

DR KEZIA GAITSKELL (Orcid ID : 0000-0002-2474-1159)

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Merkel cell carcinoma with divergent differentiation: two case reports

K. Gaitskell¹ and H. Ibrahim^{1,2}

¹Department of Cellular Pathology, Royal Free Hospital, Pond Street, London NW3 2QG

²Department of Dermatology, Royal Free Hospital, Pond Street, London NW3 2QG

Corresponding author: Dr Kezia Gaitskell

E-mail: kezia.gaitskell@ndcls.ox.ac.uk

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Abstract

Merkel cell carcinoma (MCC) is a rare primary neuroendocrine carcinoma of the skin, usually occurring at sun-exposed sites in the elderly. Divergent differentiation in MCC, though rare, has been reported in previous case series. We describe two new cases of MCC with divergent differentiation. Case 1 was a 96 year-old male with a scalp lesion; on biopsy, the morphology and immunoprofile suggested MCC with divergent squamous differentiation. Case 2 was an 87 year-old female, with a lesion on the leg, originally reported as squamous cell carcinoma, later showing extensive local recurrence. On review, primary histology showed a Merkel cell carcinoma with divergent differentiation, most likely trichilemmal carcinoma; the recurrence showed only MCC. These cases illustrate that Merkel cell carcinoma is capable of divergent differentiation, including squamous and adnexal morphologies. Correct diagnosis is essential for appropriate prognosis and management, as later recurrence or metastases may only show the Merkel-cell component.

Learning points

- Merkel cell carcinoma (MCC) is a rare neuroendocrine tumour of the skin, with a poor prognosis
- MCC is capable of divergent differentiation, including squamous and adnexal morphologies
- The diagnosis of MCC may be missed if initial biopsy shows mostly the area of divergent differentiation
- Recurrence of MCC may show only the classical Merkel-cell morphology, even if divergent differentiation was present on initial biopsy
- Missed diagnosis of MCC in the context of divergent differentiation may lead to incorrect management

Introduction

Merkel cell carcinoma (MCC) is a rare primary neuroendocrine carcinoma of the skin, which usually occurs at sun-exposed sites in the elderly, particularly in the head and neck.¹ The cell of origin for MCC is traditionally held to be the Merkel cell, located primarily in the basal layer of the epidermis and follicular epithelium;² although some argue that MCC may in fact arise from pro/pre-B-cell lymphocytes, or even from dermal fibroblasts.^{3,4} Prognosis for MCC is poor, with overall mortality rates estimated to be worse than melanoma.⁵

Divergent differentiation in Merkel cell carcinoma, though rare, has been reported in previous case series. Most cases show squamous or skin adnexal differentiation,⁶⁻¹² although reports also exist of MCC with rhabdomyoblastic, neuroblastic, and sarcomatous differentiation.^{6,8,9,13-16} Here, we report on two cases of Merkel cell carcinoma with divergent differentiation.

Report

The first case was a 96 year old male, presenting with a scalp lesion. Punch biopsy showed skin containing part of an atypical proliferation of basophilic cells and nests of squamous cells. Both basophilic and squamous cells showed nuclear atypia and mitotic and apoptotic figures (Fig. 1). Some of the basophilic cell nuclei had a smudged appearance. On immunohistochemistry, the basophilic cells were positive for BerEP4 and EMA, with patchy positivity for CD56, chromogranin and synaptophysin (perinuclear dot-like staining), and with very focal positivity for CK20. There was focal staining for neurofilament with perinuclear dot-like positivity. TTF1 was negative. The squamous cells expressed EMA (focal) and were negative for all other markers, including chromogranin and synaptophysin. The morphology and immunoprofile were in keeping with Merkel cell carcinoma with divergent squamous differentiation.

The second case was an 87 year old female, who presented with a lesion on the left leg, which was excised. The initial histology report suggested a squamous cell carcinoma, and excision appeared complete. On review of the case for discussion at the multidisciplinary team meeting, doubt was raised as to the diagnosis, and the case was sent for specialist review.

Histology showed a large, polypoid, ulcerated tumour, with widespread connection to the epidermis, and changes of carcinoma in situ. There was a transition to a population of cells with neuroendocrine morphology, composed of nests and lobules of hyperchromatic cells with scant cytoplasm and brisk mitotic activity (Fig. 2). Another area of the tumour showed areas of clear cell change, abrupt keratinisation, and dystrophic calcification. On immunohistochemistry, the cells with neuroendocrine morphology were positive for synaptophysin, CD56, and neuron specific enolase. Much of the tumour was also immunopositive for CK20, Bcl-2, and P63, with some positivity for CK7. Expert review diagnosed the case as a Merkel cell carcinoma with divergent differentiation. The non-neuroendocrine component of the tumour was considered to be a trichilemmal carcinoma, in view of the clear cell change, abrupt keratinisation, and dystrophic calcification.

The tumour showed aggressive clinical behaviour, recurring within a few months at the site of the previous excision, and also showing extensive spread, involving the left lower leg, left groin, left hemipelvis, and left common iliac nodes. The recurrent lesion was excised, and radiotherapy planned for the multiple associated smaller lesions. Histology of the recurrence showed an exclusively Merkel cell-type morphology, with no evidence of the divergent trichilemmal differentiation seen on the original excision (Fig. 3).

Discussion

Merkel cell carcinoma is most common in the elderly, with an average age at diagnosis of 75, and incidence appears to be increasing.¹⁷ MCC is also associated with various causes of immunodeficiency/ immunosuppression.^{1,5} The aetiology of MCC is uncertain, but most cases appear to be related to either ultraviolet light exposure or Merkel cell polyomavirus (MCPyV)³ – though why these common exposures should lead to MCC in a small subset of people is unclear. A proportion of MCCs show integration of Merkel cell polyomavirus (MCPyV) within their DNA; the presence of virus can be detected using either tests based on polymerase chain-reaction, or immunohistochemistry, in about 70-90% of cases.¹⁸ Several studies have found that Merkel cell carcinomas with divergent differentiation tend to be negative for MCPyV, suggesting a non-MCPyV-driven aetiology for these tumours,^{6,18-21} though others report evidence of MCPyV (by PCR or immunohistochemistry) in some cases.^{13,22}

Clinically, MCC has a fairly non-specific appearance, usually presenting as a solitary, painless, dome-shaped cutaneous nodule, with an erythematous to violaceous colour.^{1,5} Histologically, the tumour is characterised by small, basaloid cells with scanty cytoplasm, granular, dusty, or smudged chromatin, and frequent mitoses.²³ Diagnosis is confirmed by the characteristic profile on immunohistochemistry, including positivity for EMA, CK20 (with typical perinuclear dot staining), neurofilament, and neuroendocrine markers such as chromogranin and synaptophysin.²³

Disease extent at diagnosis is strongly predictive of prognosis, with estimated 5-year overall survival for local, nodal, and distant disease being 51, 35, and 14%, respectively.²⁴ Evidence for the impact of divergent differentiation on prognosis is mixed, as the rarity of the entity means that most published case series have had small numbers.^{6,7,10,12,22,25} The main clinical import of divergent differentiation is the potential for misdiagnosis as a less-aggressive skin tumour (e.g. squamous cell carcinoma or an adnexal tumour), which would tend to have a better prognosis.

Treatment guidelines for MCC suggest wide local excision, with possible adjuvant radiotherapy, for local disease; chemotherapy has been used for some patients in an adjuvant, advanced, or recurrent disease setting, but evidence for efficacy is limited, and enrolment in a clinical trial may be appropriate.^{1,26} Several targeted approaches are in development, including PD-1/ PD-L1 immune checkpoint inhibitors, tyrosine kinase inhibitors, and somatostatin analogues.^{5,26}

In conclusion, we describe two new patients with Merkel cell carcinoma with divergent differentiation, diagnosed based on morphology and characteristic immunohistochemistry. These cases illustrate that MCC is capable of divergent differentiation, including squamous and adnexal morphologies. Diagnosis can be challenging, particularly if the divergent components are more prominent in the original histology samples. Later recurrences or metastases may show only the Merkel cell component. However, correct diagnosis on the primary lesion is important to ensure appropriate management and prognostication, especially as Merkel cell carcinoma tends to have a more aggressive behaviour than other skin epithelial tumours.

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FIGURE LEGENDS

Figure 1

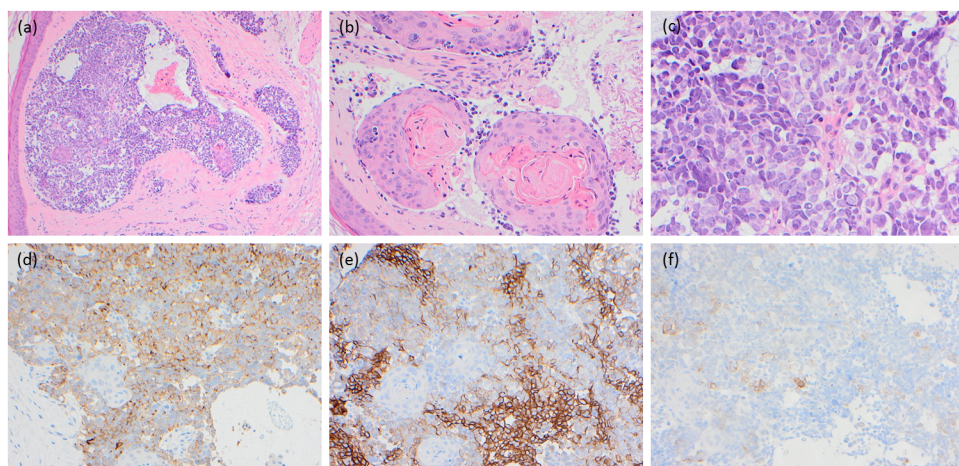
Case 1. (a) The tumour showed a mixture of neuroendocrine and squamous differentiation; (b) detail of squamous differentiation; (c) detail of neuroendocrine differentiation. (a-c) Haematoxylin and eosin. On immunohistochemistry, the neuroendocrine component showed patchy staining for (d) synaptophysin, (e) CD56, and (f) CK20 (dot-like positivity).

Figure 2

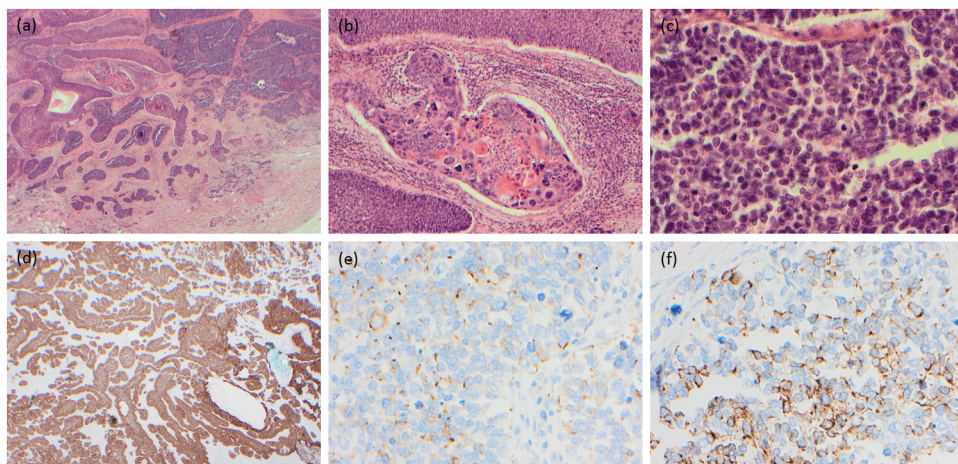
Case 2. The tumour showed a mixture of neuroendocrine and trichilemmal differentiation, visible at (a) low power magnification, and (b) medium power magnification; (c) detail of neuroendocrine differentiation. (a-c) Haematoxylin and eosin. On immunohistochemistry, the neuroendocrine component was positive for (d) CD56, (e) chromogranin, and (f) CK20.

Figure 3

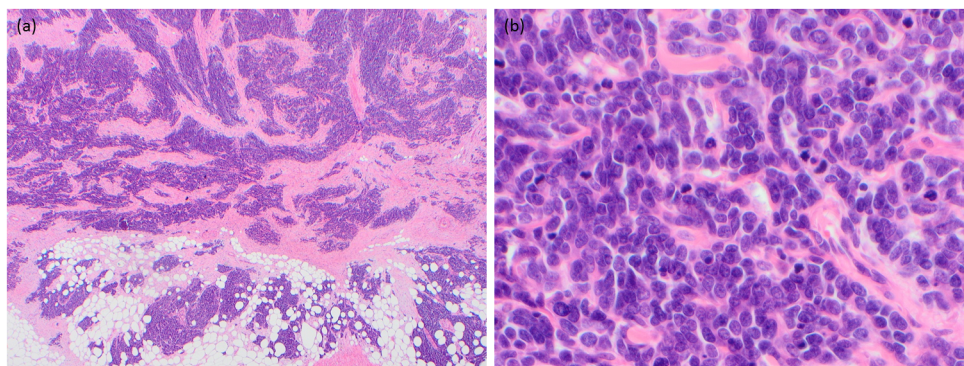
Case 2. At recurrence, the tumour showed exclusively Merkel-cell morphology. (a) Low power magnification. (b) High power magnification. (a-b) Haematoxylin and eosin.



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