Surgical and Experimental Pathology

REVIEW

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Merkel cell carcinoma: a review from the preanalytical to the postanalytical phase by the Brazilian society of pathology

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Abstract

Background Merkel cell carcinoma is a very rare and aggressive primary cutaneous neuroendocrine carcinoma with rapid growth and a risk of early metastasis and regional recurrence despite treatment.

Main body This review covers the diagnostic and staging process for Merkel cell carcinoma, from preanalytical clinical reporting and biopsy selection to gross examination and essential histopathological findings for accurate diagnosis.

Conclusion Understanding the necessary steps for a definitive diagnosis, beginning with the appropriate biopsy type, detailed clinical reporting, proper processing and handling of specimens, and thorough gross and microscopic evaluation, is crucial for all clinicians and pathologists, leading to accurate diagnosis and staging.

Keywords Merkel cell carcinoma, Merkel cell polyomavirus, Neuroendocrine carcinoma

Background

Merkel cell carcinoma (MCC) is a very rare and aggressive primary cutaneous neuroendocrine carcinoma with rapid growth and a risk of early metastasis and regional recurrence despite treatment (Wang et al. 2011; Lugowska et al. 2024). Owing to the rarity of this neoplasm, the therapeutic guidelines are not yet well established, especially in locally advanced cases, as there is a shortage of long-term prospective studies with an adequate number of patients to correlate histopathological characteristics and prognosis (Duprat et al. 2011).

This review addresses all the stages involved in diagnosing and staging MCC, from the preanalytical phase, includes the clinical information required in the specimen request form, the choice of biopsy, and gross examination, to the analytical phase (histopathological findings necessary for diagnostic conclusions) and the postanalytical phase (the pathology report). All these steps are described and discussed below.

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Preanalytical phase

Performing the biopsy

Types of biopsies

When suspecting MCC, there are several ways to perform a biopsy, which depend on the site of the lesion, first excision or re-excision, and then widening of margins. In the first approach, an incisional (for example, punch or shaving) or excisional biopsy (wide resection with a total sample of the lesion) can be chosen (Gauci et al. 2022). After confirming MCC diagnosis, a wide margin between 10 and 20 mm with deep resection down to the fascia is recommended (Busam et al. 2019; Divino et al. 2019; Duprat et al. 2011; Schmults et al. 2024; Slater et al. 2019). In this case, enlargement of margins with re-excision might be necessary, and, when indicated, lymphadenectomy and sentinel lymph node resection should also be performed (Schmults et al. 2024). When a free margin of 10–20 mm cannot be ensured in large tumors, excisions might be done with less than a 10 mm margin if followed by adjuvant radiotherapy (Schmults et al. 2024).

Fine needle aspiration and core biopsy are only used to assess clinically positive lymph nodes, which will require confirmation by immunocytochemistry and/or immunohistochemistry (Fig. 1). Frozen section evaluations are not recommended to diagnose this type of lesion or to assess lymph node involvement. MCC diagnosis and lymph node analysis must be evaluated in paraffin-embedded tissue and after immunohistochemical examination (Slater et al. 2019).

The only exception for intraoperative assessment is in cases where a 10 mm minimum margin resection is not possible. In lesions on the face, for example, Mohs surgery is accepted to preserve the skin surface for reconstruction or to spare nerves in the region. Wide resection and Mohs micrographic surgery are equally accepted, with similar results in terms of recurrence and survival rates (Gauci et al. 2022; Schmults et al. 2022).

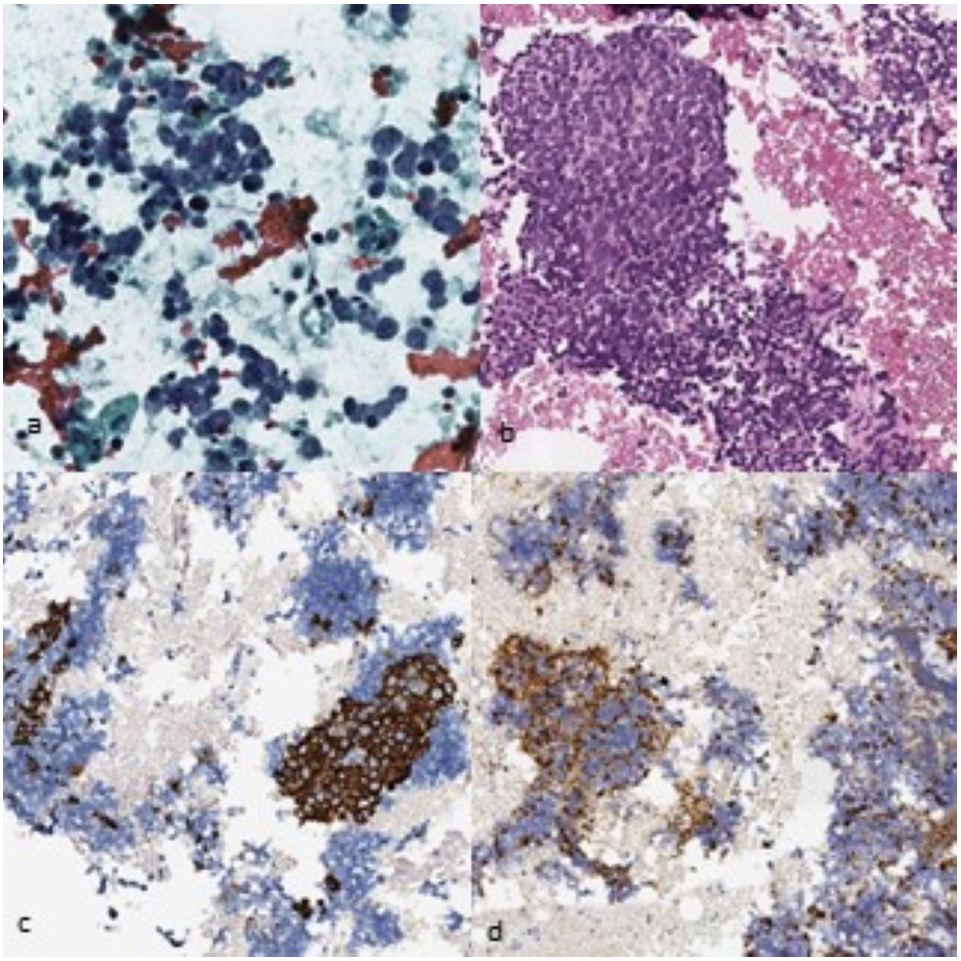

Fig. 1 **a**) Inguinal lymph node fine needle aspiration biopsy showing round to oval cells forming cellular aggregates between lymphocytes (Papanicolaou, 20x) **b**) In the cell block the aggregates exhibit nuclear molding and "salt and pepper" chromatin (H&E, 14x) **c**) CK20 positive membrane staining pattern (CK20, 12x) and **d**) synaptophysin confirm the diagnosis of Merkel cell carcinoma (Synaptophysin, 10x) (Figures are courtesy of Dr. Luciana Carvalho Costa)

Fixation

The sample obtained for histopathological examination must be submerged immediately after removal in a 10% buffered formalin container with a volume approximately 10 to 20 times the sample size. This thorough and uniform tissue fixation is essential for preserving cellular structures and preventing autolysis.

Requisition form

When a request for histopathological examination is submitted, clinicians must ensure that essential patient data are documented. The most important information for pathologists is listed below.

- Age and immunosuppression: MCC predominantly affects elderly individuals (particularly those older than 50 years), caucasians, and immunosuppressed patients, such as transplant recipients, individuals with HIV, and those with chronic lymphocytic leukemia. Additionally, MCC is often linked with polyomavirus (PyV) infection (Divino et al. 2019; Duprat et al. 2011; Gauci et al. 2022; Lugowska et al. 2024; Wang et al. 2011).
- Lesion topography and clinical features: MCC typically manifests as a rapidly growing, reddish or violet asymptomatic nodule. These lesions might be associated with ultraviolet ray exposure and commonly arise in sun-exposed areas, notably the head and neck, followed by the extremities and trunk (Divino et al. 2019; Duprat et al. 2011; Wang et al. 2011). UV-induced DNA damage may contribute to the oncogenic transformation of Merkel cells, emphasizing the role of sun protection measures in MCC prevention (Becker et al. 2017).
- History of neoplasia: MCC may be associated with secondary malignancies such as chronic lymphocytic leukemia and squamous cell carcinoma (Becker et al. 2017; Duprat et al. 2011; Wang et al. 2011).
- Size of the lesion: Measurement of the lesion's longest axis before biopsy or excision is important for staging MCC as tissue shrinkage post-biopsy can lead to sub-staging. When this information is unknown, gross measurements should be used for staging (Amin et al. 2017; Busam et al. 2019; Slater et al. 2019).
- Clinical or imaging evidence of lymph node involvement: The detection of lymph node involvement, whether through clinical examination or imaging studies, is necessary for adequate pN staging (Busam et al. 2019).

The acronym AEIOU serves as a mnemonic reminder of the major clinical information related to MCC. Each letter represents one of the clinical characteristics discussed above. Therefore, the letter A represents the "asymptomatic lesion", the letter E represents the "fast expansion", the letter I represents the "immunosuppression state", the letter O represents the "older individuals" and the letter U represents the "chronic exposure to ultraviolet radiation" (Divino et al. 2019; Wang et al. 2011; Walsh and Cerroni 2021).

Gross examination and sampling for microscopy

Skin biopsy

The gross examination report must include skin measurement in three dimensions and determine whether a visible tumor is present. The largest tumor dimension is important because it can be used for pT staging when there is no information about clinical tumor size (Busam et al. 2019; Slater et al. 2019; Smoller et al. 2021). Additional dimensions and the distance of the lesion from the nearest circumferential and deep margins must also be reported, as well as extracutaneous extension (i.e., fascia, cartilage, muscle, and bone) (Busam et al. 2019).

In excisional samples, if there is a mark for anatomical positioning, different inks should be used to identify the respective margins via microscopic analysis (Fig. 2a and b). The excisional biopsy should be sectioned every 2–3 mm, perpendicular to its longest axis ("bread-loaf technique") (Fig. 2c). The larger the sample, the more accurate the assessment. In the report, the margins and their respective inks must be indicated (Fig. 3a and b). Inserting more than two skin fragments per cassette is not recommended (Fig. 3c) (Slater et al. 2019).

Gross identification of the tumor may not be possible in cases of incisional biopsy, margin extension, re-excision, fragmented samples, etc. In this case, the whole sample must be included for histopathological evaluation. In margin extension or re-excision, total inclusion ensures the assessment of possible residual or satellite neoplasia. Other indications for total inclusion are an ill-defined lesion after consecutive sections and/or samples smaller than 10 mm. In cases of re-excision, it is also important to report whether the scar has been completely removed (Slater et al. 2019).

In specimens larger than 10 mm, a well-defined and visible lesion may be partially sampled, considering various factors, such as the closest margins, representativeness of the lesion, maximum tumor thickness, and unusual features (Slater et al. 2019).

Lymph nodes

Sentinel lymph node biopsy showed a rate of microscopic metastases between 24% and 48%. This supports the recommendation to use sentinel lymph node biopsy as routine staging in patients with Merkel cell carcinoma, even when there's no clinical or imaging evidence of nodal or distant metastases. (Gauci et al. 2022). The gross analysis

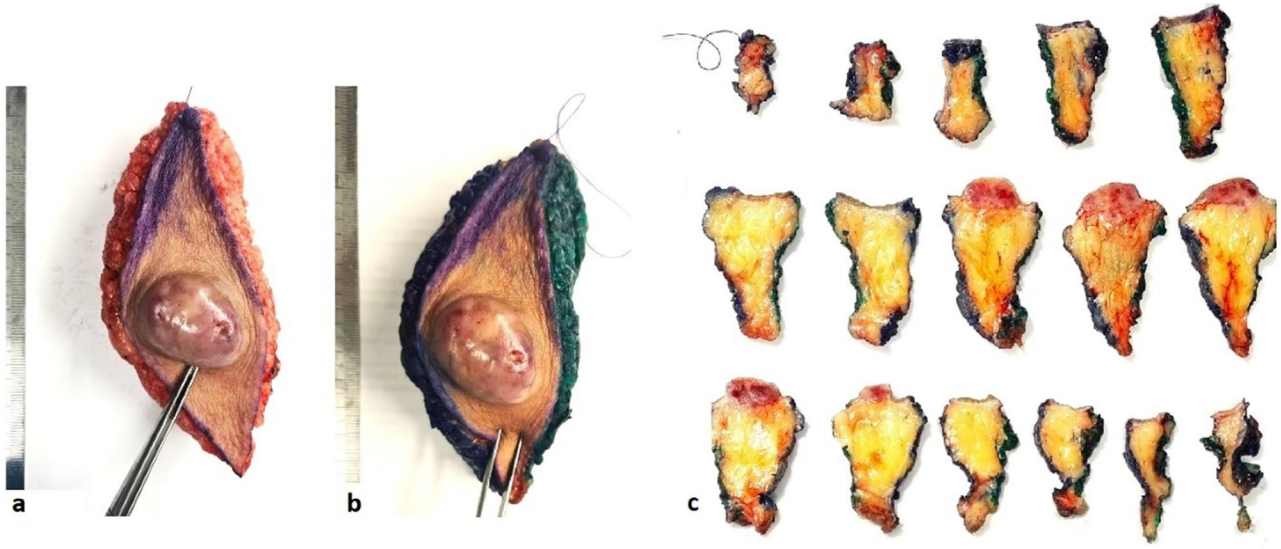

Fig. 2 (**a**) Merkel cell carcinoma excisional biopsy with a suture wire in the superior margin. (**b**) To prevent loss of anatomical orientation and to ensure accurate margin analysis after histological processing, the margins were stained in green and blue (**c**) Sequential sections, perpendicular to its longest axis every 2–4 mm. The fragment in the upper left corner corresponds to the superior margin, and the fragment in the lower right corner corresponds to the inferior margin. Both should be identified in separate cassettes and referred to in the gross report for microscopic orientation

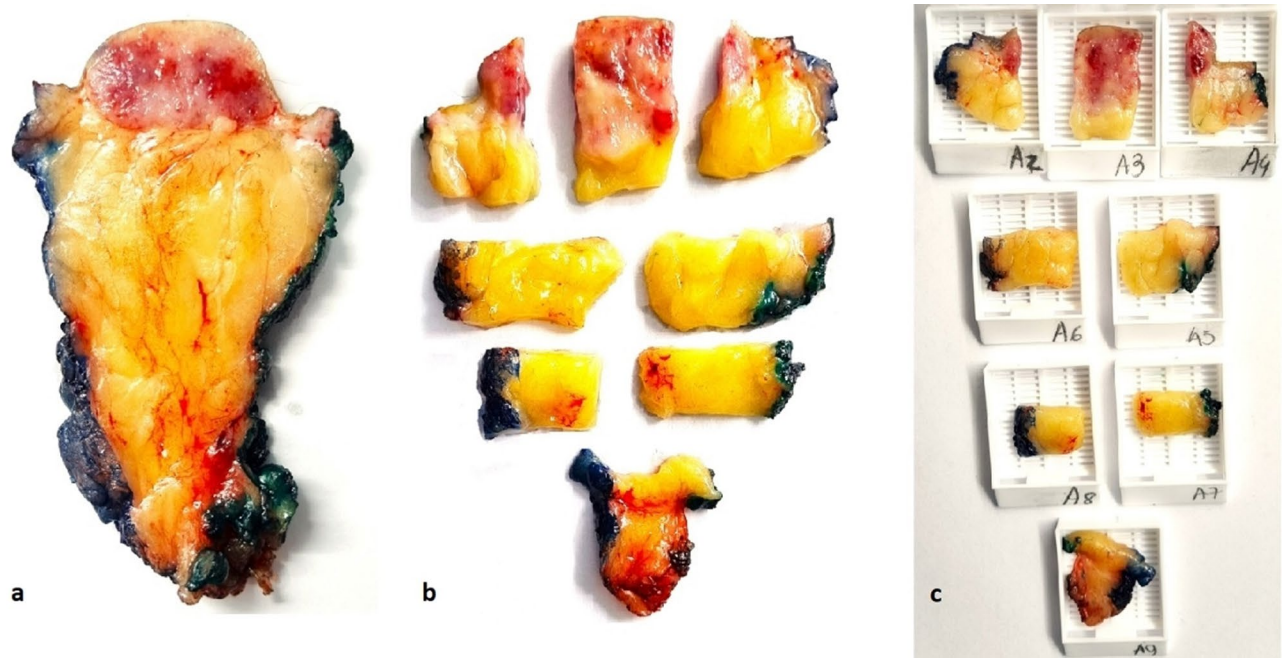

Fig. 3 (**a**) A slice was selected (**b**–**c**) to demonstrate how it can be represented and mapped in the cassettes. Other slices with tumors and margins must be chosen for greater diagnostic accuracy. In this case, it was well-delimited, and margin representation was partial and oriented according to the nearest margins

of the lymph nodes revealed three dimensions (Fig. 4a), the number of dissected lymph nodes (Fig. 4b), and the measurements of the largest and smallest isolated nodes. Each lymph node should be separated from the surrounding fat, minding not to damage the capsule or slice into the lymph node (Slater et al. 2019). Lymph nodes must be sectioned every 2–4 mm perpendicular to their longest axis ("bread-loaf technique") (Fig. 4c) to ensure thorough examination and detection of microscopic metastases (Busam et al. 2019). All lymph nodes must be submitted when macroscopically negative (Fig. 4d). Each lymph node is placed in its cassette and identified via cleavage mapping (Fig. 4d). Macroscopically positive

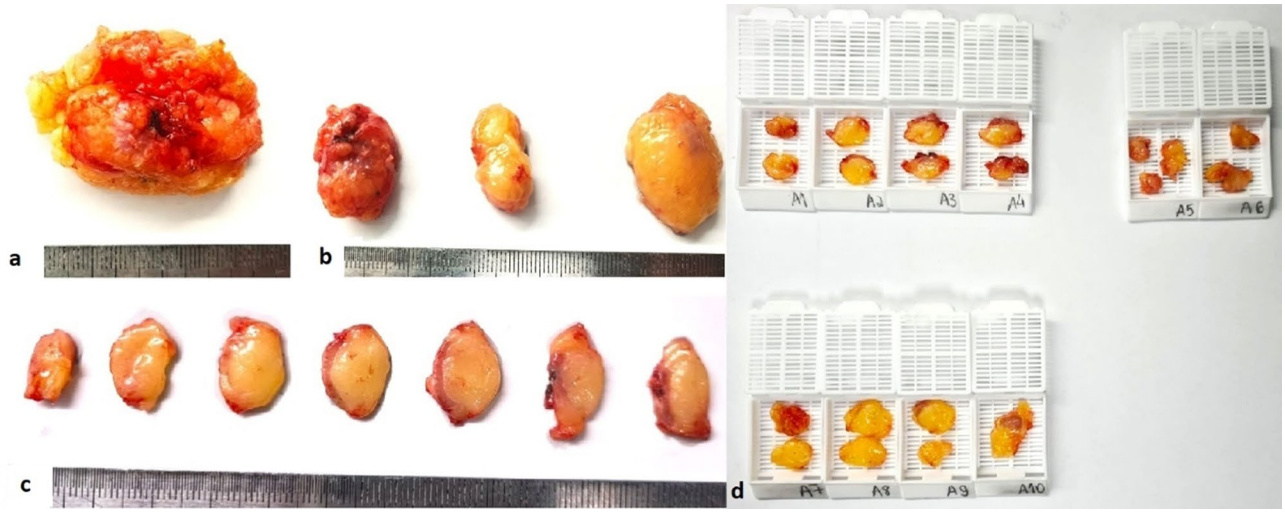

Fig. 4 (**a**) Lymphadenectomy, sentinel lymph nodes, and total samples sent. (**b**) The sample was dissected, and three lymph nodes were identified. (**c**) Example of sequential "bread slice" sections every 2–4 mm, showing macroscopically negative lymph nodes. (**d**) The lymph nodes were completely submitted for histological analysis due to the absence of macroscopic metastasis. Cleavage: A1-A4 corresponds to the first lymph node, A5-A6 corresponds to the second lymph node, and A7-A10 comprises the third lymph node

lymph nodes can be partially represented. (Slater et al. 2019).

Analytical and postanalytical phases

Histopathological report

Primary cutaneous lesion

The histopathological report following an excisional biopsy should detail the type of procedure chosen, specimen laterality, tumor size in mm and site, mitotic rate in 1 mm^2, tumor extent (involvement of surrounding tissues such as dermis, subcutaneous tissue, fascia, muscle, cartilage, or bones), surgical margins and distance from the closest, tumor thickness (Breslow in mm), lymphovascular invasion, intratumoral lymphocyte infiltration, tumor growth pattern (nodular or infiltrative), lymph node status, presence of a second malignancy if present in the same specimen, immunohistochemical profile and MCC-associated polyomavirus (MCCPyV) status (Lugowska et al. 2024; Schmults et al. 2022; Slater et al. 2019; Smoller et al. 2021). A second skin malignancy should be reported as a core item, detailed in free text or, if applicable, using a separate cancer dataset (Slater et al. 2019).

Histopathological features of MCC include uniform small-blue round-cell tumors with vesicular nuclei and scant cytoplasm with a 'salt and pepper' chromatin pattern, large lobulated nucleoli, high mitotic rate, and occasional necrotic cells (Gauci et al. 2022; Lugowska et al. 2024) (Fig. 5). Small cell variants also show nuclear molding and crush artifact (Pulitzer 2017). Histological subtypes include intermediate (showing a sheet-like, diffuse growth pattern with large cells), small cell (small and round cells), trabecular (forming columns 2 to 3 cells thick and possibly spindle cells), and combined (containing two or more of the previously described subtypes) (Lugowska et al. 2024; Slater et al. 2019). Although this subcategorization is obsolete, recognizing these subtypes is important, as the presence of large, pleomorphic, or clear cells often indicates the absence of MCCPyV. The combined form may contain carcinomatous (mainly squamous differentiation) and/or sarcomatous elements (Walsh and Cerroni 2021). The growth pattern should be classified as nodular (well-circumscribed) or infiltrative (irregular infiltrative areas and lack of circumscription), with infiltrative classification if both patterns are present (Schmults et al. 2022) (Figs. 6 and 7) (Table 1).

Invasion level should be detailed, and any free structures must be informed (e.g., "cartilage free of neoplasia"). Tumor thickness, measured from the stratum granulosum to the lesion's depth, should be stated. Lymphovascular invasion should be categorized as present, undetected, or undetermined (Schmults et al. 2022).

Tumor lymphocyte infiltration assessment determines the relationships between lymphocyte infiltration and the tumor base and stroma. It is considered brisk if it surrounds the tumor base and/or permeates the tumor; otherwise, it is not identified or nonbrisk (Schmults et al. 2022).

Surgical margins should be reported, indicating the distance from the nearest circumferential and deep limits (<1 mm, between 1 and 5 mm, >5 mm) if free of neoplasia, or specifying which margins are compromised (Busam et al. 2019; Slater et al. 2019).

Lymph node

The regional lymph node status must also be reported, indicating the number of lymph nodes, sentinel or

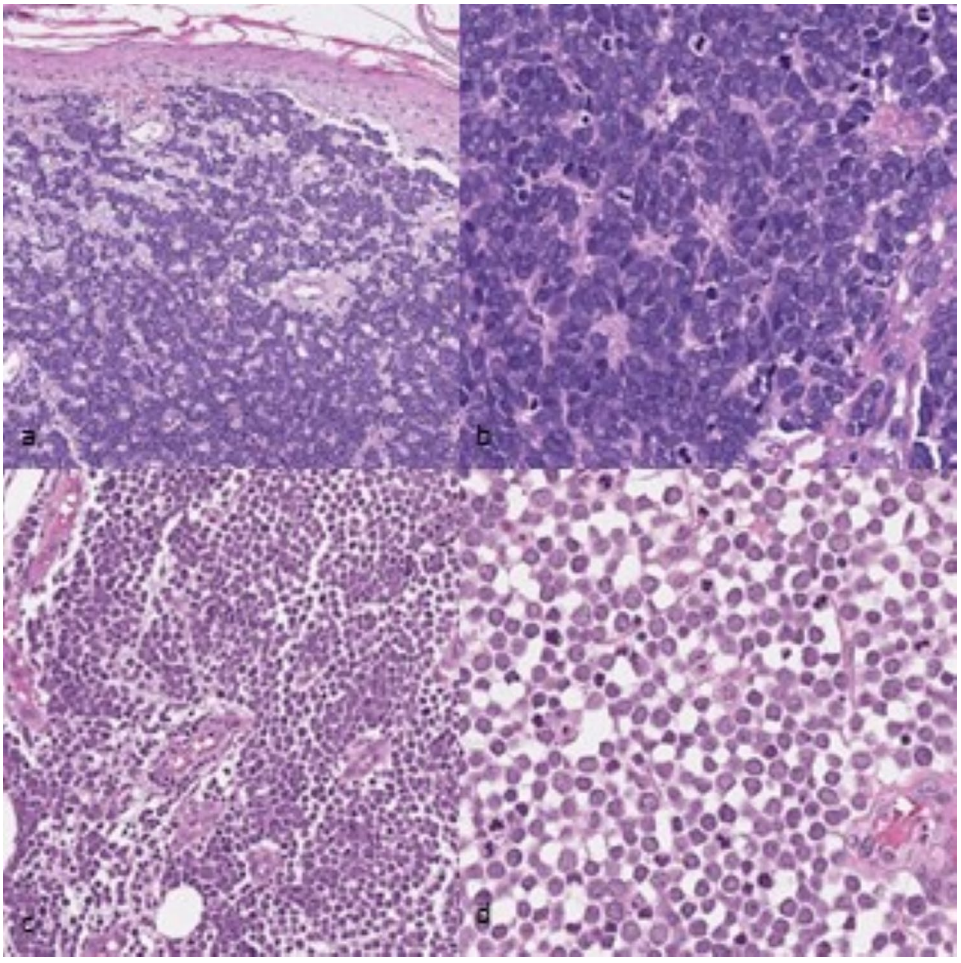

Fig. 5 Two cases of Merkel cell carcinoma **a**) Case 1 shows large cells forming pseudorosettes and trabecular pattern (H&E, 6x) **b**) there is nuclear molding with 'salt and pepper' chromatin pattern and a high mitotic index (H&E, 20x) **c**) Case 2 exhibit sheet-like growth pattern (H&E, 10x) **d**) with small and round cells with the same cytologic features (H&E, 20x)

non-sentinel nodes, the number of free and compromised lymph nodes, the size of the largest metastatic deposit, and the presence of extranodal extension (Smoller et al. 2021). The size of the largest metastatic focus is not a staging criterion (Slater et al. 2019). Negative lymph nodes on hematoxylin–eosin (H&E) staining should undergo serial histological sectioning on 2 slides and immunohistochemical studies for confirmation. Isolated tumor cells in a lymph node are classified as micrometastases and staged as pN1a (Schmults et al. 2022).

Metastatic lesion

Metastasis in transit is defined as a lesion distinct from the primary neoplasm (separated by normal dermis, not fibrosis or inflammation), located far from the primary lesion or between it and the respective lymph node chain (Slater et al. 2019; Smoller et al. 2021). Owing to the rarity of multiple simultaneous MCC lesions, these lesions are best interpreted as metastases in transit. If in-transit or distant metastasis is present, the site is indicated. Tumor deposits or affected lymph nodes near any surgical margin should be referred to according to the distance to the nearest margin (Slater et al. 2019).

Staining and immunohistochemistry

Microscopic examination requires H&E-stained slides and immunohistochemistry to distinguish MCCs from potential histopathologic simulators and to detect lymph node metastasis (Gauci et al. 2022; Slater et al. 2019).

The latter should include CK20 (preferably, due to its 90% sensitivity and characteristic membranous (Fig. 6d) and/or paranuclear dot-like staining pattern (Fig. 7d) and at least one neuroendocrine marker (e.g., chromogranin, synaptophysin, NSE, neurofilament and CD56) for diagnostic confirmation in cutaneous specimens (Divino et al. 2019; Duprat et al. 2011; Gauci et al. 2022; Lugowska et al. 2024; Slater et al. 2019; Wang et al. 2011).

TTF-1, CD45, S100 and Melan A are also important for ruling out the cutaneous metastasis of small cell lung carcinoma, lymphoma and melanoma, respectively (Divino

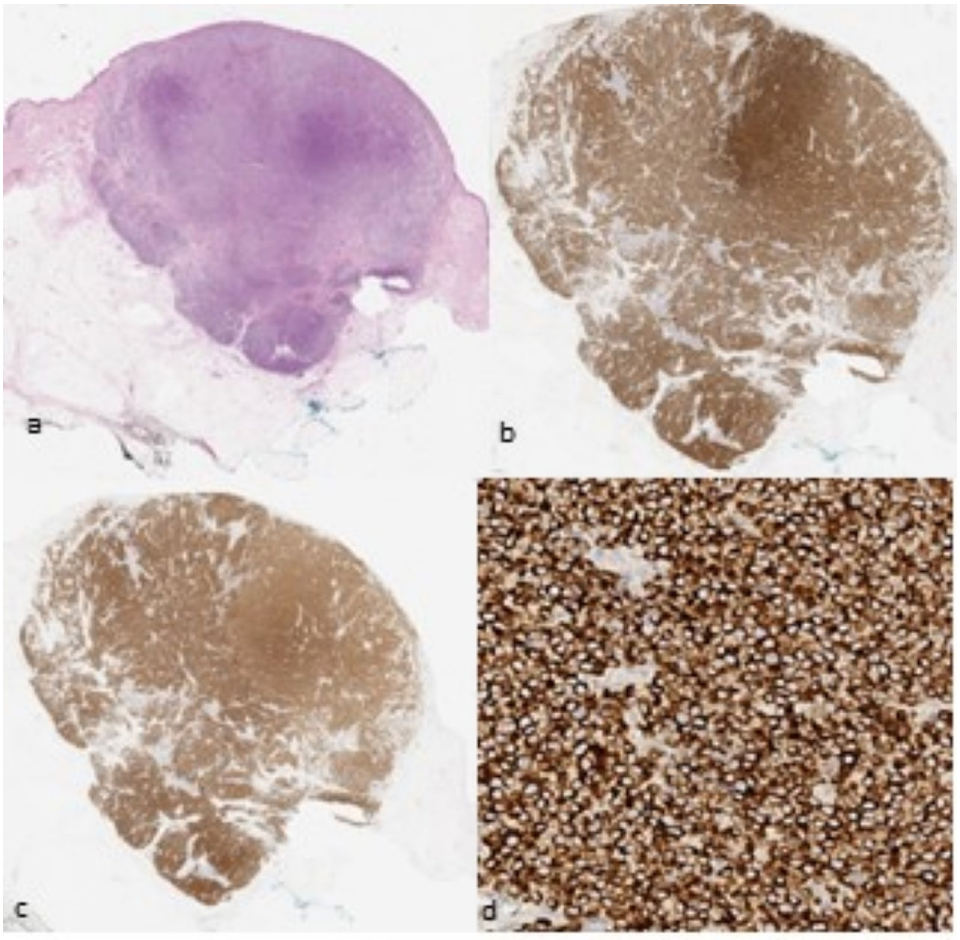

Fig. 6 Merkel cell carcinoma showing a nodular and diffuse growth pattern. The morphology is highlighted in **a**) H&E, 3X. **b**) CK20 positive immunostaining (CK20, 4X). **C**) Synaptophysin positive immunostaining (Synaptophysin, 3X). **d**) CK20 positive with membrane pattern (CK20, 15X)

et al. 2019; Slater et al. 2019; Wang et al. 2011) (Table 1). The pattern of immunopositivity can vary between antibodies, with the "dot" or "cap" type perinuclear pattern, membrane marking, or cytoplasmic granules being well recognized (Slater et al. 2019).

Investigation of MCCPyV is not mandatory for MCC diagnosis, although it can be performed via immunohistochemistry using the mouse monoclonal antibody CM2B4 and by researching viral DNA via real-time polymerase chain reaction in tumor tissue (Divino et al. 2019).

Immunohistochemistry has been proven to increase the sensitivity of identifying occult lymph node metastases. In this case, immunostaining should be performed in every lymph node tissue block as it is known to be positive in the primary tumor, preferably CK20 (Busam et al. 2019; Schmults et al. 2022) (Fig. 1c). If the immunophenotype of the primary tumor is not known, one may apply two immunostains to reduce the risk of false negatives (Fig. 1d) (Busam et al. 2019; Slater et al. 2019).

Molecular studies

Two distinct subsets of MCCs have been identified, each with different molecular pathogenetic pathways: ultraviolet-induced MCC (high tumor mutational burden subtype) and virus-positive MCC (low tumor mutational burden subtype), the latter of which has a better prognosis (Gauci et al. 2022; Walsh and Cerroni 2021).

The high tumor mutational burden subtype is associated with mutations related to ultraviolet radiation exposure, mutations in the TP53 and RB1 genes, and lack of the MCCPyV genome (Divino et al. 2019; Schmults et al. 2024; Walsh and Cerroni 2021). Consequently, this molecular subtype shows immunopositivity for p53 and p63 and is immunonegative for Rb (the retinoblastoma protein is lost in PyV-negative cases) (Stachyra et al. 2021) (Table 1).

In contrast, the low tumor mutational burden subtype presents the opposite molecular profile, characterized by the absence of genetic mutations, the presence of polyomavirus DNA (Divino et al. 2019; Schmults et al. 2024), the immunoexpression of Rb, and the negativity for p53

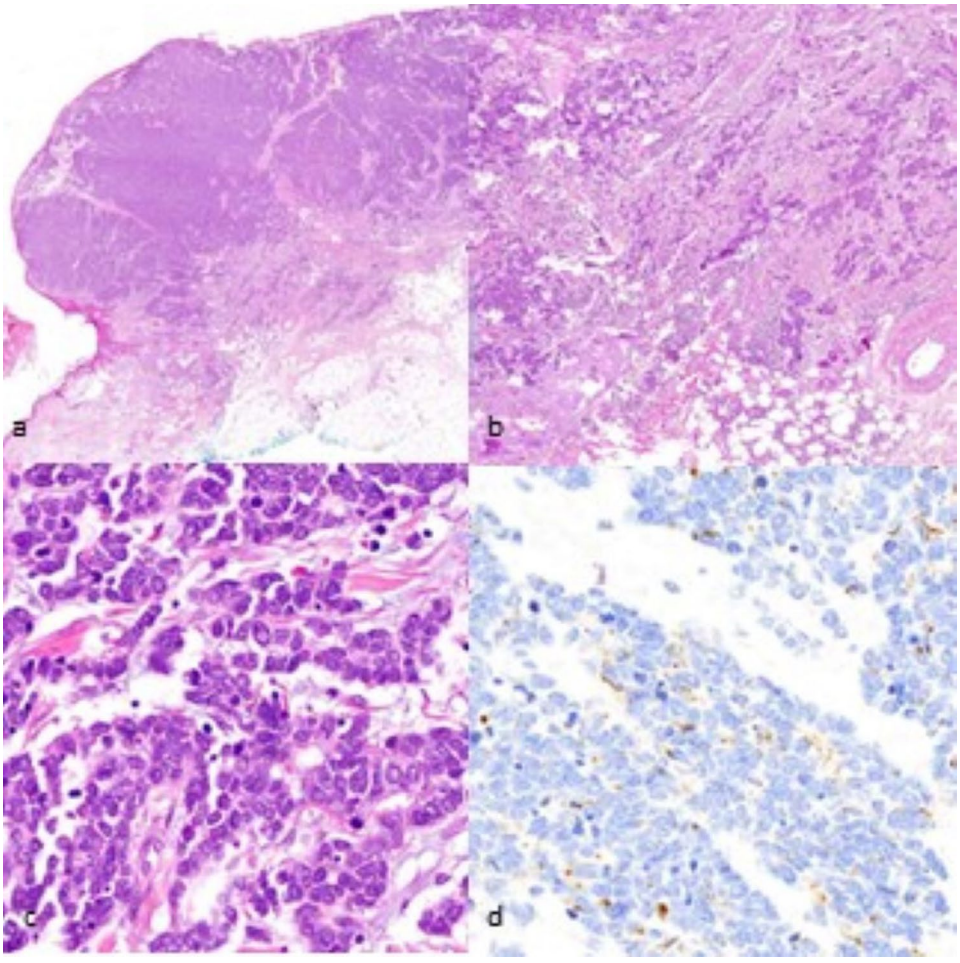

Fig. 7 **a**) Merkel cell carcinoma with an infiltrative pattern (H&E, 1X). The base of the lesion is irregular, with cells infiltrating the dermal collagen and adipocytes in small aggregates (H&E, 10X). **c**) Round blue cells tumors exhibit nuclear molding and a "salt and pepper" chromatin pattern (H&E, 40X). **d**) CK20 positive dot-like pattern (immunohistochemistry, 40X)

and p63 (Stachyra et al. 2021; Walsh and Cerroni 2021) (Table 1).

Potential diagnostic pitfalls

The CK20 negative variant of MCC is broadly known. Given its unusual immunophenotype, other immunomarkers such as desmin and myogenin must be performed to exclude potential mimicking such as alveolar rhabdomyosarcoma (Lindsey et al. 2022) (Table 1). Rhabdomyosarcoma rarely arises as a primary skin tumor and may express keratins and neuroendocrine markers, making it easy to confuse with Merkel cell carcinoma (Lindsey et al. 2022).

In situ MCC may also reveal a CK7 and CK20 negative staining pattern, and other in situ pathologies must be excluded (Richardson et al. 2022).

Rare cases of MCC can regress spontaneously and present as nodal metastasis and can be misinterpreted as other neuroendocrine carcinomas such as small cell carcinoma. Nodal MCCs of unknown primary were reported to have a significantly lower association with MCPyV than the cutaneous MCCs. Cases can exhibit atypical immunostaining patterns and can be either MCPyV-positive or MCPyV-negative. Initial immunostaining should include pan-CK, CK7, CK20, TTF1, chromogranin A, synaptophysin, and S100 to rule out a metastatic neuroendocrine carcinoma or melanoma. CK20-negative MCC cases are associated with a low incidence of MCPyV positivity (Miner et al. 2015) and should not exclude the diagnosis of metastatic MCC if clinically suspected (Mohamed et al. 2023).

In the setting of a neuroendocrine carcinoma metastatic to lymph node, SATB2 and NF expression (Table 1) and Merkel cell polyomavirus real-time PCR are useful in CK20 negative MCC cases and are accurate tools to distinguish MCC from extracutaneous neuroendocrine carcinoma metastasis (Kervarrec et al. 2019). In CK20 negative MCC cases, neurofilament is sensitive regardless of MCPyV status and is useful in detecting sentinel lymph node deposits (Stanoszek et al. 2019).

Table 1 †"AEIOU" - mnemonic reminder of the major clinical information related to MCC; *MCC - Merkel's cell carcinoma; ★MCCPyV - Merkel's cell carcinoma-associated polyomavirus, #IHC - Immunohistochemistry

Essential features for Merkel Cell Carcinoma specimen analysis	
Clinical information	
	A†: **A**symptomatic nodule
	E†: fast **E**xpansion
	I†: **I**mmunosupression state
	O†: **O**lder than 50 years
	U†: **U**ltraviolet exposure
	Caucasian
	Polyomavirus infection
	Head and neck, extremities and trunk
	History of neoplasia
	Size of lesion before biopsy
	Clinical or imaging evidence of lymph node involvement
Histopathology	
	Small-blue round-cell tumors with 'salt and pepper' chromatin pattern
	High mitotic rate
	Large cells or small cells
	Nodular, trabecular or infiltrative pattern
IHC#	
	CK20 + (90% sensitivity, membranous and/or paranuclear dot-like staining pattern)
	Neuroendocrine marker + (chromogranin, synaptophysin, NSE, neurofilament, CD56)
	TTF-1 - (rule out small cell lung carcinoma)
	CD45 - (rule out lymphoma)
	S100 - (rule out melanoma)
	Melan A - (rule out melanoma)
	CK20 - (complement with desmin/ myogenin to rule out alveolar rhabdomyosarcoma; complement with SATB2 and NF to look for lymph node metastasis)
Molecular subtypes	
Ultraviolet-induced MCC* (high tumor mutational burden subtype)	Ultraviolet radiation exposure
	TP53 and RB1 mutations
	Absence of the MCCPyV★ genome
	IHC#: p53 +, p63 + and Rb -
Virus-positive MCC* (low tumor mutational burden subtype)	Presence of the MCCPyV★ genome
	Absence of genetic mutations
	IHC#: Rb+, p53 - and p63 -

Prognosis

Factors correlated with a worse prognosis include clinical findings such as >75 years of age, male sex, location in the head and neck or trunk, immunosuppression, tumor size>2 cm, region and distant metastases, and histological findings such as extension to subcutaneous tissue, nodal disease, angiolymphatic invasion, >10 mitoses per high-power field (currently, counting in 1 mm^2 using the method defined for cutaneous melanoma can be used for greater standardization and interobserver reproducibility), Ki67>50%, positive margins after resection, infiltrative growth pattern, high tumor mutational burden subtype, and absence of polyomavirus association (Becker et al. 2017; Duprat et al. 2011; Gauci et al. 2022; Lugowska et al. 2024; Schmults et al. 2024; Slater et al. 2019).

The current AJCC staging system is based on tumor size and is considered the best predictor of survival. However, no consensus has been reached on the best staging methodology, and increasing evidence suggests that tumor thickness is better correlated with local recurrence, lymph node metastasis, and poorer survival than tumor size itself (Amin et al. 2017; Slater et al. 2019).

Conclusion

This review highlights the importance of a systematic approach, from the preanalytical phase—including clinical reporting, biopsy selection, and gross examination—to the analytical and postanalytical phases, which involve microscopic, immunohistochemical, and molecular studies for diagnosing and staging MCC. The process begins by measuring the clinical lesion before biopsy, followed by detailed clinical reporting, gross examination, and subsequent microscopic, immunohistochemical, and molecular analyses. Understanding these steps is crucial for ensuring a precise and accurate diagnosis.

Abbreviations

MCC	Merkel cell carcinoma
MCCPyV	Merkel cell carcinoma-associated polyomavirus
PyV	Polyomavirus

Authors' contributions

All authors contributed to the working group discussions and the manuscript review. All authors read and approved the final manuscript.
The manuscript is original, has not been published elsewhere, and is not under consideration by another journal.

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Consent for publication

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