

## CASE REPORT

### Merkel cell carcinoma: Preparing to go the distance

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#### Abstract

**Introduction:** Merkel cell carcinoma (MCC) is a rare and aggressive malignancy of the skin, with poor clinical outcomes. Typical conditions include a rapidly growing, solitary dome-shaped, violaceous nodule. Several root causes have been identified - sun exposure, age, lighter skin, immunocompromised state, and polyomavirus infection. Wide local excision is the best treatment. The tumour is radiotherapy-responsive. However, the success rate of the treatment with chemotherapy is rather limited. Immunotherapy has shown promising results. Early detection is important to prevent morbidity and mortality. **Case Report:** In this literature work, we reported on a particular case of MCC, as exhibited by an 84-year-old Chinese woman, and discussed the clinical features and management of MCC. **Discussion:** We highlighted that MCC cases have a link to the polyomavirus 5. Patients who were identified with the Polyomavirus 5, and underwent immunotherapy, were seen to depict much better prognosis.

**Keywords:** Merkel cell carcinoma, neuroendocrine tumour, Polyomavirus

#### INTRODUCTION

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine cutaneous malignancy.<sup>1</sup> It affects 0.6 per 100,000 people per year, in the United States, 1.6 per 100,000 people per year in Australia, and 0.3 per 100,000 people per year in Sweden.<sup>2,3</sup> In Malaysia, only 6 cases were reported in the Malaysian Cancer Registry between 2007 and 2011.<sup>4</sup> The 5-year relative survival rate stands between 30-64%, depending on the stage at which diagnosis takes place, as well as the site of the tumour.<sup>5</sup> MCC is typically presented as a solitary nodule in sun-exposed areas, which may be mistaken for a benign lesion during the initial presentation.<sup>1</sup> It also typically occurs amongst the elderly with light skin and immunocompromised states.<sup>1</sup> MCC was first introduced by Toker in 1972.<sup>1,5</sup> While it was initially thought that MCC arose from Merkel Cells in the epidermis, this was now found to be less likely.<sup>1</sup> This point has been further elaborated in the discussion. Recent advances describe an association with polyomavirus, with one study reporting that as many as 8 out of 10 cases were

positive for polyomavirus.<sup>1,3,5,6</sup>

#### CASE REPORT

An 84-year-old Chinese woman was presented to the dermatology clinic with a 4 months' history of an ulcerated nodule in her left arm. She described the lesion as a pruritic pinkish nodule at first, which later become ulcerated. It was non-tender. She did not have constitutional symptoms, or a history of skin trauma prior to the development of the nodule. There was no family history of cancer either. There was no history of allergies, and she denied excessive sun exposure. She did not use any topical or traditional medication on the skin before the lesion appeared. She had a long-standing type II diabetes mellitus, and hypertension for over 40 years. She also had diabetic retinopathy, stage IV chronic kidney disease (CKD) stage IV (EGFR 22). However, she refused renal replacement therapy. She had generalised dry skin and pruritus due to her CKD over the last 1 year or so. She required no medications for her diabetes, and hypertension over the past 8 months. Prior to

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that, she was on an ACE inhibitor, Perindopril and a Calcium channel blocker, Amlodipine. She had previously worked for more than 30 years as a hawker.

On clinical examination, she was not cachectic, with a normal body mass index (BMI). Her skin was generally dry. Mild excoriations were observed over both forearms and legs. There was no axillary or cervical lymphadenopathy. The chest and cardiovascular examinations were unremarkable. There was a dome-shaped nodule over the lateral aspect of her left arm, measuring 3 x 3 cm. The nodule was crusted and violaceous (Fig. 1). Her laboratory investigation results were as follows: full blood count: Hb 9.1g/dL; total white cell count  $10.1 \times 10^9/L$ ; platelet  $253 \times 10^9/L$ , renal profile: urea- 15.3mmol/l, creatinine  $173.8 \mu\text{mol/l}$ ; total cholesterol 5.20mmol/l, LDL 3.56mmol/l; albumin: 29g/dl and HbA1c: 6.5%. The chest X-ray did not show any significant points of concern. The provisional diagnosis concluded that she depicted Squamous Cell Carcinoma, with a differential diagnosis of Basal Cell Carcinoma. An underlying diagnosis of asteatotic eczema was also made. Histopathological examination



FIG. 1: A crusted, dome-shaped, and violaceous nodule over lateral aspect of the proximal left arm.

(HPE) of the excised lesion revealed diffuse dermal infiltration by malignant cells disposed in lobules and cords with areas of necrosis seen (Fig. 2). Neoplastic cells were positive for CK AE1/AE3, CK20, synaptophysin and

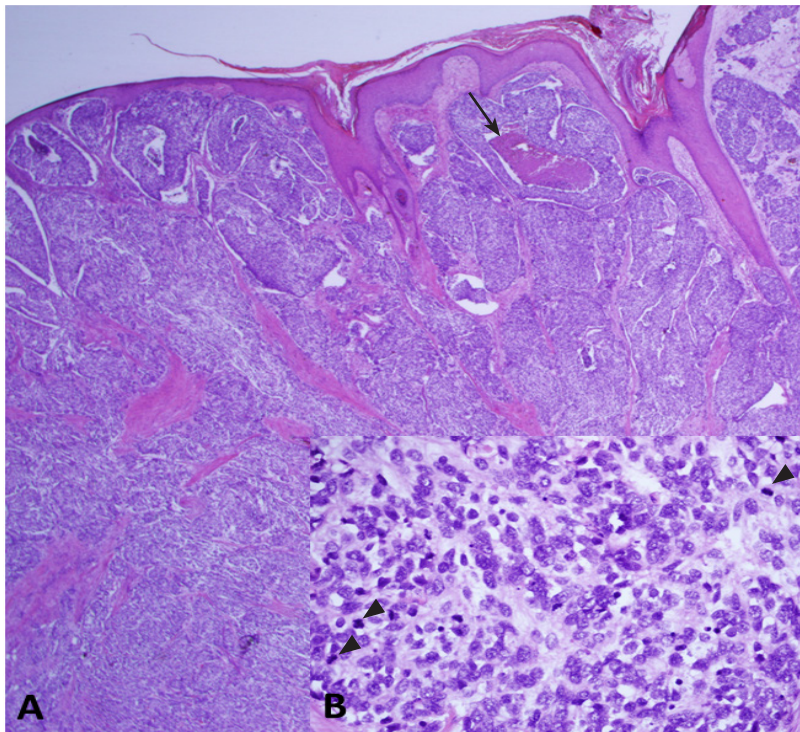


FIG. 2: (A) Sections from the skin show diffuse dermal infiltration by malignant cells disposed in lobules and cords. Areas of necrosis (arrow) are also seen. (H&E, 10x). (B) The cells display round to oval hyperchromatic vesicular nuclei, inconspicuous nucleoli and scanty cytoplasm. Numerous mitotic figures are seen (arrowhead) (H&E, 40x).

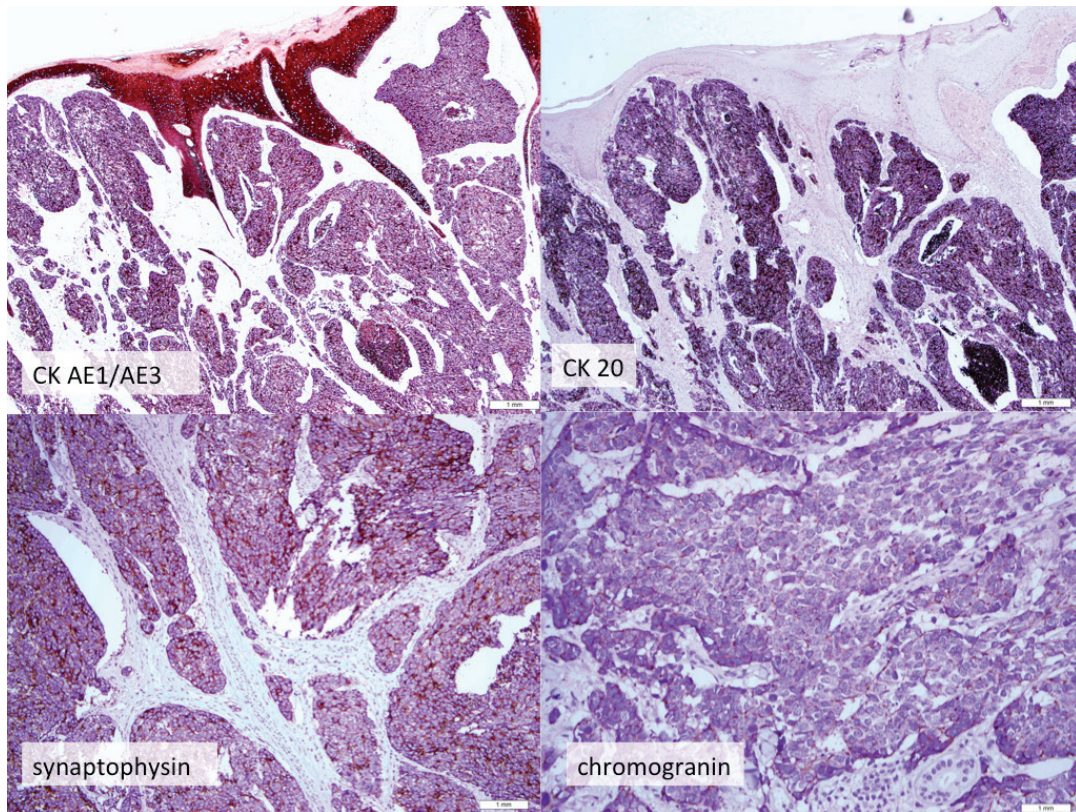


FIG. 3: The neoplastic cells are positive for CK AE1/AE3, CK20, synaptophysin and chromogranin immunostains. (CK AE1/AE3, 4x; CK20, 4x; synaptophysin, 10x; chromogranin, 20x)

chromogranin immunostains (Fig. 3). The final diagnosis was Merkel Cell Carcinoma based on the HPE.

The patient was well post-excision. A thoraco-abdomino-pelvic CT scan for staging was planned, but she declined. She was referred to the oncology department for further follow-up. She was not keen on further intervention, due to her age and multiple comorbidities. She was managed conservatively. Four months' post excision, there were no signs of local recurrences or distant metastases.

## DISCUSSION

The cell origin of MCC cells has not been identified. Merkel cells are post-mitotic cells, which makes it least likely to be the cell of origin for MCC.<sup>1</sup> Post-mitotic cells are mature cells, that are no longer capable of undergoing mitosis. Possible cells that may be cells of origin for MCC are the epidermal stem cells, and keratinocytes. Other candidates such as dermal fibroblasts, pro-B-cells and pre-B-cells, which lie in the deeper dermis, are not possible to be treated with UltraViolet (UV) mediated carcinogenesis.<sup>1</sup>

MCC carcinogenesis has been linked with polyomavirus 5 (MCPyV)<sup>6</sup> and chronic sun (ultraviolet) exposure.<sup>1,7</sup> Clonal integration MCPyV genome disrupts the expression of the early transforming gene and leads to specific DNA damage and rapid tumour growth.<sup>1,8</sup> This may indicate that the deeper dermal cells may be linked to polyoma 5 virus infections. MCPyV oncoprotein antibody titres have been shown to increase preceding clinically evident recurrent diseases.<sup>9</sup> Testing for polyomavirus was not available in our setting.

Typically, MCC is presented as a painless, dome-shaped nodule, or indurated plaque, that grows rapidly and is usually red or violaceous in colour, as well as asymptomatic.<sup>5,1</sup> People with a high risk of MCC are the elderly, with a median age between 75 and 80 years old, immunocompromised individuals with HIV, people with haematological malignancy, and individuals who have had previous cutaneous tumours.<sup>1</sup> There were reports that MCC was more common amongst Asians compared to Caucasians<sup>2,3</sup>, however in mainland China, MCC is uncommon.<sup>10</sup> MCC is more prevalent in men

than women.<sup>1</sup> A previous history of melanoma has a three-fold greater risk of developing MCC.<sup>1</sup> Our patient was an elderly woman of Asian-Oriental origin. She was immunocompromised (chronic kidney disease) which fell into the high-risk category for MCC. She also had an underlying asteatotic eczema, which probably resulted in the non-typical appearance of MCC. MCC is usually not crusted or symptomatic. The crusting observed in our patient and the pruritus might have been due to the patient's underlying CKD, and asteatotic eczema. Patients with CKD may frequently complain of pruritus because of the high serum urea. MCC is located mostly on sun-exposed areas such as head and neck (50%), extremities (40%) and trunk or genitalia (<10%).<sup>1,10</sup> Our patient worked as a hawker for over 3 decades, and was exposed to the sun daily. Skin pigmentation may be protective against MCC, which might explain the lower number of MCC amongst African ethnicities reported so far.<sup>1</sup> The rarity of MCC, did not prompt the attending physician to list it down as a provisional diagnosis. This clinical decision was also influenced by the non-typical presentation in our case.

MCC usually spreads to the lymph node first, thus the involvement of lymph nodes is important for staging.<sup>1</sup> The survival rate for stage I is 62%, and decreases to around 10 to 20% if the disease progresses further. Stage III and above might have local or distant metastases in 2-3 years' time.<sup>1,11</sup> Ultrasound of the lymph nodes, CT scan, MRI and/or PET CT are effective in ruling out distant metastases.<sup>1</sup>

Management of MCC should be based on the tumour's appearance and its grade.<sup>1</sup> Excision of the tumour is the first line of therapy. Sentinel lymph node biopsy (SLNB) during excision of the tumour is beneficial in identifying the nodal micrometastasis in up to one-third of patients.<sup>7</sup> The presence of sentinel lymph node metastases is a strong predictor for the 3-year overall survival rate (88% for negative SLNB and 57.6% for positive SLNB).<sup>1</sup> For stage I and II local primary tumours, the excision of the lesion with a clear margin of more than 1 cm is much preferred as a method for the removal of sentinel lymph nodes, followed by adjuvant radiotherapy.<sup>7</sup> The National Comprehensive Cancer Network (NCCN) and the European Association of Dermato-Oncology (EADO)-European Organisation for Research and Treatment of Cancer (EORTC) guidelines recommend a 1-2 cm excision margin down to the muscle fascia, or the pericranium (the

membrane that externally covers the skull), regardless of tumour size.<sup>11</sup> Almost one-third of MCC patients are presented in Stage III of the disease, which encompasses a clear node-positive disease.<sup>7</sup>

Radiotherapy after wide surgical excision is the mainstay of therapy for stage III of MCC. The role of adjuvant chemotherapy remains vague with varied outcomes.<sup>7</sup> The response rates to adjuvant chemotherapy were reported at 55%.<sup>1</sup> Chemotherapy was not associated with the overall survival benefit for the patient who was presented with either local or nodal MCC.<sup>1</sup> In MCC cases with distant metastases (Stage IV), palliative chemotherapy with platinum and etoposide is a common practice. The response rates vary between 60% to 75% with poor sustainability, as most patients relapse within 4 to 15 months. Many patients may not be fit for palliative chemotherapy due to their age, and multiple comorbidities.<sup>7</sup> Immunotherapy and targeted therapy such as antisense oligonucleotide, which targets bcl-2 (Oblimesen), monoclonal ab against CD56 (Lorvotuzumab mermantazine) are promising, but its use in routine management is yet to be defined.<sup>7</sup> Avelumab, pembrolizumab and nivolumab are anti-PD-L1 monoclonal antibodies that are approved by the FDA for stage IV MCC with distant metastasis.<sup>11</sup>

Follow up after treatment is needed as half of MCC cases are recurrent with a median time of 9 months to 2 years.<sup>7</sup> The National Comprehensive Cancer Network guidelines recommend clinical review every 3 to 6 months over the period of 2 years, and then 6 to 12 months thereafter.<sup>11</sup> Routine surveillance imaging is not recommended.<sup>11</sup> The EADO-EORTC guideline however recommends ultrasound of the lymph node basin every 4 months for 3 years, then 6 months for 5 years, with consideration of annual PET-CT scans.<sup>1,7</sup>

## CONCLUSION

The patient discussed in this case had opted for conservative management post excision, with a 4-monthly follow-up, in view of her advanced age and other comorbidities. In this case, serology for MCPyV oncoprotein may be useful in monitoring for the reoccurring disease. Dermatologists, oncologists, and surgeons, who attend to such cases should come up with a collaborative plan for the management of such cases in Malaysia. Resources for the screening of polyomavirus nearest to Malaysia should be sought, and made available to patients. A

comprehensive plan, availability of screening, and prognostication options will be most useful when treating MCC cases who are younger, have fewer comorbidities, and are ready to go the distance, more so, with the progress shown in immunotherapy.

*Conflict of interest:* The authors declare they have no conflict of interests.

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