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Case Report

Spontaneous regression of primary extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) colliding with invasive ductal carcinoma of the breast: a case report

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Abstract: Malignant lymphomas of the breast, whether they are primary or secondary, are rare diseases, constituting only around 0.1 to 0.15% of the primary neoplasm of the breast. Although the most prevalent histological subtype is diffuse large B-cell lymphoma, primary extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) also occurs in the breast as in other extranodal sites, comprising about 15% of malignant lymphomas of the breast. In many cases, primary MALT lymphoma of the breast is low grade lymphoma, localized in the breast with indolent behavior and good prognosis. Here we report a case of spontaneous regression of primary MALT lymphoma of the breast. The lymphoma collided with invasive ductal carcinoma in the breast. Both tumors were identified in the Vacora biopsy specimen before the operation. However, the lymphoma disappeared, while the carcinoma remained, in the resected mass. To our knowledge, this is the first case report of spontaneous regression of MALT lymphoma of the breast colliding with breast cancer.

Keywords: MALT lymphoma, invasive ductal carcinoma, breast, spontaneous regression

Introduction

Malignant lymphomas of the breast, whether they are primary or secondary, are rare diseases, constituting only around 0.1 to 0.15% of the primary neoplasm of the breast [1]. Although the most prevalent histological subtype is diffuse large B-cell lymphoma, primary extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) also occurs in the breast as in other extranodal sites, comprising around 15% of malignant lymphomas of the breast [2]. It is difficult to distinguish breast lymphoma from breast carcinoma by imaging studies alone. Therefore, histopathological examination by needle or excisional biopsy is often required to make the diagnosis of breast lymphoma.

Lymphomas and breast cancers may coexist in the same organ. Lymphomas may be incidentally found in the axillary lymph nodes resected for examination of metastasis of breast cancer [1]. This pitfall may complicate the pathological diagnosis of lymph node metastasis of the breast cancer. In these cases, the most prevalent subtype of the lymphomas is small lymphocytic lymphoma/chronic lymphocytic leukemia [1].

Spontaneous regression of cancer was reviewed for neuroblastoma [3], renal cancer, choriocarcinoma, malignant melanoma [4-7]. Spontaneous regression of breast cancer was comparatively rare among these. However, two cases of spontaneous regression of metastatic breast cancer were reported by famous Sir William Osler in 1901 [4]. There are several factors involved in spontaneous regression of cancer, including infection, host immunity, hormonal factors, and trauma [5]. Spontaneous regression of lymphomas was also reviewed [8]. In non-Hodgkin's lymphoma, spontaneous regression has been reported in indolent histologic subtypes, with a frequency of 10 to 20% in selected series [8]. The importance of host

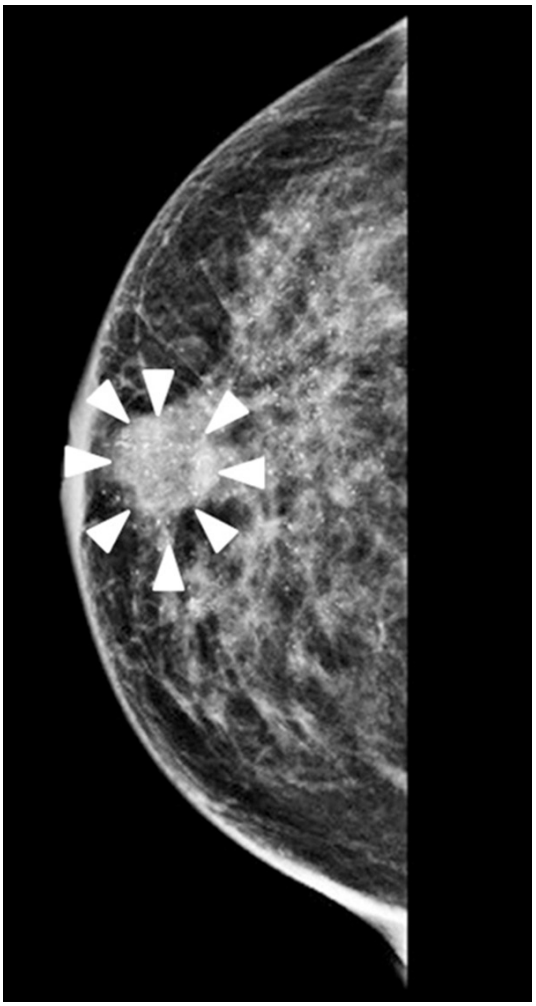

Figure 1. Mammography image of the mass of the right breast. It was composed of a 3.5 cm-sized subnipple mass together with dysplastic calcification scattered diffusely in the right breast. The subnipple mass was indicated by white arrowheads.

immunity against lymphomas may be illustrated by spontaneous regression of methotrexate-associated lymphoproliferative disorder after cessation of methotrexate medication.

Here we report a case of spontaneous regression of primary MALT lymphoma of the breast, colliding with invasive ductal carcinoma in the breast. Both tumors were identified in the Vacora biopsy specimen before the operation. However, the lymphoma disappeared, while the carcinoma remained, in the resected mass.

Case report

A 47-year-old Japanese female was admitted to our hospital for examination of a mass of her right breast. Mammography study showed a 3.5 cm-sized subnipple mass together with dysplastic calcification scattered diffusely in the right breast (**Figure 1**). Cytological examination of the needle aspiration of the mass showed scattered epithelial cells with inflammatory infiltrate and necrotic debris (data not shown). Vacora biopsy of the mass revealed that most of the tumor was composed of diffuse albeit vaguely nodular lymphoid infiltration (**Figure 2A**) by small to medium-sized lymphoid cells (**Figure 2B**). In addition, a tiny part of the tumor was occupied by invasive ductal carcinoma (**Figure 2A**). Although the carcinoma cells were inconspicuous by lymphoid infiltrate (**Figure 2C**), they were clearly identified by immunohistochemistry of cytokeratin AE1/AE3 (**Figure 2D**). Immunohistochemical examination of the carcinoma cells showed that the carcinoma cells were strongly positive for HER2 with around 20% positivity for Ki-67, but negative for both estrogen receptor and progesterone receptor (data not shown). On the other hand, the vaguely nodular lymphoid tumor contained small aggregates composed of homogeneous centrocyte-like cells (**Figure 2B**). The rest of the tumor cells exhibited extensive differentiation into plasma cells and diffusely circumscribed the small aggregate (**Figure 2B**). Immunohistochemical examination demonstrated that the proliferating lymphoid tumor cells were partly positive for CD20 (**Figure 3A**), extensively positive for plasma cell marker CD138 (**Figure 3B**), but negative for CD3 (data not shown), CD23 (data not shown), and Cyclin D1 (data not shown). *In situ* hybridization of immunoglobulin light chains showed restricted expression of κ (**Figure 3C**) compared with λ light chains (**Figure 3D**), confirming the diagnosis of low grade B-cell lymphoma with plasmacytic differentiation. The lymphoma lesion was localized in the breast without apparent involvement of peripheral lymph nodes (data not shown). The past history of the patient did not suggest the precedence of malignant lymphomas. Furthermore, M protein was not apparently detected serologically (data not shown). No evidences for the involvement of autoimmune diseases were obtained, although serum antinuclear antibody was not examined (data not shown). Taken together, the final diagnosis was primary extranodal marginal zone lymphoma of mucosa-associated tissue (MALT lymphoma), colliding with invasive ductal carcinoma of the right breast.

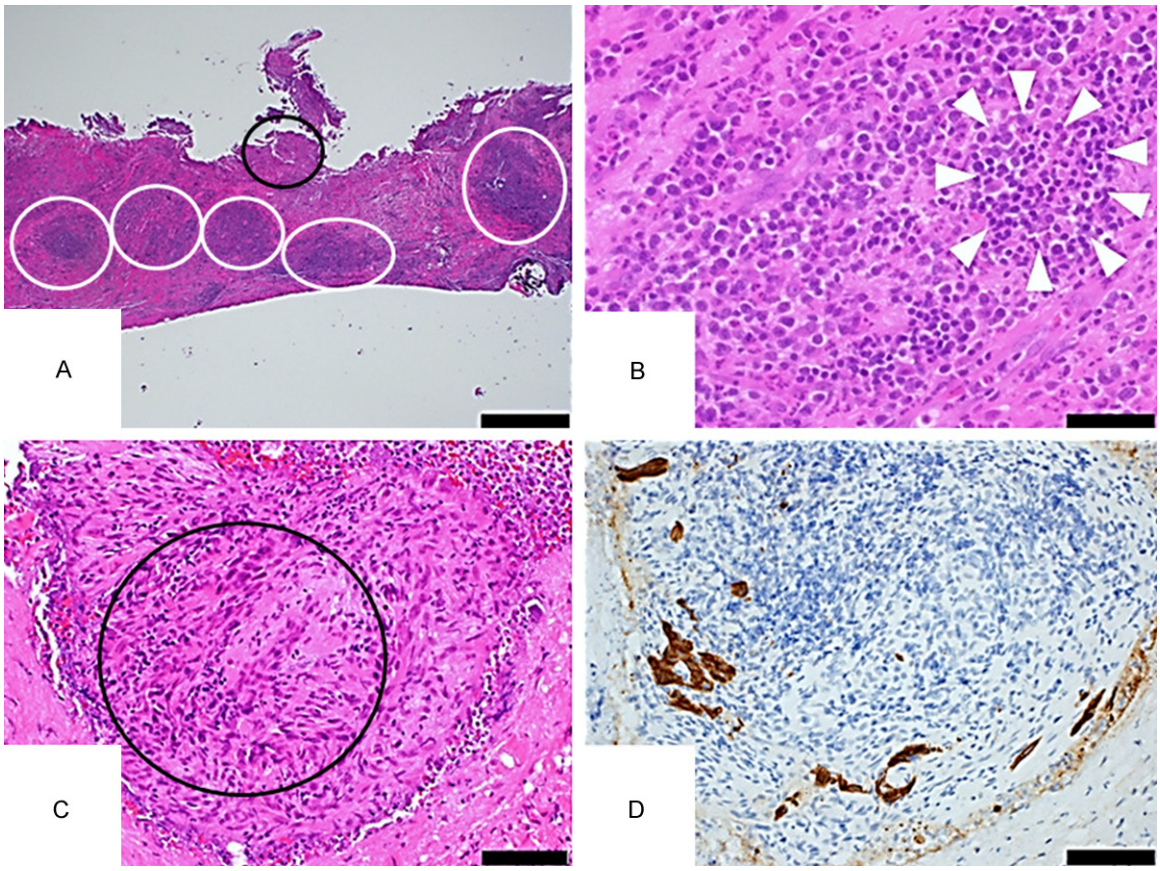

Figure 2. Histology of the Vacora specimen of the mass of the right breast. (A) Low power view of the mass lesion by hematoxylin and eosin (HE) stain. Most of the mass were extensively infiltrated with vaguely nodular lymphoid tumor composed of small to medium sized lymphoid cells (indicated by white circles). The carcinomatous lesion was not apparent by low power (indicated by a black circle). Original magnification: ×20. Bar: 1 mm. (B) High power view of the vaguely nodular lymphoid tumor by HE stain. Part of the nodule contained small aggregates composed of homogeneous centrocyte-like tumor cells (indicated by white arrowheads). The rest of the lymphoid nodule consisted of plasmacytic tumor cells (in the left-hand side of the figure). Original magnification: ×400. Bar: 50 μm. (C) High power view of the lesion inside the black circle in (A). Note clusters of atypical cells inside a black circle, masked by heavy inflammatory infiltrate. Original magnification: ×200. Bar: 100 μm. (D) Immunohistochemistry of cytokeratin AE1/AE3 of the same lesion in (C). The clusters of the atypical cells were stained brown, revealing the presence of the invasive ductal carcinoma. Original magnification: ×200. Bar: 100 μm.

Based on this diagnosis, right mastectomy with sentinel lymph node biopsy and axillary lymph node dissection was performed approximately 1 and a half month later. Macroscopically, the resected mass was associated with scatteredly punctated calcification. Histological examination of the resected mass revealed a profoundly different view at low power (**Figure 4A**), compared with that of the preoperative Vacora biopsy (**Figure 2A**). Diffuse albeit vaguely nodular infiltration of lymphoid cells present in the preoperative biopsy diminished or disappeared (**Figure 4A**). The main portion of the tumor was composed of solid- or comedo-type ductal carcinoma *in situ*, presumably related to dystrophic calcification observed in the preoperative mammography, with invasive components (**Figure 4B**). The lymphoid infiltrate was dramatically decreased, only remaining in the narrow vicinity of the flourishing cancerous lesion as a feathery cuff (**Figure 4A** and **4B**). Basically, the residual lymphoid lesion was a reactive lymphoid hyperplasia with occasional germinal centers, which partly surrounded clusters of invasive cancer cells (**Figure 4C**). Plasmacytic differentiation was not evident as observed in the preoperative biopsy (**Figures 2B** and **3B**). We did not observe any histological evidence of the residual MALT lymphoma in the vicinity of the carcinoma. We further examined the rest of the resected specimen but did not observe the residual MALT lymphoma (data not shown).

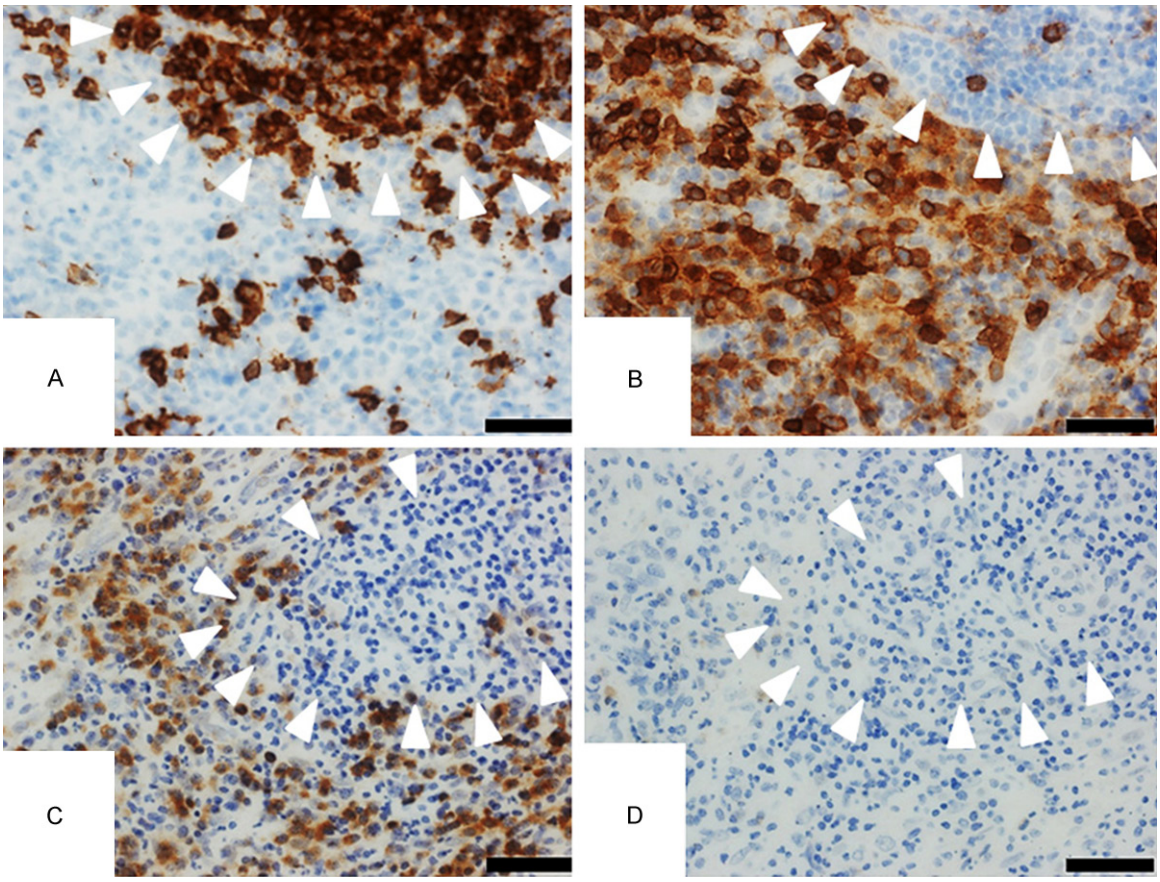

Figure 3. Immunohistochemical and *in situ* hybridization analyses of the lymphoid tumor nodules. (A, B) Immunohistochemistry. (C, D) *In situ* hybridization. (A) CD20. (B) CD138. (C) Immunoglobulin κ light chain. (D) Immunoglobulin λ light chain. Positive cells were stained brown. The small aggregates in **Figure 2B** are indicated by white arrowheads (in the upper-right quadrant of the figures). The centrocyte-like tumor cells forming vague nodules were positive for CD20 (A) but negative for CD138 (B). The rest of the lymphoid tumor cells were stained negative for CD20 (A) but positive for CD138 (B), confirming their plasmacytic differentiation. Original magnification: ×400. Bar: 50 μm. These plasmacytic tumor cells were showed restricted expression of κ (C) compared with λ light chains (D).

Thus we confirmed spontaneous regression of the MALT lymphoma originally detected in the preoperative Vacora biopsy, while the invasive ductal carcinoma remained. Examination of the sentinel lymph nodes showed no evidence of lymphoma cells as well as cancerous metastasis (data not shown).

The patient was followed-up for around six months after the operation without any evidences of the relapse of the both lesions.

Discussion

Here we report a rare case of coexisting primary MALT lymphoma and invasive ductal carcinoma of the breast. By imaging studies, both tumors were considered to be localized and primary tumors of the breast, which were found to be collided by histological examination. Our case of MALT lymphoma occurred in a premenopausal women, which is also rare because the MALT lymphoma of the breast most often occurs in postmenopausal women [1].

There were some reports of the collision of lymphoma with metastatic breast cancer in the sentinel or axillary lymph nodes, which may complicate pathological diagnosis of the lymph node metastasis of the breast cancer [9-12]. In these cases, the most prevalent subtype of the lymphomas is small lymphocytic lymphoma/chronic lymphocytic leukemia [1]. However in our case, there was a collision of the breast cancer and MALT lymphoma inside the breast. By reviewing the literature, there were several reports on coexisting primary breast lymphoma and breast carcinoma inside the breast [13-

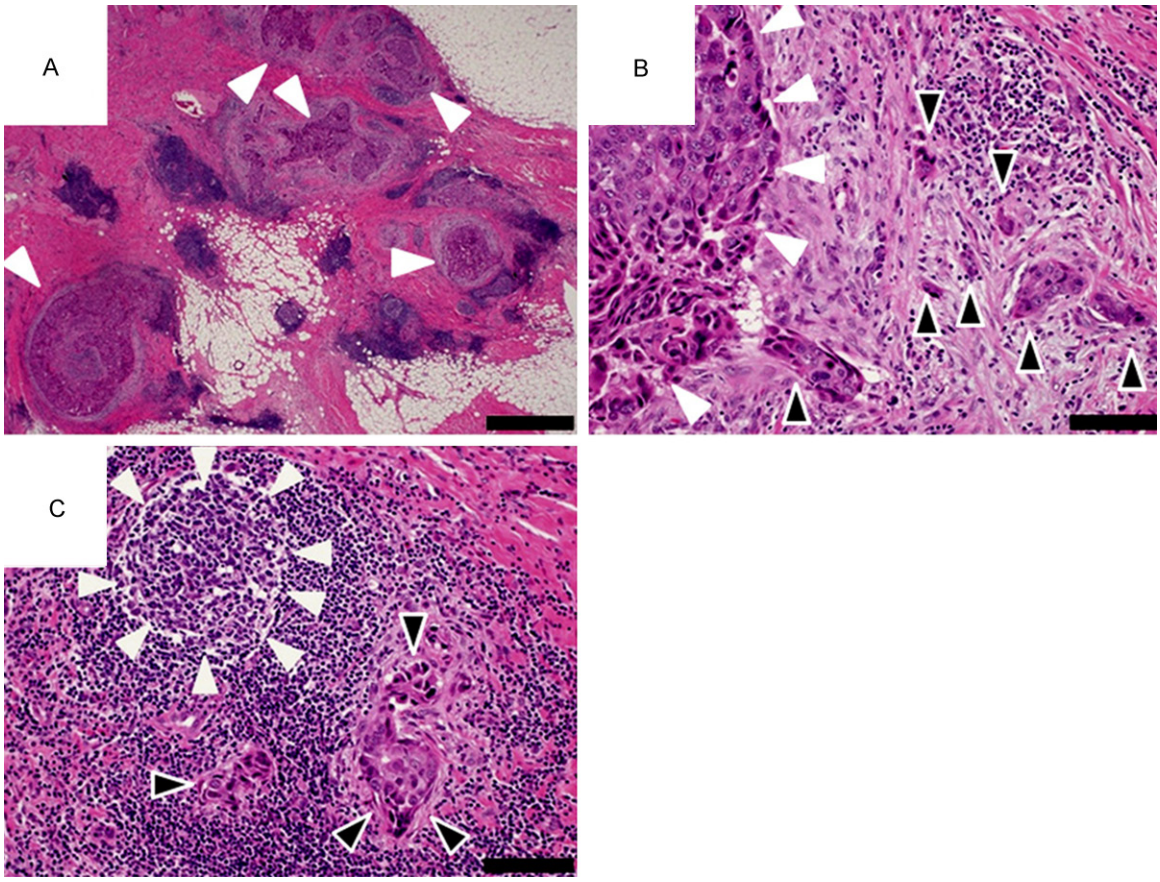

Figure 4. HE image of the resected specimen of the mass of the right breast. A: Low power view of the main tumor. Mainly observed was the breast carcinoma (indicated by white arrowheads), mostly composed of ductal carcinoma *in situ* (DCIS), with tiny amount of invasive components. The amount of lymphoid infiltrate was smaller than that of the carcinoma and was decreased compared with that in the preoperative biopsy in **Figure 1A**. Original magnification: ×20. Bar: 1 mm. B: High power view of the invasive ductal carcinoma associated with reactive lymphoid infiltration. The DCIS component is indicated by white arrowheads (in the right-hand side of the figure), while the invasive components are by black arrowheads. Original magnification: ×200. Bar: 100 μm. C: High power view of the reactive lymphoid infiltration associated with the invasive ductal carcinoma. A germinal center is indicated by white arrowheads. The invasive carcinomas are indicated by black arrowheads. Original magnification: ×200. Bar: 100 μm.

17]. The histological subtypes of the lymphoma include three cases of primary MALT lymphoma of the breast [13, 14, 16], chronic lymphocytic leukemia/small lymphocytic lymphoma [15], and intravascular large B-cell lymphoma [17]. Susnik et al. and Quilon et al. reported collision tumors of invasive ductal carcinoma with primary MALT lymphoma of the breast [13, 14]. Susnik et al. reported that the initial diagnosis of the breast tumor was medullary carcinoma due to massive infiltration of lymphoid cells, and the coexistence of the MALT lymphoma was missed [13]. Anavekar et al. reported a collision of invasive lobular carcinoma and primary MALT lymphoma [16]. A potential pitfall of this case may be that the lobular carcinoma cells mimic plasma cells, which may be a component of the MALT lymphoma. However, spontaneous regression of the lymphoma was not reported in any of these cases of the collision tumor as in our case.

It is generally thought that the developmental origin of MALT lymphoma is the underlying MALT. The MALT is considered to be induced in the breast as a part of the common mucosal immunity system. Two major causes of the MALT induction are infection/inflammation and autoimmunity. In the case of human breast, there have been no established pathogens involved in MALT induction and/or lymphomagenesis, as Helicobacter pylori in MALT lymphomas in the gastrointestinal tracts. In addition, evidences for autoimmunity were not apparent

in our patient. In the situation of the breast, it is generally known that lymphocytic mastitis or diabetic mastopathy are often associated with lymphoid cell infiltration [18, 19]. However, the relationship between these and MALT induction is uncertain.

Are there any relationships between co-development of the MALT lymphoma and the ductal carcinoma in our case? There are reports suggesting a possible association of malignant lymphoma of the breast and the presence of lymphocytic mastopathy [20] or nodular adenosis [21]. In the stomach, there are more than ten case reports on gastric adenocarcinoma coexisting with synchronous MALT lymphoma [22]. The co-occurrence of this combination is not unexpected in view of epidemiologic association of the both with Helicobacter pylori infection. It is known that MALT lymphoma of the stomach is frequently associated with lymphoepithelial lesions. Lymphoepithelial lesions may play a role as replicative and regenerative stresses for gastric epithelia, which may be a basis for the reported case of gastric adenocarcinoma coexisting with MALT lymphoma [22]. It is intriguing to speculate that a similar mechanism may operate in carcinogenesis in the breast in our case. In view of the coexistence of ductal carcinoma with lymphoid cell infiltration in the breast, involvement of Epstein Barr virus (EBV) or mouse mammary tumor virus-like DNA sequences were suggested but not established [23, 24]. *In situ* hybridization of EBV-encoded small RNA (EBER) showed that both the carcinoma cells and lymphoma cells were negative in our case (data not shown), excluding the possibility of EBV-positive carcinoma like nasopharyngeal carcinoma.

We observed spontaneous regression of primary MALT lymphoma of the breast in the present case. In non-Hodgkin's lymphoma, spontaneous regression has been reported in indolent histologic subtypes, with a frequency of 10 to 20% in selected series [8]. There are four reports on spontaneous regression of MALT lymphomas arising in the digestive tracts and the conjunctiva [25-28]. There are only two case reports on spontaneous regression of primary lymphoma of the breast [29, 30]. In addition, there is a report on spontaneous regression of lymphoma cell infiltration in the breast, which was originated from the central nervous system [31]. However, in these reports, the histological subtypes of the lymphomas were diffuse large B-cell lymphoma. Thus, as far as we know, our case is the first report on spontaneous regression of the MALT lymphoma of the breast. In the above two cases, the intervals between the diagnostic biopsy and the confirmation of the regression were 4 weeks [29] and 11 days [30], respectively. In our case, the interval was approximately 1 and a half month, which was comparable to that of the previous two cases.

There are several factors involved in spontaneous regression of cancer, including infection, host immunity, hormonal factors, and trauma [5]. The involvement of infection and host immunity against cancer has been strongly suggested by the success of Corey's toxin and the recent development of various immunotherapies. The importance of host immunity against lymphomas may be illustrated, for example, by spontaneous regression of methotrexate-associated lymphoproliferative disorder after cessation of methotrexate medication. In the above reports on the primary breast lymphomas, spontaneous regression of the lymphomas was observed after the needle biopsy [29, 30], suggesting the involvement of needle biopsy-triggered trauma. In our case, since that patient is at the pre-menopausal, hormonal factors cannot be excluded in addition to needle biopsy-triggered trauma.

In conclusion, we reported a rare case of spontaneous regression of primary MALT lymphoma of the breast, colliding with invasive ductal carcinoma of the breast. In histological viewpoint, one of the lessons from the present case may be the differential diagnosis of the collision tumor of carcinoma and MALT lymphoma from medullary carcinoma of the breast, which is often associated with massive lymphoid cell infiltration. In view of a possibility of spontaneous regression of lymphoma, it may be a better strategy to treat carcinoma first, when the lymphoma and the carcinoma collide or coexist in the breast as in the present case. However, the long-term outcome of the strategy is not known and not guaranteed because such a situation as ours may be very rare. Prudently, close follow-up will be desirable until the long-term prognosis of such a case as ours will be clarified in the future.

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Disclosure of conflict of interest

None.

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