BMJ Best Practice

Merkel cell carcinoma

Straight to the point of care

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Summary

Merkel cell carcinoma (MCC) is a rare cutaneous cancer with a high risk of regional and distant metastases and a higher case fatality rate than melanoma. The primary cutaneous tumor is typically rapidly growing but usually asymptomatic and is often initially misdiagnosed as a benign lesion.

Key risk factors for MCC are advancing age, immunosuppression, and light skin type. Two distinct etiologies are now recognized: exposure to ultraviolet radiation and oncogenic transformation by Merkel cell polyomavirus (MCPyV).

Diagnosis is confirmed with skin biopsy and histopathologic evaluation including immunohistochemistry. Occult metastasis is common, and sentinel lymph node biopsy and imaging are important tools for staging the disease.

Management requires a multidisciplinary approach as evidence is scarce and optimal treatment is not well established. Localized disease is managed with surgical wide local excision with or without radiation therapy. Lymph node disease requires radiation therapy to the nodal basin or lymph node dissection or a combination of the two, with consideration of neoadjuvant immunotherapy. For patients with stage IV metastatic disease, enrollment in a clinical trial (if available) is the preferred option according to US and European guidelines; otherwise, any one or a combination of immunotherapy with an immune checkpoint inhibitor, radiation therapy, or surgery is recommended.

MCC recurs in up to half of patients; hence, ongoing monitoring is important.

Definition

Merkel cell carcinoma (MCC) is a rare, aggressive cutaneous neuroendocrine neoplasm that primarily affects white adults, with incidence increasing with advancing age. MCC carries a high risk of recurrence and locoregional and distant metastases.[1] The primary MCC tumor typically presents as an asymptomatic, rapidly growing, pink-to-violaceous or skin-colored dermal or subcutaneous nodule on sun-exposed skin.[2]

Epidemiology

MCC accounts for less than 1% of all skin cancers, with approximately 2500 cases detected annually in the US.[3] Incidence is increasing (postulated to be as a result of an aging population and improved recognition) and is projected to reach >5000 cases a year in the US by 2030.[4] [5] [6]

Based on available data, the highest recorded incidence of MCC globally is in Australia, where it is reported to be as high as 2.5 per 100,000 people, followed by New Zealand with 0.96 per 100,000, then the US with 0.7 cases per 100,000 people. In Europe, incidence ranges from 0.12 to 0.6 per 100,000 people.[5] [6] [7] [8]

Incidence increases with age and is highest among those >85 years of age.[4] [5] The incidence of MCC is higher in men than in women, with various studies reporting that 61% to 66% of cases are in men.[1] [4] [5] [9][10] MCC is predominantly seen in white patients and is very rare in people of color.[7] There is an 8-fold increased incidence in white individuals compared with non-Hispanic black people.[11]

An estimated 80% of MCC tumors in North America occur in people who are positive for Merkel cell polyomavirus (MCPyV), whereas in Australia, only 24% of MCCs are estimated to be MCPyV-associated.[12] Australia has the highest reported prevalence of ultraviolet light-associated MCC tumors.[13]

Etiology

Risk factors include chronic ultraviolet (UV) radiation exposure, immunosuppression, advancing age, male sex, and white skin.[14]

MCC is strongly associated with lower latitudes and high UV radiation indexes, as evidenced by MCC tumors often arising on sun-exposed skin.[7] [13]

Immunosuppression due to hematologic malignancy, organ transplantation, immunosuppressive medication (e.g., for autoimmune disease), decreased immune function associated with advancing age, or HIV infection is associated with an increased risk of MCC.[15] [16] [17] MCC patients who are immunocompromised also have an increased risk of disease recurrence.[18]

Oncogenic transformation by Merkel cell polyomavirus (MCPyV) is associated with up to 70% to 80% of MCC tumors in the US and Europe, with lower associations in Australia.[7][12] [14] It is an oncogenic process that requires viral integration into the host genome, resulting in inactivation of a viral replication protein.

Pathophysiology

MCC is a highly aggressive primary cutaneous neuroendocrine carcinoma with epithelial and endocrine features. Its origin is disputed, with epidermal Merkel cell precursors, pre-B cells, pro-B cells, or dermal fibroblasts all suggested.[7]

MCC tumorigenesis is attributed to two main etiologies with distinct molecular pathogenetic pathways: integration of MCPyV into the host genome, or exposure to UV radiation.[7] [19]

MCPyV is a ubiquitous polyomavirus with 60% to 80% seropositivity in the US adult population.[20] MCPyV infection is typically asymptomatic.[20] While viral infection is common, oncogenic transformation by MCPyV is rare as it requires integration into the host genome.[20] [21] MCPyV-positive MCCs have a low tumor mutational burden but harbor clonal integration of the virus.[7]

UV-associated MCCs, which usually occur on sun-exposed parts of the body, are characterized by a high tumor mutational burden, with enrichment of the UV-DNA damage signature seen in MCPyV-negative MCC tumors.[7] [22] [23] [24] [25] [26] Retinoblastoma protein and p53 are among the most significantly mutated genes.[7]

Case history

Case history #1

An 80-year-old white man who continues to work as a farmer presents with a rapidly growing lesion on the left forearm. Past medical history is significant for immunosuppression due to kidney transplant. Examination reveals a 2 cm pink papulo-nodule on the left forearm. There is no associated pain, itching, or bleeding. Skin biopsy confirms MCC, and Merkel cell polyomavirus (MCPyV) immunohistochemistry is negative. Physical exam reveals palpable lymphadenopathy in the left axilla. Fine-needle biopsy demonstrates metastatic MCC to the axillary lymph node basin. Staging imaging reveals no distant disease.

Case history #2

A 75-year-old black man presents with a long-standing history of an asymptomatic 5 cm subcutaneous mass on the buttock. On examination, there are no overlying skin changes and the lesion is not tender to the touch. Skin biopsy confirms MCC, and MCPyV serology is positive. Physical exam reveals no clinical adenopathy in the groin. Staging imaging shows no distant disease. Sentinel lymph node biopsy (SLNB), undertaken at the same time as surgical excision of the primary tumor, is negative.

Approach

MCC is a rare, aggressive cutaneous neuroendocrine malignancy that carries a high risk of metastasis to regional lymph nodes and distant organ sites and has a higher case fatality rate than melanoma.[3] [19] The primary cutaneous tumor typically presents as a solitary, nonspecific, rapidly growing nodule or plaque, generally on sun-exposed white people who are >65 years of age and/or immunosuppressed.[2] [9] [30] [31] [32] [33] [34] [35] [36] [37] [38]

The diagnosis is confirmed with skin biopsy and histopathologic evaluation.[3] [19] [39]

Diagnosis of MCC requires a high index of suspicion, because the primary tumor lacks distinguishing features and is usually asymptomatic.[3] Always ensure prompt biopsy of any asymptomatic nodule or plaque that is firm, red or flesh-colored, and expanding rapidly.[2] [7]

- MCC is often initially misdiagnosed clinically as a benign lesion. In one prospective cohort study of 195 patients with MCC, 56% of lesions were presumed by the physician to be benign; the most common incorrect diagnosis (32%) was a cyst or acneiform lesion.[2]
- The clinical differential diagnosis includes other types of skin cancer such as basal or squamous cell carcinoma, amelanotic melanoma, or a benign skin lesion such as an epidermal inclusion cyst or a pyogenic granuloma. Another differential diagnosis to consider would be cutaneous metastasis of a primary visceral tumor, such as metastatic small cell lung cancer, which has similar histopathology to MCC; immunohistochemistry, and sometimes imaging, is needed to distinguish between the two.[3]

It is important to diagnose MCC early because the 5-year overall survival for stage IV disease (distant metastases) has been reported at just 14% to 29%, whereas the prognosis is significantly better for earlier stages.[10] [19]

Use the mnemonic **AEIOU** to recall five common presenting features of MCC. The presence of three or more should prompt suspicion of the diagnosis.[2] [40] Bear in mind that not all patients present with all five features; of 62 patients studied, 89% met ≥3 of the AEIOU criteria, 52% met ≥4 criteria, and 7% met all 5 criteria.[2]

- **A**symptomatic/lack of tenderness. One study of 195 patients with pathologically confirmed MCC found 88% of tumors were asymptomatic.[2]
- **E**xpanding rapidly over ≤3 months.
- **I**mmunosuppressed. Immunosuppression is an important risk factor for MCC (although it is also important to note that most patients who develop MCC are not immunosuppressed).[30] Studies have reported that an estimated 6% to 12% of MCC cases are associated with immunosuppression.[7] [19]
- **O**lder than 50 years of age. The median age of MCC diagnosis is 77 years.[6] [7] [10]
- **U**ltraviolet (UV)-exposed site on a person with light skin. Less than 10% of MCCs occur on partially sun-protected areas (trunk, thighs, and hair-bearing scalp) or on highly sun-protected sites (e.g., buttocks).[7]

History

Take a detailed history with a particular focus on:

- How long the lesion has been present, whether it has increased in size, and if any other changes have occurred.
    - Early growth of MCC lesions is typically rapid, over weeks or months.[7]

- Although ulceration and bleeding are infrequent at first presentation, they might occur at advanced stages.[7] [19]

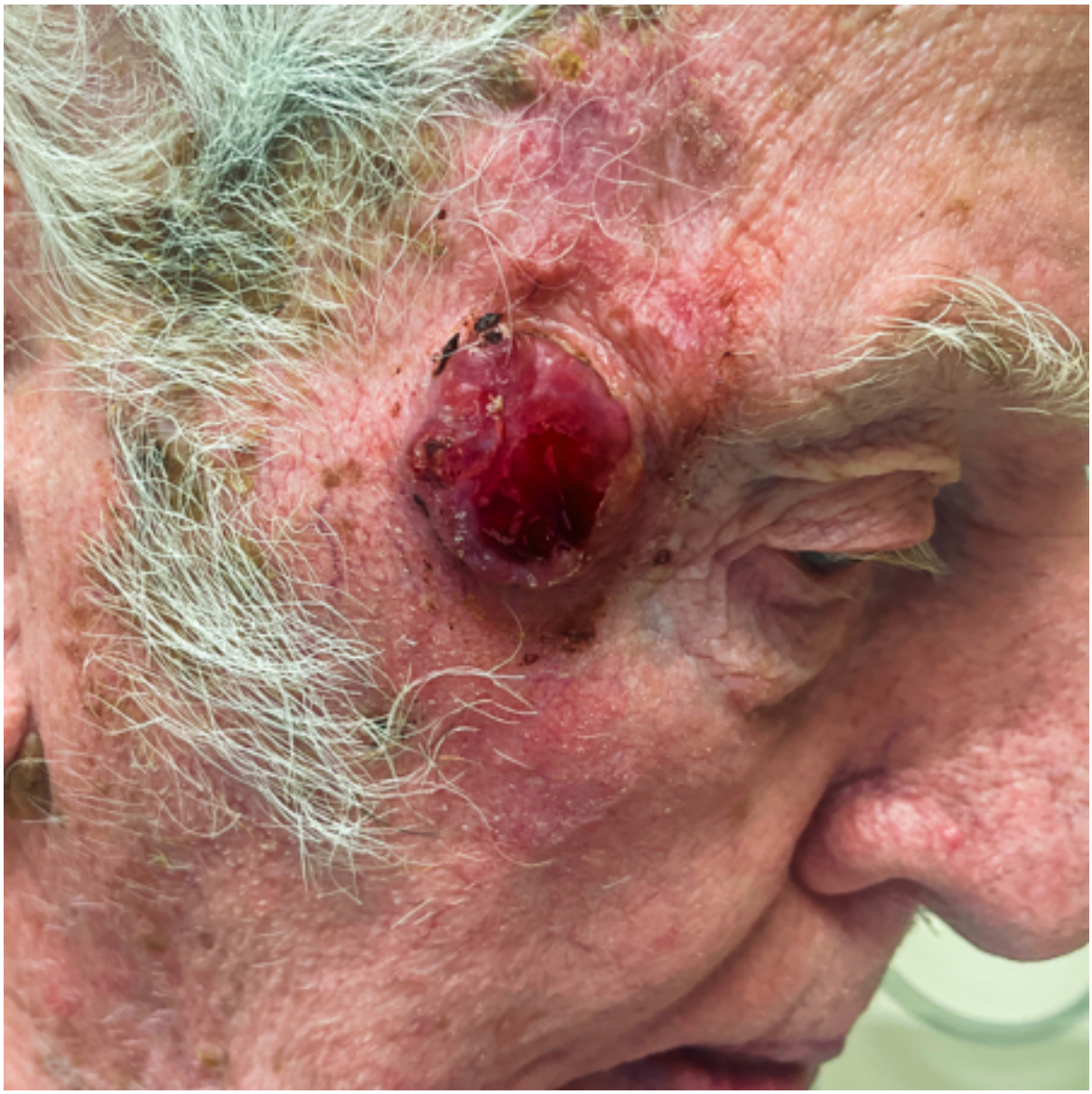
- Any associated pain or pruritus.
  - MCC is not typically tender or pruritic.
- History of UV exposure.[30]
  - MCC is strongly associated with lower latitudes and a high UV radiation index.[13]
  - The primary tumor typically occurs on sun-exposed skin.[7] It may sometimes be commingled with or adjacent to other lesions caused by UV exposure.[3]
  - Note that UV induction is understood to be one of the two pathogenetic pathways for MCC development; the second pathway is associated with oncogenic transformation by Merkel cell polyomavirus.[7]
- Immunosuppression, including any history of hematologic malignancies, HIV/AIDS, solid organ transplant, and use of immunosuppressant medications.[30]
  - MCC is strongly associated with immunosuppression, with an estimated 6% to 12% of all patients with MCC being immunosuppressed.[7] The European Society for Medical Oncology (ESMO) guideline states that 10% of patients with MCC are organ transplant recipients, or have either a hematologic malignancy or human immunodeficiency virus (HIV) infection.[19]
- Other risk factors. These include:[7]
  - Advancing age. The median age at diagnosis is 77 years.[6] [10] Incidence rates increase with age; the highest incidence is reported in those ages over 85 years.[6]
  - Light skin type. MCC is very rare in people who are not white.[5] [32]
  - Male sex. Studies have reported that 61% to 66% of cases are in men.[1] [4] [5] [9] [10]

Physical exam

Perform a thorough examination of any suspicious lesion(s).

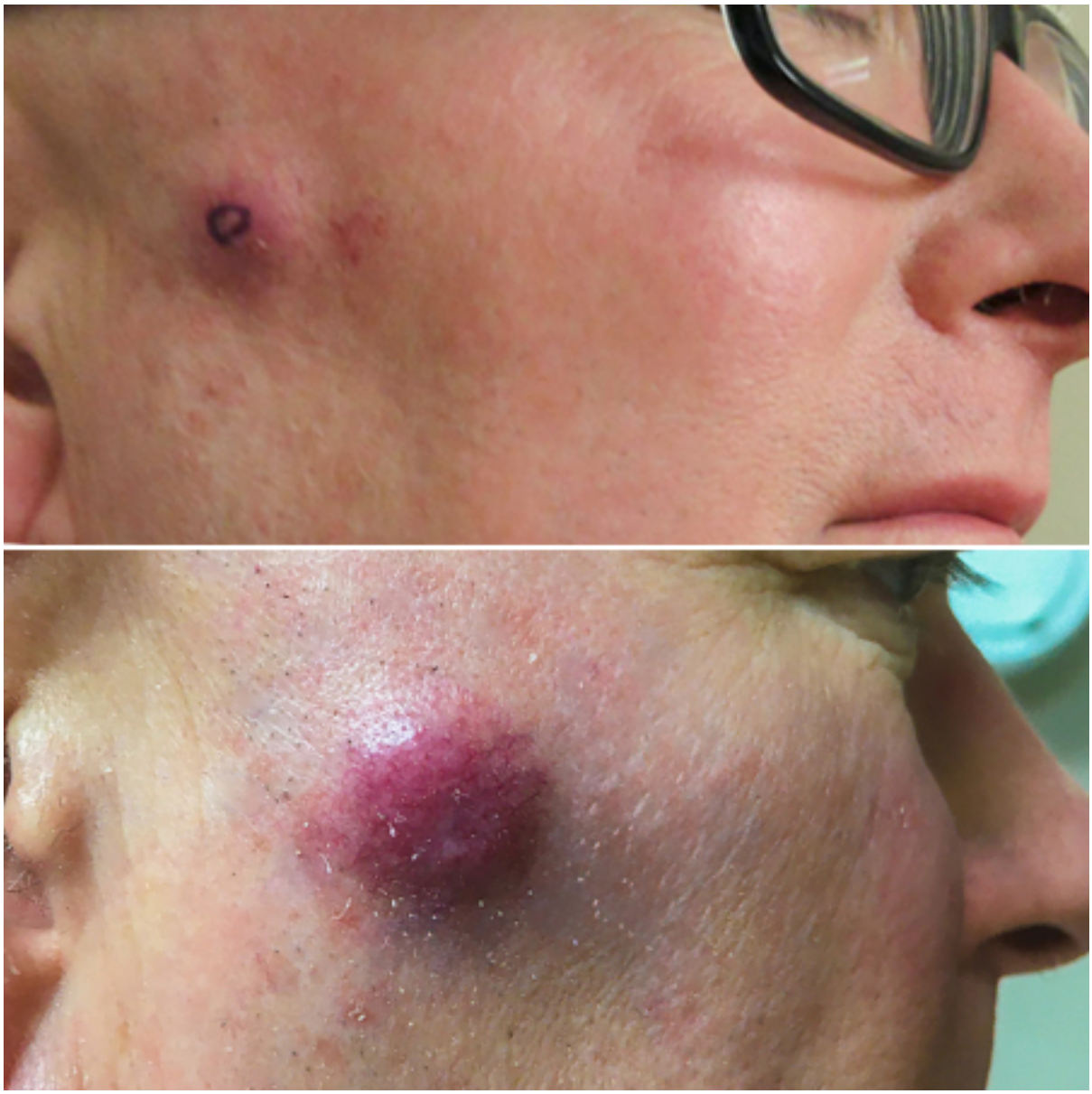
- The primary cutaneous MCC tumor usually presents as a solitary, firm, rapidly-growing, erythematous or pink-to-violaceous or skin-colored papule or subcutaneous nodule.[19]
- MCC most frequently develops on the sun-exposed areas of head and neck (29% to 44%) and the extremities (37% to 45%). Less than 10% of MCCs occur on partially sun-protected areas (trunk, thighs, and hair-bearing scalp) or highly sun-protected areas (buttocks). Extracutaneous sites (e.g., vulva, vagina, oral mucosa parotid gland, nasal cavity) are very rarely involved.[7] Note that in black and Hispanic patients, MCC more often presents on sites other than the head and neck.[41]
- MCC lesions are usually asymptomatic and not tender to the touch.[7]
- Measure the clinical size of the lesion prior to any biopsy, as the diameter of the primary tumor will determine the T-stage. Moreover, increased clinical tumor diameter and depth are associated with a worse prognosis.[42] The National Comprehensive Cancer Network (NCCN) guideline lists a primary tumor >1 cm as one of several adverse risk factors for a worse outcome, warranting different treatment recommendations.[3]

Dermoscopy for MCC is nonspecific, but can show prominent red or milky-red background color or smaller clods of milky-red areas, polymorphous vessels, and white areas.[7] It can be particularly helpful to use dermoscopy for patients with multiple skin lesions as MCC can sometimes be contiguous to, or intermingled with, other skin cancers that can be more easily identified with dermoscopy.[19]



A primary MCC tumor in an 87-year-old man who presented with a large, fast-growing, red, eroded nodule on the right temple

From the collection of Dr Kelly Harms and Dr Alison Lee, University of Michigan; used with patient consent



A rapidly-growing MCC on the right cheek of a 64-year-old man, which started as a small erythematous cyst-like papule then developed within a few months into a larger, violaceous nodule with associated pruritus

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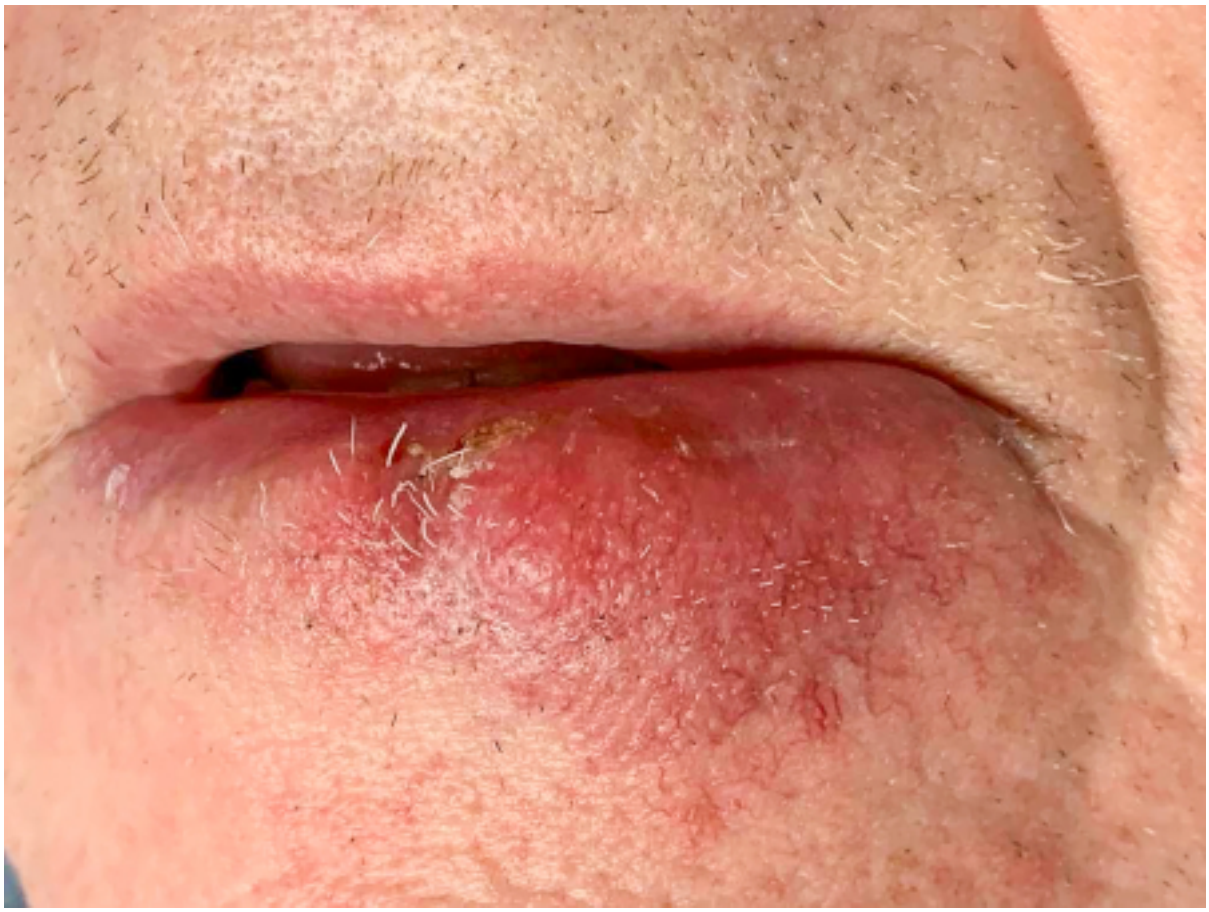

MCC on the left lower lip of a 68-year-old man. The asymptomatic tumor is an ill-defined reddish-pink, scaly plaque blurring the lower vermillion of the lip

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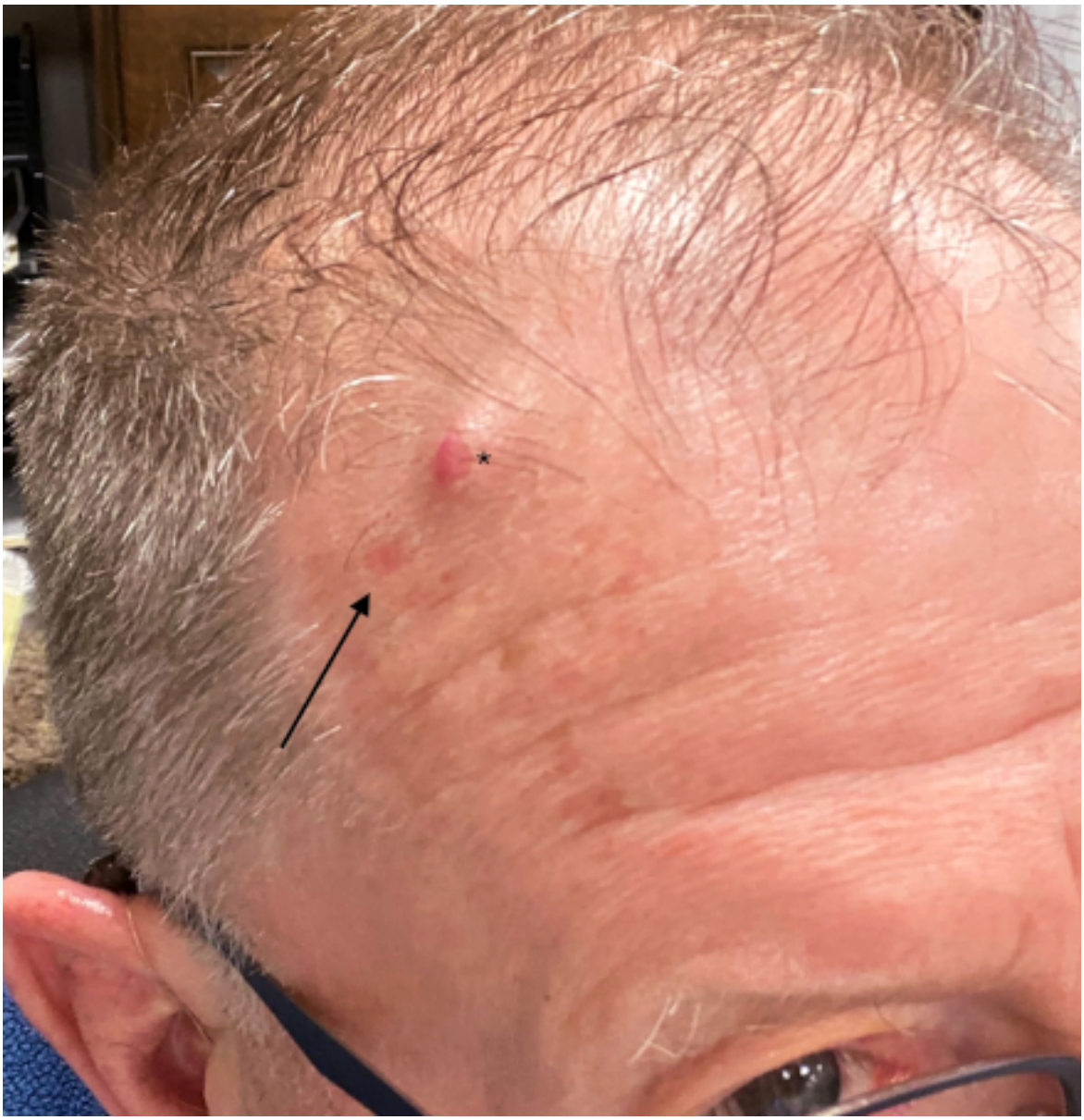

Primary MCC on the right frontal scalp (asterisk) of a 73-year-old man, with a biopsy scar of an in-transit metastasis (arrow). The primary tumor initially presented as an asymptomatic, fast-growing subcutaneous nodule that was misdiagnosed as an epidermoid cyst

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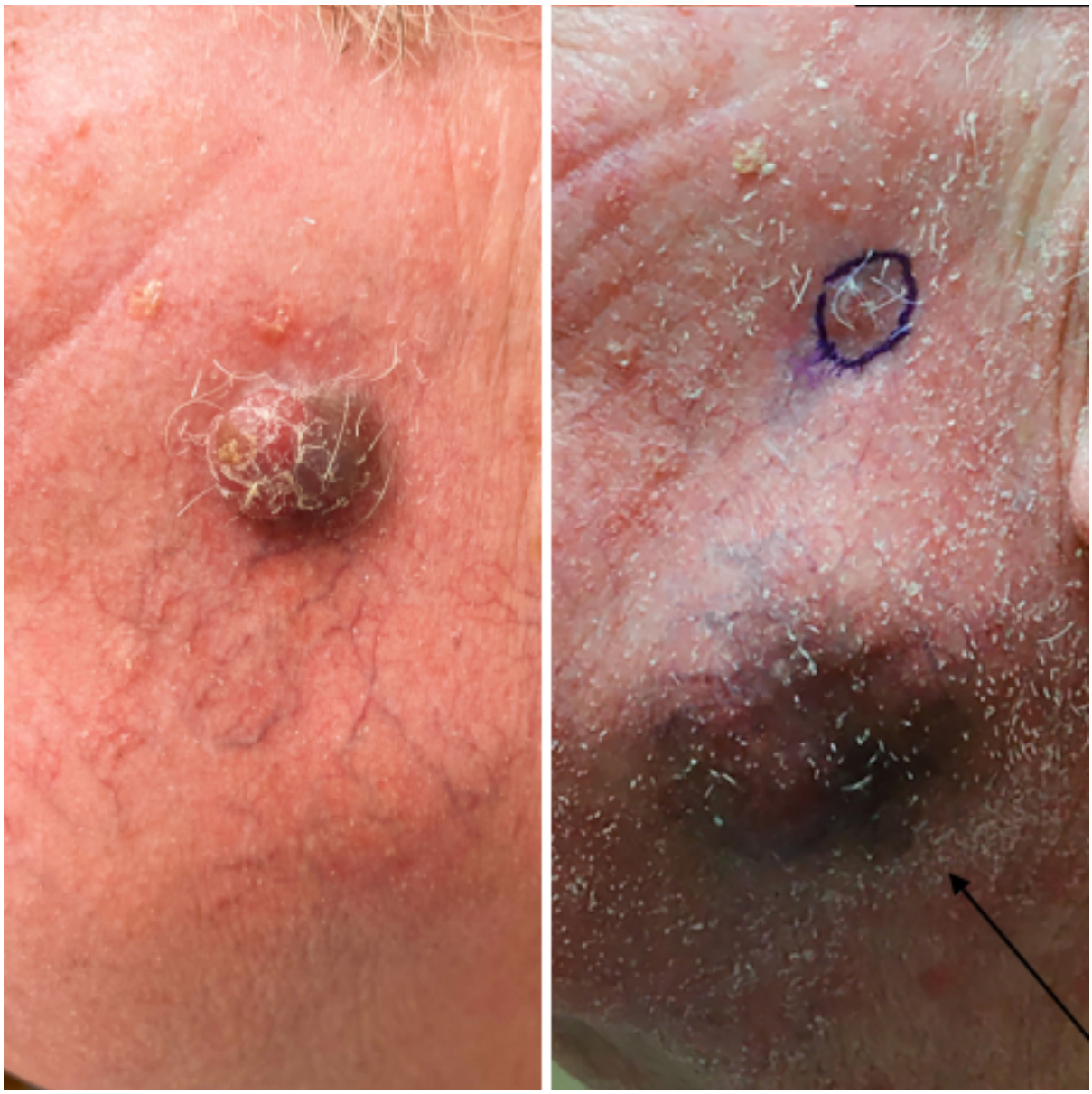

MCC presenting as a well-defined, rapidly growing, asymptomatic, brightly violaceous nodule on the left cheek of a 71-year-old man. The patient developed a golf-ball sized subcutaneous mass in the left parotid (original biopsy site marked with blue ink, subcutaneous metastasis marked with arrow). Fine needle aspiration of the mass in the left parotid gland confirmed MCC

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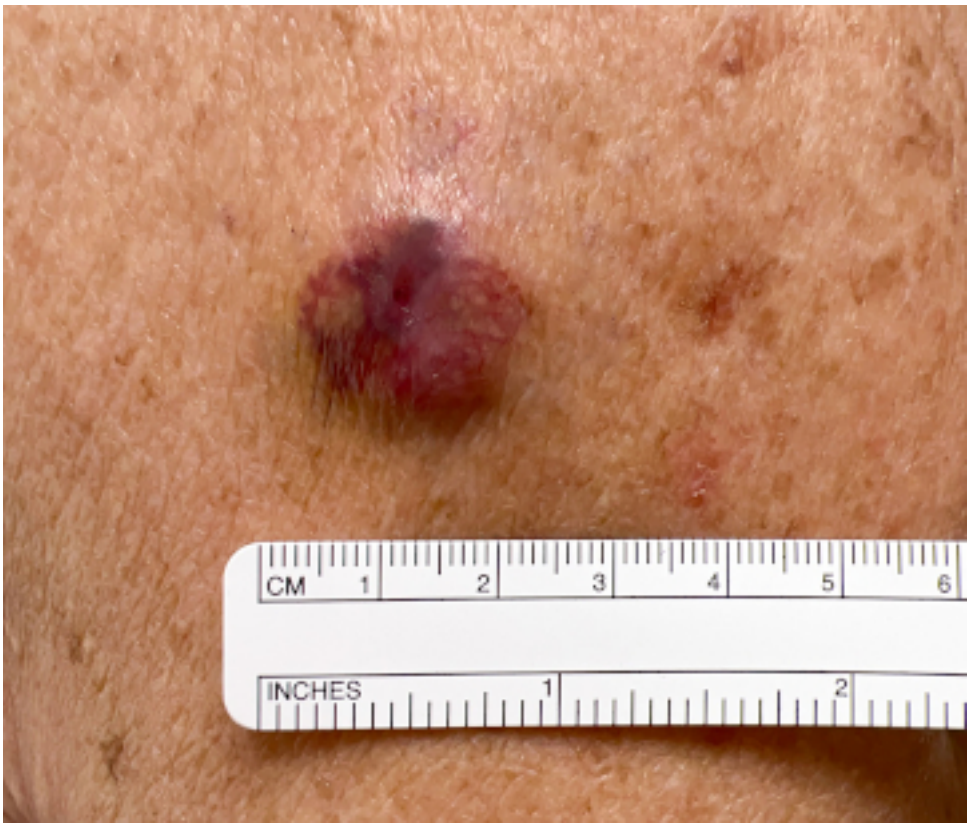

A 2 cm red, nodular MCC with varied vessel patterns on the right upper arm of an 80-year-old man

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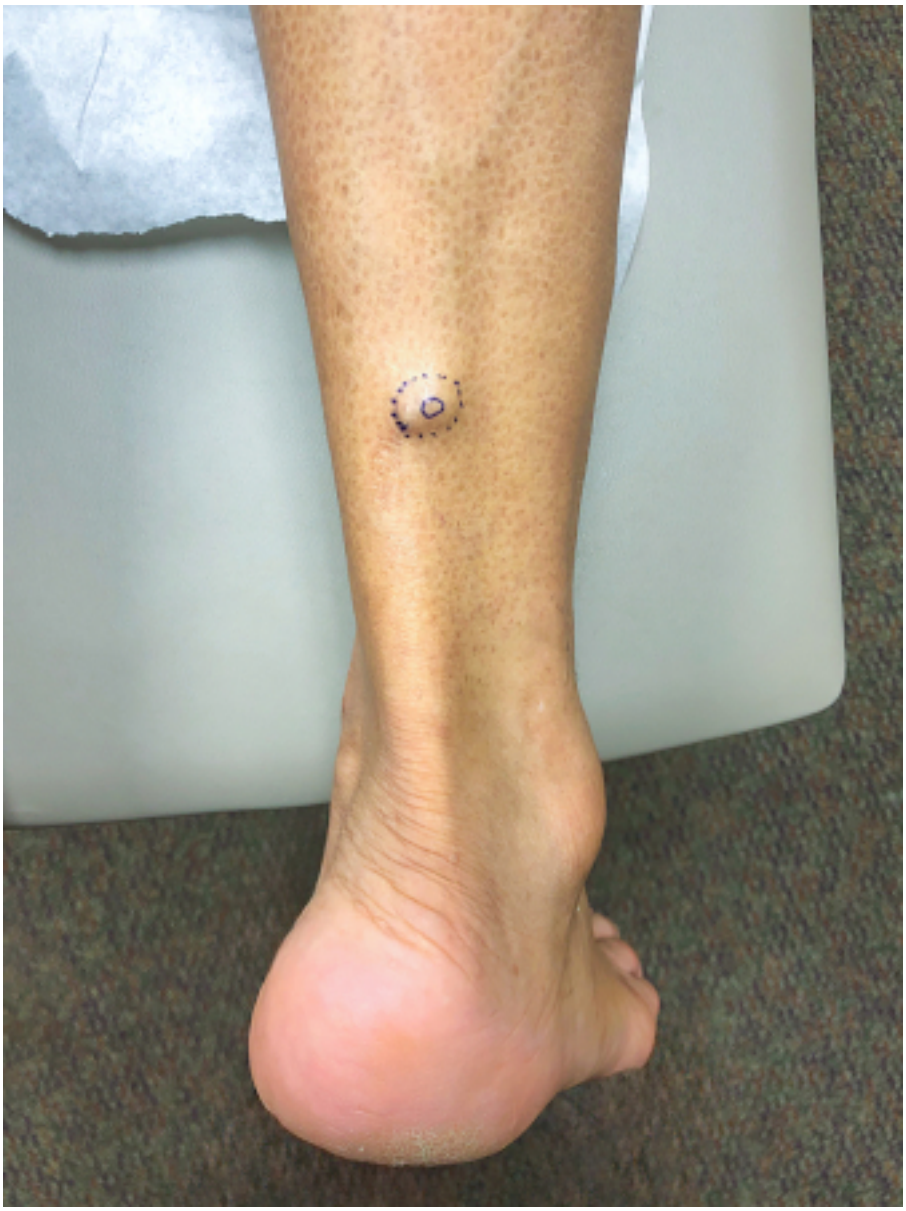

MCC on the right posterior ankle of a 66-year-old African-American man, which presented as a subtle 1.5 cm subcutaneous nodule without overlying epidermal changes. This can often be confused with benign entities such as an epidermal cyst or a lipoma

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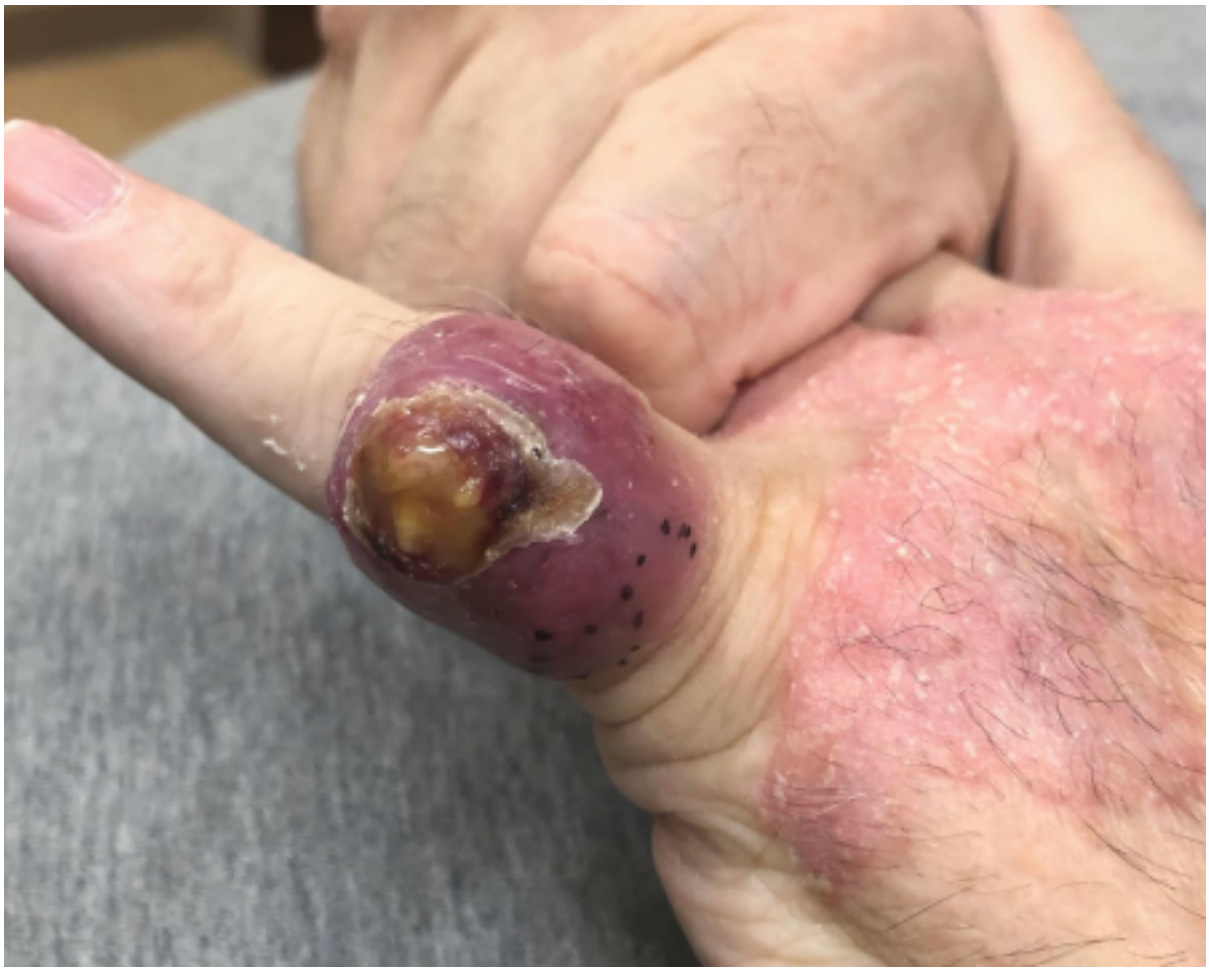


A 2x3 cm MCC lesion in a white man aged in his late 60s who had a history of taking immunosuppressive medication for psoriasis. The nodule was violaceous with central ulceration, tan crusting, and serous drainage. Note that ulceration is unusual in MCC

Tomtschik J et al. BMJ Case Reports CP 2022; 15: e249288; used with permission

Biopsy

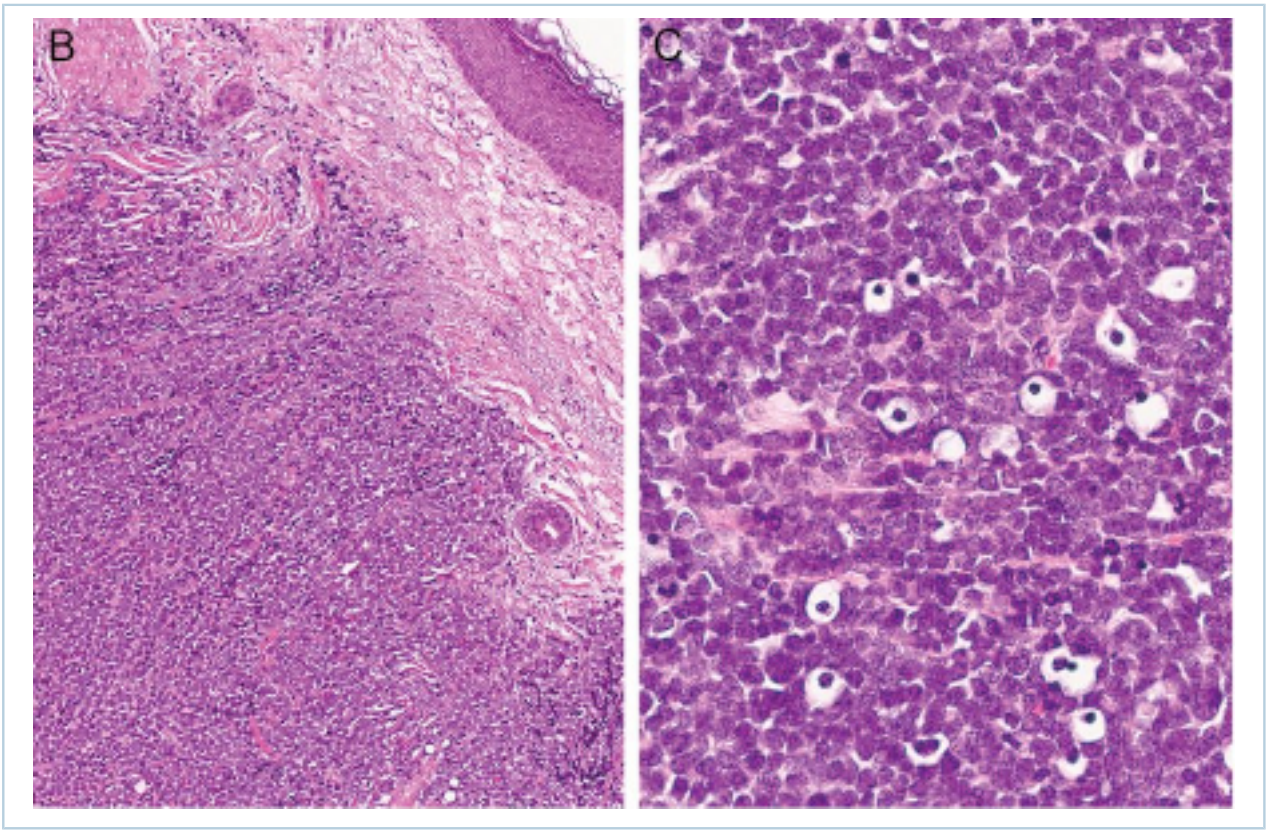
Any nontender nodule with nonspecific morphology that is fast growing should be biopsied rather than monitored.[7]

- Skin biopsy confirms the diagnosis and provides prognostic information.
- Ensure the clinical size of the lesion is measured prior to biopsy as this has implications for the T-staging, prognosis, and recommended treatment pathway.[3] [42]

A punch, incisional, or excisional biopsy should be performed on any suspicious lesion.[3] [7] [39] [43] The most appropriate method will depend on the size and location of the tumor.

- Immunohistochemistry (IHC) must be used in conjunction with hematoxylin and eosin (H&E) for confirmation of the diagnosis and to rule out histologic mimics (most notably other small cell tumors, including basal cell carcinoma, small cell lung cancer, and small cell melanoma).[3] [7] [29] [39] [43] Staining that is positive for cytokeratin 20 (CK20) and negative for thyroid transcription factor (TTF-1) is usually considered sufficient to confirm the MCC diagnosis, although variations are sometimes reported.[3]

- H&E typically shows a dermally-based tumor of small round blue cells with hyperchromatic nuclei, a "salt and pepper" chromatin pattern, and high mitotic activity.[7][40] [43]



Histologic features of MCC from biopsy of a primary tumor. Image B shows small round blue cells and image C shows characteristic nuclei, finely granular and dusty "salt and pepper" chromatin, and abundant mitotic figures

Mauzo SH et al. J Clin Pathol 2016; 69: 382-90; used with permission

Subsequent diagnostic workup

Once the diagnosis of MCC is confirmed, consult with the multidisciplinary team.[3] [7] Clinical exam and initial imaging studies (if indicated) are used to make an initial determination of the clinical N-stage and M-stage, which then determines the recommended approach to pathologic evaluation of lymph nodes.[3]

Staging

Initial staging involves a complete examination of the patient's skin and palpation of lymph nodes, which may reveal clinical signs of metastatic disease.[2] [3] [7] [19][29] [44]

- Clinical size of the primary tumor lesion, as measured prior to biopsy, is needed for T-staging.[45]
- MCC presents with a primary tumor without regional metastases in 65.4% of cases. However, it has a high risk of loco-regional metastasis, and presents with nodal and distant metastasis in 26.3% and 8.3% of patients, respectively.[10]
- Cutaneous satellite or in-transit metastases present as smaller papules or nodules surrounding the primary tumor. In-transit metastases are defined as lesions that are discontinuous from the primary tumor, located between the primary tumor and the draining regional nodal basin or distal to the primary tumor site.[3] Regional lymph node metastases present as enlarged lymph nodes or masses in the draining nodal lymph node basin.
- In addition, MCC can present with clinically detectable metastatic disease in a lymph node without a primary tumor (unknown primary MCC).[35] [46] [47] Around 11% of patients with MCC have no

identifiable primary lesion.[19] These patients have significantly higher survival rates compared with those who have a similar extent of disease but with a known primary lesion.[29]

Histopathologic confirmation of metastatic disease with biopsy is recommended.[3] [7] [48]

- A skin biopsy should be performed on suspected satellite/in-transit metastases.[3] [7]
- Fine-needle aspiration (FNA) or core biopsy should be performed on suspected lymph node metastases.[3] [7]

Imaging

Imaging is recommended for most cases of MCC to evaluate for regional lymph node metastases and distant disease and for staging of the disease.[3] [44]

- This is because occult metastatic disease has been detected in 12% to 20% of patients who presented with no suspicious findings on history and examination.[3] [48]
- Data indicate that whole-body fluorodeoxyglucose-positron emission tomography (FDG-PET) with fused axial imaging is the most reliable method for detecting occult metastatic MCC at baseline.[49] [50] It is therefore recommended as the preferred cross-sectional imaging modality, if available, to assess local and distant disease.[3] [19]
- An acceptable alternative is CT with contrast of chest/abdomen/pelvis (and neck if the primary tumor is on the head/neck).[3] [19]
- Use MRI of the brain with or without contrast if there is clinical suspicion of brain metastases (e.g., if the patient has neurologic symptoms).[3]
- European guidelines recommend ultrasound of the regional lymph nodes in patients with clinical stage I or II disease to further evaluate for regional lymph node involvement.[19]

Imaging is also an important tool to evaluate for underlying, noncutaneous, visceral neuroendocrine tumor mimics such as small cell lung cancer that may have metastasized to the dermis.

Sentinel lymph node biopsy (SLNB)

SLNB is recommended for any patient who presents without detectable metastatic disease and who is a candidate for surgery.[19][33] [34] [35] [42] [44] [51] It is performed prior to, or at the time of, excision of the primary tumor.[3] [7]

- SLNB is the most reliable tool to identify subclinical metastatic disease in the regional nodal basin.[3] [7]
- SLNB has been demonstrated to detect lymph node spread in up to one third of patients who would have otherwise been staged as node-negative.[52]

Merkel cell polyomavirus (MCPyV) serology

Consider baseline serum testing of antibodies to MCPyV (AMERK test), if available.[3] Virus-positive MCC is one of two subtypes of the disease and carries a better prognosis than UV-induced MCC.[7]

- The AMERK test can be considered as part of initial workup, and if used, should be undertaken within 3 months of initial treatment.[3]
- A proportion of patients with MCC caused by MCPyV develop antibodies to MCPyV oncoproteins.[53] In these patients, antibody titers can be monitored to detect changes in MCC disease burden.[53] [54]
- Among those who are seropositive, titers are expected to decrease after the elimination of clinically evident disease, hence a rising titer may be an early indicator of recurrent disease. Consider re-

testing every 3 months for surveillance, to detect recurrence and to help determine frequency of radiologic imaging.[53] [54]

- Among those who are seronegative, more intensive surveillance is indicated as virus-negative patients have a worse prognosis.[3] [7]

Integration of MCPyV into the host genome is associated with up to 70% to 80% of MCC tumors in North America and Europe. The proportion of virus-positive cases is lower in Australia, where the UV index is higher.[7][12] [14] [19]

- MCPyV is a ubiquitous virus, with seroprevalence in the adult population of 60% to 80%.[20] Oncogenic transformation by MCPyV is a rare event and requires viral integration into the host genome, resulting in inactivation of a viral replication protein.

Emerging test

Circulating tumor DNA (ctDNA) analysis, which measures circulating cell-free DNA from tumor cells, is an emerging blood test for molecular disease monitoring of different cancers, including MCC.[55] [56] Additional studies are needed to further define its role in MCC.

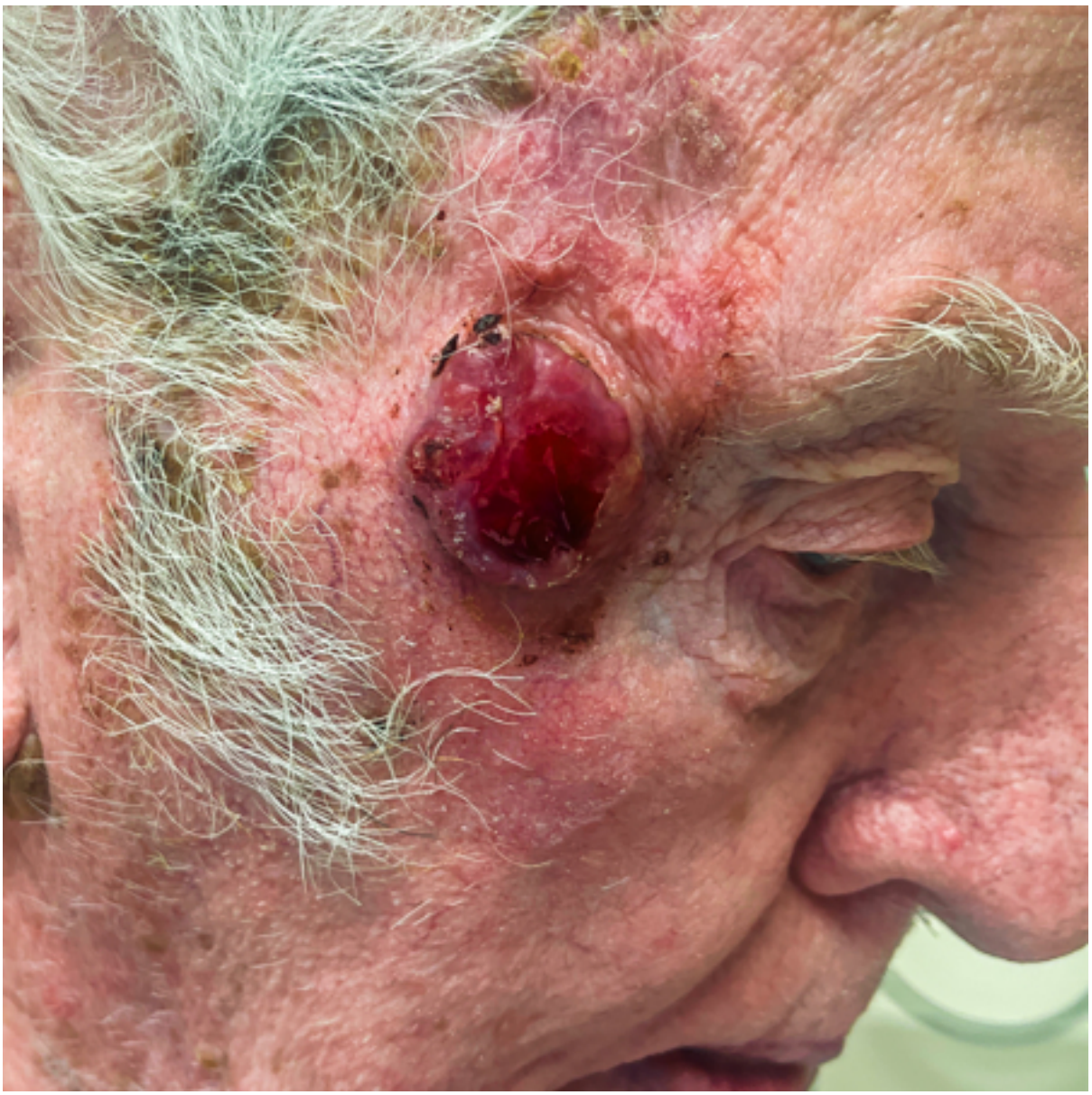
History and exam

Key diagnostic factors

firm, nontender, red or pink-to-violaceous or skin-colored papule or subcutaneous nodule (common)

- The primary cutaneous MCC tumor usually presents as a solitary, firm, erythematous or pink-to-violaceous or skin-colored papule or subcutaneous nodule, typically on sun-exposed skin.[7] [19]
- MCC lesions most frequently develop on the sun-exposed areas of head and neck (29% to 44%) and the extremities (37% to 45%). Less than 10% of MCCs occur on partially sun-protected areas (trunk,

thighs, and hair-bearing scalp) or highly sun-protected areas (buttocks). Extracutaneous sites (e.g., vulva, vagina, oral mucosa, parotid gland, nasal cavity) are very rarely involved.

- MCC lesions are typically asymptomatic and not tender to the touch.[7] One study of 195 patients with pathologically confirmed MCC found 88% of tumors were asymptomatic.[2]
- 

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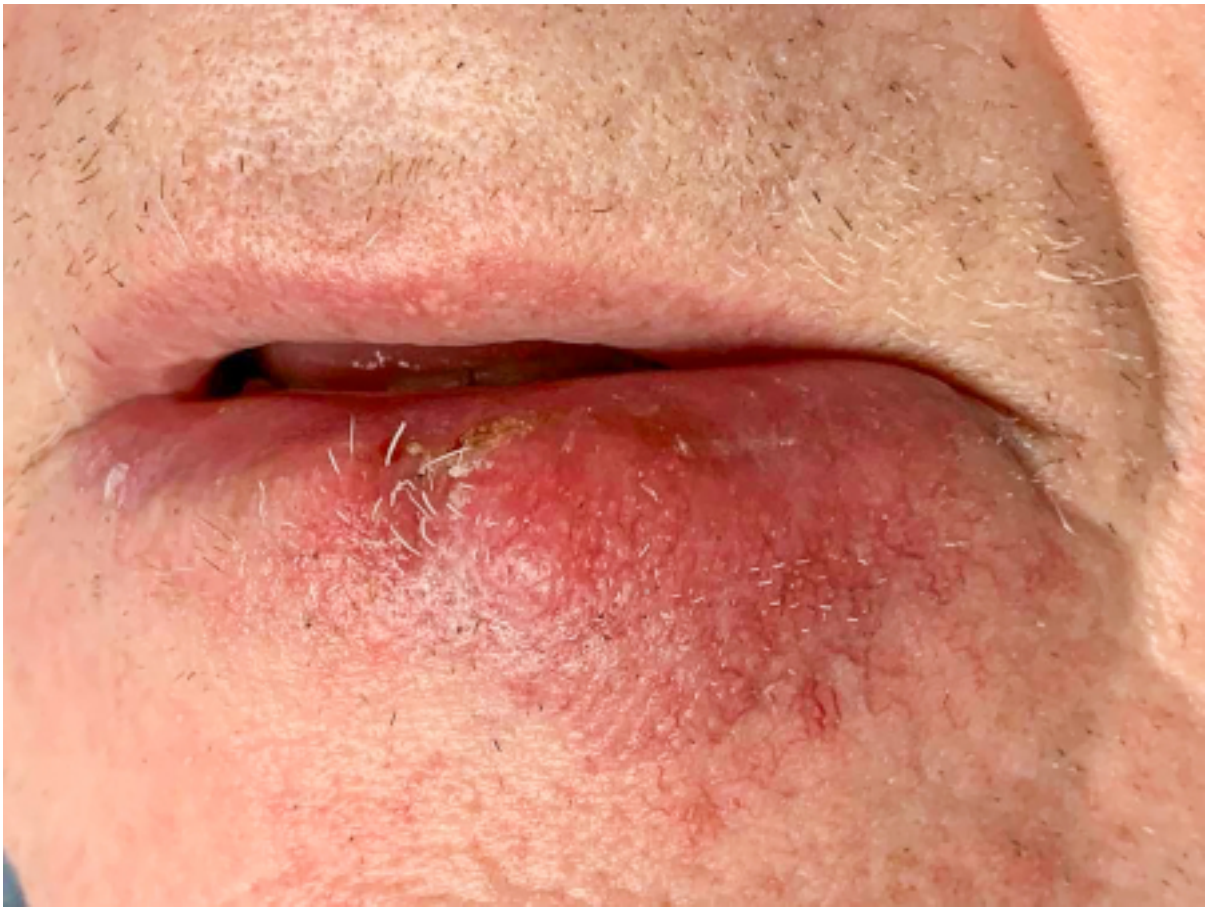

MCC on the left lower lip of a 68-year-old man. The asymptomatic tumor is an ill-defined reddish-pink, scaly plaque blurring the lower vermillion of the lip

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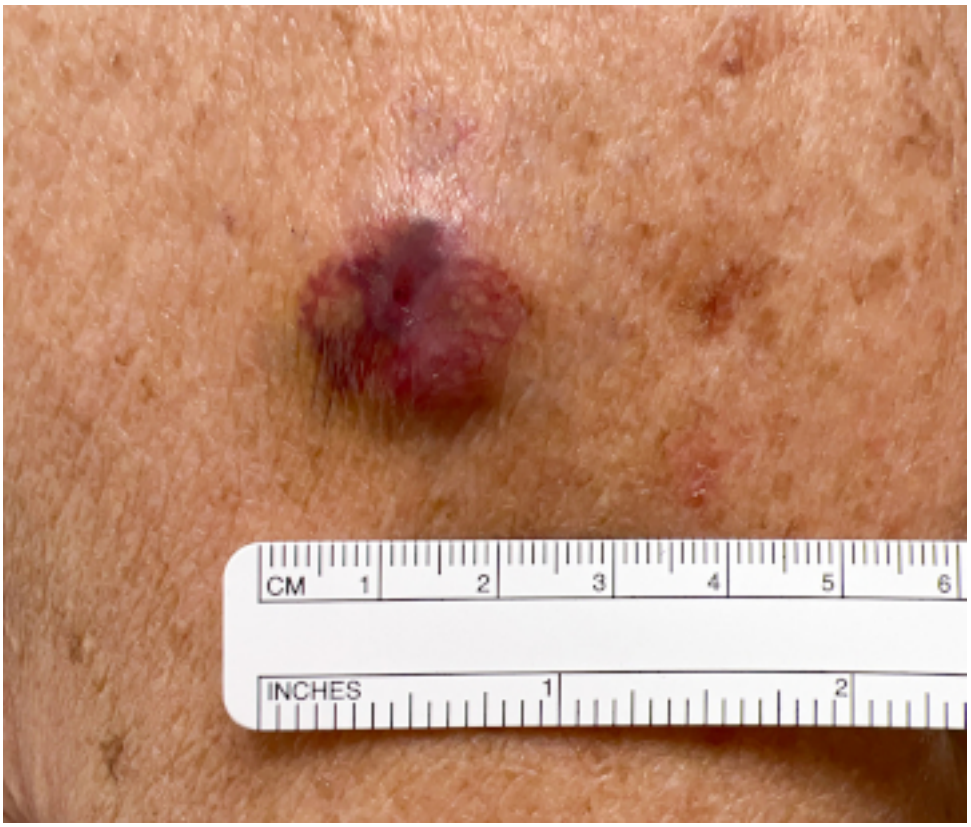

A 2 cm red, nodular MCC with varied vessel patterns on the right upper arm of an 80-year-old man

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- For further clinical images of MCC, see Diagnosis approach .

rapidly growing lesion (common)

- The primary MCC tumor typically grows rapidly over the first 3 months.[2]

Other diagnostic factors

enlarged lymph nodes (common)

- Regional lymph node metastases present as enlarged lymph nodes or masses in the draining nodal lymph node basin.
- Rarely, MCC can present with clinically detectable disease in a lymph node without a primary tumor (unknown primary MCC).[35] [46] [47]

ulceration or bleeding cutaneous lesion (uncommon)

- Ulceration and bleeding are infrequent at first presentation of MCC but might occur at advanced stages.[7] [19]

small papules or nodules surrounding a primary lesion (uncommon)

- Cutaneous satellite or in-transit metastases present as smaller papules or nodules surrounding the primary tumor.

Risk factors

Strong

cumulative ultraviolet (UV) exposure

- UV-mediated DNA damage is a significant risk factor for MCC.
- MCC is strongly associated with lower latitudes and high UV radiation indexes.[13] The primary tumor typically occurs on sun-exposed skin.[2] [7]
- MCC tumors that do not harbor integration of Merkel cell polyomavirus (MCPyV) demonstrate a high burden of UV-signature mutations, and UV-mediated DNA damage is considered a pathogenic mechanism of MCC tumorigenesis.[22] [23]

immunosuppression

- MCC is strongly associated with immunosuppression, with an estimated 6% to 12% of all patients with MCC being immunosuppressed.[7] [19]
- There is a greater than 34-fold increased risk of MCC in patients with chronic lymphocytic leukemia (CLL).[15] [17] Patients with solid organ transplantation have a 23% increased risk of MCC.[16] [27] Other immunosuppression mechanisms, such as human immunodeficiency virus (HIV) infection and use of immunosuppressive medications, have also been associated with a higher risk of developing MCC.[7] [28]
- The European Society for Medical Oncology (ESMO) guideline states that 10% of patients with MCC are organ transplant recipients, or have either a hematologic malignancy or HIV infection.[19]

advancing age

- The median age of MCC diagnosis is 77 years.[6] [7] [10] Incidence rates increase sharply with age, and the highest incidence is reported in those ages over 85 years.[4] [5] [7]

male sex

- There is a higher incidence in men than in women.[7] Studies have reported that 61% to 66% of cases are in men.[1] [4][5] [9] [10]

white skin

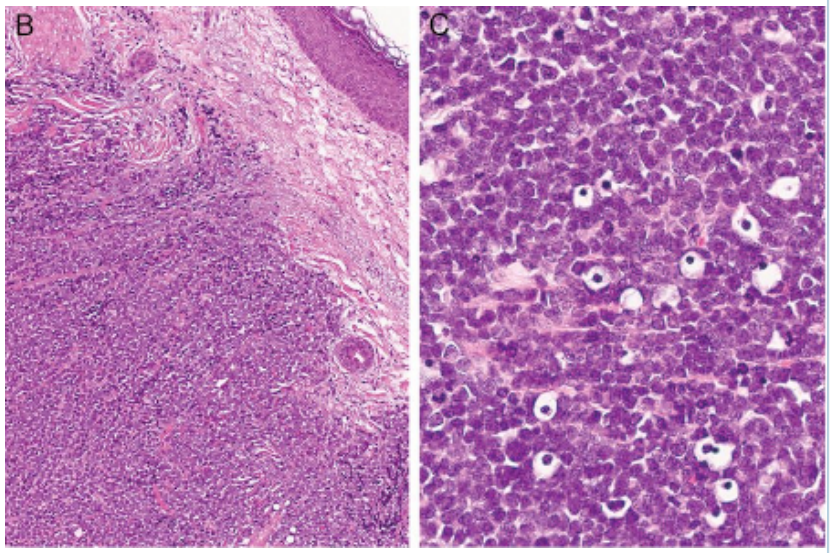
- MCC is predominantly seen in white patients and is very rare in people of color.[7] There is an 8-fold increased incidence in white individuals compared with non-Hispanic black people.[11]

Merkel cell polyomavirus (MCPyV) infection with oncogenic transformation

- Oncogenic transformation by MCPyV is a key risk factor for MCC.[29] MCPyV is a ubiquitous virus, with seroprevalence in the adult population of 60% to 80%.[20] Oncogenic transformation by MCPyV is a rare event and requires viral integration into the host genome, resulting in inactivation of a viral replication protein. MCPyV is associated with up to 70% to 80% of MCC tumors in North America and Europe, with lower associations in Australia, where a higher proportion of cases are associated with UV exposure.[7] [12] [14]

Tests

1st test to order

Test	Result
biopsy and histopathologic assessment • Skin biopsy confirms the diagnosis and provides prognostic information. Any nontender cutaneous nodule with nonspecific morphology that is fast growing should be biopsied rather than monitored.[7] • A punch, incisional, or excisional biopsy should be performed on any suspicious lesion.[3] [7] [39] [43] The most appropriate method will depend on the size and location of the tumor. • Immunohistochemistry (IHC) must be used in conjunction with hematoxylin and eosin (H&E) for confirmation of the diagnosis and to rule out histologic mimics (most notably, other small cell tumors, including basal cell carcinoma, small cell lung cancer, and small cell melanoma).[3] [7] [29] [39] [43] • Cytokeratin 20 (CK20) positivity and thyroid transcription factor (TTF-1) negativity is characteristic of MCC, although variations are reported. MCC also stains positive for epithelial markers AE1/AE3, and CAM5.2, and for neuroendocrine markers such as neuron-specific enolase (NSE), synaptophysin, CD56, and chromogranin A. MCPyV large T expression is a specific but not wholly sensitive marker. • In addition to TTF-1 negativity, MCC is negative for S-100 and HMB-45, cytokeratin 7, carcinoembryonic antigen (CEA), leukocyte common antigen, and lymphoma-specific lymphocytic markers. •  *Histologic features of MCC from biopsy of a primary tumor. Image B shows small round blue cells and image C shows characteristic nuclei, finely granular and dusty "salt and pepper" chromatin, and abundant mitotic figures* *Mauzo SH et al. J Clin Pathol 2016; 69: 382-90; used with permission*	**H&E: dermally-based tumor of small round blue cells with hyperchromatic nuclei, "salt and pepper" chromatin pattern, and high mitotic activity; confirmatory IHC stains distinguish MCC from histopathologic mimics**
dermoscopy • Dermoscopy can be useful in raising suspicion of malignancy, although the dermoscopic pattern of MCC is nonspecific.[7] It can be particularly helpful for patients with multiple skin lesions as MCC can	**may show prominent red or milky-red background color or smaller clods of milky-red areas,**

Test	Result
sometimes be contiguous to, or intermingled with, other skin cancers that can be more easily identified with dermoscopy.[19]	**polymorphous vessels, and white areas**

Other tests to consider

Test	Result
lymph node ultrasound • European guidelines recommend ultrasound of the regional lymph nodes in patients with clinical stage I or II disease to further evaluate for regional lymph node involvement.[19]	**may show regional disease**
whole-body PET scan • After confirmation of the diagnosis of MCC, imaging is recommended for most patients to evaluate for regional lymph node metastases and distant disease and for staging of the disease.[3] [44] • Data indicate that whole-body fluorodeoxyglucose-positron emission tomography (FDG-PET) with fused axial imaging is the most reliable method for detecting occult metastatic MCC at baseline.[49] [50] It is therefore recommended as the preferred cross-sectional imaging modality, if available, to assess local and distant disease.[3] [19]	**may show metastases**
CT scan with contrast chest/abdomen/pelvis (± neck) • A CT scan with contrast of chest/abdomen/pelvis (and neck if the primary tumor is on the head/neck) is an acceptable alternative to FDG-PET for evaluation of regional lymph node metastases and distant disease.[3] [19]	**may show metastases**
brain MRI • MRI of the brain (with or without contrast) is recommended if there is clinical suspicion of brain metastases (e.g., neurologic symptoms).[3]	**may show metastases**
fine-needle aspiration or core biopsy • Perform in any patient with MCC who has a clinically enlarged lymph node concerning for metastatic disease.[3] [7]	**may show metastases**
sentinel lymph node biopsy (SLNB) • In patients presenting without detectable metastatic disease, use SLNB to identify subclinical metastatic disease in the regional nodal basin.[33] [34] [35] [42] [44] [51] • SLNB should be performed prior to or at the time of excision of the primary tumor.[3] [7] • SLNB has been demonstrated to detect lymph node spread in up to one third of patients who would have otherwise been staged as clinically node-negative.[52]	**may show metastases**
Merkel cell polyomavirus serology • Consider baseline serum testing of antibodies to MCPyV (AMERK test) as part of initial workup, if available.[3] If used, this should be undertaken within 3 months of initial treatment. • Results may guide subsequent surveillance; antibody titers can be monitored to help detect disease recurrence in those who are seropositive, whereas those who are seronegative have a worse prognosis and may need more intensive surveillance.[3] • In seropositive patients, consider re-testing every 3 months for surveillance, to detect recurrence and to help determine frequency of radiologic imaging.[53] [54] Rise of antibody titer correlates with disease recurrence and fall of antibody titer correlates with treatment effect.[54] Two consecutive increasing titers of more than 20% have a positive predictive value for disease recurrence of 99%; decrease	**positive result indicates oncogenic transformation by MCPyV; post-treatment decreased oncoprotein antibody titer may indicate positive response; increasing titer may indicate disease recurrence**

Test	Result
by 20% has a 99% negative predictive value for clinically detectable disease.[53] [54]	

Emerging tests

Test	Result
circulating tumor DNA (ctDNA) analysis • ctDNA is a blood test that measures circulating cell-free DNA from tumor cells, thereby offering molecular disease monitoring of different cancers, including MCC. ctDNA for MCC is an emerging area of interest for disease monitoring with few published data.[55] [56]	**may detect minimal residual MCC ctDNA**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Basal cell carcinoma (BCC)	• Slow growing. • Presents as pearly papules or plaques with rolled borders, telangiectasias, and ulceration when tumors become larger.	• Dermoscopy: crisp and well-defined arborizing vessels, spoke wheel-like pigment clods and maple leaf structures, milky-white background.[57] • Histopathology: hematoxylin and eosin (H&E) features consistent with BCC include basaloid tumor with peripheral palisading, clefting, and distinctive stroma.
Squamous cell carcinoma (SCC) of the skin	• Typically grows more slowly, although keratoacanthoma is a fast-growing variant. • Hyperkeratotic scale is more common in cutaneous SCCs compared with MCC.[58] [59]	• Dermoscopy: white circles and glomeruloid vessels. • Histopathology: H&E features consistent with SCC include atypical squamous cells infiltrating into dermis.
Amelanotic/ hypomelanotic melanoma	• Younger age of presentation compared with MCC. More than two-thirds of melanoma cases in the California Cancer Registry over a 15-year period occurred in people younger than 70 years, with a median age of 57 years.[60] • Occurs more frequently on the trunk than MCC.[60]	• Dermoscopy: hypomelanotic melanoma can show pigmented structures or blue-gray veil.[61] • Histopathology: skin biopsy with H&E features diagnostic of melanoma (e.g., severely cytologically atypical melanocytes, with an asymmetric growth pattern, Pagetoid spread of melanocytes, and confluent growth with

Condition	Differentiating signs / symptoms	Differentiating tests
		a loss of the normal nested pattern). Immunohistochemical markers for melanocytic lesions include S100, HMB45, Sox10, and MelanA.
Cutaneous metastasis of small cell lung carcinoma (SCLC) or other pulmonary neuroendocrine tumor	• Favors the scalp or trunk.[62] [63] • Typically accompanied by respiratory symptoms.	• Immunohistochemistry: SCLC is generally positive for TTF-1 and CK7, and negative for CK20.[43] • Imaging: mass or adenopathy on chest CT.[3]
Cutaneous metastasis of other nonpulmonary visceral neuroendocrine tumor (gastrointestinal, mammary, urothelial/ renal, pancreatic)	• In one case series, metastatic neuroendocrine tumors were characterized by a single well-defined nodular neoplasm in the dermis and subcutis.[63] • Another study of 14 patients showed the most common locations for metastasis were the head and neck (n=7), chest, and breast (n=4).[64]	• Broad immunohistochemistry panel including CK20, TTF-1, neurofilament (NF), CK7, CDX2, GATA-3, SATB2, and progesterone receptors.[64] [65] Gastrointestinal: positive for CDX2, negative for CK20, TTF-1, NF. Appendix and rectum: positive for SATB2, negative for TTF-1. Breast/mammary and urothelium: positive for GATA 3. Pancreatic: positive for progesterone receptor (PR), negative for SATB2. • Imaging: complete radiologic imaging with clinical correlation to identify a noncutaneous primary neuroendocrine tumor.[64]
Epidermal inclusion cyst	• Fluctuant nodules that can be found on the head, neck, and upper torso, often	• Often a clinical diagnosis, based on history and physical exam.

Condition	Differentiating signs / symptoms	Differentiating tests
	with a central opening (punctum).[66] [67] • Inflamed cysts are often painful.	• Histopathology: cystic structure with a cell wall that has a granular layer and is filled with keratinaceous material.[67]
Pyogenic granuloma	• Raised (exophytic), red papule that is friable, with a collarette of scale that bleeds easily. • Commonly on sites of trauma, such as the face, hands, or mucous membranes.[68]	• Often a clinical diagnosis. • Dermoscopy: milky-red areas, but often with a base with a collarette of scale.[68] • Histopathology: a lobular lesion with many capillaries made up of bland endothelial cells.[68]

Criteria

Histopathologic classification

- Hematoxylin and eosin (H&E) staining demonstrates a dermal tumor of small round blue cells.
- Immunohistochemistry should be used to exclude mimics:
  - Positive staining with CK20 (membranous or paranuclear dot pattern) and negative staining with thyroid transcription factor 1 (TTF-1) may be sufficient to confirm MCC.
  - Additional immunophenotyping with neuroendocrine markers or for MCPyV may be helpful.
- The College of American Pathologists (CAP) recommends a synoptic report including tumor depth in mm, tumor-infiltrating lymphocytes, tumor growth pattern, and presence of a second malignancy within the specimen, among other features.[39] [69]

American Joint Committee on Cancer (AJCC) TNM staging system (8th edition)[70]

The AJCC staging system describes the extent of disease based on the following anatomic factors: size and extent of the primary tumor (T); regional lymph node involvement (N) (assessed clinically [cN] and pathologically [pN]); and presence or absence of distant metastases (M).

Approach

Owing to the aggressive nature of MCC and the scarcity of evidence to guide management, optimal treatment is not well established. A multidisciplinary approach to care coordination is recommended and requires the expertise of pertinent specialties, including:[3] [7] [29] [30] [40]

- Dermatologists/dermato-oncologists
- Surgeons (dermatologic surgeons, head and neck surgeons, surgical oncologists, and/or plastic surgeons)
- Radiation oncologists
- Medical oncologists
- Pathologists.

As with all cancers, the National Comprehensive Cancer Network (NCCN) encourages participation in available clinical trials.[3]

The most suitable treatment depends on staging according to the 8th Edition of the American Joint Committee on Cancer (AJCC8). Patients may present with localized disease (cN0), clinically detected regional disease (cN1, cN2, or cN3), or disseminated disease (M1).

Immunocompromised patients

For patients who are immunocompromised, it is important to reduce any immunosuppressive treatments as clinically feasible, in consultation with the relevant managing physician.[3] [7] More frequent follow-up may be indicated for patients who are immunosuppressed.[3]

- Immunosuppression in MCC is associated with an increased risk of recurrence and poorer outcomes.[18] [27] [76] [77]

Localized disease

In patients who present with localized disease (AJCC8 clinical stage I or II: i.e., T-any cN0 M0) that is surgically resectable, the recommendation is for concomitant management of the primary tumor and staging of the lymph node basin with sentinel lymph node biopsy (SLNB).[3] [19][40] [44]

- First-line treatment for the primary MCC tumor is surgical wide local excision to remove the lesion with histologically clear margins. Postoperative radiation therapy may be appropriate to manage a positive histologic margin or narrow (<1 cm) surgical margin, or to decrease the risk of local recurrence, based upon the clinical size of the primary tumor (>1 cm) and/or other adverse risk factors.[3]
- It is imperative to identify occult lymph node metastases in patients with early-stage localized disease. SLNB is recommended to be performed at the time of, or prior to, wide local excision of the primary tumor to stage the nodal basin.[1] [3][7] [19][35] [51]
- Adjuvant systemic therapy is not recommended outside of a clinical trial for this patient group.[3]
- After initial treatment, the patient should be monitored for disease recurrence with clinical surveillance and imaging studies as indicated.[3] [7] [29] If there are clear margins and no risk factors present, observation may be appropriate, with regular follow-up to monitor for recurrence.[3] See *Monitoring* below.

Surgical wide local excision of the primary tumor

There is a lack of consensus regarding the ideal surgical margin due to a paucity of evidence; therefore, multidisciplinary consultation and local guidelines should steer the approach.

The National Comprehensive Cancer Network (NCCN) recommends a 1-2 cm margin while noting that surgical margins should be balanced with the morbidity associated with surgery.[3]

- For clear margins in a patient with no adverse risk factors, observation can be considered.
- For microscopically positive margins, adjuvant radiation therapy is preferred over re-excision +/- adjuvant radiation.
- For narrow clinical margin (<1 cm) and/or the presence of additional risk factors, excision should be followed by adjuvant radiation therapy. Relevant risk factors include: tumor size (primary tumor >1 cm); immunosuppressed state (chronic T-cell immunosuppression, HIV, chronic lymphocytic leukemia (CLL), solid organ transplant); tumor location (head/neck primary site); presence of lymphovascular invasion (LVI).
- If adjuvant radiation therapy is indicated, this should be initiated as soon as wound healing permits.[3] A delay > 8 weeks in starting radiation therapy has been associated with worse outcomes.[78]

European guidelines recommend a 1-2 cm margin. If this is difficult or not feasible (e.g., in cosmetically sensitive locations such as the face or in proximity to joints), a narrower margin of 0.5 to 1.0 cm with adjuvant radiation therapy may be acceptable.[7] [19]

- Adjuvant radiation therapy to the tumor bed is recommended for tumors ≥1 cm and/or with negative prognostic features.

In selected patients (e.g., for sensitive areas such as the head and neck), a tissue-sparing approach such as Mohs or another form of peripheral and deep en face margin assessment (PDEMA) may be appropriate in place of wide local excision.[3][7] [19]

Sentinel lymph node biopsy (SLNB)

SLNB is an important staging tool, and every effort must be made to coordinate surgical management so that it can be performed before, or at the same time as, excision of the primary tumor.[3] [19]

- SLNB has been demonstrated to detect occult spread to the lymph node basin in up to one third of patients who have no clinical evidence of node disease and would therefore have otherwise been staged as node-negative.[52]
- Patients found to have occult lymph node disease on SLNB are upstaged to stage IIIA.

Unresectable primary tumor

In patients with locally advanced MCC for whom curative surgery and curative radiation therapy are not feasible, multidisciplinary consultation should inform management.[3] [7] [29]

- In patients who are candidates for surgery, neoadjuvant nivolumab may be considered prior to excision and SLNB.[3] [19] If progression on nivolumab means surgery is not feasible, radiation therapy may be considered.[3]
- In nonsurgical candidates (due to tumor characteristics or comorbidities), the tumor may be treated with radiation therapy.[3] [19] [29]

Regional disease

For those with regional disease, management differs depending on whether the lymph node disease is occult or clinically detectable.

Stage IIIA patients are those who present with occult lymph node metastasis, as confirmed by a positive SLNB during management of the primary tumor.

Stage IIIB covers patients who have clinically palpable/radiologically detected lymph node metastasis and/or in-transit disease but no distant metastatic disease. Lymph node metastasis is pathologically confirmed by fine-needle aspiration or core biopsy of the draining nodal basin with appropriate immunohistochemistry panel. In-transit metastasis is confirmed by skin biopsy.[3]

AJCC8 stage IIIA disease

For patients with SLNB-positive stage IIIA disease (i.e., with identified occult lymph node metastasis), treatment of the nodal basin is recommended along with baseline imaging studies to screen for distant metastases if not already performed. Multidisciplinary consultation should be sought.[3] [7]

For treatment of the nodal basin, the NCCN recommends:[3]

- Radiation therapy to the nodal basin *or*
- Lymph node dissection, which can be combined with adjuvant radiation therapy when indicated (e.g., for multiple involved nodes and/or in the presence of extranodal extension [ENE]).

The European Society for Medical Oncology (ESMO) recommends:[19]

- Adjuvant radiation therapy alone as an option or complete lymph node dissection with adjuvant radiation therapy, with the decision made following multidisciplinary team discussion.
- Consideration of entry into a clinical trial for neoadjuvant or adjuvant systemic therapy is also recommended, if available.

AJCC8 stage IIIB

Multidisciplinary consultation is recommended for any individual with stage IIIB disease.[3] [7] Patients with stage IIIB disease have a primary tumor together with one of the following:[45]

- Metastases to the draining lymph node basin (clinically/radiologically detected and pathologically confirmed), *without* in-transit disease (stage pN1b). In this group, the primary tumor is managed in the same way as for stages I/II.
- In-transit metastasis *without* lymph node disease (stage pN2).
- Both lymph node metastasis (clinically/radiologically detected and pathologically confirmed) *and* in-transit disease (stage pN3).

For management of the metastatic draining nodal basin in patients with stage IIIB MCC, the NCCN recommends:[3]

- Lymph node dissection with postoperative radiation therapy (preferred, although either dissection or radiation therapy alone may also be used).
- Clinical trial enrollment, if available.
- Consideration of neoadjuvant systemic immunotherapy prior to surgery, based upon multidisciplinary recommendations (e.g., nivolumab).

In Europe, ESMO recommends a multidisciplinary team discussion to determine the best therapy options. Entry into a clinical trial is preferred. Surgical options include complete regional lymph node dissection with postoperative radiation therapy (or definitive radiation therapy in patients who are not surgical candidates).[7] [19]

- The ESMO guideline also recommends consideration of entry into a clinical trial of adjuvant or neoadjuvant immunotherapy, if available, on the basis that neither adjuvant radiation therapy nor adjuvant chemotherapy has been found to have any statistically significant impact on overall survival.[19]

Stage III: in-transit disease

For management of in-transit disease (pN2/3), various factors will determine the most appropriate approach, including a decision on whether the disease is resectable. There is a lack of evidence to direct care in this scenario. The NCCN recommends multidisciplinary consultation for consideration of:[3]

- Clinical trial enrollment, if available
- Surgery and/or radiation therapy
- Case-by-case consideration of systemic therapy, according to clinical judgment, if neither curative surgery nor radiation therapy is feasible. In practice, this scenario would generally be managed in the same way as stage IV disease.

The European guideline from ESMO recommends surgery and/or radiation therapy or entry into a clinical trial for patients with in-transit disease, but recommends against adjuvant chemotherapy.[19]

Unknown primary MCC

Patients with MCC with unknown primary site present with a clinically identified, pathologically confirmed MCC metastasis to a lymph node without a primary MCC tumor.

- In AJCC8, these patients were downstaged to IIIA (T0pN1bM0) as their prognosis aligns with the prognosis for patients with occult lymph node metastasis.[10][35] [45] [46] [47][70]
- Multidisciplinary consultation will guide the preferred treatment approach in these patients, with modalities including node dissection with or without radiation therapy.[3] [7]

Distant metastatic disease

Note that local protocols for metastatic MCC vary between countries and institutions, and the management plan for each individual is agreed on a case-by-case basis following discussion among the multidisciplinary team.

For disseminated metastatic MCC (AJCC8 stage IV), multidisciplinary consultation is recommended together with comprehensive imaging.[3] [7] [29]

The recommended approach to these patients (according to both US and European guidelines) is one of the following:[3][7] [19] [29]

- Enrollment in a clinical trial, if available (preferred) *or*
- Any one of, or a combination of, the following therapies:
    - Systemic immunotherapy with a PD-1/programmed death-ligand 1 (PD-L1) inhibitor (preferred agents include avelumab, pembrolizumab, nivolumab, and retifanlimab).[3] [29]
    - For patients who have contraindications to immune checkpoint inhibitors, systemic chemotherapy with cisplatin or carboplatin with or without etoposide, topotecan monotherapy, or cyclophosphamide plus doxorubicin (or epirubicin) plus vincristine (CAV) can be considered.[3]
    - Radiation therapy.
    - Surgery.

- Note that systemic therapy and radiation therapy are the primary options in most patients, with surgery reserved for selective circumstances (e.g., for resection of oligometastases or symptomatic lesions).[3]

- Best supportive care
  - Depending on the extent of the disease and other individual patient circumstances, palliative care alone may be the most appropriate option for some patients, which may include radiation or systemic therapy.

Monitoring

Follow-up should aim to:[7]

- Detect recurrence early
- Detect second primary cancers at an early stage
- Manage adverse effects of local or systemic treatment.

MCC will recur in up to half of patients.[3] Recurrence risk is highest within the first year, with most recurrences occurring within 3 years.[79] [80] If baseline AMERK testing for antibodies to Merkel cell polyomavirus (MCPyV) was available and showed the patient was seropositive, antibody titers can be monitored to help detect disease recurrence.[3][53] [54] For more detail, see Diagnosis approach .

The NCCN recommends that follow-up visits should include:[3]

- Physical exam including complete skin and complete lymph node exam every 3-6 months for 3 years and every 6-12 months thereafter. The precise frequency can be individualized according to risk of recurrence and stage of disease.
- Imaging and other studies as clinically indicated, with routine imaging surveillance considered for those at high risk (e.g., immunosuppression, advancing age, stage II–IV disease, men, non-sentinel lymph node metastases, Merkel cell polyomavirus [MCPyV]-negative status).

The ESMO guideline recommends:[19]

- Follow-up exams for all radically treated patients every 3-6 months for the first 3 years, and then every 6 months up to year 5; thereafter a lifelong annual general physical exam, including a complete skin check-up.
- Routine cross-sectional imaging may be appropriate in higher-risk patients.

Patients with MCC should be advised to perform self-examination of skin and lymph nodes every month.[29]

- ESMO recommends patient education for self-examination of the whole skin because patients with a history of MCC have a higher risk of developing another skin cancer.[19]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)			
localized disease: stage I or II (T-any cN0 M0)			
■	**surgically resectable**	**1st**	**surgical wide local excision ± radiation therapy to tumor bed**
		plus	**sentinel lymph node biopsy (SLNB)**
		adjunct	**reduction of any immunosuppressive treatment for another condition**
■	**curative surgery/curative radiation therapy not initially feasible and surgical candidate**	**1st**	**multidisciplinary team consideration of neoadjuvant immunotherapy plus surgery and sentinel lymph node biopsy (SLNB)**
		adjunct	**reduction of any immunosuppressive treatment for another condition**
■	**curative surgery/curative radiation therapy not feasible and nonsurgical candidate**	**1st**	**radiation therapy**
		adjunct	**reduction of any immunosuppressive treatment for another condition**
regional disease: stage IIIA			
		1st	**radiation therapy to nodal basin and/or lymph node dissection**
		adjunct	**reduction of any immunosuppressive treatment for another condition**
regional disease: unknown primary tumor with clinically apparent nodal disease			
		1st	**lymph node dissection ± radiation therapy**
		adjunct	**reduction of any immunosuppressive treatment for another condition**
regional disease: stage IIIB			
■	**with lymph node metastasis but no in-transit disease (pN1b)**	**1st**	**lymph node dissection and radiation therapy to nodal basin ± neoadjuvant immunotherapy**

Acute (summary)		
	plus	surgical wide local excision of primary tumor ± radiation therapy to primary tumor
	adjunct	reduction of any immunosuppressive treatment for another condition
with in-transit disease with or without lymph node metastasis (pN2/ pN3)	1st	enrollment in clinical trial, surgery and/or radiation therapy, or systemic therapy
	adjunct	reduction of any immunosuppressive treatment for another condition
distant metastatic disease: stage IV		
	1st	enrollment in clinical trial; immunotherapy or chemotherapy and/or radiation therapy and/or surgery
	adjunct	reduction of any immunosuppressive treatment for another condition

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

localized disease: stage I or II (T-any cN0 M0)

surgically resectable — **1st** — **surgical wide local excision ± radiation therapy to tumor bed**

» A multidisciplinary approach involving specialists with expertise in management of rare skin cancers is recommended for management of MCC, regardless of stage.[3] [7] [19]

» In patients who present with localized disease (AJCC8 clinical stage I or II: i.e., T-any cN0 M0) that is surgically resectable, the recommendation is for concomitant management of the primary tumor and staging of the lymph node basin with sentinel lymph node biopsy.[3] [19][40] [44]

- Adjuvant systemic therapy is not recommended outside of a clinical trial for this patient group.[3]

»

Surgical wide local excision of the primary tumor ± radiation therapy

» First-line treatment for the primary MCC tumor is surgical wide local excision to remove the lesion with histologically clear margins. Multidisciplinary consultation and local guidelines should steer the approach regarding surgical margins.

» The National Comprehensive Cancer Network (NCCN) recommends a 1-2 cm margin while noting that surgical margins should be balanced with the morbidity associated with surgery.[3]

- For clear margins in a patient with no adverse risk factors, observation can be considered.
- For microscopically positive margins, adjuvant radiation therapy is preferred over re-excision +/- adjuvant radiation.
- For narrow clinical margin (<1 cm) and/or the presence of additional risk factors, excision should be followed by adjuvant

Acute

radiation therapy. Relevant risk factors include: tumor size (primary tumor >1 cm); immunosuppressed state (chronic T-cell immunosuppression, HIV, chronic lymphocytic leukemia (CLL), solid organ transplant); tumor location (head/neck primary site); presence of lymphovascular invasion (LVI).

- If adjuvant radiation therapy is indicated, this should be initiated as soon as wound healing permits.[3] A delay > 8 weeks in starting radiation therapy has been associated with worse outcomes.[78]

» European guidelines recommend a 1-2 cm margin. If this is difficult or not feasible (e.g., in cosmetically sensitive locations such as the face or in proximity to joints), a narrower margin of 0.5 to 1.0 cm with adjuvant radiation therapy may be acceptable.[7] [19]

- Adjuvant radiation therapy to the tumor bed is recommended for tumors ≥1 cm and/or with negative prognostic features.

» In selected patients (e.g., for sensitive areas such as the head and neck), a tissue-sparing approach such as Mohs or another form of peripheral and deep en face margin assessment (PDEMA) may be appropriate in place of wide local excision.[3] [7] [19]

»

Ongoing monitoring

» After initial treatment, the patient should be monitored for disease recurrence with clinical surveillance and imaging studies as indicated.[3] [7] [29] If there are clear margins and no risk factors present, observation may be appropriate with regular follow-up to monitor for recurrence.[3]

plus **sentinel lymph node biopsy (SLNB)**

Treatment recommended for ALL patients in selected patient group

» It is imperative to identify occult lymph node metastases in patients with early-stage localized disease. SLNB is an important staging tool, and every effort must be made to coordinate surgical management so that it can be performed before, or at the same time as, excision of the primary tumor.[3] [19]

- SLNB has been demonstrated to detect occult spread to the lymph node basin

Acute

in up to one third of patients who have no clinical evidence of node disease and would therefore have otherwise been staged as node-negative.[52]

- Patients found to have occult lymph node disease on SLNB are upstaged to stage IIIA.

adjunct **reduction of any immunosuppressive treatment for another condition**

Treatment recommended for SOME patients in selected patient group

» For patients who are immunocompromised, it is important to reduce any immunosuppressive treatments as clinically feasible, in consultation with the relevant managing physician.[3] [7] More frequent follow-up may be indicated for patients who are immunosuppressed.[3]

- Immunosuppression in MCC is associated with an increased risk of recurrence and poorer outcomes.[18] [27] [76] [77]

curative surgery/curative radiation therapy not initially feasible and surgical candidate

1st **multidisciplinary team consideration of neoadjuvant immunotherapy plus surgery and sentinel lymph node biopsy (SLNB)**

Primary options

» nivolumab

» A multidisciplinary approach involving specialists with expertise in management of rare skin cancers is recommended for management of MCC, regardless of stage.[3] [7] [19]

» For patients with locally advanced MCC in whom curative surgery and curative radiation therapy are not feasible due to tumor characteristics or comorbidities, multidisciplinary consultation should inform management.[3] [7] [29]

- In patients who are candidates for surgery, neoadjuvant nivolumab may be considered prior to excision and SLNB.[3] [19]
- If progression on nivolumab means surgery is not feasible, radiation therapy may be considered.[3]

» See local specialist protocol for dosing guidelines.

adjunct **reduction of any immunosuppressive treatment for another condition**

Treatment recommended for SOME patients in selected patient group

Acute

» For patients who are immunocompromised, it is important to reduce any immunosuppressive treatments as clinically feasible, in consultation with the relevant managing physician.[3] [7] More frequent follow-up may be indicated for patients who are immunosuppressed.[3]

- Immunosuppression in MCC is associated with an increased risk of recurrence and poorer outcomes.[18] [27] [76] [77]

curative surgery/curative radiation therapy not feasible and nonsurgical candidate

1st **radiation therapy**

» A multidisciplinary approach involving specialists with expertise in management of rare skin cancers is recommended for management of MCC, regardless of stage.[3] [7] [19]

» For patients with locally advanced MCC in whom curative surgery and curative radiation therapy are not feasible and who are nonsurgical candidates (due to tumor characteristics and/or comorbidities), multidisciplinary consultation should inform management.[3] [7] [29]

- The tumor may be treated with radiation therapy.[3] [19] [29]

adjunct **reduction of any immunosuppressive treatment for another condition**

Treatment recommended for SOME patients in selected patient group

» For patients who are immunocompromised, it is important to reduce any immunosuppressive treatments as clinically feasible, in consultation with the relevant managing physician.[3] [7] More frequent follow-up may be indicated for patients who are immunosuppressed.[3]

- Immunosuppression in MCC is associated with an increased risk of recurrence and poorer outcomes.[18] [27] [76] [77]

regional disease: stage IIIA

1st **radiation therapy to nodal basin and/or lymph node dissection**

» A multidisciplinary approach involving specialists with expertise in management of rare skin cancers is recommended for management of MCC, regardless of stage.[3] [7]

» For patients with sentinel lymph node biopsy (SLNB)-positive stage IIIA disease (i.e., with identified occult lymph node metastasis), treatment of the nodal basin is recommended along with baseline imaging studies to screen for distant metastases if not already performed.

Acute

Multidisciplinary consultation should be sought.[3] [7]

- Note that because regional disease will only have been detected by SLNB, the primary tumor will already have been resected, together with consideration of adjuvant radiation therapy to the primary site. See the *Localized disease* patient group for details.

» For treatment of the nodal basin, the National Comprehensive Cancer Network (NCCN) recommends:[3]

- Radiation therapy to the nodal basin *or*
- Lymph node dissection, which can be combined with adjuvant radiation therapy when indicated (e.g., for multiple involved nodes and/or in the presence of extranodal extension [ENE]).

» European guidelines recommend:[19]

- Multidisciplinary team discussion to consider adjuvant radiation therapy alone *or* complete lymph node dissection with adjuvant radiation therapy.[7]
- Consideration of entry into a clinical trial for neoadjuvant or adjuvant systemic therapy is also recommended, if available.

adjunct **reduction of any immunosuppressive treatment for another condition**

Treatment recommended for SOME patients in selected patient group

» For patients who are immunocompromised, it is important to reduce any immunosuppressive treatments as clinically feasible, in consultation with the relevant managing physician.[3] [7] More frequent follow-up may be indicated for patients who are immunosuppressed.[3]

- Immunosuppression in MCC is associated with an increased risk of recurrence and poorer outcomes.[18] [27] [76] [77]

regional disease: unknown primary tumor with clinically apparent nodal disease

1st **lymph node dissection ± radiation therapy**

» A multidisciplinary approach involving specialists with expertise in management of rare skin cancers is recommended for management of MCC, regardless of stage.[3] [7]

Acute

» Patients with MCC with unknown primary site present with a clinically identified, pathologically confirmed MCC metastasis to a lymph node without a primary MCC tumor.

- In the 8th edition of the American Joint Committee on Cancer (AJCC8) staging system, these patients were downstaged to IIIA (T0pN1bM0) as their prognosis aligns with the prognosis for patients with occult lymph node metastasis.[10][35][45][46][47] [70]

» Multidisciplinary consultation will guide the preferred treatment approach in these patients, with nodal lesions managed similarly to those in patients with stage IIIB MCC.[19] See the *Regional disease: stage IIIB, with lymph node metastasis but no in-transit disease* patient group.

adjunct **reduction of any immunosuppressive treatment for another condition**

Treatment recommended for SOME patients in selected patient group

» For patients who are immunocompromised, it is important to reduce any immunosuppressive treatments as clinically feasible, in consultation with the relevant managing physician.[3] [7] More frequent follow-up may be indicated for patients who are immunosuppressed.[3]

- Immunosuppression in MCC is associated with an increased risk of recurrence and poorer outcomes.[18] [27] [76] [77]

regional disease: stage IIIB

with lymph node metastasis but no in-transit disease (pN1b)

1st **lymph node dissection and radiation therapy to nodal basin ± neoadjuvant immunotherapy**

Primary options

» nivolumab

» Multidisciplinary consultation is recommended for any individual with stage IIIB disease.[3] [7]

» Stage pN1b patients have metastases to the draining lymph node basin (clinically/radiologically detected and pathologically confirmed), without in-transit disease.

» For management of the metastatic draining nodal basin in patients with stage IIIB MCC, the National Comprehensive Cancer Network (NCCN) recommends:[3]

Acute

- Lymph node dissection with postoperative radiation therapy (preferred, although either dissection or radiation therapy alone may also be used)
- Clinical trial enrollment, if available
- Consideration of neoadjuvant systemic immunotherapy prior to surgery, based upon multidisciplinary recommendations (e.g., nivolumab).

» The European guidelines recommend a multidisciplinary team discussion to determine the best therapy options. Entry into a clinical trial is preferred. Surgical options include complete regional lymph node dissection with postoperative radiation therapy (or definitive radiation therapy in patients who are not surgical candidates).[7] [19]

- The European Society for Medical Oncology (ESMO) guideline also recommends consideration of entry into a clinical trial of adjuvant or neoadjuvant immunotherapy, if available, on the basis that neither adjuvant radiation therapy nor adjuvant chemotherapy has been found to have any statistically significant impact on overall survival.[19]

» See local specialist protocol for dosing guidelines.

plus **surgical wide local excision of primary tumor ± radiation therapy to primary tumor**

Treatment recommended for ALL patients in selected patient group

» In patients with stage IIIB MCC, the primary tumor is managed in the same way as for localized disease, with surgical wide local excision to remove the lesion with histologically clear margins and consideration of adjuvant radiation therapy. For details, see the *Localized disease* patient group.

adjunct **reduction of any immunosuppressive treatment for another condition**

Treatment recommended for SOME patients in selected patient group

» For patients who are immunocompromised, it is important to reduce any immunosuppressive treatments as clinically feasible, in consultation with the relevant managing physician.[3] [7] More frequent follow-up may be indicated for patients who are immunosuppressed.[3]

Acute

- Immunosuppression in MCC is associated with an increased risk of recurrence and poorer outcomes.[18] [27] [76] [77]

with in-transit disease with or without lymph node metastasis (pN2/pN3) **1st** **enrollment in clinical trial, surgery and/or radiation therapy, or systemic therapy**

» Multidisciplinary consultation is recommended for any individual with stage IIIB disease.[3] [7]

- Stage pN2 patients have in-transit metastasis without lymph node disease.
- Stage pN3 patients have both lymph node metastasis (clinically/radiologically detected and pathologically confirmed) and in-transit disease.

» Various factors will determine the most appropriate approach to management of in-transit disease, including a decision on whether the disease is resectable. There is a lack of evidence to direct care in this scenario.

» The National Comprehensive Cancer Network (NCCN) recommends multidisciplinary consultation for consideration of:[3]

- Clinical trial enrollment, if available. Depending on the trial protocol, some standard management steps for MCC might also be required.
- Surgery and/or radiation therapy.
- Case-by-case consideration of systemic therapy, according to clinical judgment, if neither curative surgery nor radiation therapy is feasible. In practice, this scenario would generally be managed in the same way as stage IV disease.

» The European Society for Medical Oncology (ESMO) guideline recommends surgery and/or radiation therapy or entry into a clinical trial for patients with in-transit disease but recommends against adjuvant chemotherapy.[19]

» If surgery and/or radiation therapy rather than systemic therapy is used, the primary tumor and any lymph node disease must also be managed.

- The primary tumor is managed in the same way as for stage I/II MCC. For details, see the *Localized disease* patient group.
- Nodal disease is managed as for pN1b disease. For details, see the *With lymph*

Acute

node metastases but no in-transit disease (pN1b) patient group.

adjunct **reduction of any immunosuppressive treatment for another condition**

Treatment recommended for SOME patients in selected patient group

» For patients who are immunocompromised, it is important to reduce any immunosuppressive treatments as clinically feasible, in consultation with the relevant managing physician.[3] [7] More frequent follow-up may be indicated for patients who are immunosuppressed.[3]

- Immunosuppression in MCC is associated with an increased risk of recurrence and poorer outcomes.[18] [27] [76] [77]

distant metastatic disease: stage IV

1st **enrollment in clinical trial; immunotherapy or chemotherapy and/or radiation therapy and/or surgery**

Primary options

» avelumab

OR

» pembrolizumab

OR

» nivolumab

OR

» retifanlimab

Secondary options

» cisplatin

OR

» carboplatin

OR

» cisplatin
-or-
» carboplatin
--AND--
» etoposide

Acute

OR

» topotecan

OR

» cyclophosphamide

--AND--

» doxorubicin

-or-

» epirubicin

--AND--

» vincristine

» Local protocols for metastatic MCC vary between countries and institutions, and the management plan for each individual is agreed on a case-by-case basis following discussion among the multidisciplinary team.

» For disseminated metastatic MCC (AJCC8 stage IV), multidisciplinary consultation is recommended together with comprehensive imaging.[3] [7] [29]

» The recommended approach to these patients (according to both US and European guidelines) is one of the following:[3] [7][19] [29]

- Enrollment in a clinical trial, if available (preferred) *or*
- Any one of, or a combination of, the following therapies:
    - Systemic immunotherapy with a programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitor (preferred agents include avelumab, pembrolizumab, nivolumab, and retifanlimab).[3] [29]
    - For patients who have contraindications to immune checkpoint inhibitors, systemic chemotherapy with cisplatin or carboplatin with or without etoposide, topotecan monotherapy, or cyclophosphamide plus doxorubicin (or epirubicin) plus vincristine (CAV) can be considered.[3]
    - Radiation therapy.
    - Surgery.
- Note that systemic therapy and radiation therapy are the primary options in most patients, with surgery reserved for

Acute

selective circumstances (e.g., for resection of oligometastases or symptomatic lesions).[3]

» Depending on the extent of the disease and other individual patient circumstances, palliative care alone may be the most appropriate option for some patients disseminated metastatic MCC. This may include radiation therapy or systemic therapy.

» See local specialist protocol for dosing guidelines.

adjunct **reduction of any immunosuppressive treatment for another condition**

Treatment recommended for SOME patients in selected patient group

» For patients who are immunocompromised, it is important to reduce any immunosuppressive treatments as clinically feasible, in consultation with the relevant managing physician.[3] [7] More frequent follow-up may be indicated for patients who are immunosuppressed.[3]

- Immunosuppression in MCC is associated with an increased risk of recurrence and poorer outcomes.[18] [27] [76] [77]

FOLLOW UP

Prognosis

MCC is an aggressive cutaneous tumor with a risk of locoregional and distant metastases. Prognosis depends on several factors, including increasing primary tumor size and advancing stage of disease.

Reported 5-year overall survival rates vary widely, ranging from:[1] [7] [10] [19][31] [32][33] [34] [35] [36] [37] [38] [81] [82] [83][84][85][86]

- 51% to 73% for local disease
- 35% to 63% for nodal disease
- 14% to 29% for distant disease.

MCC-specific survival is higher than overall survival. Based upon a Seattle-based data repository between 2003 and 2019, 5-year MCC-specific survival rates were 95% for stage I, 80% for stage III, 78% for stage IIIA, 56% for stage IIIB, and 41% for stage IV.[79] One UK study found an overall 5-year net survival estimate for MCC diagnosed at any stage of 49.4% based on 2013 diagnosis (95% CI 40.2 to 58.7), with case numbers too small to provide net survival estimates according to stage.[87]

Other than stage at diagnosis, clinical factors associated with a poorer prognosis include older age, male sex, head/neck primary site, primary tumor size >2 cm, and the presence of immunosuppression.[7] [18] [19] [27] [77] One study found that Hispanic ethnicity was associated with improved survival compared with white patients and that black patients had similar MCC-specific survival to white patients despite presenting with more advanced disease.[41] The authors postulated that these findings could be attributable to a higher proportion of cases being Merkel cell polyomavirus (MCPyV)-positive in darker-skinned individuals.

Patients who present with unknown primary MCC (i.e., nodal or distant metastases without a primary lesion) have significantly better survival rates than those who have similar extent of disease but with a known primary lesion.[29][35] [46] [47] This group was downstaged in the AJCC8 MCC staging system to IIIA, as their prognosis aligns with the prognosis for patients presenting with a primary tumor and occult lymph node metastasis.[10]

Following treatment, patients are at risk of local, regional, and/or distant recurrence. There is a high risk of recurrence in the first year, and 95% of recurrences happen within the first 3 years of diagnosis.[79] Patients whose tumors are MCPyV-negative may have a higher risk of recurrence than those whose tumors test MCPyV-positive.[3] An estimate of recurrence risk based on initial stage, time to treatment, and other risk factors such as age, sex, immunosuppression, and location of primary tumor can be calculated at: [Merkelcell.org: recurrence risk calculator] (https://merkelcell.org/recur) [79] [80]

Diagnostic guidelines

International

NCCN clinical practice guidelines in oncology: Merkel cell carcinoma (https://www.nccn.org/guidelines/category_1) [3]

Published by: National Comprehensive Cancer Network **Last published:** 2024

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of nonmelanoma skin cancer (https://www.sitcancer.org/research/cancer-immunotherapy-guidelines/cpg) [29]

Published by: Society for Immunotherapy of Cancer **Last published:** 2022

A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal (https://www.nature.com/articles/s41379-018-0110-y) [71]

Published by: International Agency for Research on Cancer; World Health Organization **Last published:** 2018

Merkel-cell carcinoma: ESMO-EURACAN clinical practice guideline for diagnosis, treatment and follow-up (https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-endocrine-and-neuroendocrine-cancers) [19]

Published by: European Society for Medical Oncology and EURACAN European Reference Network for Rare Adult Solid Cancers **Last published:** 2024

Diagnosis and treatment of Merkel cell carcinoma: European consensus-based interdisciplinary guideline - update 2022 (https://www.ejcancer.com/article/S0959-8049(22)00253-2/fulltext) [7]

Published by: European Dermatology Forum; European Association of Dermato-Oncology; European Organization for Research and Treatment of Cancer **Last published:** 2023

S2k guideline - Merkel cell carcinoma (MCC, neuroendocrine carcinoma of the skin) - update 2022 (https://onlinelibrary.wiley.com/doi/10.1111/ddg.14930) [44]

Published by: Association of the Scientific Medical Societies in Germany (AWMF) **Last published:** 2023

Radiation therapy of cutaneous cancers (https://pubmed.ncbi.nlm.nih.gov/34955421) [72]

Published by: French Society of Oncological Radiotherapy (SFRO) **Last published:** 2022

International

Nationwide multidisciplinary consensus on the clinical management of Merkel cell carcinoma: a Delphi panel (https://jitc.bmj.com/content/10/6/e004742) [40]

Published by: DELPHI Panel members, Italy; Journal for Immunotherapy of Cancer **Last published:** 2022

Diagnosis and treatment of Merkel cell carcinoma in specialized dermatology units: a clinical practice guideline of the Spanish Academy of Dermatology and Venereology (https://pubmed.ncbi.nlm.nih.gov/30961887) [73]

Published by: Spanish Academy of Dermatology and Venereology **Last published:** 2019

Sunlight exposure: risks and benefits (https://www.nice.org.uk/guidance/ng34) [74]

Published by: National Institute for Health and Care Excellence (UK) **Last published:** 2016

Guidelines of the French Society of Otorhinolaryngology (SFORL), short version: extension assessment and principles of resection in cutaneous head and neck tumors (https://www.sciencedirect.com/science/article/pii/S1879729614001276) [75]

Published by: French Society of Otorhinolaryngology (SFORL) **Last published:** 2014

Treatment guidelines

International

NCCN clinical practice guidelines in oncology: Merkel cell carcinoma (https://www.nccn.org/guidelines/category_1) [3]

Published by: National Comprehensive Cancer Network **Last published:** 2024

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of nonmelanoma skin cancer (https://www.sitcancer.org/research/cancer-immunotherapy-guidelines/cpg) [29]

Published by: Society for Immunotherapy of Cancer **Last published:** 2022

A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal (https://www.nature.com/articles/s41379-018-0110-y) [71]

Published by: International Agency for Research on Cancer; World Health Organization **Last published:** 2018

Merkel-cell carcinoma: ESMO-EURACAN clinical practice guideline for diagnosis, treatment and follow-up (https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-endocrine-and-neuroendocrine-cancers) [19]

Published by: European Society for Medical Oncology and EURACAN European Reference Network for Rare Adult Solid Cancers **Last published:** 2024

Diagnosis and treatment of Merkel cell carcinoma: European consensus-based interdisciplinary guideline - update 2022 (https://www.ejcancer.com/article/S0959-8049(22)00253-2/fulltext) [7]

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S2k guideline - Merkel cell carcinoma (MCC, neuroendocrine carcinoma of the skin) - update 2022 (https://onlinelibrary.wiley.com/doi/10.1111/ddg.14930) [44]

Published by: Association of the Scientific Medical Societies in Germany (AWMF) **Last published:** 2023

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Published by: DELPHI Panel members, Italy; Journal for Immunotherapy of Cancer **Last published:** 2022

International

Radiation therapy of cutaneous cancers (https://pubmed.ncbi.nlm.nih.gov/34955421) [72]

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Published by: Spanish Academy of Dermatology and Venereology **Last published:** 2019

Sunlight exposure: risks and benefits (https://www.nice.org.uk/guidance/ng34) [74]

Published by: National Institute for Health and Care Excellence **Last published:** 2016

Guidelines of the French Society of Otorhinolaryngology (SFORL), short version: extension assessment and principles of resection in cutaneous head and neck tumors (https://www.sciencedirect.com/science/article/pii/S1879729614001276) [75]

Published by: French Society of Otorhinolaryngology (SFORL) **Last published:** 2014

Online resources

1. Merkelcell.org: recurrence risk calculator (https://merkelcell.org/recur) *(external link)*

Key articles

- National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Merkel cell carcinoma [internet publication]. Full text (https://www.nccn.org/guidelines/category_1)
- Gauci ML, Aristei C, Becker JC, et al; the European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO), and the European Organization for Research and Treatment of Cancer (EORTC). Diagnosis and treatment of Merkel cell carcinoma: European consensus-based interdisciplinary guideline - update 2022. Eur J Cancer. 2022 Aug:171:203-31. Full text (https://www.ejcancer.com/article/S0959-8049(22)00253-2/fulltext) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35732101?tool=bestpractice.bmj.com)
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Images

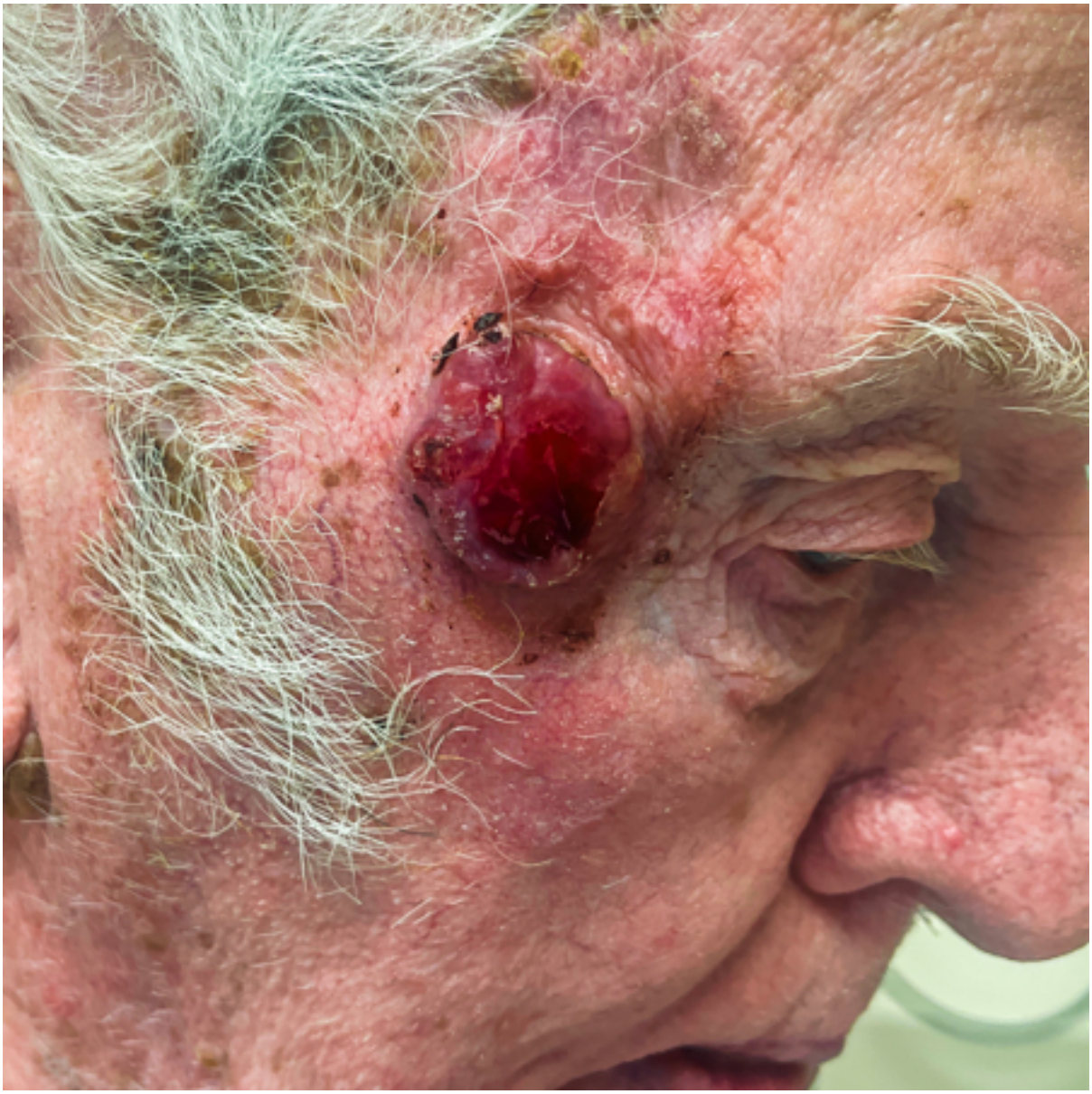

Figure 1: A primary MCC tumor in an 87-year-old man who presented with a large, fast-growing, red, eroded nodule on the right temple

From the collection of Dr Kelly Harms and Dr Alison Lee, University of Michigan; used with patient consent

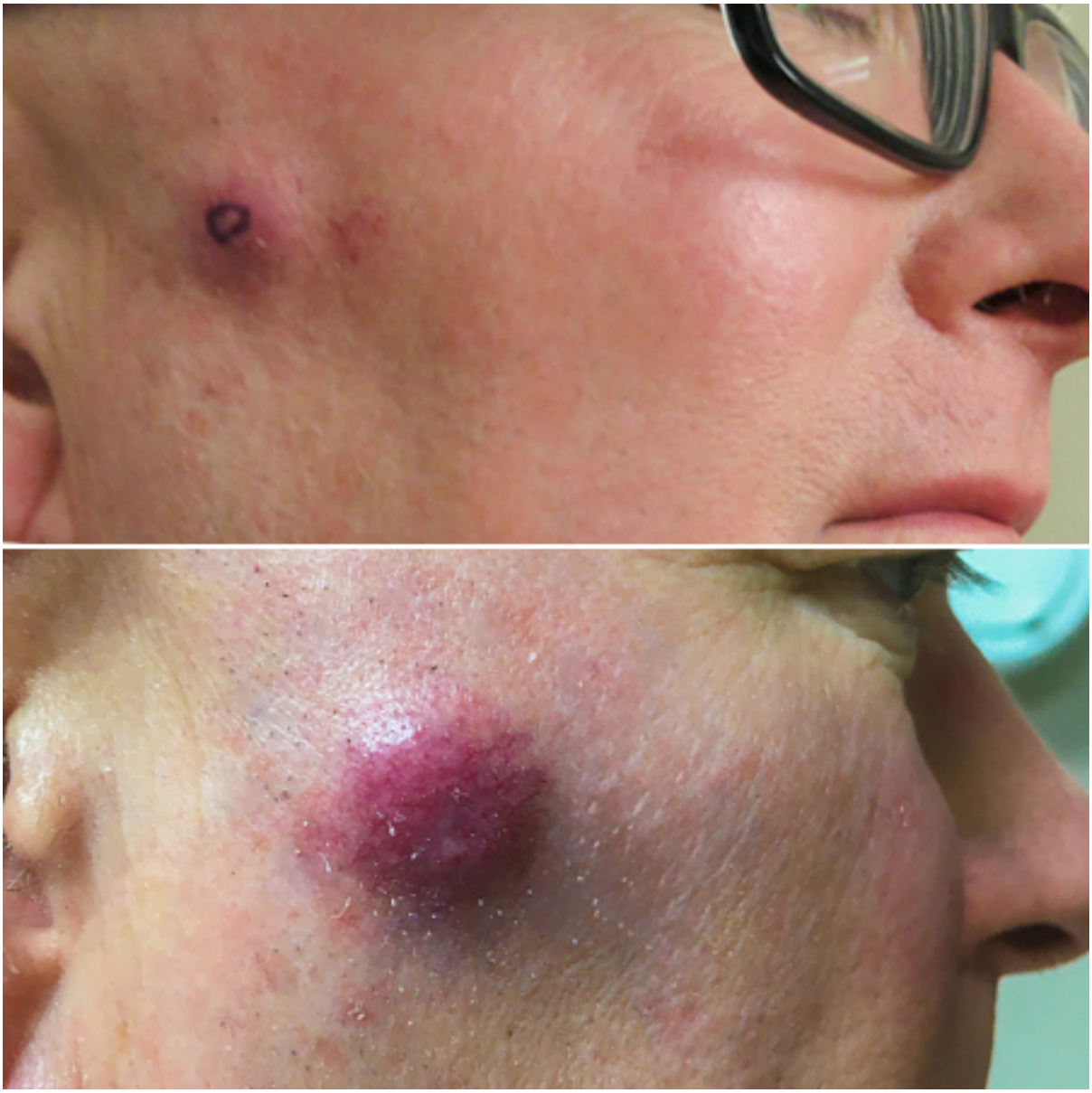

Figure 2: A rapidly-growing MCC on the right cheek of a 64-year-old man, which started as a small erythematous cyst-like papule then developed within a few months into a larger, violaceous nodule with associated pruritus

From the collection of Dr Kelly Harms and Dr Alison Lee, University of Michigan; used with patient consent

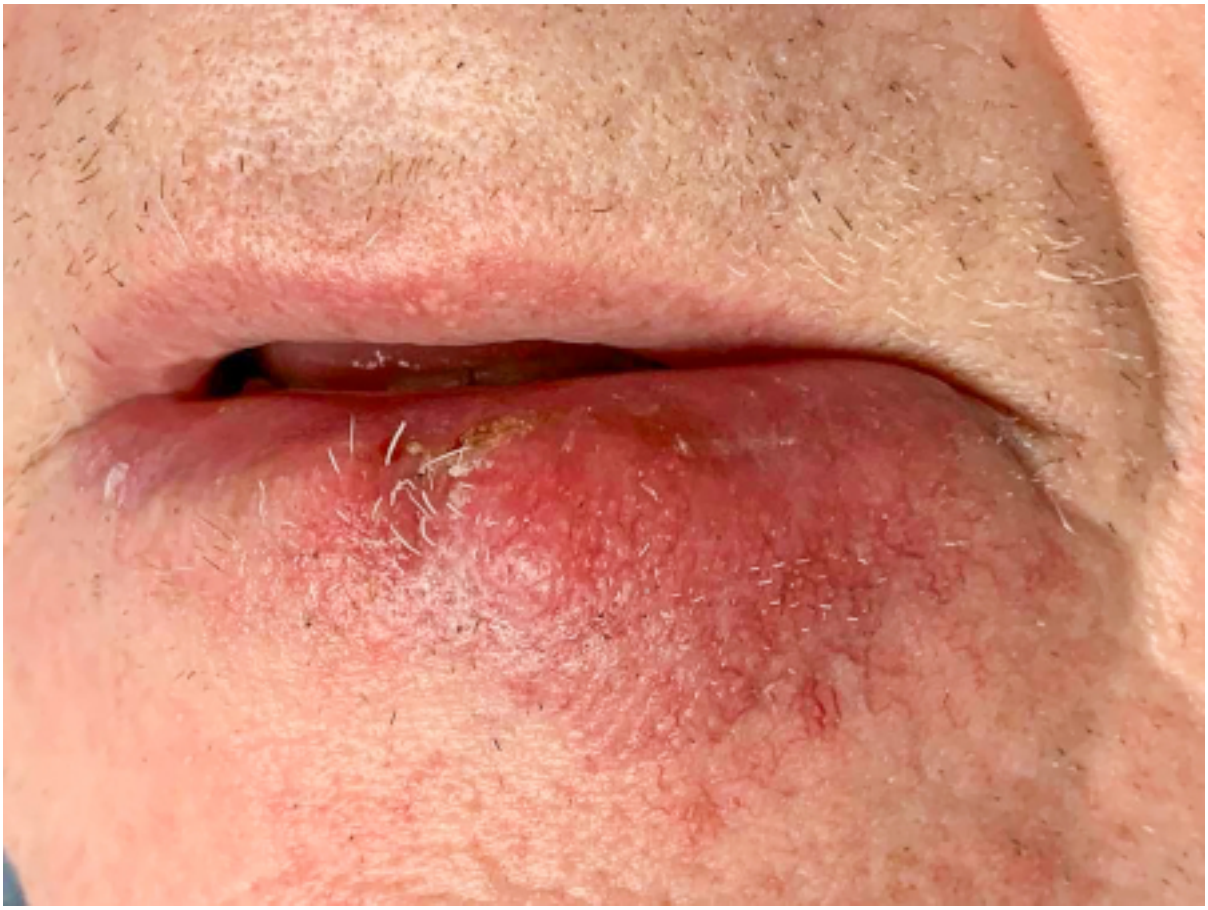

Figure 3: MCC on the left lower lip of a 68-year-old man. The asymptomatic tumor is an ill-defined reddish-pink, scaly plaque blurring the lower vermillion of the lip

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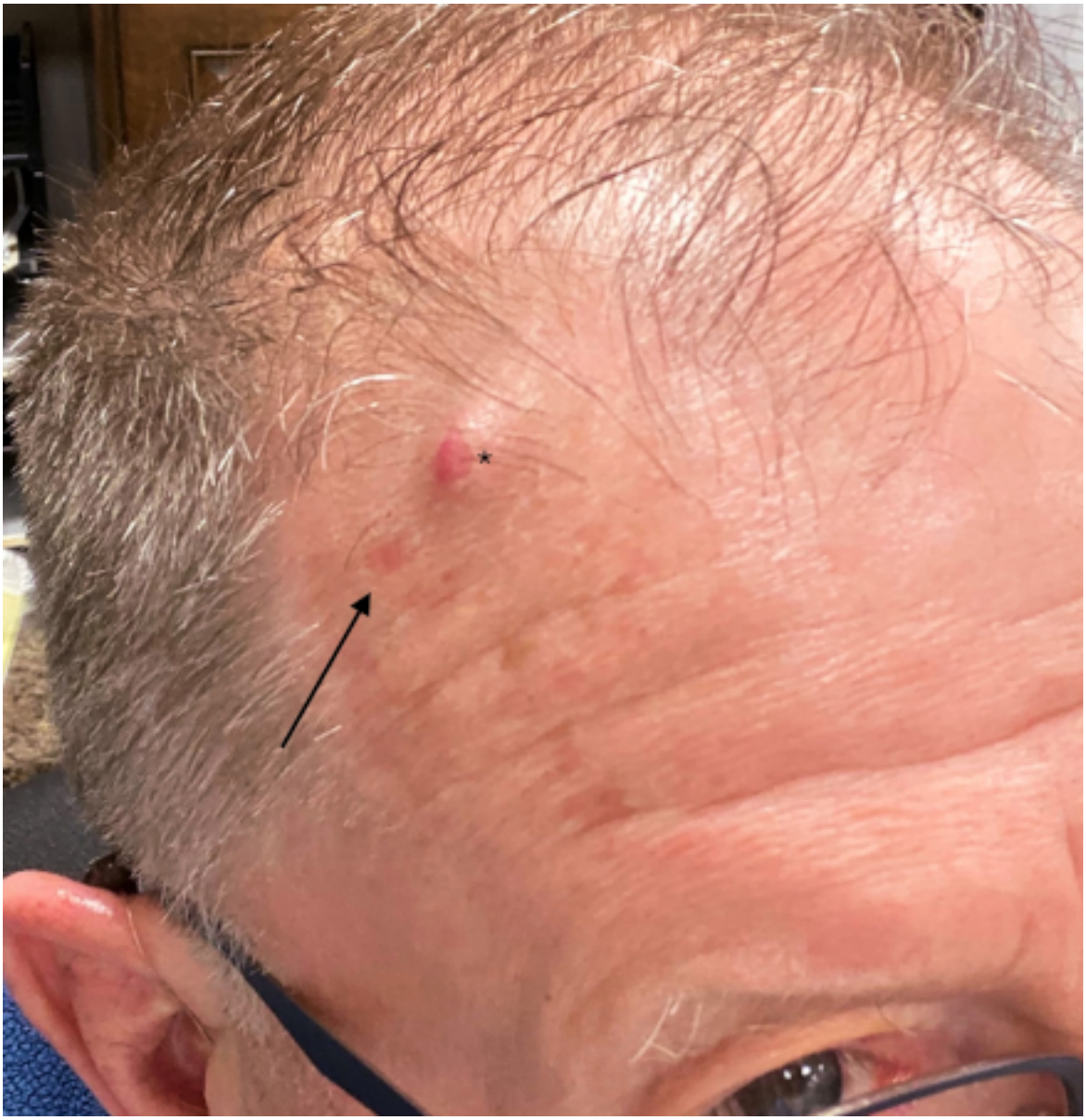

Figure 4: Primary MCC on the right frontal scalp (asterisk) of a 73-year-old man, with a biopsy scar of an in-transit metastasis (arrow). The primary tumor initially presented as an asymptomatic, fast-growing subcutaneous nodule that was misdiagnosed as an epidermoid cyst

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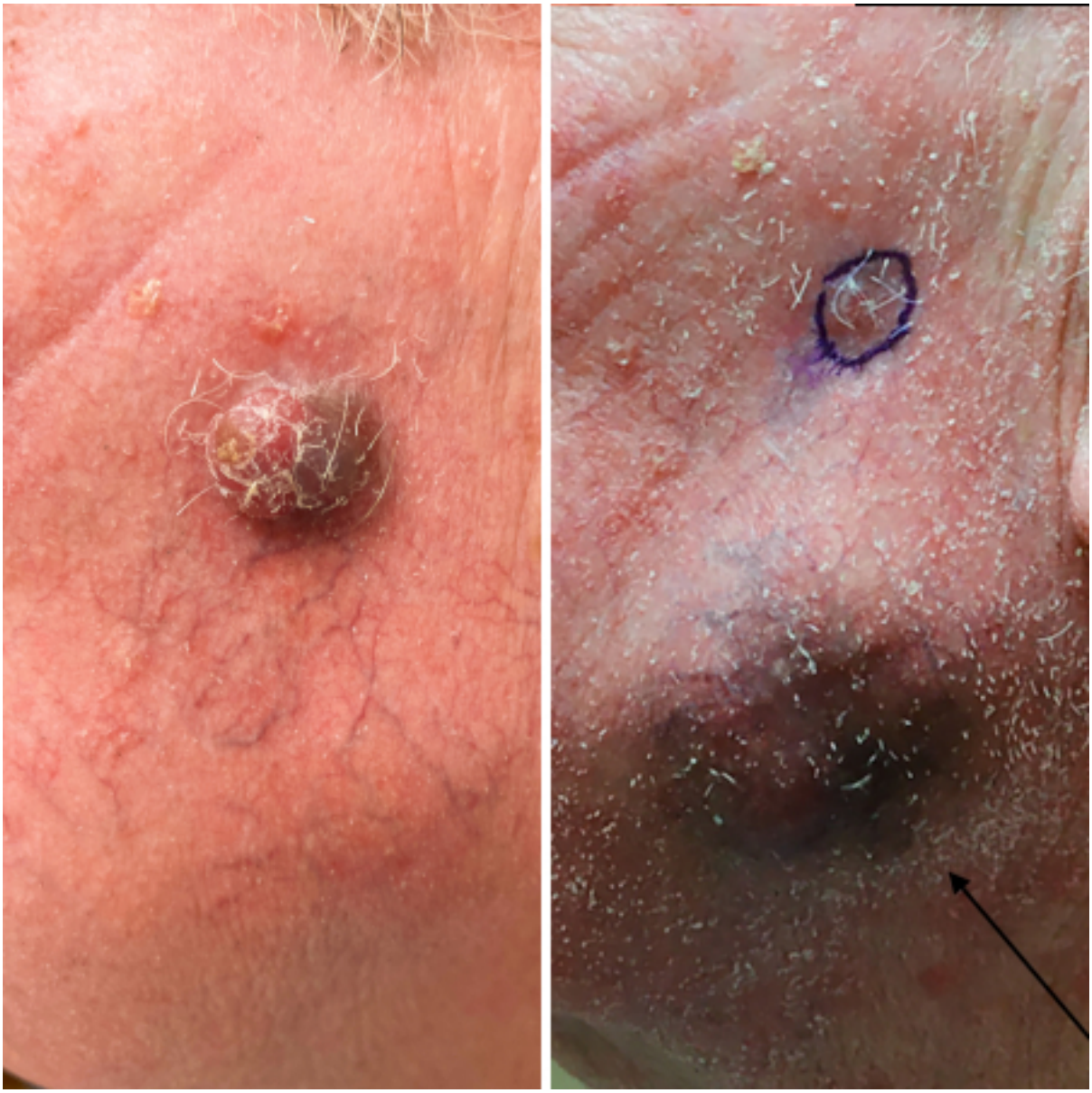

Figure 5: MCC presenting as a well-defined, rapidly growing, asymptomatic, brightly violaceous nodule on the left cheek of a 71-year-old man. The patient developed a golf-ball sized subcutaneous mass in the left parotid (original biopsy site marked with blue ink, subcutaneous metastasis marked with arrow). Fine needle aspiration of the mass in the left parotid gland confirmed MCC

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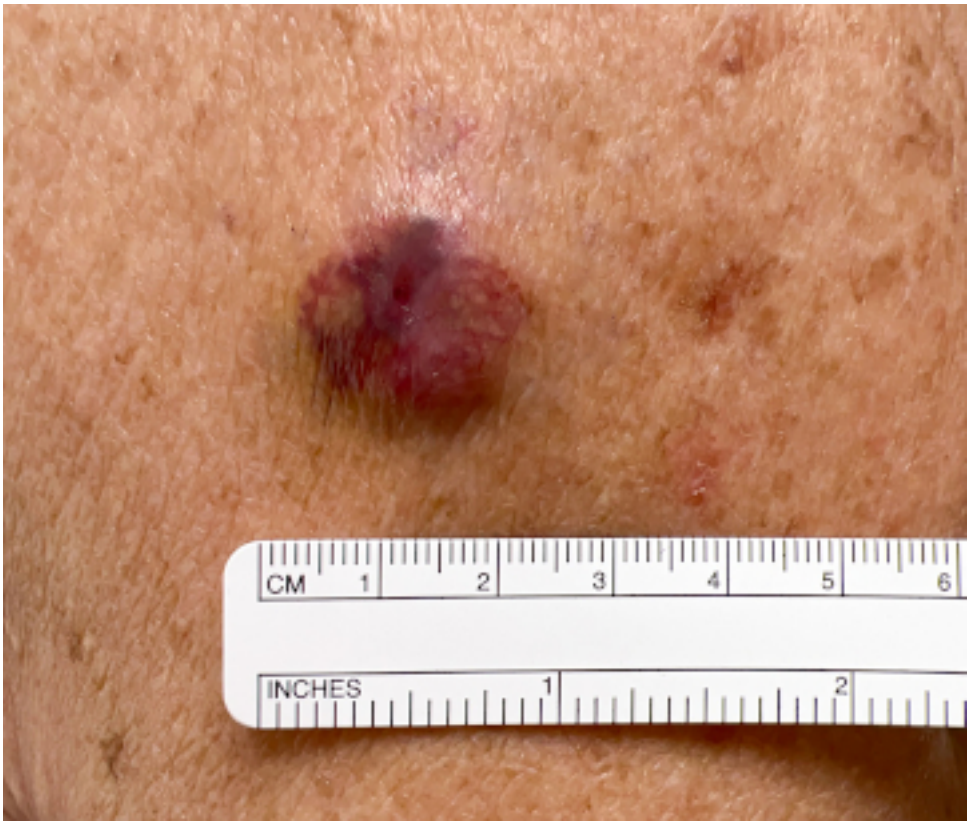

Figure 6: A 2 cm red, nodular MCC with varied vessel patterns on the right upper arm of an 80-year-old man

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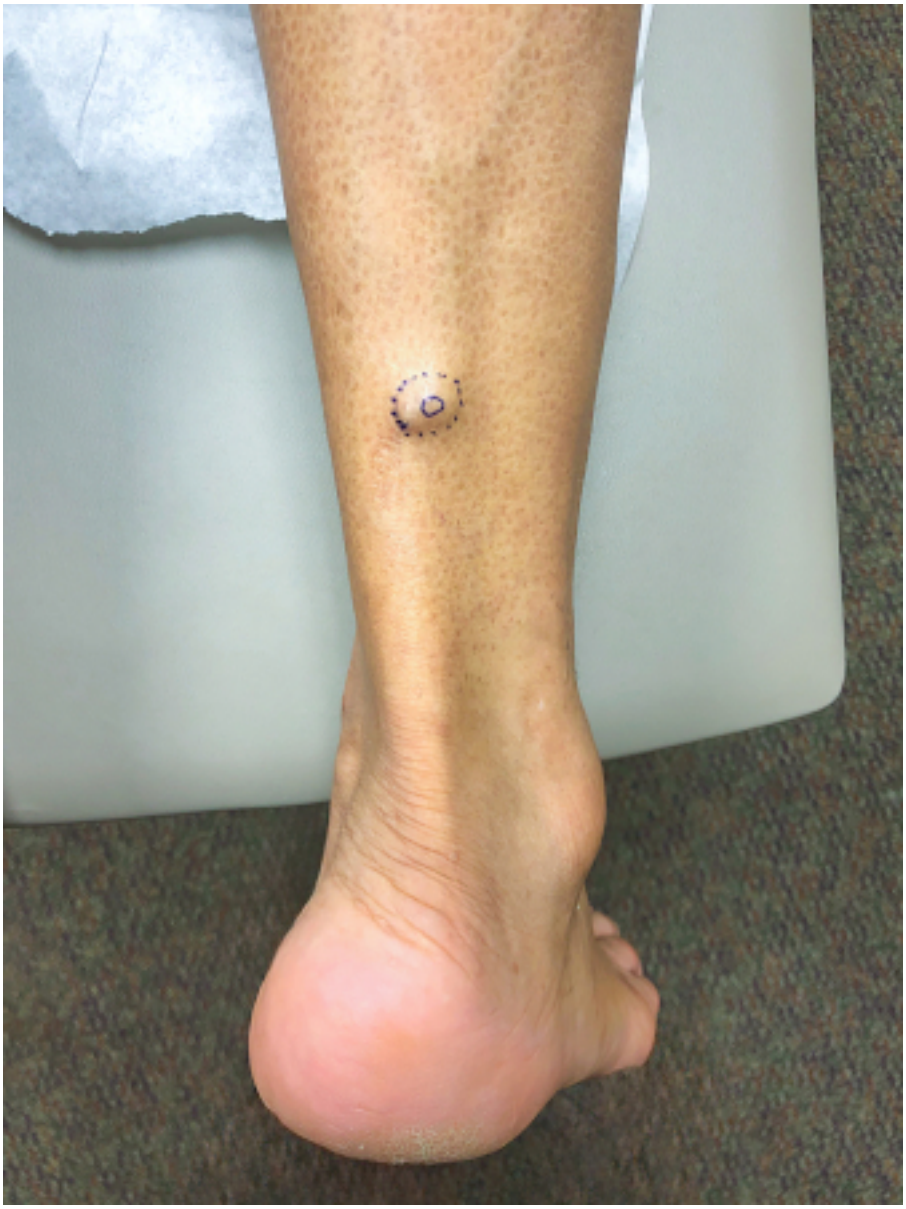

Figure 7: MCC on the right posterior ankle of a 66-year-old African-American man, which presented as a subtle 1.5 cm subcutaneous nodule without overlying epidermal changes. This can often be confused with benign entities such as an epidermal cyst or a lipoma

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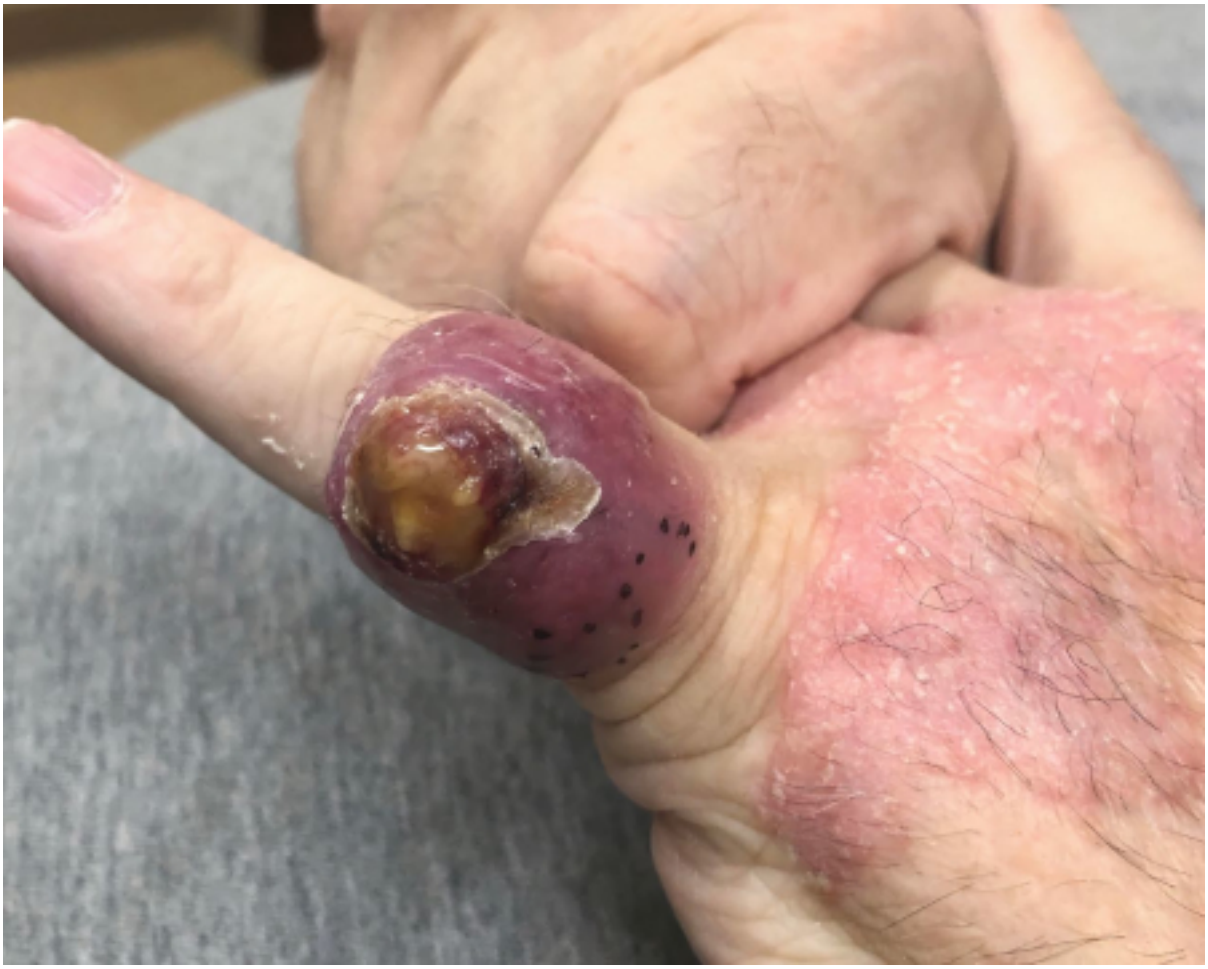

Figure 8: A 2x3 cm MCC lesion in a white man aged in his late 60s who had a history of taking immunosuppressive medication for psoriasis. The nodule was violaceous with central ulceration, tan crusting, and serous drainage. Note that ulceration is unusual in MCC

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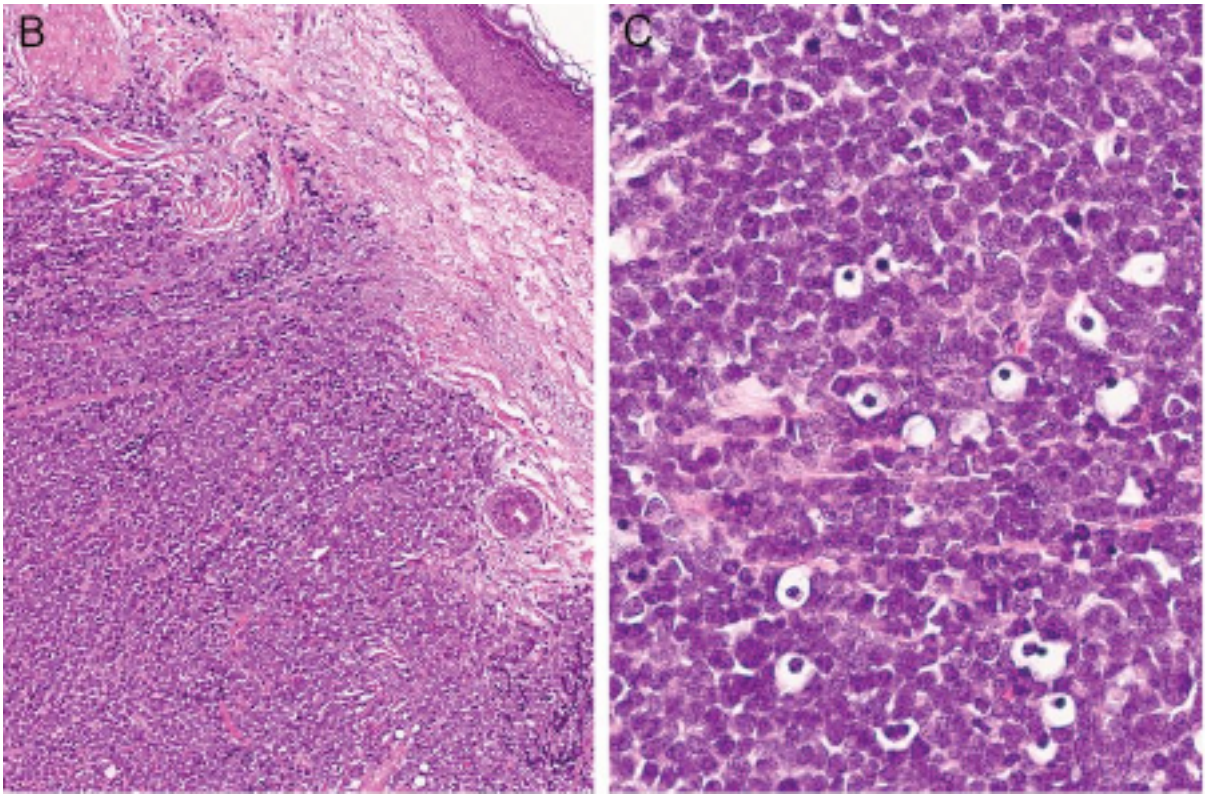

Figure 9: Histologic features of MCC from biopsy of a primary tumor. Image B shows small round blue cells and image C shows characteristic nuclei, finely granular and dusty "salt and pepper" chromatin, and abundant mitotic figures

Mauzo SH et al. J Clin Pathol 2016; 69: 382-90; used with permission

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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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