Digital Merkel cell carcinoma

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Merkel cell carcinoma (MCC) is a rare and biologically aggressive neuroendocrine tumour of the skin. Recent analysis of a surveillance, epidemiology and end results program has shown a statistically significant increase of 8% per year in the age-adjusted rates for MCC of the skin over the past 15 years. MCC commonly presents as a painless, rapidly growing, single red or purple cutaneous nodule. Diagnosis is often delayed until histopathological examination due to the relative rarity of the disease. MCC-specific immunohistochemical markers are available for definitive diagnosis, including anticytokeratin-20-positive stain and thyroid transcription factor-1-negative stains. Because there are no phase III trials to guide management, treatment is often tailored to the individual patient by integrating surgery, radiation and chemotherapy.

Key Words: *Hand tumour; Merkel cell carcinoma; Ray amputation*

Un merkelome digital

Le merkelome est une forme rare et biologiquement agressive de tumeur neuroendocrinienne de la peau. La récente analyse d'un programme de surveillance, d'épidémiologie et de résultats finaux démontre une augmentation statistiquement significative de 8 % par année des taux ajustés selon l'âge de markelomes cutanés après l'âge de 15 ans. D'ordinaire, le merkelome ressemble à un simple nodule cutané rouge ou mauve, indolore et à croissance rapide. Le diagnostic est souvent retardé jusqu'à l'examen histologique en raison de la rareté relative de la maladie. Il existe des marqueurs immunohistochimiques propres aux merkelomes pour poser un diagnostic définitif, y compris une coloration positive à l'anticytokératine-20 et des colorations négatives au facteur 1 de transcription thyroïdienne. Parce qu'aucun essai de phase III n'oriente la prise en charge, le traitement est souvent adapté au patient et intègre chirurgie, radiation et chimiothérapie.

CASE PRESENTATION

A 78-year-old man with multiple comorbidities presented with a painless, purple lesion on his left small finger that he first noticed one month before. He stated that the lesion had increased in size and ulcerated before presentation. The patient denied recent injury to the area. Previous dermatological history was significant only for actinic keratosis, although he was found to have a concurrent in situ squamous cell carcinoma of the thigh at the time of presentation. He was evaluated by dermatology with subsequent biopsy of the lesion, which revealed a neuroendocrine carcinoma consistent with Merkel cell carcinoma (MCC).

Past medical history included Dupuytren's contracture release of the small and ring finger of the same hand, hepatic cirrhosis with resulting anemia, leukopenia and thrombocytopenia. The patient had a remote 60 pack per year smoking history. There was no history of immunosuppression or HIV.

Examination showed a 1.5 cm ulcerating, exophytic lesion on the left dorsal small finger middle phalanx (Figure 1). Computed tomography (CT) of the thorax revealed a 3.3 cm left axillary mass consistent with metastatic adenopathy. CT of the abdomen and pelvis, as well as magnetic resonance imaging of the brain, were negative for metastatic disease. Operative intervention involved ray amputation of the small finger with concurrent complete left axillary lymph node dissection (Figures 2 and 3). Pathology from the operative specimen was positive for a 1.7 cm × 1.4 cm × 0.7 cm MCC at least 1.5 cm from the nearest surgical skin margin. Six of 18 axillary lymph nodes were involved with metastatic disease. The largest involved node was 3.8 cm in diameter with an extracapsular tumour present. The patient was classified as having stage II disease (local disease with regional lymph node metastases).

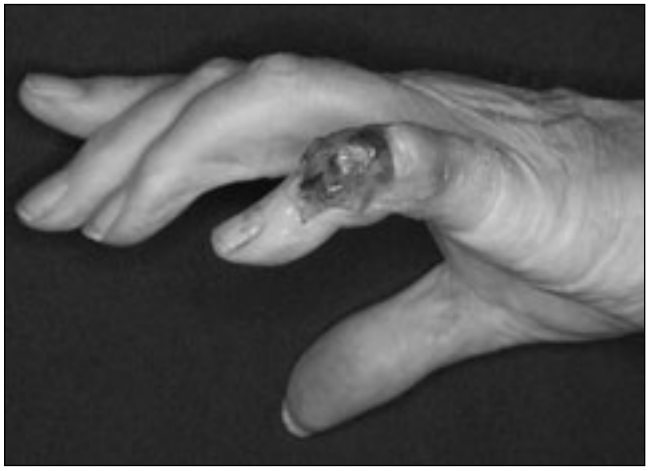

Figure 1) *Preoperative appearance of Merkel cell carcinoma of the left small finger*

The patient was evaluated by medical oncology but was not a candidate for chemotherapy due to his comorbidities. Regional radiotherapy was planned but, unfortunately, the patient died from complications of his disease before treatment.

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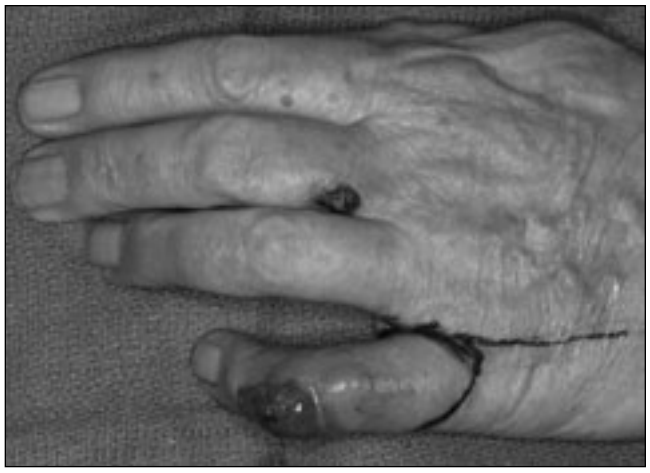

Figure 2) *Preoperative markings for planned ray amputation of left small finger*

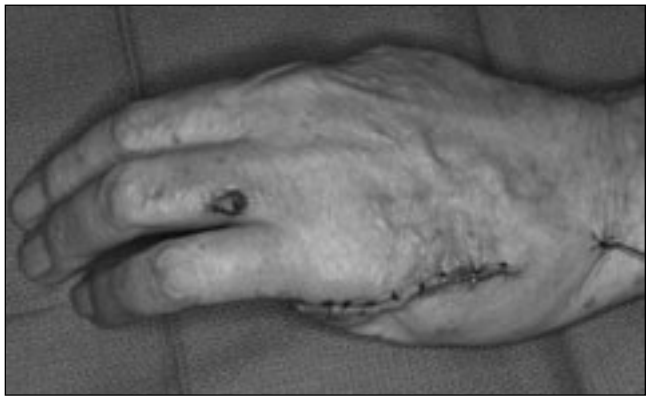

Figure 3) *Postoperative closure following ray amputation of left small finger*

DISCUSSION

Frederick Merkel first described Merkel cells in 1875. They reside in the basal layer of epidermis and are thought to be mechanoreceptors that conduct information about touch and hair movement (1). The cells are of neuroendocrine origin and migrate from the neural crest to the skin before differentiation (1). Toker (2) first described five cases of trabecular cell carcinoma of the skin in 1972. In 1978, Tang and Toker (3) further characterized the cellular ultrastructure with electron microscopy as being consistent with Merkel cells. Merkel cell carcinoma commonly presents as a painless, rapidly growing, single red or purple cutaneous nodule (4).

The highest incidence of MCC is seen in Caucasian men, older than 65 years of age. According to the surveillance, epidemiology and end results (SEER) data, only 49% of patients present with localized disease, with 19.3% presenting with a primary lesion of the upper limb (3). There is a statistically significant increase of 8% per year in the age-adjusted rates for MCC of the skin over the past 15 years (5). The five-year relative survival rate is 75%, 59% and 25% for localized, regional and distant disease, respectively, with female sex, limb presentation, localized disease and young age associated with improved survival (6). MCC has been associated with sun exposure and has been documented in patients with congenital ectodermal dysplasia and Hodgkin's disease (7). Increased risk is also seen in the face of HIV infection, immunosuppression and chronic lymphatic leukemia (8,9).

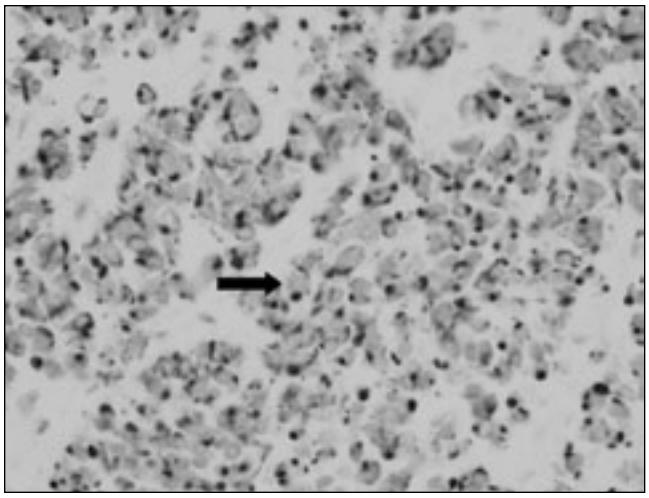

Figure 4) *Multiple mitosis (arrow) characteristic of Merkel cell carcinoma (hematoxylin and eosin stain, original magnification ×600)*

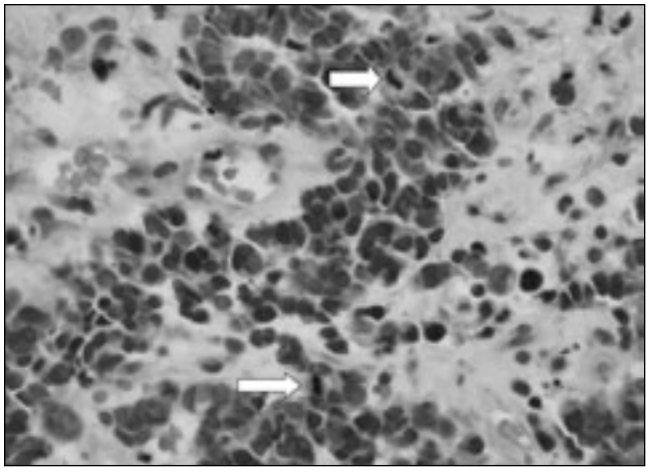

Figure 5) *Photomicrograph reveals perinuclear staining (arrows) in Merkel cell carcinoma (anticytokeratin-20 stain, original magnification ×600)*

Clinically, these lesions can be misdiagnosed as other, more common, cutaneous malignancies. The majority of primary lesions are less than 20 mm in diameter, but the ability of MCC to spread through the dermal lymphatics can lead to multiple satellite lesions. Nodal status is the strongest predictor of distant metastasis, with approximately one-third of patients presenting with regional node involvement. Metastasizes can be found in the skin (28%), lymph nodes (27%), liver (13%), bone (10%) and brain (6%) (10).

Histologically, MCC is composed of small, monomorphic basophilic tumour cells with round to oval shaped nuclei (Figure 4). Tumour cells occupy the dermis and may extend into the subcutaneous fat; the epidermis is generally spared although ulceration can occur (11). The differential diagnosis includes other poorly differentiated small cell tumours, including small cell carcinoma of the lung and metastatic carcinoid (11). Subsequently, immunohistochemistry is required for definitive diagnosis of MCC. Anticytokeratin antibodies are the most sensitive markers, with most studies suggesting that anticytokeratin-20 is highly specific for MCC; it is thought to be highly suggestive of MCC when determining the diagnosis of

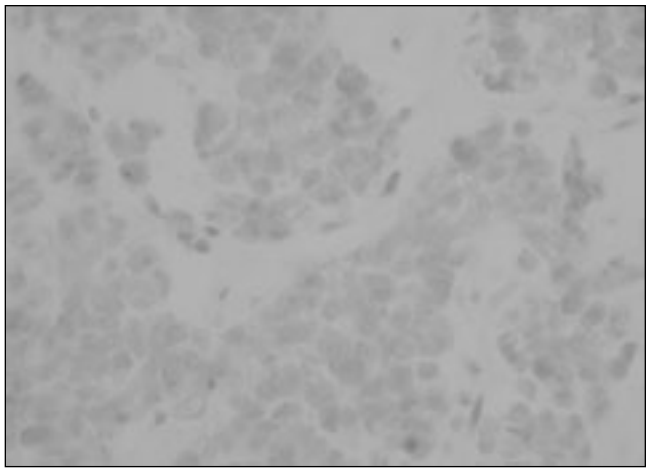

Figure 6) *Immunological stain for thyroid transcription factor-1 (TTF-1) is negative in Merkel cell carcinoma (TTF-1 stain, original magnification ×600)*

small cell carcinoma (Figure 5) (11). Thyroid transcription factor-1 is both sensitive and specific for small cell lung cancer but is not expressed at all in MCC (Figure 6) (11). It has been recommended that anticytokeratin-20 and thyroid transcription factor-1 should be used routinely in conjunction to provide the best sensitivity and specificity when distinguishing MCC from other small cell carcinomas (12).

Although there is not a specific staging system for MCC, patients are generally classified into one of three groups based on the extent of disease (Table 1). The presence of nodal involvement is the strongest predictor of survival, with one series demonstrating a median survival of 13 months with involved nodes, and 40 months with no nodal disease (13). Other factors associated with a poor prognosis include male sex, primary lesion greater than 2 cm, age older than 60 years and lack of radiotherapy in management (14). Accordingly, assessment of MCC should include careful examination of the primary site to detect satellite lesions and dermal seeding with careful palpation of the draining nodes (14). CT scan of the regional nodal basins should be performed, as well as the chest and liver, to exclude a primary small cell lung cancer and distant disease.

Treatment of MCC centres on the control of the primary site as well as the relevant nodal basins. For stage I disease, the primary modalities of treatment are surgery and radiation, with a five-year survival quoted at 64% (15). Although there are no controlled trials for direct comparisons, most authors recommend wide local excision with a margin of 2.5 cm to 3 cm (14). Postoperative radiation is employed based on a retrospective review of patients with stage I disease demonstrating a reduction of local failure from 39% to 26% and a reduction in regional failure from 46% to 22% with the addition of radiotherapy (16). It is recommended that radiotherapy begin as soon as the wounds have healed, given a recent review that suggests a median wait of 24 days before initiation of treatment is associated with increased risk of disease progression (17). Elective treatment of the nodes with radiation or surgery is recommended, given recurrence rates of 46% to 76% when they are not treated (18). There is no demonstrated survival advantage with elective lymph node dissection, and prophylactic lymphadenectomy is not currently recommended (19). Some authors (20) have advocated lymphscintigraphy and sentinel lymph node biopsy in this setting. Currently, there are no definitive data to support the use of chemotherapy in stage I disease.

TABLE 1
Stages of Merkel cell carcinoma

Stage	Description
IA	Disease confined to skin and <2 cm in diameter
IB	Disease confined to skin and >2 cm in diameter
II	Involvement of regional lymph nodes
III	Metastatic disease

Treatment principles for stage II disease are similar to those for stage I. Five-year survival with stage II disease is approximately 47% (15). Nodal dissection can de done at the same time as the resection of the primary lesion; however, radiation can be used as the definitive treatment as well (14). There are currently insufficient data to determine which modality has superior survival outcomes. There is increasing evidence for the use of adjuvant chemotherapy in stage II disease. The Trans-Tasman Radiation Oncology Group (21) demonstrated a 76% overall survival, with a protocol of synchronous chemoradiotherapy and adjuvant chemotherapy in a group of high-risk patients (two-thirds of whom had stage II disease) (21). In stage III disease, the presence of distant disease carries a grave prognosis. Consequently, the intent of treatment is primarily palliative (14).

MCC has been traditionally thought of as a relatively rare carcinoma of the skin. However, the increasing incidence of these lesions over the past 15 years in concert with their biologically aggressive nature demand prompt diagnosis and treatment of this disease.

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