Cases of the Day

Breast Imaging Case of the Day[1]

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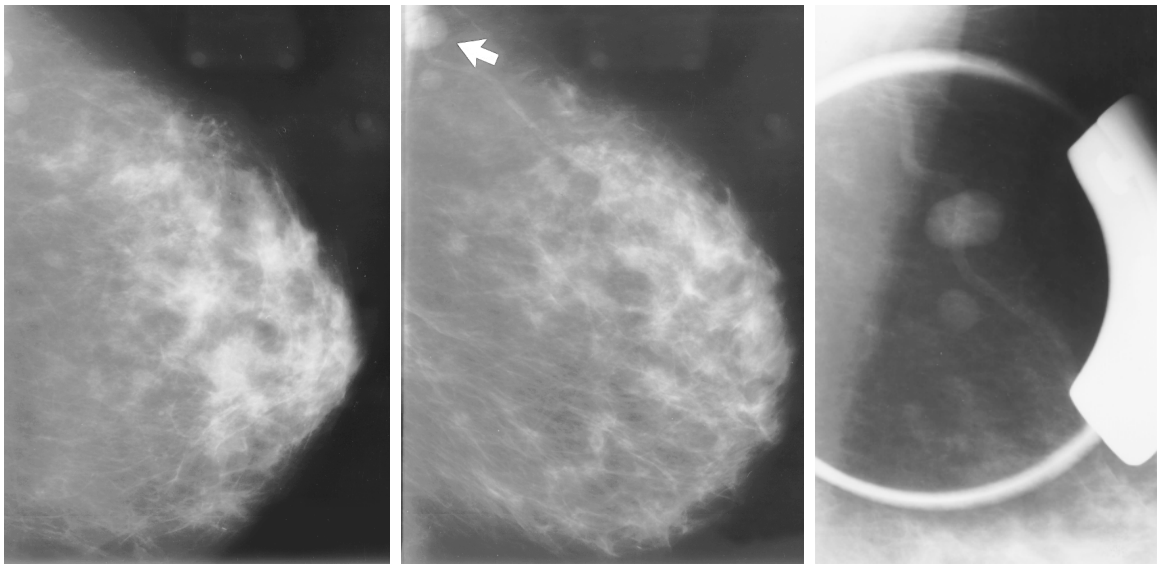

a. **b.** **c.**

Figure 1. **(a, b)** Craniocaudal **(a)** and mediolateral oblique **(b)** mammograms demonstrate an abnormally enlarged (1.7-cm) and dense node in the left axillary tail (arrow in **b**). An additional mediolateral oblique mammogram (not shown) was obtained to evaluate the region of the pectoral muscle. The node had more than doubled in size since a previous mammogram (not shown) obtained 1 year earlier. **(c)** Coned-down mediolateral oblique mammogram better depicts the abnormal density of the node without a clearly defined, radiolucent hilus. Subtle asymmetry and distortion of the left breast, apparent only on the craniocaudal view (cf **a**), was identified retrospectively.

■ HISTORY

A 55-year-old asymptomatic woman presented for annual screening mammography. She had been undergoing therapy with conjugated estrogens ever since undergoing a hysterectomy at age 36. Her mother was diagnosed with breast cancer at age 65. Mammography, computed tomography (CT), and scintimammography were performed.

■ FINDINGS

Craniocaudal and mediolateral oblique mammograms demonstrated an intramammary node with increased size and density in the left axillary tail (Fig 1a, 1b). Coned-down magnification mediolateral oblique mammography better demonstrated the abnormal density of the

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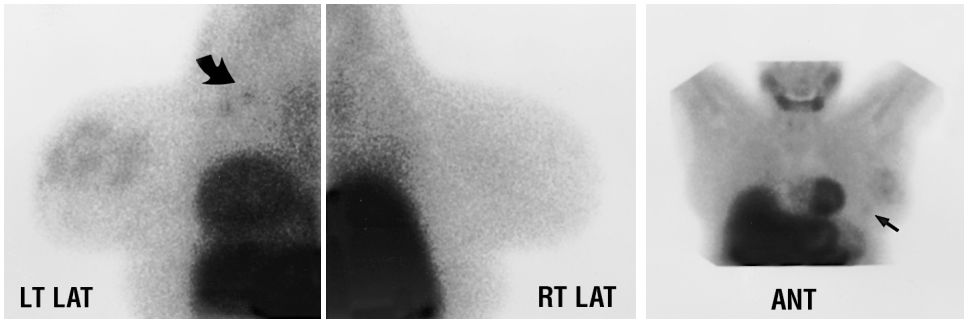


a. **b.**

Figure 3. Prone lateral **(a)** and supine anterior **(b)** scintimammograms demonstrate a large, multiloculated area of uptake in both the medial and lateral left upper breast. An additional focus of uptake is identified in the lower inner breast (arrow in **b**) as well as two foci of uptake in the left axilla (arrow in **a**).

node without a well-defined, radiolucent hilus (Fig 1c). The node was palpable, as were deeper left axillary nodes. However, clinical evaluation of the breasts demonstrated fibrocystic changes bilaterally without a dominant mass. CT of the chest demonstrated left intramammary and axillary adenopathy. Asymmetric density was present in the left breast compared with the right (Fig 2). Scintimammography demonstrated a large, multiloculated area of uptake in the left upper breast involving both medial and lateral breast tissue (Fig 3). An additional small focus of uptake was identified in the left lower inner breast, and two foci of uptake were seen in the left axilla. Lymph node biopsy was performed.

DIAGNOSIS: Intramammary and axillary lymph node metastases from infiltrating lobular carcinoma of the breast.

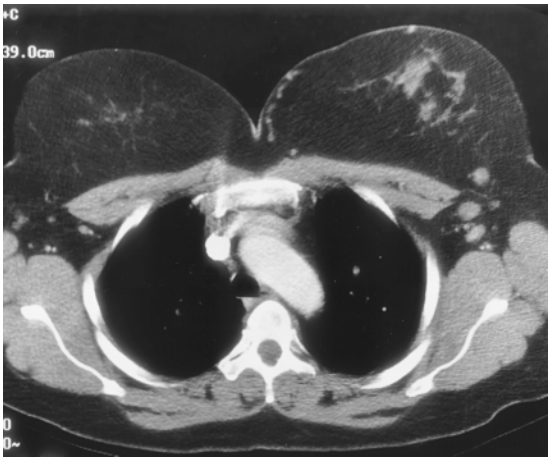


Figure 2. Chest CT scan demonstrates enlarged intramammary and axillary nodes as well as asymmetric density in the left breast.

■ DISCUSSION

Metastatic involvement of intramammary or axillary lymph nodes is a rare first sign of breast cancer (1,2). Few if any mammographic findings may be evident that suggest the location of the primary lesion, even if the lesion is large (2). This is particularly true when breast tissue is mammographically dense or there is a complex parenchymal pattern.

Adenopathy involving either intramammary lymph nodes or lymph nodes in the axilla (lower level I nodes) may be demonstrated at standard mediolateral oblique mammography

(3,4). Because both intramammary lymph nodes located high in the axillary tail (tail of Spence) and inferior axillary lymph nodes overlie the region of the pectoral muscle at mammography, differentiating between the two may be difficult (5). Strictly speaking, intramammary lymph nodes should be surrounded by breast parenchyma (5). They are generally found in the upper outer quadrant but may manifest in any quadrant of the breast (6).

Axillary or intramammary lymph nodes are considered normal if they are of overall low to moderate density, sharply defined, round to oval, and contain a radiolucent fatty hilus (7). The fatty hilus may not always be evident, however, and further work-up is required. In a series of 64 nonpalpable intramammary nodes detected at mammography and confirmed with stereotactically guided fine-needle aspiration, 78% had a radiolucent center and 22% were of similar density throughout (6).

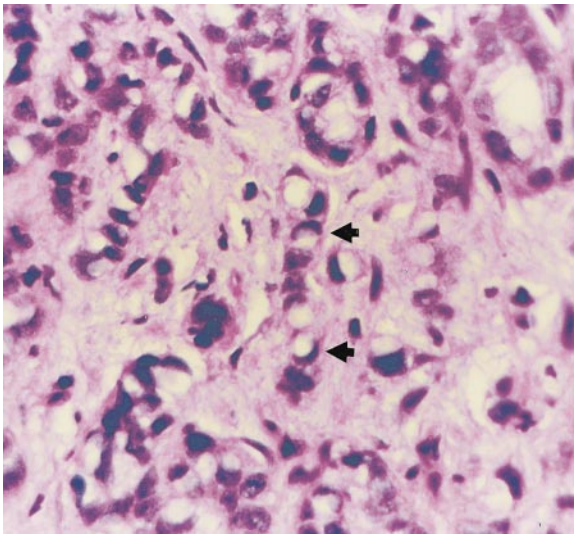
Intramammary lymph nodes are considered abnormal if they are larger than 1 cm (8), whereas axillary lymph nodes are considered abnormal if they are larger than 1.5 cm (3,7). However, axillary nodes may be as large as 3 cm and still be considered normal if they are mostly replaced by fat. Small changes in node size are of no concern if the fatty hilus is preserved, the nodes are nonpalpable, and the patient has no history of malignancy (4,9).

Unilateral enlargement of axillary or intramammary lymph nodes on an otherwise negative mammogram is rare (9). Differentiation of benign from malignant causes may be impossible on the basis of imaging findings (1,10,11). Bilateral axillary adenopathy favors the diagnosis of lymphoproliferative disease, whereas ill-defined, spiculated adenopathy favors the diagnosis of metastatic breast carcinoma (3). Benign causes include nodal hyperplasia, collagen vascular disease, granulomatous disease, human immunodeficiency virus infection, and silicone adenopathy (3,12). Malignant causes include lymphoproliferative disease, breast cancer, and metastases arising from extramammary tumors (especially lung metastases and melanoma, but also thyroid and gastrointestinal tumors) (2,3, 12). In patients in whom there is no clinically evident primary tumor, breast carcinoma is the most likely primary tumor for axillary lymph node metastasis; however, mammographic sensitivity may be low (29%) (2). Even when breast tissue is obtained, including by means of mastectomy, the primary breast lesion will not be confirmed in about one-third of cases (2).

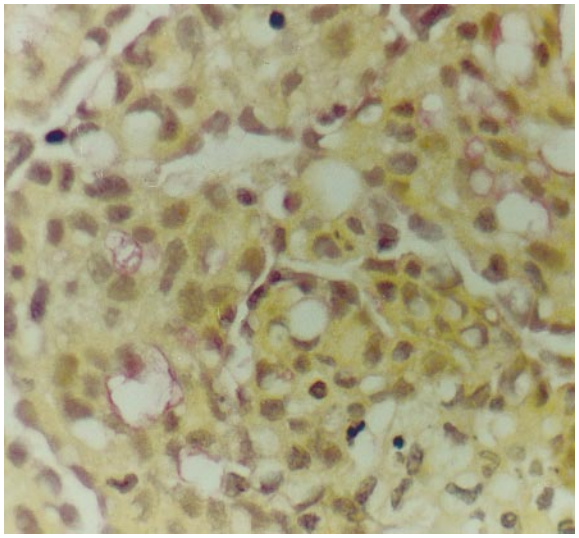
If metastatic disease is found in intramammary lymph nodes, staging and management proceed as if the patient had axillary lymph node involvement (stage II), even if no such involvement is demonstrated (1).

In our patient, axillary tail adenopathy was seen at screening mammography (Fig 1). The larger of two nodes measured 1.7 cm in diameter, compared with 0.7 cm on a previous mammogram. No other focal lesion was identified initially at mammography, and metastatic lesions such as melanoma and lymphoma as well as infectious causes were included in the differential diagnosis. In retrospect, slight asymmetry and subtle diffuse distortion was evident in the left breast at craniocaudal mammography. Likewise, results of physical examination of the breast by multiple clinicians were believed to be "within normal limits" or "compatible with bilateral fibrocystic changes without a focal mass." Adenopathy in the left axillary region was clinically palpable.

Axillary lymph node biopsy demonstrated metastatic adenocarcinoma (Fig 4a). The tumor

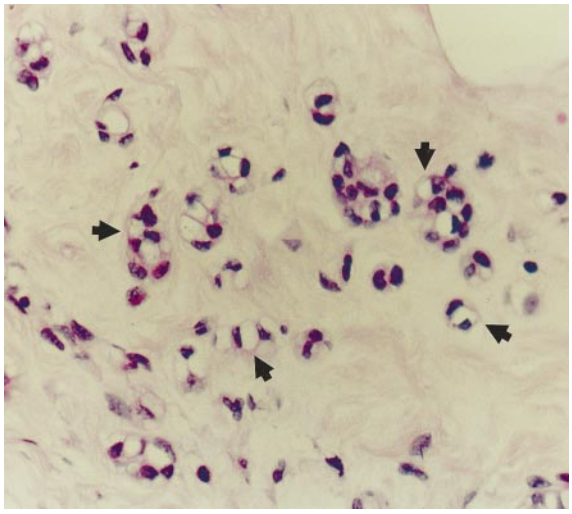


a.



b.

Figure 4. **(a)** Photomicrograph (original magnification, ×400; hematoxylin-eosin stain) shows cancerous cells in the lymph node, occasionally in single file arrangements (arrows), including signet ring cells with numerous cytoplasmic vacuoles. **(b)** Photomicrograph (original magnification, ×400; mucicarmine stain) demonstrates that the signet ring cells contain mucin, which is apparent from the pink color of the droplets. **(c)** Photomicrograph (original magnification, ×400; hematoxylin-eosin stain) of a left mastectomy specimen demonstrates infiltrating lobular carcinoma of the breast. The diagnostic characteristics of the tumor include relatively small, uniform tumor cells in single file or small nests or occasionally as single cells. Some of the tumor cells are vacuolated signet ring cells (arrows).



c.

consisted of cells in nests, cords, and small glands. The cells were small, fairly uniform in size and shape, and contained clear cytoplasmic vacuoles. These vacuole-containing cells, which are known as signet ring cells because of their shape, were shown to contain mucin on histologic sections stained with mucicarmine (Fig 4b). The presence of these signet ring cells suggested that the tumor was either a metastasis from a breast carcinoma, a poorly differentiated stomach carcinoma, or some other type of gastrointestinal tract adenocarcinoma. To further characterize the tumor, immunohistochemical analysis with antibodies against gross cystic disease fluid protein–15 (GCDFP-15) and estrogen receptors was performed. Both antibodies yielded a positive staining reaction, providing strong evidence that the tumor was mammary in origin (13–15). GCDFP-15 immunoreactivity is a specific means of confirming a mammary origin for a primary lesion (15) and is a particularly sensitive marker for signet ring carcinoma, a rare variant of infiltrating lobular carcinoma (14,15). Because the tumor was observed only in lymph nodes, the pattern of the primary breast tumor could not be determined with certainty. However, the vacuolation, the small, uniform nuclei, and the occasional single file arrangements of the tumor cells were suggestive of infiltrating lobular carcinoma of the breast (14).

Histologic findings at lymph node biopsy as well as earlier clinical and mammographic findings were consistent with infiltrating lobular carcinoma. The absence of a clear-cut, clinically palpable breast mass or of discrete mammographic findings (although there was evidence for a large breast lesion at scintimammography) (Fig 3) was compatible with the pattern of manifestation and spread of infiltrating lobular carcinoma.

Infiltrating lobular carcinoma is a neoplasm that arises from terminal ductules of the breast lobules and manifests as small, uniform cells in a single file linear pattern or scattered individually throughout fibrous stroma (14,16). The infiltrating cells spread along and around ducts in a targetlike pattern (14,16) without a discrete tumor nidus. The pattern of spread of infiltrating lobular carcinoma may explain why results of physical examination are often considered normal (ie, no focal masses are palpated) and why discrete mass lesions or increased density may not be apparent at mammography. Findings at mammography may be negative, especially in dense breasts or in breasts with heterogeneously distributed parenchyma, or may be positive but very subtle.

Infiltrating lobular carcinoma is notoriously difficult to detect both clinically and mammographically (16–20). Mammographic findings include asymmetric density with no definable margins, a spiculated mass, distortion, dense breasts with no apparent lesions, a discrete or ill-defined mass, and, less commonly, microcalcifications (16,17). Microcalcifications are usually found in cases with mixed histologic findings (16). Studies have shown mammographic findings to be normal or to cause little suspicion in 19%–24% of cases irrespective of tumor size (17,19).

Infiltrating lobular carcinoma accounts for a disproportionately high percentage of breast cancers that are evident on only one standard mammographic projection: In a large screening study by Sickles (21), this disease entity represented only about 10% of all breast cancers but 33% of all cancers that were evident on just one view. The craniocaudal view demonstrated significant findings more often than mediolateral or mediolateral oblique views in several series (17,20). Difficulties in making an early diagnosis of infiltrating lobular carcinoma result in a disproportionate potential for malpractice suits (18).

The role of ultrasonography (US) in improving diagnostic sensitivity in infiltrating lobular carcinoma is controversial. Paramagul et al (22) found low sensitivity (68% overall, 25% in masses less than 1 cm) in US diagnosis of infiltrating lobular carcinoma. In contrast, Butler et al (23) found high sensitivity (88%) in lesions that were mammographically subtle or invisible.

Scintimammography has been extensively evaluated as an adjunct in the evaluation of women with mammographically "difficult" breasts due to marked breast density or scarring (24). Although multiple agents have been evaluated, the most widely used is technetium-99m methoxyisobutylisonitrile (also known as Tc-99m MIBI and Tc-99m sestamibi). After injection of this agent, a gamma camera is used to scan the breasts with the patient in the prone lateral and supine anterior positions with the arms raised for better imaging of the axilla.

Tc-99m MIBI is a lipophilic molecule that passively diffuses across cell membranes and is taken up by mitochondrial membranes (25). It is taken up more in breast cancer than in normal tissue, probably because of active uptake by the mitochondria (26). Hypercellular lesions including epithelial hyperplasia, atypia, and severe sclerosing adenosis also demonstrate increased uptake, resulting in false-negative findings (26). This increased uptake likely reflects increased mitochondrial density in areas with abnormal histologic findings. Although women with these lesions do not have breast cancer, they are at increased risk (24).

Factors that affect the accuracy of imaging with Tc-99m MIBI include the following (25):

1. The resolution of the best gamma camera is greater than 7 mm. Therefore, even if there is significant tracer uptake, smaller tumors are not likely to be detected.

2. Tc-99m MIBI may be actively removed from mitochondria or cytoplasm by a substrate P-glycoprotein. This substrate is encoded by a gene that makes cells resistant to chemotherapeutic drugs and is called the multidrug resistance (MDR) gene–1. In patients with resistance to cytotoxic drugs, there will be less uptake of Tc-99m MIBI.

3. Angiogenesis will increase perfusion to a tumor, resulting in increased delivery of Tc-99m MIBI to breast cancer cells compared with normal breast tissue.

Scintimammography is not competitive with standard mammography for screening in terms of sensitivity, cost-effectiveness, or radiation exposure (24,25,27). The overall sensitivity and specificity of scintimammography are both about 80% (24). Sensitivity for lesions less than 1 cm is poor (28,29) and is lower for nonpalpable lesions than for palpable lesions (24). The sensitivity of Tc-99m MIBI scintimammography in detecting breast cancer increases with maximum tumor size: less than 1 cm, 25% sensitivity; 1.0–1.5 cm, 78% sensitivity; and greater than 1.5 cm, 94% sensitivity (28). Sensitivity for lymph node metastases is about 75% (29). If findings at scintimammography are positive and those at mammography and US are negative, preoperative localization of the area of abnormality is difficult.

The accuracy of Tc-99m MIBI scintimammography, unlike that of standard mammography, is independent of breast density (24,27). Tc-99m MIBI scintimammography has shown promise in the evaluation of palpable masses (24,28). It may also play a role in the assessment of patients with poorly defined palpable masses not seen at mammography or of high-risk patients with equivocal mammographic findings (24). Other potential roles include searching for mammographically occult multifocal disease in patients who are candidates for lumpectomy, evaluating therapeutic response to chemotherapy prior to definitive surgery, and searching for a primary breast lesion in patients who present with adenocarcinoma in an axillary mass (24).

Women with metastatic adenocarcinoma in the axillary nodes are most likely to have a primary breast lesion; however, the lesion may be difficult to identify at mammography or US. Use of Tc-99m MIBI scintimammography has been suggested in such cases (24). In our patient, scintimammography clearly helped identify a primary breast lesion, multicentric disease, and lymph node metastases (Fig 3). The primary advantage of Tc-99m MIBI scintimammography as an ancillary technique to mammography, in addition to its accuracy irrespective of breast density, is its ability to produce semiquantitative results: Either there is uptake, or there is no uptake. This is in contrast to mammography, in which qualitative changes in the breast parenchymal pattern or subtle changes in density occur (25).

Our patient underwent adjuvant chemotherapy followed by left mastectomy. No lesion was identified at gross examination of the mastectomy specimen, but microscopic examination showed multiple, signet ring cell–type foci of infiltrating lobular carcinoma (Fig 4c). This finding confirmed the tumor in the lymph node as a metastasis from infiltrating lobular carcinoma.

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