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Abnormal axillary lymph nodes on negative mammograms: causes other than breast cancer

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ABSTRACT
Enlargement of lymph nodes can be due to a variety of benign and malignant causes. The most common malignant cause is invasive ductal carcinoma, which is usually visualized with mammography. Excluding breast cancer, other causes of abnormal lymph nodes that produce a negative mammogram include lymphoma, metastases from other malignancies, and benign etiologies such as inflammatory processes, infectious diseases, collagen vascular diseases, and miscellaneous causes. In this essay, we described common causes of abnormal axillary lymph nodes on negative mammograms excluding breast cancer.

Key words: • *mammography* • *lymph nodes* • *ultrasonography* • *axilla*

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Normal and abnormal axillary lymph nodes are commonly seen on mediolateral oblique (MLO) mammograms (1). Normal axillary lymph nodes are frequently identified and are typically small and oval with a lucent center due to hilar fat (Fig. 1). Abnormal lymph nodes are characterized by high density, absence of hilar fat, and a round, irregular, ill-defined shape with or without intra-nodal calcifications on the MLO view (2, 3). The spectrum of calcifications within lymph nodes comprises microcalcifications, punctate or amorphous calcificatons, and coarse calcifications. An abnormal density can sometimes be partially seen on the MLO view, and to better view the lesion, a tangential axillary view is taken. This helps to enlarge the axillary region and to see abnormal densities that are not clearly demonstrated on the MLO view. Ultrasonography (US) of the axillary region is another available imaging method that can be used when an abnormal lymph node is detected on a negative mammogram. On US, a normal lymph node has a thin hypoechogenic cortex in the periphery and an echogenic hilum (Fig. 1). Abnormal nodes tend to become more rounded. Eccentric enlargement with focal thickening of the cortex is a strong indicator of malignant transformation. Indentation of the hilum, and especially obliteration of the hilum, is highly suggestive of malignancy (4).

Peripheral flow and transcapsular vessels seen on color Doppler favor malignancy compared with central flow in normal axillary lymph nodes (Fig. 1). For an accurate diagnosis, needle aspiration or biopsy should be performed under US guidance. Enlargement of lymph nodes can be due to a variety of benign and malignant causes. The most common malignant cause of abnormal axillary lymph nodes is breast cancer; however, when lymph nodes enlarge because of metastatic breast cancer, the primary tumor within the breast is usually visualized mammographically. Conversely, occult breast cancer presenting as axillary metastasis is uncommon, accounting for less than 1% of all patients with primary breast cancer at diagnosis (5, 6).

In addition to metastatic breast cancer, another malignant cause of lymph node enlargement with a negative mammogram is metastases from other primary tumors (e.g., lymphoma, malignant melanoma, or lung, stomach, or ovarian carcinomas) (6, 7). Benign causes of abnormal axillary lymph nodes occuring with negative mammography include systemic inflammatory processes (sarcoidosis), infectious diseases (bacterial lymphadenitis, tuberculosis), collagen vascular diseases, and several miscellaneous causes (silicon implants, tattooing).

Here, we discuss the common causes of abnormal lymph nodes excluding breast cancer on negative mammograms and provide the imaging findings from our retrospective review of adult cases including patients with lymphoma, human immunodeficiency virus (HIV), silicone implants, histiocytosis, sarcoidosis, bacterial lymphadenitis (abscess formation), and tattoos.

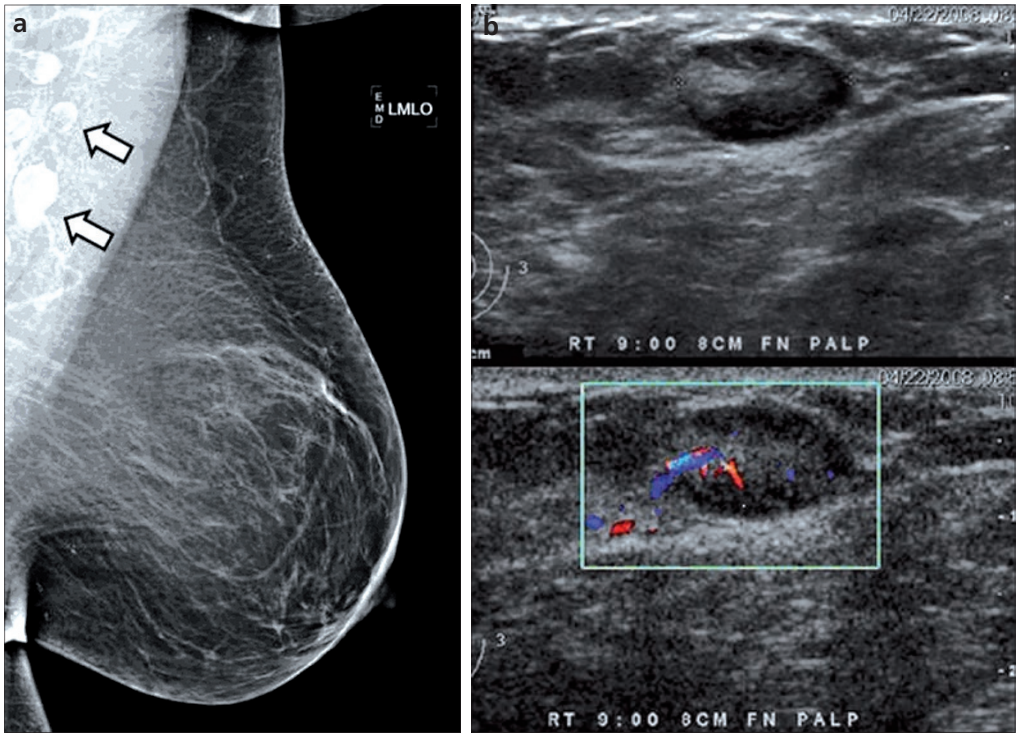

Figure 1. a, b. Mediolateral oblique (MLO) view of a mammogram **(a)** shows slightly enlarged lymph nodes with a lucent center due to the fatty hilum (*arrows*). On US normal lymph-node is seen with its echogenic fatty hilum, and central flow is noted on Color Doppler US **(b)**.

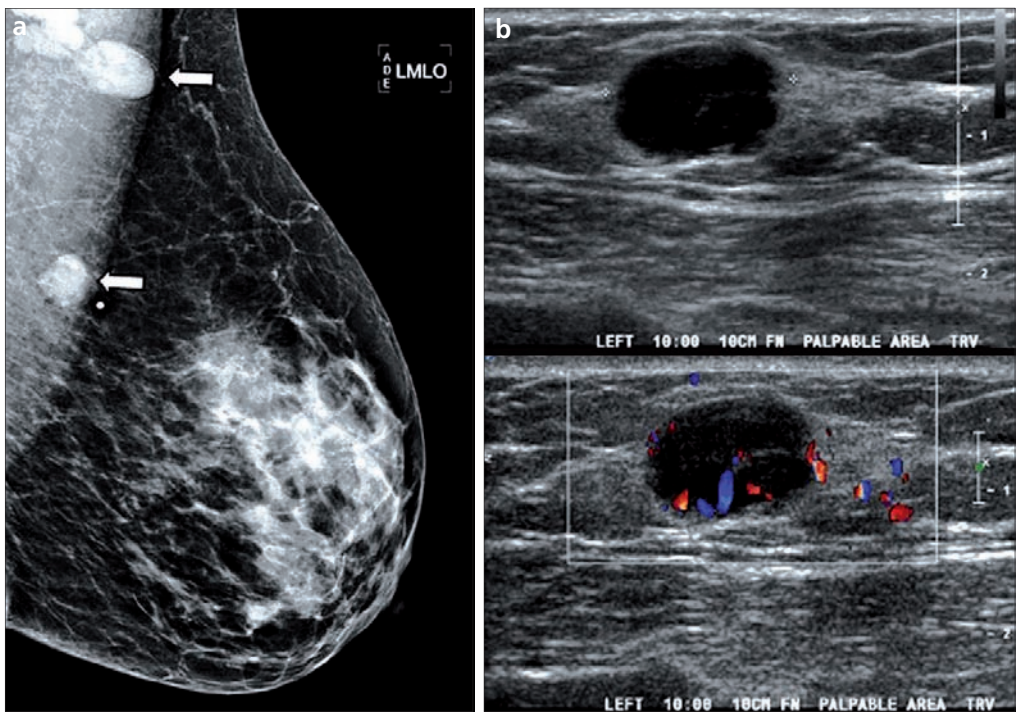

Figure 2. a, b. A 52-year-old patient with a history of non-Hodgkin lymphoma presented with a left axillary lump. MLO view **(a)** shows dense, round left axillary lymph nodes (*arrows*). Transverse US of a palpable area shows a round, hypoechoic lymph node with an eccentric hilum, and color Doppler US shows increased peripheral flow **(b)**.

Malignancies other than breast cancer

Systemic lymphoid dissemination of a malignancy may result in multiple abnormal lymph nodes. The clinical history of a patient with a known primary malignancy provides important information. It is therefore important to consider metastases when abnormal lymph nodes are observed in any body region. Lymphoma is the first on the diagnostic checklist of abnormal axillary lymph nodes with a negative mammogram and unknown primary tumor after occult breast cancer (5). Non-Hodgkins lymphoma is the most common type of breast lymphoma. There are two types of Non-Hodgkins lymphoma. Primary lymphoma of the breast, which is an extra-nodal lymphoma arising from periductal and perilobular lymphoid tissue, or intramammary lymph nodes, represents 0.04% to 0.5% of all primary malignant breast tumors. Secondary lymphomatous (systemic lymphoma) involvement of the breast, which is more commonly encountered in breast imaging, usually presents with unilateral or bilateral abnormal axillary lymph nodes of variable sizes (Fig. 2).

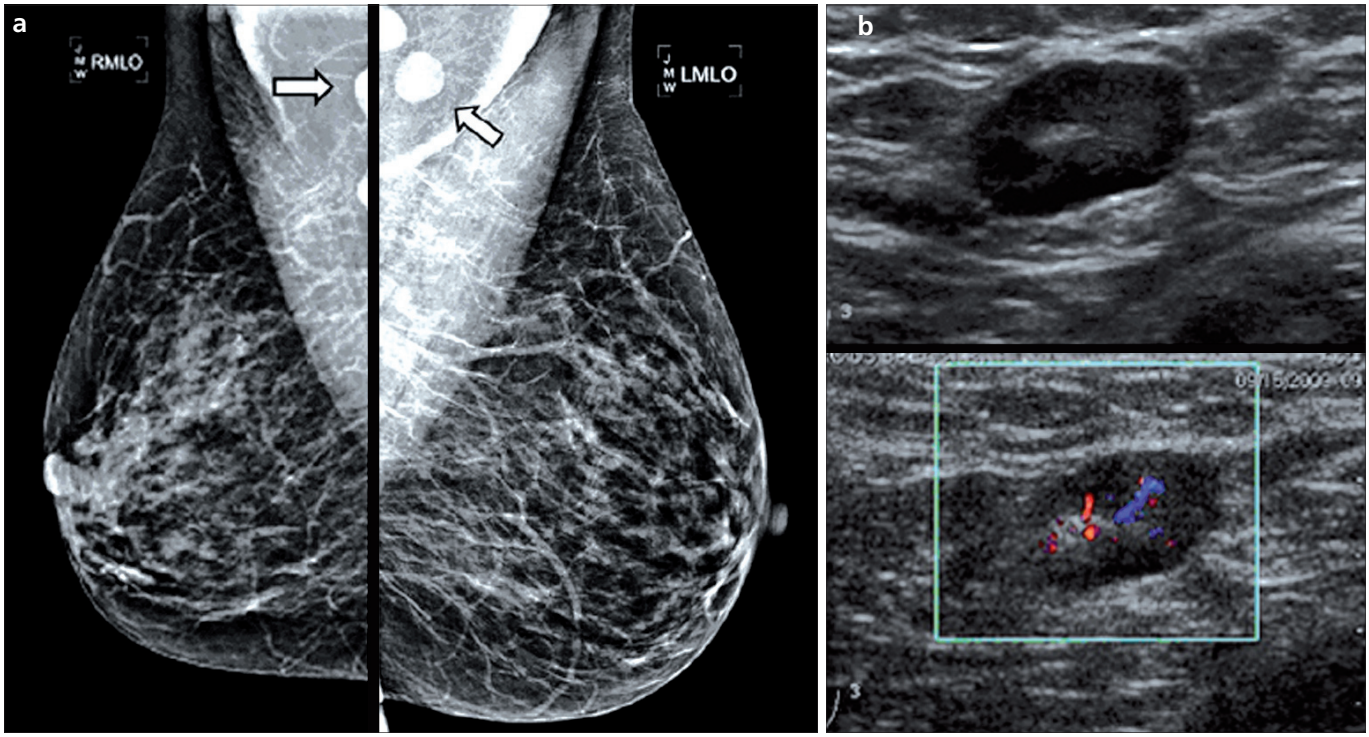

Figure 3. a, b. MLO views **(a)** of bilateral breasts show multiple round, dense, enlarged lymph nodes in a patient with history of stomach cancer who presented with bilateral lumps in the axillary regions *(arrows)*. A round hypoechoic lymph node with a diffusely enlarged cortex is seen on US, and color Doppler US shows increased central flow **(b)**.

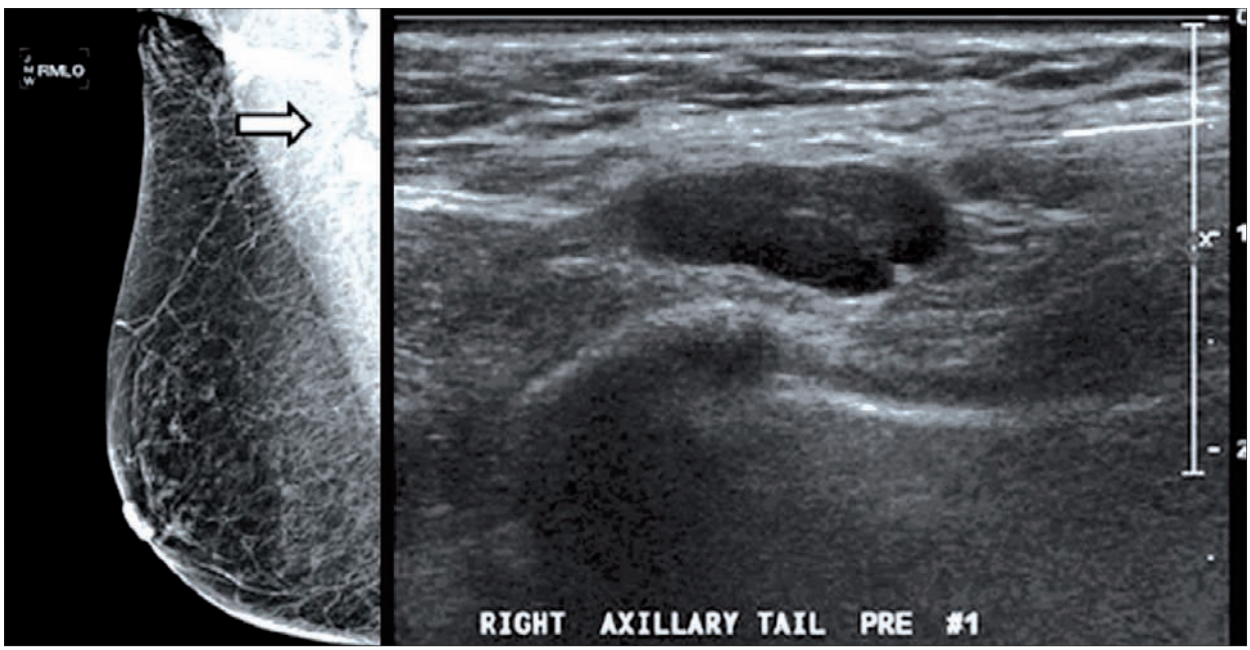

Figure 4. An 84-year-old woman with Langerhans cell histiocytosis. There are enlarged axillary lymph nodes in the right axillary region on the right MLO view (*arrow*). US of the right axillary region shows a plump node with an enlarged, somewhat lobular, and hypoechoic cortex. However, the fatty hilum is preserved.

Other metastases from primary tumors, such as malignant melanoma, lung carcinoma, or stomach or ovarian carcinoma, are also on the list of causes of abnormal lymph nodes detected on mammograms (Fig. 3). As a rare multisystemic disease, Langerhans cell histiocytosis (LCH) can involve many different anatomical sites including the bone, skin, neurohypophysis, oral cavity, anogenital region, lungs, liver, spleen, kidney, and lymph nodes (8). The occurrence of LCH in lymph nodes, either as a primary isolated manifestation of the disease or as part of a systemic disease, has been previously described in the literature. There is no specific imaging finding to diagnose lymphadenopathy caused by LCH (Fig. 4).

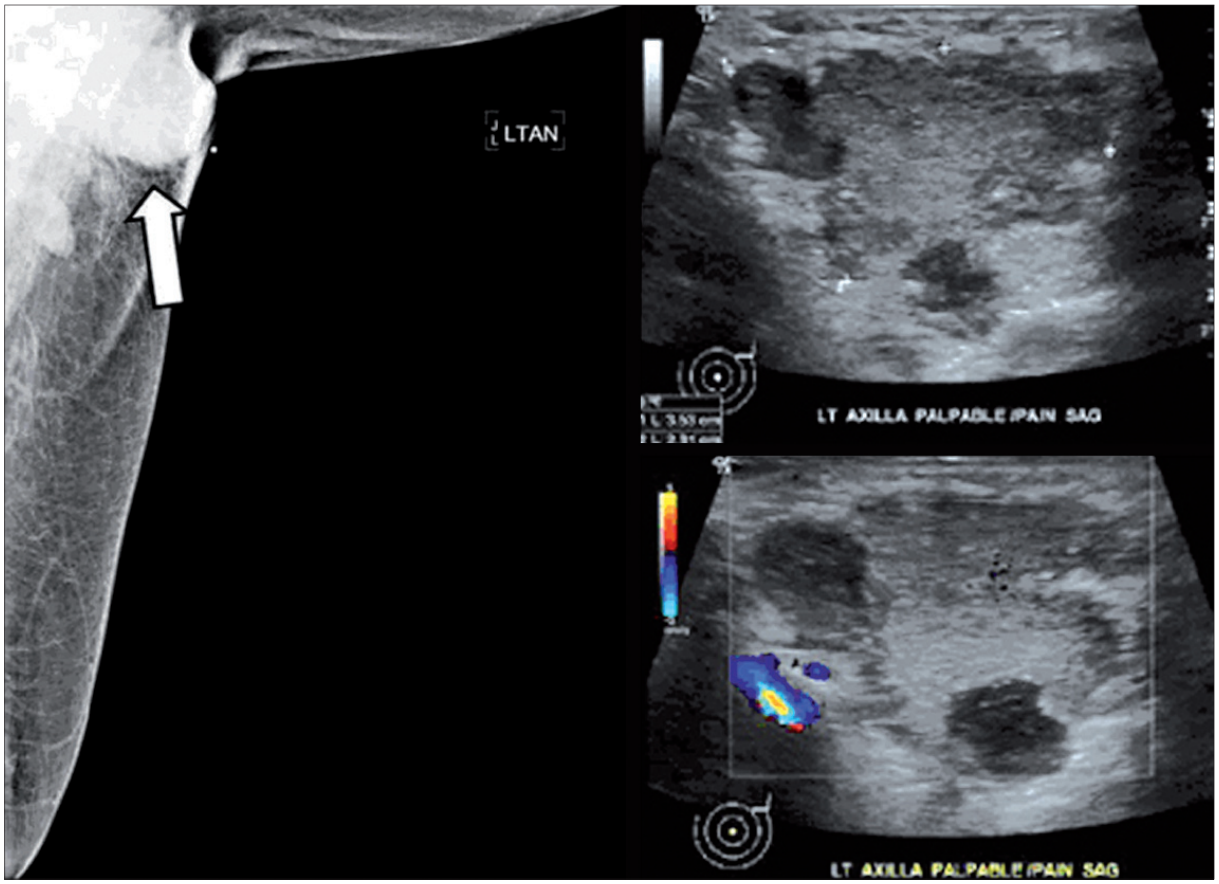

Figure 5. A 53-year-old female patient with a tender left axillary lump. On the spot tangential view of the left axilla (BB marker is over palpable lesion), there is a dense, ill-defined mass, and surrounding enlarged axillary lymph nodes are easily seen (*arrow*). The sagittal US image shows a complex mass with adjacent hypoechoic nodules that have the appearance of enlarged lymph nodes lacking a normal fatty hilum. Color Doppler US demonstrates no flow within it. The diagnosis was abscess formation secondary to bacterial lymphadenitis.

Benign diseases: infections and inflammatory diseases

Inflammation of lymph nodes by bacterial or granulamotous infections such as tuberculosis is known as lymphadenitis. The most common causes of axillary lymphadenitis are bacterial agents that are located in the normal flora of the skin. Focal lymphadenitis is prominent in streptococcal infection, tuberculosis, nontuberculous mycobacterial infection, tularemia, plague, and cat-scratch disease. Multifocal lymphadenitis is common in infectious mononucleosis, cytomegalovirus infection, toxoplasmosis, brucellosis, secondary syphilis, and disseminated histoplasmosis (3, 4). Tuberculous lymphadenitis (or tuberculous adenitis) is a chronic specific granulomatous inflammation with caseation necrosis of the lymph nodes. On physical examination, tenderness, redness, swelling, fluctuation, or abscess formation are detected as a result of bacterial lymphadenitis, while tuberculosis lymphadenitis may result in cold abscesses, which develop so slowly that there are no signs of inflammation unless it becomes complicated (Fig. 5).

HIV infection is associated with a range of lymphoid alterations, from generalized lymphadenopathy to abnormal lymphoid proliferations and malignant lymphomas. Multiple bilateral, enlarged, dense axillary lymph nodes may be seen on screening mammograms in female patients infected with HIV (Fig. 6).

Sarcoidosis is an idiopathic systemic inflammatory granulomatous disorder. It usually invades the lungs with fibrosis and may also involve lymph nodes, skin, liver, spleen, eyes, phalangeal bones, and parotid glands. Pathologically, the most characteristic feature of sarcoidosis is the presence of noncaseating granulomas in a lymphatic or perilymphatic distribution. The list of differential diagnoses should also include other granulomatous infections due to specific organisms such as tuberculosis and histoplasmosis. Enlarged, dense axillary lymph nodes can be detected on mammograms. Coarse calcifications within lymph nodes are seen in other specific granulomatous diseases, such as histoplasmosis and tuberculosis. US shows hypoechoic, round, abnormal lymph nodes of variable sizes (Fig. 7).

Collagen vascular diseases

Collagen vascular diseases are diseases of connective tissue and are caused by immune disorders. Because this is a group of diseases, no unique symptoms exist. The symptoms generally include anemia, fever, joint inflammation, and persistent fatigue. The list of collagen vascular diseases comprises rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, dermatomyositis, and polyarteritis nodosa. It is possible to observe enlarged lymph nodes secondary to a spectrum of diseases, and punctate or amorphous densities mimicking calcifications in enlarged lymph

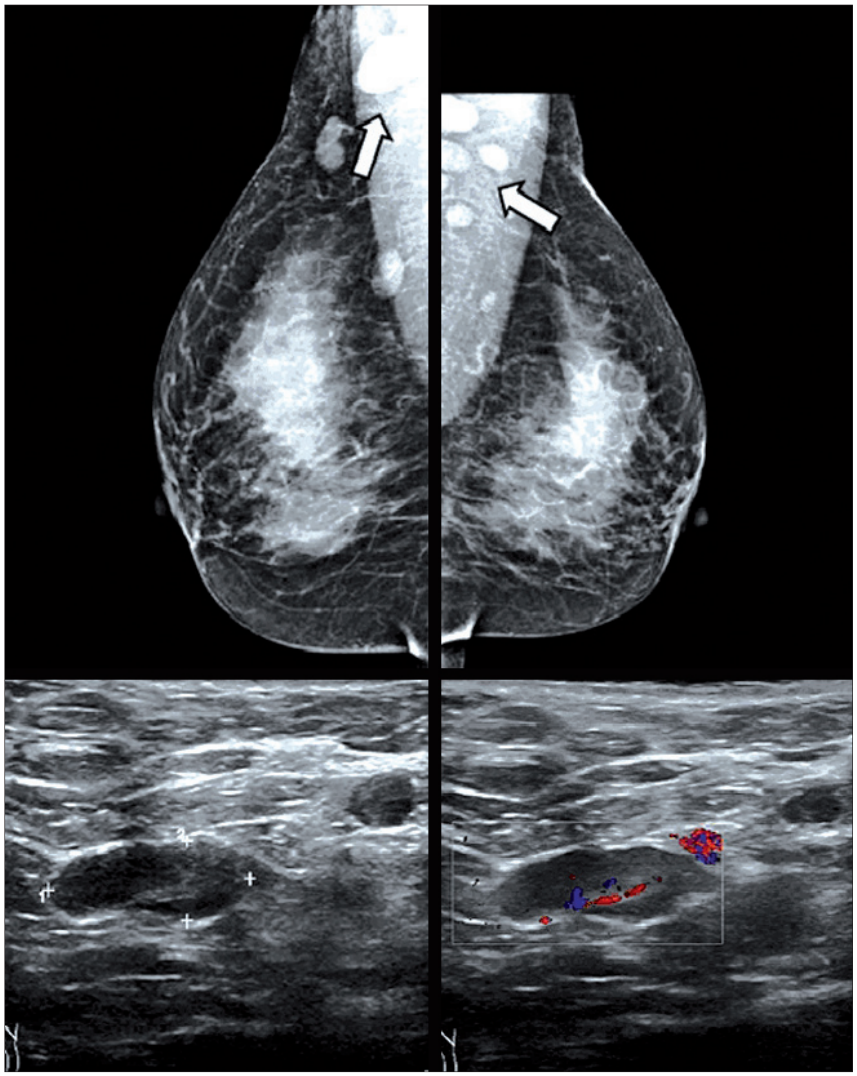

Figure 6. Multiple bilateral, enlarged, dense lymph nodes were detected on a screening mammogram of a 48-year-old woman with HIV (*arrows*). Transverse and oblique US and Color Doppler of the bilateral axillae show hypoechoic, round lymph nodes with central flow.

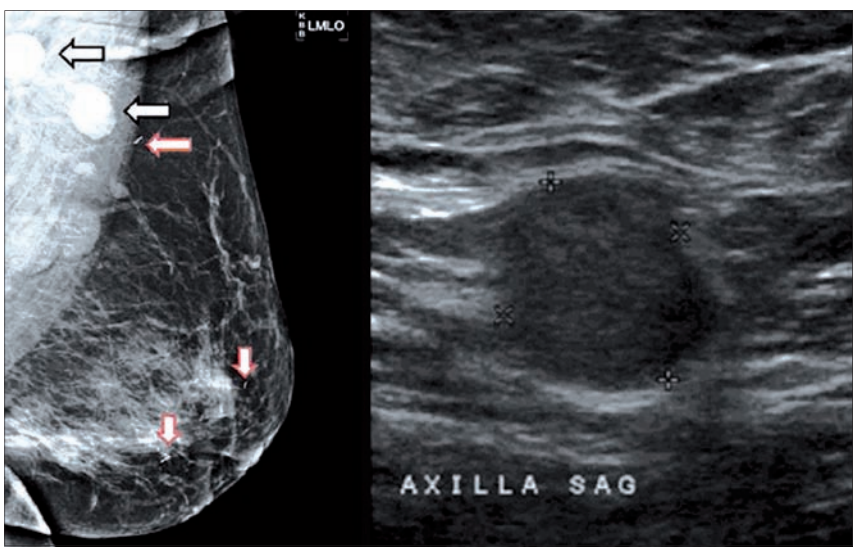

Figure 7. A 51-year-old woman presented after six-month follow-up of US-guided biopsy of the left breast with findings of sarcoidosis. MLO mammography shows round-to-oval, dense axillary lymph nodes *(black arrows)* and three biopsy clips *(red arrows)* in the left breast. Sagittal US images of the left axilla reveal well-circumscribed, diffusely hypoechoic lymph nodes.

nodes can be detected on MLO views after gold injections for treatment of rheumatoid arthritis (3, 4).

Calcifications within lymph nodes

Three types of calcifications in enlarged axillary lymph nodes may be seen on mammograms: 1) microcalcifications; e.g., metastatic breast carcinoma with secondary calcifications that are similar to the primary tumor; 2) punctate or amorphous densities mimicking calcifications; e.g., secondary to gold injections for treatment of rheumatoid arthritis or rarely secondary to tattoo injections; and 3) benign, coarse calcifications; e.g., secondary to granulomatous diseases such as tuberculosis and sarcoidosis (Fig. 8). Calcifications can be identified as echogenic foci with posterior acoustic shadowing on US (9).

Miscellaneous causes

Silicone implants

Silicone gel implants have been used for breast augmentation and reconstruction since 1963. In the USA, more than one million women have undergone implant surgery. The silicone gel-filled variety is the most common type of implant used, although other types are available, such as the saline-inflatable implant and double-lumen implant (combination of outer saline solution and inner silicone compartments). A silicone leak, which can be gross or microscopic, is defined as free silicone found anywhere outside the implant envelope. This could be intra-capsular (contained by a capsule) or extra-capsular (within the soft tissues of the breast or axilla). Microscopic leakage of gel, which is called gel bleed, through an intact envelope occurs in all silicone implants to some extent. This represents a microscopic leak without a rupture. Silicone gel particles can migrate by the lymphatic system and be deposited in the axillary nodes (10). Enlarged, dense axillary lymph nodes are seen on mammograms. A snowstorm appearance (echogenicity in the node with incoherent posterior shadowing) is typical for silicone from current or prior rupture or a microscopic leak (Fig. 9).

Tattoos

Tattooing is a popular cosmetic practice, and the technique has been adopted in breast reconstruction. Intradermally injected pigment is

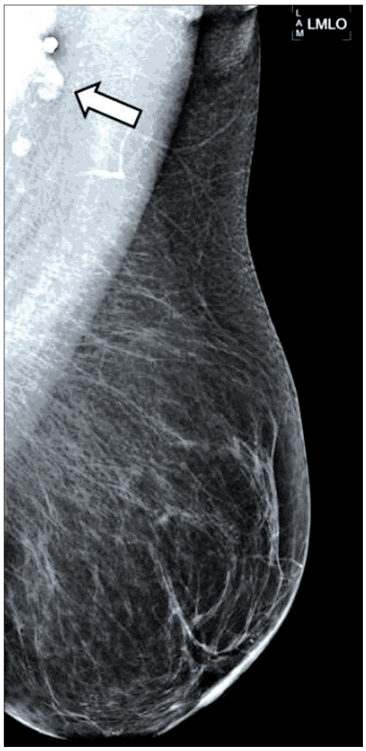

Figure 8. On the screening mammogram of a 50-year-old female patient, the MLO image of the left breast shows a group of benign calcifications in enlarged axillary lymph nodes (*arrow*), which was related to old granulomatous disease. There was no history of rheumatoid arthritis or gold injection.

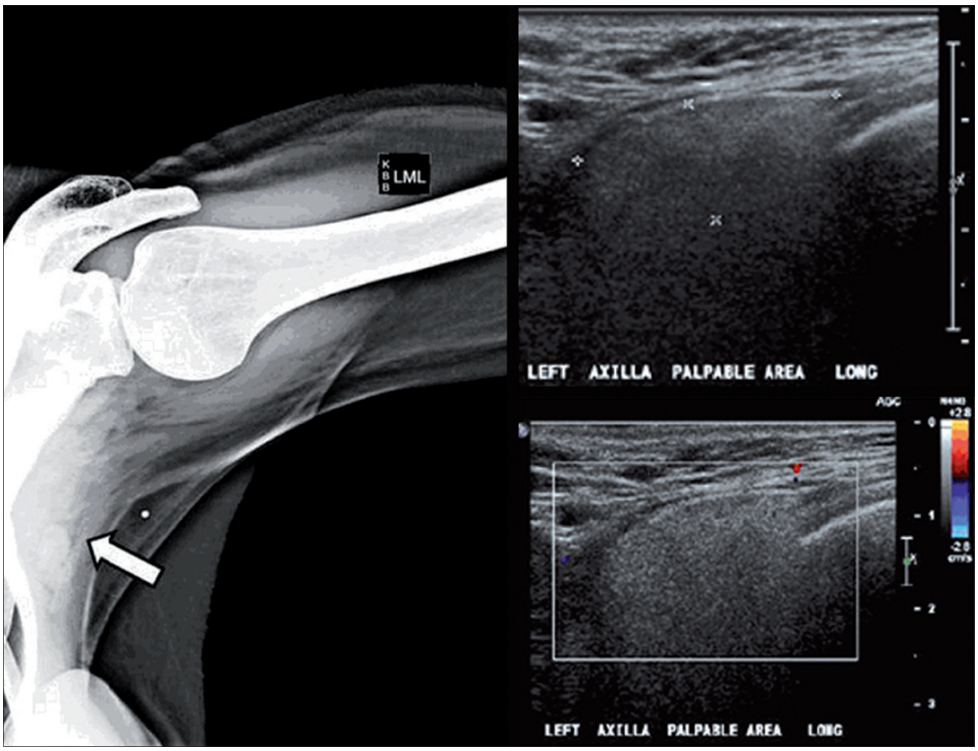

Figure 9. MLO spot compression mammogram of a palpable axillary lump in a 56-year-old woman shows enlarged lymph nodes of varying sizes (*arrow*). She had silicone implants without perceptible changes or other symptoms of leakage. Longitudinal US of the palpable nodes shows well-defined, echogenic, enlarged lymph nodes with a snowstorm appearance and incoherent posterior shadowing and silicone within nodes. There is no flow in the lymph nodes on color Doppler US.

transported to lymph nodes, leading to permanent pigmentation. Enlarged, pigmented lymph nodes are seen in both melanoma and tattoo pigmentation. The differential diagnosis between tattoo and melanotic pigmentation of lymph nodes is made microscopically. Pigmentation of lymph nodes can also occur by deposition of anthracosilicotic pigment, which appears similar to high-density deposits simulating calcium from dental amalgam, aluminium, gold, and titanium (Fig. 10) (9).

Conclusion

In addition to occult breast malignancies, causes of non-breast malignant as well as benign processes should be included in the differential diagnosis of abnormal axillary lymph nodes on negative mammograms. Although the MLO view has been very useful for detecting abnormal axillary lymph nodes, the tangential axillary view, US, and color Doppler US of the axillary region also give useful information about

Figure 10. A 35-year-old woman with extensive tattooing on her arms and back. A photograph of the patient's right arm and posterior shoulder shows extensive tattooing with black, blue, red, and yellow pigments. MLO mammogram of the right breast shows an axillary lymph node (*arrow*) containing foci of calcification densities. A photomicrograph of a fine-needle aspiration biopsy specimen from the lymph node reveals abundant black granular tattoo pigment obscuring lymphocytes. *Arrows* indicate some of the pigment (Diff-Quick [Dade-Behring, Deerfield, Illinois, USA], ×60). *Reprinted with permission from ref. 9.*

abnormal lymph nodes and may help to shorten the list of differential diagnoses and aid the physician in making an accurate diagnosis by needle aspiration or biopsy.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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