Pathology of Merkel Cell Carcinoma (Primary Neuroendocrine Carcinoma of the Skin)

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Introduction

Merkel cell carcinoma (MCC), also known as primary cutaneous neuroendocrine carcinoma and historically as trabecular carcinoma and as "APUDoma," is a rare skin tumor with an aggressive clinical behavior and a predilection for the elderly and the immunosuppressed. Dr. Cyril Toker first described this entity in 1972 under the rubric of trabecular carcinoma [1]. Dr. Toker characterized this tumor as a primary cutaneous carcinoma composed of small round blue cells that could be potentially confused for metastatic carcinoma. In subsequent papers, he attributed sudoriferous and neurosecretory features to the tumor cells, speculating that the tumor may have originated from normal Merkel cells, sweat glands, or a pluripotential precursor [2]. The term Merkel cell carcinoma, the most widely accepted name for the entity, was coined by De Wolff-Peeters in 1980 [3]. The question of the "cell of origin" from which MCC arises has been a matter of much controversy. Since MCC tumor cells share many immunophenotypic and ultrastructural features with normal Merkel cells, it was long believed that these cells act as a precursor for MCC. This notion has been further reinforced by the fact that a fraction of MCC cases can exhibit a prominent intraepidermal component as well as by the existence of an in situ MCC variant.

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A. Nasir, D. Coppola (eds.), *Neuroendocrine Tumors: Review of Pathology, Molecular and Therapeutic Advances*, DOI 10.1007/978-1-4939-3426-3_21

Normal Merkel cells, first characterized by Friedrich Sigmund Merkel in 1875, are intraepidermal neural crest-derived cells that are thought to serve as slow-acting mechanoreceptors responsible for touch and hair movement sensitivity. They occur singly or in clusters in touch domes (*haarscheibe*) in close relationship with sensory axons and along the basilar layer of the epidermis, in hair disks, and in the bulge region of the follicle [4]. As far as anatomical distribution of Merkel cells is concerned, they are widely and numerously present in sensitive areas of the skin as well as of the oral and anal mucosal surfaces. Merkel cells can also be found in high numbers populating tongue taste buds, whisker pads, palatine mucosa rugae, and the vermillion border of the lips and in hairy and glabrous sensitive skin and even in sweat glands [5]. Interestingly enough, normal Merkel cells tend to be more abundant in sun-exposed areas [5].

Recently, the concept that MCC most likely originates from a pluripotential stem cell precursor with acquired immunophenotypic and ultrastructural characteristics akin to normal Merkel cells has gained more traction [6]. This concept is further supported by the presence of divergent differentiation in some MCC cases, a phenomenon to be discussed below. Some authors have recently proposed that a possible precursor of MCC could be represented by pre-/pro-B lymphoid stem cells [7], particularly after the observation that MCC cells can express primitive B-cell markers such as PAX5 and TdT [8, 9]. It is important to point out that the discovery of the Merkel cell polyomavirus (MCPyV) [10] has truly revolutionized our understating of MCC. MCPyV is a polyomavirus, first characterized in 2008, that is found in about 80 % of MCC cases. This finding prompted a classification of MCC into two groups: the MCPyV-positive MCCs and the MCPyV-negative MCCs. This dichotomous view of MCC will be expanded below.

Epidemiological and Clinical Features

Due to the combination of an aging population, increased disease awareness, and improved diagnostic tools and criteria, the yearly incidence rate of MCC in the United States has been steadily increasing from less than 0.1 cases per 100,000 in the 1980s to 0.24 cases per 10,000 toward the end of the twentieth century [11] to up to 0.6 cases per 10,000 in 2006 [12]. A similar trend has been observed in other industrialized nations [13]. Caucasian men are the most frequently affected, with MCC only rarely affecting blacks and other ethnic groups. MCC is a tumor of the elderly with average age at presentation being 76 years old for women and 72 years old for men [12]. This entity thrives in an immunosuppressed milieu [14], and patients with HIV/AIDS [15], hematologic conditions [16], and in the post-transplant status [17–19] are at increased risk of developing MCC. The frequent link between MCC and immunosuppression triggered a suspicion for an infective agent being an etiologic factor, ultimately leading to the discovery of the MCPyV [10]. Individuals afflicted by MCC are also at increased risk of developing additional malignancies [13, 20, 21], a finding likely related to the above-mentioned fact that

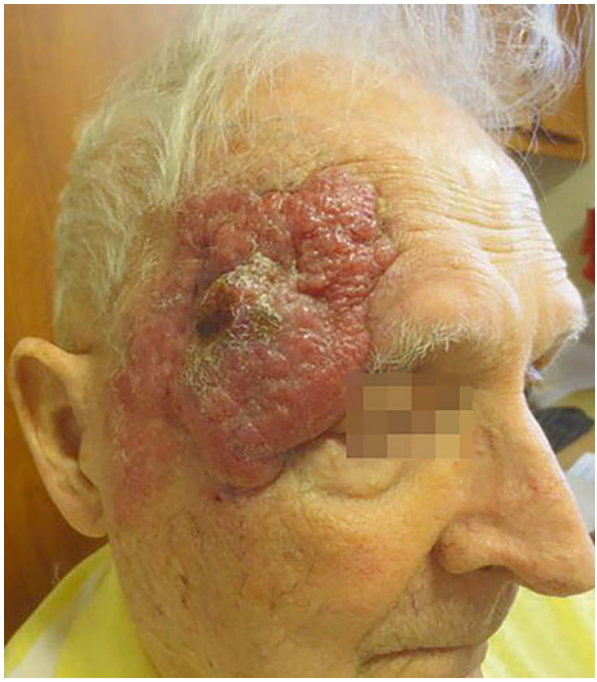

Fig. 1 Clinical presentation of MCC. Image representing the most commonly seen clinical features of MCC: a non-ulcerated erythematous head and neck mass arising in an elderly individual

these patients are frequently immunosuppressed. With regard to anatomic location, MCC frequently arises on chronically sun-damaged skin of the head and neck and extremities with rare cases arising from the trunk [12, 22–25]. However, MCC can arise in a variety of non-sun-exposed sites such as mucosal surfaces of the mouth [26–29], tongue [30], nasopharynx [31], and skin from the external genitalia [32, 33]. Lymph nodes are also mentioned as primary sites for MCC [34–37], probably representing nodal metastases from completely regressed cutaneous tumors. Rare cases of MCC-like tumors have been documented arising from the parotid gland [37–39], stomach [40], and vagina [41, 42]. Clinically, MCC often presents as a rapidly-growing painless and often firm nodule or mass with erythematous, pink, violaceous, or even bruise-like-colored overlying skin that is often non-ulcerated [14, 43] (Fig. 1). Some tumors can even exhibit a pigmented appearance [44, 45]. Due to this relatively nonspecific clinical presentation, MCC is more often included as part of a clinical differential diagnosis that includes basal cell carcinoma (BCC), squamous cell carcinoma (SCC), amelanotic melanoma, cyst, adnexal tumor, or lymphoma cutis [46]. Multicentric presentations [47] and in-transit metastatic spread [48, 49] have been reported. MCC is characterized by frequent regional nodal metastasis, and a positive lymph node status, particularly if clinically detected, is negatively correlated with outcome [50, 51]. Distant metastatic spread can affect a wide variety of organs and anatomical sites including the iris [52], brain [53–55], meninges [56, 57], gingiva [58],oropharynx [59], heart [60–63], gastrointestinal tract [64–66] (Fig. 2), pancreas [67, 68], genitourinary system [69–73], and soft

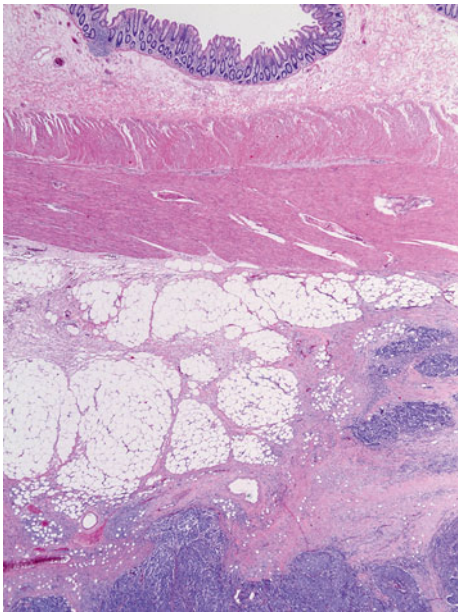

Fig. 2 MCC can metastasize to a variety of anatomical sites, including the gastrointestinal tract as in this case where tumor nodules can be appreciated involving the pericolic adipose tissue (H&E, 1.5×)

tissue [74]. Cases of MCC exhibiting massive involvement of bone marrow [75] and leukemic dissemination [76] have been described, and although they are extremely rare events, such occurrences carry an obvious dismal prognosis. Spontaneous regression of MCC is an unusual but well-documented phenomenon [77–86] that may account for a good proportion of cases described as "primary" lymph node MCCs [34–36, 87–90] as well as for cases with unknown primary [91–94]. As is the case with other small cell carcinomas with neuroendocrine features, MCC can very rarely exhibit paraneoplastic manifestations such as thrombocytopenia [95], hyponatremia from ectopic ACTH production [96], and Lambert-Eaton syndrome [97].

Light Microscopic Findings

MCC is most often a dermal tumor, centered in the mid-dermis and exhibiting a Grenz zone. A fraction of the cases (up to 10 %) will display a prominent intraepidermal component, sometimes even more prominent than the dermal component [18, 98–102]. Pure in situ intraepidermal variants can be rarely encountered [103, 104]. On H&E-stained tissue sections, the presence of dark-blue dermal nodules "grossly" distinguishable on the glass slide section even before placing it under the microscope is a characteristic of this tumor. The tumor's deeply basophilic hue reflects the fact that it represents a "small round blue cell" (SRBC) proliferation, thus composed of monomorphic small- to medium-sized cells bearing hyperchromatic nuclei and scant cytoplasm. These cells can be arranged in a variety of

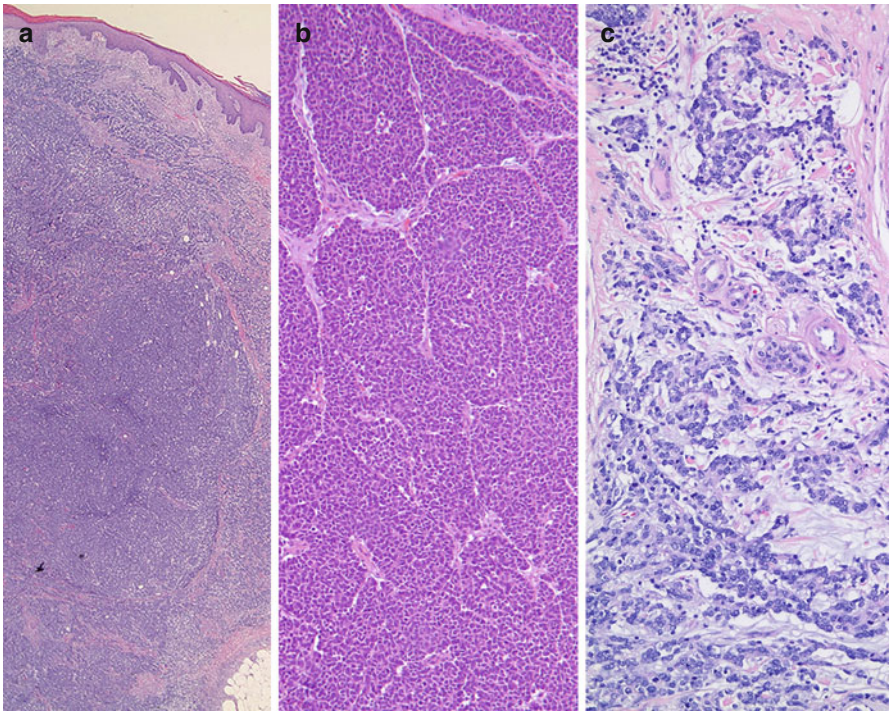

Fig. 3 Panel exhibiting some of the growth patterns seen with MCC including sheets (**a**), nests (**c**), and trabecular (**c**). Note the Grenz zone on image **a** (H&E, **a**: 1.5×, **b**: 100×, **c**: 200×)

patterns: large sheets, nests, and cords or the characteristic trabeculae that prompted the tumor's first moniker (Fig. 3). As is characteristic of small cell carcinomas and SRBC tumors, the lesional cells are often closely packed but lack intercellular cohesion, a consequence of dysfunctional E-cadherin/beta-catenin machinery, which mediates intercellular adhesion [105, 106]. This growth pattern can make evaluation for lymphovascular invasion (LVI) and margin status a quite difficult task. Nevertheless, *Bona fide* LVI is a frequent finding in MCC, particularly in thick tumors (Fig. 4). The tumor borders can be pushing or infiltrative, a distinction that might carry prognostic significance, as will be discussed below. Other features akin to SRBC and high-grade neuroendocrine tumors can be often seen in MCC, such as nuclear molding as well as signs of high cell turnover with numerous readily identifiable mitotic figures and apoptotic bodies. Classically, three morphologic patterns have been recognized: trabecular, intermediate, and small cell (Fig. 5). However, these morphologic variants have no correlation with clinical outcome [107] and are commonly found in combination in a single tumor. Furthermore, MCCs can exhibit a myriad of additional growth patterns, including organoid [108] and spindle cell patterns (Fig. 6), as well as tumors forming Homer-Wright rosettes [18, 98, 109] and some exhibiting a pseudo-follicular type of arrangement (Fig. 7). Cytologically distinctive tumor cell features include pleomorphic and plasmacytoid forms and

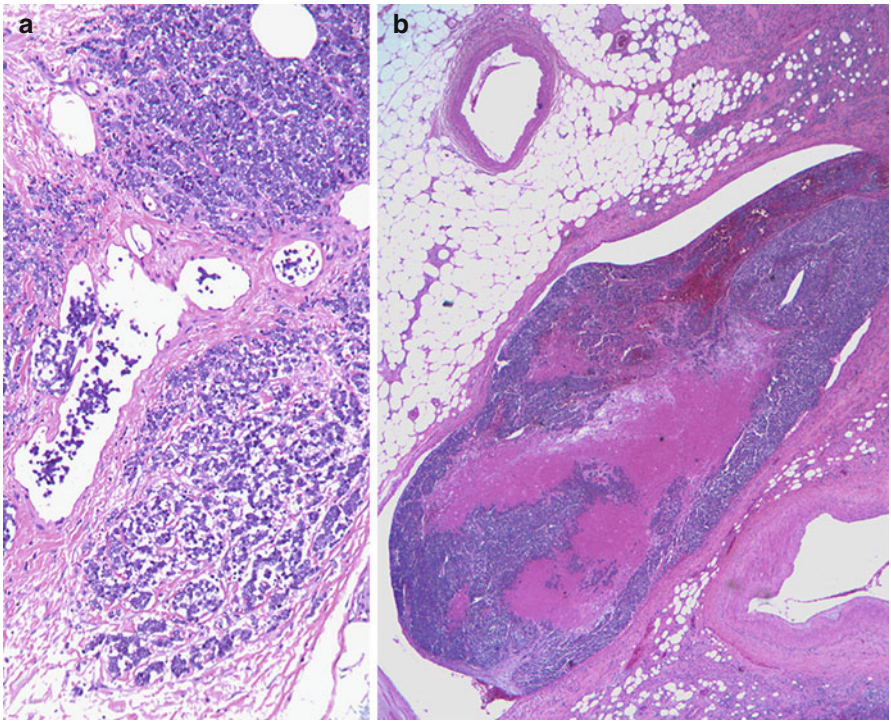

Fig. 4 Lymphovascular invasion (LVI) is a frequent finding in MCC and is an adverse prognostic factor. One can either find intravascular small nests and tumor cells at the edge of the tumor (**a**) or even extreme cases of large tumor emboli (**b**) (H&E, **a**: 100×, **b**: 1.5×)

cells with "washed-out" nuclear chromatin (Fig. 5) [110]. The so-called Azzopardi phenomenon, a feature frequently seen in SRBC and high-grade neuroendocrine tumors that relates to the increased cell fragility due to a practically absent cytoplasm, can be identified in MCCs [111, 112]. The stroma surrounding the tumor cells often shows a mucinous/myxoid appearance (Fig. 5), but it can also be sclerotic or show deposition of amyloid-like material [110]. Varying amounts of newly formed vessels, a product of reactive angiogenesis, can be identified surrounding MCCs [112]. In addition, it is not unusual to find prominent peri-tumoral lymphocytic infiltrates [110], sometimes adopting a follicular pattern [113]. Since MCC likely originates from a pluripotential stem cell precursor [6], this entity has the potential to exhibit quite varied types of divergent differentiation. Some of the described associated divergent phenotypes associated with MCC include squamous, glandular (Fig. 8), basal cell carcinoma, melanocytic, rhabdomyosarcomatous, leiomyosarcomatous, fibrosarcomatous, neuroblastic, and even atypical fibroxanthoma-like [114–128]. The most common associated neoplasm identified closely associated with MCC is squamous cell carcinoma (either in situ or invasive), which is recognized in approximately one-third of cases. Rare variants of MCC mimicking other

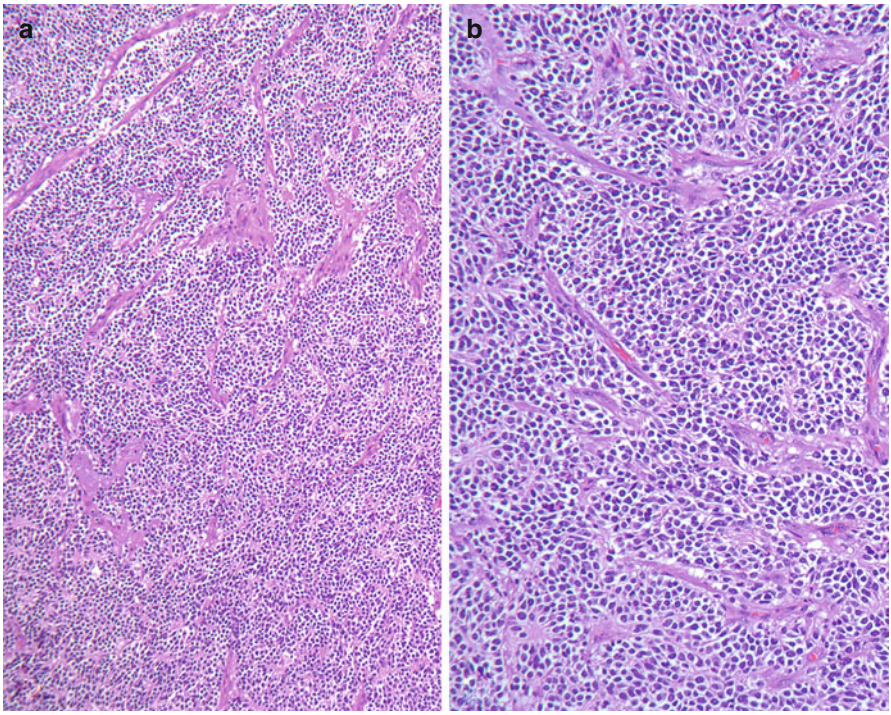

Fig. 5 MCC with small cell pattern, indistinguishable from other small cell carcinomas. Some authors claim it corresponds to the MCPyV-positive tumors. Note the nuclear molding (H&E, **a**: 40×, **b**: 200×).

skin neoplasms have been described, such as lymphoepithelioma-like [129, 130] and microcystic adnexal carcinoma-like [131] patterns.

As previously mentioned, MCC tends to arise in chronically sun-damaged skin. Thus, concomitant actinic keratosis, both invasive and in situ SCC (Fig. 9) and BCC, is often recognized [18, 103, 115, 128, 132–141]. In fact, similar UV-signature *TP53* mutations can be found in both squamous cell carcinoma and MCC [142] suggesting a similar tumorigenesis pathway, and these MCC examples are often MCPyV negative [133, 141, 143]. Recent studies claim that there are somewhat specific morphologic features that will distinguish MCPyV-positive from MCPyV-negative MCCs, with a decent correlation when compared against immunohistochemical and molecular tests for the virus. The features associated with MCPyV-negative MCC include an association with SCC, cells with abundant cytoplasm, and larger pleomorphic and irregular nuclei, roughly corresponding to the "intermediate cell" type. On the other hand, MCPyV-positive MCC will have smaller cells with higher nuclear to cytoplasmic ratio and round nuclei, corresponding to the previously described "small cell variant" [144, 145]. Aside from the above-mentioned association between MCC and SCC, several other cutaneous lesions have been described to arise in conjunction with MCC including sebaceous

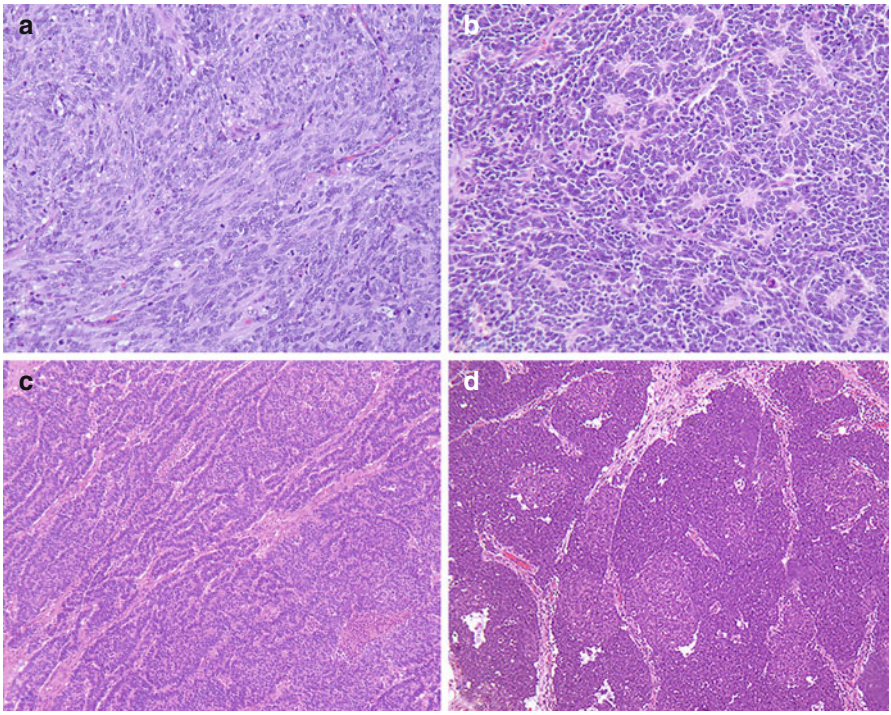

Fig. 6 Composite image demonstrating less frequent growth patterns in MCC, a spindle cell (**a**), an example with well-formed Homer-Wright rosettes (**b**), an example with a striking organoid arrangement (**c**), and a tumor exhibiting a "pseudo-follicular" pattern, in the manner of medulloblastoma (**d**) (H&E, **a** and **b** 200×, **c** and **d**: 100×)

carcinoma [146], atypical fibroxanthoma [147], and trichilemmal [148, 149] and infundibular follicular [150] cysts. Another well-documented and worth mentioning association is that with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (Fig. 10) [13, 16, 151–154]. As commented above this phenomenon is likely related to both the immunosuppressed milieu and the older population of patients in which MCC arises. Interestingly, although recent findings have suggested shared molecular events between CLL/SLL and MCC [16], it is likely that these two entities do not share the same pathogenesis [155].

The main morphologic differential diagnosis of MCC includes metastases from small cell carcinomas of other origins, particularly pulmonary, from which it can be practically indistinguishable by morphology. The possibility of a lymphoid neoplasm should also be ruled out. Other less frequently encountered differential diagnostic possibilities include other primary SRBC tumors that can rarely arise in the skin such as the superficial variant of Ewing sarcoma [156–159] and the rare small cell melanoma. In the unique and unusual occurrence of a purely in situ MCC, one should consider the differential of pagetoid entities such as superficial spreading melanoma and cutaneous T-cell lymphoma [98, 99, 103]. Fortunately, in the majority of the

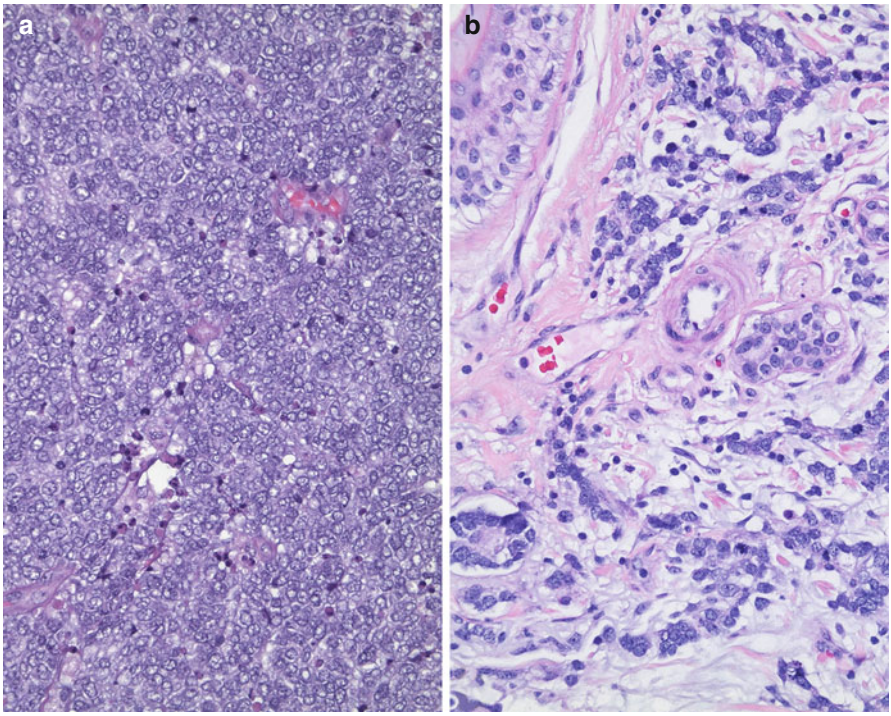

Fig. 7 "Cleared out" chromatin in MCC tumor cells (**a**) and the frequently encountered myxoid stromal reaction adjacent to MCC (H&E, **a** and **b**: 400×)

cases, immunohistochemical staining patterns differ between these entities, allowing for correct classification. Please refer to the immunohistochemistry section for a complete discussion.

Immunohistochemical Aspects of MCC

Just like their normal "counterparts," MCC cells usually and characteristically express cytokeratins and neuroendocrine markers with the prototypical immunoprofile of CK7 negative, CK20 positive, synaptophysin, and chromogranin positive [160]. Albeit quite nonspecific and thus rarely used, another neuroendocrine/neural marker that is frequently described as positive in MCC is neuron-specific enolase (NSE). Regarding the cytokeratins, it is important to emphasize the quite distinctive staining pattern with CK20 found in MCC cells: a strong, paranuclear dot-like signal that either can be found in its "pure" form or accompanied by a diffuse perinuclear or membranous staining. In the latter case, the pattern is best characterized as paranuclear dot-like "accentuation" [107, 161, 162] (Fig. 11) (Importantly, *peri* is a Greek prefix for "around" or "about," while the *para* prefix means "alongside" or

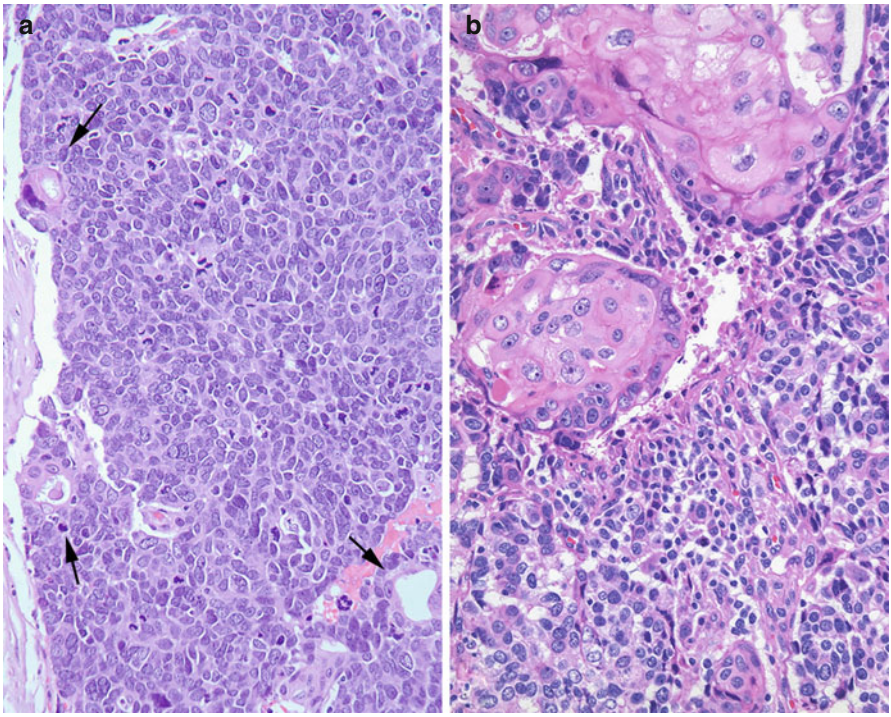

Fig. 8 Glandular (**a**, *arrows*) and squamous (**b**) differentiations in MCC tumors are rarely encountered features (H&E, **a** and **b**: 400×)

"beside"). CK20 and keratin cocktails (CAM 5.2 and AE1:AE3) are particularly useful when evaluating lymph nodes for metastatic disease [163], a procedure that can be quite challenging if one were to use only morphology, particularly in small metastatic deposits (Fig. 12). The distinctive staining pattern with CK20 is replicated in staining for neurofilament [164, 165] and/or CAM 5.2 and AE1:AE3 keratin cocktails and translates to paranuclear accumulation of intermediate filaments, a constant ultrastructural feature of MCC tumor cells. Nevertheless, it is worth emphasizing that both of these immunohistochemical and ultrastructural features can also be observed in a wide variety of other SRBC tumors and small cell (high-grade neuroendocrine) carcinomas from other organs [166–170]. Another important caveat to take in account is that up to 38 % of MCCs can exhibit CK7 positivity [171] with some cases having a CK7+/CK20− immunophenotype [172, 173]. Interestingly enough, normal Merkel cells exhibit a strong, diffuse, and homogeneous cytoplasmic pattern when stained with CK20 and keratin cocktails, and they can also exhibit CK7 positivity [174]. Other epithelial markers expressed in MCC include BerEP4 [100] and p63. Expression of p63 in early-stage MCC has been correlated with progression of disease and worse prognosis [175–177]; however, subsequent studies yielded only a small fraction of MCC expressing p63 without correlation with survival, raising questions about the prognostic utility of this

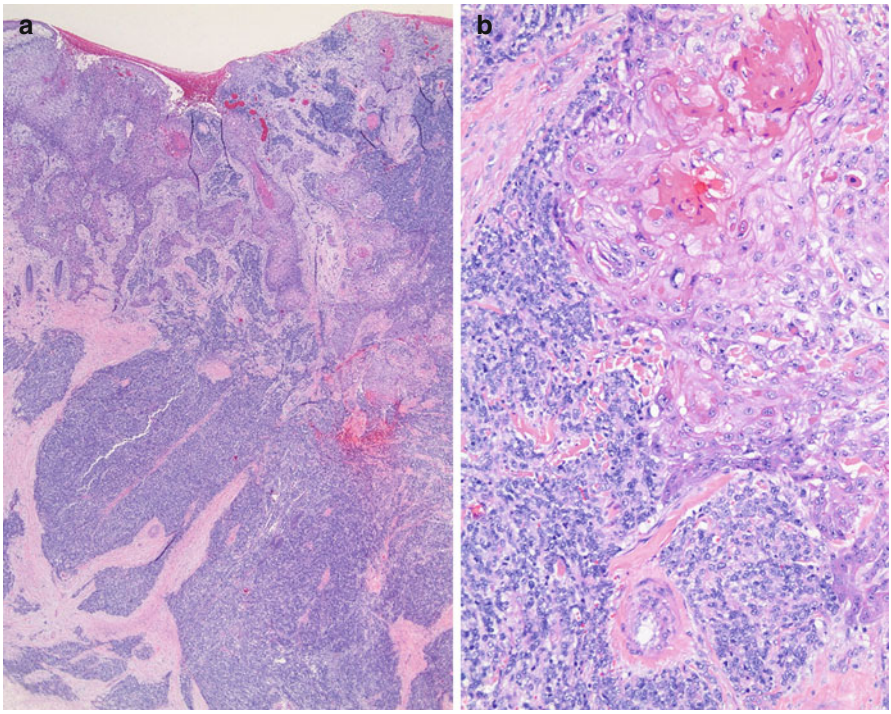

Fig. 9 MCC arising in association with a squamous cell carcinoma (SCC). These tumors tend to be MCPyV negative (H&E, **a**:1.5×, **b**: 200×)

marker [176, 178]. Following the discovery of the MCPyV [10], an antibody clone directed to the large T antigen (LT-Ag) of the virus (CM2B4) was developed [179]. This antibody shows a diffuse nuclear signal by immunohistochemistry (Fig. 13) and performs fairly well and has been shown to have a sensitivity ranging from 77 to 95 % and specificity of 83 %, when compared to MCPyV detection via molecular techniques [133, 145, 179]. The Ab3 clone, a recently developed antibody directed to a different epitope of LT-Ag, has allegedly outperformed CM2B4, with a sensitivity of 97 % [180]. Importantly, these antibodies can certainly be used as diagnostic tools since it is usually not expressed in tumors within the differential diagnosis [133, 180]. Along the lines of the proposed dichotomous model of two tumor pathways (UV-damage *TP53* mutated and MCPyV driven), expression of p53 has been more frequently found in the context of MCPyV-negative MCC tumors, with the p53-positive cases accounting for around 20 % [181] which corresponds to both the proportion of MCPyV-negative tumors and the *TP53*-mutated tumors [142, 182, 183]. Likewise, loss of expression of Rb protein by immunohistochemistry has been related to the MCPyV-negative group of tumors; however, recent data suggest that an underlying dysfunction of the *RB* gene is present in both MCC groups (MCPyV positive and negative) via two different mechanisms [184]. This interplay will be further discussed in the pathogenesis and prognosis sections. Several studies have

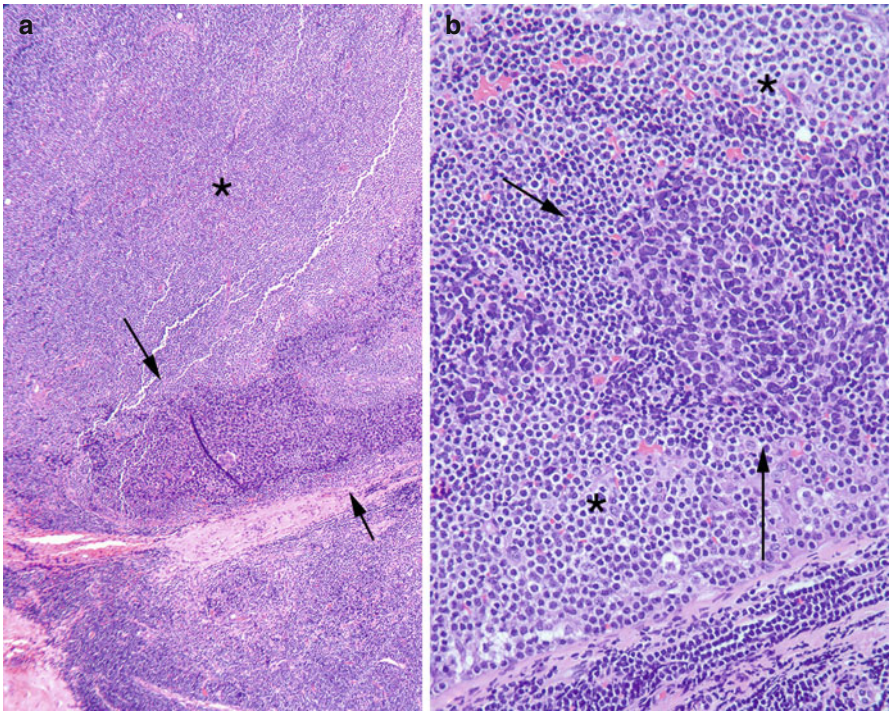

Fig. 10 MCC metastatic deposits (*arrows*) in a lymph node affected by CLL/SLL (*asterisks*). This association is not surprising due to MCC relationship with immunosuppressed and older individuals (H&E, **a**: 40×, **b**: 200×)

demonstrated that MCC is positive for c-kit (CD117) immunohistochemical staining in approximately 50 % of patients [185–188], without a clear correlation with clinical outcome. Unfortunately, this feature is not related to activating *KIT* mutations; MCC is virtually unresponsive to small molecule tyrosine kinase inhibitor therapeutic agents such as imatinib [181, 189–191].

As previously mentioned, the morphologic differential diagnosis of MCC includes several completely unrelated entities requiring immunohistochemical evaluation to be solved. In the following section, we will describe these entities and their different staining patterns. Please see Table 1 for a concise review of the main immunohistochemical differential diagnosis of MCC. First and foremost, a crucial distinction to be made is between MCC and metastatic small cell carcinoma, particularly of pulmonary origin. In this setting, immunohistochemistry for thyroid transcription factor 1 (TTF-1) is of paramount importance. The great majority of MCC are negative for TTF-1, while a large proportion of pulmonary small cell carcinomas and other small cell carcinomas will be positive with this marker [167, 171, 192, 193]. There are rare but well-documented examples of TTF-1-positive MCC, with two cases in which the TTF-1 positivity was present in MCC metastases [55, 194–196]. These unusual examples comprise about 1.1 % of the MCC cases that

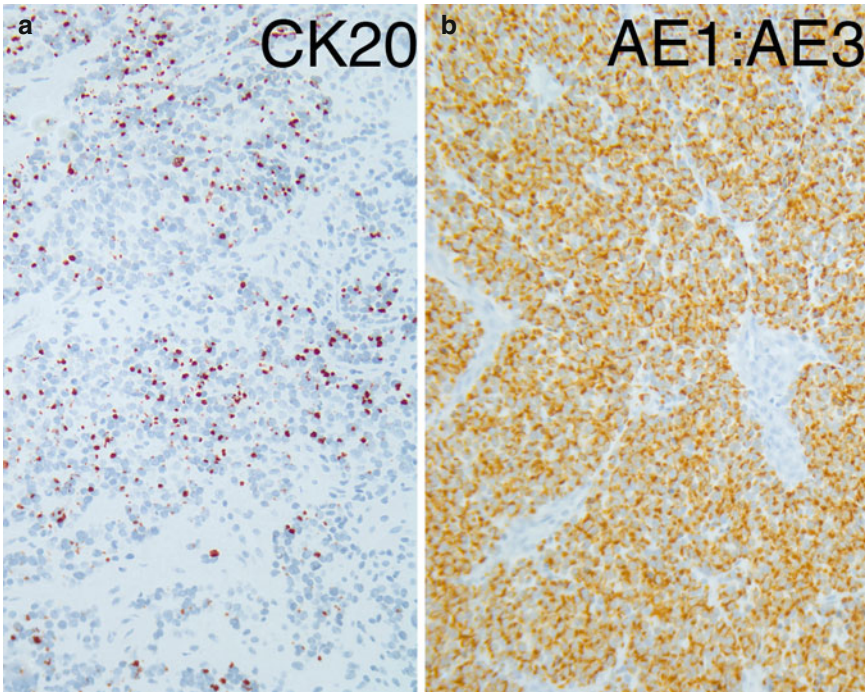

Fig. 11 Cytokeratin immunohistochemistry for MCC, either CK20 or cytokeratin cocktails (AE1:AE3 and Cam 5.2) can potentially exhibit these patterns, the "globular" or "dot-like" paranuclear signal (**a**) or the "dot-like" paranuclear accentuation of the signal (**b**) (**a**: CK20 immunohistochemistry, 400×, **b**: AE1: AE3 immunohistochemistry, 400×)

were tested for TTF-1 according to a recent review [143]. A newly described marker that has been deemed as helpful in the MCC versus small cell lung carcinoma (SCLC) differential is the mammalian/human achaete-scute complex homolog 1 (MASH1/hASH1). This is a transcription factor related to neuroendocrine development that is retained in the majority of SCLCs tested, suggesting that it may be more specific than TTF-1 [195] in this differential diagnosis. Interestingly enough, Notch-1, which is a transcription factor that suppresses MASH1/hASH1, is expressed in MCC and is negative in other neuroendocrine tumors including SCLC [105], yet another available diagnostic tool for this differential diagnosis. Lymphoid neoplasms are also included in the differential diagnosis. Although MCC is consistently negative for CD45 (LCA) [8], it can exhibit considerable overlap with hematologic malignancies in terms of immunohistochemical markers, since MCCs can express a variety of lymphoid-related markers such as CD56 (NCAM) [171, 197], the B-cell-associated transcription factor PAX5 and the primitive lymphoid marker TdT [7–9, 194, 198]. Additionally, the majority of MCC will express the apoptosis-related marker bcl-2 [8, 106, 199], an apparently major player in MCC tumor cell survival [200]. Furthermore, another lymphoid-related marker that can be expressed by MCC cells is anaplastic lymphoma kinase (ALK), specifically with the D5F3

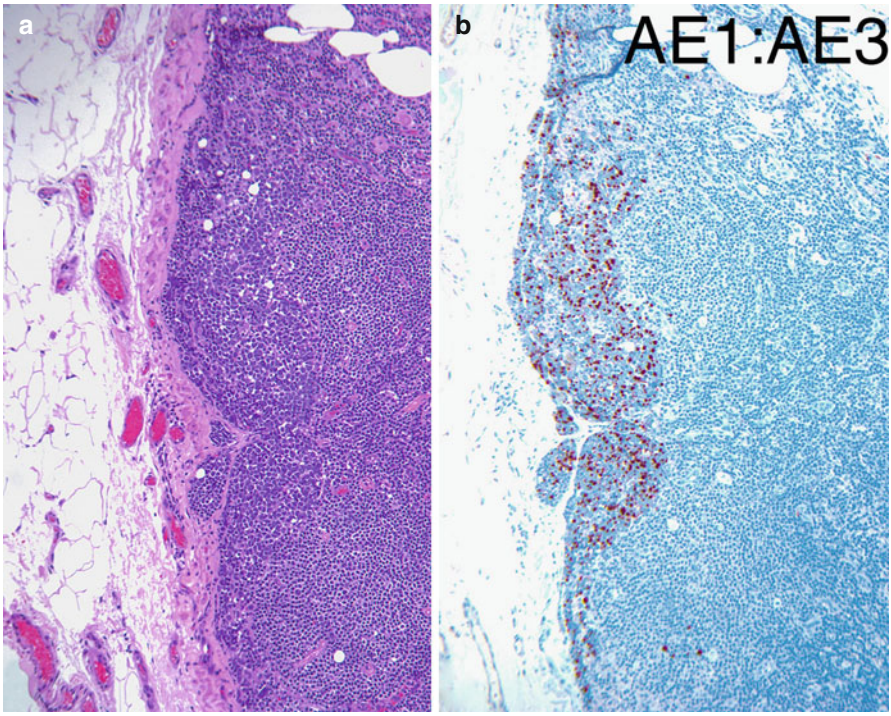

Fig. 12 Cytokeratin immunohistochemistry is an invaluable tool when evaluating for lymph node metastatic disease, particularly if they are small deposits (**a**: H&E and **b**: AE1: AE3, both 100×)

clone but less so with the ALK-1 clone [201]. Finally, consideration must be given to the SRBC group of tumors, particularly the superficial variant of Ewing sarcoma/primitive neuroectodermal tumor (PNET) group, since MCC can frequently express CD99 and Friend leukemia integration 1 (FLI1), while conversely up to 20 % of Ewing sarcoma/PNET can show expression of keratins, particularly with CAM 5.2 and AE1:AE3 cocktails [170]. In potential cases of PNET that are indistinguishable morphologically and immunohistochemically from MCC, one could resort to cytogenetic studies, since MCCs completely lack the cytogenetic aberrations found in those tumors [159].

Ultrastructural Features of MCC

As previously stated, MCC tumor cells exhibit many shared ultrastructural characteristics with normal Merkel cells, the main reason behind the tumor's nomenclature. Under the transmission electron microscope, normal Merkel cells are identified as cells measuring about 15 μm size, oval shaped with their long axis oriented parallel to the basement membrane plane [4, 5]. Close relationship to a sensory axon is

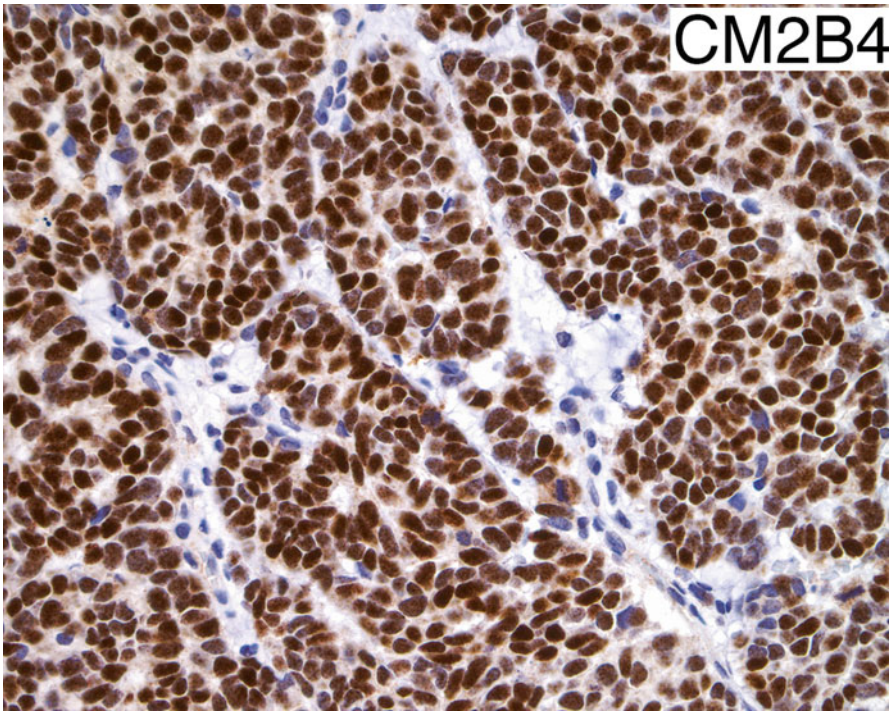

Fig. 13 Immunohistochemistry directed to the LT-Ag of MCPyV in an MCC case. Note the clean and strong nuclear signal denoting integration of the viral genome in the tumor cells (MCPyV immunohistochemistry (CM2B4 clone, 400×) (Image courtesy of Gauri Panse M.D. from Baystate Medical Center-Tufts University, Springfield, MA)

Table 1 Immunohistochemical differential diagnosis between MCC and mimickers

Tumor type	Cam 5.2	CK7	CK20	TTF-1	S100	LCA	CD99	PAX5	MASH1
MCC	100 %	27 %	92 %	1.1 %	20 %	0 %	25 % (C)	91 %	0 %
Small cell carcinoma	60–80 %	40 %	3 %	91 %	0 %	0 %	12 % (C)	78 %	83 %[a]
EWS/ PNET	20 %	ND	ND	ND	50 %	0 %	92 % (M)	0 %	ND
Lymphoma	0 %	0 %	0 %	ND	6 %	98 %	7 %	Near 100 %[b]	ND
Small cell melanoma	0 %	0 %	0 %	0 %	97 %	0 %	8 %	0 %	ND

Table constructed with data from the following references: McKee's Pathology of the Skin [45], Kuwamoto [143], Fan [240], Desouki et al. [241]

Abbreviations: *MCC* Merkel cell carcinoma, *EWS/PNET* Ewing sarcoma/primitive neuroectodermal tumor, *C* cytoplasmic, *M* membranous, *ND* no data

[a]Specifically in small cell lung carcinoma origin

[b]Particularly in B-cell processes and classic Hodgkin lymphoma

often evident. Normal Merkel cell bears a large, usually bilobulated nuclei, and their cytoplasm is scant, relatively scarcely populated by organelles but containing many free ribosomes. Numerous neurosecretory granules can be appreciated close to the area where the cell is in relationship with a sensory axon. Other salient ultrastructural features of normal Merkel cells are the abundant spikelike spinous cytoplasmic processes interdigitating with the surrounding keratinocytes to which they are attached by sparse, small, and poorly formed desmosomes [4, 5, 202]. Interestingly, melanosomes have been described to occur in normal Merkel cells.

Neoplastic Merkel cells replicate the majority of the above-cited ultrastructural features of normal Merkel cells, including the very characteristic spinous processes and the neurosecretory granules. However, MCC tumor cells exhibit a prominent perinuclear ball-like collection of intermediate filaments contrasting to the sparse collections of simple keratin-intermediate filaments found in the cytoplasm of normal Merkel cells [4, 5]. This cytoplasmic ball of intermediate filaments is an ultrastructural feature common among neuroendocrine tumors and small cell carcinomas. This accumulation of intermediate filaments translates to the immunohistochemical pattern that is observed in MCC with CK20, keratin cocktails, and neurofilament immunostains.

Molecular Aspects, Pathogenesis, and Association with the Merkel Cell Polyomavirus (MCPyV)

The discovery of the MCPyV has indeed completely changed our understanding of MCC pathogenesis and behavior. MCPyV is a novel polyomavirus that belongs to the same family as the JC, BK, KI, and WU as well as the recently discovered trichodysplasia-associated polyomavirus (TSPyV) [203]. However, so far, only MCPyV has an associated oncogenic potential. Several recent studies have demonstrated that MCPyV is quite prevalent in the healthy adult population, and it is detected in peripheral blood both by molecular DNA amplification techniques and serology. Evidence of the virus has also demonstrated from cutaneous swabs [143, 204–208]. A recent prospective study has correlated high serum MCPyV antibody titers in healthy individuals with an increased risk of subsequent MCC development in older age [209]. Transmission is likely to occur in early childhood, especially between family members [210], and the virus remains dormant in a wide variety of tissues [211] until immunosuppression-triggered reactivation, as is characteristic of this viral group. The importance of MCPyV resides in that it is part of the two proposed models of MCC pathogenesis, the other being a UV-damage-induced pathway, which involves *TP53* mutations and is to MCPyV. The causative oncogenic role of MCPyV in MCC is nowadays widely accepted, since the viral genetic material is integrated and clonally expanded in viral-positive MCC tumor cells [10]. Numerous studies on the subject have shown that MCPyV can be detected in about 70–80 % of MCC tumors [133, 145, 205, 207, 211–218]. However, a recent study claims that if one were to use sensitive enough molecular techniques, all MCC tumors will show integrated MCPyV genome [180]. Along this line of thought,

some authors claim that the two pathways could be unified into one that is driven by mutagenic effects of preexisting MCPyV, which has been reactivated itself in an immunosuppressed host that has been accumulating deleterious UV-induced mutations [219]. As we discussed before in this chapter, there is a well-documented and clear link between MCC and various types of immunosuppressive states, including chronic solar damage. The main oncogenic mechanism of MCPyV is exerted via the interaction between LT-Ag and the retinoblastoma (Rb) group of proteins. It is important to understand the fact that the oncogenic gene LT-Ag present in the infected MCC tumor cells has undergone a signature truncating mutation [179, 220]. The product of this mutated LT-Ag, through its LxCxE motif, binds and sequesters hypophosphorylated Rb leading to its accumulation and thus allowing E2F-mediated transcription that leads to the entry of the cell into S-phase [221]. The p53 protein system also becomes affected by LT-Ag, albeit in an indirect fashion [220, 222]. Additionally, the LT-Ag protein also serves to allow detection of MCPyV by immunohistochemistry. Regarding the MCPyV-negative MCC group, Rb function is also impaired but through different mechanisms that include hypermethylation and heterozygous deletions [184]. Characteristically, p53 is more often suppressed and immunohistochemically overexpressed (accumulated) in this particular group. These alterations in Rb are reflected on immunohistochemistry with LT-Ag-positive MCC tumors expressing the accumulated Rb and conversely with 87 % of LT-Ag-negative tumors being predominantly Rb negative due to the deletions and silencing hypermethylation [212, 223]. Likewise, it seems that there is an inverse relationship between p53 overexpression and MCPyV viral abundance [181, 224] with overexpression of p53 being also negatively related to survival. Furthermore, recent studies have correlated both tumor positivity for MCPyV and an effective viral-directed immune response with better survival [15, 181, 223–225]. After reviewing these models, one could draw comparisons with what occurs in other organ systems such as in the lower female genital tract SCC (HPV driven versus p53 driven) and head and neck SCC (p16-positive/HPV-positive tumors having better prognosis than HPV-negative tumors).

Prognostic Factors, Staging, and Management

Several clinical and histopathologic features in MCC are associated with clinical outcome. In terms of clinical features, a large Surveillance, Epidemiology, and End Results (SEER)-based National Cancer Institute (NCI) study [12] demonstrated that women have a 10-year survival advantage compared to men with the rates being 64.8 % and 50.5 %, respectively. Additionally, tumor location yielded survival differences, and if one were to align the anatomical sites from best to worse prognosis, it would show the following pattern: upper limbs, head and neck, lower limbs, and trunk. Furthermore, this study added tumor diameter to the prognostic factors, demonstrating that tumors equal or less than 2 cm have statistically significant better survival (61 %) than tumors larger than 2 cm (39.6 %). In fact, tumor size is the main

focus of tumor staging [14, 226]. In the 2010 American Joint Committee on Cancer (AJCC) guidelines, a four-tier staging system is used for MCC: tumors are designated as stage I or stage II if they are localized to the skin at the primary site (stage I/T1 is less or equal than 2 cm in diameter, and stage II/T2 is more than 2 cm in size); stage III denotes spread to regional lymph nodes; and stage IV indicates spread beyond the regional lymph nodes. According to some recent studies, tumor thickness measured utilizing the Breslow technique has emerged as a strong and important independent prognostic factor. Studies indicate that thicker tumors are related to advanced stage [185], predict positive sentinel lymph node (SLN) status [227, 228], and are associated with both higher recurrence rate and worse survival [178, 229, 230]. A suggested cutoff of equal or greater than 10 mm in thickness [178] was proposed to indicate increased risk for the mentioned complications. Tumor growth pattern and tumor borders have also been reported to be associated with prognosis with both infiltrative tumor borders [229] and diffuse growth pattern [230] being negatively associated with survival. It is likely that the development of thick tumors with irregular borders is correlated with higher expression of several types of metalloproteinases by the tumor cells, which has been found to impact prognosis by itself [186, 231]. The presence of LVI, a rather frequent finding in MCC, is also considered a strong adverse prognostic factor [228, 229, 232]. Unsurprisingly, a high proliferative rate, represented by either an elevated Ki-67 proliferation index of equal or more than 35 or 50 % and/or a high mitotic rate, has also been correlated with both disease progression and worse survival [24, 185, 233, 234].

While a comprehensive discussion of management is beyond the scope of this chapter, the mainstay of treatment, particularly in localized disease, is surgical. The data related to the role of the sentinel lymph node biopsy is somewhat less clear in MCC in comparison to melanoma and breast carcinoma. Current National Comprehensive Cancer Network (NCCN) treatment recommendations include surgical excision of the primary tumor with wide margins (1–2 cm) followed by sentinel lymph node biopsy (SLNB) or elective lymphadenectomy (for clinically node-negative cases), as 25–30 % patients have regional nodal disease at presentation [22, 227, 235]. Chemotherapy and radiation therapy are reserved for advanced stage patients. A recent study from a large cohort of patients underscored the beneficial impact of SLNB and completion lymphadenectomy on survival while finding that chemotherapy and radiotherapy had no effect on survival in node-negative patients [235]. Other studies pointed out that clinically detectable metastatic lymph node deposits were more predictive of outcome than lymph nodes with microscopic deposits [232]. More data need to be accumulated in this regard to be able to make stronger evidence-based management recommendations.

MCC tumors can be accompanied by a brisk immune response. However, as is the case with other highly immunogenic tumors such as melanoma, the relationship between this immune host response and survival has had conflicting results in the literature, with some studies attributing a worse prognosis to either the presence [230] or absence [185] of immune response, while in other study the presence of an immune response was associated with good prognosis particularly in lymph node-negative tumors with nodular growth pattern [229]. It appears that

MCPyV might play a role in this issue since it has been recently suggested that the MCPyV status of the tumor is reflected in patient survival with patients with a higher viral load and mounting an appropriate immune response having better clinical outcome [15, 181, 223, 224]. Another interesting new finding is that in MCPyV-positive tumors, there is evidence of tumor-driven immune suppression, as a high proportion of PD-L1-positive tumor-infiltrating lymphocytes (TILs) and macrophages found particularly at the tumor-stroma interface [236]. Furthermore, the same study showed that expression of PD-L1 in MCC tumor cells is correlated with better survival. The innate immune system is apparently also affected by the tumor [237]. In addition, it has been shown that specific T-cell populations directed to MCPyV are detected peripherally in MCC patients and also express the immune exhaustion markers PD-1 and Tim-3 [238]. Other studies demonstrated that presence of specific T-cell [239] TIL subpopulations without impaired function might also predict improved survival. These observations open exciting opportunities for potential immune modulatory therapy with recently developed monoclonal antibodies [219] in this particular group of virus-driven MCC.

Abbreviations

AJCC	American Joint Committee on Cancer
APUD	Amine precursor uptake and decarboxylation
BCC	Basal cell carcinoma
CK	Cytokeratin
CLL	Chronic lymphocytic leukemia
ACTH	Adrenocorticotropic hormone
HIV/AIDS	Human immunodeficiency virus/acquired immunodeficiency syndrome
LT-Ag	Large T antigen
LVI	Lymphovascular invasion
MASH1/hASH1	Mammalian/human achaete-scute complex homolog 1
MCC	Merkel cell carcinoma
MCPyV	Merkel cell polyomavirus
NCCN	National Comprehensive Cancer Network
NSE	Neuron-specific enolase
PNET	Peripheral neuroectodermal tumor
Rb	Retinoblastoma
SCC	Squamous cell carcinoma
SCLC	Small cell lung carcinoma
SEER	Surveillance, Epidemiology, and End Results
SLN	Sentinel lymph node
SRBC	Small round blue cell
TILs	Tumor-infiltrating lymphocytes
TTF-1	Thyroid transcription factor 1

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