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Granular cell tumour of the mammary gland simulating malignancy

A report on two cases with light microscopy, transmission electron microscopy and immunohistochemical investigation

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Summary. Primary granular cell tumours of the breast in 35 and 55 year old women were studied by light microscopy, transmission electron microscopy and immunohistochemistry. Light and electron microscopy revealed a neural origin of the tumours and this was further substantiated by immunohistochemical studies, with positive S-100 protein reaction and negative reactions for surface heavy and light chains, CEA, alfa-1-antitrypsin, muramidase and GFA-protein. Granular cell tumour of the mammary gland is a very rare tumour. Clinically it sometimes simulates carcinoma because of its fibrous consistency, fixation to pectoral fascia and skin retraction. The diagnosis of granular cell tumour should be included in the differential diagnosis of carcinoma of the breast.

The granular cell tumour is derived from neuro-ectodermal tissue. Whether it represents a neurogenic cell-confined metabolic disturbance with lysosomal activation, or a true neoplasm remains to be elucidated.

Key words: Immunohistochemistry – Electron microscopy – Light microscopy – Granular cell tumour – Mammary gland neoplasm

In 1926 Abrikosoff described a tumour of the tongue composed of granular cells which he believed to be derived from striated muscle. Since then identical lesions have been described from a varity of organs including the female breast parenchyma (van Toth 1972). In this localisation, however, the entity is distinctly uncommon (Azzopardi 1979). Mulcair (1968) found a total of only 15 granular cell tumours of the breast parenchyma and added another 15 of his own. Umansk and Bullock (1968) reported 19 cases including both breast and overlying skin. Van Toth (1972) tabulated 100 cases from

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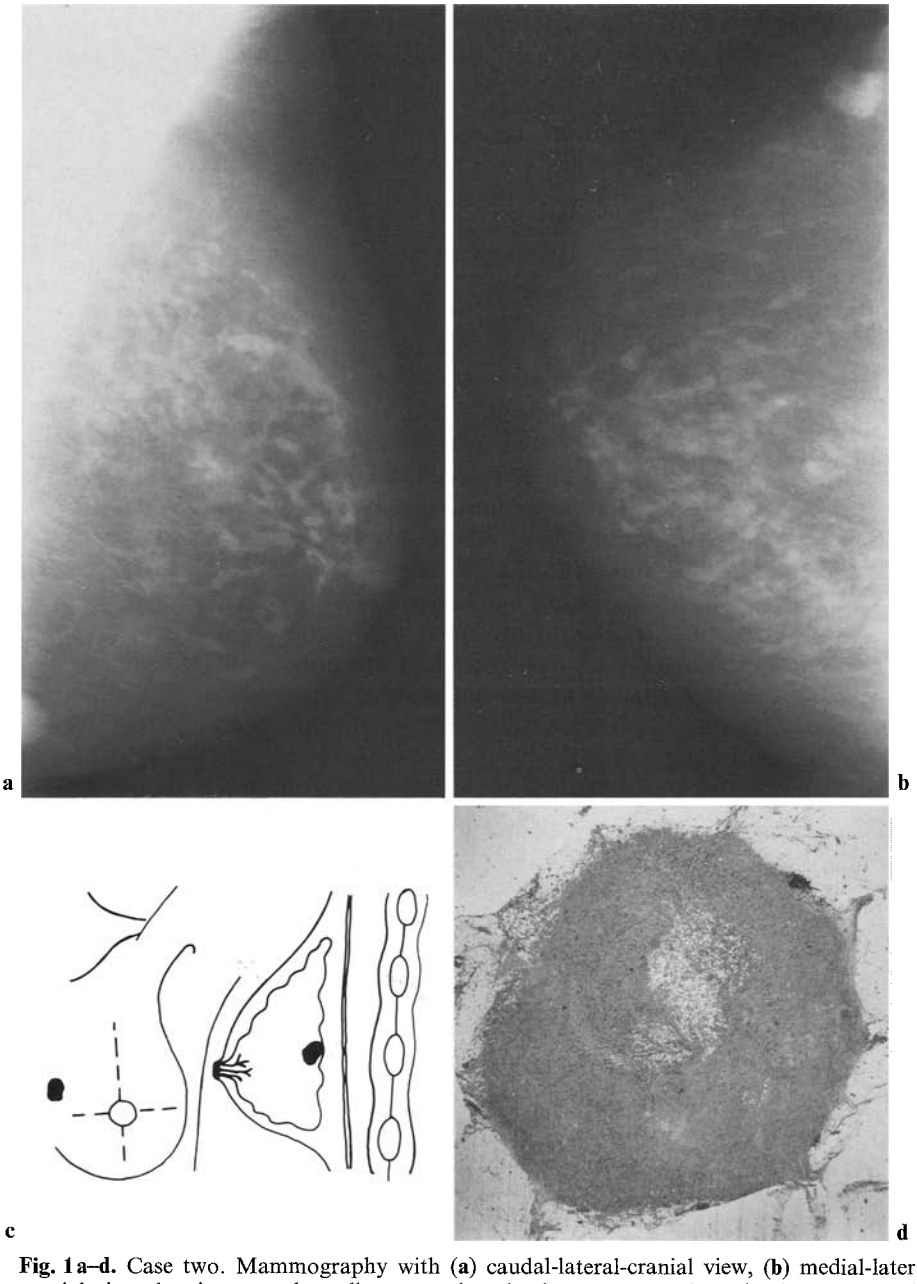


Fig. 1a–d. Case two. Mammography with (**a**) caudal-lateral-cranial view, (**b**) medial-lateral-cranial view showing granular cell tumour deep in the mammary tissue in the upper medial quadrant. (**c**) simplified illustration of the tumour location. (**d**) section of non-encapsulated tumour in case two within atropic breast tissue. HE ×4

the world literature, 93 in female and 7 in male patients but included cases which more properly should be classified as cutaneous lesions. Cytologically diagnosed granular cell tumours are also on record (Sussman et al. 1973; Zajdela 1975; Löwhagen and Rubio 1977). According to Weitzner et al. 1981 only 52 true intramammary granular cell tumours were on record. They made a survey of these cases and added two of their own. Since then another 3 cases have been reported (McCracken et al. 1979; Jena et al. 1982). The aim of this investigation is to study two examples of a granular cell tumour of the female breast parenchyma, not involving skin or fascial tissue. The tumours were studied by light microscopy, transmission electron microscopy and immunohistochemically.

Case reports

Case one. A previously healthy 35 year old woman was admitted for a tumour in the left breast. She had two children and regular menstrual flow. One year earlier she had noticed the tumour and had been examined twice at another hospital. No biopsies were taken and no mammography was performed at that time. At clinical examination a hard, well defined tumour situated in the upper medial quadrant near the areolar margin deep in the mammary tissue was palpated. The size was estimated to be about 10×10 mm, and the tumour was not fixed to the skin or to the pectoral muscle. As malignancy was suspected the tumour was excised for histological examination. The postoperative cause was uneventful and no recurrence has been noticed at fullow up.

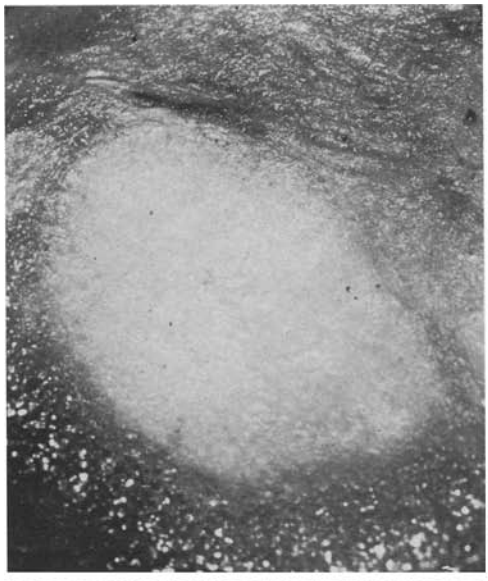
Case two. Fifty-five year old immigrant, with past history of malaria, tonsillectomy and uterine myomata, presented with a 1.5 cm firm mass in the upper inner quadrant of the left breast. The tumour was fixed to the deeper structures at palpation. Cytology revealed naked polymorpic nuclei having large nucleoli and malignancy was suspected. Two plain mammography examinations revealed a lesion of uncertain nature, possibly a carcinoma (Fig. 1 A–C). A mastectomy with axillary dissection was performed. The postoperative cause was uneventful and no recurrence has been detected at follow up.

Methods

Light microscopy. Formalin-fixed, paraffin-embedded tumour tissue was sectioned at 5 mμ and stained with Haematoxylin-eosin, van Gieson's connective tissue staining, Gordon-Sweet procedure for reticulin and PAS for neutral mucins and glucogen.

Table 1. Survey of the antisera used and the immunoreactions of the granular cell tumors of the breast

Antisera raised against	Immunocytochemistry of the tumour
IgA	Neg
IgG	Neg
IgM	Neg
Kappa-chains	Neg
Lambda-chains	Neg
GFA-protein	Neg
Muramidase	Neg
CEA	Neg
alfa-1-antitrypsin	Neg
S-100 protein	Pos



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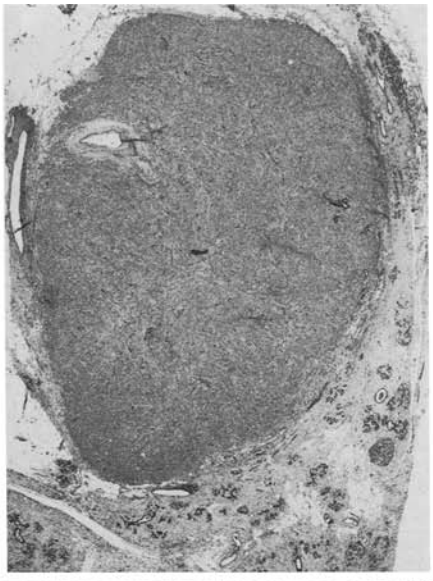

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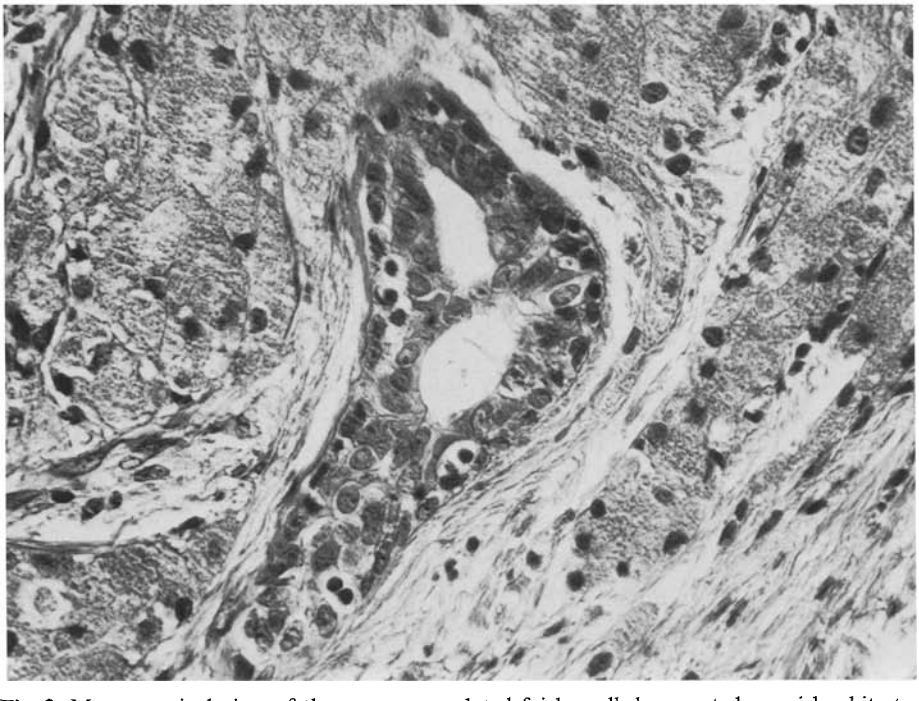

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Fig. 2. Macroscopical view of the non-encapsulated fairly well demarcated, greyish-white tumour (case one)

Fig. 3. Section of tumour showing the obvious intramammary location. (case one) HE ×7

Fig. 4. Higher magnification of tumour, with small dark nuclei and granular cytoplasm, growing within mammary tissue. Note tubular structures surrounded by tumour cells. (case one) HE ×210

Electron microscopy. One mm^3 blocks of tumour tissue were postfixed in glutaraldehyde and osmium-textroxide, counterstained in uranylacetate and embedded in Epon as described previously (Willén et al. 1975).

Immunocytochemistry. The immunohistochemical demonstration of immunoglobulins was performed by an indirect immunoperoxidase conjugate technique (Taylor and Burns 1974; Burns 1978). The antisera used are given in Table 1. The method has in detail been described elsewhere (Alm et al. 1983). All the immunoglobulin antisera, normal swine serum and peroxidase conjugated swine antirabbit immunoglobulin were purchased from DAKO Immunoglobulins AB, Stockholm, Sweden. Purification, production and staining levels of antisera against S-100 protein has previously been described in detail (Haglid et al. 1973; Angervall et al. 1984; Kindblom et al. 1983).

Results

Gross appearance. The specimen from case one consisted of a $6 \times 4 \times 3$ cm mammary tissue fragment without skin or fascial tissue. Centrally a non-encapsulated $2{,}5 \times 2 \times 2$ cm well demarcated, solid, greyish-white tumour was seen (Fig. 2). The specimen from case two consisted of a small left breast with fatty, atrophic breast tissue. In the upper inner quadrant a 1.5 cm firm greyish non-encapsulated tumour was seen.

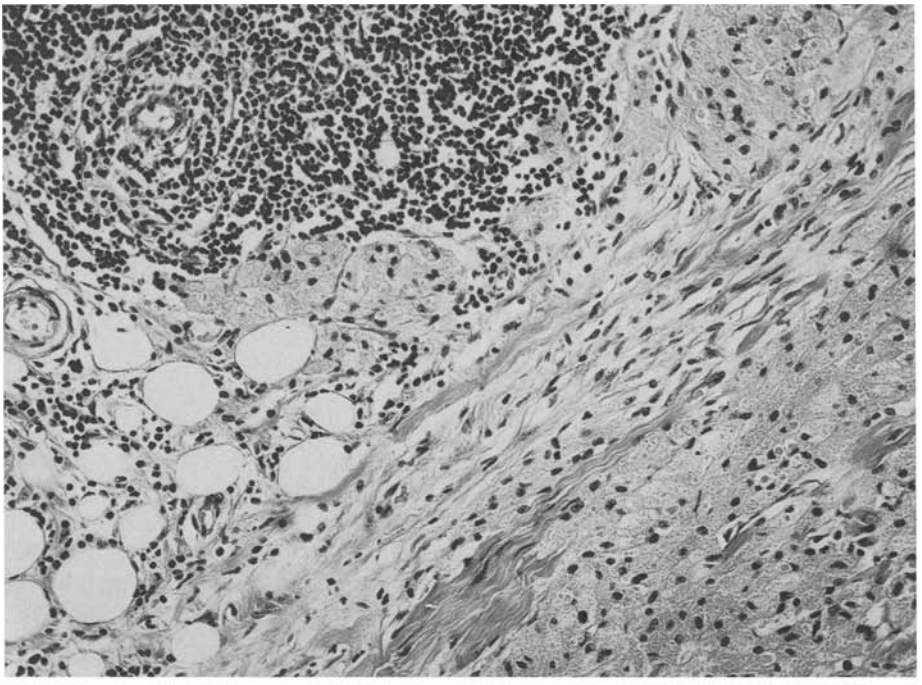
Microscopy. Light microscopy from both tumours revealed tumour cells arranged in nests and clusters of varying size and randomly placed within ordinary mammary tissue (Fig. 1D and 3). The cells themselves had indistinct cell borders and abundant cytoplasm that contained numerous small eosinophilic granules and a few small vacuoles. The granules stained positively with PAS staining (Fig. 4 and 5).

Immunohistochemical findings. The result of the immunohistochemical reactions are shown in Table 1; only S-100 protein was positive. Interestingly, the cytoplasm and nuclei of a peripheral nerve also showed a positive reaction for S-100 protein (Fig. 6).

Electron microscopy. The tumour cells were arranged in compact groups of cells surrounded by abundant collagen and a few histiocytes. Each of the granular cells was surrounded by a distinct basement membrane (Fig. 7). Unmyelinated axons were present and neurotubles, neurofilaments and mitochondria were observed (Fig. 8). Cell inclusions of three types were detected: osmophilic bodies with concentric lamellae, homogenous lighter bodies and aggregates of tubular filaments (Fig. 9).

Discussion

The histogenesis of granular cell tumour is still unsettled. Abrikosoff (1926) thought that granular cell tumours originated from striated muscle. In 1935 Feyrter proposed that they could be derived from neural tissue, an idea that has received considerable support in recent years. It has been suggested that these tumours are derived from Schwann cells (Sobel et al. 1971), peri-



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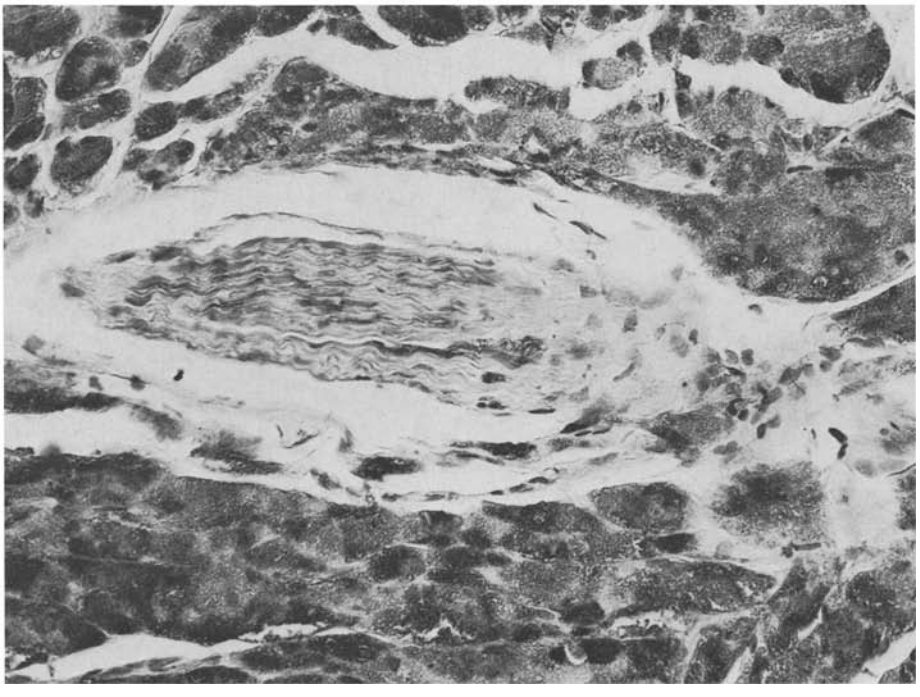

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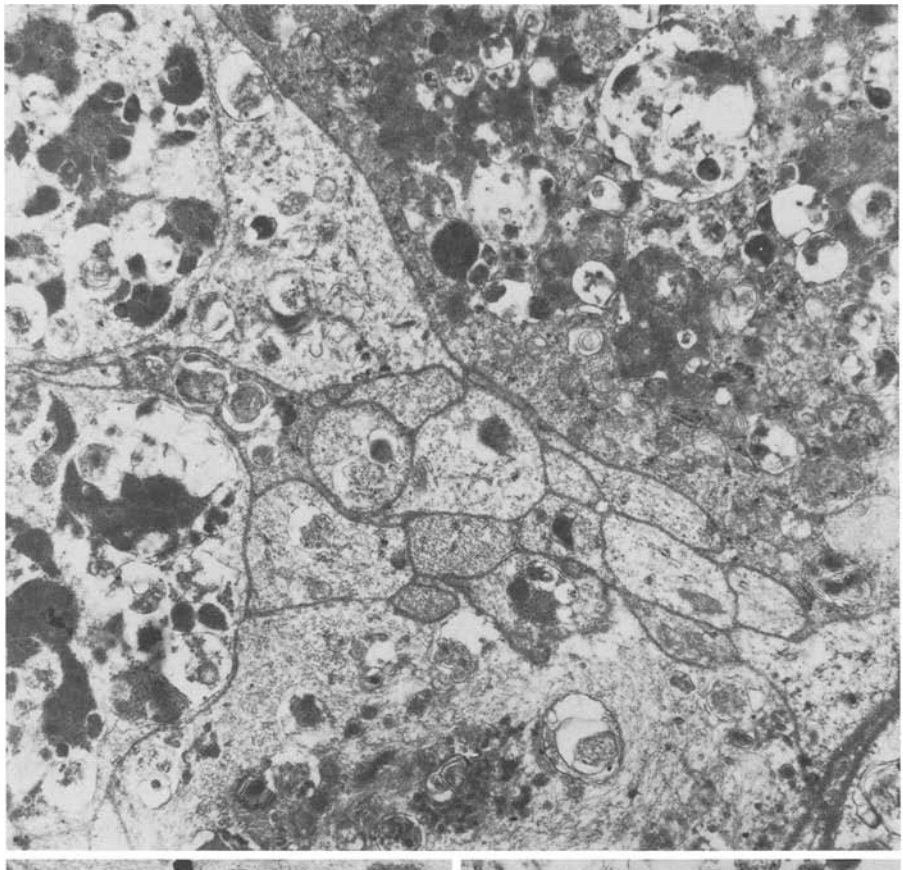
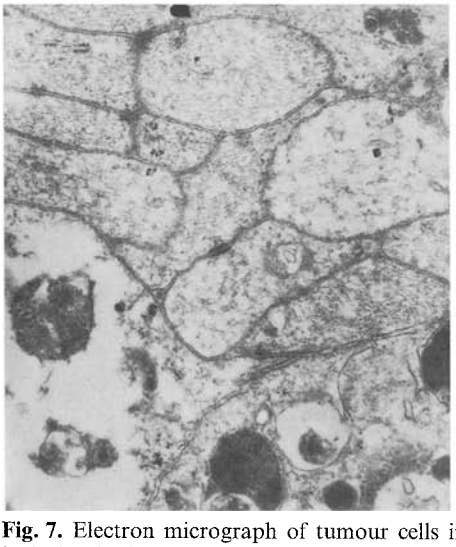
Fig. 5. Higher magnification of tumour in case two, growing in atropic breast tissue. HE $\times 90$

Fig. 6. Immunoperoxidase staining against S-100 protein within the granular cell tumour. Note extensive cytoplasmic staining of the tumour cells as well as cytoplasmic granules within Schwann cells in peripheral nerve (center). $\times 285$





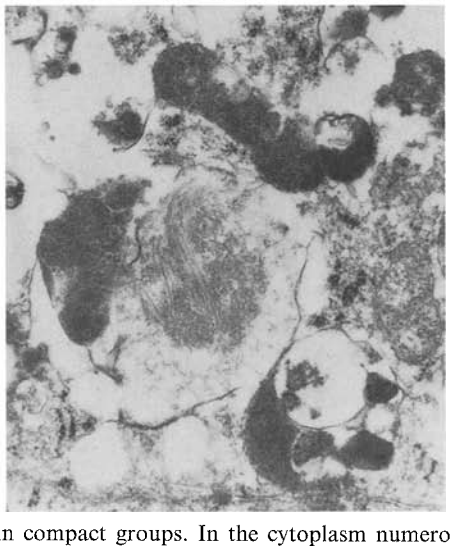


Fig. 7. Electron micrograph of tumour cells in compact groups. In the cytoplasm numerous inclusion bodies are seen. Electron micrograph × 10,000

Fig. 8. Unmyelinated axons containing tubular filaments, focal densities and inclusion bodies. Electron micrograph × 26,400

Fig. 9. Cytoplasm of a granular tumour cell containing three types of inclusion bodies; osmophilic bodies with concentric lamellae, homogenous light bodies and aggregates of tubular filaments. Electron micrograph × 44,800

neural fibroblasts or primitive mesenchymal cells (Sobel and Marquet 1974; Garancis et al. 1970) or even histocytes (Azzopardi 1956).

By immunohistochemical studies, using S-100 protein antibody localisation, both glial and neuronal cells have been demonstrated to contain S-100 protein (Yamaguchi 1980; Ludwin et al. 1976). In the peripheral nervous system S-100 has been found in Schwann cells (Yamagushi 1980).

The presence of this protein has also been shown in neural tissue neoplasm such as gliomas, astrocytomas, ependymomas and schwannomas (Haglid et al. 1973; Rydén and McEwen 1966).

Outside the central nervous system S-100 protein is found in granular cell tumours, neurofibromas, Schwann cell tumours (Nakazato et al. 1982; Stefansson and Wollman 1982), plexiform nerve sheath myxoma (Angervall et al. 1984), clear cell sarcoma of tendons and aponeuroses (Kindblom et al. 1983), melanomas (Stefansson and Wollman 1982) as well as in cultured human melanoma cells (Gaynor et al. 1980).

Our two cases contained S-100 protein immunohistochemically in the tumour as well as in adjacent peripheral nerve tissue. We therefore support the view that our tumour was of neuro-ectodermal origin.

Shousha and Lyssiottis (1979) demonstrated the presence of carcinoembryogenic antigen (CEA) in 10 cases of granular cell tumours. They did not find CEA in Schwann-cells, schwannomas or neurofibromas, but found it in some cells within the perineural sheath. They suggested that this supports the original view by Pears (1950) that granular cells tumours were derived from perineural cells rather than Schwann cells. In our case no CEA could be detected and this again speaks for a schwann cell origin.

A negative stain for muramidase is against a histiocytic genesis and negative reactions for light and heavy chains, against a lymphocytic one. Negative reactions for CEA and alfa-1-anti-trypsin are not in favour of an epithelial histogenesis. GFA-protein is never seen positive in perpheral neural tumours, thus supporting the view that our tumour was derived from peripheral nerve tissue.

By electron microscopy Apparicio and Lumbsden (1969) thought the tumour to be derived from an undifferentiated mesenchymal cell. Sobel et al. (1971) originally argued for an Schwann cell genesis but subsequently (Sobel and Marquet 1974) derivating from a primitive mesenchymal cell. The electron microscopic picture of the granular cell tumour in our case is in keeping with the findings of Becher-Carstens 1970 and Ahmed 1978 e.g. derivation from Schwann-cells and unmyelinated axons.

Granular cell tumours of the breast can simulate cancer both clinically and macroscopically (Azzopardi 1979). They may be fixed to the skin or pectoral fascia with signs of skin retraction, have a very firm consistency, they are not frequently mobile and usually not well circumscribed. The yellowish colour and fibrous consistency makes it difficult to differentiate them from carcinoma. Only microscopical examination will reveal the proper diagnosis, as demonstrated by this case. The diagnosis of granular cell tumour can also be made cytologically, provided that this rare type of tumour is kept in mind (Lövhagen and Rubio 1977). Granular cell tu-

mours of the breast are mostly situated within the upper medial quadrant of the breast (Mulcare 1968; Weitzner 1981) which was also the case in this report. Differentiation from traumatic (reactive) noduls is easily based on light and electronmicroscopical uniform granules, staining reactions including haemosiderin (Sobel et al. 1974). Differentiation for other granular cell lesions have been outlined elsewhere in great detail (Sobel and Marquet 1974).

Only a few of these tumours have been reported to be malignant or have an aggressive growth pattern (Crawford and De Bakey 1953; Kirschner 1962; Van Toth 1972). However, they can easily be reported as malignant tumours on frozen sections, if the pathologist is not aware of this entity (Umansky and Bulloch 1968; Mulcare 1968; Mc Cracken et al. 1979 and Weitzner et al. 1981).

As regards therapy a simple excision is adequate as this type of tumour is benign. In very rare cases, when malignant forms are found, more aggresive surgery may be required (Umanski and Bullock 1968).

The granular cell tumour is derived from neuro-ectodermal tissue. Whether it represents a neurogenic cell-confined metabolic disturbance with lysosomal activation, or a true neoplasm remains to be elusidated.

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