

A rare case of bilateral breast lobular carcinoma coexisting with primary breast follicular lymphoma

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ABSTRACT

CLINICAL PRACTICE POINTS

- Co-existence of breast cancer and lymphoma is a rare condition. A few cases of synchronous breast ductal carcinoma and lymphoma have been reported in the literature. However, to our knowledge this is the first case report of a bilateral breast lobular carcinoma co-presenting with follicular lymphoma.
- Little is known about the pathophysiology of synchronous cancers of different tumor types, especially solid tumors co-existing with hematologic malignancies. In-depth review of these cases can shed light on underlying mechanism leading to synchronous cancer development.

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1. Introduction

Breast cancer is the most common cancer and the leading cause of cancer death in women worldwide [1]. The high rate of breast cancer incidence and prolonged survival of patients have resulted in an increase in metachronous breast cancer or other synchronous cancers in this patient population [2]. However, synchronous bilateral breast cancer is still an uncommon diagnosis. In one series, incidence of synchronous bilateral breast cancer was reported to be 2.1% [3]. Histology of these cancers is more likely to be infiltrating lobular carcinoma than ductal carcinoma [4].

The incidence of FL is 20% to 30% of all lymphomas, which makes it the second most common type of non-Hodgkin lymphoma (NHL) [5].

Breast cancer is the most common cancer after radiotherapy for early-stage Hodgkin lymphoma [6–8]. However, synchronous and metachronous breast cancer and follicular lymphoma is a rare condition, and the other reported cases are related to ductal breast cancer [9–13]. We report the first case of a synchronous incidence of follicular lymphoma with invasive lobular carcinoma of the breast.

2. Case report

A 71-year-old Caucasian female presented to the hematology/oncology clinic with upper outer left breast lump detected on screening mammography in December 2015. The patient had a more than 30-pack-year smoking history and had quit smoking in 2012. Her

past medical history was significant for atrial fibrillation treated with rivaroxaban and flecainide and hypertension treated with hydrochlorothiazide, amlodipine, and metoprolol. She had been on conjugated estrogens since 1997 when she underwent a TAH/BSO for multiple cysts. She did not have any breast-related or constitutional symptoms. She had chronic arthritic pain, which had been stable. She denied any new bone pain, weight loss, decreased appetite, fever, chills, or night sweats. Family history was significant only for lung cancer in the patient's brother who was a smoker. There was no known family history of breast cancer or hematologic malignancies.

On physical examination, there was a painless, firm mass in the upper outer quadrant of the left breast. The rest of the physical examination was unremarkable. Ultrasound of the left breast showed a hypoechoic shadowing mass measuring 2.2 × 0.9 × 1.6 cm at the posterior 2 o'clock location and a small complicated cyst measuring 6 mm at the 3 o'clock location. In the axilla, several lymph nodes with mild cortical thickening measuring up to 6 mm were identified. Ultrasound-guided core biopsy of the lesion revealed invasive moderately differentiated (Elston/Nottingham score 2/3) mammary carcinoma with features of an invasive lobular carcinoma. The tumor was ER/PR positive both > 90% and HER-2 negative with ki-67 of approximately 15% to 20%.

Bilateral MRI of the breast revealed a mirror-image possible malignancy measuring 1.6 cm in the right breast at the 10 o'clock location. Ultrasound-guided core needle biopsies revealed invasive

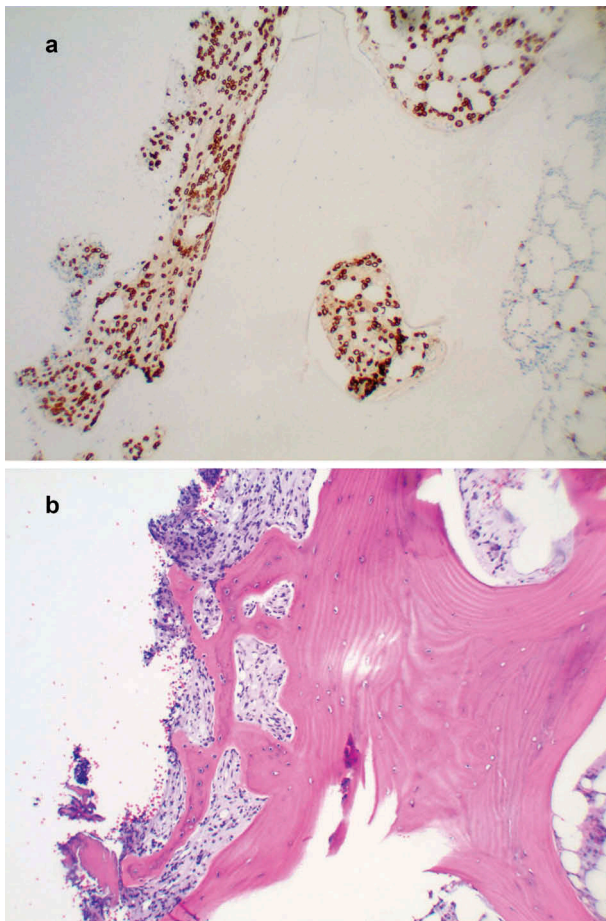


Figure 1. Histological specimens of bone marrow biopsy with. (a) cytokeratin and (b) H and E staining revealed bone metastasis of breast cancer.

moderately differentiated lobular carcinoma associated with a focus of in situ ductal carcinoma (DCIS), cribriform type, intermediate nuclear grade with central necrosis and in situ lobular carcinoma (LCIS). CT of the chest, abdomen and pelvis raised the question of possible skeletal metastasis but was nonspecific. Radiology recommended nuclear medicine bone scan, which was performed and was negative for malignancy.

The patient underwent bilateral partial mastectomy in January 2016. The right side showed a 2.7-cm grade 2 invasive lobular carcinoma that was ER/PR positive (>90%, strong nuclear staining), HER-2 negative (staining intensity of 0) in IHC staining. All margins were clear. Four sentinel lymph nodes were negative for malignancy. The 21-gene recurrence score was low at 13. She was found to have exactly the same findings on the left side with a 2.7-cm invasive lobular cancer, which was grade 2, ER/PR positive, and HER-2 negative. Four sentinel lymph nodes were negative for malignancy.

The left sub-mammary mass was completely excised and was found to be follicular lymphoma (WHO grade 3 A). Immunohistochemical stains for CD3, CD20, CD21, CD23, CD10, BCL2, BCL6, and

Ki-67 were performed. The CD20 was strongly positive on B-lymphocytes. These B-cells were also positive for CD10 and BCL6. BCL-2 showed a two-toned pattern of expression with dim positivity on nodular B-cells and bright positivity on background T-cells. CD21 and CD23 highlighted follicular dendritic meshwork. CD3 highlighted T-cells. Ki-67 was low (approximately 20%) in the majority of the nodular B-cell areas, although there are focal nodules with high proliferation index, corresponding to residual germinal centers. CBC showed white blood cell count 5.8×10^3 cells/ μL , hemoglobin 12 g/dL, platelets 383×10^3 cells/ μL ; BMP values were within normal limits.

Bone marrow biopsy performed for staging evaluation of follicular lymphoma revealed metastatic lobular breast carcinoma (Figure 1), which was ER/PR positive and HER-2 negative. On the Her2/neu immunohistochemical stain, there was some faint, predominantly incomplete tumor cell membrane staining, but the amount (although difficult to accurately quantify) of staining appeared to correlate best with the 1+ category.

Bone marrow and bilateral breast carcinomas were morphologically similar. There was no histologic, immunohistochemical, or immunophenotypic evidence of follicular lymphoma in the bone marrow. PET/CT scan showed left lower lobe pleura uptake with SUV of 4.1, suspicious for pleural metastases. Multiple sclerotic lesions were noted on the lower thoracic spine, lumbar spine, pelvic bones, sacrum, and femoral head.

The patient did not need any systemic treatment for follicular lymphoma because the left breast was the only site of disease and it was completely excised. For metastatic breast cancer, the patient was started on letrozole 2.5 mg daily and palbociclib 125 mg daily 21/28 days. Follow-up CT scans since then have shown stable diffuse osteoblastic lesions. Serial CT images also have not shown any evidence of recurrent lymphoma or suspicious lymphadenopathy. Follow-up chest CT scan with IV contrast on 11 April 2017, showed focal thickening at the posterior right mid lower pleura was markedly diminished compared to prior. The focal thickening was completely resolved on repeat CT scan on 12 July 2017. CA 27–29, which was initially elevated, was normalized and remained within normal limits. The patient is tolerating the treatment with a good performance status.

3. Discussion

Primary breast lymphoma is a rare condition; however, its incidence has increased from 0.66 (1975 to 1977) to 2.96 (2011 to 2013) per 1,000,000 women in USA [14]. Synchronous presentation of breast cancer and follicular lymphoma is rare. Limited case reports

have documented this co-incidence. In these case reports the breast cancer type is mainly ductal carcinoma. We report the first case report of synchronous incidence of follicular lymphoma and bilateral lobular carcinoma of breast. Many of the previous case reports noted involvement of axillary sentinel nodes with non-Hodgkin lymphoma, which was diagnosed through sentinel node biopsy. In our case, axillary lymph nodes did not show any evidence of breast cancer or lymphoma.

Considering the fact that primary breast lymphoma occurs mainly in women [14], some studies have proposed that estrogen plays a role in some forms of the disease [15]. However, the exact role of estrogen and its derivatives in lymphoma and lymphocyte survival is still controversial. Estrogen plays a pivotal role in regulation of the genes that are responsible for B cell growth, survival and apoptosis including Bcl-2, c-fos, c-myc, P21 and P53. Ladikou and Kassi [16] provided the evidence that although estrogen is an antiapoptotic factor in normal lymphocytes, it can induce apoptosis in cancerous B cells in Burkitt lymphoma and CLL cell lines. However, no study has yet shown the effect of estrogen in follicular lymphoma. More studies are needed to further investigate this question.

Viral origin of cancers has been suggested as one of the mechanisms of synchronous carcinomas. In 1936, Bittner identified an agent that can cause breast cancer in mice [17]. This agent was later identified as mouse mammary tumor virus (MMTV). MMTV was found to be an RNA virus that can cause insertional mutations and activation of many proto-oncogenes in human organs. Other studies reported MMTV-like ENV DNA sequences in more than one third of breast cancer tissues [18,19]. On the other hand, in vitro studies in animal models have shown that MMTV not only causes mammary tumors in inbred strains of mice, but it also induces lymphomas in these animals [20–22].

One of the other hypothesis regarding multiple primary malignant neoplasm, as in our case, is that during fetal life the cells with somatic mutations migrate to different sites and organs of the body and later on, during adulthood, these cells become malignant, possibly secondary to environmental exposure [23,24].

It has been also shown that neoplastic lymphoid cells could reduce adhesion of breast cancer malignant cells to the endothelial layer of the axillary lymph nodes and could increase lymphatic dissemination of breast cancer cells [25]. The fact that our patient did not have any evidence of axillary lymph node involvement of breast carcinoma or lymphoma supporting the hypothesis that neoplastic lymphoid cells have decreased the adhesion of breast cancer

malignant cells to the axillary lymph nodes and have facilitated breast cancer metastasis to the bones.

In conclusion, primary breast lymphoma and its coincidence with breast cancer is rare, but this case and other case reports suggest that more detailed studies are required to identify the risk factors and optimal treatment modalities in these patients.

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