Case report

Synchronous breast cancer and non-Hodgkin lymphoma: A case report

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ABSTRACT

Introduction: Among women, breast cancer (BC) is the most prevalent type of cancer and the top cause of cancer deaths. Although non-Hodgkin lymphoma (NHL) is the most prevalent hematological cancer, it is rarely reported synchronous with BC. Moreover, which malignancy appears first can rarely be explained because they are usually detected incidentally while diagnosing and treating other malignancies. This paper reports a case of invasive ductal carcinoma (IDC) concomitant with NHL.

Presentation of case: A 35-year-old woman presented with simultaneous IDC in the left breast and NHL in a lymph node in the neck. The patient underwent a modified radical mastectomy for stage IIIA IDC and received rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy for stage I NHL.

Clinical discussion: Treating BC and NHL remains challenging due to their significantly different management, the lack of guidelines for treating BC and lymphoma simultaneously, and uncertainty about whether synchronous tumors should be treated separately as distinct clinical entities or as one disease with treatment covering both. Therefore, the best approach continues to be focusing on the most biologically aggressive malignancies.

Conclusion: The enlargement of lymph nodes not in the lymphatic drainage of the primary tumor should be suspected of indicating multiple primary malignancies until proven otherwise. For patients with luminal-B BC, NHL chemotherapy can involve receiving the R-CHOP regimen, including doxorubicin and cyclophosphamide, which can help to mitigate BC.

1. Introduction

Among women, breast cancer (BC) is the most prevalent type of cancer and the top cause of cancer deaths [1]. Following chemotherapy or radiotherapy, patients with BC are at greater risk of developing non-Hodgkin lymphoma (NHL), the most prevalent hematological cancer [2]. However, cases of synchronous BC and lymphoma at the time of initial diagnosis have been documented, meaning that lymphoma is not always caused by therapy [3].

BC and NHL rarely appear simultaneously; this coincidence has only been observed in a few cases. We report the first known case in Indonesia, a 35-year-old woman with synchronous invasive ductal carcinoma of the breast and NHL. We are reporting it according to the 2020 Surgical Case Report criteria [4].

2. Case presentation

A 35-year-old woman presented with the complaint of a large palpable lump in her left breast and a lump in the left side of her neck, both of which had been present for 2 years. The breast lump was initially as large as 1.0 × 1.5 cm but not painful. The patient reported usually experiencing drenching night sweats and weight loss but did not report any shortness of breath.

The patient had a history of tuberculous lymphadenopathy in the left side of her neck and had undergone treatment for tuberculosis. Her menarche had occurred at 12 years of age, and she was still menstruating at the time of presentation. A year after her marriage, she became pregnant with her first child at 26 years of age, whom she breastfed until the child was 1 year old. She had used contraceptive injections for 1 year.

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but had not sustained any radiation exposure to the thoracic wall.

The patient also had a history of fine-needle aspiration (FNA) biopsy in the past two years with adenocarcinoma of the left breast. Eighteen months ago, she had an open biopsy, and the histopathology showed invasive ductal carcinoma with no special type grade III (i.e., poorly differentiated) in the breast and NHL in the neck mass. Meanwhile, immunohistochemistry revealed luminal-B BC (i.e., positive for progesterone receptors [PR], estrogen receptors [ER], and human epidermal growth factor receptor 2 [HER-2]; Fig. 1) and small cell lymphocytic lymphoma (SLL; positive for CD20 and CD45). Immunohistochemistry also revealed that the lymphocytes were positive (Fig. 2). The patient subsequently underwent eight cycles of chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (Fig. 3). After chemotherapy, the lump in the left breast had decreased to 0.5 cm in diameter based on ultrasonography (US) examination (i.e., partial clinical response according to RECIST criteria [1,5]), whereas the lump in the neck had disappeared (i.e., complete clinical response according to RECIST criteria [6]) (Fig. 4). Table 1 shows the timeline of the case.

At admission, the patient’s vital signs and body mass index were within normal limits, and her Karnofsky Performance Status score [7,8], a measure used to gauge whether chemotherapy or palliative care is appropriate and whether dose adjustment is necessary, was 90. Clinical examination revealed a firm, painless, mobile, poorly circumscribed

![Fig. 1. A) Nests of tumors growing infiltratively in the connective tissue stroma, generally in a solid, nested pattern (hematoxylin and eosin, 4×). B) Tumor cells with atypical pleomorphic nuclei, coarse chromatin, prominent nucleoli, and a mitotic appearance (arrow; hematoxylin and eosin, 40×).](image-url)
tumor approximately 5 × 4 × 4 cm in the upper outer quadrant of the left breast with no associated lymphadenopathy. Examining the contralateral breast and axilla yielded nothing remarkable, whereas examining the lymph node in the left neck at level III revealed a firm, mobile tumor approximately 1 × 1 cm. US images showed an irregular hypoechoic mass in the left breast and abnormal regional lymph nodes in the left axilla. Laboratory evaluation also yielded nothing remarkable, and a chest X-ray and abdominal ultrasonography showed no signs of metastasis. We, a team of surgical oncologists, thus diagnosed stage IIIA invasive ductal carcinoma in the left breast and stage I SLL according to the Lugano classification.

The patient underwent a left mastectomy followed by adjuvant chemotherapy with paclitaxel and trastuzumab. She remains in follow up today, 8 months after mastectomy, and has shown satisfying results and no evidence of the tumor’s recurrence. We re-evaluated her stage I SLL and are treating it with hormonal therapies, including tamoxifen and goserelin.

3. Discussion

In 1889, multiple primary malignancies (MPMs) were first reported by Billroth [9,10]. In 1962, Warren and Gates proposed the following specific criteria for diagnosing MPM: (1) both tumors must have unequivocal histologic evidence of malignancy; (2) histologically, the two

![Fig. 2. A) Distribution of cells with a diffuse effect and blood vessels between them (arrow; hematoxylin and eosin, 10×). B) Distribution of oval cells with minimal small, atypical, relatively monotonous, vesicular nuclei (hematoxylin and eosin, 40×).](image-url)
tumors must be different; and (3) the second tumor cannot be a metastasis of the primary tumor. The occurrence of two or more primary malignant tumors in a single patient was classified as an MPM. MPM is divided into two types, synchronous and metachronous, depending on when the tumors are diagnosed. In synchronous MPM, a second tumor is diagnosed simultaneously or within two months of the first tumor, whereas in metachronous MPM, a second tumor is identified more than six months after the first tumor. In various settings, the prevalence of MPM has ranged from 0.52 to 11.2 % [10,11]. Over seven years, a retrospective clinical study in Shaanxi, China, revealed a 1% frequency of MPM among 15,683 patients diagnosed with malignant tumors [10].

Women with BC have a greater risk of developing a second malignancy than the overall population. Still, synchronous non-breast cancer is extremely rare in BC patients [10,12]. Synchronous BC and malignant lymphoma are infrequent. Malignant lymphoma is identified in the breast or the ipsilateral axillary lymph nodes in the majority of synchronous BC and malignant lymphoma cases [10]. However, our patient has synchronous BC and malignant lymphoma of the cervical lymph nodes.

MPMs have a complex etiology that has yet to be determined [10,13]. Several potential causal variables of MPMs have been identified, including environmental, intrinsic, therapeutic, and genetic
Fig. 4. Ultrasonography after chemotherapy: (A) A regular hypoechoic mass 1.0 × 0.5 cm in the left breast (yellow arrow), (B) no enlarged lymph nodes in the left axilla, and (C) no enlarged lymph nodes in the neck. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
of BC concurrent with lymphoma may share viral origins. Beyond that, genetic factors may include genetic
factors. Long-term exposure to pollution and/or radiation, as well as lifestyle, can also play a role, while intrinsic factors may consist of
intrinsic factors may consist of vulnerability, immune status, embryonic development, and endocrine
development. Radiation therapy and chemotherapy are the most common therapeutic factors, whereas genetic factors may include genetic
alterations [10]. Wiernik et al. [14] have hypothesized that some cases of BC concurrent with lymphoma may share viral origins. Beyond that, Subramanian et al. [15] have hypothesized that the oncogenic Epstein–Barr virus, which interacts with the Nm23-H1 metastasis suppressor protein to prevent it from inhibiting breast and lymphoma cell
migration, is the causative factor of the dissemination of both invasive BC and lymphomas.

Indolent lymphomas, such as the SLL variety, make lymphoma and BC diagnosis difficult. Patients with NHL present with fever, night
sweats, and weight loss, also known as B symptoms. Patients with a high-grade variety of NHL are more likely to have systemic B symptoms.

Table 1
Timeline of the case.

| Dates                  | Relevant medical history | Summaries from initial and follow-up visits | Diagnostic testing | Interventions               |
|------------------------|--------------------------|--------------------------------------------|--------------------|-----------------------------|
| January 2019           | Painless lump in the left side of necks at levels IIA and III | FNA: Tuberculous lymphadenopathy | Antitubercular drugs for 9 months, after which the patient has remained well and shown no further symptoms |
| January 2020           | The breast lump was initially as large as 1.0 × 1.5 cm but painless. | FNA: Adenocarcinoma in the left breast and NHL in the neck mass | – | – |
| February–October 2020  | The Indonesian government imposed a lockdown due to the COVID-19 pandemic so that hospitals temporarily only provided emergency treatment for an emergency case. | Open biopsy: | Eight cycles of chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) |
| November 2020          | The breast lump was enlarged (3.8 × 2.6 cm), as was the lump in the left side of the neck (1.5 × 1 cm). | | | |
| April 2021             | The lump in the left breast had decreased in size. | US images showed an irregular hypoechoic mass in the left breast and abnormal regional lymph nodes in the left axilla. | Surgery scheduled for the following week to remove the tumor. The patient did not return for surgery, however, due to residing in a rural village with little access to public transportation. No follow-up |
| May–August 2021        | The patient presented with the complaint of a large palpable lump in her left breast and a lump in the left side of her neck. Clinical examination revealed a firm, painless, mobile, poorly circumscribed tumor approximately 5 × 4 × 4 cm in the upper outer quadrant of the left breast with no associated lymphadenopathy. Examining the contralateral breast and axilla yielded nothing remarkable, whereas examining the lymph node in the left neck at level III revealed a firm, mobile tumor approximately 1 × 1 cm. | | Left mastectomy |
| October 2021           | The patient remained in follow-up, with no symptoms or evidence of the tumor’s recurrence. | | Chemotherapy with paclitaxel and trastuzumab |
| December 2021          | The patient remained in follow-up, with no symptoms or evidence of the tumor’s recurrence. | | Chemotherapy with paclitaxel and trastuzumab |
| June 2022              | The patient remains in follow-up, with no symptoms or evidence of the tumor’s recurrence. | | Tamoxifen and goserelin |

Notes: FNA = fine-needle aspiration; NHL = non-Hodgkin lymphoma; COVID-19 = coronavirus disease of 2019; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; PR = progesterone receptors; ER = estrogen receptors; HER-2 = human epidermal growth factor receptor 2; US = ultrasonography; CD20 = cluster of differentiate 20; CD45 = cluster of differentiate 45; Ca-153 = carcinoma antigen 15-3; CEA = carcinoembryonic antigen.
Painless peripheral lymphadenopathy affects more than two thirds of individuals [16]. The majority of patients with early-stage NHL have no obvious symptoms or abnormalities in their lab tests. NHL frequently manifests with adenopathy. In addition to the breast tumor, patients with BC may have axillary adenopathy. Atypical signs and symptoms, as in early-stage BC and distant adenopathy, may lead the treating physician to believe that the patient has synchronous cancer rather than metastatic disease. The diagnosis of synchronous pathology may be overlooked if adenopathy arises only in the axillary lymph nodes or if BC is locally progressed. Therefore, the pathologist should consider performing various IHC stains to differentiate the different diagnoses. When lymphoma is suspected, clinicians should consider running a comprehensive IHC panel, including CD3, CD5, BCL6, CD10, CD20, CD23, and cyclin D1 [17,18]. We conducted an IHC, CD20, and CD45 examination of this patient, with positive results.

The management of BC and SLL differs significantly, creating yet another challenge. No guidelines presently exist for treating BC and lymphoma simultaneously, and it is unclear whether synchronous tumors should be treated as two different clinical entities with separate treatments or as a single disease with treatment that covers both tumor types. Therefore, the best approach is to focus on the most biologically aggressive malignancies. According to the best practice statement, multidisciplinary teams should discuss and make treatment recommendations based on the initial presentation of each cancer’s type and stage, as well as the prognosis of malignancy and current status.

According to the National Comprehensive Cancer Network (NCCN), the first choice of therapy for SLL depends on the disease stage, the presence or absence of TP53 or del(17p) mutations, immunoglobulin heavy-chain variable region gene mutation status, patient age, performance status, presence of comorbid disease, and the toxicity profile of chemotherapeutic agents [18]. The NCCN recommends observation versus locoregional radiotherapy plus anti-CD 20 monoclonal antibody (rituximab, obinutuzumab) therapy. Chemotherapy may be added if the patient has systemic B symptoms or if progressive bulky disease, progressive anemia, and progressive thrombocytopenia are indicated [18,19]. Before therapy, evaluating the fluorescent in situ hybridization for del(17p), TP53 mutation status, and CpG-stimulated karyotype is advisable [18]. However, this examination does not exist in Indonesia. Therefore, we administered R-CHOP chemotherapy. The components of this regimen also contain an AC (doxorubicin/adriamycin and cyclophosphamide) regimen, so it can be helpful for BC as well.

According to NCCN recommendations, tumor, node and metastasis staging is used to determine treatment for invasive BC. The standard of care is still surgery with a modified radical mastectomy or a lumpectomy followed by radiation therapy (breast-conserving therapy [BCT]). BCT is the therapy of choice for early-stage BC, according to recent studies [17]. Chemotherapy regimens for luminal B type are:

- Dense AC dosages, followed by dense paclitaxel doses.
- AC at a high dose, followed by paclitaxel every week.
- Docetaxel in combination with cyclophosphamide.

Surgical oophorectomy and ovarian irradiation are two options for treating ovarian ablation. Luteinizing hormone-releasing hormone (LHRH) agonists can be used to inhibit ovarian estrogen synthesis by inhibiting the secretion of the pituitary follicle-stimulating hormone and luteinizing hormone [20,21]. In Indonesia, the LHRH agonist drugs available, goserelin and leuprolide, to be administered every 1 or 3 months. Adjuvant endocrine therapy with selective estrogen receptor modulators (SERMs) such as tamoxifen or aromatase inhibitors (i.e., letrozole, exemestane, and anastrozole) is recommended for all patients with hormone receptor positive (HR+) BC [17,20]. According to the Early Breast Cancer Trialists’ Collaborative Group [22], women with early-stage HR+ BC who received adjuvant SERM or tamoxifen medication for 5 years had a nearly 30 % lower risk of death. In our premenopausal patient with luminal-B BC, we administered AC chemotherapy with paclitaxel and trastuzumab, followed by endocrine therapy with tamoxifen and ovarian suppression therapy with goserelin.

The prognosis of lymphoma and breast cancer alone is usually poor, and synchronous malignancies will worsen the prognosis. But in our patients, the follow-up to 8 months post-mastectomy indicated satisfying results, with no evidence of the tumor recurrence. Repeated histology and laboratory tests spaced approximately three to six months apart for five years, then annually, are recommended for surveillance. Imaging such as a contrast chest, abdominal, and pelvic computed tomography scan every six months is suggested for up to two years, then every year [17].

4. Conclusion

The enlargement of lymph nodes not in the lymphatic drainage of the primary tumor should be suspected of indicating MPM until proven otherwise. As our rare case of synchronous BC with NHL and brief review of the literature have shown, MPMs can challenge diagnosis and treatment and consequently require the complete staging assessment of both types of tumors in order to determine the best treatment option. For patients with luminal-B BC, NHL chemotherapy can involve receiving the R-CHOP regimen, including doxorubicin and cyclophosphamide, which can help to mitigate BC.

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Ethical approval

The study is exempt from ethical approval in our institution.

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.

Author contribution

Salman Ardi Syamsu: study concept and surgical therapy for this patient. Salman Ardi Syamsu and Rino Setiady: Data collection and Writing-Original draft preparation. Nilam Smaradania and Prihantono: senior author and the manuscript reviewer. Salman Ardi Syamsu, Rino Setiady and Muhammad Faruk: Editing and Writing. All authors read and approved the final manuscript.

Registration of research studies

Not applicable – single case report.

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Declaration of competing interest

Nothing to declare.
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