 but low incidence of PTEN mutations in Merkel cell carcinoma. Int J Cancer. 2001;92:409–13.

31. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science. 2008;319:1096–100.

32. Tai P. Merkel cell cancer: Update on biology and treatment. Curr Opin Oncol. 2008;20:196–200.

33. Skelton HG, Smith KJ, Hitchcock CL, McCarthy WF, Lupton GP, Graham JH. Merkel cell carcinoma: Analysis of clinical, histologic, and immunohistologic features of 132 cases with relation to survival. J Am Acad Dermatol. 1997;37:734–9.

34. Katenkamp D, Watzig V. [Neuroendocrine carcinoma of the skin. Morphology and differential diagnosis based on 2 clinical cases]. Zentralbl Allg Pathol. 1984;129:383–92.

35. Eftekhari F, Wallace S, Silva EG, Lenzi R. Merkel cell carcinoma of the skin: Imaging and clinical features in 93 cases. Br J Radiol. 1996;69:226–33.

36. Hitchcock CL, Bland KI, Laney RG 3rd, Franzini D, Harris B, Copeland EM 3rd. Neuroendocrine (Merkel cell) carcinoma of the skin. Its natural history, diagnosis, and treatment. Ann Surg. 1988;207:201–7.

37. Mamalis N, Medlock RD, Holds JB, Anderson RL, Crandall AS. Merkel cell tumor of the eyelid: A review and report of an unusual case. Ophthalmic Surg. 1989;20:410–4.

38. Dinh V, Feun L, Elgart G, Savaraj N. Merkel cell carcinomas. Hematol Oncol Clin North Am. 2007;21:527–44.

39. Pitale M, Sessions RB, Husain S. An analysis of prognostic factors in cutaneous neuroendocrine carcinoma. Laryngoscope. 1992;102:244–9.

40. Smith DE, Bielamowicz S, Kagan AR, Anderson PJ, Peddada AV. Cutaneous neuroendocrine (Merkel cell) carcinoma. A report of 35 cases. Am J Clin Oncol. 1995;18:199–203.

41. Yiengpruksawan A, Coit DG, Thaler HT, Urmacher C, Knapper WK. Merkel cell carcinoma. Prognosis and management. Arch Surg. 1991;126:1514–9.

42. Llombart B, Monteagudo C, Lopez-Guerrero JA, Carda C, Jorda E, Sanmartin O, et al. Clinicopathological and immunohistochemical analysis of 20 cases of Merkel cell carcinoma in search of prognostic markers. Histopatholog. 2005;46:622–34.

43. Ratner D, Nelson BR, Brown MD, Johnson TM. Merkel cell carcinoma. J Am Acad Dermatol. 1993;29:143–56.

44. Bottles K, Lacey CG, Goldberg J, Lanner-Cusin K, Hom J, Miller TR. Merkel cell carcinoma of the vulva. Obstet Gynecol. 1984;63:61S–5S.

45. Copeland LJ, Cleary K, Sneige N, Edwards CL. Neuroendocrine (Merkel cell) carcinoma of the vulva: A case report and review of the literature. Gynecol Oncol. 1985;22:367–78.

46. Rocamora A, Badia N, Vives R, Carrillo R, Ulloa J, Ledo A. Epidermotropic primary neuroendocrine (Merkel cell) carcinoma of the skin with Pautrier-like microabscesses. Report of three cases and review of the literature. J Am Acad Dermatol. 1987;16:1163–8.

47. Eusebi V, Capella C, Cossu A, Rosai J. Neuroendocrine carcinoma within lymph nodes in the absence of a primary tumor, with special reference to Merkel cell carcinoma. Am J Surg Pathol. 1992;16:658–66.

48. Foote M, Veness M, Zarate D, Poulsen M. Merkel cell carcinoma: The prognostic implications of an occult primary in stage IIIB (nodal) disease. J Am Acad Dermatol. 2012;67:395–9.

49. Cirillo F. Spontaneous regression of primitive Merkel cell carcinoma. Rare Tumors. 2015;7:5961.

50. Val-Bernal JF, Garcia-Castano A, Garcia-Barredo R, Landeras R, de Juan A, Garijo MF. Spontaneous complete regression in Merkel cell carcinoma after biopsy. Adv Anat Pathol. 2011;18:174–7.

51. Requena C, Traves V, Llombart B, Guillen C. Incipient Merkel cell carcinoma: A report of 2 cases. Actas Dermosifiliogr. 2013;104:71–4.

52. Ferringer T, Rogers HC, Metcalf JS. Merkel cell carcinoma in situ. J Cutan Pathol. 2005;32:162–5.

53. Al-Ahmadie HA, Mutasim DF, Mutema GK. A case of intraepidermal Merkel cell carcinoma within squamous cell carcinoma in-situ: Merkel cell carcinoma in-situ. Am J Dermatopathol. 2004;26:230–3.

54. Arias S, Sierra M, Gutiérrez MT, García V. Características clínicas del carcinoma de Merkel. 1st ed. Madrid: Editorial Aula Médica; 2013. Vol. 26. p. 49-52.

55. Heath M, Jaimes N, Lemos B, Mostaghimi A, Wang LC, Penas PF, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: The AEIOU features. J Am Acad Dermatol. 2008;58:375–81.

56. Harting MS, Ludgate MW, Fullen DR, Johnson TM, Bichakjian CK. Dermatoscopic vascular patterns in cutaneous Merkel cell carcinoma. J Am Acad Dermatol. 2012;66:923–7.

57. Suarez AL, Louis P, Kitts J, Busam K, Myskowski PL, Wong RJ, et al. Clinical and dermoscopic features of combined cutaneous squamous cell carcinoma (SCC)/neuroendocrine [Merkel cell] carcinoma (MCC). J Am Acad Dermatol. 2015;73:968–75.

58. Smith PD, Patterson JW. Merkel cell carcinoma (neuroendocrine carcinoma of the skin). Am J Clin Pathol. 2001;115 Suppl:S68–78.

59. D'Agostino M, Cinelli C, Willard R, Hofmann J, Jellinek N, Robinson-Bostom L. Epidermotropic Merkel cell carcinoma: A

case series with histopathologic examination. J Am Acad Dermatol. 2010;62:463–8.

60. Smith KJ, Skelton HG 3rd, Holland TT, Morgan AM, Lupton GP. Neuroendocrine (Merkel cell) carcinoma with an intraepidermal component. Am J Dermatopathol. 1993;15:528–33.

61. LeBoit PE, Crutcher WA, Shapiro PE. Pagetoid intraepidermal spread in Merkel cell (primary neuroendocrine) carcinoma of the skin. Am J Surg Pathol. 1992;16:584–92.

62. Gould VE, Lee I, Hammar SP. Neuroendocrine skin carcinoma coexpressing cytokeratin and neurofilament proteins. Ultrastruct Pathol. 1985;9:83–90.

63. Martin B, Poblet E, Rios JJ, Kazakov D, Kutzner H, Brenn T, et al. Merkel cell carcinoma with divergent differentiation: histopathological and immunohistochemical study of 15 cases with PCR analysis for Merkel cell polyomavirus. Histopathology. 2013;62:711–22.

64. Saeb-Lima M, Montante-Montes de Oca D, Albores-Saavedra J. Merkel cell carcinoma with eccrine differentiation: A clinicopathologic study of 7 cases. Ann Diagn Pathol. 2008;12:410–4.

65. Koba S, Nagase K, Ikeda S, Aoki S, Misago N, Narisawa Y. Merkel cell carcinoma with glandular differentiation admixed with sweat gland carcinoma and spindle cell carcinoma: Histogenesis of Merkel cell carcinoma from hair follicle stem cells. Am J Dermatopathol. 2015;37:e31–6.

66. Gould E, Albores-Saavedra J, Dubner B, Smith W, Payne CM. Eccrine and squamous differentiation in Merkel cell carcinoma. An immunohistochemical study. Am J Surg Pathol. 1988;12:768–72.

67. Foschini MP, Eusebi V. Divergent differentiation in endocrine and nonendocrine tumors of the skin. Semin Diagn Pathol. 2000;17:162–8.

68. Tan KB, Murali R, Karim RZ, Dutta B, Dutta R, McCarthy SW, et al. Merkel cell carcinoma with fibrosarcomatous differentiation. Pathology. 2008;40:314–6.

69. Covello R, Licci S, Ferrari A, Morelli L, Catricala C. Merkel cell carcinoma of the thumb with squamous and leiomyosarcomatous differentiation. Eur J Dermatol. 2010;20:529–30.

70. Plaza JA, Suster S. The Toker tumor: Spectrum of morphologic features in primary neuroendocrine carcinomas of the skin (Merkel cell carcinoma). Ann Diagn Pathol. 2006;10:376–85.

71. Walsh NM. Primary neuroendocrine (Merkel cell) carcinoma of the skin: Morphologic diversity and implications thereof. Hum Pathol. 2001;32:680–9.

72. Tilling T, Moll I. Which are the cells of origin in Merkel cell carcinoma? J Skin Cancer. 2012;2012:680410.

73. Casari A, Argenziano G, Piana S, Lallas AE, Moscarella E, Lombardi M, et al. Merkel cell carcinoma arising on a pre-existing Bowen's disease: Is it just by chance? G Ital Dermatol Venereol. 2015 Jul 29. [Epub ahead of print].

74. Molina-Ruiz AM, Bernardez C, Requena L, Rutten A. Merkel cell carcinoma arising within a poroma: Report of two cases. J Cutan Pathol. 2015;42:353–60.

75. Takenaka H, Kishimoto S, Shibagaki R, Nagata M, Yasuno H. Merkel cell carcinoma with partial spontaneous regression: An immunohistochemical, ultrastructural, and TUNEL labeling study. Am J Dermatopathol. 1997;19:614–8.

76. Rao P, Balzer BL, Lemos BD, Liegeois NJ, McNiff JM, Nghiem P, et al. Protocol for the examination of specimens from patients with Merkel cell carcinoma of the skin. Arch Pathol Lab Med. 2010;134:341–4.

77. Wang TS, Byrne PJ, Jacobs LK, Taube JM. Merkel cell carcinoma: Update and review. Semin Cutan Med Surg. 2011;30:48–56.

78. Bichakjian CK, Lowe L, Lao CD, Sandler HM, Bradford CR, Johnson TM, et al. Merkel cell carcinoma: Critical review with guidelines for multidisciplinary management. Cancer. 2007;110:1–12.

79. Goepfert H, Remmler D, Silva E, Wheeler B. Merkel cell carcinoma (endocrine carcinoma of the skin) of the head and neck. Arch Otolaryngol. 1984;11070:7–12.

80. Aneiros J, Almodóvar A, Caba M. Carcinoma de células de Merkel: estudio histopatológico, inmunohistoquímico, ultra-estructural y molecular. 1st ed. Madrid: Editorial Aula Médica; 2013. Vol. 26. p. 58-64.

81. Calder KB, Coplowitz S, Schlauder S, Morgan MB. A case series and immunophenotypic analysis of CK20-/CK7+ primary neuroendocrine carcinoma of the skin. J Cutan Pathol. 2007;34:918–23.

82. Weiler R, Fischer-Colbrie R, Schmid KW, Feichtinger H, Bussolati G, Grimelius L, et al. Immunological studies on the occurrence and properties of chromogranin A and B and secretogranin II in endocrine tumors. Am J Surg Pathol. 1988;12:877–84.

83. Krasagakis K, Tosca AD. Overview of Merkel cell carcinoma and recent advances in research. Int J Dermatol. 2003;42:669–76.

84. McNiff JM, Cowper SE, Lazova R, Subtil A, Glusac EJ. CD56 staining in Merkel cell carcinoma and natural killer-cell lymphoma: Magic bullet, diagnostic pitfall, or both. J Cutan Pathol. 2005;32:541–5.

85. Chan JK, Suster S, Wenig BM, Tsang WY, Chan JB, Lau AL. Cytokeratin 20 immunoreactivity distinguishes Merkel cell (primary cutaneous neuroendocrine) carcinomas and salivary gland small cell carcinomas from small cell carcinomas of various sites. Am J Surg Pathol. 1997;21:226–34.

86. Sibley RK, Dehner LP, Rosai J. Primary neuroendocrine (Merkel cell?) carcinoma of the skin. I. A clinicopathologic and ultrastructural study of 43 cases. Am J Surg Pathol. 1985;9:95–108.

87. Nicholson SA, McDermott MB, Swanson PE, Wick MR. CD99 and cytokeratin-20 in small-cell and basaloid tumors of the skin. Appl Immunohistochem Mol Morphol. 2000;8:37–41.

88. Bickle K, Glass LF, Messina JL, Fenske NA, Siegrist K. Merkel cell carcinoma: A clinical, histopathologic, and immunohistochemical review. Semin Cutan Med Surg. 2004;23:46–53.

89. Byrd-Gloster AL, Khoor A, Glass LF, Messina JL, Whitsett JA, Livingston SK, et al. Differential expression of thyroid transcription factor 1 in small cell lung carcinoma and Merkel cell tumor. Hum Pathol. 2000;31:58–62.

90. Leech SN, Kolar AJ, Barrett PD, Sinclair SA, Leonard N. Merkel cell carcinoma can be distinguished from metastatic small cell carcinoma using antibodies to cytokeratin 20 and thyroid transcription factor 1. J Clin Pathol. 2001;54:727–9.

91. Fuertes L, Santonja C, Kutzner H, Requena L. Immuno-histochemistry in dermatopathology: A review of the most commonly used antibodies (part II). Actas Dermosifiliogr. 2013;104:181–203.

92. Ralston J, Chiriboga L, Nonaka D. MASH1: A useful marker in differentiating pulmonary small cell carcinoma from Merkel cell carcinoma. Mod Pathol. 2008;21:1357–62.

93. Warner TF, Uno H, Hafez GR, Burgess J, Bolles C, Lloyd RV, et al. Merkel cells and Merkel cell tumors. Ultrastructure, immunocytochemistry and review of the literature. Cancer. 1983;52:238–45.

94. Gould VE, Dardi LE, Memoli VA, Johannessen JV. Neuroendocrine carcinomas of the skin: Light microscopic, ultrastructural, and immunohistochemical analysis. Ultrastruct Pathol. 1980;1:499–509.

95. Van Gele M, Leonard JH, Van Roy N, Van Limbergen H, Van Belle S, Cocquyt V, et al. Combined karyotyping, CGH and M-FISH analysis allows detailed characterization of unidentified chromosomal rearrangements in Merkel cell carcinoma. Int J Cancer. 2002;101:137–45.

96. Plettenberg A, Pammer J, Tschachler E. Merkel cells and Merkel cell carcinoma express the BCL-2 proto-oncogene. Exp Dermatol. 1996;5:183–8.

97. Van Gele M, Kaghad M, Leonard JH, Van Roy N, Naeyaert JM, Geerts ML, et al. Mutation analysis of P73 and TP53 in Merkel cell carcinoma. Br J Cancer. 2000;82:823–6.

98. Harms PW, Collie AM, Hovelson DH, Cani AK, Verhaegen ME, Patel RM, et al. Next generation sequencing of Cytokeratin 20-negative Merkel cell carcinoma reveals ultraviolet-signature mutations and recurrent TP53 and RB1 inactivation. Mod Pathol. 2016;29:240–8.

99. Goh G, Walradt T, Markarov V, Blom A, Riaz N, Doumani R, et al. Mutational landscape of MCPyV-positive and MCPyV-negative Merkel cell carcinomas with implications for immunotherapy. Oncotarget. 2015;19:3403–15.

100. Lemos BD, Storer BE, Iyer JG, Phillips JL, Bichakjian CK, Fang LC, et al. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: Analysis of 5,823 cases as the basis of the first consensus staging system. J Am Acad Dermatol. 2010;63:751–61.

101. Gupta SG, Wang LC, Penas PF, Gellenthin M, Lee SJ, Nghiem P. Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma: The Dana-Farber experience and meta-analysis of the literature. Arch Dermatol. 2006;142:685–90.