



Case report

Sarcoid-like reaction in a HER2-positive breast cancer patient: A case report

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ABSTRACT

Introduction and importance: Sarcoid-like reaction is a systemic granulomatous reaction that may develop in the lymph nodes and organs of cancer patients. Distinguishing a sarcoid-like reaction from metastasis is difficult. Accurate diagnosis of this reaction is key to preventing overtreatment.

Case presentation: A 51-year-old woman presented with a lump in her left breast and swollen lymph nodes in her left axilla and infraclavicular fossa. A core biopsy was performed, leading to the diagnosis of grade 2 infiltrating ductal carcinoma, clinical stage T2N3M0 with estrogen and progesterone receptor negativity and human epidermal growth factor receptor-2 positivity. After neoadjuvant therapy, the tumor in her left breast reduced in size, but the lymph nodes remained swollen. Mastectomy and axillary lymph node dissections were performed. In the pathological findings, epithelioid cell granuloma was observed in the lymph nodes. Based on these findings, lymph node swelling was attributed to a sarcoid-like reaction.

Clinical discussion: SLRs have been reported in 4–14% of cancer patients. Although there are various imaging modalities for detecting swollen lymph nodes, the differential diagnosis of cancer metastasis is often difficult.

Conclusion: Histological evaluation of swollen lymph nodes is required to prevent overtreatment; especially in cases where the tumor size is reduced by chemotherapy, but the lymph nodes remain swollen.

1. Introduction

Sarcoidosis is a systemic disease of unknown cause characterized by the formation of immune granulomas in the lymphatic system and various organs, mainly the lungs [1]. It is characterized by the presence of non-caseating epithelioid cell granulomas [1,2]. Sarcoid-like reactions (SLRs) are granulomas that develop in the lymph nodes that do not meet the criteria for the diagnosis of systemic sarcoidosis [2]. SLRs can be caused by an immune response to infection, inflammatory disease, malignancy, drugs, radiation therapy, and foreign bodies. SLRs are benign and do not need treatment; however, they may mimic lymph node metastasis or recurrence in cancer patients [3]. In recent years, SLRs have been reported as rare adverse events associated with treatments such as immune checkpoint inhibitor therapy and targeted therapy [4]. Erroneous diagnosis may lead to overtreatment. Here, we report a case of SLRs diagnosed after neoadjuvant chemotherapy in HER2-positive breast cancer.

This work was written in accordance with the SCARE criteria [5].

2. Case presentation

A 51-year-old postmenopausal Asian woman presented with a lump in her left breast. A hardened mass measuring approximately 3 cm was detected. There were several palpable axillary nodes. The patient's history included type 2 diabetes mellitus. She had no family history of malignancy. Mammography was not performed because she was in pain at the time of presentation. Breast ultrasonography showed an indistinct hypochoic mass measuring 3 cm in the lower outer quadrant of the left breast. Several swelling lymph nodes were detected in her left axilla and subclavian fossa (Fig. 1). Computed tomography revealed swelling of the lymph nodes in the left axilla extending to the infraclavicular fossa. CT scan report did not show any evidence of distant metastasis. A core biopsy was performed, leading to the diagnosis of grade 2 infiltrating ductal carcinoma with estrogen and progesterone receptor negativity and human epidermal growth factor receptor-2 (HER2) positivity, by immunohistochemical staining (3+) (Fig. 2). Based on the diagnosis of breast cancer (cT2N3M0), she received four cycles of doxorubicin (60 mg/m²) plus cyclophosphamide (600 mg/m²), followed by four cycles of docetaxel (80 mg/m²) plus trastuzumab (initial dose of 8 mg/kg,

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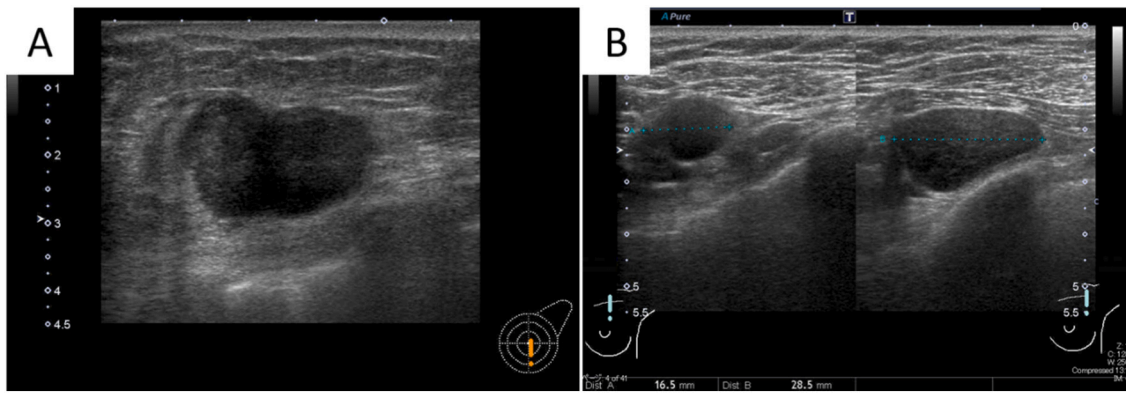


Fig. 1. Ultrasonography images before starting chemotherapy. (A) The left breast tumor measured 3 cm; (B) swollen infraclavicular lymph nodes were detected.

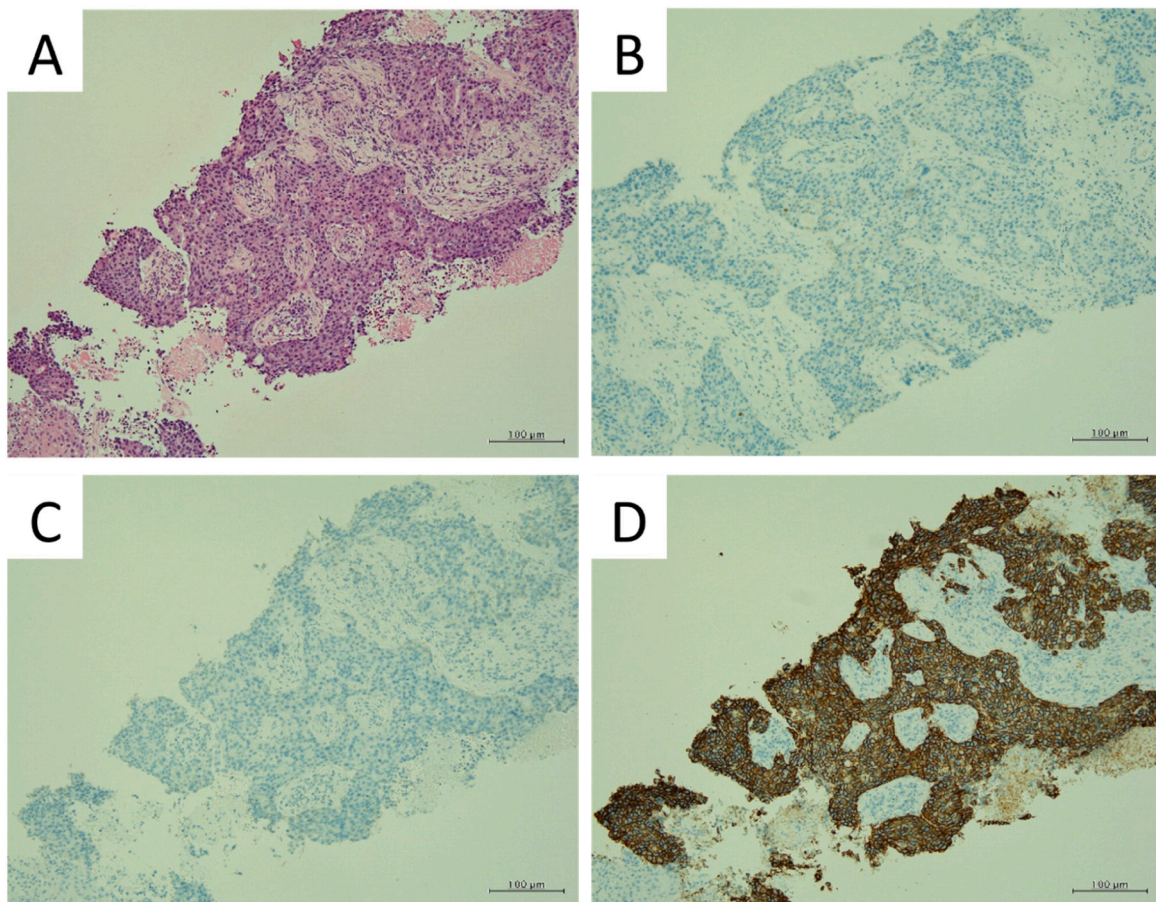


Fig. 2. Histopathology of the breast core biopsy. (A) Hematoxylin-eosin staining revealed invasive ductal carcinoma; (B) estrogen receptor was negative; (C) progesterone receptor was negative; (D) human epidermal growth factor receptor-2 (HER2) was positive by immunohistochemical staining (3+).

followed by 6 mg/kg) plus pertuzumab (initial 840 mg/kg, followed by 420 mg/kg).

After neoadjuvant therapy, mammography showed that the mass had shrunk in the lower area of her left breast. Ultrasonography revealed the remaining mass measuring 1.5 cm, which had reduced in size; meanwhile, magnetic resonance imaging showed the remaining mass measuring 9 mm, with decreased enhancement (Fig. 3).

Infraclavicular lymph nodes and axillary lymph nodes remained swollen on ultrasound and CT images. At a multidisciplinary conference, we diagnosed that neoadjuvant therapeutic effect was partial in HER2-

positive breast cancer with lymph nodes metastasis.

In line with her request, mastectomy and axillary lymph node dissection were performed. Post-operative pathological evaluation revealed that the residual invasive tumor measured 13 × 7 mm. Peritumoral lympho-vascular invasion was not detected. The therapeutic response was classified as grade 2a. No neoplastic cells were detected in any of the 24 extracted axillary or subclavian lymph nodes. Instead, epithelioid cell granuloma was observed in every lymph node that stained negative upon Ziehl-Neelsen staining (Fig. 4). Based on these findings, lymph node swelling was attributed to an SLR. Although the

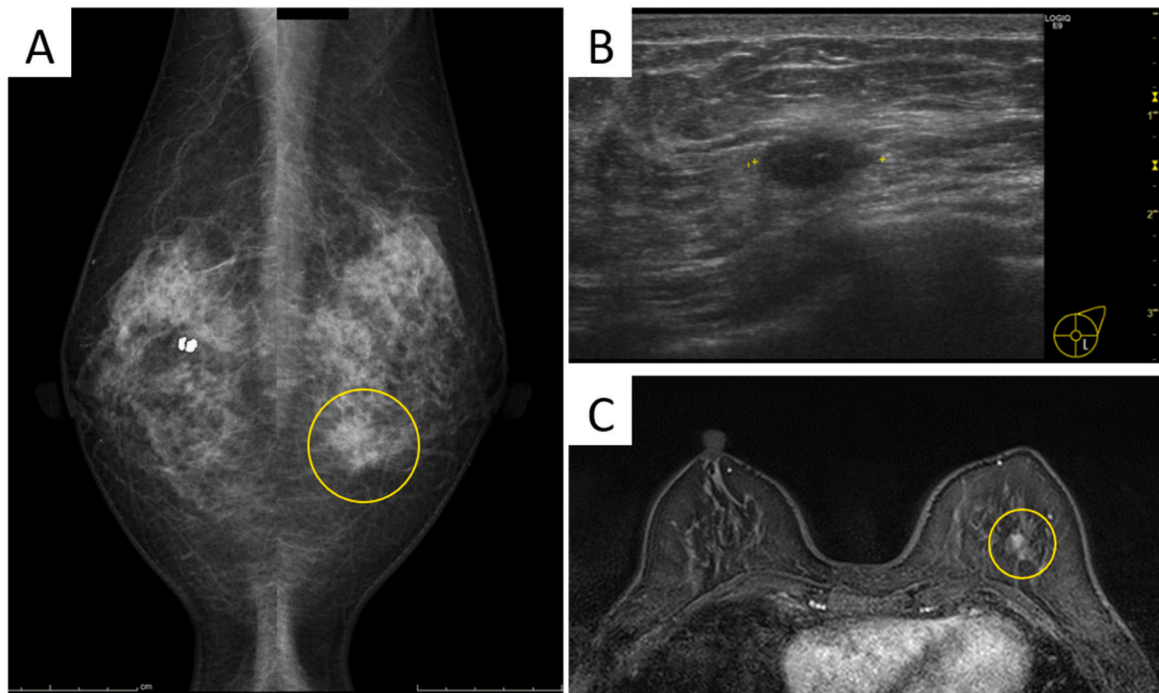


Fig. 3. Imaging findings after neoadjuvant therapy.

(A) Mammography and (B) ultrasonography revealed the remaining mass measuring 1.5 cm that had reduced in size. (C) Magnetic resonance imaging showed the remaining mass measuring 9 mm with decreased enhancement.

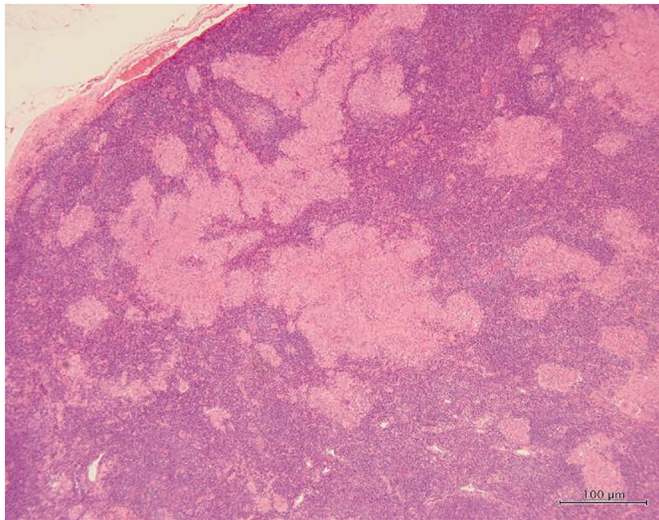


Fig. 4. Histopathology of non-caseating granulomas in regional lymph nodes. Epithelioid cell granuloma was observed in all the extracted lymph nodes. No cancer cells were detected.

initial diagnosis was T2N3M0 HER2-positive breast cancer, the patient continued to receive only trastuzumab as an adjuvant therapy because there was no firm evidence to prove that the SLR was caused by cancer metastasis. Additionally, radiation therapy for regional lymph nodes was not administered. The possibility of sarcoidosis was considered, but her serum angiotensin-converting enzyme level was within the normal range, and cardiac function was normal. Follow-up visits included a physical examination of the breast and regional lymph nodes twice a year and mammography and sonography once a year. Eighteen months after the surgery, the patient showed no evidence of local recurrence or distant metastasis.

3. Discussion

Sarcoidosis is diagnosed on the basis of clinical and pathological presentation, including the presence of non-caseating granulomas and the absence of evidence suggesting other diseases [6]. Granulomas are considered to represent SLRs when they develop in the lymph nodes of patients who do not meet the criteria for systemic sarcoidosis [6]. SLRs have been reported in various carcinomas [7]. SLRs have been reported in 4–14% of cancer patients [8]. SLRs typically develop in regional lymph nodes, in particular, in non-metastatic lymph nodes of cancer patients [7,9]. Although various imaging modalities are used for detecting swollen lymph nodes, the differential diagnosis with cancer metastasis is often difficult. Chowdhury et al. reported that based on positron emission tomography-computed tomography findings, SLRs were suspected in 1.1% of cancer patients [10]. Both morphological studies of the lymph nodes and metabolic analysis may be necessary. Chemotherapeutic treatments, targeted therapy, radiation therapy, and the carcinoma itself may cause SLRs [4,6]. Categories of drugs that are associated with the development of SLRs include immune checkpoint inhibitors, highly active antiretroviral therapy, interferons, and tumor necrosis factor- α antagonists [4]. It has been suggested that the relationship between a malignant tumor and an SLR may be mediated by the host's resistance to cancer or by the response to metabolic disintegration substances released by tumor cells [1]. T-cell mediated immune response to cancer antigens or other factors may be involved in SLRs. CD4⁺ T-cells activated by antigen-presenting cells secrete interleukin-2 or interferon-gamma and activate macrophages. This process accelerates granuloma formation [11]. The occurrence of SLRs does not seem to affect the prognosis of breast cancer [6]. In addition, asymptomatic SLRs do not require any treatment.

In the present case, lymph node swelling was observed before the start of chemotherapy. It remains unclear whether the cause of the present SLR was malignancy, chemotherapy, targeted therapy, or a combination of these aspects. Cases in which lymph node metastasis is not pathologically confirmed, axillary lymph node dissection might result in overtreatment. However, in patients with HER2-positive breast

carcinomas, lymph node metastasis from T2 primary tumors is often reported. It is difficult to differentiate between SLR and metastasis using imaging studies alone [12]; pathological confirmation is often required. Although fine-needle aspiration cytology is a relatively non-invasive and highly effective method for differentiating SLRs from cancer metastases, puncturing all swollen lymph nodes is not a reasonable approach and may yield false-negative results. SLRs may occur several years after primary cancer treatment [12,13] and should be considered in cancer patients presenting with unexpected lymph node swelling.

4. Conclusion

In conclusion, the present report documents a case of regional lymph node swelling caused by an SLR. Using pre-treatment imaging alone to distinguish between SLRs and lymph node metastasis remains a challenge. Thus, histological evaluation of swollen lymph nodes in cancer patients is recommended.

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Ethical approval

Our institution does not require ethical approval for case reports that are deidentified and collected retrospectively.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Registration of research studies

Not applicable.

Guarantor

Chikako Sekine.

CRedit authorship contribution statement

Chikako Sekine: Conceptualization, Investigation, Resources, Writing – Original draft preparation, Writing – Review and editing.

Kazumi Kawase: Conceptualization, Investigation, Review.
Kazuhiko Yoshida: Administration, Review.

Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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