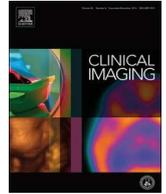




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# Methotrexate (MTX)-associated malignant lymphoma of the bilateral breast: imaging features in comparison to other nipple-areolar tumors

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## ARTICLE INFO

## Keywords:

Nipple-areolar complex  
Methotrexate  
Rheumatoid arthritis  
Breast  
Lymphoma  
Neoplasm

## ABSTRACT

Tumors originating from the nipple-areolar complex of the breast are rare. We herein report the case of a patient with metachronous bilateral areolar methotrexate (MTX)-associated lymphoma. The patient was a 67-year-old woman who presented with a rapidly enlarging tumor in the areolar region of her left breast. She had a long history of rheumatoid arthritis and had taken MTX for many years. On ultrasonography, the tumor showed well-demarcated margins and hyper-vascularity. On magnetic resonance imaging, the tumor showed a homogeneous low-to-moderate signal intensity that was similar to that of the nipple on both T1- and T2-weighted imaging; the diffusion was significantly reduced on diffusion-weighted images. The tumor showed a medium-plateau pattern on dynamic contrast-enhanced imaging. No necrotic change was observed. Based on the imaging findings, we considered the tumor to have originated from the areola. According to the internal homogeneity, the rapid growth and hyper-cellularity, the potential diagnoses included a small round cell tumor (including malignant lymphoma) and a mesenchymal neoplasm (especially leiomyoma or leiomyosarcoma, which frequently originate from the areolar region).

An excisional biopsy of the tumor was performed. The pathological diagnosis was diffuse large, non GC B-cell lymphoma that we suspected was associated with MTX. The tumor shrank rapidly after the withdrawal of MTX.

After three months, we detected a B-cell lymphoma of the same type originating in the contralateral areola. We compared the characteristics of the imaging findings of the MTX-associated lymphoma with the nipple-areolar or periareolar tumors and primary breast lymphoma.

## 1. Introduction

Tumors originating from the nipple-areolar complex (NAC) of the breast are rare. Although Paget's disease and nipple adenoma are often encountered, other tumors are extremely rare, and few reports have described the imaging findings in detail. We herein present the case of a patient with metachronous bilateral areolar tumors, which were diagnosed as methotrexate (MTX)-associated malignant lymphomas. To our knowledge, no other reports have described MTX-associated malignant lymphoma of the breast.

## 2. Case report

We experienced the case of a patient with MTX-associated lymphoma in a left areolar tumor that rapidly grew within a few months and which relapsed three months later in the contralateral areolar

region of the breast. The patient was a 67-year-old woman who visited our hospital with a rapidly enlarging mass in the areolar region of her left breast. She had a long history of rheumatoid arthritis (RA), which had been treated with MTX. A biochemical examination on the first visit, revealed the elevation of her rheumatoid factor (196 IU/ml) and hemoglobin A1c (7.3%) levels. Her other values were normal.

The patient stated that the mass had rapidly grown over a two-month period, and that she had no pain, itchiness or discharge. A physical examination revealed an elastic hard mass in the left areola of her breast. No abnormalities were found on the skin covering the surface of the mass. On mammography, a mass with smooth margins was depicted in the areolar region of her left breast (Fig. 1). The mass, which had a diameter of 3.5 cm, showed well-demarcated margins, heterogeneous hypoechogenicity with posterior echo enhancement (Fig. 2A) and hyper-vascularity on ultrasonography (Fig. 2B). We also evaluated the elasticity by ultrasound elastography. The elastography

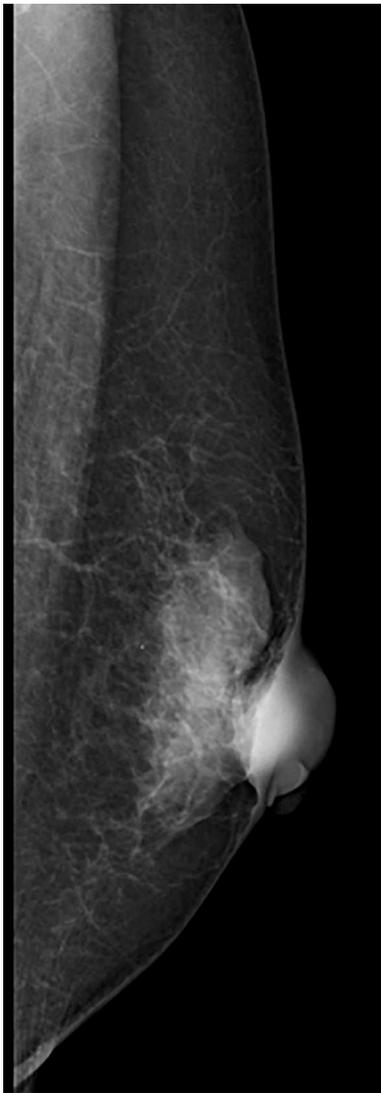
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<https://doi.org/10.1016/j.clinimag.2018.10.004>

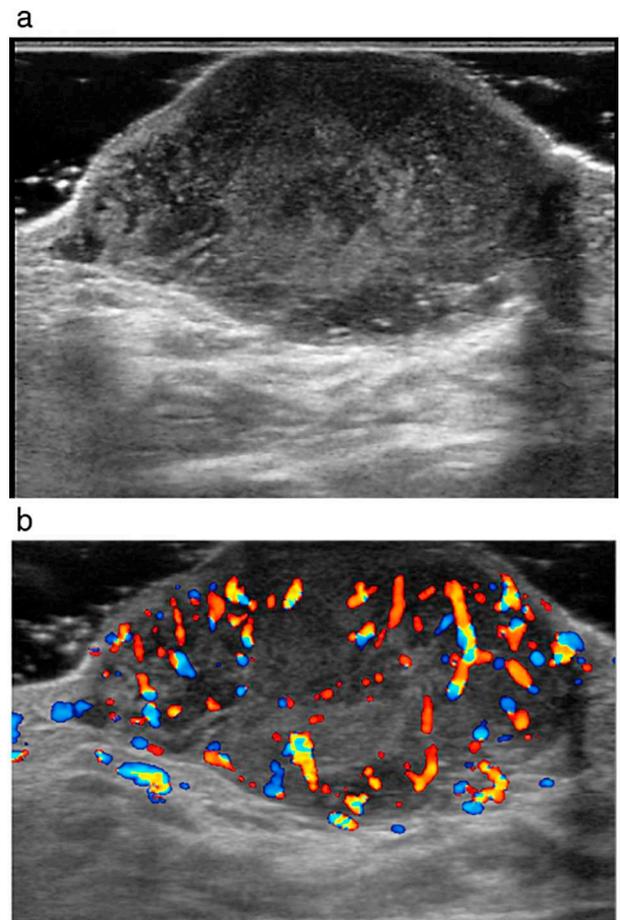
Received 20 June 2018; Received in revised form 6 September 2018; Accepted 2 October 2018

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**Fig. 1.** A well-demarcated mass with smooth margins in the areolar region of the left breast was observed on mammography (MMG).

score (based on the Tsukuba elastography score) of the mass was almost 4 (Fig. 2C). On magnetic resonance imaging (MRI), the mass showed a homogeneous low-to-moderate signal intensity that was similar to the nipple both on T1-(Fig. 3A) and T2-weighted (Fig. 3B) images, and significantly reduced diffusion on diffusion-weighted imaging. No tumor was observed on the contralateral side at the time of the initial examination. The apparent diffusion coefficient (ADC) was  $0.459 \times 10^{-3} \text{ mm}^2/\text{s}$  (Fig. 3C). On a dynamic contrast-enhanced study, the mass showed a medium-plateau pattern and homogeneous enhancement (Fig. 3D, E and F). The mass was localized in the areola, and the continuity with the mammary gland was unclear. No obvious necrotic change was observed. Based on the imaging findings, we considered that the tumor originated from the areolar region. According to the internal homogeneity, the rapid growth and hyper-cellularity, the most likely diagnosis was a small round cell tumor including lymphoma, followed by a mesenchymal neoplasm (especially leiomyoma or leiomyosarcoma which frequently originate from the areolar region). An excisional biopsy of part of the tumor was performed. The pathological diagnosis was diffuse large, non-GC (germinal center) B-cell lymphoma (Fig. 3G). No malignant lymphoma lesions were detected in other sites by whole body FDG PET-CT. We suspected that the tumor



**Fig. 2.** A. On ultrasonography, the tumor showed a well-demarcated margins, heterogeneous echogenicity with posterior echo enhancement. B. The tumor showed hyper-vascularity on color-Doppler ultrasonography. C. The elastography score (based on the Tsukuba elastography score) of the mass was almost 4.

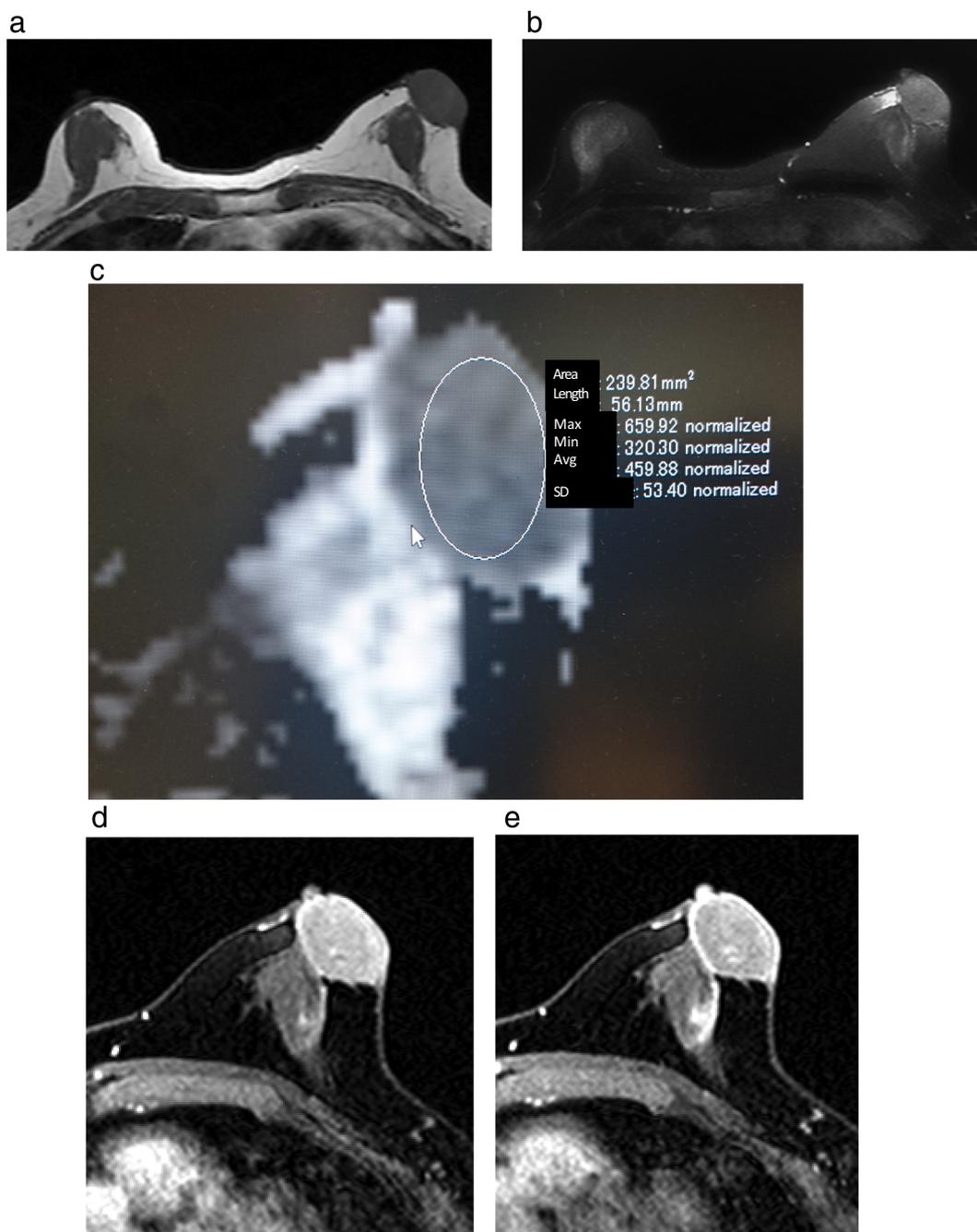
was associated with the administration of methotrexate (MTX). The tumor rapidly shrank both macroscopically and on imaging, including ultrasonography (not shown) after the withdrawal of MTX.

After three months, she became aware of a new mass in the areolar region in the contralateral breast. A well-demarcated hypoechoic mass with posterior echo enhancement and hyper-vascularity was depicted on ultrasonography (Fig. 4). A pathological analysis revealed that the tumor was the same type of B-cell lymphoma. Chemotherapy (R-CHOP regimen: Rituximab, Cyclophosphamide, Hydroxydaunorubicin [doxorubicin], ONCOVIN® [vincristine], Prednisone) was added, after which the tumors rapidly shrank.

### 3. Discussion

RA patients have been reported to have an increased risk of developing non-Hodgkin lymphoma. Kamel et al. [1] reported two cases of lymphoma in patients taking MTX for RA. Both cases were associated with Epstein-Barr virus (EBV) infection. The patients' tumors showed spontaneous regression after the withdrawal of MTX. Since then, a large number of cases involving MTX-related EBV-associated lymphomas have been reported [2–7]. The pathogenesis of RA-associated lymphomas is not clear; however, the increased risk may be related to the high inflammatory activity in patients with rheumatologic disease, the administration of immunosuppressive agents (including MTX) for RA, or EBV infection [4].

To the best of the knowledge, there have been no other cases of



**Fig. 3.** A. T1-weighted MRI.

B. T2-weighted MRI.

The mass showed a homogeneous low-to-moderate signal intensity that was similar to that of the nipple on both T1-(Panel A) and T2-weighted (Panel B) imaging. There was no continuity between the mammary gland and the tumor. No tumor was observed on the contralateral side at the time of the initial examination.

C. The ADC map of the tumor showed significantly reduced diffusion. The mean apparent diffusion coefficient (ADC) was  $0.459 \times 10^{-3} \text{ mm}^2/\text{s}$  ( $b = 1000$ ).

D. Initial phase of dynamic contrast-enhanced MRI (120 s).

E. Delayed phase of dynamic contrast-enhanced MRI (240 s).

F. Kinetic curve of dynamic contrast-enhanced MRI.

The tumor showed a medium-plateau pattern on dynamic contrast-enhanced MRI, and prolonged homogeneous enhancement on delayed-phase imaging.

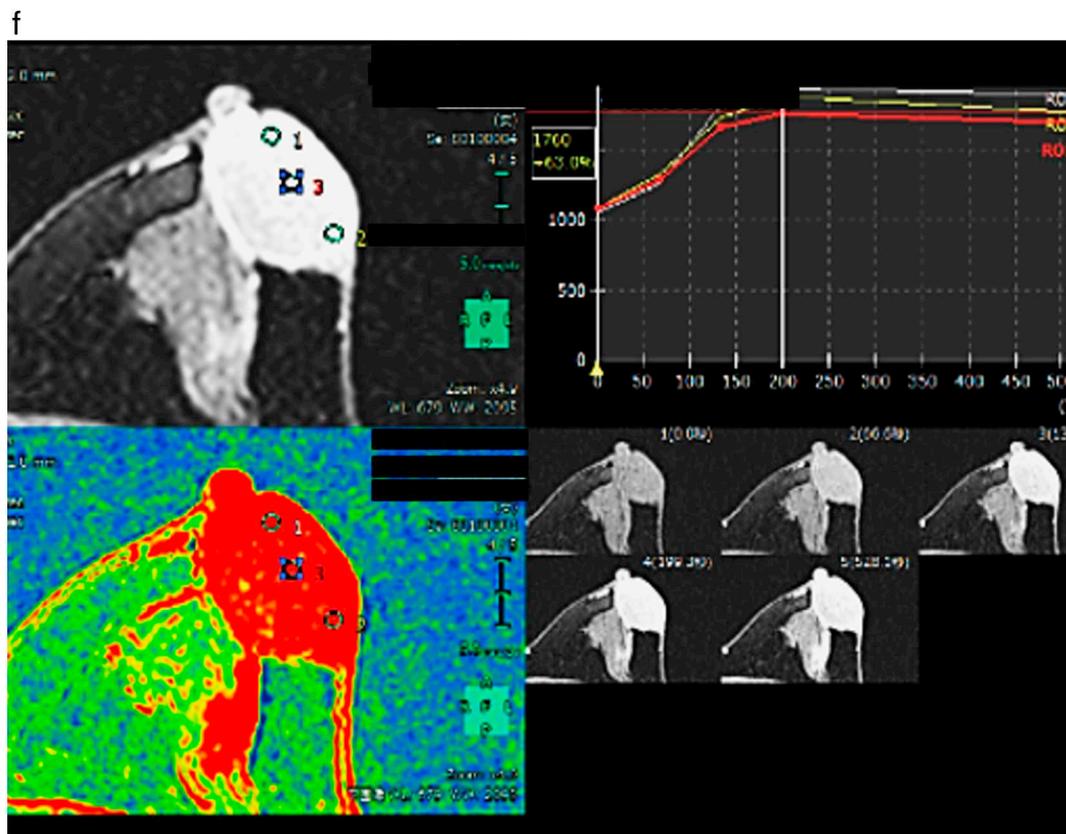
G. Histologically, the tumor was composed of a diffuse proliferation of large lymphoid cells (HE staining,  $\times 100$ ).

Immunohistochemically, these cells were positive for CD20 and CD79a; thus, the tumor was diagnosed as diffuse large non GC (germinal center) B-cell lymphoma.

metachronous MTX-related lymphoma occurring in the bilateral NAC. Such cases may be difficult to diagnose; thus, we compared our case with the reported cases in order to clarify the points of discrimination from other reported tumors originating from the NAC (Table 1).

**4. Comparison of the characteristics of the imaging findings of the present case with nipple-areolar tumors and primary breast lymphoma**

Two common lesions originating from the areolar region are Paget's disease and nipple adenoma. Other reported lesions, which have



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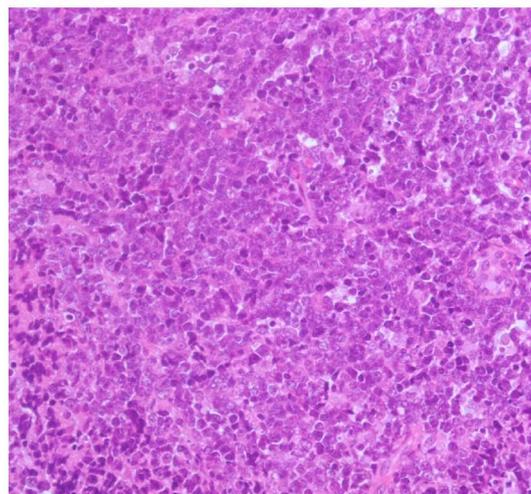


Fig. 3. (continued)

originated in the NAC, have included syringomatous adenoma, melanoma and leiomyoma or leiomyosarcoma [8]. Furthermore, pleomorphic adenoma usually originates in the periareolar region. Additionally, intraductal papilloma originates in the lactiferous duct near the nipple.

Most Paget's disease patients present with eczematous or erythematous changes and occasionally show the redness of the nipple with frank ulceration [9]. The underlying ductal carcinoma *in situ* may be demonstrated by MRI [10]. Imaging does not usually detect a huge mass. On mammography, almost half of the patients show negative findings [10].

Clinically, nipple adenoma is an uncommon condition of the breast. It often presents as a palpable nipple nodule and skin erosion; it can mimic a case of Paget's disease [11]. The lesion of our case showed

early strong rim enhancement and washout of the internal part on dynamic contrast-enhanced MRI. These findings reflected the surrounding dense collagenous change with intermingled large vessels, and weak fibrosis of the internal part [11]. In comparison to the imaging finding of MTX-associated lymphoma, the internal enhancement of the nipple adenoma was inhomogeneous.

Intraductal papilloma also shows early enhancement. However, the tumor is likely to show early homogeneous or delayed heterogeneous rim-like enhancement [12].

Syringomatous adenoma of the nipple is a rare neoplasm of the breast. To our knowledge, only 34 cases of syringomatous adenoma have been reported [13]. Despite its benign behavior, syringomatous adenoma usually shows infiltrative proliferation into the adjacent tissue [14]. AlSharif et al. reported a case of syringomatous adenoma that

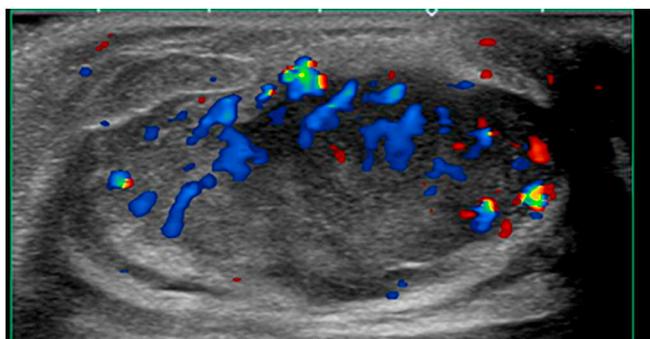


Fig. 4. After three months, ultrasonography depicted a well-demarcated hypoechoic mass with posterior echo enhancement and hyper-vascularity in the periareolar region of the contralateral breast.

showed nipple enlargement with microcalcification that was detected by ultrasonography and mammography [15]. There have been no reports of the MRI findings of syringomatous adenoma of the nipple; however, the infiltrative feature may be the most important finding for distinguishing syringomatous adenoma from MTX-associated lymphoma.

We also experienced a pleomorphic adenoma and a leiomyoma. Pleomorphic adenoma is a rare tumor of the breast that is morphologically similar to pleomorphic adenoma of the salivary glands that tends to originate in periareolar region [16]. The tumor showed a strong high signal intensity on T2-weighted MRI, which is a characteristic of myxoid stroma as well as salivary gland tumors.

Leiomyoma of the breast is a rare benign tumor that shows distinct smooth-muscle differentiation. Most lesions occur superficially in the

skin, especially around the NAC [17]. Since the smooth muscle cells are densely proliferated, the tumor exhibits a low signal intensity, similar to skeletal muscles on T2-weighted MRI. The MRI findings, especially the signal intensity on T2-weighted imaging of these tumors, are different from those of MTX-associated lymphomas.

In our search of the literature, we found no reports of imaging findings of melanoma in the NAC.

In the present case, the ultrasonography and MRI findings both reflected the pathological features of the tumor. The tumor showed hyper-vascularity with internal homogeneity on MRI as well as marked hyper-cellularity on DWI.

There have been few reports on the imaging findings in malignant lymphoma of the breast, which is also a rare tumor. In 2013, we reported the detailed MRI findings of primary breast lymphoma [18]. The imaging features of the reported case were similar to those of the present case.

Based on the internal homogeneity and enhancement, the high signal intensity (reflecting the uniform proliferation of tumor cells) on DWI, the lack of severe invasion into the surrounding tissue and the patient's clinical information (the use of MTX for the treatment of RA), we considered that it was possible to correctly diagnose the patient's tumor. The accumulation of further cases and a detailed comparison of images will be necessary to judge the diagnostic usefulness of the above-mentioned imaging findings.

### 5. Conclusion

We reported the case of a patient with rare MTX-associated lymphomas in the areolar region of the bilateral breast. The imaging features of the tumor resembled those observed in patients with primary breast lymphomas. MTX-associated lymphoma should be considered

Table 1  
Comparison of other tumors and MTX-associated lymphoma in nipple-areolar region

Tumor	Shape	Margin	Clinical features	Imaging findings
MTX-associated lymphomas (presented case)	Oval	Smooth	Rapid growth No nipple discharge Normal skin	MMG: Mass with smooth margins US: Heterogeneous mass with posterior echo enhancement MRI: Homogenous fashion with high intensity on DWI Homogenous prolonged enhancement
Nipple adenoma	Round or Oval	Smooth	Enlargement of nipple Nipple discharge Nipple erosion	MMG: Enlargement of nipple Mass with smooth margins US: Well demarcated mass in the nipple MRI: Early rim-enhancement with inhomogenous fashion
Paget's disease	(not applicable)	Ill-defined	Nipple redness or scaling, frank ulceration	MMG: Nipple and areolar thickening Almost half are negative US: Not visualized MRI: The underlying DCIS may be demonstrated
Syringomatous adenoma	(not applicable)	Ill-defined	A firm discrete mass in the nipple limited in the dermis	MMG/US: Multiple pleomorphic microcalcifications
Intraductal papilloma	Round or Oval	Smooth	Nipple discharge Palpable mass	MMG: usually not visualized Round to oval mass US: Intraductal mass near the nipple Cystic and solid mass MRI: Early homogeneous or delayed rim-enhancement
Pleomorphic adenoma	Multinodular Lobulated	Smooth	Palpable mass in periareolar region	MMG: lobulated mass with smooth margins US: Lobulated mass with smooth margins MRI: Strong high signal intensity on T2-weighted image reflected the myxoid stroma
Leiomyoma	Round or Oval	Indistinct	Most occur in the skin around the NAC Small (0.5 to 1 cm)	MMG: Not visualized US: hypoechoic mass in the nipple MRI: Low-signal intensity similar to skeletal muscle on T2-weighted image
Primary lymphoma	Oval or Lobulated "Cerebroid"	Smooth or irregular	Normal or thickening of skin	MMG: lobulated mass with smooth margins US: Oval or Lobulated hypoechoic mass with posterior enhancement MRI: Homogenous fashion with strong high intensity on DWI Homogeneous early and prolonged enhancement

Abbreviations: MTX, methotrexate, MMG, mammography, US, ultrasonography, MRI, magnetic resonance imaging, NAC, nipple-areolar complex, DWI, diffusion-weighted imaging.

when RA patients receiving MTX present with rapidly growing tumors that display internal homogeneity and a high cellular density.

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