Spontaneous Regression of a Clinically-Advanced Histologically Low-Grade Follicular Lymphoma Involving the Breast: Case Report and Review of the Literature

Yasunobu Sekiguchi · Asami Shimada · Hidenori Imai ·
Mutsumi Wakabayashi · Keiji Sugimoto · Noriko Nakamura ·
Tomohiro Sawada · Norio Komatsu · Masaaki Noguchi

Received: 15 November 2013 / Accepted: 28 March 2014 / Published online: 16 April 2014
© Indian Society of Haematology & Transfusion Medicine 2014

Abstract A 68-year-old woman was diagnosed as having grade 1 follicular lymphoma of the left breast in November 2012. Bone marrow infiltration was noted histologically and confirmed by Southern blot analysis of the IgHJH locus. The clinical stage was IVA, advanced stage. According to the Follicular Lymphoma International Prognostic Index, the patient was classified into the high risk group. The general condition was good and there were no organ symptoms, therefore, the patient was kept under observation without treatment. After one year and 2 months of follow up, The mass was regressed spontaneously. As previous studies have suggested a poor prognosis of patients with an advanced clinical stage of the disease, careful follow-up of our patient is necessary.

Keywords Follicular lymphoma · Breast · Primary · Secondary

Introduction

Breast lymphomas, including primary and secondary lymphomas, are rare, accounting for less than 0.5 % of all breast tumors [1] and 0.38–0.7 % of all non-Hodgkin's lymphomas [2]. In addition, previous studies have shown that most breast lymphomas are mostly diffuse large B cell lymphomas (DLBCL) [1, 3–5], and there have been only two reports of small-scale studies of follicular lymphoma (FL) of the breast: one report of primary FL [6] and another of secondary FL [2]. According to these two reports, both primary and secondary FLs have a poor prognosis. Therefore, it is necessary to conduct large-scale studies after accumulating further cases to determine the clinical features, molecular biological characteristics and prognosis of FL of the breast.

Case Report

The patient was a 68-year-old woman with a category 3 mass (according to the Breast Imaging Reporting and Data System [7]) in the left breast detected by mammographic screening for breast cancer. Her medical history included surgery for acute appendicitis at age 19, surgery for uterine myoma at age 39, and sudden right hearing loss at age 64. She had no significant family history. Screening for breast cancer by mammography in October 2012 revealed a mass in the left breast, and the patient visited the Department of Breast Surgery of our hospital in November. Needle biopsy of the left breast mass led to the diagnosis of grade 1 FL, and she was referred to our department.

At the time of hospitalization, general physical and systemic examination was unremarkable except for a palpable mass in the left breast that was about 12.5 mm in

Y. Sekiguchi (✉) · A. Shimada · M. Wakabayashi ·
K. Sugimoto · M. Noguchi
Department of Hematology, Juntendo University Urayasu
Hospital, 1-1, 2-chome, Tomioka, Urayasu,
Chiba Prefecture 279-0021, Japan
e-mail: yasu_sek@juntendo-urayasu.jp

A. Shimada · N. Komatsu
Department of Hematology, Juntendo University Hospital,
3-1-3 Hongo, Bunkyo-ku, Tokyo 113-8431, Japan

H. Imai
Shibanishi Clinic, Shimada-Setsubi Building 1F, 27-16,
2-chome, Shibanishi, Kawaguchi, Saitama Prefecture 333-0855,
Japan

N. Nakamura · T. Sawada
Department of Laboratory Medicine, Juntendo University,
Urayasu Hospital, 1-1 2-chome, Tomioka, Urayasu,
Chiba Prefecture 279-0021, Japan

Fig. 1 **a** Mammography showed a high-density mass with a smooth border measuring 9 mm in diameter in the *left upper quadrant* of the left breast (*red arrow*) **b**, Breast ultrasound revealed a hypoechoic lesion measuring $9.4 \times 6.7 \times 9.3$ mm in size, with evidence of rich blood flow (*blue arrows*)

diameter, non-tender, elastic-soft in consistency, and mobile. The overlying skin and the nipple were normal. There was no palpable lymphadenopathy or abdominal organomegaly.

At the first examination, laboratory findings revealed no abnormalities of the blood counts, coagulation profile, immunological indices, or urinalysis results. Biochemical tests revealed only a mild increase of the serum LDH (260 IU/l, institutional reference range 119–229 IU/l). Serum soluble IL-2 receptor levels were within normal range (381 U/ml, institutional reference range 145–519 U/ml).

Fig. 2 ^{18}F -fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET-CT) revealed FDG accumulation in the left mammary gland (standardized uptake value [SUV] max = 1.5; *yellow arrows* in **a**, **b**), mesentery (SUV max = 1.8; *yellow arrow* in **c**)

Mammography showed a high-density mass with a smooth border in the left upper quadrant of the left breast (*red arrow* in Fig. 1a); Ultrasound revealed a hypoechoic lesion measuring $9.4 \times 6.7 \times 9.3$ mm in size, with evidence of rich blood flow (*blue arrows* in Fig. 1b) ^{18}F -fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET-CT) revealed FDG accumulation in the left mammary gland (standardized uptake value [SUV] max = 1.5; *yellow arrows* in Fig. 2a, b), mesentery (SUV max = 1.8; *yellow arrow* in Fig. 2c),

Histopathologic findings of needle biopsy specimens obtained from the breast mass were as follows: Examination of hematoxylin-eosin (HE)-stained sections under low magnification showed formation of somewhat indistinct lymphoid follicles (Fig. 3a); examination under high magnification showed that the germinal center was composed mainly of small cells (Fig. 3b). Positive staining for Bcl 2, CD10 and CD20 was observed, and the MIB 1 index was 10 % (Fig. 3c–g). The B-cells showed surface kappa light chain restriction. Fluorescence in situ hybridization of the needle biopsy specimens revealed the IgH-BCL 2 reciprocal translocation (not shown). Histopathologic examination of bone marrow biopsy specimens raised the suspicion of bone marrow infiltration, as small paratrabeular lymphoid aggregates (*yellow arrows*) were found on the slide (Fig. 3h). Southern blot analysis of the bone marrow blood cells revealed rearrangement of the IgHJH gene (Fig. 4). Based on the above, the patient was diagnosed as having grade 1 FL, and the clinical stage was diagnosed as stage IVA, based on the detection of bone marrow infiltration. The patient was classified as a high-risk patient according to the Follicular Lymphoma International Prognostic Index, based on the age, increased

Fig. 3 Histopathologic findings of needle biopsy specimens obtained from the breast mass **a** HE staining ($\times 40$) show formation of somewhat indistinct lymphoid follicles. **b** HE staining ($\times 600$) showed that the follicles were composed mainly of small cells. **c** Follicles showing positive staining for Bcl 2 ($\times 40$). **d** Positive CD10 staining

of the follicles ($\times 40$). **e** Positive CD10 staining of the follicles ($\times 600$). **f** Positive CD20 staining of the follicles ($\times 40$). **g** The MIB 1 index was 10 % ($\times 40$). **h** Histopathologic findings of HE-stained sections of the bone marrow ($\times 40$) showed small paratrabecular lymphoid aggregates (yellow arrows)

LDH levels, and clinical stage. Her general condition was good and there were no organ symptoms, therefore, the patient was kept under observation without treatment. As of November 2013, after one year and 2 months of follow up, her general condition remains good, with no palpable mass in the breast. The mass was regressed spontaneously.

Discussion

A strict definition of primary breast lymphoma was first proposed by Wiseman and Liao as follows: (1) adequate pathological evaluation, (2) presence of both mammary tissue and lymphomatous infiltrate in close association, and (3) exclusion of systemic lymphoma or previous extramammary lymphoma [8]. There is also a report that a breast lesion is defined as a primary lesion if it is the main lesion, regardless of the disease stage and the presence/absence of infiltration of other organs [9]. Thus, there are differences in the definition of the primary lesion among

reports, but lesions other than the primary lesions are considered to be secondary lesions.

It has been reported that the incidence of primary breast lymphoma is almost the same as [10] or slightly lower than [11] that of secondary breast lymphoma, but most of both primary and secondary breast lymphomas are B cell lymphomas. DLBCL is common among primary breast lymphoma [5, 12, 13]. However, there are some reports suggesting that DLBCL is also common among secondary breast lymphomas [10, 14–17] and some reports that FL is common [11, 18].

Most detailed analyses of breast lymphomas have involved patients with DLBCL [1, 3–5], and there have been only two reports of studies analyzing FL of the breast in detail: a retrospective study of 36 patients with primary FL [6] and another retrospective study of 15 patients with secondary FL [2].

To the best of our knowledge, there have been a total of 179 reported cases of FL of the breast, including 91 cases of primary FL, 73 cases of secondary FL (including the

Fig. 4 Southern blot analysis for Ig(H)JH in bone marrow blood cells: The restriction enzymes are: lane 1, EcoR I; lane 2, BamH + Hind III; and lane 3, Hind III. A gene rearrangement band was detected (red arrow), leading to the diagnosis of bone marrow infiltration

present case) and 15 cases of primary or secondary FL (Table 2) [1, 2, 4–6, 9–12, 14–16, 18]. Most of these cases have been described in case reports or additionally described in reports of other lymphomas such as DLBCL, and the molecular biological characteristics, clinical symptoms, prognosis, etc., of FL of the breast have not yet been clarified in detail. However, Talwalkar et al. [2] described that the molecular biological characteristics of secondary FL were similar to those of nodal FL, based on a study of 15 patients with secondary FL. Future studies on a larger number of cases are expected.

In the study reported by Martinelli et al. [6], who retrospectively analyzed the data of 36 primary FL patients followed up for a mean observation period of 44 months, 14 patients died, the 10-year overall survival was 47 %, and the progression-free survival was 28 %, the outcome being worse than that in patients with localized nodal FL treated by a “watch-and-wait” approach.

A retrospective study by Talwalkar et al. [2] of 15 patients with secondary FL of the breast showed that the outcome of this disease was extremely poor, with a median overall survival of 24 months and a median disease-free survival of 14 months. From the above, it is speculated that the prognoses of both primary and secondary FL are poor. Actually, Ganjoo et al. [4] reported that the usual treatment for low-grade lymphoma should be given to patients with advanced stages or clinical symptoms. However, these data were obtained before rituximab became available for treatment, and it is considered essential to analyze the data after accumulation of patients treated with rituximab.

The prognoses of both primary and secondary FL may be poor, and it is necessary to conduct large-scale studies after accumulating a larger number of cases in the future to determine the molecular biological characteristics and prognostic factors of FL of the breast. Furthermore, it will be desirable to establish new treatment strategies including rituximab. This case was due to distant LN involvement, there is a possibility of secondary involvement of breast by grade 1 FL which is also an uncommon instance.

References

1. Gualco G, Bacchi CE (2008) B-cell and T-cell lymphomas of the breast: clinical–pathological features of 53 cases. *Int J Surg Pathol* 16:407–413. doi:10.1177/1066896908316784
2. Talwalkar SS, Miranda RN, Valbuena JR, Routbort MJ, Martin AW, Medeiros LJ (2008) Lymphomas involving the breast: a study of 106 cases comparing localized and disseminated neoplasms. *Am J Surg Pathol* 32:1299–1309. doi:10.1097/PAS.0b013e31865eb50
3. Ryan G, Martinelli G, Kuper-Hommel M, Tsang R, Pruneri G, Yuen K, Roos D, Lennard A, Devizzi L, Crabb S, Hossfeld D, Pratt G, Dell’Olio M, Choo SP, Bociek RG, Radford J, Lade S, Gianni AM, Zucca E, Cavalli F, Seymour JF, International Extranodal Lymphoma Study Group (2008) Primary diffuse large B-cell lymphoma of the breast: prognostic factors and outcomes of a study by the International Extranodal Lymphoma Study Group. *Ann Oncol* 19:233–241
4. Ganjoo K, Advani R, Mariappan MR, McMillan A, Horning S (2007) Non-Hodgkin lymphoma of the breast. *Cancer* 110:25–30
5. Fruchart C, Denoux Y, Chasle J, Peny AM, Boute V, Ollivier JM, Genot JY, Michels JJ (2005) High grade primary breast lymphoma: is it a different clinical entity? *Breast Cancer Res Treat* 93:191–198
6. Martinelli G, Ryan G, Seymour JF, Nassi L, Steffanoni S, Alietti A, Calabrese L, Pruneri G, Santoro L, Kuper-Hommel M, Tsang R, Zinzani PL, Taghian A, Zucca E, Cavalli F (2009) Primary follicular and marginal-zone lymphoma of the breast: clinical features, prognostic factors and outcome: a study by the International Extranodal Lymphoma Study Group. *Ann Oncol* 20:1993–1999. doi:10.1093/annonc/mdp238
7. Bae MS, Moon WK, Chang JM, Koo HR, Kim WH, Cho N, Yi A, La Yun B, Lee SH, Kim MY, Ryu EB, Seo M (2014) Breast cancer detected with screening US: reasons for nondetection at mammography. *Radiology* 270(2):369–377
8. Wiseman C, Liao KT (1972) Primary lymphoma of the breast. *Cancer* 29:1705–1712. doi:10.1002/1097-0142(197206)29:6<1705:AID-CNCR2820280640>3.0.CO;2-I
9. Loughrey MB, Windrum P, Catherwood MA, Alexander HD, Markey GM, McManus DT, Morris TC (2004) WHO reclassification of breast lymphomas. *J Clin Pathol* 57:1213–1214
10. Cohen PL, Brooks JJ (1991) Lymphomas of the breast. A clinicopathologic and immunohistochemical study of primary and secondary cases. *Cancer* 67:1359–1369
11. Domchek SM, Hecht JL, Fleming MD, Pinkus GS, Canellos GP (2002) Lymphomas of the breast: primary and secondary involvement. *Cancer* 94:6–13
12. Liu MT, Hsieh CY, Wang AY, Pi CP, Chang TH, Huang CC, Huang CY (2005) Primary breast lymphoma: a pooled analysis of prognostic factors and survival in 93 cases. *Ann Saudi Med* 25:288–293

13. Park YH, Kim SH, Choi SJ, Ryoo BY, Kang YK, Lee SS (2004) Primary malignant lymphoma of the breast: clinicopathological study of nine cases. *Leuk Lymphoma* 45:327–330
14. Arber DA, Simpson JF, Weiss LM, Rappaport H (1994) Non-Hodgkin's lymphoma involving the breast. *Am J Surg Pathol* 18:288–295
15. Sabaté JM, Gómez A, Torrubia S, Camins A, Roson N, De Las Heras P, Villalba-Nuño V (2002) Lymphoma of the breast: clinical and radiologic features with pathologic correlation in 28 patients. *Breast J* 8:294–304
16. Kuper-Hommel MJ, Snijder S, Janssen-Heijnen ML, Vrints LW, Kluin-Nelemans JC, Coebergh JW, Noordijk EM, Vreugdenhil G (2003) Treatment and survival of 38 female breast lymphomas: a population-based study with clinical and pathological reviews. *Ann Hematol* 82:397–404
17. Au WY, Chan AC, Chow LW, Liang R (1997) Lymphoma of the breast in Hong Kong Chinese. *Hematol Oncol* 15:33–38
18. Mattia AR, Ferry JA, Harris NL (1993) Breast lymphoma. A B-cell spectrum including the low grade B-cell lymphoma of mucosa associated lymphoid tissue. *Am J Surg Pathol* 17:574–587