PRIMARY BILATERAL BREAST LYMPHOMA: A REVIEW OF LITERATURE AND REPORT OF FOUR CASES FROM A SINGLE CENTRE

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Abstract

Primary Breast lymphoma is a rare entity and carries poor prognosis, bilateral breast lymphoma is even rarer and carries worst prognosis. Bilateral breast lymphoma is a rare disease and lacks treatment. Out of the 2, 766 cases of Non-Hodgkin’s lymphoma, registered at our institute from 1994 to 2013, 31 cases of breast lymphoma were found, out of which 4 cases had bilateral involvement. In this review, we describe, clinical presentation, histopathological subtypes, treatment administered and outcome of those 4 cases retrospectively. All patients were female with a median age 31 years (range 24 to 64 years). Three patients were diagnosed with Diffuse Large B Cell Lymphoma (DLBCL), and MALT-Lymphoma detected in 1 patient. Chemotherapy remained the main treatment modality and surgery (excision biopsy) was reserved for diagnostic purpose only, none of the patients received radiation therapy.

Keywords: Breast lymphoma, histopathological subtypes, palliation

Introduction:

Primary Breast lymphoma (PBL) is a rare form of breast malignancy and accounting 0.4-0.5% of all breast cancers and 1.7-2.2 % of extra-nodal Non-Hodgkin’s Lymphoma (NHLs) [1]. Primary breast lymphomas are classified as disease confined to the breast only in the absence of previously existing lymphoma [2]. According to Wiseman and Liao criteria, PBL is defined by the presence of following features: (1) breast should be the primary site (2) there should be no evidence of the distant organ involvement (3) tissue sample should be adequate (4) there should be a close association between breast tissue and lymphoma [3]. According to this definition, lymphoma confined to the breast alone will be classified as PBL. However some researchers would also categories PBL when bone marrow is involved in addition to lymphoma in the breast [4]. Bilateral breast lymphoma accounts for about 11% of lymphoma involving the breast, whereas a study of 204 primary DLBCL patients by Ryan et al showed bilateral breast involvement by lymphoma in only 5% cases [5,6]. Cancer Registry at Shaukat Khanum Memorial Cancer Hospital & Research Centre (SKMCH & RC) Lahore recorded 12, 866 cases of breast cancer between December 1994 to December 2013. Among those patients 4 cases of PBL were identified whose details are given in this case report.

Materials and Methods

Data on 4 PBL patients treated at Shaukat Khanum Memorial Cancer Hospital and Research Centre was collected by review of their case notes using hospital electronic medical records in a retrospective manner. Following patient variables searched: patients’ demographics like age, gender, presenting clinical symptoms like B-symptoms, pathological characteristics like histopathology and immunohistochemistry of breast biopsy as well as bone marrow infiltration and its response to chemotherapy if positive at baseline, details of treatment and measurement of outcome. A formal ethical approval was obtained from the Institutional Review Board.
Case Series:

Baseline patient characteristics are shown in table 1. All patients were females median age at the time of diagnosis was 31 years (range 24 to 64 years). All patients underwent breast ultrasound, mammogram, bone marrow biopsy and whole body computed tomography for staging of lymphoma at presentation. Diagnosis was made on review of the blocks as all four patients had undergone lumpectomy at peripheral hospitals before being referred to our institute for further. Ann Arbor system was used for staging of lymphoma according to which bilateral cases were classified as stage IVE due to poor prognosis, and according to Wiseman and Liao criteria.

At presentation, 1 patient has multiple bilateral skin nodules, 2 were diagnosed with pregnancy/ lactation associated breast lumps. Two of our patients had B-symptoms and another 2 had bone marrow involvement at baseline. Histopathological diagnosis of DLBCL was made in 3 patients and 1 case had morphology consistent with MALT lymphoma. Immunohistochemistry consistent with the given diagnosis was the positivity of CD 20, CD 30, Ki 67 in 3 cases however immunohistochemistry was unknown for a single patient. There were no distant organ involvement at the time of presentation in all four cases.

The main stay of treatment was R-CHOP chemotherapy (Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone). Surgery was limited for diagnostic purpose only, none of our patients received radiation therapy to breast. Response to the treatment was assessed by bone marrow biopsy after chemotherapy and PET scan. One patient died during the chemotherapy, second patient had complete response (CR), while rest of the two patients had progressive disease after chemotherapy, none of the patient received extensive surgery or radiation therapy, survival period ranges from 1-13 months, three patients died, and two were lymphoma specific deaths.

Discussion:

Primary breast lymphoma is a rare entity, it represents 0.04-0.5 % of all breast malignancies [6]. Breast lymphomas are staged according to Ann Arbor staging system, although staging of bilateral PBL is still controversial, Ryan et al classified bilateral PBL in stage IVE [5] this was the largest study of PB-DLBCL, they reviewed retrospectively 204 patients whereas other studies include in stage IE and IIE [7,8]. We included bilateral involvement in stage IVE as they had poor prognosis. Bilateral PBL have some association with pregnancy as mentioned in some studies [9]. It is difficult to differentiate radiologically between breast lymphoma, fibroadenoma or breast cancer [10,11].

The most common subtype is DLBCL accounts for about 50% of all B cell lymphomas, others rare types include, MALT Lymphoma, Burkitt lymphoma, anaplastic, follicular, small lymphocytic [12]. Aggressive form of PBL is known to have association with younger age group; three of our patients were young [13].

Another largest study by Jeanneret-Sozzi et al, included a review of 84 cases of PBL from 20 institutions they concluded that PBL has better prognosis if managed by combined chemotherapy and radiotherapy [14]. MALT Lymphoma breast is an extremely rare entity amongst the Non-Hodgkin’s lymphoma, and bilateral involvement is even rarer, we found only single patient with bilateral MALT lymphoma [15].

Chemotherapy stays the main treatment modality for breast lymphomas; RCHOP is the preferred regime, as it increases five year survival. Aviv et al recommended addition of Rituximab to chemotherapy may reduce central nervous system relapse, may be given intrathecal injections, [16,17] whereas other studies describe it as ineffective [18]. Radiotherapy can be combined with chemotherapy but the role of surgery is limited only to diagnosis and palliation of symptoms in progressive disease. Jennings et al observed high mortality rate in patients undergoing mastectomy and axillary dissection, therefore they concluded that there is no role of
axillary lymph-nodal dissection and extensive surgery for breast lymphoma [19].

**Conclusion:**

Bilateral breast lymphoma is very rare but aggressive disease with poor prognosis usually present at younger age group, aggressive treatment with chemotherapy should be considered and surgery should be reserved for diagnosis and palliation.

**Acknowledgement:**

We are thankful to Dr Sajid Mushtaq, Misbah (Pathology department), Dr Farhana Badar and Mr Shahid Mehmood (Cancer Registry department) for helping us in retrieving the data of breast lymphoma.

**Table 1. Demographics**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Diagnosis</th>
<th>B-symptoms</th>
<th>Pre-treatment Bone marrow</th>
<th>Post-treatment Bone marrow</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>DLBCL</td>
<td>No</td>
<td>Positive</td>
<td>Negative</td>
<td>Pregnancy associated</td>
</tr>
<tr>
<td>2</td>
<td>35</td>
<td>DLBCL</td>
<td>No</td>
<td>Negative</td>
<td>Negative</td>
<td>Multiple skin lesions</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>MALT-Lymphoma</td>
<td>Yes</td>
<td>Positive</td>
<td>Positive</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>DLBCL</td>
<td>Yes</td>
<td>Negative</td>
<td>Negative</td>
<td>Lactation associated</td>
</tr>
</tbody>
</table>

**Table 2. Treatment and Outcome**

<table>
<thead>
<tr>
<th>Case</th>
<th>Chemotherapy</th>
<th>Radiotherapy</th>
<th>Response</th>
<th>Local relapse</th>
<th>Distant relapse</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RCHOP X 6</td>
<td>No</td>
<td>PR</td>
<td>No</td>
<td>No</td>
<td>Dead</td>
</tr>
<tr>
<td>2</td>
<td>RCHOP X 6</td>
<td>No</td>
<td>CR</td>
<td>No</td>
<td>No</td>
<td>Dead</td>
</tr>
<tr>
<td>3</td>
<td>RCHOP X 5</td>
<td>No</td>
<td>Progressive</td>
<td>No</td>
<td>No</td>
<td>Dead</td>
</tr>
<tr>
<td>4</td>
<td>RCHOP X 4, RICE X 5</td>
<td>No</td>
<td>Progressive</td>
<td>No</td>
<td>No</td>
<td>Alive</td>
</tr>
</tbody>
</table>

**References:**