Case Reports

Four Cases of Central Nervous System Involvement of Breast Malignant Lymphoma

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Although malignant lymphoma of the breast is a rare disease, we recently experienced a high incidence of central nervous system (CNS) involvement. Thus, we retrospectively reviewed clinical records of 921 patients with breast tumors, treated from 1990 to 2002, to examine CNS involvement. Eight patients were found to have malignant lymphomas during this period. Of these, four patients ranging from 46 to 80 years of age had CNS involvement, one with Burkitt type and three with diffuse large B-cell lymphoma. The patients received surgery and/or chemotherapy and/or radiotherapy. The four other patients without CNS involvement are alive without tumor, whereas three of four patients with CNS involvement died of the disease. It should be noted that CNS involvement in breast lymphoma is not so rare. It is difficult, but important, to determine whether malignant lymphoma of the breast originates in the breast or is of systemic origin. Although brain metastasis could be treated effectively by radiotherapy and/or chemotherapy, the prognosis was poor. Further intensive treatment is required for breast malignant lymphoma with CNS involvement.

Key words: malignant lymphoma – breast – central nervous system

INTRODUCTION

The breast is rarely a primary site of extranodal malignant lymphoma. The reported incidence of primary breast lymphoma varies from 0.04% to 0.53% of all malignant diseases of the breast, and comprises 2.2% of extranodal malignant lymphoma (1). The most frequent histology is a non-Hodgkin lymphoma of B-cell phenotype (2). Between January 1990 and June 2002, 921 cases of malignant breast tumor were treated in our hospital, and eight cases (0.9%) were identified as malignant lymphoma of the breast. Of these, we experienced four cases (50%) of central nervous system (CNS) involvement with poor prognosis, especially in three recent cases between 2000 and 2001. Four patients without CNS involvement are alive without tumor, whereas three of the four patients with CNS involvement died of the disease. These cases prompted us to perform a review of CNS involvement in malignant lymphoma of the breast, and treatment modality (Table 1).

CASE REPORT

CASE 1

An 80-year-old woman presented with a mass in the upper-inner quadrant of the left breast in November 1999. She had no contributory past or family history. Fine needle aspiration cytology (FNAC) showed malignant lymphoma. On admission, blood chemistry, including serum levels of tumor marker CEA, CA 15–3 showed no abnormal values except for a slightly high level of LDH (240 IU/l). The tumor, measuring 53 mm, was not fixed to the chest wall. Nipple discharge and axillary lymphadenopathy were not detected. An ultrasonogram revealed lobulated hypoechoic and heterogeneous masses. We diagnosed the tumor as primary malignant lymphoma of the breast, Stage IE, by Ann Arbor staging, and classified her as...
belonging to the high-intermediate risk group as her international prognostic index (IPI) score was 3 (age over 60, elevated serum LDH level, and extranodal involvement). We performed an extended mastectomy, followed by external radiotherapy (50 Gy/25 fractions/5 weeks). Although histology of the tumor revealed diffuse large B-cell lymphoma, she refused chemotherapy. One month later, she showed motor disability with brain metastasis, which was confirmed by CT and MRI examinations. Whole brain radiotherapy was initially planned at 45 Gy/25 fractions/5 weeks. However, radiotherapy was stopped at 32.4 Gy, because pleural effusion and ascites with abdominal mass lesion appeared. Although subsequent chemotherapy was started with etoposide and carboplatinum, she died, without improvement, 4 months after first presentation.

CASE 2

The second case was that of a 50-year-old woman who presented with a rapidly growing induration in the right breast. She was an ATLA carrier and her younger brother suffered from leukemia. She underwent surgical excision (690 g), and histology of the tumor revealed diffuse large B-cell lymphoma. No skin or chest wall invasion was found. She underwent five cycles of CHOP regimen, including high-dose chemotherapy (HDC) by etoposide followed by peripheral blood stem cell transplantation (PBSCT) and breast irradiation (40 Gy/20 fractions/4 weeks). Three months after completing radiotherapy, she had convulsions and a 3 cm brain lesion was found in the left temporal lobe. She underwent surgical excision, which revealed a diffuse large B-cell lymphoma concurrent with the breast tumor. Post-operative radiotherapy, she had convulsions and a 3 cm brain lesion was found in the left temporal lobe. She underwent surgical excision, which revealed a diffuse large B-cell lymphoma concurrent with the breast tumor. Post-operative radiotherapy (50 Gy/25 fractions/5 weeks; 30 Gy/15 fractions of whole brain radiotherapy, and local boost radiotherapy (20 Gy/10 fractions/2 weeks) were performed. However, leukemic changes subsequently occurred in peripheral blood (35% of blast cells) and bone marrow (15% of blast cells) just after completion of radiotherapy. High-dose Methotrexate, with leukovoline rescue reduced blast cells in bone marrow to <10%. She achieved a good partial response and was discharged from the hospital. Although small nodular lesions <1 cm appeared in the right breast, left lateral abdominal wall, and right lateral chest wall, she was still alive, with the disease, 3 months after completion of treatment.

CASE 3

The third case was a 49-year-old woman who had several neurological symptoms; memory disturbance, vomiting, abnormal behavior, a tendency to fall asleep, loss of self-identification. CT and MRI scans revealed a 5 cm brain SOL. The tumor was located at the corpus callosum and fornix between the anterior horns of the lateral ventricle. Biopsy confirmed this to be a diffuse large B-cell lymphoma. She was first diagnosed as having a primary brain non-Hodgkin malignant lymphoma. High-dose Methotrexate was administered followed by radiotherapy (54 Gy/27 fractions/6 weeks; whole brain irradiation 30 Gy, limited field 20 Gy and a localized 4 Gy boost of radiotherapy). The tumor regressed into a small spot enhancement as revealed

Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>ID</th>
<th>CNS involvement</th>
<th>Age</th>
<th>Sex</th>
<th>Year presented</th>
<th>Stage</th>
<th>She</th>
<th>Histology</th>
<th>Largest diameter (mm)</th>
<th>Rapid growth</th>
<th>IPI</th>
<th>Treatment</th>
<th>Response</th>
<th>Relapse</th>
<th>Treatment for CNS</th>
<th>Outcome</th>
<th>Follow-up (months)</th>
<th>CNS involvement</th>
<th>Treatment for CNS (months)</th>
<th>CNS involvement (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>4</td>
<td>46</td>
<td>F</td>
<td>1998</td>
<td>Bil</td>
<td>4</td>
<td>Burkitt</td>
<td>80</td>
<td>+</td>
<td>0</td>
<td>PD</td>
<td>4</td>
<td>PD</td>
<td>CNS</td>
<td>PD</td>
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<td>PD</td>
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<td>50</td>
<td>F</td>
<td>2000</td>
<td>R</td>
<td>2</td>
<td>DLB</td>
<td>110</td>
<td>+</td>
<td>0</td>
<td>PD</td>
<td>1</td>
<td>PD</td>
<td>R</td>
<td>PD</td>
<td>12</td>
<td>PD</td>
<td>CNS</td>
<td>PD</td>
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<tr>
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<td>3</td>
<td>49</td>
<td>F</td>
<td>2000</td>
<td>brain + brain + DLB</td>
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<td>DLB</td>
<td>40</td>
<td>+</td>
<td>0</td>
<td>PD</td>
<td>3</td>
<td>PD</td>
<td>DLB</td>
<td>PD</td>
<td>0</td>
<td>PD</td>
<td>CNS</td>
<td>PD</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>80</td>
<td>F</td>
<td>1999</td>
<td>Bil</td>
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<td>DLB</td>
<td>53</td>
<td>+</td>
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<td>PD</td>
<td>0</td>
<td>PD</td>
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<td>PD</td>
<td>2</td>
<td>PD</td>
<td>CNS</td>
<td>PD</td>
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</table>

DLB, diffuse large B-cell; R, radiotherapy; S, surgery; C, chemotherapy; AT, alive with tumor; NED, no evidence of disease; D, dead; CR, complete response; PR, partial response; PD, progressive disease; IPI, international prognostic index.
in an MRI examination. However, simultaneously, a 4 cm tumor, which was thought to be a primary tumor, showed rapid progress in the left breast during radiotherapy. Although she underwent chemotherapy (two cycles of CHOP regimen), a recurrence was identified in the pituitary region (inside the 50 Gy irradiated field) and dissemination into CSF. She received four more cycles of chemotherapy, but did not respond to the treatment and died 10 months after her first symptoms.

CASE 4

The fourth case was that of a 46-year-old female with Burkitt type lymphoma originating in the oral gum. She showed diffuse intestinal wall thickening, peritoneal dissemination, and bilateral breast tumors (both sides 8 cm and 4 cm), presenting with a rapidly fatal course including cytology proven meningeal dissemination (1 month after the onset). Chemotherapy (VEPA, high-dose AraC, carboplatinum) was ineffective and palliative bypass surgery was performed for her ileus condition due to malignant peritonitis. She died 6 months after her first presentation.

DISCUSSION

Malignant lymphoma is a neoplasm originating from lymphatic tissue and extranodal lymphoma occurring in the intestinal tract and Waldeyer's ring. In Japan, the incidence rates of lymphoma have increased steadily from 2.4 in 1975 to 6.5 in 1995 in females and from 4.2 in 1975 to 9.0 in 1995 in males per 100 000 people (3).

Wiseman and Liao reported that a diagnosis of primary malignant lymphoma of the breast must satisfy the following criteria: (i) adequate pathological evaluation, (ii) both mammmary tissue and lymphomatous infiltration must be in close association, (iii) the exclusion of either systemic lymphoma or previous extramammary lymphoma (the presence of ipsilateral axillary node involvement is considered acceptable) (4). It is important to determine whether malignant lymphoma of the breast actually originates in the breast or is systemic. For staging the disease, we used CT scans of the chest, abdomen, pelvis, and other areas if required. Chest radiography, bone marrow biopsy, and gallium scan were also performed. In addition, an MRI, upper gastrointestinal or small bowel series, and cytologic evaluation of effusion were also performed if disease was anticipated. In the case 3 patient, brain metastasis was initially identified and the breast tumor appeared rapidly during radiotherapy, which left the possibility of there being another primary site of lymphoma. Since we did not find any other lesions, and brain lymphoma rarely shows metastasis to other regions, we included this case in this report even though it did not fulfil the criteria of malignant lymphoma originating in the breast (5).

In addition, the case 4 patient was an apparent disseminated case, so she did not fulfil the criteria of lymphoma originating in the breast either. We included this case to emphasize the relationship between the breast and the brain. All four cases involving CNS, excluding the third, showed systemic manifestations of lymphoma within a very short period after the diagnosis of the manifestation in the breast. Alternatively, as in the fourth case, systemic manifestations had preceded the diagnosis of breast lymphoma. Thus, it is difficult but important to determine whether malignant lymphoma of the breast originates in the breast or is of systemic origin.

Several authors have reported on CNS involvement of malignant lymphomas. Hoerni-Simon et al. reported that out of 498 patients with NHL, 30 (6%) showed secondary CNS involvement (6). Of these 30 patients, 26 had high-grade malignancy and 21 had lymphoblastic lymphoma, mainly convoluted (n = 8) or Burkitt type (n = 6) according to the Kiel classification. In the case of breast lymphoma, most reports on CNS involvement are case reports concerning a small number of cases (Table 2). In a Japanese literature review, an incidence of 7% (9/121) of CNS involvement was reported (10). Recently, Ribrag et al. reported a high incidence of CNS involvement of malignant lymphoma originating from the breast. Four out of 20 patients (20%) treated with chemotherapy (CHOP or CHOP like regimen), with or without radiotherapy, showed CNS relapse (9). Breast lymphoma, which shows a propensity for CNS dissemination, seems to be different from that observed in most localized nodal lymphomas when no CNS prophylaxis is given in first-line therapy (9). Au et al. also reported a high incidence of CNS involvement of breast lymphoma among Hong Kong Chinese (3/14) with poor prognosis (13). Our data concurs with their observations and we need to accumulate further data on a multi-institutional scale to examine whether the ratio to CNS involvement in breast lymphoma is increasing.

Therapeutic management of this disease is controversial and has not yet been fully established. Cohen and Brooks reported their experience of 35 patients with primary and secondary breast lymphoma (14). In those patients with primary breast lymphoma (16 patients), they found a predominance of diffuse large cell lymphoma, B-cell in origin, and stage-related survival. Brogi reported 60–70% 5-year survival in Stage I, and 30–40% in Stage II localized breast lymphoma, which is somewhat lower than that reported for other lesions (15). Jeon et al. divided primary breast lymphoma into a unilateral type that occurred in older women and a bilateral type that affected younger women (1). They reported poor prognosis for the age group <45 years (mostly Burkitt lymphomas) compared to older patients (B-cell lymphomas). We also experienced a Burkitt lymphoma (ID4) with rapidly progressing disease resulting in early death, even though the patient was over 45 and had not been pregnant or lactated. We would like to raise the question of whether the subgroup of breast lymphoma patients, with poor prognosis, have a tendency of CNS involvement. If so, similar to NHL of the orbit, nasal sinus, testis, and marrow, breast lymphoma may be another disease site commonly associated with CNS involvement. Combined-modality treatments were recommended in patients with intermediate- and high-grade lymphomas (16). Only patients with low-grade limited lymphomas may be successfully treated with local...
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therapy such as radiotherapy. Regardless of age and type, breast lymphoma showing brain metastasis is an aggressive disease that requires intensive treatment — combined intrathecal and/or systemic chemotherapy and/or cranial irradiation and high-dose chemotherapy with marrow/stem cell rescue in case of relapse. Ribrag et al. suggested that CNS prophylaxis associated with systemic chemotherapy should be given to all patients with high-grade histology, especially those with bulky or bilateral disease (9). Although this prophylaxis strategy should be considered for high-risk cases, we are not in a position to recommend prophylactic treatment excluding systemic chemotherapy, because prophylactic treatment would become excessive for more than half the patients who do not exhibit CNS relapse. We need to accumulate further data on a multi-institutional scale to examine whether prophylactic treatment improves the outcome in breast lymphoma.

In conclusion, we presented in this report four cases of CNS involvement of breast malignant lymphoma. CNS involvement in breast lymphoma is not so rare. It is difficult, but important, to determine whether malignant lymphoma of the breast originates in the breast or systemically. Although brain metastasis could be treated by radiotherapy and/or chemotherapy effectively, the prognosis is poor. Further intensive treatment is required for breast malignant lymphoma with CNS involvement.

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References


