Nodular sclerosing Hodgkin's lymphoma with breast involvement: Case report and review of the literature

Yashpal Modi, David Thomas, Hamid Shaaban, Trevor Layne, Gunwant Guron

Abstract
Extranodal disease in Hodgkin’s lymphoma (HL) is very rare and it occurs in 15%-30% of all cases. The intrathoracic area is the most common extranodal presentation. There are very few cases in the medical literature of breast involvement with HL. We report a 25-year-old woman who had been managed and treated for nodular sclerosing HL for 6 months, but she was noncompliant with chemotherapy. She presented 1 year later with a palpable left breast mass and B symptoms. The fluorine-18 fluorodeoxyglucose-positron emission tomography images revealed disseminated disease with a left breast mass demonstrating fluorodeoxyglucose uptake. Histopathology of the ultrasound-guided biopsy specimen of the breast mass was consistent with recurrence. This case highlights the need for an awareness of HL presenting in this way because the diagnosis has therapeutic and prognostic implications.

Key words: Breast neoplasms, Hodgkin’s disease, lymphoma

INTRODUCTION
Hodgkin’s lymphoma (HL) is almost always restricted to the lymph nodes. The extranodal manifestations of this disease entity are not very common. In fact, extranodal presentation of HL with or without lymphatic involvement occurs in 15%-30% cases. The most affected extranodal site of involvement is the intrathoracic region. HL of the breast, as a primary malignancy or as recurrent disease is unusual. In general, lymphoproliferative disorders constitute about 0.15% of all breast neoplasms. Less than 0.5% of all malignant lymphomas have secondary breast involvement. Primary breast lymphomas are less common than secondary involvement by lymphoma with other nodal or extranodal sites of disease. We report a rare case of HL with the breast as an atypical extranodal site of involvement.

CASE REPORT
A 25-year-old woman diagnosed as having nodular sclerosing HL from the left axillary lymph node biopsy almost 2 years ago presented to our clinic for evaluation of a 1 month history of a palpable left breast mass. At the time of initial diagnosis, she was staged at stage 2B. However, she was noncompliant with treatment with the chemotherapy regimen containing adriamycin, bleomycin, vinblastin, and dacarbazine (ABVD), receiving a total of only 2 cycles and was then subsequently lost to follow-up. She never received any radiation therapy. She had received her last course approximately 6 months ago. In addition to the left breast mass, the patient denied any weight loss and night sweats in the 1 month duration. On examination, she had a hard 2 cm diameter fixed mass proximal to the left nipple. No lymphadenopathy or organomegaly was detected. Full blood count revealed a mild lymphocytosis for her age (total leukocyte count, 9.53 × 10^9/L; lymphocyte count, 5.01 × 10^9/L; neutrophil count, 7.04 × 10^9/L). The erythrocyte sedimentation rate was 35 mm/h and biochemical screening tests (including urea and electrolytes, liver function tests, lactate dehydrogenase, and immunoglobulins) were within normal limits. Ultrasound studies revealed an asymmetric hypoechoic density above the left nipple, with moderate distortion of the surrounding breast tissue, but no evidence of calcifications [Figure 1]. Fine-needle aspiration cytology was suspicious of malignancy. A core biopsy with the aid of ultrasound was then taken. The histopathology demonstrated nodular sclerosing HL with neoplastic Reed-Sternberg cells [Figure 2] that were positive for CD30 [Figure 3a] and CD15 [Figure 3b], and negative for...
CD20, CD3, and CD79a. No abnormal cell populations were identified on flow cytometry study. She had a fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography FDG-PET/CT scan for restaging, which revealed FDG-avid hypermetabolic lymphadenopathy in the left cervical, left axillary, and left inguinal regions. Because the patient was never adequately treated with the first chemotherapy regimen (ABVD), because of her noncompliance issues, we have opted to resume the same regimen this time.

**DISCUSSION**

This case report documents an atypical clinical presentation of extranodal HL with breast involvement. Over 90% of cases of breast masses in patients who present to a breast clinic are benign. There is an increased risk for breast carcinoma at young age secondary to the radiation therapy for HL. Although breast carcinoma is of major concern as a differential diagnosis, other uncommon causes of breast mass include granular cell tumor, chronic fungal infection, tuberculosis of breast, and lymphoma. Diffuse large B-cell lymphoma and Burkitt’s lymphoma are the more frequent types of lymphoma in the breast. Rare cases of breast involvement with MALT lymphoma, follicular lymphoma, and T-cell and histiocytic lymphomas have also been reported.

HL of the breast is a very unusual occurrence. The first case report of HL involving the breast was described by Kuckens in 1928. Wood *et al.* reviewed 354 localized extranodal HL cases reported until 1973 and discovered eight cases of primary HL limited to the breast. Park *et al.* reviewed 30 cases of breast involvement of HL in the literature. Interestingly, those cases were initially suspected to be primary breast carcinoma until the diagnosis of HL was confirmed by immunohistochemistry. Hoimes *et al.* recently reported a patient with breast mass and ipsilateral axillary lymph nodes revealed nodular sclerosing HL by a core biopsy. That patient has stage 4A disease with bone and bone marrow involvement. Ergul *et al.* reported a patient with recurrent HL with disseminated lymphadenopathy along with bilateral breast involvement. In our patient, left cervical, axillary, and inguinal lymphadenopathy along with a left breast mass was noted. On review of the literature, it is clear that metastatic involvement of breasts with lymphoma is a more common clinical presentation than the primary breast lymphoma.

From our review, the mean age of patients with HL in the breast was 33.5 (SD 16.6) years. Aksu *et al.* reported the first case of HL of the breast in a child, a 12-year-old girl, with bulky cervical and axillary lymphadenopathy and two masses in the right breast. Biopsy of the supraclavicular node was done and histopathology confirmed nodular sclerosing HL. The breast masses and lymphadenopathy regressed after the administration of chemotherapy.

Only two cases of HL in the breast have been described in males. The most common mammographic finding, in breast lymphoma, is a well-defined hyperdense mass without
calcification. Hypoechoic solitary uncaldified masses with indistinct margins are classically seen on ultrasound.\(^6,7\)

Younger patients have dense breast parenchymal tissue and so there is an increasing use of PET/CT scan to identify and also better delineate the extent of breast involvement with HL. The accuracy of this modality is not affected by breast parenchymal density.\(^8,9\)

As in our case, the diagnosis of HL in the breast is usually made by biopsy and the histopathological identification of the classic Reed-Sternberg cells. It is also important to stress the importance of immunohistochemical staining to confirm the diagnosis.\(^10\)

Specific poor prognostic markers of HL in the breast have not been identified. Our patient did not exhibit B symptoms (weight loss, intermittent fever, and profuse night sweating) or any laboratory findings related to worse prognosis such as elevated erythrocyte sedimentation rate, low serum albumin, low hemoglobin, and low lymphocyte count. In cases of breast lymphoma that showed low lymphocyte count, the survival was roughly 9 months after initial presentation.\(^19\)

Our review of the literature, however, suggests that the presence of B symptoms appear to be associated with a poor prognosis.\(^19-21\)

**CONCLUSION**

We describe an unusual case of HL in a young patient who presented with a fixed breast mass with no B symptoms and no palpable lymphadenopathy. These clinical findings are typically worrisome for breast carcinoma. The imaging studies could not accurately differentiate HL from primary breast carcinoma. Subsequently, the pathological findings of Reed-Sternberg cells on the solid core biopsy specimen confirmed the diagnosis of HL. Our case should alert physicians to consider lymphoma-like HL as a differential diagnosis because the diagnosis has prognostic and therapeutic implications. Its accurate identification using a repertoire of diagnostic tests including immunohistochemical analysis is important, and pathologists should be equally aware that HL may present in this unusual way.

**REFERENCES**

1. Guermazi A, Brice P, de Kerviler EE, Fermé C, Hennequin C, Meignin V, et al. Extranodal Hodgkin disease: Spectrum of disease. Radiographics 2001;21:161-79.
2. Yang WT, Lane DL, Le-Petross HT, Abruzzo LV, MacApinlac HA. Breast lymphoma: Imaging findings of 32 tumors in 27 patients. Radiology 2007;245:692-702.
3. Talwalkar SS, Miranda RN, Valbuena JR, Routhert MJ, Martin AW, Medeiros LJ. Lymphomas involving the breast: A study of 106 cases comparing localized and disseminated neoplasms. Am J Surg Pathol 2008;32:1299-309.
4. Codd R, Gateley CA. Management of benign disease of the breast. Surgery (Oxford) 2007;25:264-7.
5. Alm El-Din MA, Hughes KS, Finkelstein DM, Betts KA, Yock Tl, Tarbell NJ, et al. Breast cancer after treatment of Hodgkin’s lymphoma: Risk factors that really matter. Int J Radiat Oncol Biol Phys 2009;73:69-74.
6. Sabate JM, Gomez A, Torrubia S, Camins A, Roson N, De Las Heras P, et al. Lymphoma of the breast: Clinical and radiologic features with pathologic correlation in 28 patients. Breast J 2002;8:294-304.
7. Cao YB, Wang SS, Huang HQ, Xu GC, He YJ, Gauan ZZ, et al. Primary breast lymphoma: A report of 27 cases with literature review. Ai Zheng 2007;26:84-9.
8. Kuckens H. Localised breast lymphogranuloma as a form of mammary tumor. Beitr Path Anat 1928;80:135.
9. Wood NL, Coltman CA. Localized primary extranodal Hodgkin’s disease. Ann Intern Med 1973;78:113-8.
10. Park J, Rizzo M, Jackson S, Bates SR, Green V, Oprea-Ilie G. Reed-Sternberg cells in breast FNA of a patient with left breast mass. Diagn Cytopathol 2010;38:663-8.
11. Hoimes CJ, Selbst MK, Shaff NJQ, Rose MG, Rosado MF. Hodgkin’s lymphoma of the breast. J Clin Oncol 2010;28:e11-3.
12. Ergül N, Güner ŞI, Sağır S, Huq GE, Çiçtiç H, Çermik TF. Bilateral breast involvement of Hodgkin lymphoma revealed by FDG PET/CT. Med Oncol 2012;29:1105-8.
13. Garg NK, Bagul NB, Rubin G, Shah EF. Primary lymphoma of the breast involving both axilla with bilateral breast carcinoma. World J Surg Oncol 2008;6:32.
14. Aksu G, Inan N, Corapcioglu F, Tugay M, Anik YA. Breast involvement in nodular lymphocyte predominant type Hodgkin lymphoma in childhood. Pediatr Hematol Oncol 2008;25:159-61.
15. Adair FE, Craver LF, Herrmann JB. Hodgkin’s disease of the Breast. Surg Gynecol Obstet 1945;80:205-10.
16. Frauolini C, Mauro E, Rigolim GM, Bissoli S, Chierichetti F, Panareo S, et al. A case of advanced Hodgkin lymphoma with breast involvement treated with a combination of gemcitabine and pegylated liposomal doxorubicin. Eur J Haematol 2005;75:515-7.
17. Kumar R, Xiу Y, Dhurairaj T, Yu JQ, Alavi A, Zhuang H. F-18 FDG positron emission tomography in non-Hodgkin lymphoma of the breast. Clin Nucl Med 2005;30:246-8.
18. Tantisattamo E, Bello EF, Acoba JM, Torrubia D, Melnick. Neutrophilic granulomatous mediastinal tumor. Hawaii J Med Public Health 2009;73:69-74.
19. Adair FE, Craver LF, Herrmann JB. Hodgkin’s disease of the Breast. Surg Gynecol Obstet 1945;80:205-10.
20. Fraulini C, Mauro E, Rigolim GM, Bissoli S, Chierichetti F, Panareo S, et al. A case of advanced Hodgkin lymphoma with breast involvement treated with a combination of gemcitabine and pegylated liposomal doxorubicin. Eur J Haematol 2005;75:515-7.
21. Kumar R, Xiу Y, Dhurairaj T, Yu JQ, Alavi A, Zhuang H. F-18 FDG positron emission tomography in non-Hodgkin lymphoma of the breast. Clin Nucl Med 2005;30:246-8.
22. Tantisattamo E, Bello EF, Acoba JM, Torrubia D, Melnick. Neutrophilic granulomatous mediastinal tumor. Hawaii J Med Public Health 2009;73:69-74.