Merkel cell carcinoma

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Merkel cell carcinoma (MCC) is a rare yet highly aggressive tumour of the skin. While the dangers of other skin cancers like malignant melanoma are ingrained in most physicians' minds—with the changing or atypical nevus often inciting an urgent biopsy—MCC remains an unfamiliar and neglected disease. Yet, the annual incidence of MCC is rising more quickly than that of melanoma, at 8% annually, and one-third of patients die within 3 years of diagnosis.[1,2] Despite these sobering figures, a timely diagnosis followed by excision and radiotherapy can be curative in early disease. This article seeks to familiarize family physicians with both the characteristics and the management of MCC, so that they can quickly identify MCC patients and direct them to the appropriate specialists for care.

Case description

A 93-year-old white woman presented to the emergency department with an asymptomatic tumour on her left ear (**Figure 1**). She claimed that the lesion had appeared 2 months earlier and had been growing rapidly. The patient was otherwise healthy and not taking any medications. On physical examination, her skin showed moderate photodamage. A 5- by 4-cm erythematous, dome-shaped nodule was noted in her left conchal bowl. Findings from lymph node and abdominal palpation were normal. A 4-mm skin biopsy of the tumour was performed, and results confirmed a diagnosis of MCC. The patient refused further investigation but agreed to surgical debulking and radiotherapy of the left ear. She has since been lost to follow-up.

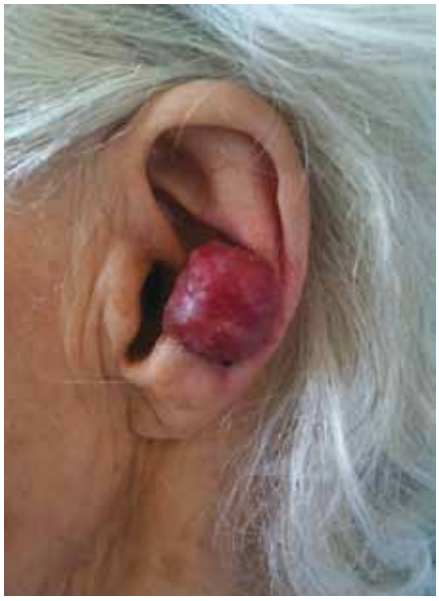

Figure 1. Asymptomatic tumour on left ear

Epidemiology

Merkel cells function as mechanoreceptors in the skin, hair follicles, and oral mucosa.[1-3] Ultrastructurally, they can be identified by characteristic cytoplasmic, electron-dense neurosecretory granules.[1] Merkel cell carcinoma is classified as a neuroendocrine carcinoma and is believed to be derived from Merkel cells because it also contains cytoplasmic, electron-dense neurosecretory granules.[3]

The annual incidence of MCC is approximately 3 per million in the United States.[1] Disease rarely occurs before the age of 50, after which the incidence rises sharply. In one large review, the median age of patients at diagnosis was 69 years.[4] However, MCC occurs more frequently and at a substantially younger age among immunosuppressed patients, with an incidence between 5 and 11 times greater in individuals

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EDITOR'S KEY POINTS

- Merkel cell carcinoma (MCC) is a rare but highly aggressive cutaneous neoplasm with a rising incidence among elderly patients. The 3-year mortality rate is greater than 30%, surpassing that of malignant melanoma.
- The most common clinical features of MCC have been summarized by the acronym *AEIOU:* asymptomatic, expanding rapidly, immunosuppression, older than 50 years, and UV-exposed location. Definitive diagnosis of MCC requires a skin biopsy.
- Guidelines for the management of MCC recommended excision of the primary tumour whenever possible, with adjuvant radiation therapy to the excised tumour bed and draining lymph node basin to minimize locoregional recurrence.

POINTS DE REPÈRE DU RÉDACTEUR

- Le carcinome à cellules de Merkel (CCM) est un néoplasme cutané rare mais très agressif dont l'incidence augmente chez les patients plus âgés. Le taux de mortalité après 3 ans dépasse 30 %, soit un niveau supérieur à celui du mélanome malin.
- Les caractéristiques cliniques les plus fréquentes du CCM sont résumées par l'acronyme AEIOU: asymptomatique, expansion rapide, immunosuppression, au-dessus (O) de 50 ans et emplacement exposé aux rayons UV. Le diagnostic définitif du CCM exige une biopsie de la peau.
- Les lignes directrices pour la prise en charge d'un CCM recommandent l'excision de la tumeur primaire dans la mesure du possible, une radiothérapie adjuvante du siège tumoral et le drainage du bassin des ganglions lymphatiques pour minimiser la récurrence locorégionale.

with organ transplants and AIDS, respectively.[1,2] Merkel cell carcinoma is more common in men and predominantly affects white individuals of European ancestry. Incidence is inversely related to latitude of residence, and exposure to ultraviolet radiation is an important risk factor for MCC, although it is thought to play an immunosuppressive rather than a mutagenic role.[1] Studies have found that patients with MCC are at increased risk of other skin cancers, as well as hematologic malignancies like chronic lymphocytic leukemia, non-Hodgkin lymphoma, and multiple myeloma.[1]

In 2008, researchers identified the genome of a novel polyomavirus that was subsequently named the *Merkel cell polyomavirus* (MCPyV).[5] While tumoral skin samples from patients with MCC show the highest frequency of positivity and the greatest levels of MCPyV DNA, the virus is also present in the skin of patients with other cutaneous disorders, as well as in healthy individuals.[3,6] Thus, MCPyV DNA detection is not a specific marker for MCC, and its presence is not sufficient for the disease to develop. The exact role of MCPyV in MCC oncogenesis is still under investigation and might include viral integration into the host genome followed by specific signature mutations that lead to overstimulation of the cell cycle.[6]

Diagnosis

Merkel cell carcinoma usually develops rapidly over weeks to months on chronically sun-damaged skin.[2,3] The most frequent site of involvement is the head and neck region, followed by the extremities, the trunk, and the oral and genital mucosa.[3] It typically presents as an asymptomatic pink, red, or bluish firm dome-shaped nodule. Acneform and plaquelike lesions, particularly on the trunk, have also been described. Tumours are usually smaller than 2 cm at the time of presentation and quickly increase in size. Ulceration is rare but can be observed in very advanced tumours, and satellite metastases might be present.[2,3] The most common clinical features of MCC have been summarized by the acronym *AEIOU:* asymptomatic, expanding rapidly, immunosuppression, older than 50, and UV-exposed location.[4]

Because of its nonspecific clinical features, definitive diagnosis of MCC requires a skin biopsy. Tumours are predominantly located in the reticular dermis and might spread to the subcutaneous fat, but they generally spare the epidermis, papillary dermis, and skin appendages.[3] They are classified into 3 histologic subtypes, although mixed or transitional variants are frequent. The intermediate subtype is the most common and consists of large nests of basophilic cells with characteristic round to oval nuclei, powdery chromatin, and inconspicuous nucleoli. The small cell subtype consists of nests of small round cells with scant cytoplasm, oval hyperchromatic nuclei, and prominent nucleoli. The trabecular subtype is the least common and consists of strands of round to polygonal cells with abundant cytoplasm, round centrally located vesicular nuclei, and inconspicuous nucleoli.[1,2] The histologic differential diagnosis includes metastatic small cell lung carcinoma, hematologic malignancies involving the skin such as B- and T-cell lymphomas, Ewing sarcoma, and malignant melanoma. A unique tumoral immunohistochemistry profile—including reactivity to keratin 20 and neuron-specific enolase as well as an absence of reactivity to thyroid transcription factor 1—permits definitive diagnosis of MCC.[1,2]

Staging and prognosis

Currently there is no standard protocol for the management of MCC. Reasonable investigations include a chest x-ray scan, as well as ultrasonography of the abdomen and regional lymph nodes with further imaging based on symptoms.[1] Sentinel lymph node biopsy (SLNB) is also required for staging and reveals metastatic disease in up to one-third of patients without palpable lymph nodes.[1,7,8] False-negative SLNB, however, is possible and particularly worrisome in the head and neck region because of variable drainage patterns that can lead to inadequate sampling. In fact, the draining lymph nodes remain the most common site of metastasis. Other sites include distant lymph nodes, the skin and subcutaneous tissue, the liver, the lungs, the bones, and the brain.[8]

The American Joint Committee on Cancer defines stage I and II MCC as consisting of a localized tumour smaller or larger than 2 cm, respectively. Stage IIIa and IIIb disease implies regional micrometastases or macrometastases, while stage IV disease implies distant metastases.[8] Most patients present with either stage I or II disease.[3] Patients with stage I disease have an 81% survival rate at 5 years compared with an 11% survival rate for those with stage IV disease.[3,8] Overall, one-third of patients will die from MCC within 3 years of diagnosis.[1-3] Thus, MCC has a mortality rate that exceeds that of malignant melanoma.[2]

Clinically, poor prognostic factors include advanced tumour stage; advanced age; male sex; primary tumour located on the head, neck, or trunk; and immunosuppression. Histologic poor prognostic factors include small cell subtype, angioinvasion, presence of mitotic figures, absence of an inflammatory reaction, overexpression of Ki-67 and p63, and CD44 positivity of tumour cells.[2,3]

Management

Multiple different guidelines exist for the management of MCC, although none are universally accepted and all are based on limited data. Surgery remains the cornerstone of therapy. The National Comprehensive Cancer Network 2010 guidelines for the management of MCC recommended excision of the primary tumour when-

ever possible.[7] Options include wide local excision extending to the fascia with 1- to 2-cm lateral margins, or Mohs micrographic surgery. Complete local lymph nodal dissection is recommended for SLNB-positive or palpable-nodal disease. Adjuvant radiation therapy to the excised tumour bed and draining lymph node basin regardless of SLNB results is suggested as a means of minimizing locoregional recurrence. Radiation alone is also listed as an acceptable alternative to surgery when excision is not feasible or is refused by the patient. Chemotherapy with or without surgery and radiation therapy is reserved for stage IV disease and is generally palliative. Regimens include cyclophosphamide in combination with doxorubicin and vincristine, as well as cisplatin or carboplatin with or without etoposide. Remission rates as high as 70% can be achieved, but disease often recurs within a few months and response does not lead to a substantial increase in survival time.[1]

Follow-up of MCC patients should include a complete skin and lymph node examination every 1 to 3 months for the first year, every 3 to 6 months for the second year, and every 6 to 12 months thereafter. The median time to recurrence in patients with MCC is about 8 months, and 90% of recurrences occur within 24 months following the initial diagnosis.[7] Suspicious skin lesions should be biopsied, and a chest x-ray scan as well as abdominal and draining lymph node ultrasounds should be obtained once yearly.[2]

Conclusion

While MCC remains an aggressive carcinoma, elevated mortality rates are also related to delays in diagnosis and treatment. Fortunately, increased recognition by primary care physicians and urgent referral for excision and radiotherapy will likely help improve disease prognosis in many patients.

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Competing interests
None declared

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