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Carcinoma of the Breast with Multinucleated Reactive Stromal Giant Cells

A Light and Electron Microscopic Study of Two Cases

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Summary. Two unusual carcinomas of the breast are described, containing nests of infiltrating neoplasm situated within stromal lacunar spaces, and surrounded by numerous benign appearing multinucleated giant cells. Within the stroma, there was extensive hemorrhage, hemosiderin pigment deposition, and large numbers of mononucleated inflammatory cells. The morphology of both tumors resembled the giant cell tumor of bone. Although a similar giant cell reaction has recently been described in association with a uterine leiomyosarcoma, we are aware of only two other examples of this entity in the breast, both reported over 40 years ago in the French literature. This is the first report in which electron microscopy confirmed the benign histiocytic nature of the giant cells. These cells had many of the ultrastructural features of multinucleated giant cells described in tissue culture, skeletal osteoclastomas, and foreign body granulomas. We propose that the giant cells arise from fusion of mononucleated stromal cells, and most likely are reactive histiocytic elements which are in some way related to the tumor cell nests. Further studies of these unusual neoplasms are needed to determine if the giant cell reaction in any way affects the prognosis of the patient.

Key words: Breast carcinoma – Stromal giant cells.

Introduction

Tumors of the breast containing large numbers of benign osteoclast-like giant cells comprise one of the rarest forms of mammary neoplasm. Fry (1927), recorded a case of osteoclastoma of the breast having the typical appearance of a giant-cell tumor of bone. This author also reviewed the literature up to that

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time and tabulated 27 cases of breast tumor in which giant cells played a prominent role. Although osteoclastomas have been described in diverse extra-skeletal locations (Schmaman et al., 1963; Andreev et al., 1964; Dorney, 1967; Salm et al., 1972) there has been no report of a similar breast lesion since Fry's detailed paper.

Osteoclastic giant cells intimately associated with otherwise typical duct cell carcinoma of the breast have been described only twice, by Leroux (1931) and Duboucher et al. (1933). Leroux (1931) considered that the giant cells arose from stromal elements reactive to the malignant epithelium which was behaving like a foreign body. A similar admixture of malignant neoplasm and benign stromal reactive giant cells has recently been described in the uterus (Darby et al., 1975). The authors adhered to the concept that osteoclasts were derived from the monohistiocyte group of cells. Unfortunately, though the tumor was studied ultrastructurally, none of the giant cells was available for examination.

We recently had the opportunity to examine two carcinomas of the breast containing large numbers of benign osteoclast-like giant cells clearly differentiated from malignant duct cell elements by both light and electron microscopy. Both tumors appear to be identical to the tumors recorded in the French literature cited above, and are to the best of our knowledge the only examples of this entity in the English literature. We are reporting both cases not only because of their rarity, but to clarify further the pathogenesis of these unusual neoplasms.

Case Reports

Case 1. A 45 year old woman had a right lower quadrant breast mass, 2 cm from the alveolar margin for several months. On May 1, 1975 an excisional biopsy was done. The specimen revealed a 1.5 cm irregular soft and hemorrhagic tumor. The frozen and permament sections showed an infiltrating carcinoma with giant cells, and benign fibrocystic disease. One week later the patient underwent a modified right radical mastectomy. The histopathological study of the specimen demonstrated no residual carcinoma, and axillary lymph nodes were free of tumor. The patient was alive and well 4 months following the operation.

Case 2. A 40 year old woman complained of a right breast mass for 6 weeks. Initially, the breast showed inflammatory changes in the overlying skin which were self-limited, but reappeared and responded to local therapy. However, the mass enlarged and the skin became discolored. The lesion was slightly tender but not painful. The right breast in its upper half contained a tumor mass 10 cm in diameter. It had involved the overlying skin which was discolored and fixed, with a peau d'orange appearance. An enlarged mobile lymph node was palpable along the pectoralis major border. On November 10, 1972 excisional biopsy and a modified right radical mastectomy were performed. Gross pathological examination revealed a large soft and hemorrhagic tumor mass with irregular borders. Histologically, the tumor was an infiltrating carcinoma with giant cells, which invaded the skin and metastasized to one axillary lymph node. The post-operative course was uneventful. She was then lost to further follow-up.

Materials and Methods

The biopsy specimens from both cases were fixed in 4% buffered formaldehyde and processed for light microscopy. Paraffin sections were stained with hematoxylin and eosin, Masson's trichrome, phosphotungstic acid hematoxylin, periodic acid Schiff, Perl's iron, Gomori's reticulin, and elastic van Gieson's stains.

A small portion of the biopsy specimen from Case 1 was available for electron microscopy. The tissue had been fixed in formaldehyde for approximately 1 month. This tissue was diced into 1 mm cubes, was washed in cacodylate sucrose buffer pH 7.4 for 1 h, and was osmicated for 1 h in 1 per cent osmium tetroxide. The tissue was then dehydrated in graded alcohols and embedded in epoxy resin. Thick sections were stained with alkaline toluidine blue, and appropriate areas were selected and photographed. Thin sections were cut on an MT2B ultramicrotome, stained with uranyl acetate and lead citrate, and examined in an RCA EMU-3C electron microscope.

Results

Light Microscopy

The basic morphology of both tumors was similar and they will be described together except where noted. The tumors were predominantly composed of large, often anastomosing cords and nests of cohesive polygonal cells arranged in solid masses (Figs. 1–4). The tumor cells were regular with only rare pleomorphic forms, and contained single vesicular round or oval nuclei. The cytoplasm was faintly granular, often vacuolated (particularly in Case 2), and was eosinophilic to amphophilic when stained with hematoxylin and eosin. Mitotic figures were rare. Smaller agglomerations of cells as well as individual cells within the larger tumor nests were frequently noted to be degenerating or undergoing obvious necrosis. The tumor were hemorrhagic (see below), and relatively well circumscribed with areas of active infiltration into the surrounding adipose tissue. Additionally, foci of intraductal carcinoma as well as small groups of tumor cells produced a dense desmoplastic stromal response.

The most striking aspect of the tumors was the association with osteoclastlike multinucleated giant cells (Fig. 1–5). The neoplastic epithelium was situated within large spaces, often containing variable numbers of red blood cells, necrotic debris, and inflammatory cells. These stromal spaces were not lined by recognizable endothelium. The stroma surrounding the spaces and delimiting the carcinomatous nests, was loose and hemorrhagic. Numerous multinucleated giant cells resembling osteoclasts or foreign-body type cells (Figs. 3, 4) extended through gaps in the stroma to protrude into the spaces containing tumor nests. The cells varied in size, shape, and nuclear number from area to area within the tumor, and between the two cases. The largest cells, with well over 100 densely packed nuclei were noted in Case 2, while in Case 1, cells having up to 20 nuclei were seen. The smaller cells were often rounded or ovoid in shape with a smooth contour. The larger cells, however, demonstrated pseudopodal extensions, often remarkably attenuated, which surrounded or apposed tumor masses (Fig. 5).

There was a distinctive difference between the giant cells and the neoplastic epithelium (Fig. 5). The giant cell nuclei were ovoid, reniform, or convoluted in shape, with prominent peripheral heterochromatin, and a large densely stained nucleolus. The cytoplasm was dense, finely granular and homogeneous, and amphophilic to basophilic with hematoxylin and eosin. Both large and small vacuoles, rarely containing white or red blood cells were noted in the larger giant cells in Case 2, while vacuoles were infrequent in Case 1. No mitosis was ever observed within a giant cell. Phosphotungstic acid hematoxylin produced

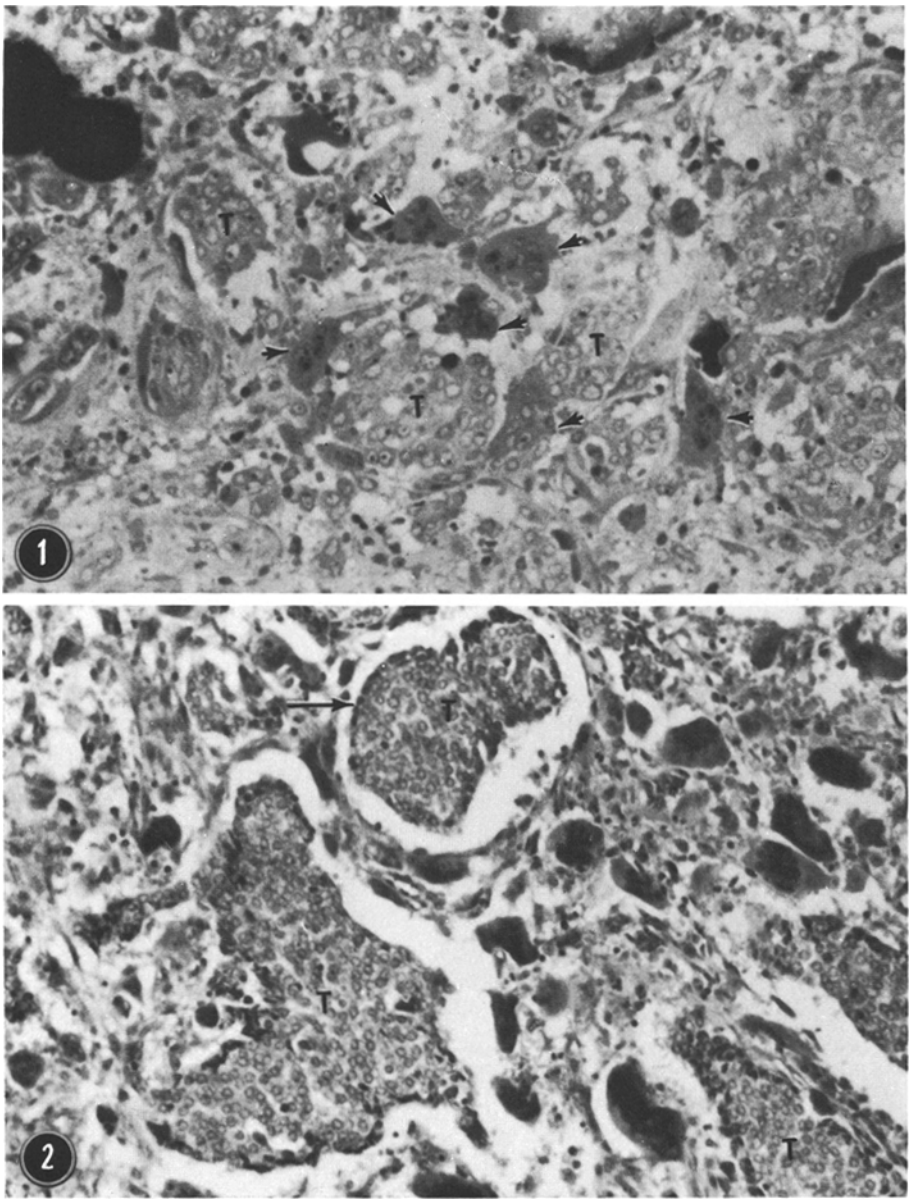
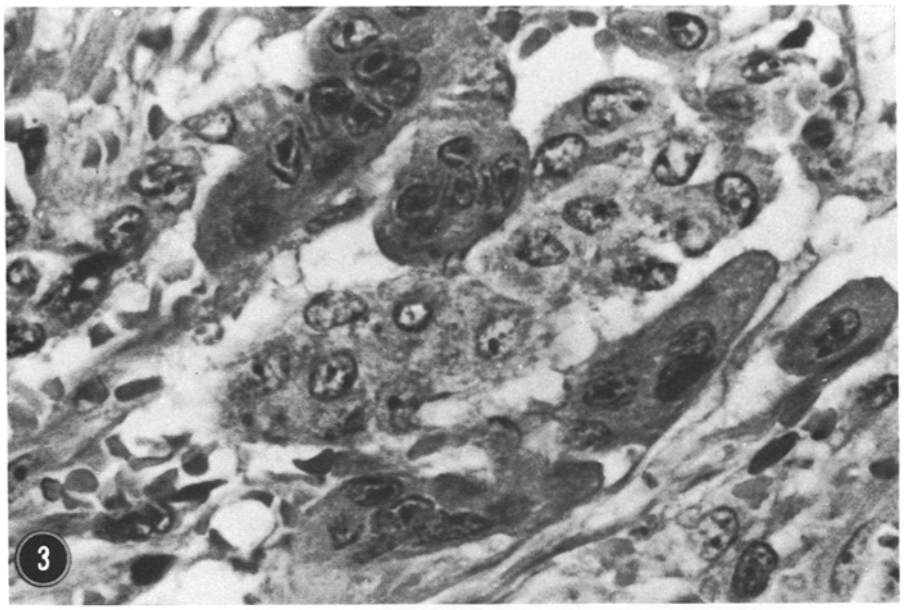


Fig. 1. Low power view, Case I. Numerous multinucleated giant cells (arrowheads) with darkly stained cytoplasm, surround nests of breast tumor epithelium (*T*) within lacunae. Mononucleated cells, small giant cells, and hemorrhage are present within the stroma. (Epon embedded, alkaline toluidine blue. ×80)

Fig. 2. Low power view, Case 2. Several large nests of tumor (*T*) are noted within lacunae. The tumor nests are rimmed by a layer of dark staining spindle cells consistent with myoepithelium (arrow). Numerous multinucleated giant cells are present within the stroma and along the lacunar margins. These cells are larger than those in Case 1, and contain many more nuclei. The nuclei are so densely packed in some cells that they are difficult to visualize. (Hematoxylin and eosin. ×80)



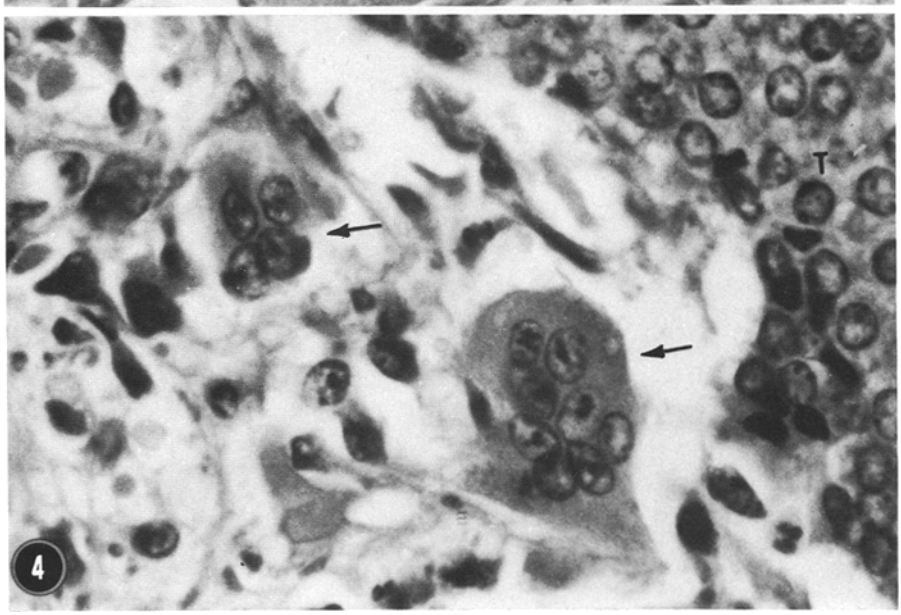


Fig. 3. A central nest of tumor is surrounded by multiple small giant cells. The darkly stained giant cell cytoplasm, and the distinctive nuclei clearly differentiate these cells from the breast epithelium. The giant cells are present in the stroma and protrude into the cleft containing the breast tumor. Scattered red blood cells and mononucleated cells are also noted within the stroma. (Case 1. Hematoxylin and eosin. $\times 175$)

Fig. 4. Two small giant cells (arrows) are partially embedded within the stroma, with the larger of the two protruding into a space containing a nest of breast tumor (*T*). Numerous mononucleated stromal cells are noted in the vicinity of the giant cells, with nuclei which resemble those in the osteoclast-like cells. The lacunar space has no recognizable endothelial lining. (Case 1. Hematoxylin and eosin. $\times 150$)

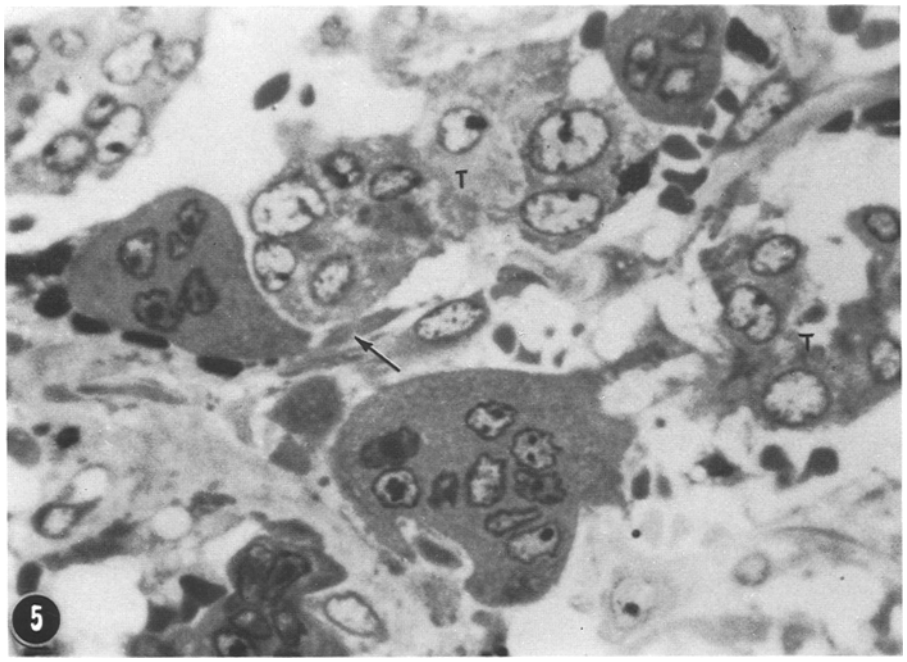


Fig. 5. A high magnification view of the Epon embedded tissue, reveals the clear differentiation between the multinucleated giant cells and the tumor nests (*T*). One of the giant cells has partially extended a pseudopod (arrow) around the tumor. (Epon embedded, alkaline toluidine blue. × 1000)

intense dark staining of the giant cell cytoplasm, in contrast to the scanty or absent staining of the breast tumor cells. This reaction was attributed to the large number of mitochondria within the cytoplasm (see below).

The loose connective tissue stroma contained large numbers of mononuclear cells, highly suggestive of histiocytes, with convoluted nuclei having dense heterochromatin and a large nucleolus, and abundant cytoplasm (Fig. 4). These cells were identical to the multinucleated giant cells in nuclear morphology and cytoplasmic staining characteristics with phosphotungstic acid hematoxylin.

Electron Microscopy

The multinucleated syncitial giant cells and the mononuclear stromal cells differed significantly from the breast epithelium (Fig. 5). The giant cells typically contained numerous small distinctive nuclei (Fig. 5). The nuclei were irregular and convoluted in shape, often displaying a lock and key arrangement. Dense clumped chromatin was arrayed along the nuclear membrane, and a single large central nucleolus was prominent. The cytoplasm was tightly packed with organelles and the ground substance invariably appeared more electron dense than the infiltrating nests of breast epithelium. Mitochondria were small, round or oval, with a dark matrix. They were diffusely scattered throughout the cytoplasm,

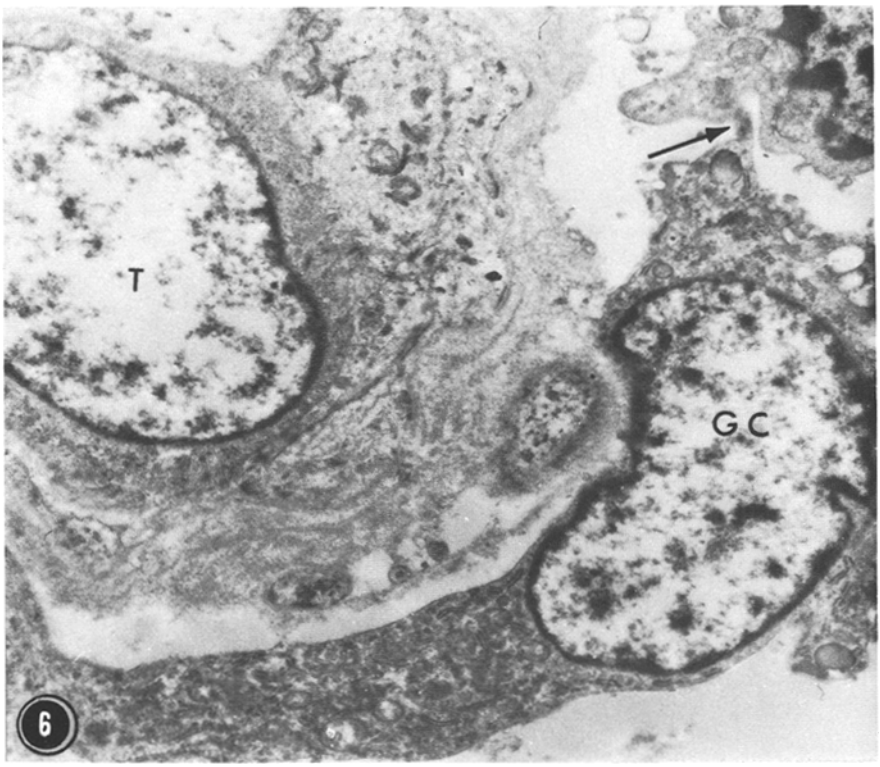


Fig. 6. Intralacunar tumor (*T*) contains a large nucleus with clear nucleoplasm, and scanty cytoplasmic organelles. The cell is surrounded by irregularly thickened basal lamina. A giant cell (*GC*) pseudopodal process wraps around the breast neoplasm. The giant cell cytoplasm is tightly packed with mitochondria, profiles of rough endoplasmic reticulum, and rare lysosomes. In the right upper portion of the field, a mononuclear cell is apparently adherent to the giant cell plasma membrane (arrow). ($\times 3600$)

displaying no tendency toward segregation. Interspersed between the mitochondria but somewhat segregated peripherally were numerous profiles of rough endoplasmic reticulum. Free ribosomes and polysomes, rare lysosomes, and occasional small vesicles were commonly seen. No fibrillar material was found. Hemosiderin pigment and degenerated red blood cells were infrequently noted, but no other evidence of active phagocytosis was observed. A consistent feature was a condensation of the cytoplasm along the inner surface of the plasma membrane, producing a thin electron dense zone. The plasma membrane displayed pseudopodal extensions which enwrapped nests of tumor cells (Fig. 6). There was no indication that the giant cells were attached or fused to the tumor cells. Desmosomes were not present between the giant cells and the tumor epithelium, nor were they seen when individual giant cells were closely apposed with interdigitation of their pseudopods. Basal lamina was never observed around the giant cells.

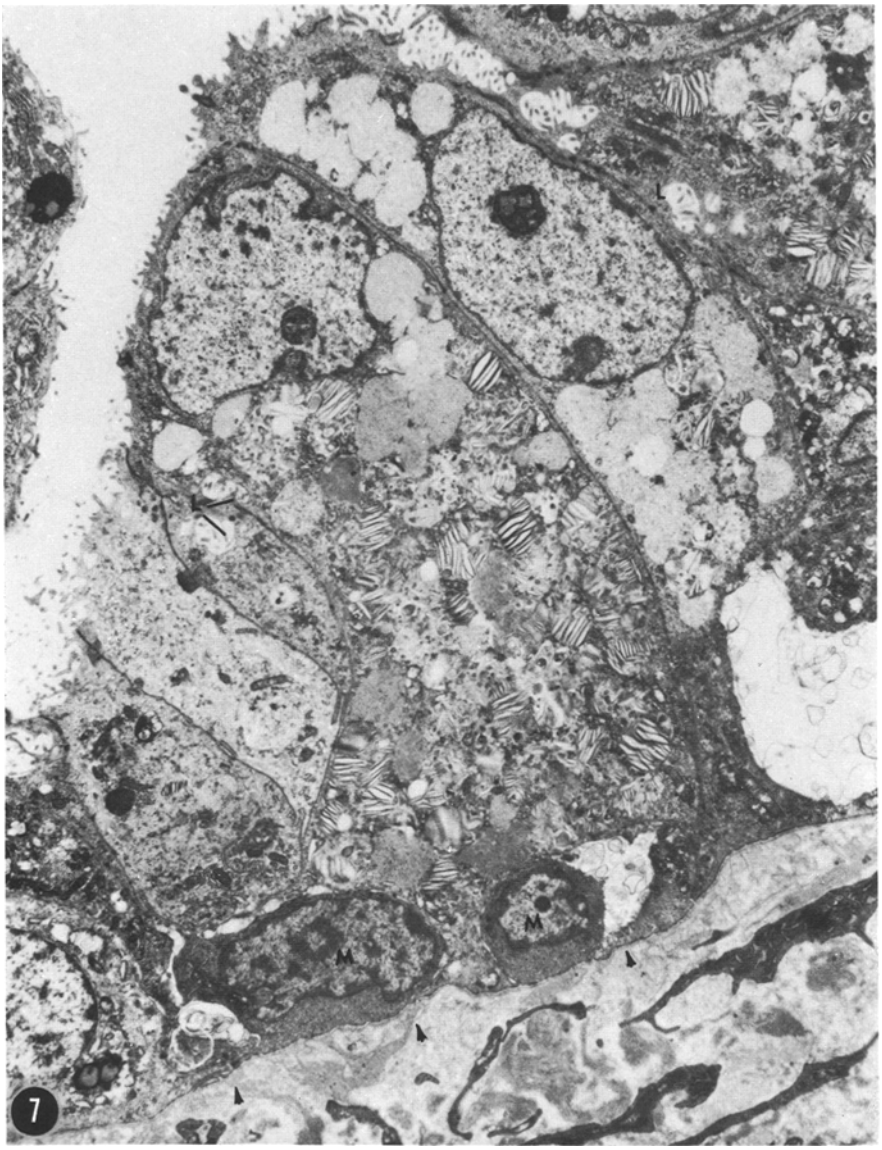


Fig. 7. Low power electron micrograph of intraductal tumor. Both light and dark staining tightly packed ductal cells are noted which maintain their polarity. The luminal surface is covered by microvilli. The cells focally abut on myoepithelium (*M*), and underlying basal lamina (arrowheads) and stroma. The cytoplasm is packed with numerous membrane bound lysosomal structures, many of which contain "zebra-like" lipid inclusions. Others display a moderate electron dense background and a fine granularity. Only rare mitochondria are observed. Intracytoplasmic lumina (*L*) are present in several cells. Desmosomal attachments are noted between cells. ($\times 3600$)

The mononucleated stromal cells included lymphocytes, monocytes, and histiocytes containing phagocytosed material. The lacunar spaces were occasionally lined by thin and elongated cells appearing to be fibroblasts. No continuity was demonstrated between these fibroblasts and the giant cells. Rare mast cells, plasma cells, and polymorphonuclear leukocytes were also observed. Although unequivocal fusion of mononucleated stromal cells into giant cells was not found, it was not infrequent to observe groups of cells with features of lymphocytes or monocytes in the vicinity of the giant cells. Rarely, it appeared that partial fusion or adherence of cell membranes had occurred.

In one instance, one of these cells was noted to adhere to a pseudopodal extension of a giant cell (Fig. 6).

The malignant breast epithelium, whether intraductal or infiltrating, showed great variability from area to area, but demonstrated no similarity with the giant cell elements. Intraductal tumor generally maintained its polarity, with the luminal surface raised into numerous microvilli and the base abutting on either myoepithelial cells or directly on basal lamina (Fig. 7). Cells were noted in which the cytoplasm was packed with large amounts of membrane bound lipid material, of varying electron density, with small profiles of myelin figures, and numerous prominent "zebra-like" bodies (Fig. 7). Interspersed among the lipid containing bodies were frequent enlarged membrane enclosed structures containing granular electron dense material, probably lysosomes. Mitochondria were few in number, and were rarely seen in the cells with excessive lipid. Scattered small profiles of rough endoplasmic reticulum, small vesicles, and haphazardly organized microfibrils were other features noted in the malignant epithelial cells.

The intralacunar nests of infiltrating breast carcinoma were less well differentiated than the intraductal tumor. Nuclei were enlarged, with swelling or clearing of the nucleoplasm, slight condensation of chromatin along the nuclear membrane, and absent or small nucleoli (Fig. 6). The cytoplasm did not have the heterogeneous population of organelles and lipid inclusions seen in the intraductal epithelium. A few profiles of rough and smooth endoplasmic reticulum, rare mitochondria and lysosomes, and an irregular scattering of fine filaments were commonly noted features (Fige 6). The cells within the tumor nests were joined by desmosomal attachments. Basal lamina was generally noted surrounding groups of cells.

Discussion

Tumors of the breast resembling the giant cell tumor of bone or containing significant numbers of osteoclast-like cells, are extremely unusual. Three tumors of the breast have been described in which these cells are present: metaplastic carcinoma, extraskeletal osteoclastoma, and infiltrating carcinoma with reactive stromal giant cells.

The metaplastic carcinomas reported by Huvos and associates (1973), consist of epithelial neoplasms in which the stroma contains varying amounts of bone and cartilage. The bone and cartilage has been interpreted as a metaplastic transformation of the mesenchymal tissues, although there is some evidence that

epithelial breast tumor cells may form these substances (Gonzalez-Licea et al., 1967). In several of these tumors bony seams were illustrated which had associated osteoclastic activity. It appears however, that these elements are not intrinsic features of the tumors, and serve to link these neoplasms only superficially with either the extraskeletal osteoclastoma or the tumors described in the present report.

The extraskeletal osteoclastoma reported by Fry (1927) is analogous in all respects to the giant cell tumor of bone. Although such extraskeletal neoplasms are rare, they have been found in the heart (Dorney, 1967), skin (Andreev et al., 1964), and soft tissues (Schmaman et al., 1963; Salm et al., 1972). Additionally, Fry reviewed the historical literature to 1861 and was able to tabulate three similar giant cell tumors of the breast out of a total of 27 cases in which osteoclast-like cells were described. The osteoclastoma of the breast contained typical multinucleated giant cells present in clefts, mononucleated stromal cells, hemorrhage and hemosiderin pigment, and osteoid material. No obvious epithelial elements were noted, and the giant cells demonstrated no pleomorphism or atypicality, features which have been described in malignant epithelial giant cell tumors of the breast (Ferlito, 1974).

The infiltrating carcinoma of the breast with reactive stromal giant cells appears to be a unique lesion which is not related either to the metaplastic carcinoma or to the extraskeletal osteoclastoma. To the best of our knowledge only two other identical tumors have been reported, both over 40 years ago (Leroux, 1931; Duboucher et al., 1933). What classifies these tumors apart from other neoplasms of the breast containing osteoclastic giant cells is the intimate association of these benign, probably histiocytic cells, with clearly malignant epithelial elements. Although a similar association of benign giant cells and malignant uterine sarcoma has recently been reported (Darby et al., 1975), our study represents the only one in which the benign histiocytic nature of the giant cells has been confirmed by electron microscopy.

The ultrastructural morphology of the multinucleated giant cells and the mononucleated stromal cells clearly established that they were not derived from the epithelial tumor. The distinctive features of both the breast tumor cells and the myoepithelium and the absence of these features in the giant cells leads us to conclude that these latter cells were not of epithelial or myoepithelial derivation but rather arose from other cells within the stroma.

That the light microscopic pattern of the tumors superficially resembled a giant cell tumor of bone appears evident. The essential difference however, was the presence of malignant epithelial tumor within characteristic clefts or lacunae. The similarity between the skeletal and mammary tumors may then be more apparent than real. In fact, though the giant cells are similar to the so-called osteoclast of the giant cell tumor of bone, they also have a light and electron microscopic appearance consistent with foreign body or Langhans type multinucleated cells. It is relevant to recall that in Leroux's original description of the breast tumor, he considered that the giant cells were histiocytes reacting to tumor recognized as foreign body (Leroux, 1931).

Supporting this concept, there is evidence that osteoclasts are derived from fusion of histiocytic stromal cells. In our two cases, light and electron microscopic

observation revealed cells within the stroma with the morphologic characteristic of lymphocytes, monocytes, and histiocytes. These cells were frequently closely associated with the giant cells. In several areas there was an ultrastructural appearance which suggested fused membranes although unequivocal evidence of cell fusion was not obtained. Other investigators (Hanaoka et al., 1970; Steiner et al., 1972), in ultrastructural studies of the giant cell tumor of bone, considered that the giant cells evolved from fused stromal cells having features of macrophages. Tissue culture (Sutton et al., 1966), autoradiography (Silverman et al., 1963), and experimental induction of foreign body granulomas (Elias et al., 1968) have provided evidence suggesting that multinucleated giant cells have a common origin from undifferentiated mesenchymal cells.

The giant cells of our two cases had many features associated with normal osteoclasts (Lucht, 1972A, B), and osteoclast-like cells described in the giant cell tumor of bone (Hanaoka et al., 1970; Steiner et al., 1972), and the reparative giant cell granuloma of the jaw (Soskolne, 1972; Sapp, 1972). A relative paucity of lysosomes and lack of phagocytosis by the giant cells has been noted by others (Soskolne, 1972; Steiner et al., 1972). Our findings were in accord with these observations. Organelles consistent with lysosomes were only rarely seen (Fig. 6) and phagocytic activity was invariably associated with the mononuclear stromal cells. True osteoclasts morphologically contain large numbers of lysosomes (Scott, 1967; Lucht, 1972A, B), and histochemically have abundant acid phosphatase (Schajowicz, 1961). The relative absence of lysosomes is more consistent with the morphology of multinucleated giant cells in tissue culture (Sutton et al., 1966), which have been observed to progressively lose these organelles as they mature.

Several hypotheses may be suggested regarding the functional relationship of these cells to the tumor epithelium. It is possible that the giant cells may not be directly related to the tumor tissue, but may be associated with the stromal proliferation and hemorrhage stimulated by the neoplasm. It has been consistently observed that osteoclastomas arising in bone, in extraskeletal tissues, or in conjunction with a malignant tumor are hemorrhagic. There are numerous small vessels in the stroma, and presumably their rupture leads to the hemorrhage. However, since there is little demonstrable phagocytosis of red cells and hemosiderin by the giant cells, it appears unlikely that hemorrhage per se is the stimulus for their formation.

It is conceivable that Leroux's original concept may be correct and that the giant cells may be reacting to antigenic stimulation associated with the tumor. If this is in fact the case, it would be interesting to have long term follow-up on similar tumors to establish if a better prognosis is associated with the presence of these giant cells. Unfortunately, follow-up data are not available on our two cases. It may be significant, however, that the tumor metastasis in Case 2 did not display a giant cell reaction. Although this may be related to the lack of stromal proliferation in the lymph node, it may also reflect an altered state of the tumor allowing it to escape the surveillance of the giant cells and other inflammatory elements.

In conclusion, we feel there is unequivocal evidence supporting a benign and probably histiocytic origin of the multinucleated giant cells in these two

neoplasms. Although the tumors superficially resemble osteoclastomas of bone, it is more likely that the giant cells are of the foreign body type, and are reacting in some unknown manner with the malignant cell nests. It will be interesting in the future to observe the behavior of similar tumors, to determine if in fact the presence of reactive giant cells portends an altered prognosis.

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