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Case report

Granular cell basal cell carcinoma. Light microscopy, immunohistochemical and ultrastructural study

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Summary. Granular cell basal cell carcinoma (BCC) is a rare histological variant of BCC. In this, the fifth reported case, a 67-year-old male with BCC located on the nose, light microscopy examination showed a tumour with the classical configuration of nodular BCC, in which most cells had finely granular eosinophilic cytoplasm. Ultrastructural observation showed numerous lysosome-like granules filling the cytoplasm of tumour cells, along with numerous well-formed pentalaminate desmosomes. Immunohistochemical profile (including positivity for keratins C 5.2 and AE 1 and for Leu-M1), together with the presence of cytoplasmic tonofilament bundles and desmosomes, are consistent with the proposed epithelial origin of granular cells in this tumour.

Key words: Basal cell carcinoma – Skin tumours – Granular cell tumours – Granular cell basal cell carcinoma

Introduction

Basal cell carcinoma (BCC) is a cutaneous tumour, which occurs in a number of histological forms (Reidbord et al. 1971; Wade and Ackerman 1978; Lever and Schaumburg-Lever 1990), possibly reflecting the proposed origin of this tumour from pluripotential germ cells of the skin. A variant containing granular cells was described by Barr and Graham in 1979. In their two cases, cells with granular cytoplasm were present in the centre of the tumour islands in otherwise typical BCCs. Electron microscopy showed lysosome-like granules in the cytoplasm of tumour cells, similar to those seen in granular cell tumours (Sobel and Marquet 1974). Subsequently, Mrak and Baker (1987) and Le Boit et al. (1991) have reported two additional cases of granular cell BCC. We report a case of granular cell BCC, the fifth in the medical literature, in which most tumour cells showed abundant granularity at light microscopy, and almost all cells showed lysosome-like granules at electron microscopy.

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Case report

A 67-year-old man presented with a papular skin lesion located on the left side of the dorsum of his nose, which had been present for several years. Wide excision of the lesion was performed with immediate skin graft. The patient remains free of relapse 14 months later.

Materials and methods

For light microscopy, representative sections were fixed in 10% formalin, dehydrated in a graduated series of alcohols, and embedded in paraffin. Sections were stained with haematoxylin and eosin. Avidin-biotin-peroxidase complex staining was performed on paraffin-embedded tissue, with antibodies directed against the following antigens: epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), Leu-M1, BRST-2, S-100 protein, Mac 387, CD 68, CAM 5.2, K 903, K 904 AE 8, AE 1, K 7, K 19 and lysozyme. For electron microscopy, formalin-fixed tissue was cut in 1-mm cubes and re-fixed in 4% glutaraldehyde/1.2 M Millonig's phosphate buffer, pH 7.3, for 2–3 h at 25° C. Subsequently, it was postfixed in 1% osmium tetroxide/0.2 M Millonig's phosphate buffer at 25° C for 45 min, and dehydrated in a series of graduated ethanol solutions. The tissue was stained with 1% uranyl acetate in 50% ethanol and was later embedded in Epon 812. Semi-thin sections 0.5 μm thick, were prepared and stained with toluidine blue. Representative areas were selected for study and were cut in ultra-thin sections, stained with uranyl acetate and lead citrate and examined by electron microscopy.

Results

The resected specimen consisted of a circle of white skin measuring 2 cm in diameter, with a central 1 cm papule. On section, the tumour was grey and firm.

Histologically, it seemed to have arisen from the basal layers of the epidermis and grew deep into the dermis, forming tumour nests (Fig. 1). The dermis was replaced by such epithelial islands and well-demarcated lobules, some of which were in continuity with the epidermis. There was peripheral palisading (Fig. 2), and retraction

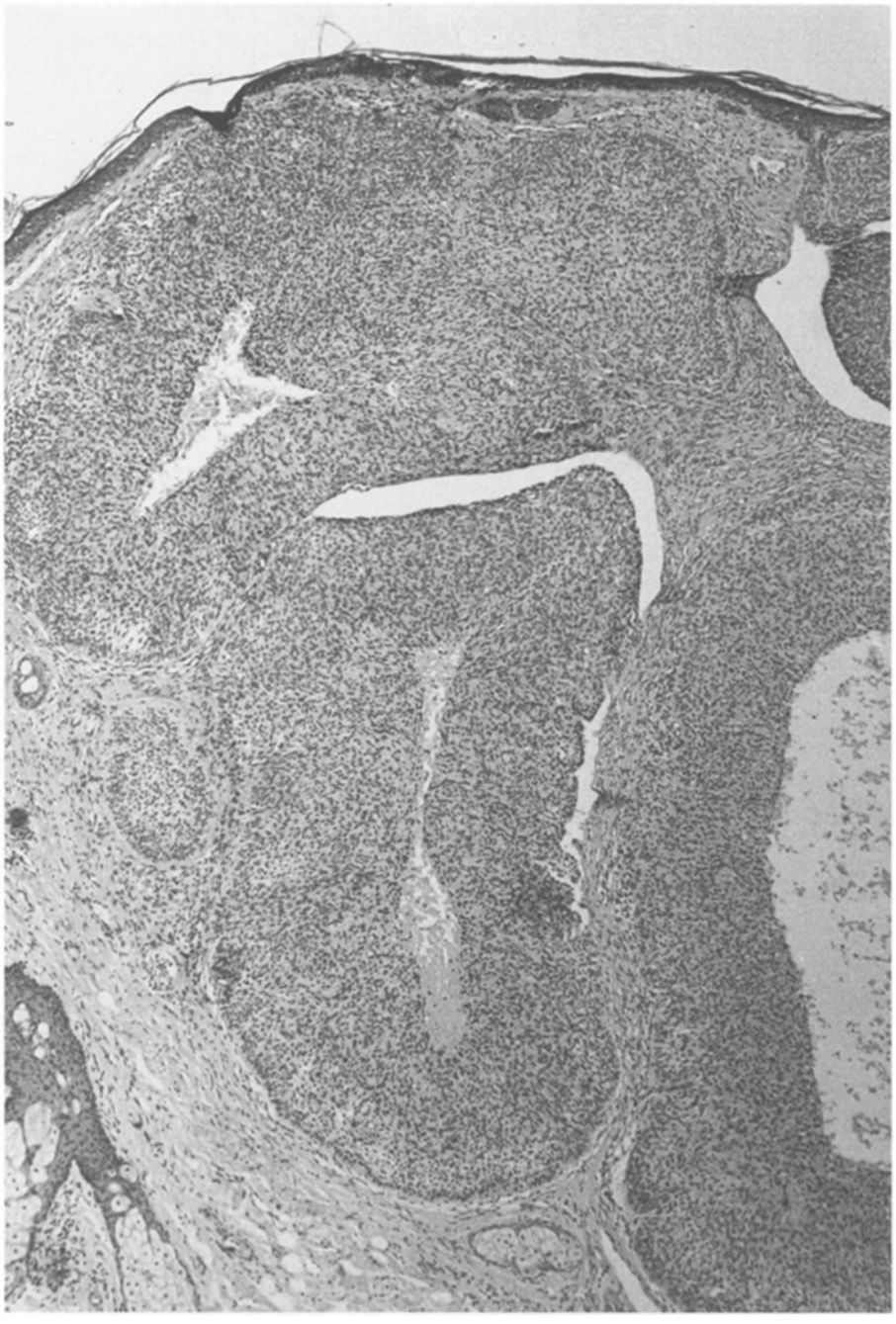

Fig. 1. Low-power photo-micrograph of the tumour, showing lobulated cell islands filling the dermis. Note peripheral palisading and retraction artefacts from adjacent stroma. H & E, ×40

artefacts from adjacent stroma, as seen in most BCCs, were evident. Tumour islands were well demarcated by a peripheral palisade of basaloid cells and all the rest consisted of monomorphic round cells with abundant eosinophilic and delicately granular cytoplasm (Fig. 3) and with vesicular nuclei. No mitosis were seen.

Electron microscopy showed a proliferation of uniform epithelial-appearing cells in scanty stroma. Tumour cells contained abundant pentalaminate desmosomes with attached tonofilaments (Fig. 4). The cytoplasm of these cells was filled with lysosome-like granules lined by unit membranes, measuring 0.2–0.4 μm. The content of such granules was pleomorphic, with round electron-dense bodies, which were either granular, homogeneous or mixed, in addition to partially degenerated membranous debris. All other organelles were few in number (Fig. 5).

Immunoperoxidase staining showed immunoreactivity for the epithelial markers Leu-M1, CAM 5.2 and AE 1 in tumour cells (Fig. 6). The most intense staining was with CAM 5.2. Tumour cells did not show positivity for EMA, CEA, BRST-2, S-100 protein, K 903, AE 8, K 7, K 19, lysozyme, Mac 387, CD 68 and K 904.

Discussion

The histogenesis of granular cell tumours has always been controversial. In the skin, the following types of

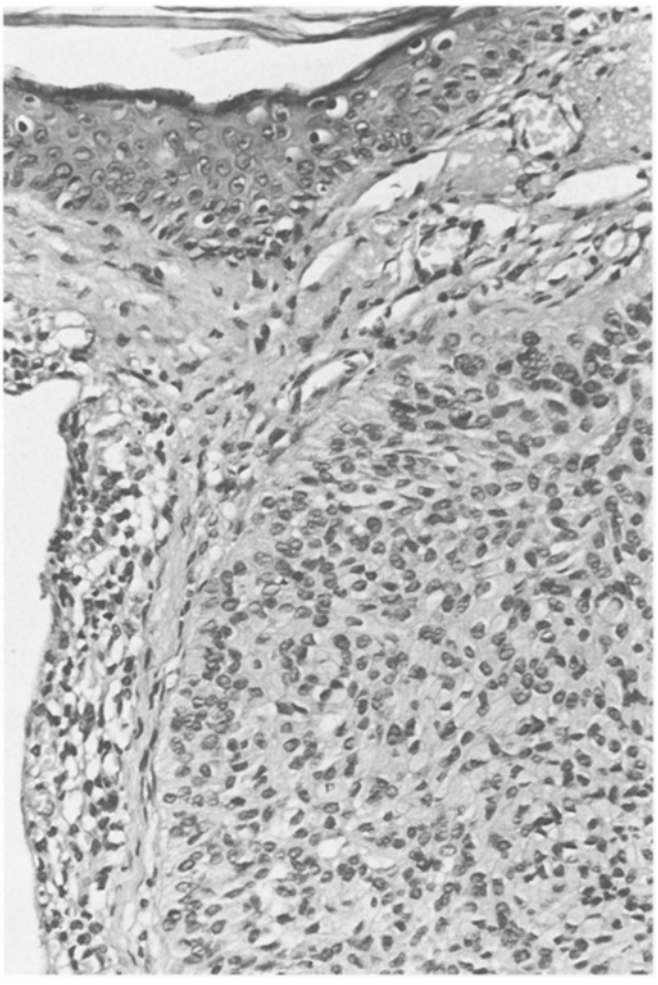

Fig. 2. High power micrograph of granular cell basal cell carcinoma. Note cytoplasmic granularity and peripheral palisading. H & E, ×100

neoplasms and reactive lesions have been noted to contain granular cells: granular cell myoblastoma (first reported by Abrikosoff in 1926), schwannoma with granular cells (Sobel et al. 1973a), granular cell BCC (Barr and Graham 1979), granular cell angiosarcoma (McWilliam and Harris 1985), granular cell leiomyosarcoma (Suster and Rosen 1988), granular cell ameloblastoma (Hartman 1974) and primitive polypoid granular cell tumour (Le Boit et al. 1991). It is now widely accepted that the presence of granular cells in a given tumour is not specific of a cell lineage, since they can appear both in epithelial and mesenchymal tumours (Le Boit et al. 1991).

The best known of these is granular cell myoblastoma. At light microscopy, this tumour is characterized by large polyhedral cells with granular eosinophilic cytoplasm. In electron microscopy, along with the presence of lysosome-like granules of variable size (identical to those seen in other granular cell tumours), two distinctive features can be seen: absence of desmosomes [except for a single report (Khansur et al. 1985] and presence of angulate bodies; oval-shaped structures that are composed of an admixture of fibrils and tubules with a limiting unit membrane. The presence of this organelle, seen also in some schwannomas (Sobel et al. 1973a), has led some authors to suggest a nerve-related origin for this tumour, probably arising from undifferentiated mesenchymal cells, potentially the precursors of Schwann cells (Sobel et al. 1973b).

Granular cell BCC was first described by Barr and Graham in 1979. To date, five cases of this rare variant of BCC have been reported (Table 1). In all of them, including this case, the diagnosis of BCC is based on the location, shape and size of nests of tumour cells, which are similar to those typical of BCC. The granular cell variant can be recognized by cytological features,

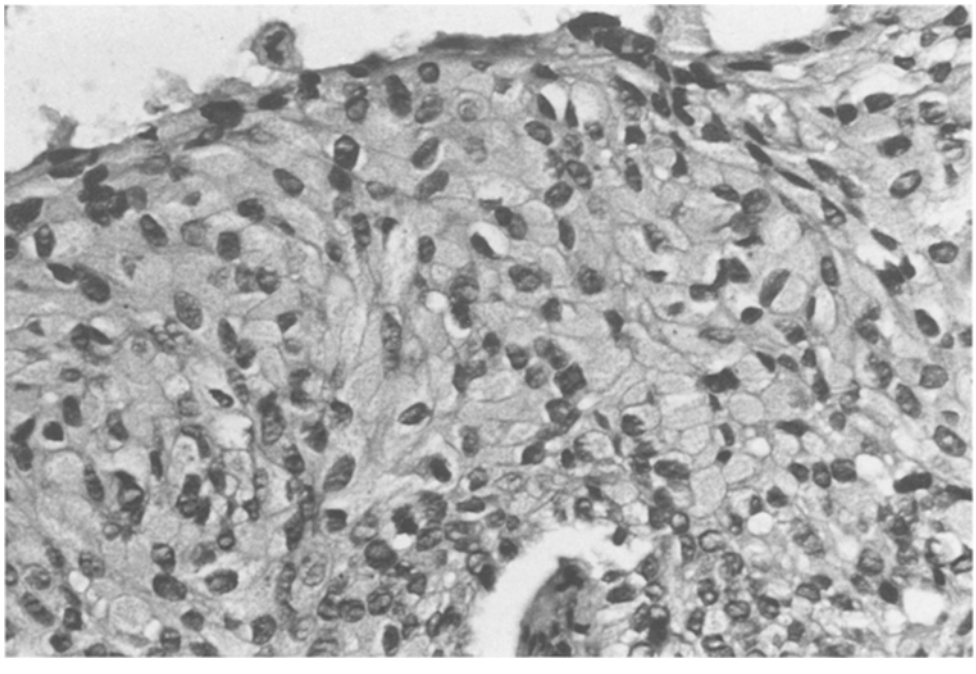

Fig. 3. Granular cell basal carcinoma. Note characteristic granular cells with eccentric nuclei. H & E, ×400

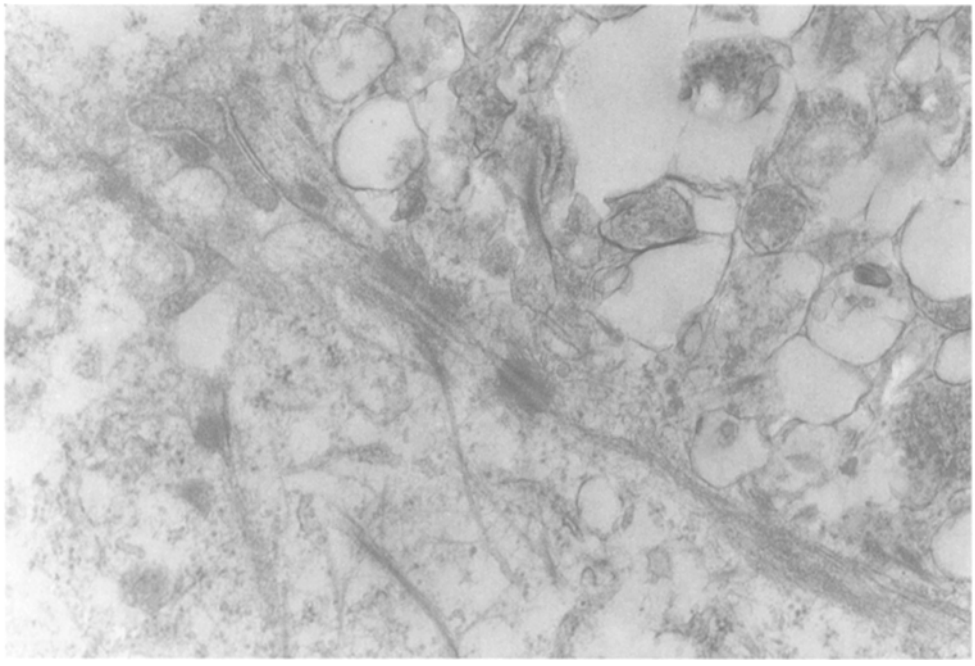

Fig. 4. Ultrastructure of granular cell basal cell carcinoma. Well-formed desmosomes with attached tonofilaments can be seen. ×48000

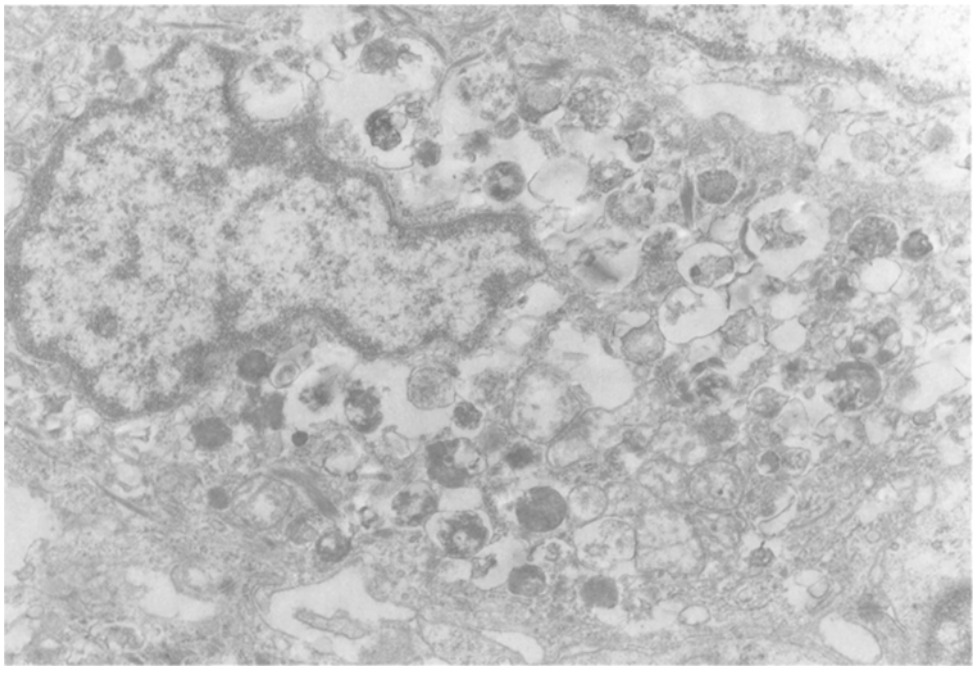

Fig. 5. Electron micrograph of granular cell basal cell carcinoma shows numerous lysosome-like granules within cytoplasm, along with tonofilaments and well-formed desmosomes. ×18000

Table 1. Clinical features of granular cell basal cell carcinoma

Reference	Age/sex	Site	Size	Treatment	Relapse	Updated status	Follow-up
Barr and Graham 1979	72/male	Nose	0.7 cm	Surgery	No	Disease-free	4 months
Barr and Graham 1979	Elderly/male	Face	1.3 cm	Surgery	NR[a]	Disease-free	NR[a]
Mrak and Baker 1987	67 female	Right supra-clavicular	NR[a]	Radiation	Yes[b]	Disease-free	12 years
LeBoit et al. 1991	30/female	Lower eyelid	"Small"	Surgery	No	Disease-free	30 months
Present case	67/male	Nose	1 cm	Surgery	No	Disease-free	2 months

[a] NR, not reported
[b] Twelve years after first diagnosis

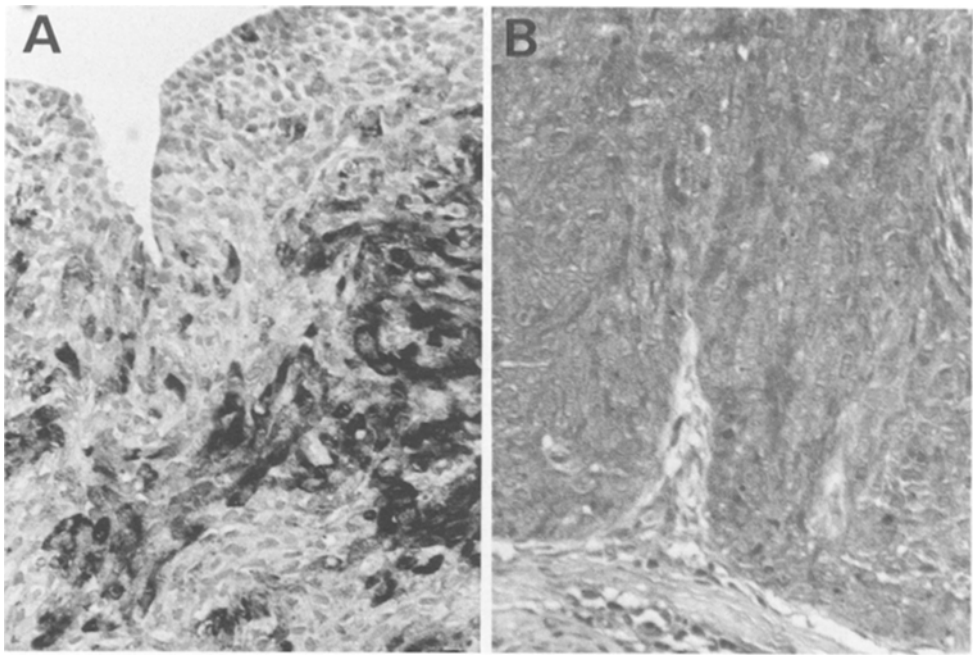

Fig. 6. A Positivity of tumour cells for low-molecular-weight cytokeratins (CAM 5.2). ×100. **B** Positivity of tumour cells for Leu-M1. ×100

with granular eosinophilic cytoplasm in most (Barr and Graham 1979; Le Boit et al. 1991) or all tumour cells (Mrak and Baker 1987). Ultrastructural features (lysosome-like granules filling the cytoplasm, presence of pentalaminate desmosomes with attached tonofilaments and absence of angulate bodies) support the diagnosis and allow differentiation from other granular cell tumours. No behaviour differing from ordinary BCC has been observed.

The only tumour with histological and ultrastructural features identical to granular cell BCC is the granular cell variant of ameloblastoma (Hartman 1974), and location readily differentiates these two tumours.

Immunohistology of granular cell BCC, reported previously in one case (Le Boit et al. 1991), includes positivity for AE 1 and AE 3 keratins and negativity for S-100 protein. In this case the immunophenotype is similar (positivity for CAM 5.2, AE 1 and Leu-M1 and negativity for S-100 protein) supporting an epithelial origin. The nature of the characteristic granules of this tumour remain a matter for speculation (Barr and Graham 1979; Mrak and Baker 1987; Le Boit et al. 1991). The immunoperoxidase stain for lysozyme was repeatedly negative in the present case, arguing against a proposed lysosomal interpretation for such granules. However, although definitive immunohistochemical demonstration of lysosomal enzymes in the granules of granular cell BCC is lacking, there seems little reason to doubt that the single-membrane-bound bodies with heterogeneous contents seen in granular BCC are in fact lysosomes, since identical granules which are characteristic of granular cell myoblastoma have been shown convincingly to be of lysosomal origin (Sobel et al. 1973b). A provocative hypothesis was suggested by Mittal and True in 1988, who showed evidence that such granules arise from infoldings of cell membrane by a process similar to myelin formation; these are subsequently phagocytosed by lysosomes. This might also be the case in granular cell BCC and other granular cell tumours, providing a tentative explanation for the presence of similar granules in tumours of different lineages.

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