Metastatic vs. non-metastatic axillary lymph nodes: helpful differential clues.

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Learning objectives

1. To describe the imaging findings of metastatic and nonmetastatic axillary lymph nodes.
2. Review of the main alterations of axillary lymph nodes, like the metastasis of breast carcinoma and hyperplastic and inflammatory diseases.
Background

The staging of the axillary lymph nodes is one of the most important factors in the prognosis of breast cancer patients. Abnormal morphology of axillary lymph nodes in patients with breast cancer may suggest involvement. However, there are other conditions that can alter the morphology of an axillary lymph node, which need to be considered.
Findings and procedure details

1. Introduction

The breast and overlying skin are derived from the ectoderm and act as a single functional unit. The lymphatic drainage of the breast occurs through three principal routes: the axillary, transpectoral, and internal mammary pathways. The skin, nipple, lactiferous tubules, and surrounding parenchyma drain into the subareolar plexus, which divides into medial and lateral trunks. The medial trunk receives lymph from the inferior breast. The lateral trunk receives lymph from the superior breast. These two trunks drain into the lower axillary lymph nodes.

Anatomical basis

Normal lymph node

The lymph node is one of the major anatomic components of the immune system. The three major regions of a lymph node are the cortex, paracortex and medulla. The cortex is situated beneath the capsule, and represents the compartment where most lymphoid follicles reside. The medulla, close to the hilum, grows in the form of cords. It is rich in lymph sinuses, arteries, and veins but contains only a minor lymphocytic component. Both cortex and medulla represent B zones and are therefore associated with humoral types of immune response. The appearance of the follicles varies according to their state of activity.

The paracortex is the zone situated between the cortex and the medulla, which contains the mobile pool of T lymphocytes responsible for cell-mediated immune responses.

Normal lymphatic drainage of the breast

The lymphatic and venous drainages of the breast are of great importance in the spread of carcinoma. About three quarters of the lymphatic drainage is to the axillary nodes: (1) Lymphatics pass around the edge of the pectoralis major and reach the pectoral group of axillary nodes; (2) routes through or between the pectoral muscles may lead directly to the apical nodes of the axilla; (3) lymphatics follow the blood vessels through the pectoralis major and enter the parasternal (internal thoracic) nodes; (4) connections may lead across the median plane and hence to the contralateral breast; (5) lymphatics may reach the sheath of the rectus abdominis and the subperitoneal and subhepatic plexuses.

The axilla is divided into three levels by the pectoralis minor muscle, just as the axillary artery is divided into three segments. There are five groups of lymph nodes in the axilla:
three in level I, which is inferolateral to the pectoralis minor; one group in level II behind
the pectoralis minor; and one group superomedial to the pectoralis minor in level III.
Drainage generally proceeds in a stepwise fashion from level I to level II, to level III, and
finally into the thorax.

The three groups of level I nodes are divided into the lateral group (deep), the subscapular
group (posterolateral), and the pectoral group (anteromedial).

Pathology of axillary lymph nodes

Hyperplasia patterns

The various components of the lymph node react to various known and unknown stimuli
by undergoing reactive changes, some being the expression of an inflammatory reaction
and some being indicative of an immune response.

Follicular hyperplasia

The reactive follicles vary considerably in size and shape; their margins are
sharply defined and surrounded by a mantle of small lymphocytes often arranged
circumferentially with an onion-skin pattern and sometimes concentrating on one pole
of the follicle.

Follicular hyperplasia can accompany a large number of inflammatory and noninfectious
conditions.

Mantle/marginal zone hyperplasia

This pattern of hyperplasia, which blends with the lymphoid subtype of hyaline vascular
Castleman disease, is characterized by a monomorphic proliferation of small lymphoid
cells with round nuclei and clear cytoplasm which may be arranged in a nodular, inverse
follicular, and/or marginal zone pattern. The main differential diagnosis is with mantle cell
lymphoma.

Paracortical hyperplasia

Expansion of the paracortical (interfollicular) region can be nodular or diffuse. The
nodular form is characteristic of dermatopathic lymphadenitis and of nodal reactions to
malignancy. The diffuse form is a feature of viral lymphadenitis, drug reactions, and
immunoblastic proliferations in general.

Sinus hyperplasia
In this pattern of hyperplasia, the sinuses appear dilated and prominent in various disorders. The most common and least significant is sinus hyperplasia seen in nodes draining infectious or neoplastic processes and characterized by an increased number of macrophages in the lumen. Other reactive disorders involving primarily the sinuses are Rosai-Dorfman disease (RDD), Langerhans cell histiocytosis, Whipple disease, vascular transformation of sinuses, and virus-associated hemophagocytic syndrome.

Autoimmune diseases

Lupus erythematosus

The lymph node changes in lupus erythematosus are generally of a nonspecific nature and consist of moderate follicular hyperplasia associated with increased vascularization and scattered immunoblasts and plasma cells.

Rheumatoid arthritis

Most patients with rheumatoid arthritis have generalized lymphadenopathy at some time during their illness. The lymph node enlargement may precede the arthritis and raise the clinical suspicion of lymphoma.

The most important changes are follicular hyperplasia and plasma cell proliferation, with formation of Russell bodies.

Castleman disease

Castleman disease (giant lymph node hyperplasia) represents a morphologically distinct form of lymph node hyperplasia rather than a neoplasm or a hamartoma. It occurs most commonly in adults but it can also affect children.

Microscopically, two major categories have been described. The first, designated as hyalinevascular type or angiofollicular, shows large follicles scattered in a mass of lymphoid tissue. The follicles show marked vascular proliferation and hyalinization of their abnormal germinal centers.

In the variant of the hyaline-vascular type described as the lymphoid subtype, the follicles have a marked expansion of the mantle zone and small, relatively inconspicuous germinal centers. This variant of Castleman disease merges with the process known as mantle zone hyperplasia, and it is the one more likely to be confused with malignant lymphoma of either follicular or mantle cell type.
The second major morphologic category of Castleman disease is known as the plasma cell type. It is characterized by a diffuse plasma cell proliferation in the interfollicular tissue, sometimes accompanied by numerous Russell bodies.

**Pigment deposits**

Several types of pigmented material have been detected in axillary lymph nodes. Histiocytes may contain black anthracotic pigment, which apparently accumulates as a result of retrograde flow from thoracic to axillary lymphatics. The pigment is usually not abundant and tends to be more prominent in apical rather than in low axillary lymph nodes.

Prior surgical trauma, or an underlying systemic condition such as hemosiderosis, can cause accumulation of brown iron pigment. Dermatopathic lymphadenitis features melanin pigment transported from inflammatory skin lesions. Pigment from cutaneous tattoos can also be transported to axillary lymph nodes. Tattoo pigment in an axillary lymph node may resemble calcification on mammography. Patients who received systemic gold therapy for rheumatoid arthritis have reportedly developed gold deposits in lymph nodes, which were visualized by mammography.

**Silicone lymphadenitis**

Reaction to silicone transported to lymph nodes has been described in association with orthopedic prostheses, cosmetic injection of silicone in the breast and other sites, and leakage from intact or ruptured silicone gel containing breast implants. In the mammary region, clinically symptomatic adenopathy is manifested by nontender or painful axillary nodal enlargement. Asymptomatic silicone lymphadenitis may be encountered when a patient with a silicone containing prosthesis undergoes an axillary dissection or lymph node biopsy for another condition such as mammary carcinoma. Involvement of an intramammary lymph node by silicone can produce mammographic changes that mimic carcinoma.

Silicone lymphadenitis caused by material from orthopedic devices is typically characterized by a prominent granulomatous reaction with clumps of granular yellowish refractile material, whereas silicone gel from mammary prostheses ordinarily produces finer vacuolated deposits that resemble soap suds. Asteroid bodies have been observed in lymphadenitis associated with silicone containing orthopedic prostheses.

**Other lymphadenitis: dermatopathic, granulomatous, necrotizing**

Dermatopathic lymphadenitis (lipomelanosis reticularis of Pautrier) is a form of nodal hyperplasia usually secondary to a generalized dermatitis, particularly those with exfoliative features. Pathogenetically, it represents a T-cell response to skin antigens processed and presented by interdigitating dendritic cells. It may occur in any skin
disorder in which itching and scratching are prominent; this includes inflammatory dermatoses such as psoriasis and neoplastic diseases such as mycosis fungoides.

Microscopically, the nodal architecture is preserved. The main change is represented by a marked pale widening of the paracortical zone, which stands out prominently on low-power examination. Most of the large nonlymphoid cells occupying this area are thought to be of three types: histiocytes, Langerhans cells, and interdigitating dendritic cells.

Chronic granulomatous disease is the result of a genetically determined enzymatic defect of granulocytes and monocytes. These cells ingest microorganisms but are unable to destroy them because of their inability to generate superoxide anion (O2 -). This is due to a defect in any one of four components of NADPH oxidases, the enzyme responsible for the generation of the antimicrobial oxidants. The main clinical features are recurrent lymphadenitis, hepatosplenomegaly, skin rash, pulmonary infiltrates, anemia, leukocytosis, and hypergammaglobulinemia. Microscopically, granulomas with necrotic purulent centers are seen in lymph nodes and other organs.

Lymphoma and leukemia

Lymphomatous proliferations are defined as the clonal malignant proliferation of a mature lymphocyte from a secondary lymphoid structure, a lymph node or an extranodal structure. They thus contrast with acute leukaemias or myeloproliferative syndromes arising from an immature cell of medullary origin. They are malignant variants of lymphocytes stuck at a specific stage in their differentiation, with their own morphological and immunophenotypic characteristics. Since there are many of these stages, malignant lymphomas cover a range of very heterogeneous conditions in terms of their forms of presentation, their development profile and their prognosis.

The diagnosis of lymphoma is based on pathological histology. Conventional examination, in the first instance, distinguishes on a morphological basis between Hodgkin's lymphoma (HL), characterised by the presence of Reed Sternberg cells (40% of lymphomas), and non-Hodgkin's lymphomas (NHL) (60%), classified according to criteria concerning their architecture (follicular or diffuse) and morphology (small or large cells).

The most well-known form of lymphoma is the lymph node form. This is the classic form of Hodgkin's lymphoma and low grade NHLs. Any lymph node area can be affected. A lymph node with a short axis of more than 1 cm is considered to be pathological.

Metastasis of breast carcinoma

Lymph nodes are the most common site of metastatic malignancy, and sometimes constitute the first clinical manifestation of the disease. Any malignant tumor can give
rise to lymph node metastases, but the incidence varies greatly depending on the tumor type. It is common with carcinomas, malignant melanomas, and germ cell tumors, and rare with sarcomas and central nervous system tumors.

The differential diagnosis between metastatic undifferentiated carcinoma and diffuse large cell lymphoma in routine sections may be difficult or even impossible in some cases. Features favoring metastatic tumor are focal nodal involvement, definite nesting, extensive necrosis, predominantly sinusal distribution, and solid tumor plugs in lymphatic vessels. The types of malignant lymphoma most likely to be misdiagnosed as metastatic carcinoma are anaplastic large cell lymphoma, large B-cell lymphoma with sclerosis resulting in prominent nesting, large B-cell lymphoma with a predominantly sinusal pattern of growth, nodular sclerosis Hodgkin lymphoma with concentration of large mononuclear variants of Reed-Sternberg cells around areas of necrosis, and signet ring cell lymphoma.

The metastatic carcinomas that most closely simulate a malignant lymphoid process are nasopharyngeal lymphoepithelial carcinoma and lobular carcinoma of the breast.

Most carcinomas metastatic to supraclavicular lymph nodes originate in the lung or breast. The large majority of metastatic tumors in axillary nodes of adult females are breast carcinoma and malignant melanoma.

**Imaging findings of axillary lymph nodes: Normality vs. abnormality**

The accurate identification and characterization of lymph nodes by imaging has important therapeutic and prognostic significance in patients with newly diagnosed cancers. The presence of nodal metastases limits the therapeutic options and also generally indicates worse prognosis in patients. Thus, it becomes crucial to have this information before commencing therapy. Current cross-sectional imaging modalities rely on insensitive size and morphologic criteria and, thus, lack the desired accuracy for characterizing lymph nodes. This is mainly because metastases can be present in non-enlarged lymph nodes and not all enlarged nodes are malignant. PET has overcome some of these limitations but is still constrained by current resolution limits for small nodal metastases.

**Mammography**

Although mammography is the most common breast imaging modality, in evaluating axillary lymph nodes is hindered by its limited visualization of the axilla because of positioning. As a result, mammography is not typically used for targeted evaluation of the axilla, nonetheless, the presence of obviously asymmetrically enlarged lymph nodes on mammogram should prompt the interpreting radiologist to further interrogate the axilla with ultrasonography and image-guided biopsy.
Ultrasound

Ultrasonography (US) is the primary imaging modality for evaluating axillary nodes. Morphologic criteria, such as cortical thickening, hilar effacement, and nonhilar cortical blood flow, are more important than size criteria in the identification of metastases.

The sonographic criteria for abnormal lymph node have been focused on node shape (length-to-width ratio) and overall echogenicity (presence or absence of hyperechoic hilum). Focal changes in the cortical morphologic features of a node may be more important because metastatic cells are first deposited in the periphery of a node.

Deepak G. Bedi et al made a study in which each node was classified into one of the following types on the basis of cortical morphologic features: type 1, hyperechoic, no visible cortex; type 2, thin (< 3 mm) hypoechoic cortex; type 3, hypoechoic cortex thicker than 3 mm; type 4, generalized lobulated hypoechoic cortex; type 5, focal hypoechoic cortical lobulation; type 6, totally hypoechoic node with no hilum. Nodes were empirically considered benign (types 1-4) or suspicious or metastatic (types 5 and 6) on the basis of experience and anatomic knowledge of nodes.

In breast cancer, axillary lymph nodes can be classified according to cortical morphologic features. Predominantly hyperechoic nodes (types 1-3) can be considered benign. Generalized cortical lobulation (type 4) is uncommonly a false-negative finding, but metastasis, if present, is invariably detected at sentinel node mapping. The presence of asymmetric focal hypoechoic cortical lobulation (type 5) or a completely hypoechoic node (type 6) should serve as a guideline for universal performance of fine-needle aspiration for preoperative staging of breast cancer.

Magnetic Resonance Imaging

The cortex of a lymph node has decreased signal intensity with T1-weighted sequences and intermediate to increased intensity with T2-weighted and inversion recovery sequences.

Nodes enhance rapidly and homogeneously at DCE MR imaging. A type III washout kinetic pattern can be seen in the cortex of a normal node and is not useful for identifying metastasis.

Lymph nodes with cortical irregularity or apparent spiculation are considered suspicious. Morphologic features that can be seen with metastasis include cortical thickening, loss of fatty hilum, heterogeneous enhancement, and round shape or a long axis to short axis ratio of less than 2.
Computed Tomography

Conventional CT is not routinely used in clinical staging of T1 and T2 tumors because the likelihood of finding distant metastases is low. Therefore, there is less routine experience with this modality in imaging the axilla in patients with these tumors. CT is often performed in patients with advanced disease, and therefore abnormal axillary nodes are occasionally encountered. Nodal size alone is a poor predictor of the presence of metastasis.

Nodes with an irregular-appearing or eccentrically thickened cortex should be considered suspicious.

Positron Emission Tomography

18F-fluorodeoxyglucose-positron emission tomography (18F-FDG-PET) is a nuclear medicine technique that relies on the increased metabolic activity of malignancies relative to normal tissue for detecting metastatic disease. 18F-FDG-PET is often performed with computed tomography (CT) to provide anatomic detail and to improve image quality with attenuation correction. Typically, metastatic axillary lymph nodes demonstrate increased radiotracer activity.
**Fig. 1:** Female 59 years old with left breast cancer. Right breast mammography without lymphadenopathy. Histopathologic diagnosis: follicular hyperplasia.

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Fig. 2: Female 59 years old with left breast cancer. Ultrasound with right axillary lymph node with suspicious morphology with focal cortical thickening 5.5mm and compression fatty hilum. Histopathologic diagnosis: folicular hyperplasia.

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Fig. 3: Female 50 years old with BIRADS 4A because of left breast nodule. Mammography with irregular nodule, hyperdense, darkened edges and popcorn calcification without lymphadenopathy. Biopsy of mammary nodule and axillary lymph node with histopathologic diagnosis of hialinized fibroadenoma and lymph node paracortical hyperplasia.

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Fig. 4: Female 50 years old with BIRADS 4A because of left breast nodule. Ultrasound of axillary region shows reactive lymph node with diffuse thickening of the cortical 2.2mm. Biopsy of mammary nodule and axillary lymph node with histopathologic diagnosis of hialinized fibroadenoma and lymph node paracortical hyperplasia.

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Fig. 5: Female 50 years old with BIRADS 4A because of left breast nodule. MRI left lymph node with diffuse thickening of the cortical. Biopsy of mammary nodule and axillary lymph node with histopathologic diagnosis of hialinized fibroadenoma and lymph node paracortical hyperplasia.
Fig. 6: Female 50 years old with BIRADS 4A because of left breast nodule. MRI left lymph node with diffuse thickening of the cortical. Biopsy of mamary nodule and axillary lymph node with histopathologic diagnosis of hialinized fibroadenoma and lymph node paracortical hyperplasia.

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**Fig. 7:** Female 50 years old with BIRADS 4A because of left breast nodule. MRI left lymph node with diffuse thickening of the cortical. Biopsy of mammary nodule and axillary lymph node with histopathologic diagnosis of hialinized fibroadenoma and lymph node paracortical hyperplasia.

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Fig. 8: Female 51 years old with a history of breast cancer right treated with mastectomy, with palpable right axillary node. Ultrasound images of reactive lymph node appearance with cortical thickening 2.7mm. Histopathologic diagnosis: sinusoidal hyperplasia.

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Fig. 9: Female 50 years old classified as BIRADS 4C because of right breast nodule and reactive node. Mammography right axillary region with rounded morphology lymph node and increased density. Histopathologic diagnosis of right breast fibrocystic changes and axillary lymph node dermatopathic lymphadenitis.

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Fig. 10: Female 50 years old classified as BIRADS 4C because of right breast nodule and reactive node. Ultrasound lymph node with increased diffuse cortical which measures 5mm and compression of the fatty hilum. Histopathologic diagnosis of right breast fibrocystic changes and axillary lymph node dermatopathic lymphadenitis.

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Fig. 11: Female 50 years old classified as BIRADS 4C because of right breast nodule and reactive node. MRI enlarged lymph node with diffuse cortical thickening. Histopathologic diagnosis of right breast fibrocystic changes and axillary lymph node dermatopathic lymphadenitis.

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**Fig. 12:** Female 50 years old classified as BIRADS 4C because of right breast nodule and reactive node. MRI enlarged lymph node with diffuse cortical thickening. Histopathologic diagnosis of right breast fibrocystic changes and axillary lymph node dermatopathic lymphadenitis.

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Fig. 13: Female 50 years old classified as BIRADS 4C because of right breast nodule and reactive node. MRI enlarged lymph node with diffuse cortical thickening. Histopathologic diagnosis of right breast fibrocystic changes and axillary lymph node dermatopathic lymphadenitis.

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Fig. 14: Female 45 years old. Mammography increased density in the right axillary region. Histopathologic diagnosis: granulomatous lymphadenitis.

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Fig. 15: Female 45 years old. Mammography in axillary projection with increased density in the right axillary region. Histopathologic diagnosis: granulomatous lymphadenitis.

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Fig. 16: Female 45 years old. Ultrasound with lymph nodes reagent aspect, some with diffuse increase in cortical which measures 6.5mm and other mass-like. Histopathologic diagnosis: granulomatous lymphadenitis.

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**Fig. 17:** Female 45 years old. Ultrasound with lymph nodes reagent aspect, some with diffuse increase in cortical which measures 6.5mm and other mass-like. No vascularity. Histopathologic diagnosis: granulomatous lymphadenitis.

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**Fig. 18:** Female 27 years old referred episode of mastitis 1 month ago, with medical treatment, which refers bulking and palpable tumor in the left axillary region. Mamography with enlarged lymph density and soft tissue swelling in the axillary region. Histopathologic diagnosis: acute necrotizing lymphadenitis.

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Fig. 19: Female 27 years old referred episode of mastitis 1 month ago, with medical treatment, which refers bulking and palpable tumor in the left axillary region. Ultrasound with enlarged lymph nodes with mass-like morphology. Histopathologic diagnosis: acute necrotizing lymphadenitis.

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**Fig. 20:** Female 27 years old referred episode of mastitis 1 month ago, with medical treatment, which refers bulking and palpable tumor in the left axillary region. Ultrasound with enlarged lymph nodes with mass-like morphology. Histopathologic diagnosis: acute necrotizing lymphadenitis.

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Fig. 21: Female 27 years old referred episode of mastitis 1 month ago, with medical treatment, which refers bulking and palpable tumor in the left axillary region. MRI with enlarged mass-like lymph node. Histopathologic diagnosis: acute necrotizing lymphadenitis.

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Fig. 22: Female 27 years old referred episode of mastitis 1 month ago, with medical treatment, which refers bulking and palpable tumor in the left axillary region. MRI with enlarged mass-like lymph node. Histopathologic diagnosis: acute necrotizing lymphadenitis.

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**Fig. 23:** Female 27 years old referred episode of mastitis 1 month ago, with medical treatment, which refers bulking and palpable tumor in the left axillary region. MRI with enlarged mass-like lymph node. Histopathologic diagnosis: acute necrotizing lymphadenitis.

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**Fig. 24:** Female 44 years old diagnosed with acute lymphoblastic leukemia in 2008, currently with new palpable tumor in the left breast fifteen days of evolution. Mammography with nodule in axillary region. Histopathologic diagnosis: leukemia infiltration.

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**Fig. 25:** Female 44 years old diagnosed with acute lymphoblastic leukemia in 2008, currently with new palpable tumor in the left breast fifteen days of evolution. Mammography with nodule in axillary region. Histopathologic diagnosis: leukemia infiltration.

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Fig. 26: Female 44 years old diagnosed with acute lymphoblastic leukemia in 2008, currently with new palpable tumor in the left breast fifteen days of evolution. Ultrasound diffuse lymph node cortical thickening 5mm, necrosis and fatty hilium compression. Histopathologic diagnosis: leukemia infiltration.

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Fig. 27: Female 44 years old diagnosed with acute lymphoblastic leukemia in 2008, currently with new palpable tumor in the left breast fifteen days of evolution. Ultrasound diffuse lymph node cortical thickening 5mm, necrosis and fatty hilium compression. Histopathologic diagnosis: leukemia infiltration.

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Fig. 28: Female 76 years old with palpable nodule in right breast and thickening and erosion of periareolar skin. Mammography with irregular, spiculated right retroareolar mass. Lymph nodes increased in size and density in right axillary region. Histopathologic diagnosis: Metastatic carcinoma of breast origin.

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**Fig. 29:** Female 76 years old with palpable nodule in right breast and thickening and erosion of periareolar skin. Mammography with irregular, spiculated right retroareolar mass. Lymph nodes increased in size and density in right axillary region. Histopathologic diagnosis: Metastatic carcinoma of breast origin.

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Fig. 30: Female 76 years old with palpable nodule in right breast and thickening and erosion of periareolar skin. Ultrasound with abnormal lymph node morphology, cortical thickening with up to 12mm which conditions compression of the central fatty hilum. Histopathologic diagnosis: Metastatic carcinoma of breast origin.

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**Fig. 31:** Female 76 years old with palpable nodule in right breast and thickening and erosion of periareolar skin. MRI with lymph node enlargement and abnormal morphology. Histopathologic diagnosis: Metastatic carcinoma of breast origin.

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Fig. 32: Female 76 years old with palpable nodule in right breast and thickening and erosion of periareolar skin. MRI with lymph node enlargement and abnormal morphology. Histopathologic diagnosis: Metastatic carcinoma of breast origin.

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**Fig. 33:** Female 76 years old with palpable nodule in right breast and thickening and erosion of periareolar skin. MRI with lymph node enlargement and abnormal morphology. Histopathologic diagnosis: Metastatic carcinoma of breast origin.
Fig. 34: Female 76 years old with palpable nodule in right breast and thickening and erosion of periareolar skin. MRI with lymph node enlargement and abnormal morphology. Histopathologic diagnosis: Metastatic carcinoma of breast origin.

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Conclusion

Examination of axillary lymph nodes is crucial in breast cancer patients. The correct characterization of the axillary lymph nodes by imaging methods is important for selection of which lymph nodes that should undergo image guided biopsy. Thereby helping clinicians obtain a more appropriate staging.
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