Metaplastic Breast Tumors with a Dominant Fibromatosis-Like Phenotype Have a High Risk of Local Recurrence

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Presented in part at the 10th International Congress on Senology, Porto, Portugal, June 1–4, 1998.

Supported in part by the Division of Anatomic Pathology, and CAPES/Brasilia, Brazil (Helenice Gobbi).

The authors thank the more than 70 clinicians and pathologists who provided clinical follow-up information, Sandy Olson for discussions, Julia Smith and Robena Ross for technical support, and Jean McClure for assistance with the article.

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Received February 5, 1999; accepted February 10, 1999.

BACKGROUND. In the current study the authors describe the clinicopathologic characteristics of a low grade variant of spindle cell metaplastic tumors of the breast. Previously these tumors have been considered within a larger group recognized as metaplastic carcinoma, including cases with higher grade features.

METHODS. Breast tumors comprised predominantly of low grade spindle cells, with sparse low grade epithelial elements, were selected. Clinical features as well as macroscopic, microscopic, and immunohistochemical findings were reviewed with emphasis on the biologic behavior and the differential diagnosis from other spindle cell lesions.

RESULTS. Of 30 tumors fulfilling strict criteria, 20 contained squamous or glandular elements associated with the spindle cells. Ten tumors were comprised entirely of low grade spindle cells with limited clustered epithelioid cells. At the periphery, all tumors showed a proliferation of bland spindle cells infiltrating the adjacent parenchyma and mimicking fibromatosis. The epithelioid cells and some spindle cells expressed both vimentin and one or more cytokeratins. Seven of eight patients treated by excisional biopsy developed local recurrence, whereas only one of ten patients treated with wide excisional biopsy developed a local recurrence. No distant or regional metastases occurred.

CONCLUSIONS. The presence of limited clusters of epithelioid cells along with a dominant fibromatosis-like pattern may be unique in the breast. The biologic potential of the fibromatosis-like, spindle cell, metaplastic breast tumors most likely is defined by their major histologic phenotype; they are capable of local recurrence with no demonstrated distant spread or regional metastases, as in pure fibromatosis of the breast. ***Cancer* 1999;85:2170–82.**

KEYWORDS: breast neoplasms, metaplastic carcinoma, spindle cell carcinoma, fibromatosis, diagnosis, prognosis, immunohistochemical study.

Metaplastic carcinomas of the breast by definition are of epithelial origin with intermixed nonepithelial elements including spindle cells, bone, cartilage, myxoid stroma, and anaplastic stroma with giant cells.[1-7] The prognostic significance of the different metaplastic changes in mammary tumors continues to be understood incompletely, largely because these tumors are rare and have been variously catalogued.[8-16]

Tumors predominantly comprised of spindle cells, frequently associated with an invasive squamous or glandular component, have been designated as spindle cell carcinoma,[10,17-19] carcinoma with pseudosarcomatous stroma,[20] and sarcomatoid carcinoma.[21,22] The metaplastic spindle cells in these tumors can vary from a relatively

bland appearance to aggressive patterns resembling high grade sarcomas.[10,17-19] The introduction of immunohistochemical markers for differentiation has not resolved problems regarding case assignment. The spectrum of their morphologic and behavioral features has not been linked directly to clinical outcome, although it generally is accepted that if histologic patterns of carcinoma are lacking, regional metastasis is unlikely.[3,14]

The purpose of this study was to describe the clinicopathologic characteristics of a low grade variant of spindle cell metaplastic tumor of the breast that previously has been reported within a larger category including cases with higher grade features. We chose the term "tumor" to avoid the word "carcinoma" because neither the phenotype nor the behavior is that of a carcinoma. Our emphasis is on the differential diagnosis from other spindle cell lesions of the breast and the prognostic implications of local recurrence without risk of metastases.

MATERIALS AND METHODS

Breast tumors coded as metaplastic carcinoma, spindle cell carcinoma, carcinoma with spindle cell metaplasia, fibrosarcoma, fibromatosis, myofibroblastic inflammatory pseudotumor, and nodular fasciitis all were selected from the files of the Breast Pathology Consultation Service at Vanderbilt University Hospital from 1988–1997. Of these, 241 tumors with metaplastic features were retrieved and the original slides were reviewed. For the purposes of this study we selected 30 tumors predominantly (95%) comprised of low grade spindle cells. Lesions with squamous or carcinomatous features were included if these elements represented $< 5\%$ of the total area of the lesion and were not present at the periphery of the tumor. The diagnosis was assigned without knowledge of clinical outcome. Initially, metaplastic tumors with a dominant low grade fibrosarcoma phenotype were selected and reviewed, but they were not included in the fibromatosis-like group. All cases with bone, cartilage, giant cell, or intermediate or high grade sarcomatous components also were excluded.

Clinical data and follow-up information were obtained from medical records and physicians responsible for patient care.

The macroscopic pathologic findings were obtained from the surgical pathology reports and included tumor size and contour (infiltrating or nodular). Histologic evaluation was performed from hematoxylin and eosin stained sections and the following microscopic findings were analyzed: growth pattern, cellularity, nuclear atypia, and mitotic rate. The microscopic growth pattern was classified as nodular, infiltrative with finger-like extensions, or partially nodular. Tumor cellularity was evaluated throughout the tissue sections after microscopic examination using a $\times 10$ objective, with emphasis on the leading edges. Cellularity was graded 1+ (25% cells, $\geq$ 75% collagen, and related intercellular elements), 2+ (50% cells and 50% collagen), and 3+ ($\geq$ 75% cells and $\leq$ 25% collagen). The spindle cell nuclear atypia was rated as absent or minimal (1+), in comparison with the nuclei of normal fibroblasts. Areas of maximum mitotic activity were identified and the number of mitotic figures expressed per ten high-power fields (HPF). The dimension of the HPF was 0.49 mm (area, 0.20 mm^2). Inflammatory infiltrate and the presence of lymphoid follicles, whether admixed with the tumor cells or present at the periphery of the tumor, were evaluated as positive if present or negative.

TABLE 1
Antibodies Used in This Study

Antibody	Clone	Dilution	Source
AE1/AE3	AE1/AE3	1:100	Dako Co. (Carpinteria, CA)
HMW-K	Polyclonal, 40–60 kD	Predilute	Signet (Dedham, MA)
CAM 5.2	CAM 5.2	1:20	Becton-Dickinson (San Jose, CA)
Cytokeratin 7	OV-TL 12/30	1:100	Dako Co.
EMA	E29	1:1000	Dako Co.
Vimentin	V9	1:300	Boehringer-Mannheim (Indianapolis, IN)
Smooth muscle actin	CGA7	Predilute	Enzo Diagnostics (Syosset, NY)
Muscle specific actin	HHF35	Predilute	Enzo Diagnostics
Factor VIII	F8/86	1:40	Dako Co.
CD31	JC/70A	1:100	Dako Co.

HMW-K: high molecular weight keratin; kD: kilodaltons; EMA: epithelial membrane antigen.

Immunohistochemical Studies

When possible the original paraffin blocks were recut and immunohistochemical stains using commercially available antibodies (Table 1) were performed on routinely processed, formalin fixed, paraffin embedded surgical material. An automated immunostainer (TechMate; Bio Tek, Tucson, AZ) and the avidin-biotin-peroxidase complex method were used. All cases examined were subjected to heat-induced epitope retrieval. Because of the limited availability of slides and blocks, not all antibodies were used in each case. Positive and negative controls were included with each assay. All stains were reviewed and scored as positive or negative in the mesenchymal and epithelial elements, noting any variations in intensity or distribution. A panel of anticytokeratin antibodies was

TABLE 2
Clinicopathologic Features of the Nonrecurrent Cases

Case no.	Age[a] (yrs)	Tumor size[b] (cm)	Growth pattern	Initial diagnosis	Initial treatment	Follow-up[c] and information
1	43	3.5	Infiltrative	Benign lesion with fibrosis	WE + AXLN	NA
2	62	2.2	Infiltrative	Bx site with fibrosis	MxT + AXLN	72 mos; L, NED
3	68	3.3	Infiltrative	SCC	WE	72 mos; L, NED
4	45	4.0	Infiltrative	Inflammatory pseudotumor	MxT + AXLN	72 mos; L, NED
5	80	NA	Nodular	Involuted fibroadenoma	NA	NA
6	80	1.3	Partially nodular	SCC	NA	NA
7	49	4.5	Infiltrative	DCIS and mastitis	NA	NA
8	69	3.5	Infiltrative	Fibromatosis	MxT + AXLN	NA
9	71	NA	Infiltrative	Immunologic disorder	MxT + AXLN	25 mos; Died with cerebral infarction
10	62	NA	Infiltrative	SCC	WE + AxLN + RT + HT	54 mos; L; NED
11	57	NA	Infiltrative	SCC	NA	NA
12	61	NA	Infiltrative	Fibromatosis	NA	NA
13	61	1.2	Nodular	ADH in a fibroadenoma	MxT + AXLN	NA
14	73	7.0	Infiltrative	FC with reactive stroma	NA	NA
15	47	2.0	Infiltrative	CSL and carcinoma	WE + CT	NA
16	54	2.5	Partially nodular	SA and marked fibroplasia	WE	NA
17	71	1.7	Nodular	SCC or reactive process	NA	NA
18	74	2.3	Infiltrative	Inflammatory pseudotumor	Excisional biopsy	10 mos; L, NED
19	75	3.0	Infiltrative	N. fasciitis or fibromatosis	WE + AXLN + CT + RT	8 mos; L, NED
20	73	2.3	Partially nodular	SCC or fibromatosis	WE + AXLN	10 mos; L, NED
21	57	1.7	Partially nodular	Fibromatosis or SCC	WE + AXLN + RT	52 mos; L, NED
22	40	3.0	Infiltrative	Fibromatosis or N. fasciitis	WE	19 mos; L, NED

WE: wide excision; AXLN: axillary lymph node dissection; NA: not available; Bx: biopsy; Mxt: mastectomy; L: alive; NED: no evidence of disease; SCC: spindle cell carcinoma; DCIS: ductal carcinoma in situ; RT: radiotherapy; HT: hormonal therapy; ADH: atypical ductal hyperplasia; FC: fibrocystic change; CSL: complex sclerosing lesion; CT: chemotherapy; SA: sclerosing adenosis; N. fasciitis: nodular fasciitis.

[a] Average age: 62.4 ± 12.1 years.

[b] Average tumor size: 2.9 ± 1.4 cm.

[c] Median follow-up: 38.5 months.

used including AE1/AE3, CAM 5.2, cytokeratin 7 (CK-7), and high molecular weight keratin (HMW-K).

RESULTS

Clinical Features

The clinicopathologic features of all cases are summarized in Tables 2 and 3. All subjects reported in this study were women. The average age at initial diagnosis was 63.4 years (range, 40–80 years). At the initial physical examination a single palpable breast mass was present in each patient. Lesions involved the left breast in 15 patients and the right breast in 9 patients. Laterality was unknown in six patients. Swelling and tenderness were present in one patient, nipple inversion was present in one patient, and recurrent cyst after aspiration was present in one patient.

Pathology

Macroscopic findings

A macroscopic description was available for 28 cases. All tumors were firm and white, and ranged from 1.2–7.0 cm in greatest dimension (average, 2.7 cm). Fifteen tumors were well circumscribed, 9 tumors had irregular borders, 3 tumors were partially nodular, and 1 tumor presented as a cyst. None was encapsulated. In two cases information regarding macroscopic contour was not available.

Light microscopic findings in the initial biopsy

The number of sections reviewed in each case ranged from 1–22 (average, 8.6 sections). In 21 cases the predominant microscopic growth pattern was infiltrative, with finger-like projections extending into adjacent mammary structures and fatty tissue (Fig. 1). In three cases the tumors were ill-defined and nodular, and in six cases the tumor was partially nodular with focal areas of finger-like extensions. In three cases the spindle cells proliferated diffusely around the periphery of adjacent ducts. In one case the spindle cells were distributed diffusely around a cystic space lined by squamous epithelium, infiltrating the adjacent tissue.

Histologically, all cases studied had a dominant low grade spindle cell component present in at least 95% of the total area of the tumor (Figs. 1 and 2).

TABLE 3
Clinicopathologic Features of the Cases that Recurred

Case no.	Age[a] (yrs)	Tumor size[b] (cm)	Growth pattern	Initial diagnosis	Initial treatment	Interval to recurrence[c]	Follow-up[d] and information
1	65	3.2	Partially nodular	Fibromatosis	Excision	8 mos	16 mos; Died 8 mos after reexcision; cause unknown
2	52	NA	Infiltrative	Fibromatosis or low grade fibrosarcoma	Excision	11 mos	11 mos
3	67	4.0	Infiltrative around a cyst	Spindle cell carcinoma	Excision	5 mos	32 mos; L, NED 27 mos after WE + RT
4	75	1.3	Partially nodular	Chronic mastitis with active stroma	Excision	36 mos	44 mos; L, NED 8 mos after WE
5	62	1.5	Infiltrative	CSL with stromal atypia	Excision	72 mos	88 mos; Second recurrence: 9 mos after reexcision, treated by MxT. L, NED 7 mos after MxT.
6	69	2.5	Infiltrative	Fibromatosis	WE	6 mos	6 mos; recurrence treated by WE
7	69	1.3	Infiltrative	CSL with active stroma and squamous metaplasia	Excision	24 mos	29 mos; Recurrence treated by MxT + AXLN; L, NED 5 mos after MxT.
8	71	2.0	Infiltrative	Reactive fibrosis	Excision	20 mos	20 mos

mos: months; NA: not available; L: alive; NED: no evidence of disease; WE: wide excision; RT: radiotherapy; CSL: complex sclerosing lesion; MxT: mastectomy; AXLN: axillary lymph node dissection.
[a] Average age: 66.3 ± 6.9 years.
[b] Average tumor size: 2.3 ± 1.0 cm.
[c] Median: 15.5 months.
[d] Median: 24.5 months.

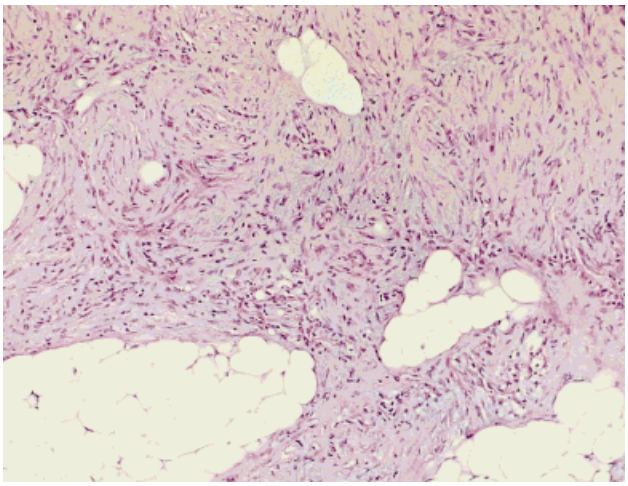

FIGURE 1. Infiltrative growth pattern with finger-like extensions into the adjacent breast stroma (H & E, ×100).

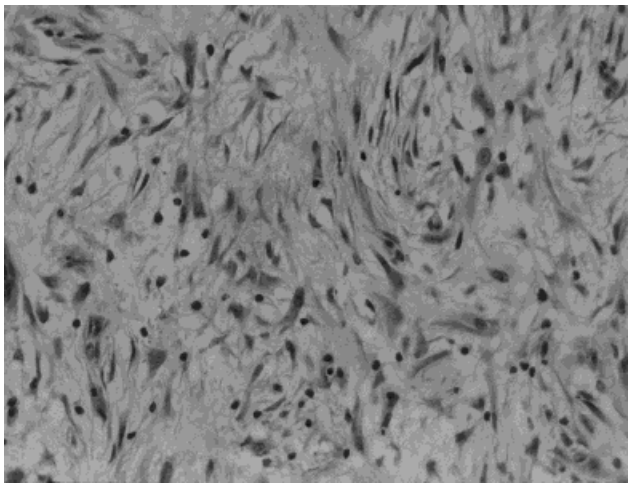

FIGURE 2. Uniform and bland spindle cells resembling fibromatosis with few lymphocytes and histiocytes, similar to nodular fasciitis (H & E, ×200).

Focally, plump fusiform and polygonal tumor cells, with more rounded nuclei, were arranged in "epithelioid" clumps (Figs. 3 and 4). Rare foci of glandular or squamous elements associated with the spindle cells were present in 20 cases, comprising < 5% of the tumor (Figs. 5 and 6). Both squamous and glandular elements were present in 11 cases, only squamous elements were present in 6 cases, and only glandular elements were identified in 2 cases. Small rudimentary glands, either without cytologic evidence of malignancy or with characteristics of low grade malignancy, represented the glandular elements (Fig. 5). Ductal carcinoma in situ was present in a limited amount in four cases. Ten tumors were comprised entirely of spindle cells with no squamous or adenocarcinomatous differentiation observed in the hematoxylin and eosin stained sections. However they had the characteristic clusters of epithelioid cells described earlier.

The lesions were characterized by spindle cell components of varying cellularity and collagenization.

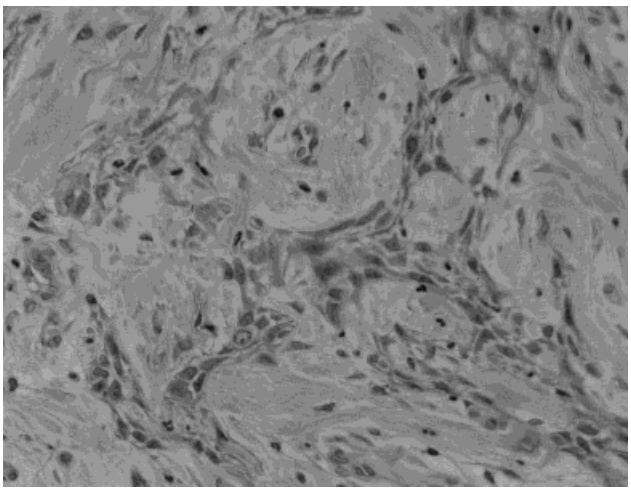

FIGURE 3. Plump fusiform and polygonal cells arranged in epithelioid clumps merging with each other and with the spindle cell component (H & E, ×400).

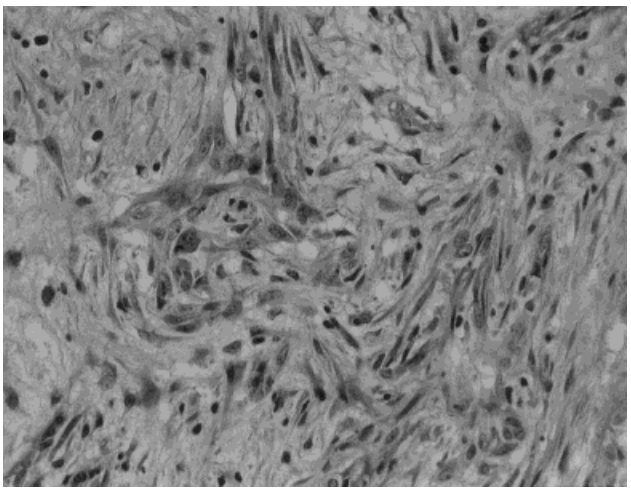

FIGURE 4. Clusters of plump epithelioid cells taper and merge with intermingled fibromatosis-like areas (H & E, ×200).

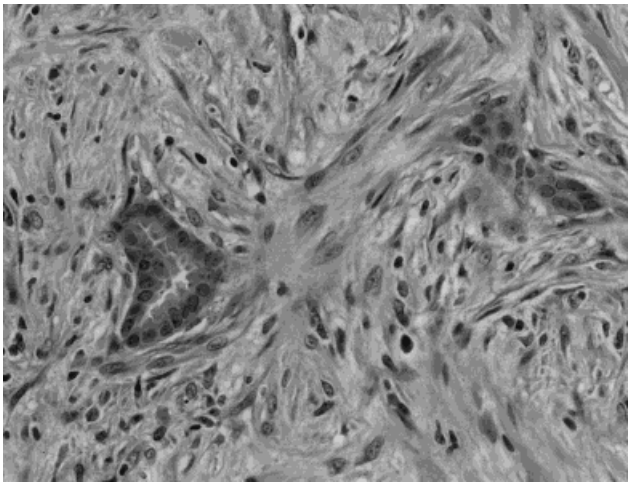

FIGURE 5. This tumor shows small neoplastic glands (upper right) and most likely normal entrapped gland (left). A gradual transition from the upper right glandular elements to the spindle cell component is observed toward the center of the photomicrograph (H & E, ×400).

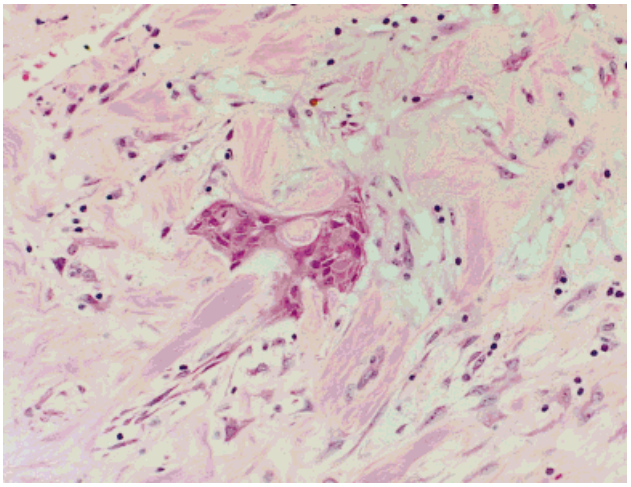

FIGURE 6. A small island of squamous cells is present intermixed with low grade spindle cells and collagen fibers (H & E, ×200).

Nineteen cases were graded as 1+ cellularity, 9 cases were graded as 2+ cellularity, and 1 case was graded as 3+ cellularity in the initial biopsy. The tumors were comprised of cytologically bland spindle cells with a pale eosinophilic cytoplasm and slender nuclei with tapered edges and finely distributed chromatin (Fig. 2). Spindle cell nuclear atypia was absent in 9 cases and was minimal in 21 cases. The spindle cells appeared mainly isolated or were arranged in wavy, interlacing fascicles. The clusters of plump epithelioid cells were common in the center but appeared less frequently at the edges of the tumors. We graded the frequency of epithelioid clumps as absent (1 case), 1+ (15 cases), 2+ (10 cases), and 3+ (3 cases). A gradual transition from plump cells to the spindle cell component frequently was observed (Figs. 4 and 5). In addition, a gradual transition also was observed from squamous and glandular elements (Fig. 5). At the periphery, the majority of tumors showed bland spindle cell proliferation, infiltrating the adjacent stroma and closely resembling fibromatosis (Fig. 1).

Other findings were present focally in a few cases such as a storiform pattern, resembling benign fibrous histiocytoma (two cases); fibromyxoid stroma (three cases); and pseudoangiomatoid stroma (two cases). Focally, spindle cells were interspersed among bands of hyaline collagen (Fig. 6). In three cases the collagen was especially abundant in the center of the tumor. In

TABLE 4
Immunohistochemical Results[a]

Antibody	No. of positive cases/no. of cases tested
AE1/AE3	10/11
HMW-K	12/16
CAM 5.2	9/14
Cytokeratin 7	5/11
EMA	4/8
Vimentin	22/23
Smooth muscle actin	2/9
Muscle specific actin	8/10

HMW-K: high molecular weight keratin; EMA: epithelial membrane antigen.
[a] Eighteen of 22 cases tested were positive for epithelial markers.

two cases the neoplastic spindle cells and some glandular or squamous elements were associated with a complex sclerosing lesion. Normal entrapped ducts and lobular structures were present in 24 cases. No lymphatic, perineural, or blood vessel invasion could be identified in any case.

Mitotic figures in the spindle cell component ranged from none to three mitoses per ten HPF. In nine cases mitoses were not present. Twelve cases showed 1 mitosis per 10 HPF and 8 cases presented with 2 mitoses per 10 HPF. Neither necrosis nor pronounced nuclear atypia was identified in any of the cases.

Scattered inflammatory infiltrate comprised of lymphocytes and plasma cells was present in 18 cases at the edges of the tumor or scattered in the lesion, resembling nodular fasciitis in minor areas (Fig. 2). Sixteen cases showed occasional lymphoid follicles, mainly at the periphery of the tumor, some with germinal centers.

Immunohistochemical Studies

Immunohistochemical analysis for epithelial differentiation was performed on 22 cases (Table 4). In 18 cases (81.8%) the spindle cells were focally positive for at least 1 cytokeratin subtype, and 4 cases (18.2%) were negative. The strongest marking was obtained with the antibodies against AE1/AE3 (Fig. 7) and HMW-K (Fig. 8). Weaker reactions were obtained for the low molecular weight keratins (CAM 5.2 and CK 7) (Figs. 9 and 10). Both types of cells, epithelioid and spindled, expressed cytokeratins, but the epithelioid cells showed stronger cytoplasm positivity. Staining intensity gradually decreased in the transition to the spindle cell component (Figs. 7 and 8). Few epithelioid cells and rare spindle cells were weakly positive for epithelial membrane antigen (EMA). The squamous and glandular elements stained for all types of cytokeratins tested. The squamous component stained more strongly with HMW-K and AE1/AE3 compared with glandular elements. Although not easily recognized in the hematoxylin and eosin stained sections, the few glandular elements could be identified easily in the sections stained for AE1/AE3, CK-7 (Fig. 10), and CAM 5.2. They stained weakly with HMW-K. Normal ducts and lobules entrapped within the tumors were positive for all epithelial markers, and were used as internal control (Fig. 10). Six of ten tumors comprised entirely of spindle cells expressed at least one keratin subtype. Three cases were negative for cytokeratin, and immunostaining was not available in the fourth case. The spindle cells and some epithelioid cells expressed vimentin, but the intensity was stronger in the spindle cells. In all cases with cytokeratin staining of

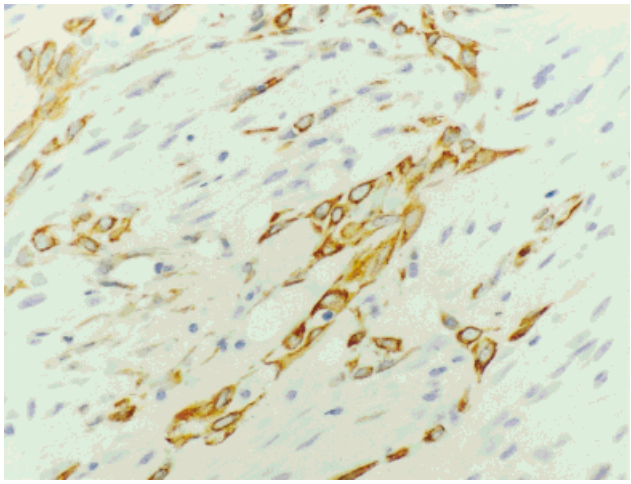

FIGURE 7. The more plump epithelioid cells and some spindle cells stained positive for AE1/AE3 (avidin-biotin-peroxidase, ×200).

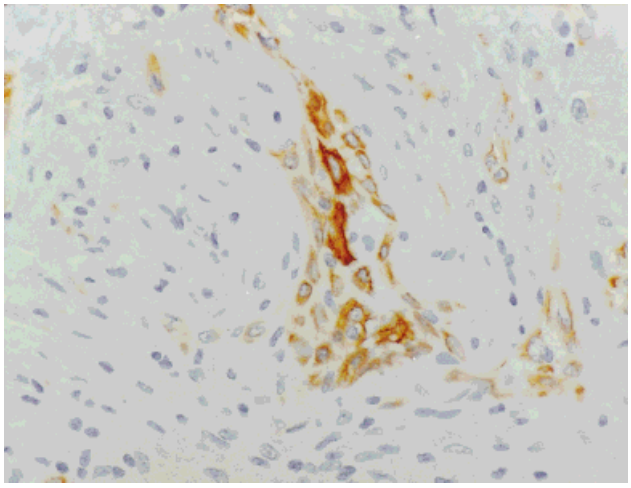

FIGURE 8. The plump epithelioid cells and some spindle cells stained positive for high molecular weight keratin (avidin-biotin-peroxidase, ×200).

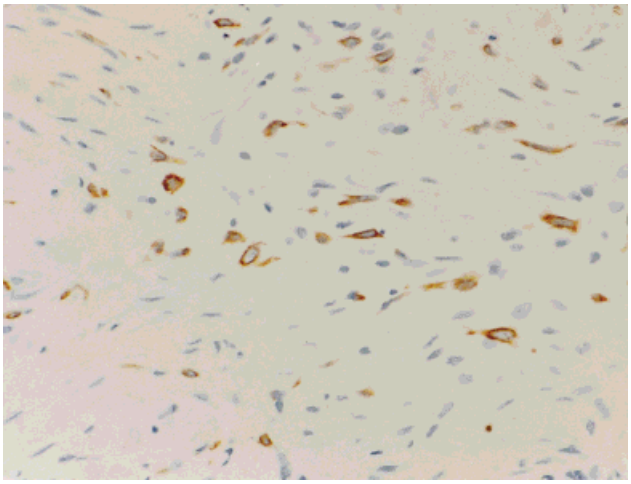

FIGURE 9. Immunohistochemical study demonstrating some spindle and plump cells positive for CAM 5.2 (avidin-biotin-peroxidase, ×200).

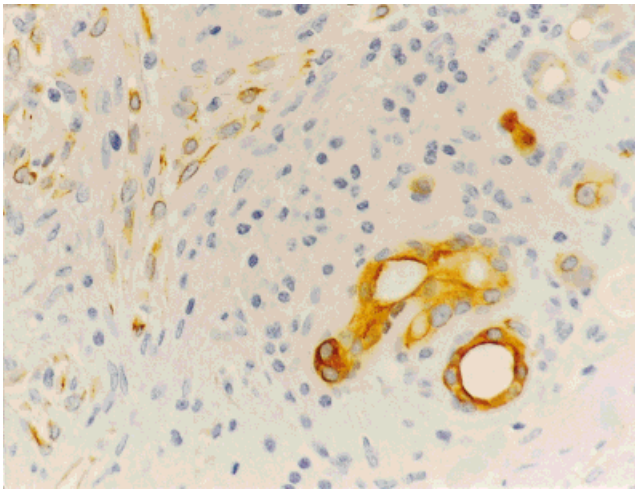

FIGURE 10. Epithelioid cells (left) and a few glandular elements (top right) were immunopositive for cytokeratin 7. Normal glandular elements (bottom right) also were positive and were used as the internal control (avidin-biotin-peroxidase, ×200).

clusters of epithelioid cells, some of these cells also expressed vimentin. In one case the spindle and epithelial cells were negative for both vimentin and HMW-K, but the normal ducts and lobules entrapped within the tumor also were negative, suggesting artifact. In eight cases the spindle cells stained for muscle specific actin and in two cases they stained for smooth muscle actin. The pseudoangiomatoid areas observed in two cases were negative for CD31 and factor VIII.

Treatment and Follow-Up

Information regarding initial treatment was available for 23 of 30 patients (76.7%) (Tables 2 and 3). All lymph nodes examined in the 11 patients who underwent axillary lymph node dissection were negative for metastases. Follow-up information was available for 18 of the 30 patients (60%) (Tables 2 and 3). The length of the follow-up period ranged from 6–88 months (median, 27 months). Eight of the 30 patients (26.7%) developed local recurrence within a period ranging from 5–72 months after the initial biopsy (median time to recurrence, 15.5 months). Seven of those eight women were treated with excisional biopsy only and the remaining patient underwent wide excision. Patients in the nonrecurrent group were treated locally with more extensive excision (mastectomy or wide excision) and had no evidence of disease between 6–72 months after the initial diagnosis (median, 38.5 months). One patient died with neurologic problems unrelated to the tumor 16 months after undergoing reexcision for tumor recurrence.

Analysis of the Recurrent Cases

Clinical and morphologic features, initial diagnosis, and data from the treatment and follow-up of the eight patients who developed local recurrences are summarized in Tables 3 and 5. The average tumor size in the initial biopsy specimens was 2.3 cm (range, 1.3–4 cm) and that for the biopsy specimens from the recurrent tumor was 2.0 cm (range, 0.7–3.8 cm). The tumor recurred within 24 months in 6 of 8 cases. In 1 patient the tumor recurred twice; the first recurrence occurred 88 months after the initial biopsy and the second recurrence developed 9 months later, after a second excisional biopsy (Fig. 11). One patient died 8 months after a biopsy of the recurrent tumor, but the cause of the death was unknown. Slides from the initial biopsy and from the recurrent lesion were available for comparison in six cases. In one case, only slides of the recurrent lesion were reviewed and in another case only slides of the initial biopsy were reviewed. Microscopic features of the initial biopsy and the recurrent lesion are summarized in Table 5. Three recurrent tumors were more cellular (Fig. 11) and had increased mitotic activity compared with the initial lesions. Selected pathologic features comparing the recurrent and nonrecurrent cases are summarized in Table 6. The age at diagnosis and the clinical features of the patients who developed a local recurrence were not appreciably different from the nonrecurrent cases. Tumor size was larger in the nonrecurrent cases (average, 2.9 cm; range, 1.2–7 cm) than in the cases that recurred locally (average, 2.3 cm; range, 1.3–4 cm). Although the macroscopic pattern of the nonrecurrent cases was dominantly nodular (54.5% of cases), the microscopic growth pattern was infiltrative with finger-like extensions in 68.2% of the cases, sim-

TABLE 5
Microscopic Features of the Cases that Recurred

Case no.	Sample	Cellularity	Mitoses/10 HPF	Atypia	Squamous elements	Glandular elements	"Epithelioid" clumps
1	Initial biopsy	+	1	+	−	−	++
	Recurrence	+++	8	++	−	−	++
2[a]	Recurrence	+	3	+	−	+	++
3[b]	Initial biopsy	+	0	+	+	−	+
4	Initial biopsy	+	0	−	−	−	+
	Recurrence	+	1	+	−	−	+
5	Initial biopsy	+	0	−	−	+	−
	1st recurrence	++	2	+/−	−	+	+++
	2nd recurrence	++	1	+	+	+	+++
6	Initial biopsy	+	2	+	+	+	+
	Recurrence	+	2	+	+	+	++
7	Initial biopsy	+	1	+	+	+	+
	Recurrence	++	1	+	+	+	++
8	Initial biopsy	+	0	+	+	−	+
	Recurrence	+	0	+	+	−	+

HPF: high-power fields.

[a] Slides from the recurrent lesion available for review.

[b] Slides from the initial biopsy available for review.

ilar to the percentage of recurrent cases (75%). Analysis of the relation between the type of treatment and local recurrence showed that the recurrences nearly were related directly to the extent of local excision, with wide excision appearing to prevent local recurrence.

DISCUSSION

The current study describes and defines 30 metaplastic breast tumors with a dominant mesenchymal component comprised of a bland spindle cell proliferation. We consider these tumors a subset of spindle cell metaplastic carcinomas, most likely with defining clusters of plump epithelioid cells. The lesions show a dominant histology of fibromatosis plus other elements that indicate that they most likely are of metaplastic origin. They are characterized by minimal nuclear atypia of the spindle cells and the outer tumor borders (edges) bear a close resemblance to fibromatosis. We prefer to use the term "fibromatosis-like metaplastic tumor" for such lesions or "metaplastic lesion with fibromatosis-like mesenchymal element" and avoid the term "carcinoma." Although low grade spindle cells have been recognized as the major element of some spindle cell carcinomas of the breast,[3,10,17] to our knowledge lesions with this predominant fibromatosis-like pattern of metaplasia previously have not been considered separately.

Various criteria have been used to classify metaplastic breast tumors.[2,3,9-13,15,16,20] Categories have been based on differentiation, without consideration of grading or substratification to prognostically relevant groups by phenotype.[1,23] This has been done despite the fact that grading of both breast carcinoma and soft tissue sarcoma is accepted widely and is extremely useful.[24-26] Wargotz et al.[10] used the term "spindle cell carcinoma" to describe neoplasms in which intraductal or infiltrating carcinomas were contiguous or merged with a bland spindle cell proliferation. However, their series included spindle cell carcinomas ranging in differentiation from a bland appearance to a marked pleomorphism. Approximately 70% of the cases in their report were low grade tumors that resembled low grade fibrosarcomas with focal areas similar to cellular fibromatosis. In the follow-up analysis the cases were not considered separately by grading of atypia or degree of malignancy of the two components.[10] Gersell and Katzenstein[17] described a series of spindle cell carcinomas of the breast with marked geographic variations in histologic patterns, and included cases in which the spindle cells had a more bland appearance. Adenosquamous carcinomas of the breast also show areas of spindle cell metaplasia that are difficult to distinguish from ordinary tumor stroma.[27,28]

In our series, only low grade metaplastic lesions were included. The selection has been consistent in removing any case with histology suggestive of sarcoma or intermediate and high grade carcinoma. We chose a cutoff of 5% for the presence of epithelial elements or a low grade carcinoma component after reviewing all metaplastic spindle cell lesions. Tumors

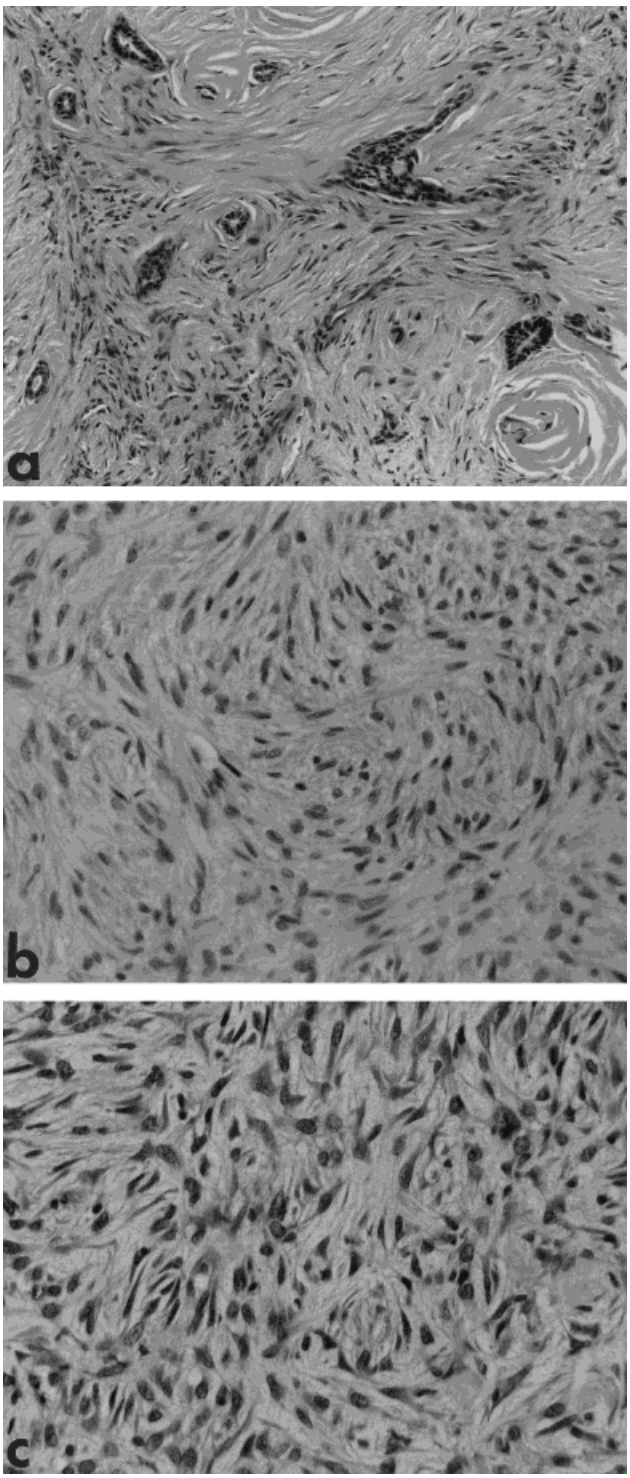

FIGURE 11. Photomicrographs from a tumor that recurred twice. a) Initial biopsy. There were few tumoral spindle cells growing adjacent to a complex sclerosing lesion. b) First recurrence. The tumor showed increased cellularity. c) Second recurrence. The tumor presented with increased cellularity and nuclear atypia. The more plump cells stained for cytokeratins (H & E; a: ×100; b and c: ×200).

TABLE 6
Selected Features of the Low Grade Spindle Cell Metaplastic Tumors in the Initial Biopsy: Recurrent versus Nonrecurrent Cases

Feature	N	Recurrent	Nonrecurrent
Average tumor size	28	2.3 cm (range, 1.3–4 cm)	2.9 cm (range, 1.2–7 cm)
Macroscopic contour	28		
Nodular	15	3 (20%)	12 (80%)
Infiltrative	9	3 (33.3%)	6 (66.7%)
Partially nodular	3	1 (33.3%)	2 (66.7%)
Cystic	1	1 (100%)	0
Growth pattern	30		
Infiltrative	21	6 (28.6%)	15 (71.4%)
Partially nodular	6	2 (33.3%)	4 (66.7%)
Nodular	3	0	3 (100%)
Cellularity[a]	30	1+	1.5+
Epithelioid areas[b]	30	1.0+	1.7+
Nuclear atypia[c]	30	0.7	0.7
Mitoses/10 HPF	30	0.6 (range, 0–2)	1.1 (range, 0–2)
Glandular elements	13	3 (23.1%)	10 (76.9%)
Squamous elements	17	4 (23.5%)	13 (76.5%)
Squamous + glandular	11	2 (18.2%)	9 (81.8%)
Entirely spindled cell	10	2 (20.0%)	8 (80.0%)
Initial treatment	23		
Excisional biopsy	8	7 (87.5%)	1 (12.5%)
Wide excision	10	1 (10%)	9 (90%)
Mastectomy	5	0	5 (100%)

HPF: high-power fields; N = number of cases.
[a] Cellularity was graded from 1+ to 3+.
[b] Epithelioid areas were graded from 1+ to 3+.
[c] Nuclear atypia was evaluated as absent (0) or minimal (1).

with the characteristics described in the current series most likely represent the lowest level of malignancy (local recurrence only) for both epithelial and mesenchymal components in the spectrum of the spindle cell carcinomas. A differential diagnostic point of fundamental importance occurs when primary tumors are similar to those described in our series but contain diagnostic carcinomatous elements or increased spindle cell atypia and cellularity. Two cases that we reviewed, but which did not meet the criteria for this study, showed a dominant fibromatosis pattern. They also presented with more cellularity of spindle cells and frequent epithelioid, glandular, and squamous elements at the edges of the tumor. One patient developed axillary lymph node metastases that were comprised entirely of squamous elements. The other patient presented with lung metastases, which were completely fibroblastic.

Ten cases in the current series (33.3%) showed spindle cell proliferation exclusively, without morphologically recognizable squamous or glandular elements. However, the presence of clusters of epithelioid cells recognized histologically in all ten cases and the immunohistochemical demonstration of cytoker-

atins in six of ten cases provided immunohistochemical evidence of epithelial differentiation.

Several spindle cell lesions, both neoplastic and nonneoplastic, must be considered in the differential diagnosis of low grade spindle cell metaplastic tumors of the breast.[10,17] These include fibromatosis, nodular fasciitis, inflammatory myofibroblastic pseudotumor, myofibroblastoma, and low grade spindle cell sarcoma.

Fibromatosis obviously is the most important differential diagnosis of the tumors described in the current series. Fibromatosis is an infiltrative lesion characterized by fibroblastic proliferation of variable cellularity and collagenization, with homogeneity of cell appearance and placement.[28,29,30] To our knowledge the majority of cases of fibromatosis of the breast reported to date had little or no nuclear pleomorphism. Mitoses are absent or rare. Inflammatory infiltrate and lymphoid aggregates, found in 50% of fibromatosis cases, tend to be present near the periphery of the lesions.[29,30] The likelihood is high that fibromatosis will recur locally, as evidenced by three studies that reported a 21–27% local recurrence rate after local excision.[29-31] In the current series, ten tumors comprised entirely of low grade spindle cell elements demonstrated a striking resemblance to breast fibromatosis. However, the cases in the current study were not fibromatoses because of the presence of clusters of epithelioid cells and cytokeratin expression in addition to the fibromatosis features. Clusters of epithelioid cells, such as those present in our series of tumors, are not described in pure fibromatosis. We have not observed the clusters of epithelioid cells in tumors of other sites. Metaplastic tumors with a fibromatosis-like phenotype may be unique in the breast.

Limited areas of the tumors described in our series showed inflammatory cells mixed with spindle cells, resembling nodular fasciitis. To our knowledge, the classic features of nodular fasciitis as reported in soft tissues of the extremities are very rare in the breast. Nodular fasciitis in the breast tends to be more rounded and circumscribed, and contains fibroblastic proliferation admixed with inflammatory, "myoid," and multinucleated cells dispersed at the periphery and within the lesion, and an increased myxoid matrix.[32-35] Mitotic figures frequently are observed in tumors that are removed or biopsied at an early stage.

Inflammatory myofibroblastic tumor, or inflammatory pseudotumor, is a spindle cell proliferation with a fibroinflammatory and pseudosarcomatous appearance that occurs in soft tissues and viscera but rarely in the breast.[24,36] In what to our knowledge is the largest series of myofibroblastic pseudotumors described, only one case was reported to occur in the breast.[36] Three major histologic patterns are recognized: 1) myxoid, vascular, and inflammatory areas, resembling nodular fasciitis; 2) compact spindle cells with intermingled inflammatory cells, resembling fibrous histiocytoma; and 3) dense collagen, resembling a scar.[36]

Myofibroblastoma, also reported as solitary fibrous tumor of the breast, is a macroscopically nodular and well circumscribed stromal tumor of the breast. It is found more frequently in the male breast.[37-40] The tumor is comprised of fascicles of uniform spindle cells separated by bands of hyalinized collagen and edematous areas.[37-41] Mitoses are rare. The spindle cells are immunoreactive for vimentin, desmin, CD34, muscle actin, and smooth muscle actin, and are negative for CD31, S-100, and cytokeratin.[37,39,41-44]

Mammary sarcomas are rare, and must be sampled exhaustively to avoid misinterpretation with spindle cell metaplastic tumors comprised nearly entirely of spindle cells.[10,14,21,45,46] The majority of the breast sarcomas with dominant spindle cells previously reported showed features of fibrosarcoma and malignant fibrous histiocytomas.[14,46] Liposarcomas presenting with myxoid areas are relatively common among breast sarcomas[47-49] but are distinguished easily from fibromatosis-like lesions. When compared with the metaplastic tumors described in the current series, sarcomas of the breast show more prominent nuclear atypia and an increased number of mitoses.[14,46] The spindle cells in the majority of breast sarcomas are positive for vimentin.[14,46] Immunopositivity for CAM 5.2 and EMA is described in the vimentin positive spindle cells of malignant fibrous histiocytoma of the breast, indicating that immunoreactivity is usually, but not always, defining.[14]

Immunostains for keratin markers demonstrated the epithelial nature of the tumors in 18 cases in the current series (i.e., 81.8% of the cases tested). Even without the demonstration of cytokeratins, we considered the tumor to be a metaplastic lesion in four cases. The element suggesting an epithelial cell origin was the clusters of cells related to each other in a more epithelioid fashion. Such epithelioid clusters of cells usually stained with cytokeratins. Using a panel of antibodies against low and high molecular weight cytokeratins allowed us to demonstrate at least one cytokeratin subtype (Table 4). Immunohistochemical results are not easily comparable to prior reports, even when the same antibodies and pretreatment are used. In our series, the low molecular weight cytokeratins (CAM 5.2 and CK-7) were only focally and weakly positive in the spindle cell component. Meis et al.[21]

did not demonstrate CAM 5.2 in the spindle cells of six sarcomatoid carcinomas of the breast. However, Ellis et al.[50] showed immunopositivity for CAM 5.2 in five of seven spindle cell tumors tested. Oberman[3] reported negative results for cytokeratin in two cases of spindle cell carcinoma.

Our strongest immunostains were obtained with antibodies against high molecular weight cytokeratins (HMW-K and AE1/AE3), similar to what previously was demonstrated in sarcomatoid carcinomas.[51,52] These results most likely indicate that the immunophenotype of the spindle cells is similar to the squamous epithelium. The low molecular weight cytokeratins (CK7 and CAM 5.2), that usually stain glandular and transitional epithelium[53,54] were better demonstrated in the more rounded epithelioid cells than in the spindle cell component. The morphologic transition from an epithelioid appearance to a more spindled shape phenotype most likely also is followed by changes in cytokeratin expression.

The coexpression of different intermediate filaments in the same cells, particularly vimentin and cytokeratin as we found in the current series of tumors, previously was described in benign and neoplastic breast epithelium, including metaplastic tumors and sarcomas.[14,19,21,50,55,56] However, in the cases in the current series, this coexpression of cytokeratin and vimentin in the clusters of epithelioid cells may represent a defining feature.

The importance of distinguishing spindle cell carcinoma from a sarcoma or a malignancy acting as a sarcoma is that the prognosis and treatment differ.[10,14,57,58] Usually patients with a diagnosis of spindle cell carcinoma undergo axillary lymph node dissection but this procedure is not required in patients with breast sarcomas.[57] However, in metaplastic tumors, such as those described in the current series, both the spindle cells and the squamous or glandular components are low grade and have extremely low potential to metastasize to regional lymph nodes (i.e., the epithelial element is limited, of low grade, and embedded in spindled components). The phenotype of metaplastic fibromatosis also would predict metastases to be an unlikely event. No metastatic tumor was found in the axillary lymph nodes dissected in seven patients in the current series. None of ten patients reported in two series of spindle cell carcinomas of the breast had metastatic neoplasms in axillary lymph nodes.[17,18] No distant metastases were detected in the patients in the current series. A similar tendency toward local containment in the breast has been recorded in patients with low grade adenosquamous tumors of the breast.[27,28]

In the current series, two cases in which the neoplastic spindle cells were associated with a complex sclerosing lesion were not recognized as metaplastic tumors in the initial biopsy. In the recurrent lesions the epithelioid clumps and glandular or squamous elements were more evident than in the initial biopsy and the diagnosis of a metaplastic tumor was made. The differential diagnosis is difficult because some radial scars and complex sclerosing lesions may show abundant spindle cells.[59] The coexistence of carcinoma in radial scars and complex sclerosing lesions had been described previously, without considering them to be premalignant lesions.[60,61]

Eight patients in the current series developed local recurrence. Microscopically, we could not find any significant morphologic element to predict recurrence. The proportion of the metaplastic components and the grade of atypia were not increased sufficiently in the recurrent cases to explain the tendency toward local recurrence. However, there were differences in the initial treatment of patients. Seven cases in the recurrent tumor group were not recognized as metaplastic tumors in the initial biopsy, and the patients were treated with excisional biopsy only. In 6 of the 8 patients the tumors recurred within 24 months (median, 15.5 months) after diagnosis. The length of follow-up for patients in the nonrecurrent group (median, 38.5 months) was longer than the time in which the majority of the tumors recurred. Although neither of the two patients treated with radiotherapy developed a local recurrence, we believe that a wide excision is more useful than radiation for these low grade lesions that appear to act clinically like fibromatosis.

Definitive conclusions regarding the biologic potential of these breast metaplastic tumors with dominant fibromatosis-like areas as the major mesenchymal element are limited by variable durations of follow-up and the differences in treatment. However, the results of the current study show that the behavior and prognosis of these metaplastic lesions with clusters of epithelioid cells most likely are the same as for pure fibromatosis lesions without epithelial elements; they have a greater tendency toward local recurrence than lymph node and distant metastases. The emphasis of the current study was on practical clinical prognosis. The challenge is that some spindled carcinomas with a dominant carcinomatous component act like carcinomas. However, when the carcinomatous component is minimal or inapparent, or low grade, and the dominant outer element of the tumor is phenotypically fibromatosis, we then expect that the clinical behavior of the majority of tumors will be that of fibromatosis. The heterogeneity of mixed epithelial-mesenchymal neoplasms is not recognized fully. The tumors described in the current study are likely to

represent a special subset of these breast neoplasms with a unique behavior.

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