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Case Report

Synchronous bilateral non-Hodgkin's diffuse large B-cell lymphoma of the breast and left breast invasive ductal carcinoma: a case report and review of literature

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Abstract: Lymphoma of the breast is unusual, and synchronous bilateral lymphoma and carcinoma of the breast is extremely rare. We present the case of a 51-year-old woman who found a mass in her left breast. Ultrasound scan findings revealed nodules at the 2 o'clock position in her left breast and focal dilation of the duct at the 8-9 o'clock and 10 o'clock position in her right and left breasts, respectively. A left breast ultrasound-guided core needle biopsy and right breast segmental excisional biopsy were performed. Pathological and immunohistochemical examination revealed left breast invasive ductal carcinoma and right breast diffuse large B-cell lymphoma of the non-germinal center type. Pathological examination of the left breast modified radical mastectomy specimen revealed synchronous invasive ductal carcinoma (grade III) and diffuse large B-cell lymphoma. The patient received chemotherapy and bone marrow transplantation in another hospital. Based on a review of the relevant literature, we discuss the diagnosis, clinical features, treatment, and prognosis of synchronous breast lymphoma and invasive ductal carcinoma.

Keywords: Breast lymphoma, invasive ductal carcinoma, diffuse large B-cell lymphoma, synchronous tumor

Introduction

Lymphoma can occur in various organs, but cases of synchronous lymphoma with other tumors are relatively rare, and their occurrence in the same organ is extremely rare. To date, reported cases of synchronous lymphoma and other neoplasms in the same organ include those of the stomach, thyroid, kidney, throat, and tonsils [1-7]. There have only been seven cases of synchronous lymphoma and carcinoma in the breast reported [8-14], among which only one case involved synchronous bilateral breast lymphoma and unilateral breast carcinoma [8]. Here, we describe the case of a 51-year-old woman with synchronous bilateral non-Hodgkin's diffuse large B-cell lymphoma and invasive ductal carcinoma of the left breast.

Case report

The 51-year-old female patient found a painless mass measuring approximately 3 × 2 cm in her left breast 15 days before we examined her. No skin dimples, erythema, rashes, or Peau d'orange ulcers were noted, and there was no nipple retraction or discharge. Neither the bilateral axillary lymph nodes nor the bilateral supraclavicular lymph nodes were palpable. Past medical history included hyperthyroidism for the preceding 20 years and diabetes over the last year. The patient had been taking thiamazole consistently up until one year ago, when she stopped. She was also taking metformin and glimepiride, and her blood glucose level was under control. She had no previous history or family history of breast cancer.

An ultrasound scan performed in our hospital showed nodules at the 2 o'clock position in the left breast (**Figure 1A**), for which an ultrasound-guided core needle biopsy was performed. The scan also showed focal dilation of the duct in the 8-9 o'clock position in the right breast (**Figure 1B**) and the 10 o'clock position in the left breast (**Figure 1C**), prompting a combination of ductoscopy and other investigations.

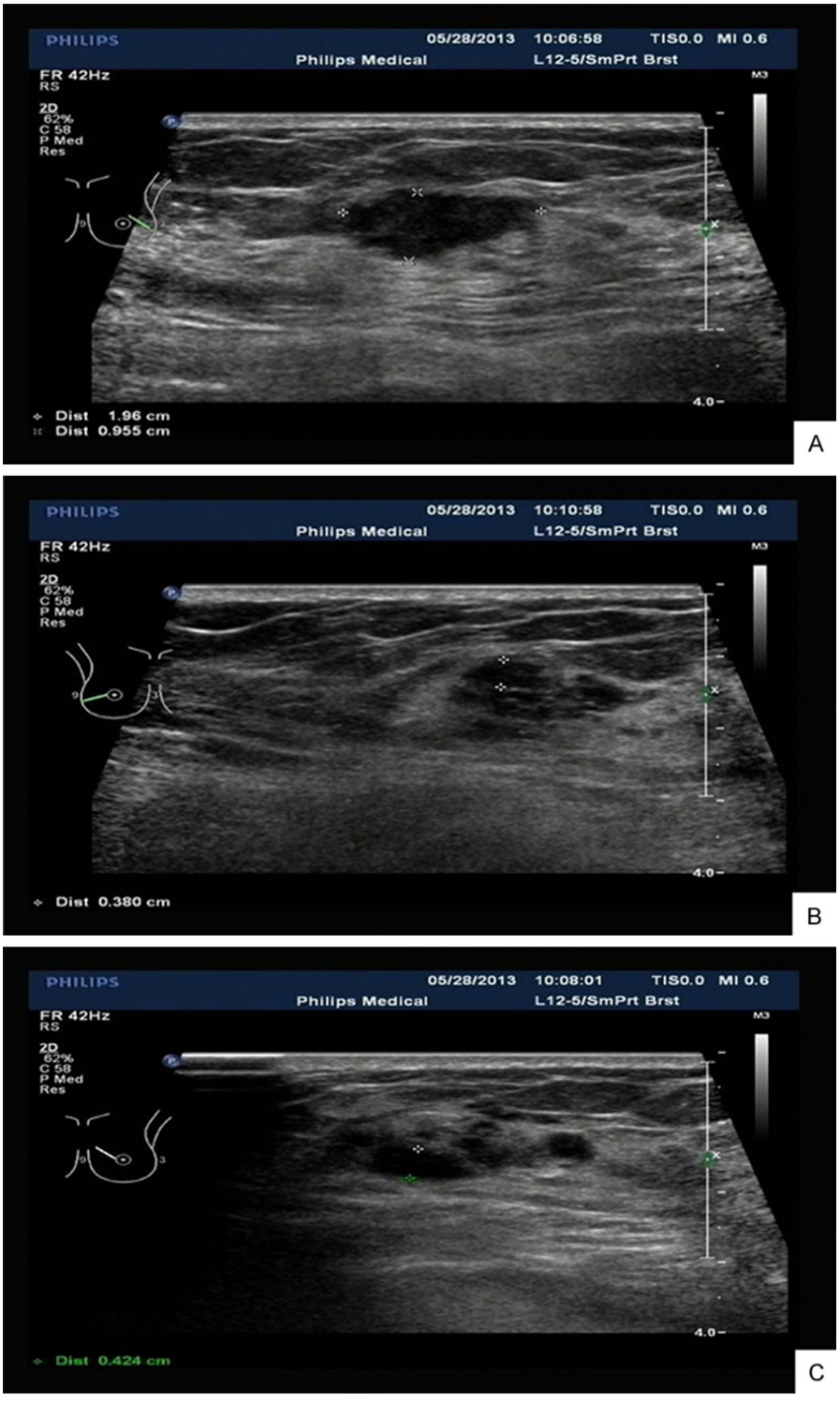

Figure 1. A. A hypoechoic nodule sized 2.0 × 1.0 cm can be seen in the 2 o'clock position of the left breast, about 4 cm from the nipple, with a clear border, irregular shape, and no significant blood flow. B. Periphery of the right breast tissue in the 8-9 o'clock position, revealing focal disorder in the fibrous tissue structure and varicose dilatation of the ductules (up to 3.8 mm in width), which are filled with indistinct hypoechoic matter and have no significant blood flow. C. Periphery of the left breast tissue in the 10 o'clock position, revealing focal disorder in the glandular tissue structure, and varicose dilatation of the ductules (up to 4.2 mm in width), which are filled with indistinct hypoechoic matter and have no significant blood flow.

The patient also underwent a right breast open biopsy and ultrasound-guided core needle biopsy of the left breast, the results of which suggested lymphoma and breast carcinoma. She subsequently underwent left modified radical mastectomy with ipsilateral axillary lymph node dissection. A postoperative bone scan showed no evidence of tumor metastasis. She received subsequent chemotherapy in another hospital and bone marrow stem cell transplantation in February 2014, and she is currently in good health.

Pathological findings

The pathology results for the ultrasound-guided core needle biopsy in the 2 o'clock position of the left breast confirmed invasive ductal carcinoma, and examination of the segmental excisional biopsy taken at the 8-9 o'clock position of the right breast suggested non-Hodgkin's diffuse large B-cell lymphoma of the non-germinal center type (**Figure 2A**).

Breast and axillary adipose tissue sized 28 × 25 × 4 cm

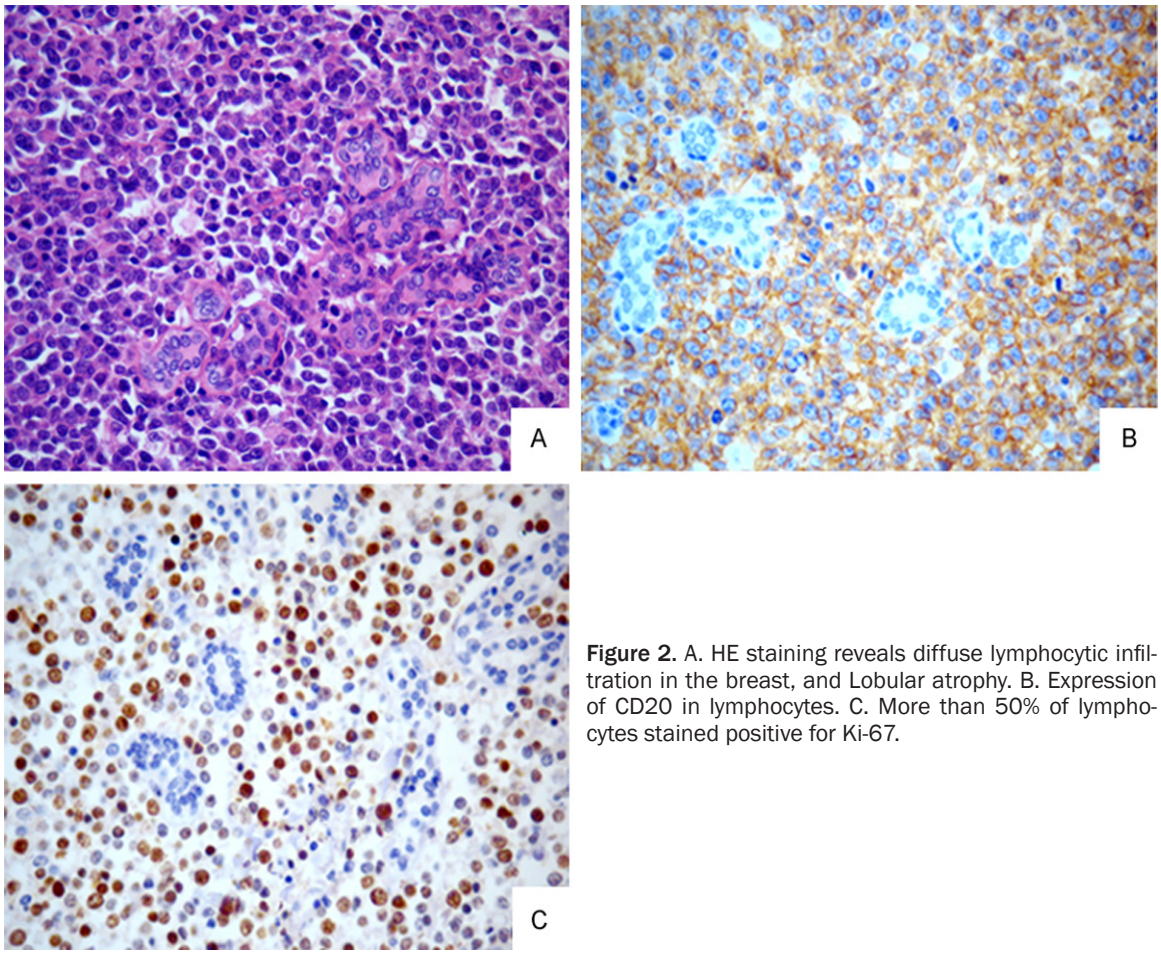

Figure 2. A. HE staining reveals diffuse lymphocytic infiltration in the breast, and Lobular atrophy. B. Expression of CD20 in lymphocytes. C. More than 50% of lymphocytes stained positive for Ki-67.

was excised during radical mastectomy of the left breast, together with spindle shaped attached skin (14 × 6 cm). A tumor was visible in the 2 o'clock position, 2 cm in diameter, and another tumor was present in the 10 o'clock position, 2.5 cm in diameter. Pathological findings for the tumor in the 2 o'clock position (**Figure 3A**) were of a solid mass, cell atypia and a paucity of glandular structure, with many mitotic cells. On this basis, it was diagnosed as poorly differentiated invasive ductal breast carcinoma (stage III). Microscopic examination of the tumor in the 10 o'clock position of the left breast revealed diffuse lymphocytic infiltration within the breast tissue, with medium sized, atypical cells. Lobular atrophy was also evident. This second tumor was diagnosed as non-Hodgkin's diffuse large B-cell lymphoma of the non-germinal center type.

Immunohistochemical findings

The breast carcinoma in the 2 o'clock position of the left breast was positive for estrogen receptor (ER) (**Figure 3B**), and progesterone receptor (PR) (**Figure 3C**), and strongly positive for CerbB-2 (**Figure 3D**). The lymphoma in the 8-9 o'clock position of the right breast and in the 10 o'clock position of the left breast stained negative for CD3, CD21, BCL-6, CD10, TDT, Cd23, CyclinD1, CD5, and CK. However, it stained positive for CD20 (**Figure 2B**), partially positive for MUM-1, and partially positive for BCL-2. More than 50% of the cells stained positive for Ki-67 (**Figure 2C**).

Discussion

Lymphoma can occur in many parts of the body, but only rarely in the breast tissue as a primary or secondary tumor. Primary breast lymphoma accounts for only 0.04-0.5% of all breast malignancies [15]. The concept of primary breast lymphoma was first proposed by Wiseman and Liao in 1972 [16], who also outlined the diagnostic criteria for this malignancy. The four major criteria are that: 1) there should be sufficient tissue for pathology; 2) the infiltration area of lymphoma should be closely associated with the breast tissue; 3) lymphoma should not

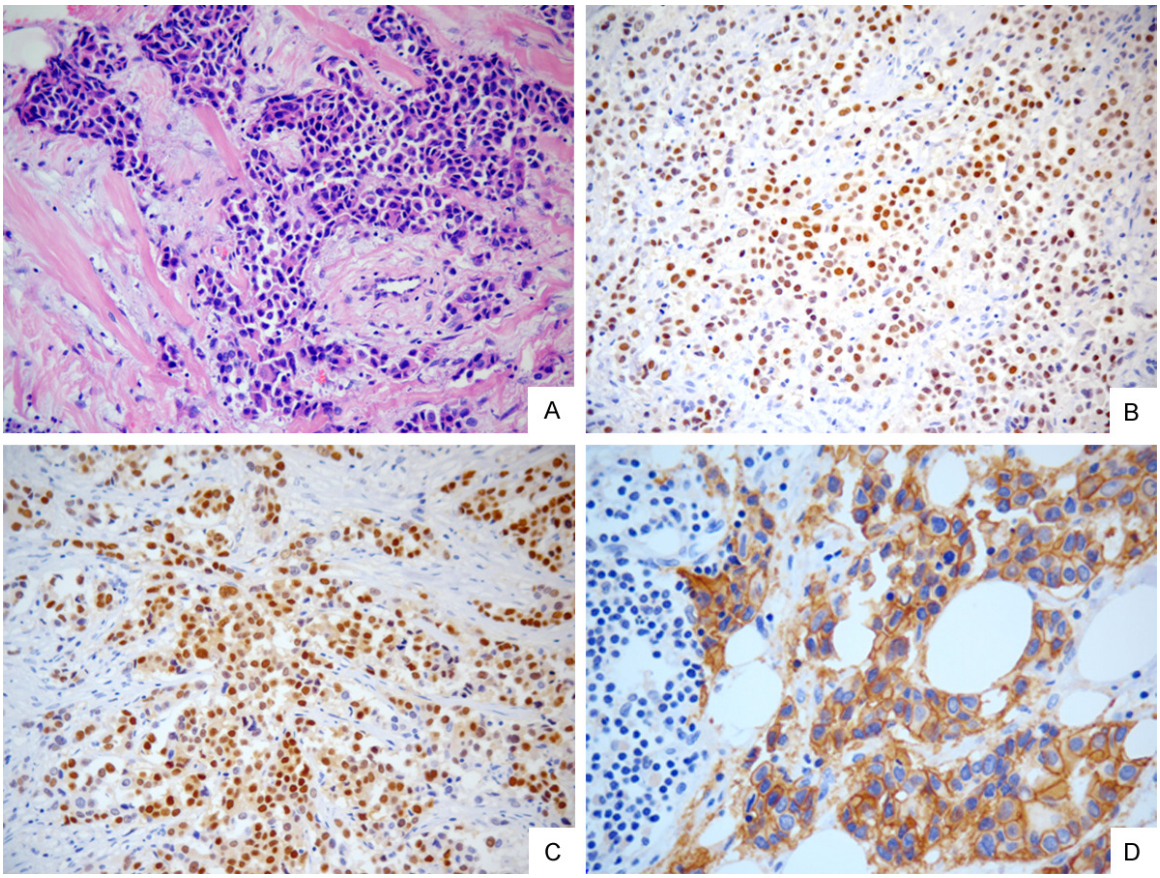

Figure 3. A. HE staining reveals poorly differentiated breast carcinoma cells in a solid arrangement. B. Tumor expression of ER. C. Tumor expression of PR. D. Tumor expression of CerbB-2, with strong membrane staining.

be present at other sites at the time of diagnosis; and 4) there may also be ipsilateral axillary lymph node involvement. However, it is difficult to determine the stage of advanced breast lymphoma. Therefore, some researchers categorize primary breast lymphomas as those occurring in or localized to breast tissue, even if there is distant lymph node metastasis or bone marrow involvement [17-19].

The most frequently encountered type of lymphoma in breast tissue is non-Hodgkin's B-cell lymphoma, usually of the diffuse large B-cell type. Breast lymphoma commonly presents as a solitary painless mass in the outer quadrants, usually without skin retraction, erythema or Peau d'orange. There is usually no nipple discharge. It is also usually associated with non-calcified lumps or diffuses hypertrophy. Microscopically, the breast tissue is atrophied, and a large number of tumor cells are diffusely distributed between the remnants of the ductules and lobules. These cells are round or oval shaped, medium-sized or larger, have little cytoplasm, sometimes exhibit vesicular nuclei, and have a mitotic count of approximately 2-8/high power field [20]. Breast lymphoma shows no obvious radiographic features, and is thus difficult to distinguish from other breast lesions using this modality. Ultrasound scans also offer no obvious benefit in differentiating breast lymphoma from other lesions.

Table 1 summarizes previously described cases that are similar to the case we report here. All of these involved synchronous breast lymphoma and invasive ductal breast carcinoma in the ipsilateral breasts, except for that described by Frei et al. [11] in which the breast carcinoma and lymphoma were in contralateral breasts. In two cases (Susnik et al. [13] and Quilon et al. [14]) there were collision tumors occurring in the same mass. In all seven cases, the patients were middle-aged women, and the overall median age was 65 years. The grade of invasive ductal carcinoma varied from I to III,

Table 1. Key characteristics of synchronous breast carcinoma and lymphoma cases

Study	Age (years)	Carcinoma				Lymphoma			Follow-up (mo)
		Site	Grade	ER/PR /HER-2	Distant metastasis	Site	Type	Distant metastasis	
Arlen et al [8]	78	LB	NS	+/+/-	No	BB	NHL-B	Yes☆	NS
Garg et al [9]	57	BB	I	+/+/NS	No	RB	MALT	BAN	6 Alive
Broco et al [10]	69	RB	PD	+/NS/NS	RAN	RB	DLBCL	No	60 Alive
Frei et al [11]	62	LB	WD	+/NS/NS	No	RB	NHL-B	No	12 Alive
Siddiqui et al [12]	47	RB	NS	NS	NS	RB	NHL-B	NS	NS
Susnik et al [13]	79	LB	II	+/-/-	LAN	LB	MALT	BM	NS
Quilon et al [14]	53	LB	III	NS	No	LB	MALT	LSN	NS

Abbreviations: LB, left breast; BB, bilateral breast; RB, right breast; NS, not stated; PD, poorly differentiated; WD, well differentiated; RAN, right axillary node; LAN, left axillary node; NHL-B, non-Hodgkin B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; DLBCL, diffuse large B-cell lymphoma; BAN, both axillae nodes; BM, bone marrow; LSN, left sentinel node. ☆Yes_ back and swelling in the right popliteal were involved.

and in the five cases in which estrogen receptor status was assessed the tumor was found to be positive. Two cases involved ipsilateral axillary lymph node metastases, but there was no evidence of distant metastases. All cases involved non-Hodgkin's B-cell lymphoma, and among them, two patients had a distant metastasis outside the axilla.

Cases of synchronous breast carcinoma and breast lymphoma in the same patient have been reported in the past. However, in most of these cases the two tumors were not found at the same time. In some patients, the breast lymphoma was found after the diagnosis; surgical resection and chemotherapeutic treatment were performed for the breast carcinoma. It has been postulated that chemotherapy for breast carcinoma can induce the development of lymphoma [21], and some researchers have suggested that the presence of breast carcinoma itself is a stimulating factor in lymphoma formation [13], through a mechanism similar to that by which *Helicobacter pylori* induces gastric mucosa-associated lymphoid tissue (MALT) lymphoma. In other patients, lymphoma formed first, which increased the susceptibility to other malignancies due to a lymphoma induced reduction in immune function [22]. Some patients were immunodeficient and were thus more susceptible to various tumors [23]. The most recent report of synchronous breast lymphoma and breast carcinoma includes evidence that [8] they may be associated with mouse mammary tumor virus (MMTV) infection, which can induce *wnt-1* gene expression in breast carcinoma and lymphoma.

Excision biopsy is recommended if lymphoma is suspected. Siddiqui et al. [12] reported a case of lymphoma diagnosed by fine needle aspiration and eventually categorized after tumor resection. Although the fine needle aspiration biopsy showed atypical lymphocytes, the structural features of the tumor could not be observed due to technical limitations. Hahm et al. [21] reported a case of delayed treatment for follicular lymphoma of breast tissue due to the difficulty of distinguishing between follicular lymphoma and benign follicular disease using fine needle aspiration.

Synchronous breast lymphoma and breast carcinoma is very rare, and there is yet no clear standard of treatment or prognostic information. In addition, the commonly used hormone therapy for breast carcinoma may promote lymphoma development [21]. Therefore, the treatment of these synchronous neoplasms is very complex, and no clear therapeutic guidelines are available. In the case we report here, the patient underwent a combination of treatment including surgical excision, chemotherapy, and bone marrow transplantation and was still in good health one year later. Only three of the previously reported cases included a follow-up period, and the survival of patients ranged from six to 60 months, with no mortality reported (**Table 1**). Furthermore, due to the limited follow-up data, the relationship between tumor grade, stage and prognosis remains unclear. More cases therefore need to be examined in order to further clarify the key diagnostic and therapeutic characteristics of these synchronous neoplasms.

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Disclosure of conflict of interest

None.

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