Although the primary purpose of periodic mammograms in screening programs is to identify lesions suspected of being carcinomas, the findings are often related to systemic (benign or malignant) diseases, rather than breast cancer. Although the involvement of breast structures in systemic diseases is unusual, it can be included in the differential diagnosis of masses, skin changes, calcifications, asymmetry, and axillary lymphadenopathy. The main diagnostic entities that can be associated with such involvement are diabetes, chronic kidney disease, heart diseases, connective tissue diseases, HIV infection, lymphoma, leukemia, and metastases from primary tumors at other sites. In many cases, information related to knowledge and treatment of chronic diseases is not available to the radiologist at the time of evaluation of the mammography findings. The purpose of this essay is to offer relevant pictorial information to the general radiologist about systemic diseases involving the breast, expanding the range of differential diagnoses in order to avoid unnecessary invasive procedures.

Keywords: Breast; Systemic diseases; Collagen disease; Lymphoma; Metastases.

INTRODUCTION

With the expansion of breast cancer screening programs, more mammographic examinations are being performed, and, as a consequence, the detection of breast findings not related to epithelial carcinomas is also more frequent. The major benign systemic diseases with radiological manifestations on mammography and breast ultrasound are diabetes, heart diseases, chronic kidney disease, HIV infection, granulomatous diseases (e.g., tuberculosis), parasitic diseases, and connective tissue diseases (e.g., dermatomyositis, scleroderma, and systemic lupus erythematosus). Within that context, patients may present, clinically, with skin changes, palpable masses and skin thickening. Malignant systemic diseases with secondary manifestations in the breasts can include lymphoma, leukemia, and metastases from primary cancer at other sites.

The initial diagnostic flow chart involves the analysis of the clinical history and previous treatments. When these tools are used in conjunction with the mammography and ultrasound findings and yet do not result in a definitive diagnosis, percutaneous biopsy can be performed. The objective of this article is to present the most common systemic diseases affecting the breasts, as well as their radiological manifestations.

DIABETES

Diabetic mastopathy is an uncommon entity, occurring mainly in young women with a long history of type I
diabetes, and affects less than 15% of insulin-dependent patients\(^{(1)}\). Although the cause is not well known, it is related to an increase in the amount of collagen, increasing the extracellular matrix in the setting of hyperglycemia\(^{(2)}\). On mammography, it manifests as focal asymmetry or a solid mass, usually in the retroareolar region, without accompanying calcifications (Figure 1). The sonographic appearance is a hypoechoic mass with indistinct or spiculated margins, with pronounced posterior acoustic shadow, and no vascularity on the Doppler evaluation\(^{(3)}\), as illustrated in Figure 2. Those presentations raise the possibility of malignancy, and, consequently, percutaneous biopsy is recommended. During the biopsy procedure, the lesion is often hard, which hampers its sampling.

**HEART DISEASES**

There are two main aspects of heart diseases with manifestation in the breasts\(^{(3)}\): arteriopathy and edema. Arterial calcifications are common and do not cause diagnostic difficulties in mammography (Figure 3), unless they are incipient, in which case they can mimic linear suspicious calcifications. It is not well established in the literature whether the detection of arterial calcifications is related to increased cardiovascular risk. It is intuitively assumed that calcifications and peripheral arteries are a consequence of ongoing cardiovascular disease and are associated with risk factors for coronary artery disease, and this assumption is supported by some studies showing a positive association between the presence of vascular calcifications and cardiovascular dis-

![Figure 1](image1.png)

**Figure 1.** Mammogram, in a craniocaudal view, showing focal asymmetry in the upper outer quadrant of the left breast (arrow) measuring 3.0 cm, in a 46-year-old patient under insulin therapy.

![Figure 2](image2.png)

**Figure 2.** Ultrasound showing an irregular, spiculated, hypoechoic mass, with posterior acoustic shadowing, with no flow on Doppler evaluation. Percutaneous biopsy of the mass resulted in a diagnosis of perilobular lymphocytic infiltrate, consistent with diabetic mastopathy.

![Figure 3](image3.png)

**Figure 3.** A 58-year-old female patient presenting with multiple vascular calcifications on mammography.

![Figure 4](image4.png)

**Figure 4.** Arteriography showing arterial calcifications.

**CHRONIC KIDNEY DISEASE**

The imaging findings most commonly seen in chronic kidney disease are related to its pathophysiology. Due to
volvement is rare and manifests in two main forms: axillary lymphadenopathy and tuberculous mastitis. When there is lymph node involvement, the lymph nodes are enlarged, the cortex is hypoechoic, and there can be calcifications. In mastitis, ultrasound shows abscess formation represented by complex (solid-cystic) masses or fluid collections (Figure 7). Granulomas may also appear as irregular masses

Figures 4-6 show examples of imaging findings in various systemic diseases.
accompanied by edema of the adjacent fat tissue\(^{3,6}\). In these situations, it is difficult to make an accurate diagnosis, given that it is often impossible to exclude a malignant lesion on the basis of imaging findings alone and a biopsy is therefore necessary.

**PARASITIC INFECTIONS**

Filariasis is a parasitic infection that can involve the breasts, caused by the helminth *Wuchereria bancrofti*. The main clinical manifestations occur as a consequence of obstruction of the lymphatic vessels by the presence of active or calcified worms. In the breast, the larva penetrates the lymphatic vessels and causes lymphangitis, fibrosis, and changes in the lymphatic drainage, resulting in global or focal asymmetry accompanied by trabecular and skin thickening. The larvae can later present as linear or serpentine calcifications\(^{7}\), as depicted in Figure 8.

**CONNECTIVE TISSUE DISEASES**

Connective tissue diseases are a heterogeneous group of diseases characterized by inflammatory processes in the connective tissues. They include systemic lupus erythematosus, scleroderma, dermatomyositis, and mixed connective tissue disease. The most common findings are bilateral axillary lymph node enlargement, skin thickening, and calcifications. In systemic lupus erythematosus, it is common to find skin thickening with multiple subcutaneous nodules, incipient linear calcifications that later become more numerous and coarse, representing areas of fat necrosis\(^{6,8}\), as can be seen in Figure 9. Scleroderma manifests as thickening of the skin, trabecular thickening of the fibroglandular tissue, and coarse superficial calcifications (Figure 10). Dermatomyositis typically presents as cutaneous and dystrophic calcifications (Figure 11).

**LYMPHOMA/LEUKEMIA**

Secondary involvement of the breasts by lymphoma is uncommon, mainly due to the rarity of lymphoid tissue.

Secondary lymphomas are associated with prior or concomitant systemic lymphoma and are more common than primary lymphomas. The most common subtype is diffuse large B-cell non-Hodgkin lymphoma. Secondary lymphomas manifest as masses, as well as focal or global asymmetry. The masses are oval or round, with circumscribed or microlobulated margins (Figure 12), mimicking benign lesions\(^{7}\).

Leukemic infiltration of the breasts is extremely rare, being most common after bone marrow transplantation.
Clinically, there are palpable masses; on mammography, the masses are rounded, microlobulated, and hyperdense, whereas they are hypoechoic or solid-cystic (complex) on ultrasound\(^9\).

**METASTASES**

Secondary lesions in the breast are uncommon, due to the limited arterial supply. The main types of primary cancer are melanoma, thyroid cancer, and ovarian cancer. Mammography shows masses with benign characteristics—oval, circumscribed, and not calcified—as depicted in Figure 13. Ultrasound shows masses that are oval or round, hypoechoic with posterior acoustic shadowing, due to the high cellularity, and presenting as calcifications in ovarian cancer (Figure 14) or thyroid cancer. The nodules are usually located in the superficial planes and are often palpable\(^{10}\).
CONCLUSION

Although the breast is not a common site of lesions caused by systemic diseases, its involvement can occur after benign or malignant changes. Knowledge of the main changes found on breast imaging can increase the range of differential diagnoses of an imaging change and occasionally avoid an unnecessary invasive procedure.

REFERENCES

1. Gouveri E, Papanas N, Maltezos E. The female breast and diabetes. Breast. 2011;20:205–11.
2. Dorokhova O, Fineberg S, Koenigsberg T, et al. Diabetic mastopathy, a clinicopathological correlation of 34 cases. Pathol Int. 2012;62:660–4.
3. Cao MM, Hoyt AC, Bassett LW. Mammographic signs of systemic disease. Radiographics. 2011;31:1085–100.
4. Chadashvili T, Litmanovich D, Hall F, et al. Do breast arterial calcifications on mammography predict elevated risk of coronary artery disease? Eur J Radiol. 2016;85:1121–4.
5. Son EJ, Oh KK, Kim EK, et al. Characteristic imaging features of breast fibroadenomas in women given cyclosporine A after renal transplantation. J Clin Ultrasound. 2004;32:69–77.
6. Dilaveri CA, Mac Bride MB, Sandhu NP, et al. Breast manifestations of systemic diseases. Int J Womens Health. 2012;4:35–43.
7. Bastarrika G, Pina L, Vivas I, et al. Calcified filariasis of the breast: report of four cases. Eur Radiol. 2001;11:1195–7.
8. Masood S, Davis CL, Kubik MJ. The clinical significance of recognizing distinct morphologic features of systemic diseases on breast biopsies. Adv Anat Pathol. 2012;19:217–9.
9. Surov A, Holzhausen HJ, Wienke A, et al. Primary and secondary breast lymphoma: prevalence, clinical signs and radiological features. Br J Radiol. 2012;85:e195–205.
10. Lee SH, Park JM, Kook SH, et al. Metastatic tumors to the breast: mammographic and ultrasonographic findings. J Ultrasound Med. 2000;19:257–62.