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Granular cell tumour of the breast

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Summary. Eight cases of benign granular cell tumour of the breast are reported. Seven patients were women and one was male. The age at the time of the excision ranged from 17 to 73 (average 40.1) years. All tumours were positive for S-100 protein and negative for keratin, myoglobin and gross cystic disease fluid protein. In two cases ultrastructural studies revealed findings identical to those in the previously reported cases of granular cell tumours. None of these cases were diagnosed preoperatively. In six cases the clinical and mammographic findings, and in one case the frozen section, led to an erroneous diagnosis of malignancy. The clinico-pathological features of the cases are delineated in order to draw attention to a benign condition which closely simulates malignancy.

Key words: Breast – Granular cell tumour – Mammography – Ultrastructure – Immunohistochemistry

Introduction

When a lump is discovered in the breast, much attention is usually given to its physical and radiological appearance. A firm consistency, poor definition of the borders, and lack of mobility are all signs considered suspicious of malignancy. These features may, however, be observed in some common benign breast conditions such as radial scar, sclerosing adenosis and fat necrosis (Azzopardi 1979).

Granular cell tumour (GCT), a rare neoplasm that may occur in a wide variety of cutaneous and visceral sites (Morrison et al. 1987) does not commonly involve the breast (Azzopardi 1979). When it does arise there, this benign tumour may be misdiagnosed as a malignancy because of its irregular margins, fixation to the pectoral muscle and retraction of the overlying skin (Haagensen 1971; Kalbfleish et al. 1978; McCracken et al. 1979; Mulcare 1968).

Here we present the clinical findings of eight cases of GCT of the breast, including mammographic findings in five of the cases. Each case was characterized histologically and immunohistochemically, and two cases were studied using electron microscopy.

Materials and methods

The cases were retrieved from the files of the Department of Pathology of the Massachusetts General Hospital, Boston (USA) (four cases), the Royal Surrey County Hospital, Guildford (UK) (two cases), St. George's Hospital of the University of London (UK) (one case) and the Bellaria Hospital of the University of Bologna, Italy (one case). Patient records, radiographs, and pathology materials from all patients were obtained.

Tissues for histology were fixed in 10% buffered formalin, embedded in paraffin and stained with haematoxylin and eosin (H &

Table 1. Antisera employed for immunohistochemistry

Antiserum	M/P	Source	Dilution
Anti-S100 protein	P	Dakopatts, Santa Barbara, California	1:3600
Anti-vimentin	M	Dakopatts, Santa Barbara, California	1:200
Anti-myoglobin	P	Dakopatts, Santa Barbara, California	1:1800
Anti-keratin (low molecular weight)	M	Ortho Diagnostic Systems, Milan, Italy	1:1500
Anti-keratin (high molecular weight)	M	Ortho Diagnostic System, Milan, Italy	1:1500
Anti-GCDFP-15	P	Dr. D.E. Haagensen, Boston, USA	1:10000

P, Polyclonal; M, monoclonal; GCDFP-15, gross cystic disease fluid protein (Haagensen et al. 1979)

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E) and periodic acid-Schiff reaction (PAS). For immunohistochemistry the strepto-avidin-biotin-peroxidase complex was used (Hsu et al. 1981). The antisera employed are reported in Table 1 together with their dilutions and sources.

For electron microscopy, samples of tissue from two cases (cases 6 and 7) were fixed in Karnovsky's II solution, postfixed in 2% osmium tetroxide, stained en bloc with uranyl acetate, dehydrated in graded ethanols, infiltrated with propylene oxide/Epon and embedded in Epon. Sections were cut (1 μm thick), stained in toluidine blue solution, and examined by light microscopy.

Representative areas were chosen for thin sectioning, and the resulting sections were examined in a Philips 301 electron microscope.

Results

Clinical findings

The most important clinical and radiological findings are summarized in Table 2.

Seven of the eight patients were females and one was male (case 7). The age at the time of the excision ranged from 17 to 73 years (average 40.1). Most patients complained of a nodule present for only a few months, but in case 2 the nodule had been present for 14 years. In all cases the nodule was evident at palpation, most often in the superior half of the breast. In six cases, the nodule was considered suspicious of malignancy because of its firm consistency (cases 1, 2, 4, 6–8), irregular margins (cases 1, 2, 4, 6, 8) fixation to the pectoral muscle (cases 2 and 7) and retraction of the overlying skin (case 1). In case 3, the patient was a 17-year-old girl with a well-defined lump that was clinically thought to be a fibroadenoma. No preoperative diagnosis was offered for case 5.

Mammography was performed in five cases. In four of cases (cases 1, 2, 4, 5) the mammogram revealed an ill-defined density with tendril-like extensions into adja-

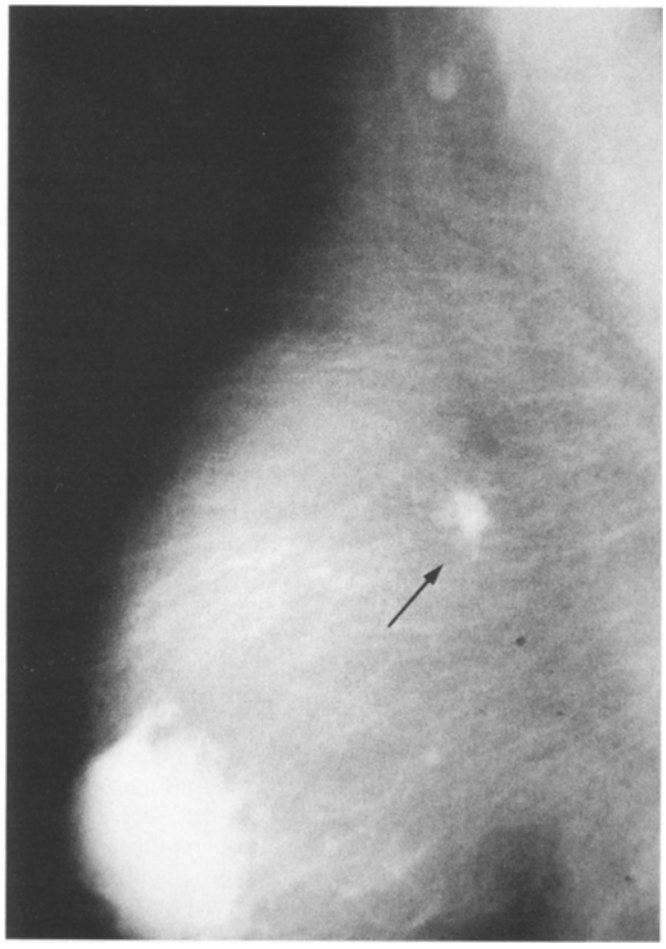

Fig. 1. Case 1. The mammography was considered suggestive of malignancy due to ill-defined density with tendril-like extensions into adjacent breast tissue (*arrow*)

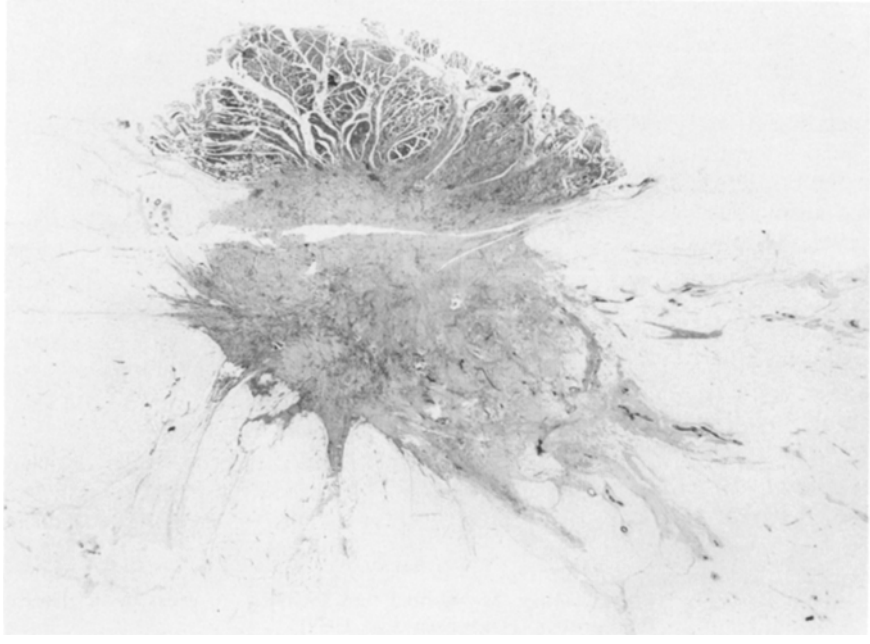

Fig. 2. Case 2. The tumour appears poorly circumscribed and invades the pectoral muscle. H & E, ×2.5

Table 2. Clinical, radiological and pathological findings of granular cell tumours of the breast

Patient sex/age/race	Duration of disease	Physical examination (location)	Mammography	Pre-operative diagnosis	Size[a] (cm)	Frozen sections
1) F 73 W	Few months	Hard, irregular nodule, skin retraction (L/UOQ)	S	Invasive carcinoma	1	GCT
2) F 45 W	14 years	Hard, irregular nodule, fixed to muscle (R/UIQ)	S	Probably carcinoma	1.5	ND
3) F 17 W	NA	Firm, well-defined nodule (L/UOQ – adjacent to areola)	ND	Fibroadenoma	1.8	ND
4) F 67 W	NA	Firm, irregular nodule (L/LIQ)	S	Probably carcinoma	1.5	GCT
5) F 30 W	Few months	Hard, well-defined nodule (L/LIQ)	ND	NA	2	ND
6) F 36 W	Few days	Firm, poorly defined nodule (L/UOQ)	S	Probably carcinoma	2	GCT
7) M 25 W	5 months	Hard, well-defined nodule, fixed to prepectoral fascia (L/NA)	ND	S	2	GCT
8) F 28 B	Few days	Hard, poorly defined, deep nodule (L/UIQ)	NE (echography: solid mass)	Invasive carcinoma	1.5	Invasive carcinoma

[a] At gross examination; F, female; M, male; W, white; B, black; L, left breast; R, right breast; UOQ, upper outer quadrant; UIQ, upper inner quadrant; LIQ, lower inner quadrant; S, suspicious of malignancy; GCT, granular cell tumour; ND, not done; NA, data not available; NE, nodule not evident mammographically

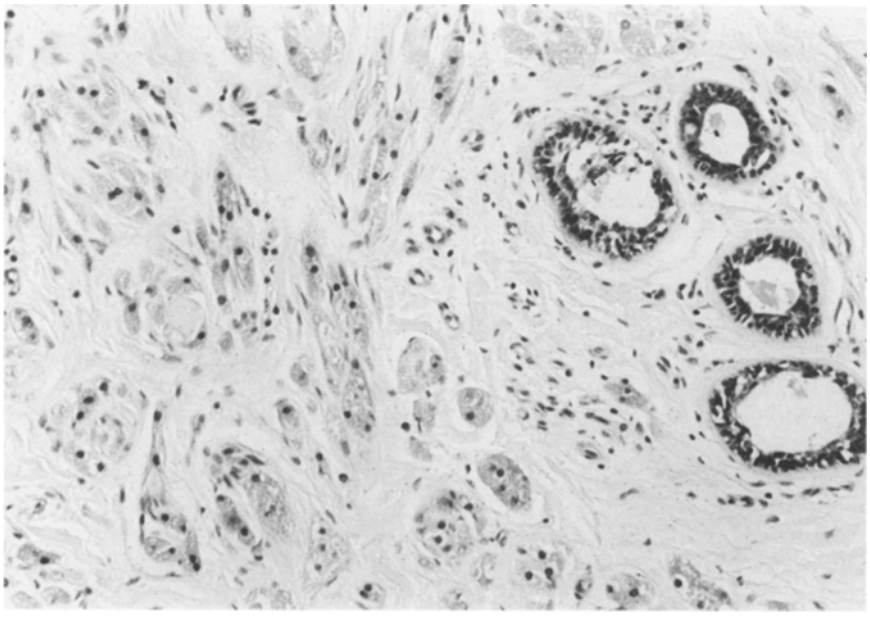

Fig. 3. Case 8. The proliferation is composed of nests and rows of cells immersed in a hyaline fibrous stroma and surrounding entrapped residual breast glands. H & E, ×150

cent breast tissue (Fig. 1). These features led the radiologist to be highly suspicious of malignancy. In case 8 mammography failed to demonstrate the nodule, but an ultrasound examination revealed a solid mass with ill-defined borders that also was considered suspicious of malignancy.

Surgical treatment consisted of wide excision in seven cases (cases 2–8). A quadrantectomy was performed in case 1. Frozen sections were performed in five cases. In four of them (cases 1, 4, 6, 7) the nodule was diagnosed as "benign granular cell tumour of the breast", whereas in case 8 the frozen section diagnosis was invasive carcinoma. In the last case, the biopsy was performed in an outpatient clinic so further immediate surgical treatment was not possible. The final diagnosis of GCT was given before a mastectomy could be scheduled.

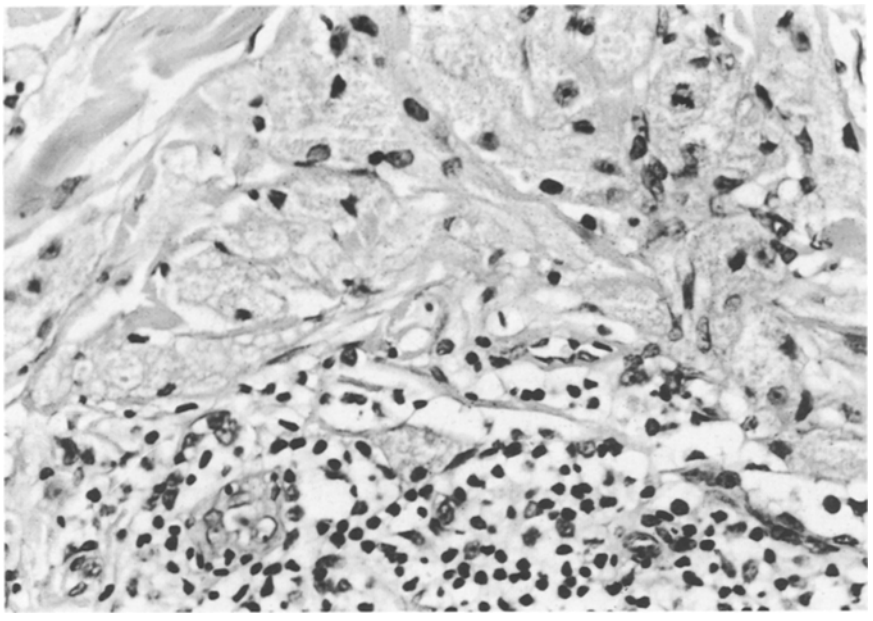

Fig. 4. Case 4. The proliferating cells show abundant granular cytoplasm. The round nuclei display prominent nucleoli. Small aggregates of lymphoid elements are often seen. H & E, ×350

Pathological findings

Macroscopical findings. Six of the eight tumours were deeply located within the breast parenchyma (cases 2, 3, 5–8), whereas the tumours from cases 1 and 4 were located in the subcutis. The nodules ranged from 1 to 2 cm (average 1.7) and varied from grey-whitish to yellow-tan.

Three of the eight tumours (cases 3, 5 and 7) showed macroscopically well-defined margins. In the remaining five cases the tumours appeared poorly circumscribed with irregular yellow streaks projecting into the surrounding tissue (Fig. 2). In case 2 the tumour appeared to invade the pectoralis major, and in case 7 the lesion was adherent to the fascia, but no muscular invasion was visible.

Microscopical findings. On histological examination, the tumours were identical. The neoplastic proliferation was composed of nests and rows of cells immersed in a hyaline, fibrous stroma (Fig. 3). The cells showed abundant, granular, eosinophilic cytoplasm and round to oval nuclei occasionally displaying cytoplasmic pseudo-inclusions. Frequently one to two nucleoli were evident (Fig. 4). Mitotic figures were not observed in any case. Well-formed nerve bundles and residual mammary structures surrounded by small aggregates of lymphocytes and rare plasma cells often appeared entrapped within the tumour (Fig. 4). In most cases, at the edge of the lesions, isolated clusters of proliferating cells invaded the surrounding adipose tissue.

The small granules visible in the cytoplasm of the cells were consistently PAS-positive. In all cases, the nuclei and the cytoplasm of the neoplastic cells were also positive with anti-S100 protein antiserum (Fig. 5). The number of positive cells varied from 20% to 80% of the total neoplastic proliferation. Anti-vimentin antiserum weakly stained the cytoplasmic borders of most of the neoplastic cells in all cases. The other antisera employed gave negative results in all cases studied.

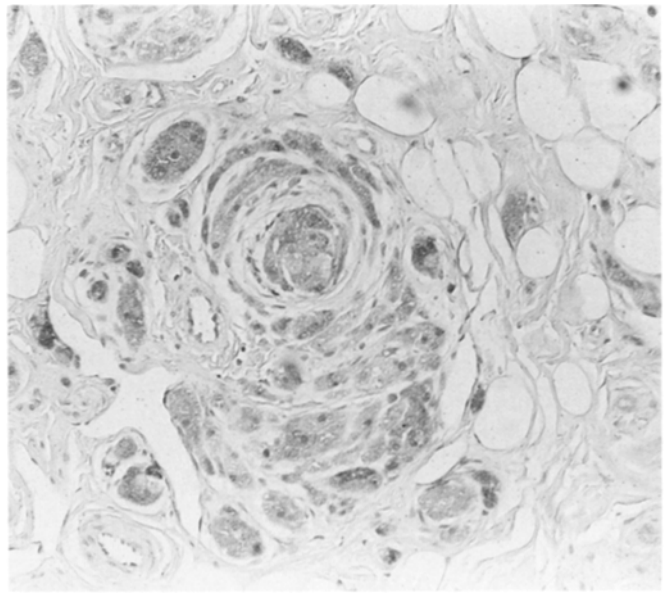

Fig. 5. Case 3. The proliferating cells are positive when anti-S100 protein antiserum is used. Strepto-avidin-biotin-peroxidase complex, ×150

Ultrastructural findings. The two neoplasms were similar ultrastructurally. Groups of round and oval cells were surrounded by basal lamina and separated by banded collagen. The basal lamina invaginated between some of the cells in the groups, but other cells had no apparent lamina or plasmalemma between their cytoplasmic compartments. The most striking feature of the cells was the filling of their cytoplasm by myriads of membrane-bound vesicles, some of which were empty but most of which contained varying amounts of membranous,

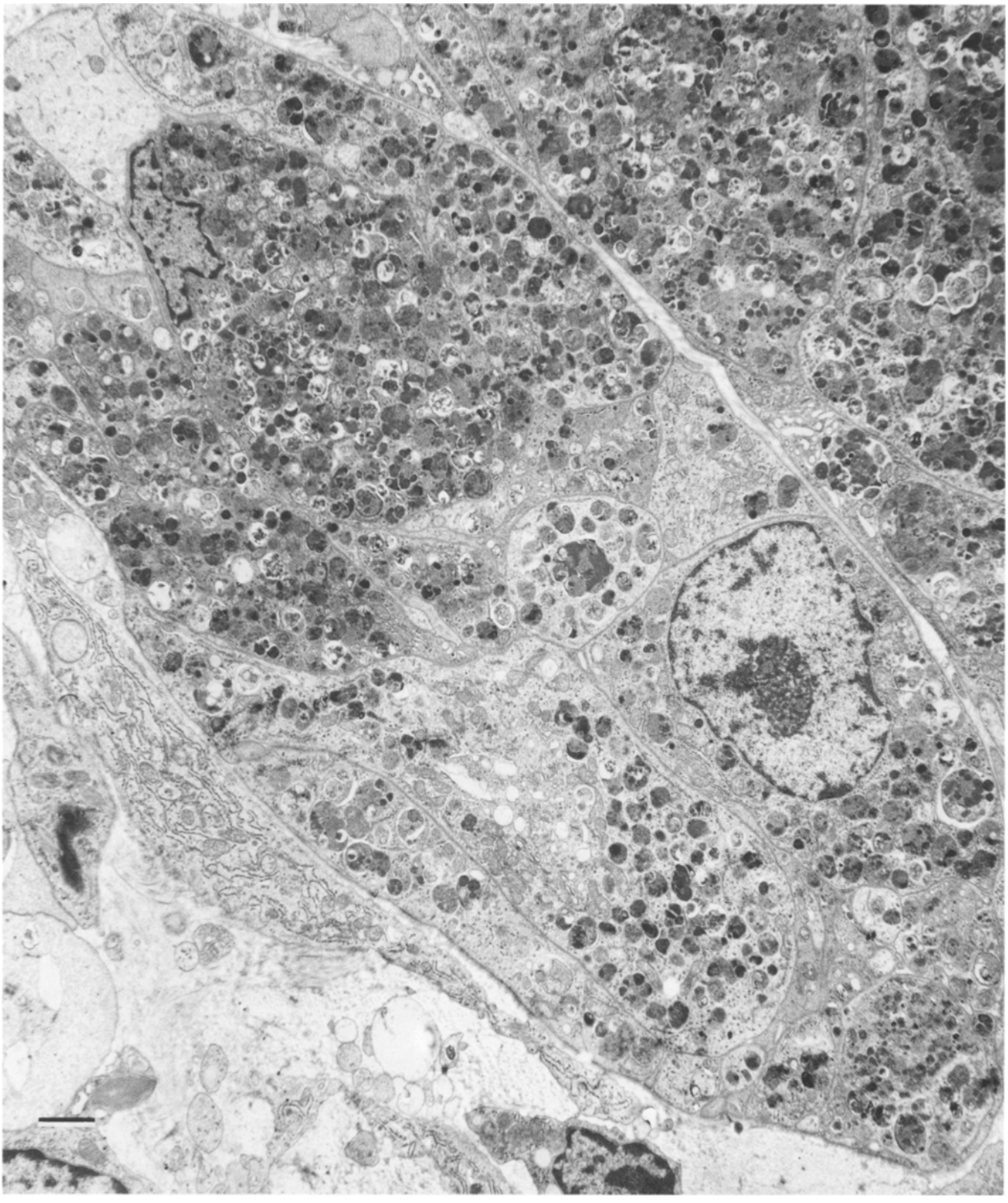

Fig. 6. Case 6. The neoplastic cells occur in groups surrounded by basal lamina. The cytoplasm of the cells is filled with innumerable electron-dense structures. Uranyl acetate, $\times 4500$; *bar* $= 2.22 \times 10^3$ nm

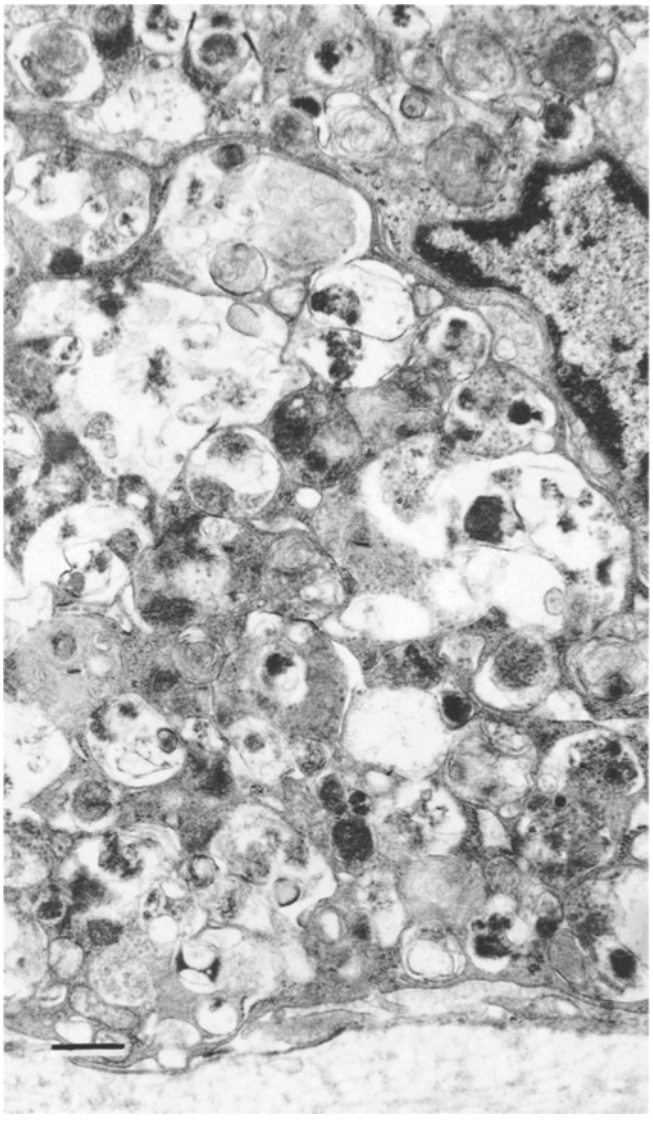

Fig. 7. Case 7. Higher magnification of the cytoplasmic granules reveals heterogeneous electron-dense and partially clear contents. Basal laminar material coats the surface of the cell. Uranyl acetate, ×15000; *bar* = 6.66 nm

flocculent and solid electron-dense material (Figs. 6, 7). Other visible organelles were sparse and included mitochondria and rough endoplasmic reticulum. Nuclei were oval or irregular in shape and had a modest amount of heterochromatin. Cytoplasmic pseudo-inclusions were confirmed in some of them. Nucleoli were large and had prominent pars amphorae.

Discussion

GCTs are unusual neoplasms that occur in many organs, but are found most commonly in the oral cavity. Between 4.6% and 16% of the neoplasms arise in or overlying the breast (Bangle 1952; Morrison et al. 1987). Patients with GCT of the breast are usually middle-aged, pre-menopausal women (DeMay and Kay 1982). Exceptional cases have occurred in women as old as 80 years (Weitzner et al. 1979) and rare examples have been reported in males (Baeten et al. 1989; DeMay and Kay 1982; Leroy et al. 1972; Mulcare 1968; Pugh et al. 1967; Sussman et al. 1973; Umansky and Bullock 1968). The tumour occurs most often in the superior medial quadrant and only rarely in the inferior lateral quadrant (Mulcare 1968; Pugh et al. 1967). This curious distribution is usually explained as reflecting the course of the supraclavicular nerve, which supplies sensory nerve fibres to the skin of the breast. The most common preoperative diagnoses are fibroadenoma and invasive carcinoma, depending on the age of the patient.

The histogenesis of the neoplasm is continually debated in the literature, and myocytes (striated, smooth and degenerating), fibroblasts, pericytes and mesenchymal cells have been proposed as the cell of origin. The general consensus (Azzopardi 1956; Sobel et al. 1971) is that the tumour arises from Schwann cells. Like GCTs arising in other sites, those in the breast are characterized by large cells with round, uniform nuclei and abundant cytoplasm containing-granules that stain with a PAS strain. Mitotic figures are few and necrosis is not seen. Using the electron microscope, one observes cells occurring in groups, ensheathed by basal lamina and filled with secondary lysosomes. The tumour cells are positive when stained for S-100 protein (Ingram et al. 1984; Nakazato et al. 1982; Nathrath and Remberger 1982; Willen et al. 1984), vimentin (Miettinen et al. 1984) and neuron specific enolase (Nathrath and Remberger, 1982). In some reports, staining for carcinoembryonic antigen is described (Ingram et al. 1984; Shousha and Lyssiotis 1979), but these results probably reflect cross-reactivity with a related antigen (Matthews and Mason 1982, 1983). In one report, GCTs of the breast were negative for oestrogen receptors and progesterone receptors using hormone binding assays (Ingram et al. 1984).

The cases reported here illustrate most of these characteristics of GCTs. Seven of the eight patients were women, and their average age was 40 years. The tumours occurred in all quadrants except the inferior lateral. The clinical impression was invasive carcinoma except in a girl of 17 years who was thought to have a fibroadenoma. Histological and ultrastructural studies revealed findings identical to published descriptions. All tumours were positive for S-100 protein and negative for keratin, myoglobin, and GCDFP-15, as also seen by Willen et al. (1984), Nathan and Remberger (1986) and Buley et al. (1988).

It is instructive to note that in six of the present cases both physical and radiological findings were considered suspicious for invasive carcinoma. The same findings emerge from most of the previously reported cases (Elias et al. 1970; DeMay and Kay 1982; Kommoss et al. 1989; McCracken et al. 1979; Mulcare 1968; Umansky and Bullock 1968). In four published cases, unnecessary mastectomies were performed on the basis of these findings (Friedman and Hurwitt 1966; Mulcare 1968; Umansky and Bullock 1968). Even ultrasound examination appears incapable of distinguishing GCT of the breast from a carcinoma (Cukierfajn et al. 1980; Kalbfleish et al. 1978; Talenti et al. 1983).

The characteristics that mislead the surgeon and the radiologist also cause difficulties for the pathologist examining the specimen macroscopically. Although a few examples have been described as well-defined, most GCTs are ill-defined, white or tan and firm to hard. The usual macroscopic diagnosis is scirrhous carcinoma.

Microscopical examination almost always clarifies the nature of these tumours. Even a frozen section preparation usually displays the diagnostic characteristics of GCT. Our case 8 serves as a reminder, however, that the unwary pathologist can continue to misinterpret these tumours as invasive carcinoma on frozen section examination. In other reports, frozen sections preparations of GCTs have been interpreted as malignant hidradenoma, fibrosarcoma and malignant melanoma (Friedman and Hurwitt 1966; Mulcare 1968; Umansky and Bullock 1968). Using paraffin sections, the histological diagnosis does not pose a difficult problem, and in our series a final correct diagnosis was made in all cases. In our experience the only malignancy which mimics GCT in the breast is invasive histiocytoid carcinomas. By definition, in these tumours most of the neoplastic invasive cells have a foamy cytoplasm (Eusebi et al. 1984). Nevertheless the nuclear pleomorphism of the neoplastic cells together with the immunohistochemical evidence of epithelial and apocrine differentiation permits the accurate distinction of these two neoplasms (Eusebi et al. 1984).

Two tumours in our series arose in the subcutaneous tissue overlying the breast (cases 1 and 4). DeMay and Kay (1982) and Haagensen (1971) prefer to separate GCT of the mammary gland from those located in the subcutis of the mammary region to avoid confusion about the true incidence and the clinical picture of GCT in the breast. Since tumours arising in the subcutaneous tissue present the same diagnostic problems as those arising within the breast, we are hesitant to hold this view. For example, the dimpling of skin seen in our case 1 made the surgeon very reluctant to accept the frozen section diagnosis of a benign lesion. Therefore, it appears to us that the distinction of these tumours into two categories, although anatomically correct, is of more theoretical than practical value.

Finally, if GCTs of the breast arise from Schwann cells, the propensity of the tumours to occur during the reproductive years is not explained. Conventional Schwann cell tumours may enlarge during puberty or pregnancy and may contain oestrogen receptors (Jay et al. 1986). Similar clinical observations of granular cell tumours of the breast have not been recorded, however, and the few tumours studied for the presence of oestrogen receptors have lacked them. It seems unlikely, therefore, that steroid hormone receptors play a role in the development of these tumours. Still, some molecule present in the physiologically active female breast must be important in the pathogenesis of these neoplasms. Identification of such a substance would provide important information in our understanding of GCTs.

In summary, GCT of the breast is a benign tumour, usually occurring in women in their reproductive years. The clinical and radiological findings almost always suggest a malignant tumour, and microscopical examination is required to establish the correct diagnosis. Since only a single case of primary GCT of the breast has been reported as malignant with documented metastatic dissemination (Crawford and DeBakey 1953) to date, the initial surgical treatment should be conservative. Once the pathologist's final report is available, further therapy can be planned as necessary.

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