Metaplastic Carcinoma of the Breast

Report of Three Cases

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BACKGROUND. Metaplastic carcinoma is a rare form of breast carcinoma that often is confused with other benign and malignant entities. The diagnosis can be difficult to establish on both a clinical and conventional histopathologic basis. One report recently described clinical and mammographic features dissimilar to the authors' experience but to the authors' knowledge no other reports have been published. Therefore a review of three cases was undertaken; all patients had undergone mammography to identify and report the mammographic features of this disease, suggesting that imaging may add to the proper diagnosis of this entity.

METHODS. Three clinical cases in which the diagnosis of metaplastic carcinoma was confirmed and for which mammography was performed were reviewed retrospectively. Follow-up on all three patients was available.

RESULTS. Metaplastic carcinoma may be manifest as a well circumscribed mass or an irregular or spiculated mass. The latter always is highly suspicious for malignancy and the former incurs suspicion if it grows, although in this series the smooth mass was biopsied immediately. The spiculated masses were associated with delayed diagnosis and poorer prognosis because immunohistochemical studies were not performed on the original excisional biopsy specimens.

CONCLUSIONS. Although spiculated masses usually are associated with invasive ductal and lobular carcinoma, they also may represent metaplastic carcinoma and immunohistochemical studies often are required to establish this diagnosis and avoid delay in proper treatment. Well circumscribed masses representing this disease may suggest benign disease but metaplastic carcinoma should be included in the differential diagnosis, especially if the mass enlarges. ***Cancer* 1998;82:1082–7.** © *1998 American Cancer Society.*

KEYWORDS: breast neoplasms, metaplastic carcinoma, fibromatosis, immunohistochemical stains, diagnosis, breast radiography.

Most benign and malignant tumors of the breast arise from glandular epithelium. However, in some cases glandular epithelium differentiates into nonglandular mesenchymal tissue, a process called metaplasia. Although both the basis and true incidence of this process is unknown because it often is not reported when it occurs microscopically, such differentiation may become such a significant component of the tumor as to characterize it as a distinct entity for purposes of diagnosis and treatment.

Various terms have been used to describe these rare tumors that demonstrate pathologic features of both carcinoma and sarcoma including pseudosarcoma, mixed tumor of the breast, sarcomatoid carcinoma, carcinoma with pseudosarcomatous metaplasia, fibrosarcoma-like squamous cell carcinoma, carcinosarcoma, and spindle cell carcinoma.[1–5] Oberman proposed the term metaplastic carcinoma to account for all mixed carcinomas of the breast.[6] The pathologic and

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Received May 20, 1997; revision received September 25, 1997; accepted September 25, 1997.

clinical aspects of these rarely encountered tumors have been described variously, but to our knowledge the radiographic features of metaplastic tumors have not been reported, except in one recent study where features described were not similar to our experience.

We report three cases of metaplastic carcinoma of the breast in which the mammographic features are demonstrated in the context of the clinical circumstances and histopathology. The range of findings are discussed with emphasis on the important role of the radiologist in proper evaluation of this unusual entity.

Case 1

A 64-year-old woman presented to her surgeon with a palpable right breast lump at the 6 o'clock position. Fine-needle aspiration biopsy showed no evidence of malignancy, but the lump was removed and diagnosed as fibromatosis. Two years later the patient developed another palpable lump at the 6 o'clock position of the right breast that was observed on mammogram as a 3-cm ill-defined mass abutting the chest wall, with irregular margins and associated architectural distortion without calcifications (Fig. 1). The mammogram was compared with prior studies that showed no mass 4 years previously and an ill-defined density observed only on mediolateral view that was not recognized as a lesion 2 years previously. At surgery, the mass was found to invade the adjacent chest wall and biopsy showed extensive fibroblast involvement diagnosed as aggressive fibromatosis and treated with mastectomy including partial resection of the fifth and sixth ribs, but no chemotherapy or hormonal therapy. The patient returned 2 years later with a lesion involving the left anterior pleura. Biopsy of the pleural mass showed extensive spindle cells that stained positive for both keratin and vimentin. Estrogen and progesterone receptors were negative. Review of prior slides within the current clinical context indicated the correct diagnosis of metastatic spindle cell carcinoma, with staging evaluation showing pulmonary nodules, as well as destruction of the remaining fifth and sixth right ribs. The patient was treated with doxorubicin and tamoxifen for 8 months with no clinical improvement, and died 3 months later from brain metastases.

Case 2

A 49-year-old woman presented with a 2-cm palpable lump at the 5 o'clock position of the left breast and no palpable adenopathy. Mammography showed a 2-cm smooth mass with macrocalcifications (Fig. 2). Excisional biopsy showed carcinosarcoma and a left modified mastectomy was performed, with the axilla showing no metastatic involvement. Estrogen and progesterone receptors were negative. At last follow-up, the patient was alive and disease free 7 years after surgery.

Case 3

A 58-year-old woman presented with a right breast lump at the 6 o'clock position. Mammography showed a 3-cm ill-defined mass with irregular margins and associated architectural distortion abutting the chest wall in the lower outer quadrant of the right breast (Fig. 3); review of a mammography study performed 2 years previously demonstrated no evidence of the mass. Modified radical mastectomy was performed. A 2.8-cm spindle cell carcinoma was found with negative surgical margins and none of 14 axillary lymph nodes involved. Estrogen and progesterone receptors were negative. Nine months later the patient developed a chest wall recurrence at the medial margin of her incision and further evaluation showed a 2-cm right upper lobe lung mass. No other metastatic foci were observed in the brain, bones, lungs, abdomen, or pelvis. Thoracotomy was performed with biopsy of the lung mass and associated bronchial lymph nodes showing metastatic spindle cell carcinoma. She was not considered a candidate for pneumonectomy because of the involvement of the tumor with the right mainstem bronchus and chemotherapy treatment for sarcoma was initiated that included doxorubicin and imidazole carboxamide. She did not respond to therapy and died 1 month later.

DISCUSSION

Most tumors in the breast arise from glandular epithelium and differentiate as carcinomas, with a small percentage of malignancies representing true mesenchymal tumors. Rarely, tumors demonstrate the apparent proliferation of more than one cell type, with the epithelium presumably undergoing a process called metaplasia presenting histopathologically in a nonglandular appearance. Squamous metaplasia has been reported to occur as microscopic foci within 0.5–3.7% of breast carcinomas.[7] When such metaplasia becomes a major component of the histopathologic findings, various terms have been applied to describe such lesions, including pseudosarcomatous carcinoma, carcinosarcoma, spindle cell carcinoma, and fibrosarcoma-like squamous cell carcinoma. The variability in terminology combined with the rarity of this form of breast carcinoma has compromised the ability to compare clinical series in terms of prognosis and treatment of such lesions and their different manifestations.[1–6]

Oberman suggested that all such tumors be categorized as metaplastic carcinoma of the breast, deemphasizing whether the metaplastic component is of mesenchymal or epithelial origin.[6] Some of these tu-

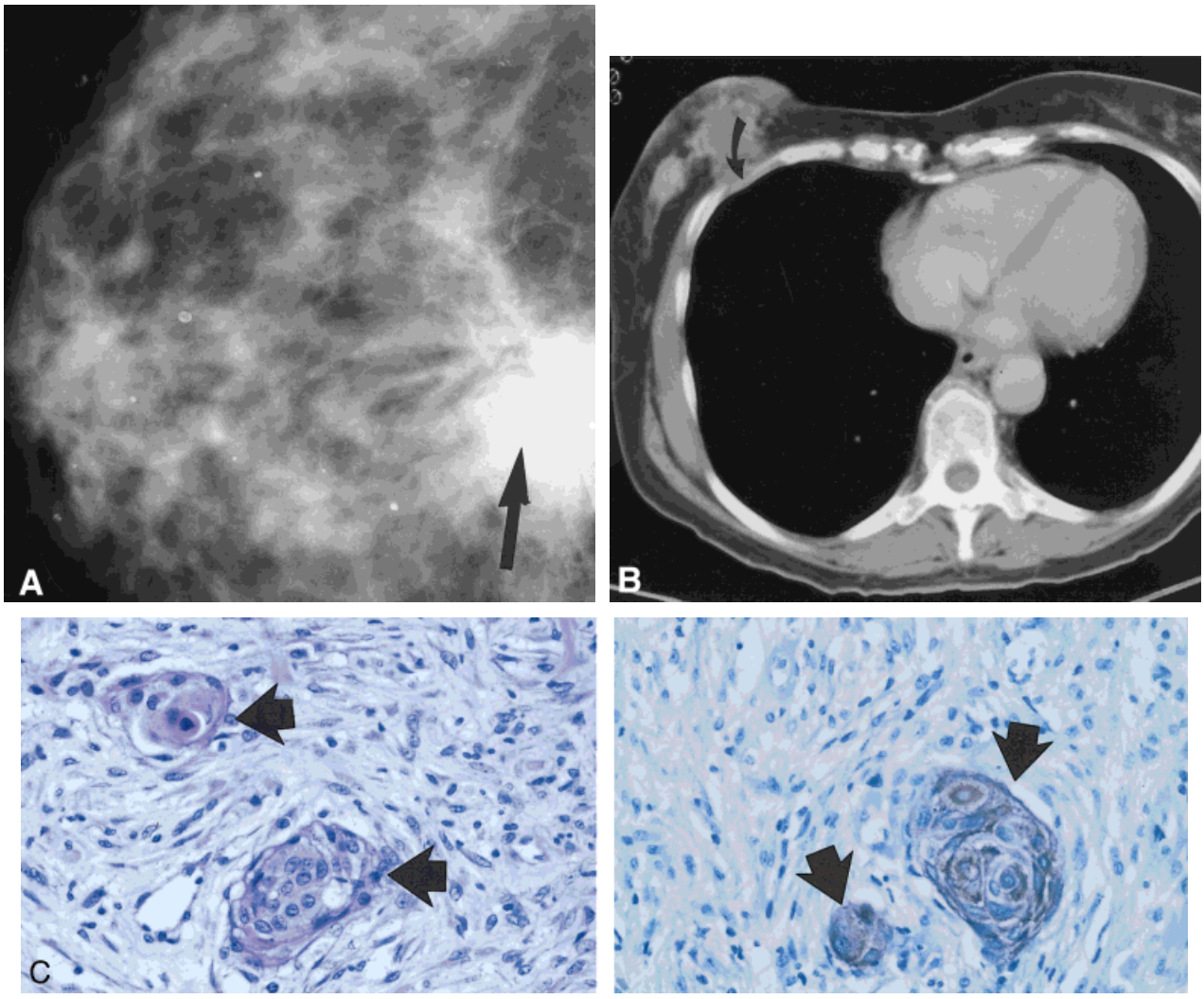

FIGURE 1. Spindle cell carcinoma. (A) Craniocaudal view shows an ill-defined mass with architectural distortion at the six o'clock position of right breast (arrow), adjacent to chest wall. (B) Computed tomography scan in 1991 shows the tumor invading the chest wall (curved arrows) on right. (C) Histopathology (H & E preparation) of mass at low power demonstrates interlacing fascicles of atypical spindled cells with small islands of squamous cells (arrows, left panel), which were immunoreactive for cytokeratin (arrows, right panel). The spindle cells were negative for cytokeratin.

mors produce a cartilaginous or osseous matrix. The mixed cell origin is corroborated by histopathologic staining for mesenchymal cells (vimentin), epithelial cells (cytokeratin), and myoepithelial cells (S-100 protein, actin, and high molecular weight cytokeratin). The cell of origin may be the myoepithelial cell in some cases, particularly spindle cell carcinomas, given the biphasic expression of the tumor.[2,7] Tavassoli also suggested the origin of this tumor to be the myoepithelial cell.[8] The mammographic appearance of the benign form of this disease (namely, myoepithelioma) has been described,[9] but to our knowledge there are no reported imaging findings for the malignant form of this disease.

Wargotz et al. collected >180 cases from the Armed Forces Institute of Pathology and suggested three variants of metaplastic carcinoma.[1–3] Carcinosarcoma was defined as a biphasic tumor with 50% of the neoplasm comprised of malignant-appearing spindle cells and 50% comprised of pleomorphic bipolar cells or polymorphic cellular populations. The tumor is less immunoreactive to cytokeratin and the high degrees of cellularity, nuclear pleomorphism, and mitotic activity in the spindle cell component distinguish it from spindle cell carcinoma.[1] Spindle cell carcinoma was characterized by a predominance of spindle cells and bland bipolar cells growing as feathered or overlapping fascicles.[2] A third variant of matrix-pro-

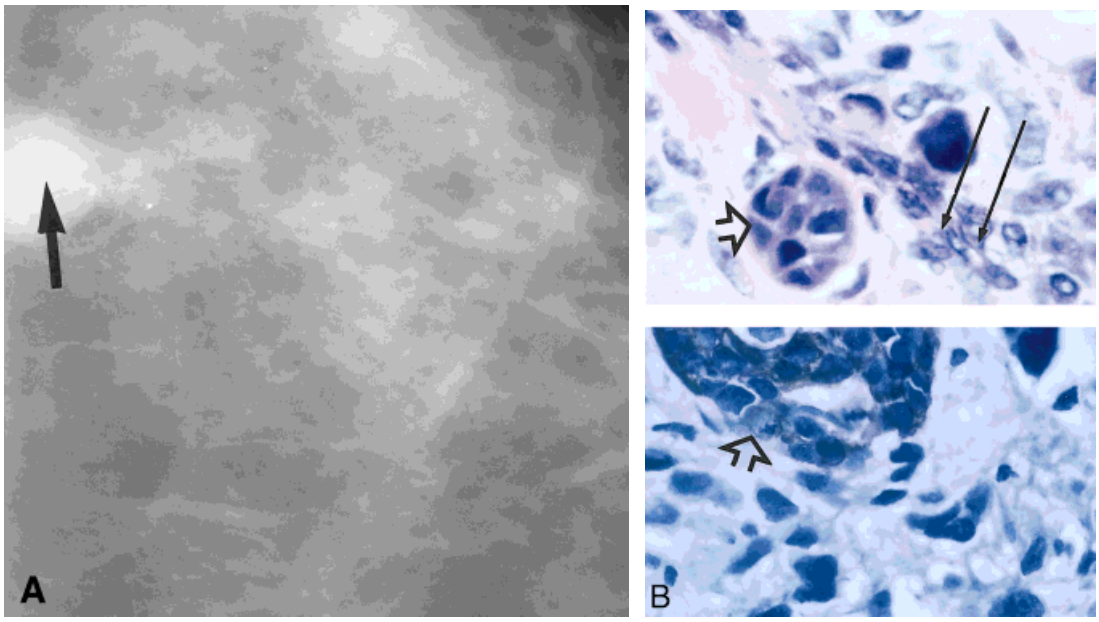

FIGURE 2. Carcinosarcoma. (A) Craniocaudal view of left breast shows a 2.2-cm, well circumscribed mass (arrow) in the lower outer (7 o'clock) quadrant adjacent to chest wall with associated macrocalcifications. (B) Histopathology (H & E preparation) of mass at high power demonstrates admixture of cohesive carcinoma cells (upper panel, short arrow) and malignant stromal spindled cells (upper panel, long arrows). Immunohistochemical stain for cytokeratin (lower panel, arrow) shows cytokeratin immunoreactivity of the carcinoma, but not the sarcoma component.

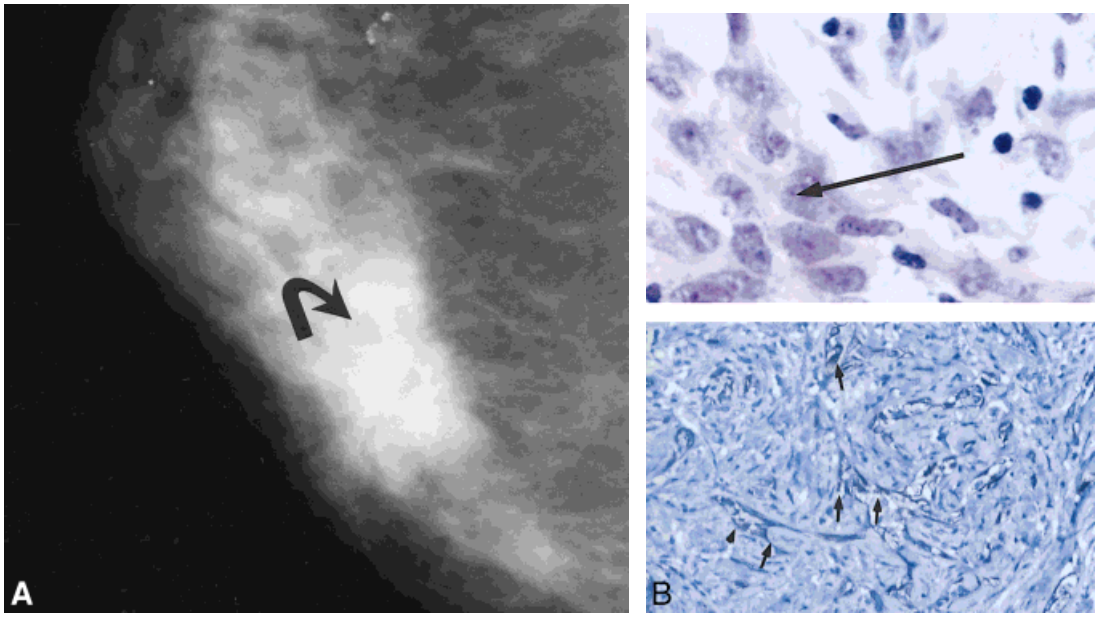

FIGURE 3. (A) Craniocaudal view of right breast show spiculated mass at the 3 o'clock position (curved arrows). (B) Histopathology (H & E preparation) of mass at low power shows interlacing bland spindled cells (upper panel, long arrow). The cells were immunoreactive for high molecular weight cytokeratin (lower panel, short arrows), supporting myoepithelial differentiation.

ducing carcinoma was defined as either of the lesions mentioned earlier associated with an osseous or cartilaginous matrix, although most breast pathologists do not recognize this last category as a distinct entity but rather as an expression of one of the other two.[3,7] The carcinomatous component may be purely intraductal, infiltrative carcinoma, or purely squamous. In cases in which carcinomatous components are not identified by histopathology, immunoreactivity for cytokeratin or electron microscopic evidence may demonstrated. Pitt et al. described three groups of patients with variable degrees of epithelial differentiation.[10]

Metaplastic carcinomas usually are not associated with estrogen or progesterone receptors, as was the case in all three patients reported here. Greater than 50% of these tumors are associated with either local or distant metastases (or both) within 5 years, with recurrence indicating very poor prognosis. Axillary lymph node metastases is uncommon for sarcoma, but metaplastic carcinoma is associated with axillary lymph node spread in 25–30% of cases, usually from the carcinomatous elements. Although no series is sufficiently large to determine overall prognosis, survival most likely depends on overall tumor size, histologic type, grade, lymph node status, and perhaps more directly on the type and grade of the mesenchymal component. The overall 5-year survival rate is approximately 40%, which may reflect the size of >2 cm at which most of these tumors are diagnosed, similar to cases presented here. In 1 series of 26 women, 5-year survival for TNM Stages I, II, and III was 56%, 26%, and 18%, respectively.[4] Chemotherapy usually is directed toward the sarcomatous component of the disease based on patterns of metastases.

Our case of the carcinosarcoma variant showed mammographic features of a smooth mass with macrocalcifications. It is notable that the mammographic features and clinical course of this lesion are similar to those described for medullary carcinoma of the breast in which squamous metaplasia is found associated with the ductal carcinoma in 16% of cases.[11,12] The axillary lymph nodes were negative and the patient's clinical course at last follow-up was disease free for 7 years. The 2.2-cm size of the lesion was smaller than the mean size of 3.3 cm reported by Wargotz et al. in a series of 80 patients.[1]

By contrast, the spindle cell carcinoma variants described here appeared as ill-defined or even spiculated masses on mammographic study and were associated with axillary lymph node disease in one case, and in both cases chest wall recurrence, with distal metastases and death occuring 9–11 months after recurrence. The misdiagnosis initially made on this tumor in one case reflects the difficulty in identifying by histopathology the mitotic figures in the spindle cell component, a distinguishing feature emphasized by Wargotz et al.[2] Approximately 41% of cases described by Wargotz et al. (717) as spindle cell carcinoma that lacked overt evidence of infiltrative or intraductal carcinoma originally were diagnosed as fasciitis, fibromatosis, or low grade mesenchymal tumors.[2] Pitt et al. reported that many of their cases resembled malignant fibrous histiocytoma.[10] The size of our tumors were slightly smaller than the mean size of 4.4 cm reported by Wargotz et al. in a series of 100 patients.[2]

The two lesions demonstrated mammographically as spiculated masses had a worse clinical course than the well circumscribed mass, which, except for the calcifications, was similar in its radiographic appearance to the benign myoepithelioma reported by Doyle et al.[9] All three lesions were >2 cm at time of diagnosis but the spiculated spindle cell carcinomas were larger than the well circumscribed carcinosarcoma at time of diagnosis, and both invaded the chest wall, which is similar to 7 cases reported by Wargotz et al.[2]

Whether or not these two distinct mammographic manifestations of metaplastic carcinoma represent different expressions of a single myoepithelial cell origin as suggested by Tavassoli or different forms of differentiation of the epithelial cell that undergoes mesenchymal, glandular, and squamous differentiation is not known. A recent report by Patterson et al. of nine metaplastic carcinoma lesions showed seven demonstrating circumscribed margins, with only two showing spiculated margins similar to two of the three lesions reported here.[13] Although they suggested that the infiltrative carcinoma portion of their tumors corresponded to irregular margins, we found no such correlation. The spectrum of histopathology that these tumors may show is demonstrated in these three cases with virtually no epithelial cells identified on hematoxylin and eosin (H & E) stains in Case 3 (Fig. 3), malignant glandular epithelium observed in Case 2 (Fig. 2), and focal squamous epithelium observed in Case 1 (Fig. 1). The two distinct populations of cells associated with the carcinosarcoma subtype and the more interlacing spindle cell predominance of the spindle cell carcinoma subtype that in the past were distinguished only by histopathology were associated with distinctly different mammographic appearances. The mammographic features of this malignancy are not distinctive, either as a well circumscribed or spiculated mass. However, it is important that physicians be familiar with this unusual form of breast carcinoma, the mammographic features of which have not been reported previously (to our knowledge). Irregular masses or well circumscribed masses that enlarge are mammographic indications for biopsy because of the high

yield of adenocarcinoma associated with such findings. When the diagnosis of fibromatosis or low grade mesenchymal tumor is made on standard H & E preparations, rather than the anticipated adenocarcinoma diagnosis, additional immunohistochemical studies should be performed to exclude metaplastic carcinoma. Indeed epithelial differentiation may be scant (Case 1) or virtually absent (Case 3) as identified by standard histopathologic H & E stains. Such error occurred in 1 of our cases and, as mentioned, in 41% of cases reported by Wargotz et al.[2] This approach is even more important if postsurgical scarring on follow-up mammography is sufficiently prominent to raise the possibility of recurrent mass, because therapy and prognosis will be altered significantly.

REFERENCES

1. Wargotz ES, Norris HJ. Metaplastic carcinoma of the breast. III. Carcinosarcoma. *Cancer* 1989;64:1490–9.
2. Wargotz ES, Deos PH, Norris HJ. Metaplastic carcinoma of the breast II. Spindle cell carcinoma. *Hum Pathol* 1989;20:732–40.
3. Wargotz ES, Norris HJ. Metaplastic carcinomas of the breast. I. Matrix-producing carcinoma. *Hum Pathol* 1989;64:1490–9.
4. Kaufman MW, Marti JR, Gallager S, Hoenn JL. Carcinoma of the breast with pseudosarcomatous metaplasia. *Cancer* 1984;53:1908–17.
5. Bauer TW, Rostock RA, Eggleston JC, Baral E. Spindle cell carcinoma of the breast: four cases and review of the literature. *Hum Pathol* 1984;15:147–52.
6. Oberman HA. Metaplastic carcinoma of the breast: a clinicopathologic study of 29 patients. *Am J Surg Pathol* 1987;11:918–29.
7. Rosen PP. Metaplastic mammary carcinoma. Harris JR, Lippman ME, Morrow M, Hellman S, editors. Diseases of the breast. Philadelphia: Lippincott-Raven, 1966:411–3.
8. Tavassoli FA. Myoepithelial lesions of the breast: myoepitheliosis, adenomyoepithelioma and myoepithelial carcinoma. *Am J Surg Pathol* 1991;15:554–68.
9. Doyle AJ, Alder SL, Rohr LR. Myoepithelial lesions of the breast: imaging characteristic and diagnosis with large-core needle biopsy in two cases. *Radiology* 1994;193:787–8.
10. Pitts WC, Rojas VA, Gaffey MJ, Rouse RV, Esteban J, Frierson HF, et al. Carcinomas with metaplasia and sarcomas of the breast. *Am J Clin Pathol* 1991;95:623–32.
11. Meyer JE, Amin E, Lindfors KK, Lipman JC, Stomper PC, Genest D. Medullary carcinoma of the breast: mammographic and US appearance. *Radiology* 1989;170:79–82.
12. Ridolfi RL, Rosen PP, Port A, Kinne D, Mike V. Medullary carcinoma of the breast: a clinico-pathologic study with a 10 year follow-up. *Cancer* 1977;40:1365–85.
13. Patterson SK, Tworek JA, Roubidoux MA, Helvie MA, Oberman HA. Metaplastic carcinoma of the breast: mammographic appearance with pathologic correlation. *AJR Am J Roentgenol* 1997;169:709–12.