

Merkel cell carcinoma: a malignant neuroendocrine tumour of the eyelid

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SUMMARY Merkel cell carcinoma is a recently described tumour which may occur on the face of the elderly. We report such a lesion which presented as a cyst on the eyelid of an 88-year-old woman. This tumour differs from other tumours of the eyelids in its propensity for local and distant spread.

The Merkel cell is an epidermal cell which is distinguished by the presence of peripherally situated dense-core cytoplasmic granules and cytoplasmic filaments, which are features of cells in the diffuse neuroendocrine system.¹ In 1973 Winkleman and Breathnach reviewed the distinctive features of the Merkel cell and predicted that it would give rise to tumours.² Several reports of probable Merkel cell carcinomas have followed.³⁻¹¹ We report a further case of the distinctive cutaneous tumour described by these authors together with histological and ultrastructural studies, which support the hypothesis that it is derived from Merkel cells. We also emphasise the need for histological diagnosis of tumorous lesions of the eyelid.

Case report

An 88-year-old woman attended the outpatient clinic at regular 4-monthly intervals for treatment of chronic simple glaucoma and early cataracts. In May 1982 she was noted to have what appeared to be an enormous chalazion of her right upper eyelid. She declined treatment, but on her next visit in August the cystic lesion was even larger, and it was incised. One month later it had recurred and occupied half of the lid, with sinuous blood vessels coursing over its surface (Fig. 1). At reincision the lesion appeared mostly cystic but was solid at the lid margin. A biopsy of the solid area was taken, on which a diagnosis of Merkel cell carcinoma was made. A full-thickness excision of almost the entire length and depth of the right upper lid (including two-thirds of the tarsal plate) was performed by Mr M. J. Absolon. The lid

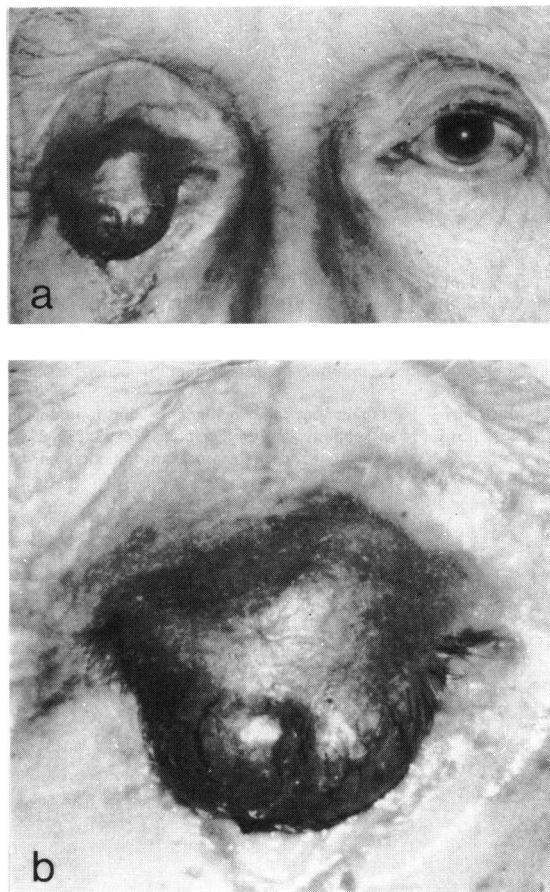


Fig. 1 (a) Eyelid with recurrent angiomatous tumour one month after initial incision. (b) Closer view of the tumour showing sinuous vessels over its surface.



Fig. 2 Postoperative appearance of the eye after opening of the tarsorrhaphy.

was reconstructed by Fox's technique. The postoperative result is shown in Fig. 2. The excision specimen was examined by both light and electron microscopy. At this time there was no evidence of regional lymphadenopathy or of distant metastasis.

Macroscopically the tumour appeared well circumscribed, pale greyish-pink in colour, and with a soft fleshy consistency. Histological examination showed cells filling the dermis in compact sheets, with peripheral areas showing a trabecular pattern. In the centre of the tumour the trabecular pattern was less easily appreciated. A narrow rim of papillary dermis separated the tumour from the epidermis. Vascular invasion was evident in many of the superficial vessels. The cells were uniform in size and shape and

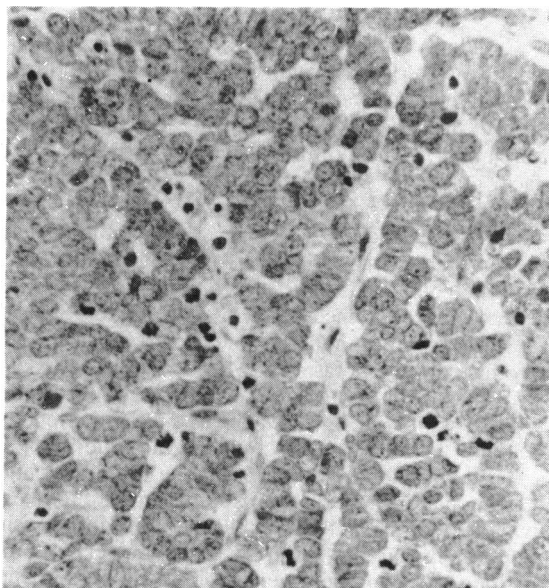


Fig. 3 The tumour cells show a trabecular pattern, with frequent mitotic figures present. (H and E, $\times 220$).

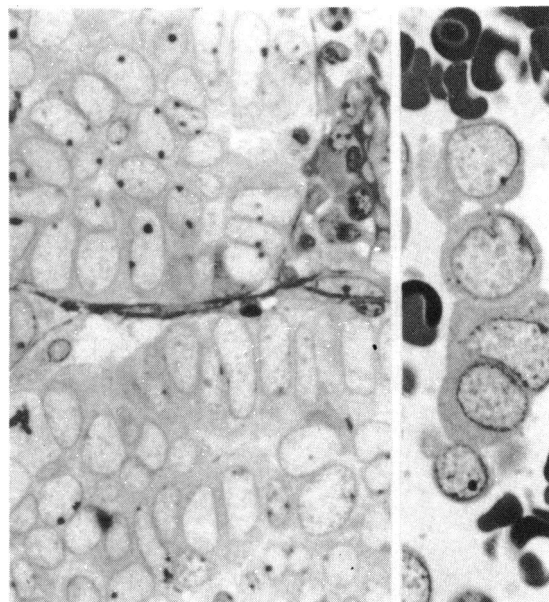


Fig. 4 Plastic section. Tumour cells are uniform with pale nuclei and scanty cytoplasm. (Toluidine blue, $\times 433$). Inset: cells from the edge of the tumour form short trabeculae. (Toluidine blue, $\times 680$).

measured up to $15\ \mu\text{m}$ in diameter. They had a thin rim of pale cytoplasm, well defined nuclei with one or more small nucleoli, and finely dispersed chromatin. A mitotic rate of $95/\text{mm}^2$ was noted. Many plasma cells were present round small blood vessels within the tumour (Fig. 3).

Examination of plastic embedded semithin sections emphasised the trabecular arrangement of tumour cells in addition to the features seen in the paraffin sections. Tumour cells from the edge of the fixed specimen were aggregated into short trabeculae 2 to 6 or 8 cells in length (Fig. 4).

Electron microscopy showed polygonal tumour cells with round to oval nuclei, one to 3 small nucleoli, and finely dispersed heterochromatin. No desmosomes were seen, but occasional macula adherens type junctions were present between tumour cells. The cytoplasm contained numerous ribosomes and polyribosomes and occasional mitochondria and profiles of smooth endoplasmic reticulum. Tangles of paranuclear microfilaments, 7–9 nm in diameter, were seen in many cells. Dense core granules were present in small numbers, with diameters ranging from 120 to 240 nm. These had a central dense body surrounded by a clear halo and were seen next to the Golgi apparatus, intermingled with filaments and aligned along the cell membrane (Fig. 5).

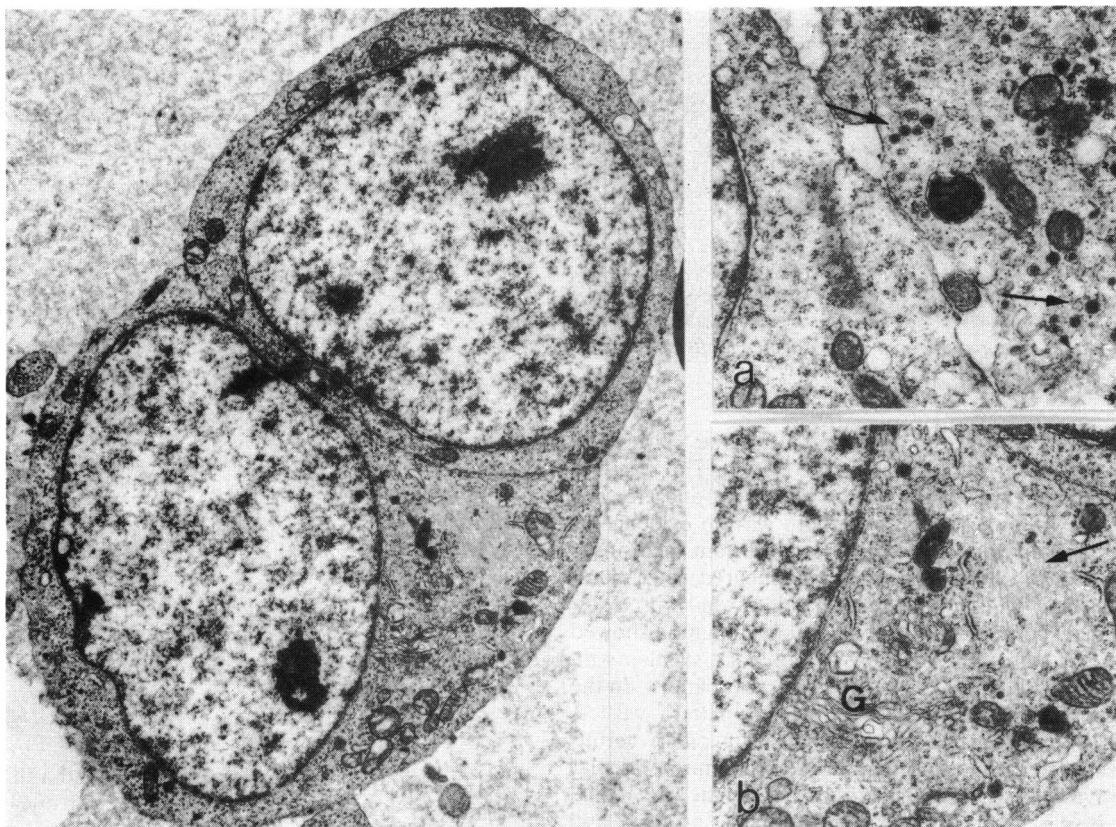


Fig. 5 Electron micrograph of 2 tumour cells. ($\times 4415$). Inset (a): cytoplasmic dense core granules (arrows) ($\times 8615$). Inset (b): cytoplasmic filaments (arrow) and prominent Golgi apparatus (G). ($\times 6892$).

Discussion

The Merkel cell was first described in the snout skin of the vole in 1875.¹² Further reports of its structure and probable neurosecretory role followed nearly a century later.^{2,13} The cells are found in a wide variety of animals. They lie in the lower epidermis in a neurite cup, forming a synaptic connection with fast conducting dermal nerve fibres. Pressure causes degranulation and produces a touch sensation.¹⁴

The origin of the cells remains uncertain. Because they contain dense core granules, a neural crest origin has been suggested.¹⁵ However, Tweedle¹⁶ has shown that the larvae of the amphibian *Ambystoma* retain the ability to develop Merkel cells after they are rendered aneurogenic by removal of the neural crest early in ontogenesis.

The cytoplasmic granules have been shown to contain the endorphin met-enkephalin.¹⁴ There are also reports of probable Merkel cell tumours associated with ectopic production of calcitonin¹⁷ and ACTH.¹⁸

Since Toker's description of trabecular carcinoma¹⁹ several reports have described similar skin tumours in terms such as APUDoma and neuroendocrine carcinoma.³⁻¹¹ The tumours occur on the skin of the face, especially around the eyes, as well as on the limbs and buttocks, as a slowly enlarging often angiomatous nodule present for several months. The patients are elderly, with an average age of 67 years, and the condition is twice as common in women as men. Local recurrence is seen in 24% of cases. Spread to regional lymph nodes is found in 24%, and 22% produce distant metastases, while 9% of patients die of widespread disease. The tumours have been treated with wide local excision, supplemented by regional lymph node dissection and radiotherapy.

Histologically the tumours show a trabecular and nesting pattern and do not usually involve the overlying epidermis. The cells have a monotonously uniform appearance with pale empty nuclei containing one to 3 small peripherally situated nucleoli and scanty pale cytoplasm, with ill defined borders. Mitoses are frequent. Individual cell necrosis and

small foci of necrosis are common. Plasma cells are present round small blood vessels within the tumour. Sidhu *et al.*⁷ described one case showing squamous pearls within the tumour, with cells at the edges of these pearls showing transitional appearances between squamous and Merkel cells. Other examples showed small clumps of cells within the tumours which could be mistaken for squamous pearls.⁸ We did not see this feature in our case.

The differential diagnosis includes other primary cutaneous tumours, together with metastatic deposits of oat cell carcinoma, extraskeletal Ewing's sarcoma, neuroblastoma, and lymphoblastic lymphoma.

Histological examination of any progressively enlarging, apparently cystic lesion of the eyelid of a middle aged or elderly patient is strongly advised to exclude the possibility of a malignant tumour such as Merkel cell carcinoma, which is likely to metastasise and even cause death. A confident diagnosis of Merkel cell carcinoma can be made with the aid of immunohistochemistry and electron microscopy.¹¹

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