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FULL RESEARCH ARTICLE

Multimodality imaging of hematologic malignancies affecting the breast: a pictorial essay

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ABSTRACT

Hematologic malignancies affecting the breast are a heterogeneous group that includes lymphomas, leukemias, and multiple myeloma. Secondary infiltration by lymphoma is the most common hematologic malignancy of the breast. This pictorial essay presents clinical cases of mammography, ultrasound, and magnetic resonance imaging (MRI) findings of lymphoma, leukemia, and multiple myeloma, with histopathologic confirmation. The most common imaging findings were mass(es), non-mass lesions, or architectural distortion, and less commonly, diffusely increased breast density. There are no specific criteria for image diagnosis of hematologic malignancies affecting the breast; therefore, it is essential to know the medical history. Although a biopsy is always necessary, knowledge of the imaging findings gives the radiologist the necessary tools to diagnose correctly.

Keywords: *Ultrasound. Mammography. Magnetic resonance imaging. Breast. Hematologic malignancies.*

INTRODUCTION

Hematologic malignancies affecting the breast are a heterogeneous group that includes different types of lymphomas, leukemias, and multiple myeloma. They comprise approximately 0.04-0.5% of all breast malignancies[1]. The manifestations in the breast are variable and may mimic a primary breast tumor. A history of hematologic malignancy should raise suspicion of a secondary breast lesion[2]. There are no specific diagnostic imaging features. Diagnosis should always be made with a pathologic examination of the suspicious lesion. This pictorial essay describes the main ultrasound, mammography, and magnetic resonance imaging (MRI) features of hematologic malignancies with infiltration of the breast and provides diagnostic pearls that should be considered in the differential diagnosis in the appropriate clinical context.

LYMPHOMAS

Lymphoma can affect the breast as a primary tumor or an extranodal manifestation[2,3]. Secondary infiltration by lymphoma is the most common hematologic malignancy of the breast[1-3]. Unilateral primary breast lymphomas affect older women and often have

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B-cell histology, whereas bilateral primary lymphomas usually affect young women and are associated with Burkitt lymphoma.

Primary breast lymphomas represent 0.85-2.2% of lymphomas and 0.1-0.5% of all primary breast neoplasms[2,3]. This low percentage is due to the small amount of intramammary lymphoid tissue. Lymphoma is considered primary if no extramammary lymphoma or disseminated disease has been previously diagnosed[4].

Secondary breast lymphoma is the most common metastatic lesion affecting the breast, with a mean age at diagnosis of 55-65 years[2] and a variable prevalence of 0.07% to 17%. Secondary disease has earlier signs of nodal disease and most commonly affects the breast in patients with diffuse non-Hodgkin lymphoma[5]. The presence of unilateral or bilateral breast masses, and trabecular or cutaneous thickening, with or without axillary adenopathy, suggests a secondary breast lymphoma in a patient with a known diagnosis of lymphoma[4-6].

The most common clinical manifestation is a palpable, painless mass (61%) in the upper outer quadrant, with palpable lymph nodes (40%) and pain (25%). There may be nipple retraction, telorrhea, and local signs of inflammation such as diffuse skin thickening and edema[3,4]. In some cases, it may be an incidental finding (12%) in asymptomatic patients[7]. B-symptoms (fever, sweating, and weight loss) are rare in primary breast lymphomas but common in secondary forms. No specific features or signs on breast imaging accurately differentiate primary and secondary lymphoma. A solitary mass with or without axillary adenopathy and a larger size can lead to the diagnosis of primary lymphoma[6].

Mammography

Lymphoma most commonly manifests as a mass (76%)[4], asymmetry, or architectural distortion of the breast. Masses may be oval, round, irregular, hyper, or isodense, with circumscribed or indistinct margins. Asymmetries occur in 20% of cases, and architectural distortion in 9%. Cutaneous edema (lymphedema) is observed in 8%. Calcifications are rare and abnormal lymph nodes can be observed in up to 28% of cases[2,4,8].

Ultrasound

The most common finding is a solid mass. Its shape is variable, with circumscribed or indistinct margins, hypoechoic or mixed echogenicity, usually with increased vascularity and a peripheral echogenic halo[4]. In both cases, axillary adenopathies may be observed in primary or secondary lymphoma. Palpable abnormal lymph nodes as an initial finding may suggest a diagnosis of secondary lymphoma[3].

MRI

As with mammography and ultrasound, the most common manifestation is an enhanced oval, or round, isointense mass in T1 with variable intensity in T2. Enhancement is variable, homogeneous, or heterogeneous. Diffuse infiltration of the breast has also been documented. Axillary and occasionally mediastinal adenopathy can be observed[4,6].

Case 1. Hodgkin lymphoma

A 63-year-old woman presented palpable abnormal lymph nodes in the right axilla. Mammography showed increased diffuse density of the right breast (global asymmetry) (Figure 1). Hyperdense round lymph nodes were identified in the right axilla. There were no masses, calcifications, or visible distortion.

Ultrasound showed multiple non-mass lesions in different quadrants without distortion or associated vascularity. The largest lesion was in the upper inner quadrant (UIQ). There were several abnormal lymph nodes in the right axilla with a thick and markedly hypoechoic cortex and some lymph nodes with loss of fatty hilum. BI-RADS Category 4C. Ultrasound-guided percutaneous biopsies (12G core needle) of the dominant non-mass lesion of the right breast and abnormal lymph nodes were performed. The histopathologic diagnosis was diffuse large B-cell non-Hodgkin's lymphoma, non-germinal center type, in the mass and the lymph node (Figure 2).

After the breast biopsy, a contrast MRI with gadolinium showed multiple non-mass enhancement with diffuse distribution in all quadrants, homogeneous and ascending contrast uptake (type I curve), increased volume and abnormal enhancement of the right nipple was also observed. Both findings presented restriction in the diffusion sequence and a low apparent diffusion coefficient (ADC) value. Abnormal axillary lymph nodes were observed in Berg levels I and II.

Case 2. Non-Hodgkin lymphoma

A 39-year-old woman with non-Hodgkin lymphoma diagnosed 2 years before in the right axilla and currently in remission presented with a lump in her right

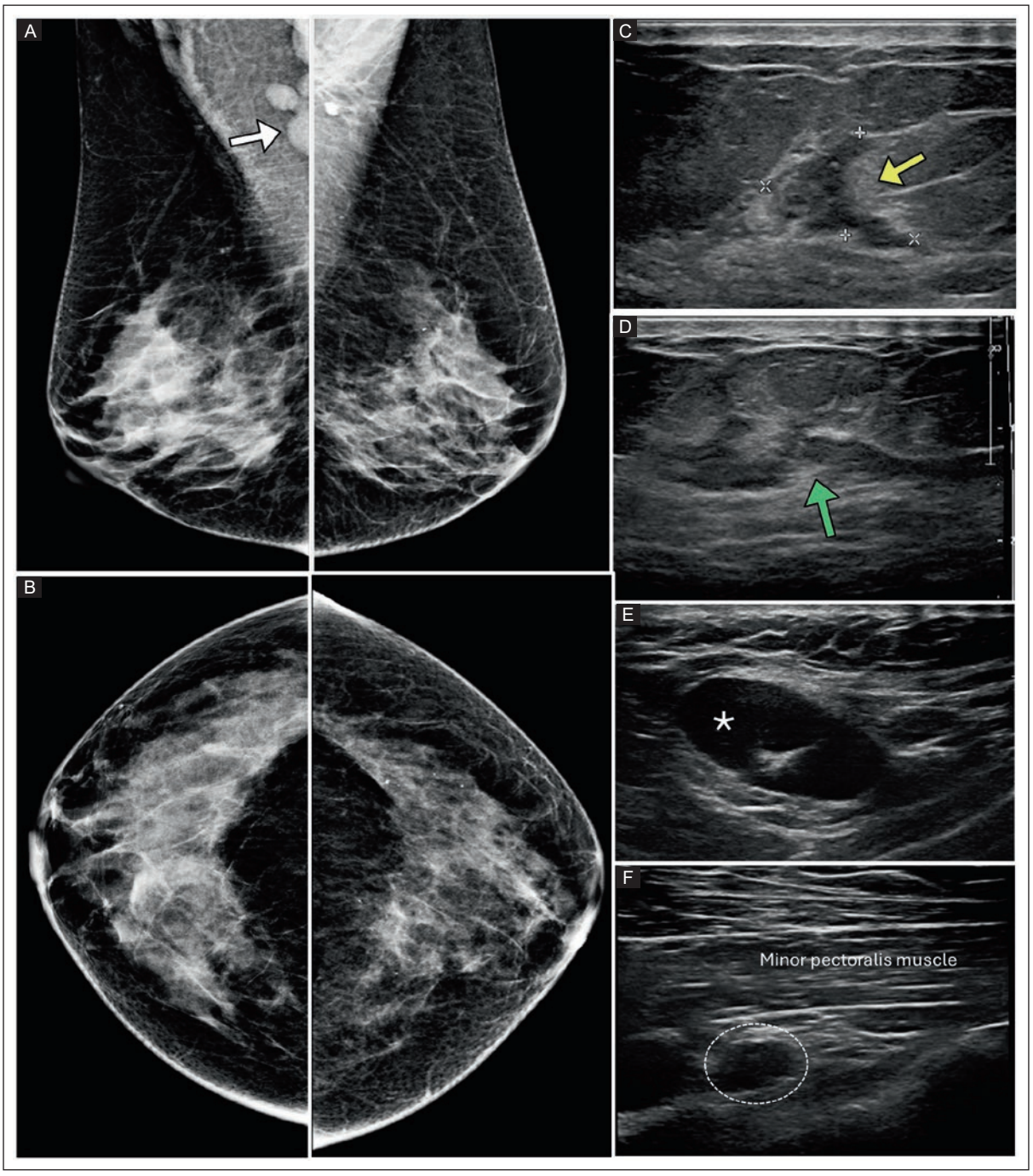

Figure 1. Case 1. A 63-year-old woman with palpable abnormal lymph nodes in the right axillary region. **A-B:** digital mammography in MLO and CC view shows global asymmetry with increased diffuse density in the right breast and no masses or architectural distortion. The right axilla has round and hyperdense lymph nodes (white arrow). **C-D:** US grayscale shows multiple non-mass lesions (yellow arrow) in different quadrants; the largest in the UIQ measures 3.2 cm (green arrow). **E-F:** there are five abnormal lymph nodes in the axilla at level I (asterisk) and two lymph nodes at level II (dotted circle), with a thick and clear hypoechoic cortex. BI-RADS Category 4C.

BI-RADS: Breast Imaging Reporting and Data System; CC: craniocaudal; MLO: mediolateral oblique; UIQ: upper inner quadrant; US: ultrasound.

breast. A mammogram showed an oval, hyperdense mass with an obscured margin at the junction of the upper quadrants (Figure 3). Another irregular, hyperdense mass was identified in the upper inner quadrant (UIQ).

Ultrasound confirmed a solid, isoechoic oval mass with a circumscribed margin and internal vascularity. Two hypoechoic irregular masses were identified in the UIQ (one was not seen on the mammogram) with spiculated margins and avascular. Abnormal lymph nodes

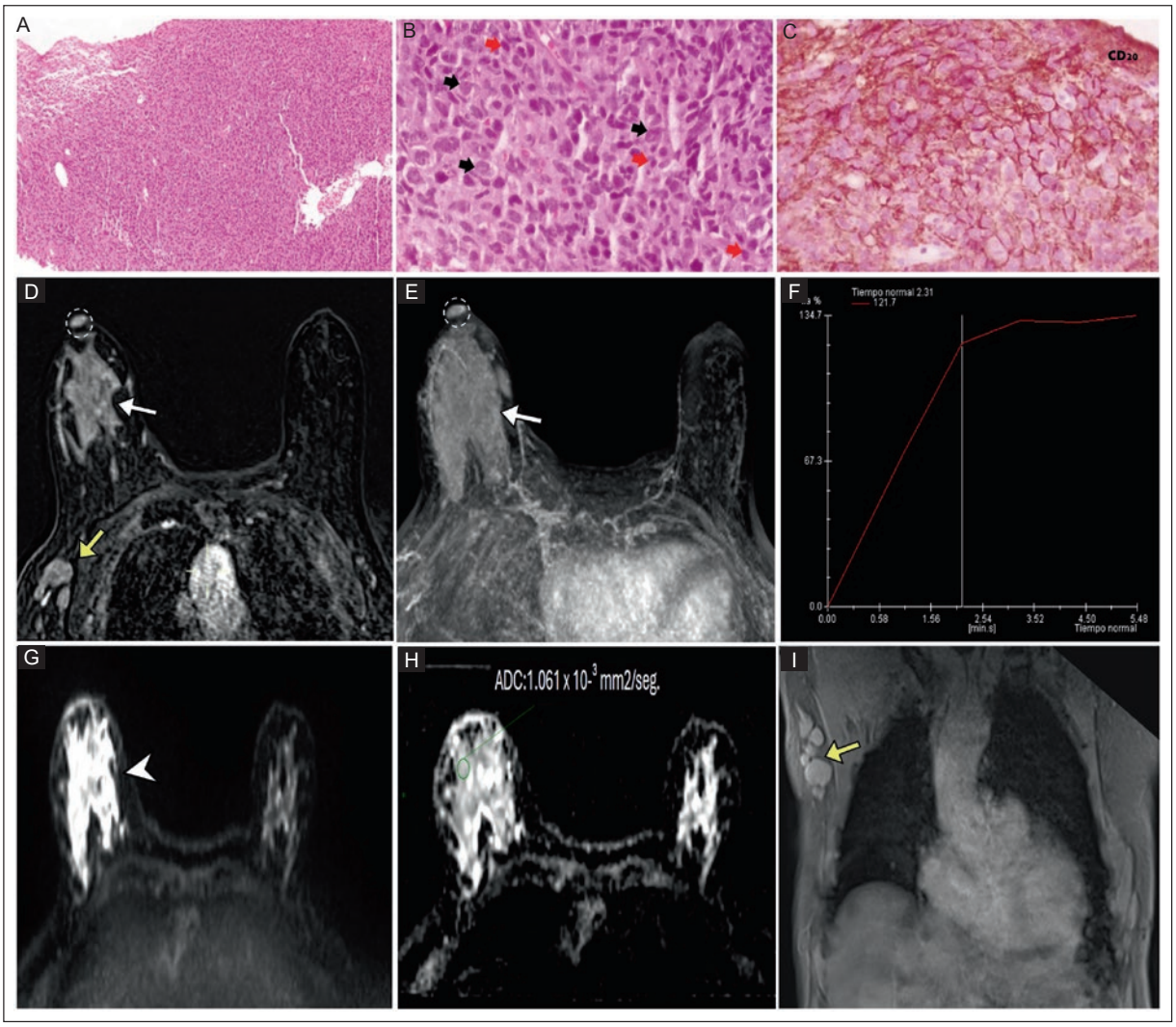

Figure 2. Case 1. A 63-year-old woman with palpable abnormal lymph nodes in the right axilla. Core biopsies of the dominant non-mass lesion in the right breast and right axilla node were performed. **A:** H&E 10×. Lymph node with loss of normal histologic architecture due to diffuse infiltration of atypical neoplastic lymphoid cells. **B:** H&E 40×. Large lymphoid cells with marked atypia, increased nucleus-cytoplasmic ratio, scant cytoplasm, vesicular chromatin, and sometimes macronucleoli (black arrows) on a polymorphic background composed of mature lymphocytes and neutrophils (red arrows). **C:** H&E 40×. IHC staining was diffusely positive for CD20 confirming B-lineage. The morphology and immunophenotype confirmed the histopathologic diagnosis of diffuse large B cell non-Hodgkin lymphoma, non-germinal center type, in the non-mass lesion and lymph node. **D-E:** T1-weighted dynamic contrast-enhanced MRI, MIP. Several areas of non-mass enhancement and diffuse distribution are seen in all quadrants (white arrows) in the right breast. Abnormal lymph nodes (yellow arrow). Increased volume and abnormal enhancement of the right nipple (dotted circles). **F:** homogeneous and ascending contrast uptake (type I curve). **G-H:** DWI and ADC. Both findings show a restriction in the diffusion sequence (white arrowhead) and an ADC value of 1.06×10^{-3} mm^2/sec. **I:** T2 MRI coronal view shows round, hyperintense axillary lymph nodes with a thick cortex and obliteration of the fatty hilum at the I (yellow arrows) and II Berg levels.

ADC: apparent diffusion coefficient; DWI: diffusion-weighted imaging; H&E: hematoxylin and eosin; IHC: immunohistochemistry; MIP: maximum intensity projection; MRI: magnetic resonance imaging.

were identified in the right axilla at Berg levels I and II. BI-RADS Category 5.

A percutaneous biopsy of the palpable mass was performed under US guidance (12G core needle) (Figure 4). The histologic diagnosis was a grade I follicular B-cell non-Hodgkin lymphoma. A biopsy of the two spiculated masses was performed at UIQ (1 o'clock). The histopathologic diagnosis was triple-negative invasive carcinoma of no special type.

After the biopsy, contrast enhanced MRI with gadolinium was performed. A dominant 3.5 cm mass with an irregular margin and heterogeneous contrast uptake

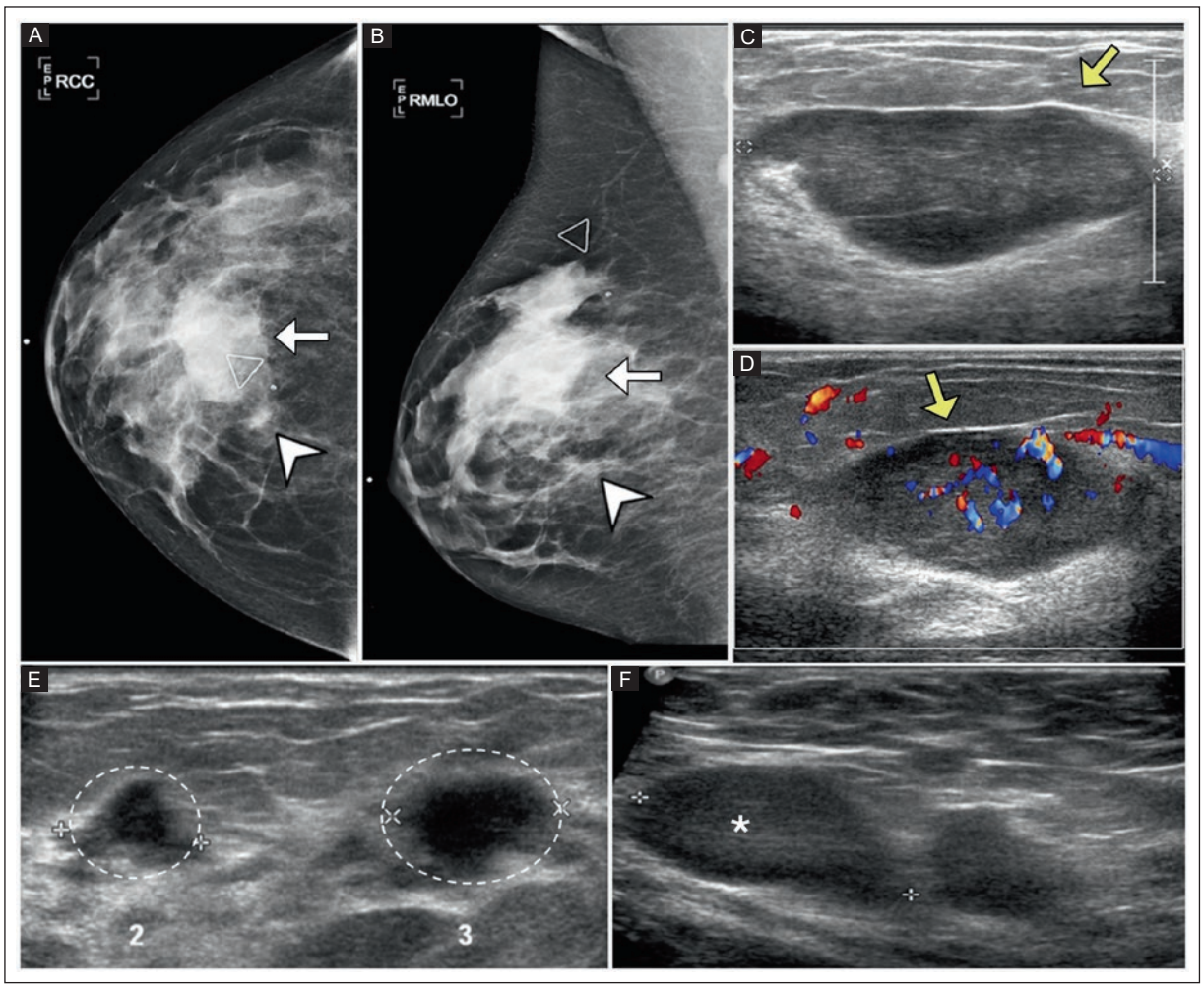

Figure 3. Case 2. A 39-year-old woman with non-Hodgkin lymphoma diagnosed 2 years earlier in the right axilla and currently in remission presented with a lump in the right breast. **A-B:** mammogram, CC, and MLO views show an oval, hyperdense mass with an obscured margin at the junction of the upper quadrants, 12 o'clock, and middle third (arrows) of the right breast. An irregular, hyperdense mass in the UIQ without associated calcifications (white arrowheads). **C-D:** grayscale and color Doppler US show a 3.8 cm solid, isoechoic, oval mass with a circumscribed margin and internal vascularity with color Doppler at 12 o'clock, 4 cm from the nipple in the right breast (yellow arrows). **E:** in the same breast, two irregular, markedly hypoechoic, avascular masses with spiculated margin (dotted circles), located at UIQ, 1 o'clock, 5 cm from the nipple. **F:** abnormal lymph nodes in the right axilla, the largest with cortical thickening up to 7 mm (asterisk) at I and II Berg levels. BI-RADS Category 5.

CC: craniocaudal; MLO: mediolateral oblique; UIQ: upper inner quadrant; US: ultrasound.

was found in the right breast. Two irregular enhanced masses in the UIQ with spiculated margins were confirmed. Multiple abnormal lymph nodes were found. The patient was treated with neoadjuvant chemotherapy and radiotherapy. MRI follow-up after treatment showed a complete absence of the dominant mass (lymphoma) and the two spiculated masses (triple-negative, no special type cancer) related to complete treatment response. Half of the abnormal lymph nodes described in the axilla disappeared, corresponding to a partial treatment response.

LEUKEMIA

Secondary infiltration of the breast by leukemia is rare. The most common subtype (60 %) is acute myeloid leukemia[2,9], while chronic leukemia infiltration is uncommon[2,9]. Premenopausal women[10] with a median age of 33 years[2,9] are usually affected. There are three clinical scenarios: the first is prior infiltration of the bone marrow, historically known as granulocytic sarcoma, in which systemic disease develops within two years; the second is during or after the diagnosis

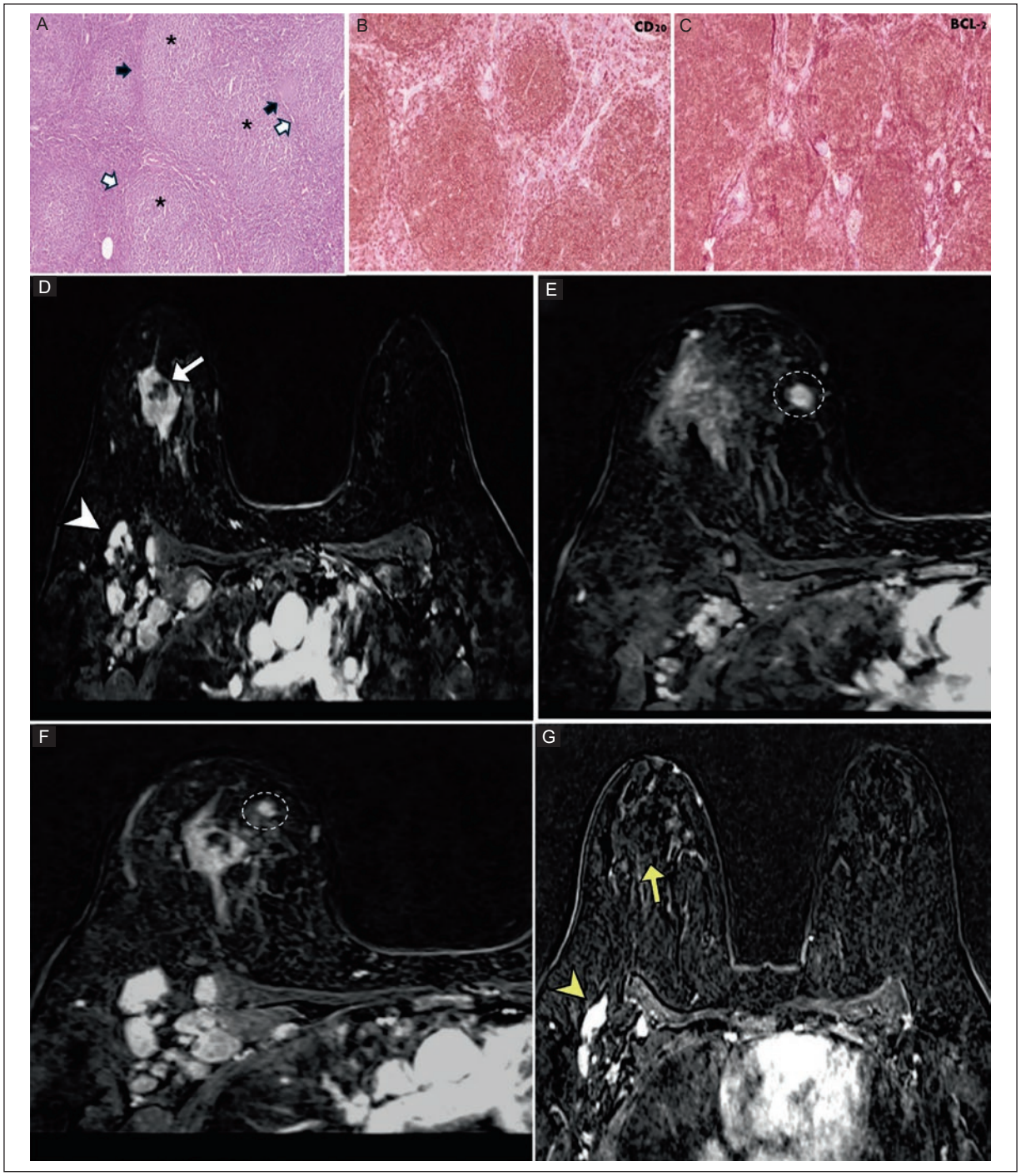

Figure 4. Case 2. A 39-year-old woman with non-Hodgkin lymphoma diagnosed 2 years before in the right axilla presented with a lump in the right breast. Core biopsies of the right breast and right axillary lymph node were performed. **A:** H&E 10×. Neoplastic follicles similar in size (white arrows) form germinal centers composed of small cells and attenuate the mantle and adjacent marginal areas (black arrows). Follicles do not polarize (asterisks) and have lack tingible bodies. **B-C:** H&E 40×. IHC stains were strongly and diffusely positive for CD20, confirming B-lineage lymphoma. BCL2 was positive in the neoplastic germinal centers. The axillary lymph node showed partial fading of the histologic architecture due to low-grade hematolymphoid proliferation in a follicular pattern. The histopathologic diagnosis was non-Hodgkin's lymphoma, grade I folicular lymphoma. **D, E,** and **F:** T1-weighted dynamic contrast-enhanced MRI axial view showing a mass with an irregular margin measuring 3.5 cm and heterogeneous contrast uptake at 12 o'clock in the right breast (white arrow). The UIQ shows two irregular, enhanced masses with a spiculated margin, measuring 1.1 cm and 9 mm, respectively (dotted circles). The axilla has multiple abnormal, round lymph nodes with cortical thickening and loss of the fatty hilum (white arrowheads). **G:** T1-weighted dynamic contrast-enhanced MRI axial view after neoadjuvant chemotherapy and radiotherapy. Absence of the dominant mass (lymphoma) at 12 o'clock and the two spiculated masses (triple-negative NST cancer) related with complete treatment response (yellow arrow). Half of the abnormal lymph nodes described in the axilla have disappeared, indicating a partial response of the lymph nodes (yellow arrowhead).

H&E: hematoxylin and eosin; IHC: immunohistochemistry; MRI: magnetic resonance imaging; NST: no special type; UIQ: upper inner quadrant.

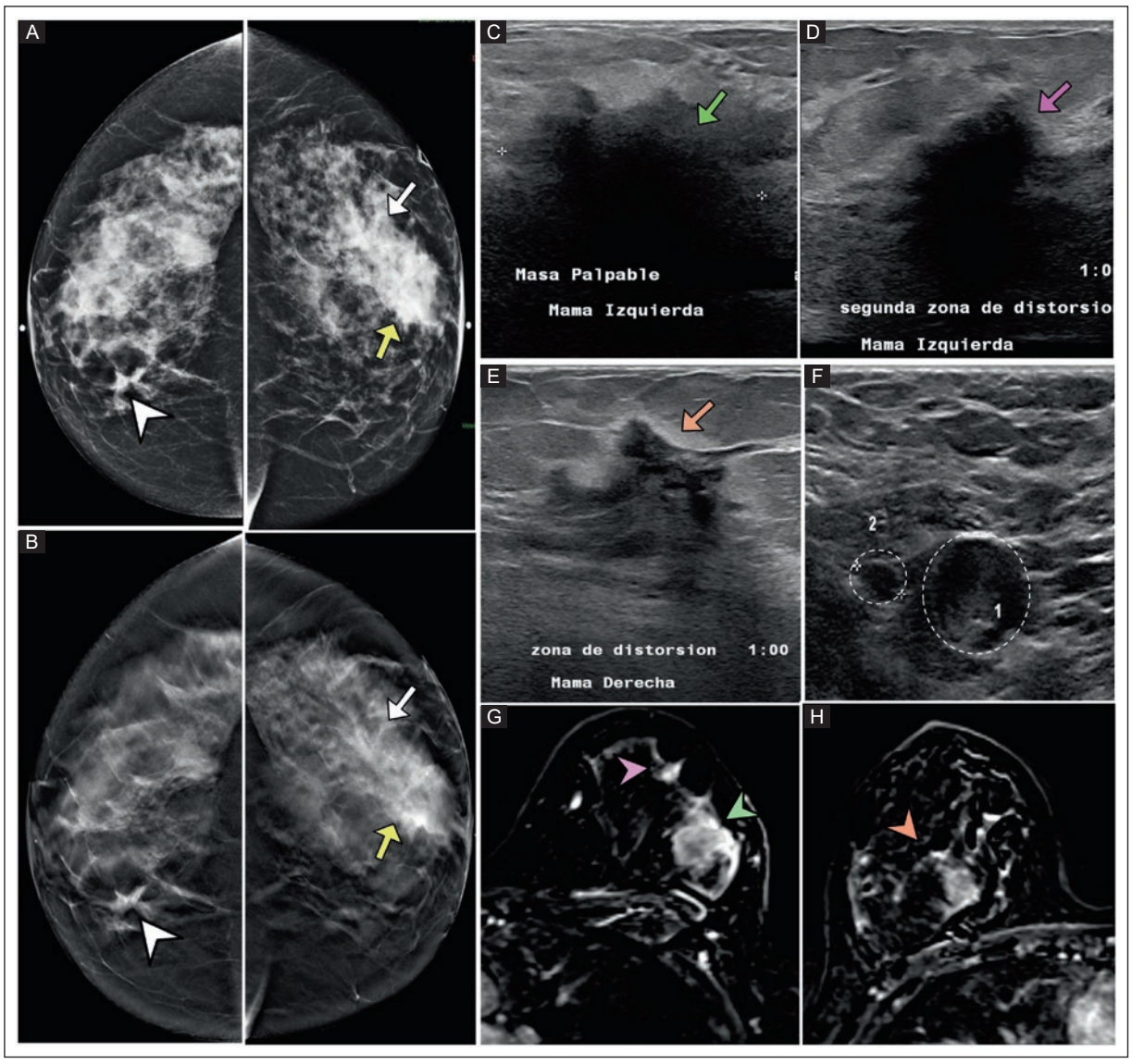

Figure 5. Case 3. A 39-year-old woman diagnosed with acute myeloblastic leukemia in remission who had recently received a bone marrow transplant. She presented with a palpable lump in her left breast. **A-B:** digital mammography and tomosynthesis, CC view, shows an irregular, dense mass with a spiculated margin at the junction of the outer quadrants at 3 o'clock, measuring 3.5 cm in the left breast (yellow arrows). An area of distortion was observed in the UOQ, which was confirmed by tomosynthesis (white arrows). In the right breast, a zone of distortion was identified in the UIQ that is only visible in the CC view and measures 1.7 cm (arrowheads). **C:** US grayscale, an irregular, hypoechoic, spiculated mass, is confirmed in the left breast at 3 o'clock, 7 cm from the nipple, measuring 3.1 × 2.8 cm (green arrow). **D:** an area of distortion in the UOQ measuring 2.0 cm at 1 o'clock and 5 cm from the nipple is seen (purple arrow). **E-F:** an area of distortion is identified in the UIQ of the right breast (orange arrow) at 1 o´clock. Two abnormal lymph nodes with a thick cortex, up to 5 mm, are observed in the left axilla (dotted circles). BI-RADS Category 5. **G:** dynamic MRI axial view shows two enhanced masses of irregular shape and margin in the UOQ of the left breast, measuring 3.5 cm (green arrowhead) and 2.3 cm (purple arrowhead), respectively. **H:** an enhanced mass with irregular morphology and margins is seen in the UIQ of the right breast (orange arrowhead), which is consistent with the area of distortion described on the mammogram.

BI-RADS: Breast Imaging Reporting and Data System; CC: craniocaudal; MRI: magnetic resonance imaging; UIQ: upper inner quadrant; UOQ: upper outer quadrant; US: ultrasound.

of systemic disease[9,10], and the third is recurrence after completing chemotherapy and/or bone marrow transplantation[11]. The latter was the most common clinical presentation (42.4%) in a study by Surov et al.[9].

The most common clinical manifestation is a palpable, painless, unilateral, or bilateral mass, which may or may not be associated with axillary lymphadenopathy (17%). Other less common clinical manifestations

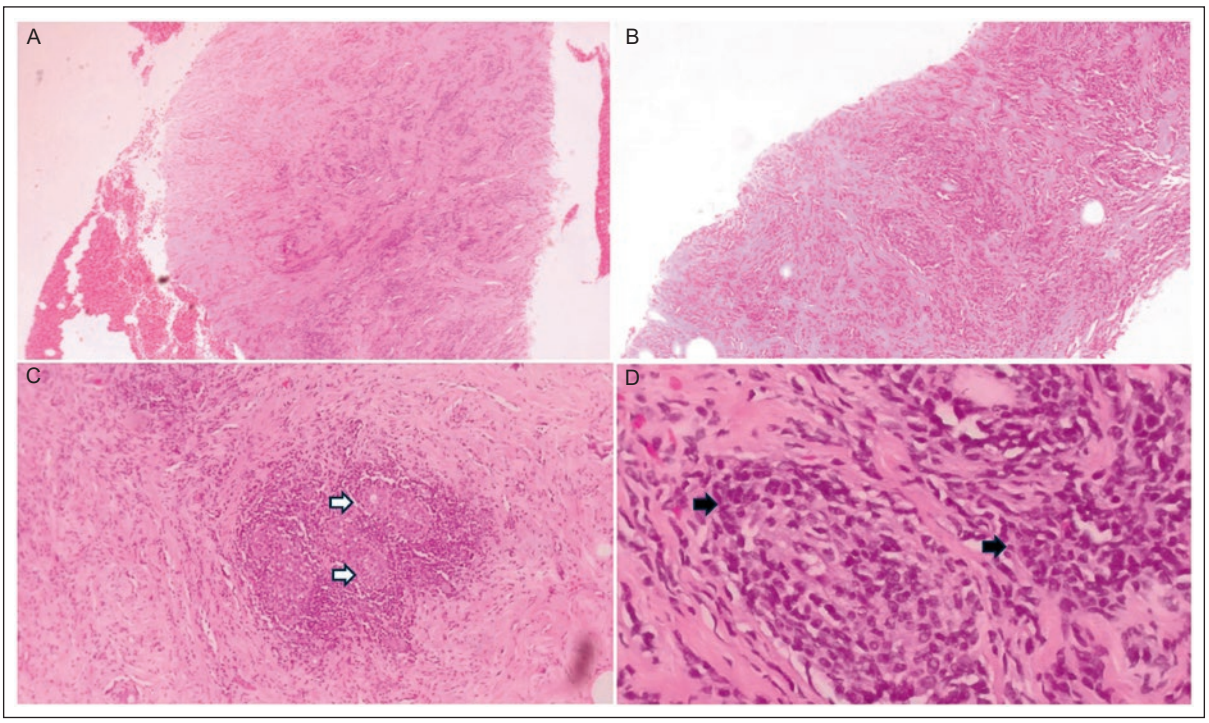

Figure 6. Case 3. A 39-year-old woman diagnosed with acute myeloblastic leukemia in remission and a recent bone marrow transplant presented with a lump in her left breast. Bilateral core biopsies were performed. **A:** H&E 2.5×. Loss of normal breast architecture due to diffuse neoplastic infiltration. **B:** H&E 2.5×. Hematolymphoid proliferation is monomorphous and occupies the entire biopsied tissue. **C:** H&E 10×. Focally preserved glands or residual epithelial elements of the breast parenchyma (white arrows). **D:** H&E 40×. Atypical lymphoid-like cells are infiltrating widely a sclerotic stromal background (black arrows). The histopathologic diagnosis was hematolymphoid infiltration related to acute myeloblastic leukemia.

H&E: hematoxylin and eosin.

in the breast include edema or skin erythema, nipple retraction, or an incidental finding in an asymptomatic patient during screening mammography[9]. Breast imaging findings are not specific for leukemia, and it is important to know the patient's medical history[12].

Mammography

The most common finding in breast infiltration secondary to leukemia is a hyperdense mass, single or multiple, with a non-circumscribed margin. There may also be breast architecture distortion and a diffuse increase in breast density; calcifications are rare. A normal mammogram may be found[2,9].

Ultrasound

The most common finding of secondary infiltration of the breast by leukemia is a single or multiple hypoechoic mass with heterogeneous echotexture and an indistinct or microlobulated margin. There is internal vascularity on color Doppler and a hard pattern on elastography[2,13].

MRI

Few cases of secondary infiltration of the breast by leukemia have been described[9,12]. The lesions are hyperintense in T2 with heterogeneous enhancement after contrast administration. Non-mass enhancement, diffuse distribution, and a heterogeneous pattern have been reported[9,12].

Case 3. Acute myeloblastic leukemia

A 39-year-old woman diagnosed with acute myeloblastic leukemia in remission with a recent bone marrow transplant presented with a lump in her left breast. On mammography, an irregular, dense mass with a spiculated margin was observed in the left breast at the junction of the outer quadrants and an area of distortion in the upper outer quadrant (UOQ), confirmed by tomosynthesis (Figure 5). An area of palpable distortion was identified in the right breast in the anterior third of the UIQ.

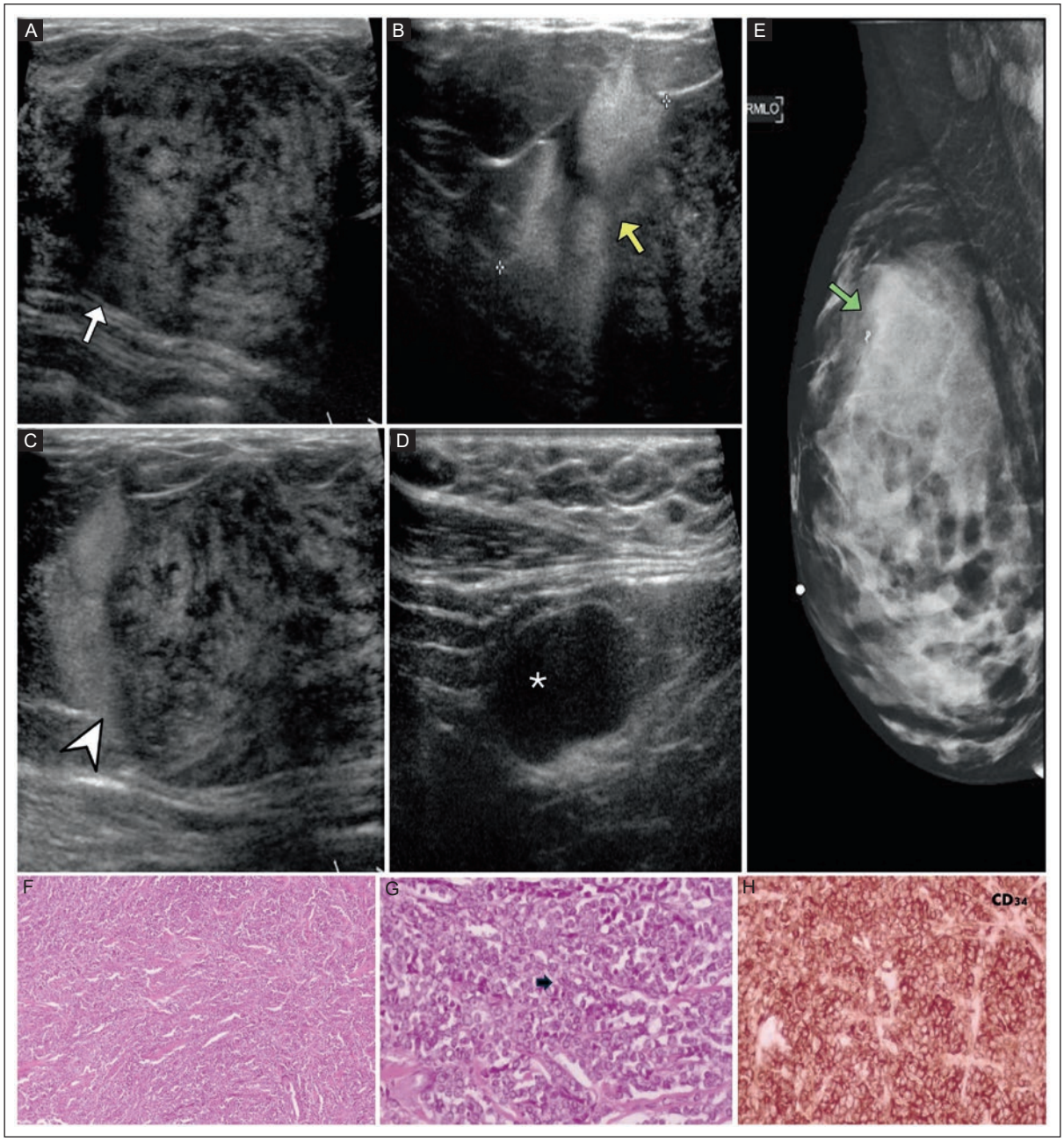

Figure 7. Case 4. A 27-year-old woman recently diagnosed with acute lymphoblastic B leukemia and treated with chemotherapy presented with a lump in the right breast. **A:** US grayscale shows a dominant solid, round mass with heterogeneous echogenicity on UOQ at 11 o'clock, 8 cm from the nipple, measuring 3.7 cm, and with internal vascularity on color Doppler in the right breast (white arrow). **B-C:** an echogenic, non-mass lesion (yellow arrow) measuring 2.7 cm in the anteroposterior diameter is adjacent to and outside this mass. Both findings completely occupy the UOQ (white arrowhead). **D:** three abnormal lymph nodes with thick cortex are seen in the axillary region, markedly hypoechoic with absent fatty hilum (asterisk), the largest with a cortical thickness of 9 mm. BI-RADS Category 4C. A core biopsy of the right breast was performed. **E:** mammogram, MLO view shows an isodense irregular mass after biopsy in the right breast (green arrow). The tissue marker of the biopsy is confirmed at the site. **F:** H&E 10×. Diffuse hematolymphoid neoplastic infiltration in a sheet-like pattern. No native epithelial elements are observed. **G:** H&E 40×. Monomorphic proliferation comprises immature cells of blast-like appearance, medium to large size with open chromatin, basophilic with scant cytoplasm (black arrow). **H:** H&E 40×. IHC staining was diffusely positive for CD34. The histopathologic diagnosis was infiltration of immature/blastic B lymphoid cells related to acute lymphoblastic B leukemia.

BI-RADS: Breast Imaging Reporting and Data System; H&E: hematoxylin and eosin; IHC: immunohistochemistry, MLO: mediolateral oblique; UOQ: upper outer quadrant; US: ultrasound.

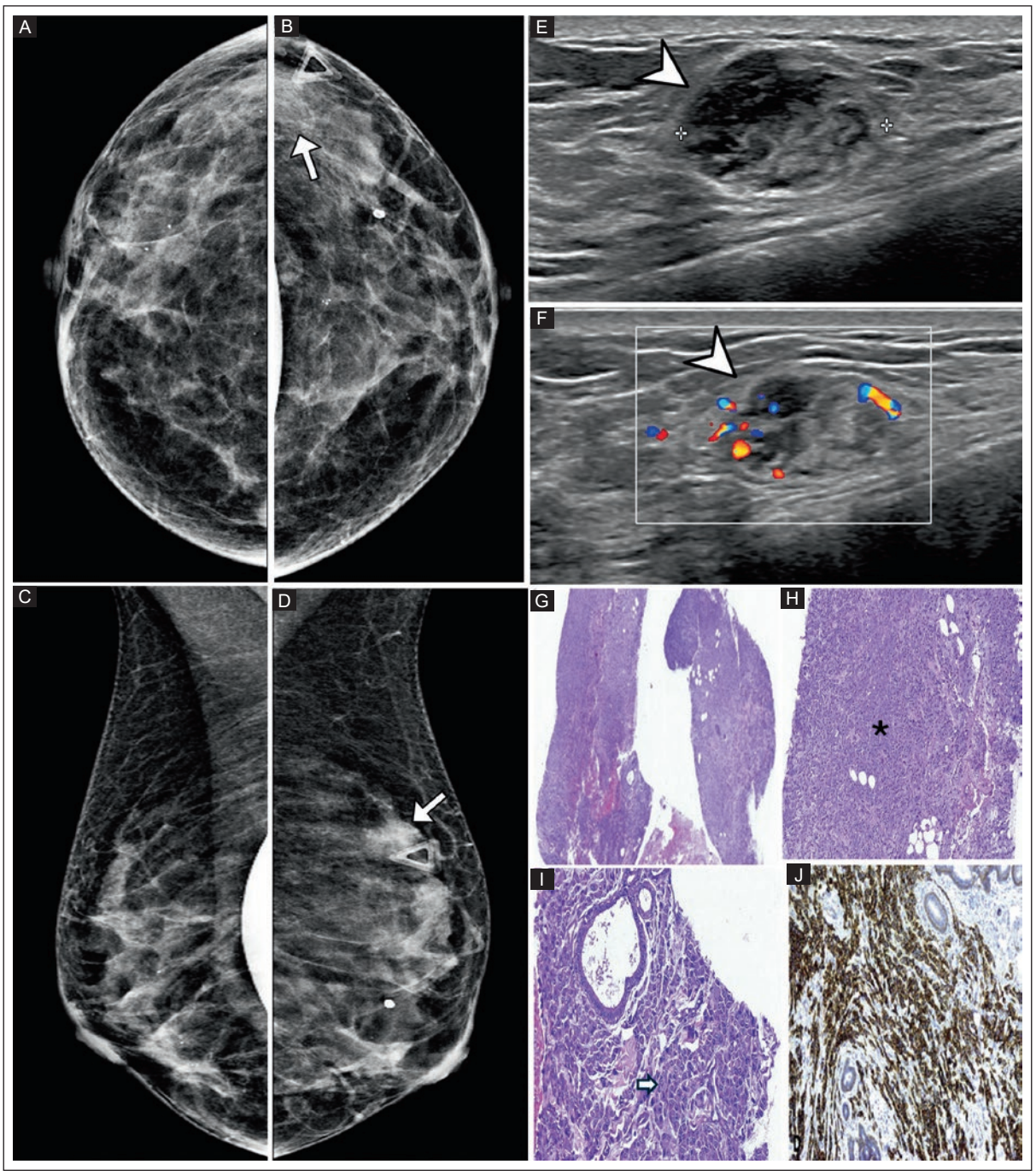

Figure 8. Case 5. A 66-year-old woman with a history of multiple myeloma presented with a lump in the left breast. **A, B, C, D:** mammogram, CC, and MLO views, with Eklund technique. A round isodense mass with an obscured margin was observed in the UOQ, middle third of the left breast (white arrows). **E-F:** US grayscale and color Doppler. A round mass with a heterogeneous echotexture and indistinct margin was confirmed, located in the UOQ at 2 o'clock, 8 cm from the nipple, measuring 1.5 cm with internal vascularity (arrowheads). BI-RADS 4B. A core biopsy of the left breast was performed. **G:** H&E 2.5×. Hypercellular neoplastic proliferation replaces the entire normal breast tissue. **H:** H&E 10×. Diffuse infiltration by plasmacytoid proliferation, discohesive, monoclonal appearance, with sheet and nest pattern (asterisk). **I:** H&E 10×. Monotonous, predominantly plasmacytoid neoplastic cells with abundant basophilic cytoplasm, eccentric nuclei (white arrow), and occasionally with clockwork chromatin (white arrow). **J:** H&E 10×. Strong and diffuse membrane-positive CD138-positive IHC in neoplastic proliferation. The histopathologic diagnosis was plasma cell neoplasm infiltration of the breast.

BI-RADS: Breast Imaging Reporting and Data System; CC: craniocaudal; H&E: hematoxylin and eosin; IHC: immunohistochemistry; MLO: mediolateral oblique; UOQ: upper outer quadrant; US: ultrasound.

Ultrasound of the left breast showed an irregular, hypoechoic mass with a spiculated margin and an area of distortion. An area of distortion was also found in the right breast. Two abnormal lymph nodes were found in the left axilla. BI-RADS Category 5.

On MRI, two irregular enhanced masses were confirmed in the UOQ of the left breast. In contrast, an enhanced mass with irregular morphology and margin in the right breast was confirmed in the UIQ and was consistent with the area of distortion described on the mammogram.

Ultrasound-guided percutaneous biopsies (12G core needle) were performed in both breasts. The histopathologic diagnosis was hematolymphoid infiltration related to acute myeloblastic leukemia (Figure 6).

Case 4. Acute lymphoblastic B leukemia

A 27-year-old woman recently diagnosed with acute lymphoblastic B leukemia and treated with chemotherapy presented with a lump in her right breast. US gray-scale showed a dominant solid, round mass with heterogeneous echogenicity and internal vascularity on color Doppler in the UOQ of the right breast (Figure 7). Three abnormal lymph nodes were identified in the axillary region, the largest with a cortical size of 9 mm. BI-RADS Category 4C.

An ultrasound-guided percutaneous core biopsy (12G core needle) was performed. Mammography after the percutaneous biopsy showed an isodense, irregular mass without calcifications. The tissue marker of the biopsy was also present. The histopathologic diagnosis was acute lymphoblastic B leukemia.

Multiple myeloma

Multiple myeloma is a plasma cell disease that occurs most frequently in the sixth decade of life. Its extramedullary location occurs as a solitary lesion (plasmacytoma) or recurrences in less than 5% of cases[14]. Plasmacytomas are rare and originate mainly in the head and neck but can occur in any organ[2]. One hundred fifty-three cases have been reported in the breast[15].

Mammography

A plasmacytoma is a round or oval mass with a circumscribed margin. Microcalcifications are rare[16].

Ultrasound

Plasmacytoma is a solid mass with variable echogenicity, a circumscribed margin, and variable vascularity[16].

MRI

Hypointense masses are observed in the T1 sequence and hyperintense in T2. After administration of a contrast agent, they are hypervascularized and show ring uptake[16].

Case 5. Multiple myeloma

A 66-year-old woman with a recent history of multiple myeloma presented with a palpable mass in the left breast. Mammography revealed a round isodense mass with an obscured margin in the UOQ of the left breast (Figure 8). Ultrasound confirmed the presence of a round mass with a heterogeneous echotexture and an indistinct margin with internal vascularity on color Doppler. BI-RADS 4B. An ultrasound-guided percutaneous core biopsy (12G needle) was performed, and the histopathologic diagnosis was plasmacytoma of the breast.

CONCLUSION

Hematologic malignancies affecting the breast include lymphomas, leukemias, and multiple myelomas. They most commonly occur as a secondary infiltration of the breast, although they can also be primary breast tumors. Infiltration of the breast can be bilateral, especially in lymphomas and leukemias**.** The most common imaging findings are mass(es), non-mass lesions, or architectural distortion, and, less commonly, diffusely increased breast density. Calcifications are rare. A complete ultrasound examination of the axilla is essential, as axillary lymphadenopathy is often present. MRI with contrast medium allows a better assessment of the extent of the disease. A biopsy is always recommended in breast imaging for accurate diagnosis of suspicious findings in patients diagnosed with a hematologic malignancy.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of individuals. This study complied with the Declaration of Helsinki (1964) and subsequent amendments.

Confidentiality of data. The authors declare they followed their center's protocol for sharing patient data.

Right to privacy and informed consent. Informed consent was not required for this observational study of information collected during routine clinical care.

Use of artificial intelligence. The authors did not use generative artificial intelligence to prepare this manuscript and/or create tables, figures, or figure legends.

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