Virchows Archiv (1994) 425:199–203

CASE REPORT

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Pleomorphic fibrohistiocytoma of the breast: a potential pitfall in breast biopsy interpretation

Received: 7 March 1994 / Accepted: 18 May 1994

Abstract We describe a benign mammary mesenchymal tumour with atypical stromal giant cells in the contralateral breast of a 66-year-old woman with infiltrating ductal carcinoma. The clinical, morphological and immunohistochemical features of this tumour suggest a pleomorphic variant of fibrous histiocytoma. This benign lesion represents a possible pitfall in breast pathology when interpreting a frozen section or fine needle aspiration biopsy.

Key words Breast · Fibrous histiocytoma · Giant cells
Flow cytometry · Immunohistochemistry

Introduction

Stromal and osteoclast-type giant cells may occur in the biopsies of both benign and malignant mammary neoplasms. The importance of these giant cells lies in their resemblance to epithelial and mesenchymal malignant neoplasm. We describe a benign mesenchymal tumour containing atypical appearing stromal giant cells in the contralateral breast of a woman with infiltrating ductal carcinoma.

Case report

The patient was a 66-year-old white woman and mother of six. She had had degenerative arthritis, arterial hypertension, mild cardiac insufficiency and a hysterectomy for fibroids at the age of 36. Her medication at the time of biopsy consisted of ibuprofen, thiazide, diltiazem and digoxin; she was receiving no hormonal treatment.

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The patient sought medical attention for a lump in her right breast that slowly increased in size over a period of 2 months. She denied trauma to the area. She was referred to a surgeon who palpated an additional smaller mass in the left breast. Mammographic examination of the right breast showed a well-defined 5 cm mass, with vascular and stromal markings throughout; sonographic examination demonstrated the mass to be solid. These imaging findings were consistent with fibroadenoma, phylloides tumour, or medullary carcinoma. A bilateral biopsy followed revealing a fibrous neoplasm containing pleomorphic giant cells in the right breast (the subject of this report), and invasive ductal carcinoma in the left breast. A left, modified radical mastectomy with ipsilateral axillary lymph node dissection followed and residual carcinoma was present in the vicinity of the initial biopsy. The patient has received tamoxifen (10 mg/b.i.d.) since her mastectomy, and is without evidence of tumour recurrence 3 years after diagnosis. No additional lesions have been detected in the remaining right breast.

Materials and methods

Formalin-fixed, paraffin-embedded tissue sections of both the mesenchymal tumour and carcinoma were studied immunohistochemically with appropriate concentrations of the the primary antibodies listed in Table 1. The primary antibody was allowed to react for 30 min at 40° C. Sections for vimentin and cytokeratin staining were pretreated with 0.5% trypsin for 10 min at 40° C. Bound antibody was detected by avidin-biotin-alkaline phosphatase technique using a kit procedure (Super-sensitive multi-link kit, Biogenex Laboratories).

For estrogen and progesterone receptor analysis formalin fixed, paraffin-embedded tissue sections were placed in 10 mM citrate buffer at pH 6.0, and warmed in the microwave oven for 5 cycles of 5 min at 750 W. This pretreatment, referred to as antigen retrieval, enhances the reactivity of some formalin-fixed antigens. The tissue sections were then incubated with appropriate primary antibody against estrogen and progesterone receptors (see Table 1). Bound antibody was detected by a commercial kit procedure employing the biotin-streptavidin-peroxidase technique (Super Sensitive Multilink Kit, Biogenex Laboratories).

DNA content analysis was performed as previously described [14]. Briefly, nuclei were extracted from a 50 μm section, treated with trypisn and ribonuclease, and stained with propidium iodide. The sample was then examined by flow cytometry (FACScan, Becton Dickinson, San Jose, Calif., USA) and 10000 events were collected. The cell cycle parameters were analysed using a rectangular model (CellFit program, Becton Dickinson).

Table 1 Immunohistochemical stains and staining results (*D* Dako Corporation, Santa Barbara, California, USA; *Bg* Biogenex Laboratories, San Ramon, California, USA; *Bo* Boehringer Mannheim Biochemicals, Indianapolis, Indianapolis, USA; *E* Enzo Diagnostics, New York, NY, USA; *Bm* Biomeda, Foster City, California, USA; *A* AMAC, Westbrook, Maine, USA; *M/P* monoclonal/polyclonal; *BFH* benign fibrous histiocytoma; *CA* carcinoma; Staining intensity: –/(+)/+/++/+++=negative/very weak/weak/moderate/strong; *N/D* not done)

Antibody	Source	Supplier	Dilution	BFH	CA
Vimentin	M-mouse	D	1:300	++	–
α_1-antitrypsin	P-rabbit	D	1:1000	(+)	–
α_1-antichymotrypsin	P-rabbit	D	1:1000	(+)	–
Desmin (D33)	M-mouse	D	1:50	(+)	–
Lysozyme	P-rabbit	Bg	1:80	–	ND
Muscle actin (HHF35)	M-mouse	E	1:1000	–	–
α-Smooth muscle specific actin	M-mouse	Bg	1:500	–	–
Myoglobin	M-mouse	D	1:1000	–	ND
KP1 (CD68)	M-mouse	D	1:100	–	ND
S100 protein	P-rabbit	D	1:100	–	–
von Willebrand Factor (factor VIII)	M-mouse	D	1:50	–	ND
Cytokeratin (AE1/AE3)	M-mouse	Bo	1:300	–	+++
Cytokeratin (CK22)	M-mouse	Bm	1:1	–	+++
ER-ICA	M-mouse	A	1:1	++	+++
PGR-ICA	M-rat	Bg	1:1	+	++
Ki-67	M-mouse	D	1:1	(+)	ND

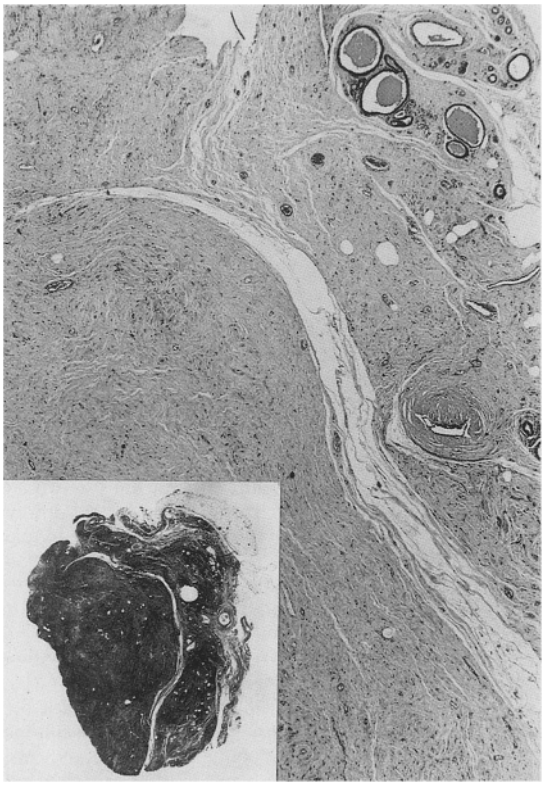

Fig. 1 Low magnification photograph at the periphery of the mesenchymal mass. The mesenchymal change extends beteen adjacent mammary epithelial structures. The tissue cleft in the photograph was accentuated by fixation and gives an erroneous impression of a sharp demarcation. The whole tissue section with peripheral fringe of benign adipose tissue is shown in the inset (haematoxylin and light green; 30×)

Results

Surgical, gross and microscopic description

The mass in the right breast was located in the upper outer quadrant, just off the areolar edge. It was situated deep in the breast and was not directly attached to the overlying skin, areolar tissue or pectoralis fascia. The surgical resection specimen consisted of a 7.5 cm mass of fibroadipose tissue that contained a 4.8 cm bosselated fibrous mass (Fig. 1). The cut surface was white and fibrous, with a slightly irregular nodular edge. Microscopic examination showed the mass to consist of of both loose and dense keloid-like collagen, with indistinct mesenchymal cells, fibroblasts and atypical-appearing stomal giant cells in the background (Fig. 2). The giant cells occurred both singly and in small clusters, and both mononuclear, lobated and multinucleated forms were noted (Fig. 3). Many of giant cells had a moderate amount of foamy cytoplasm and some had hyperchromatic nuclei. The stromal cells were not fasciculated, and neither mitotic figures, nor necrosis were identified. The mass contained some prominent thin-walled vessels, and entrapped fat cells focally. Although the mass appeared to be well-delineated grossly, the stromal change extended focally into surrounding areas of fibrocystic disease (Fig. 1). As far as we could tell, the surgical margins were free of obvious benign fibrous histiocytoma (BFH).

The tumour in the left breast was poorly differentiated, ductal carcinoma, and located directly beneath the areola. The tumour invaded subareolar smooth muscle and extended into the papillary dermis, but did not reach the epidermis. The maximum tumour dimension, including residual tumour removed at mastectomy, was estimated to be approximately 3 cm. Random sections of left breast showed fibrocystic disease, without stroma change

Fig. 2 Medium power photomicrograph of the fibrous mass showing fibroblasts and bizarre giant cells entrapped between dense collagenous fascicles (haematoxylin and light green; 200×)

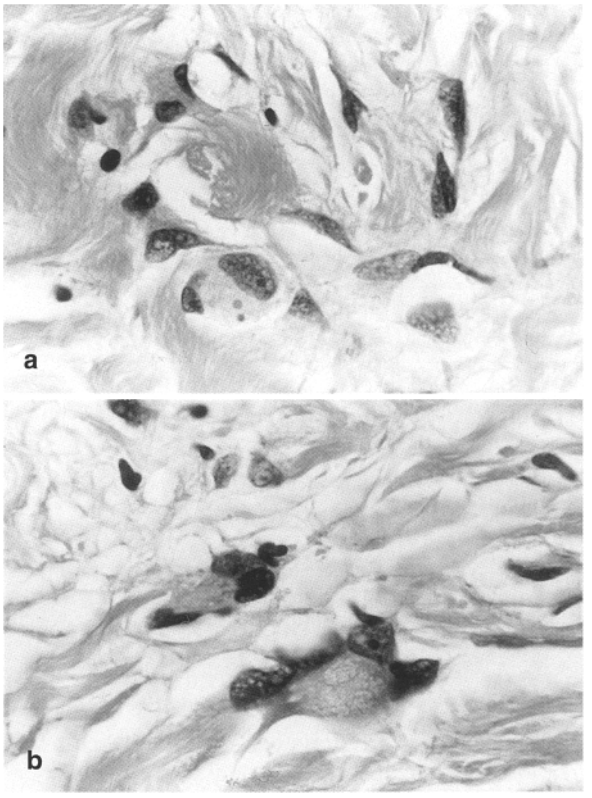

Fig. 3 Composite photomicrograph of two high power fields showing the cytomorphological features of the stromal giant cells (haematoxylin and light green; 1,000×)

as described in the contralateral breast. The axillary lymph nodes were without metastatic tumour.

Immunohistochemistry

Many of the abnormal stromal cells in the right-sided mass reacted with anti-vimentin with moderate intensity, and some reacted with anti-α_1-antitrypsin, α_1-antichymotrypsin and desmin with a weak speckled cytoplasmic staining pattern (Table 1). The other stains were negative. Very rare stromal cells reacted with the cell proliferation markier Ki-67. Approximately 50–75% of the stromal cell nuclei (including those of pleomorphic giant cells) reacted with anti-estrogen receptor (ER) and approximately 25–50% of the stromal cell nuclei reacted with anti-progesterone receptor (PR). Neighbouring benign ducts and lobules also reacted with the stains for steroid hormone receptors, and served as an internal control.

The invasive carcinoma in the left breast reacted strongly with antibodies against cytokeratin, epithelial membrane antigen, ER and PR.

DNA Content analysis

DNA content analysis of the mesenchymal tissue indicated that most of the cells were DNA diploid (Fig. 4). The S-phase and G_2/M phase (i.e., DNA tetraploid) population were both small. Despite the presence of large abnormal appearing nuclei, we were only able to detect a small (and questionable) DNA octaploid population.

Discussion

We have described a benign mesenchymal tumour with bizarre appearing giant cells in the contralateral breast of a woman with infiltrating ductal carcinoma. We interpret this lesion as a variant of BFH because of its resemblance to benign fibrohistiocytic tumours at other body sites [2] and the immunohistochemical staining pattern [5]. BFH is thought to arise from mesenchymal cells with fibroblastic, myofibroblastic and histiocytic properties. Although benign, BFH may contain atypical multinucleated giant cells, infiltrate, and recur if incompletely excised.

The differential diagnosis of this tumour includes other benign and locally aggressive mammary fibrous neoplasms, and mammary lesions associated with giant cells. Relevant fibrous neoplasms include: spindle cell lipoma, radial scar, keloid, myofibroblastoma, the "benign spindle cell neoplasm of breast," musculo-aponeurotic fibromatosis, fasciitis and primary mammary fibromatosis. This particular tumour lacks the adipose compo-

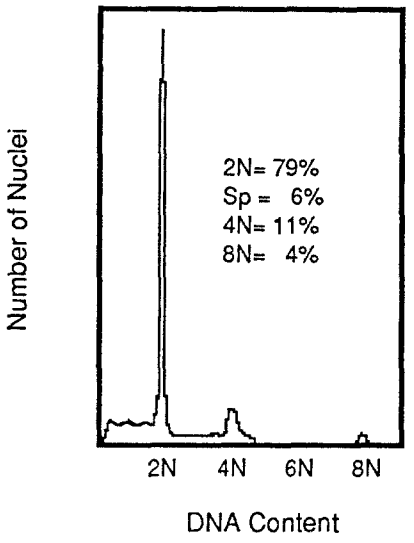

Fig. 4 DNA content analysis. Most of the nuclei were DNA diploid; the S-phase (Sp) and G_2/M-phase (i.e., 4N) populations were small, and there was a suggestion of a very small DNA octaploid peak (8N)

nent necessary for the diagnosis of spindle cell lipoma [2]. Keloid is an exuberant and dense scar, usually in the dermis, and radial scar usually contains degenerated elastic tissue and distorted ducts. Although hypocellular areas in the current tumour resemble the dense fibrous tissue of keloid or radial scar, the cellular areas did not. Myofibroblastoma, a neoplam of myofibroblasts, has a different histological appearance and is not invasive [13]. The "benign spindle cell breast tumour" is a myofibroblastic neoplasm described in 1981 [11], and appears to be related to myofibroblastoma. Musculo-aponeurotic fibromatosis typically arises from deep fascia or muscle, is aggressive and has a characteristic histological appearance, features lacking in the current lesion. The distinction from primary fibromatosis of the breast [10, 12] and nodular fasciitis is less clear, and we concede that our tumour could be interpreted as an involuted variant of either of these two neoplasms. We decided not to interpret out tumour as fibromatosis or fasciitis for the following reasons. Although primary fibromatosis of the breast may hyalinize, have a "circumscribed nodular margin" focally, and lack the aggressive behaviour of fibromatosis at other body sites, there should be cellular areas typical of fibromatosis and characteristic infiltration [12], which this lesion lacked. Nodular and proliferative fasciitis is usually a fast growing, mitotically active tumour of the fascia and soft tissue, consisting of fascicules of plump fibroblasts that may involute in later stages of maturation [2]. Our case differed from the usual case of nodular fasciitis, through its rather slow growth and lack of typical cellular areas.

Basically three types of giant cells occur in the breast: stromal giant cells, osteoclastic-like giant cells and neoplastic giant cells. Among the mammary lesions with atypical stromal giant cells, isolated cases of fibromatosis [12], fibroadenoma [1], fibrohistiocytoma of the mammary dermis [4], and carcinoma [9] deserve mention. Osteoclast-type multinucleated giant cells of histiocytic origin sometimes associate with mammary carcinoma [3]. Malignant giant cells may be seen in metaplastic carcinoma and sarcoma. The giant cells in the current tumour were stromal and not associated with obvious fibromatosis, fibroadenoma, dermis or malignant neoplasm.

In order to better define the biology of the lesion, we analysed the mesenchymal tumour for steroid hormone receptor expression and DNA content. The mesenchymal cells comprising the lesion expressed both estrogen and progesterone steroid hormone receptors suggesting a hormone dependency. There is little published data on steroid hormone expression by breast stroma, and most previous studies utilized techniques that were either unable to detect weak steroid receptor expression in formalin-fixed tissue, or analysed a macerate of both epithelium and stroma [6]. It is our impression that most mesenchymal cells do not express steroid receptors to a degree detectable by the methodology described earlier. In a review of recent mammary biopsies with carcinoma from our routine surgical service, we found ER or PR expression by mesenchymal cells in approximately 10% of cases, whereby the expression was generally variable and weak. Primary mammary fibromatosis, which appears to be related to the current neoplasm, expreses female steroid hormone receptors [8]. Most of the cells in the current tumour had a diploid DNA content (Fig. 4). This result is generally consistent with benign fibrohistiocytic neoplasm from other body sites [7]. DNA content analysis also indicated that the S-phase fraction was small. Some of the nuclei in the S-phase region may represent nuclear fragments, so that the actual S-phase of this tumour may be even less than the value measured.

In conclusion, we have described a pleomorphic variant of BFH in the breast that formed a mass lesion containing giant cells with bizarre cytomorphological features. These giant cells could lead to interpretive confusion.

Acknowledgements We thank J. W. Daucher for technical help with the immunohistochemistry, R. W. Cotie MD for clinical information, P. A. Tackman for assistance with photography, R. Paik MD and P. Malek MD for the initial pathological handling of the specimen.

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