Extracutaneous Merkel cell carcinoma or metastatic Merkel cell carcinoma with an occult primary?

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Merkel cell carcinoma (MCC) is a rare and aggressive malignancy arising from dermal neuroendocrine cells, first described by Toker in 1972 [1]. It is predominately seen in the head and neck region of older, white males and risk factors include immunosuppression, sun exposure, Merkel cell polyoma virus and a previous history of skin cancer. Approximately two-thirds of patients demonstrate local, nodal or distant metastases resulting in a five-year survival rate of 40% [2]. We present four such cases along with a review of the literature.

IHC analysis

Synaptophysin is a membrane protein indicative of neuroendocrine differentiation. Cytokeratin 20 (CK-20) is an epithelial marker commonly seen in MCC. All four cases discussed below had both markers present in over 50% of the cells, which is pathognomic on immunohistocytochemistry (IHC) for a diagnosis of MCC.

Case summaries

Four patients (two female and two male), with a median age of 70 years, presented with extracutaneous MCC without an identifiable primary skin source. All were immunosuppressed (diabetes mellitus, chronic renal disease, steroids and methotrexate), all underwent a full clinical assessment (including a detailed skin survey), core biopsy, mammography and ultrasound as appropriate, and CT or PET-CT of the chest, abdomen and pelvis. All cases were reviewed at the skin, neuroendocrine and, as appropriate, breast multidisciplinary team (MDT) meetings. In all cases, the full skin survey examining for a primary source was negative and no patient gave a history of a previous skin malignancy. All four cases were positive for both the markers, synaptophysin and CK-20 on IHC.

The location of the extracutaneous MCC was breast (one case) and nodal (three cases), with two in the axillary nodes and one in the groin.

The right breast mass was an incidental CT finding, there being nil found clinically or on CT in the axilla. Following the diagnosis of MCC from the breast core, the breast MDT advised a simple mastectomy and sentinel lymph node biopsy (SLNB). Three of the sentinel nodes were positive for MCC and the patient had adjuvant radiotherapy to the axilla.

One male patient presented with an axillary mass. He underwent an axillary dissection and had adjuvant radiotherapy to the axilla due to extracapsular and lymphovascular invasion.

The other female patient presented with an axillary mass and though other investigations were negative, the breast and neuroendocrine MDTs suspected an occult MCC in the breast and advised simple mastectomy and axillary node dissection. Two nodes were positive and an incidental finding was an occult focus of high grade ductal carcinoma in situ in the breast specimen. The patient wished no further treatment.

One female patient with MCC of the breast died of metastatic bone disease at four months and the second female patient with MCC of the axillary nodes died disease-free, of an unrelated cardiac event at 40 months.

Regarding the two males, the patient with disease in the inguinal nodes is alive and disease-free at 36 months, the other with axillary node involvement, who required postoperative irradiation and avelumab and had a complete response to treatment, was diagnosed with an asymptomatic adrenal metastasis on surveillance CT scan at 48 months and is currently undergoing assessment for surgical resection of the mass.

Discussion

Merkel cell carcinoma is a highly aggressive cutaneous malignancy arising from Merkel cells, a tactile epithelial cell located in the dermis, first described by Friedrich Merkel as Tastzellen in 1875. The UK prevalence of MCC is 1 in 100,000 annually, with the highest incidence being in the over 65-year-old male [3]. Merkel cell polyoma virus is thought to play a significant role in the malignant process [4], however despite numerous studies the potential role of the virus in the pathogenesis of MCC remains uncertain [5].

Merkel cell carcinoma presents as an asymptomatic, rapidly growing, erythematous nodule on sun-exposed areas of the skin and can be misdiagnosed as a squamous cell carcinoma or an amelanotic malignant melanoma. In 1992, Eusebi and colleagues initially described nodal MCC without an identifiable primary site [6] and two hypotheses have been proposed to explain this phenomenon.

The first recommends the spontaneous development of MCC in the lymph nodes; however, this is thought to be unlikely, as the progenitor cell of MCC, a cell of neural crest origin, has never been documented to occur naturally in lymph nodes. While the possibility of Merkel cells developing from totipotent stem cells [7], which then undergo malignant transformation, cannot be entirely excluded, the more favoured theory, advanced by Sais [8], suggests a process of primary recurrence. This postulates that the primary MCC develops intradermally and then metastasises early, due to its aggressive nature. While the metastases are in transit, a T-cell-mediated immune response occurs at the primary site, leading to regression of the primary tumour. While a very rare phenomenon, occurring in less than 1 in 60,000 of malignancies [9], spontaneous regression is a well-documented process. In 1999, Brown reported on the spontaneous regression of a primary MCC with nodal metastases [10].

While attempts to differentiate de novo nodal MCC from metastatic cutaneous MCC with regression of the primary using case analysis, have demonstrated differing behaviours [11], such as nodal disease without an identifiable primary appearing to be less aggressive than nodal disease with a documented cutaneous primary, histopathological analysis has demonstrated a common immunophenotype and supports the theory of primary regression [12]. Alternatively, Pan has noted a lower prevalence of the polyoma virus in MCCs without an identifiable primary site as compared to cutaneous neoplasms with nodal spread

[13]. This suggests the possibility of primary nodal MCC arising from a different pathophysiological to its cutaneous counterpart, contradicting the hypothesis of nodal metastases with cutaneous regression. Until the pathogenesis of MCC is more precisely understood, the development of extracutaneous MCC cannot be clearly defined as either primary nodal disease or metastatic MCC from an occult primary source.

Patients presenting with clinical features suggestive of MCC must undergo a full IHC analysis as in the National Comprehensive Cancer Network (NCCN) guidelines [14]. The tissue samples must demonstrate positivity for neuroendocrine (synaptophysin) and cytoskeletal (CK-20) markers. Both were present in over 50% of the tumour cells analysed in all four cases, which is pathognomic on IHC for the diagnosis of MCC. The staging investigations performed confirmed that all the patients were of stage 111A.

Cutaneous MCC excised with a surgical margin greater than 1cm, has an improved five-year survival as compared to those with an excision margin less than 1cm [15]. Those with no palpable regional lymphadenopathy may be offered SLNB [16] and if positive, radiotherapy or completion lymphadenectomy offered. As MCC is highly radiosensitive, the use of postoperative irradiation has demonstrated an improvement in five-year survival and the prevention of loco-regional recurrence [17]. Ngheim [18] in a large literature review, demonstrated that platinum-based chemotherapy used to treat MCC, had a varied response rate and a short mean duration of tumour responsivity and there was no demonstrable improvement when chemotherapy was used in combination with surgery. Kaufman [19] reported on a large multicentre trial, which reviewed the use of monoclonal antibody therapy in advanced chemotherapy refractory MCC, and this demonstrated an objective and ongoing response to the treatment, leading to avelumab, in 2017, becoming the first biologic agent to receive Food and Drug Administration (FDA) approval for the treatment of metastatic MCC.

Conclusion

Merkel cell carcinoma remains an exceedingly uncommon and highly aggressive form of cutaneous malignancy with a poorly understood pathogenesis and clinical course. Whilst there have been significant advances in the identification and management of this rare tumour, it poses a significant threat to the ageing Caucasian male, with its prevalence increasing steadily [20]. In particular, the development of extracutaneous MCC without an identifiable primary source remains an unexplained phenomenon, and until further advances in the understanding of the pathogenesis of MCC are made, the question of primary extracutaneous nodal disease versus metastatic MCC with an occult primary disease remains unresolved.

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TAKE HOME MESSAGES

- Merkel cell carcinoma is an aggressive neuroendocrine tumour.
- It can present ectopically without an identifiable site of skin primary.
- Some cases are associated with polyoma virus.
- Immunohistocytochemical analysis is an essential part of the diagnosis.

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