Diffuse large B-cell lymphoma of the thyroid: Seven cases with review of the literature from India

**Abstract**

**Background:** Diffuse large B-cell lymphoma (DLBCL) is the most frequent subtype of nonHodgkin’s lymphoma globally with frequent extra nodal involvement. There is sporadic data available on thyroid DLBCL in Indian population and hence we undertook this retrospective observational study at Kidwai Memorial Institute of Oncology, a tertiary care oncology center in India to analyze the clinico biological features of this disease. **Methodology:** A total of 7 consecutive cases diagnosed as DLBCL by appropriate lymph node biopsy with evidence of thyroid involvement on fine-needle aspiration cytology of thyroid or thyroid histopathology (following thyroidectomy) were confirmed by immunohistochemistry (WHO classification) between January 2008 and September 2013 were included in this study. **Results:** A total of 7 patients were included in the study. Median age was 65-years (range: 50–72 years), and all were females. Six out of seven were in stage IIAE and one was in stage IVAE. The distribution according to the international prognostic index was as follows: 3 were in low risk, 1 in low-intermediate, 2 in high-intermediate and 1 in high risk group. Regarding treatment, 5 received CHOP, 1 received COP and 1 received no treatment. 5 patients received radiotherapy. 2 patients underwent subtotal thyroidectomy. Of the 6 patients who received chemotherapy ± radiotherapy, 4 had complete response, 2 had partial response. The median survival was 15 months (3-32 months). **Conclusions:** Extranodal thyroid DLBCL presents common in elderly age group and may improve survival compared with unimodality approach. **Key words:** Diffuse large B-cell lymphoma, extra nodal, India, thyroid

**INTRODUCTION**

The global burden of nonHodgkin's lymphoma (NHL) has been steadily increasing over the last two decades and India is no exception with NHL causing significant morbidity and mortality. Around 25% of NHL arise in tissues other than the lymph node, spleen, Waldeyer's ring and thymus, and are referred to as primary extra nodal NHL (EN-NHL). It has been observed that the incidence of EN-NHL has increased more rapidly than the nodal type. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL worldwide and aggressive, high grade lymphoma with a rapid onset and progression. About one-third of DLBCLs has a primary EN origin. Primary thyroid lymphoma (PTL) is a rare disease, accounting for ~5% of all thyroid malignancies and approximately 3% of all lymphomas and 7% of extranodal lymphomas. More than 75% of thyroid lymphomas are constituted by DLBCL. There is sporadic data from India and hence we undertook this retrospective study in India.

**METHODOLOGY**

This was a retrospective observational study carried out at Kidwai Memorial Institute of Oncology, a tertiary care center in India. Diagnosis of thyroid DLBCL was made by appropriate lymph node biopsy with evidence of thyroid involvement on fine-needle aspiration cytology of thyroid or thyroid histopathology (following thyroidectomy) confirmed by immunohistochemistry (WHO classification).
between January 2008 and September 2013 at our institute were included in the study. The demographic details, clinical details, investigations and treatment details were recorded and analyzed.

Staging included patient history and physical examination; complete hemogram and serum biochemistry, including lactate dehydrogenase; echocardiography or multi gated acquisition scan, computed tomography scan of neck, thorax, abdomen, and pelvis; chest X-ray and ultrasound abdomen/pelvis in not affordable patients; as well as bone marrow biopsy from iliac crest. Patients were staged according to Ann Arbor staging as modified by Cotswold’s and international prognostic scoring (IPI) was done. Treatment was planned according to standard guidelines wherein aggressive NHL patients were planned for 6 cycles of cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² and prednisone 100 mg for 5 days every 21 days (CHOP) with or without rituximab 375 mg/m² or COP with or without rituximab with involved field radiotherapy (IFRT). Rituximab was considered in all patients, but none could afford. Response was assessed according to standard criteria. Surgery was also done in relevant cases.

RESULTS

A total of 7 patients with thyroid DLBCL were included in the study [Table 1]. Median age was 65-year (range: 50–72 years), and all were females. 6 out of seven were in stage II AE and one was in stage IVAE. The distribution according to the IPI was the following: 3 were in low risk, 1 in low-intermediate, 2 in high-intermediate, and 1 in high risk group. Regarding treatment, 5 received CHOP, 1 received COP and 1 received no treatment. 2 patients underwent subtotal thyroidectomy, 5 received radiotherapy. Of the 6 patients who received chemotherapy ± radiotherapy, 4 had complete response, 2 had partial response. The median OS was 15 months (range 3–32 months).

DISCUSSION

Primary thyroid lymphoma is an unusual entity, comprising of around 5% of all thyroid malignancies, 1–3% of lymphomas and 2.5–7% of EN lymphomas.[4] Dawson et al. defined primary EN-NHL as the site restricted to lymphomas that present with the main manifestation of their disease at that site, with or without regional lymph node involvement.[9] Primary EN lymphomas of thyroid include Stage I or II disease, but Stage III or IV disease were also included if symptoms and signs of thyroid involvement are evident, as also seen in one of our patients. PTL usually affects middle aged and elderly women with a peak incidence between 60 and 69 years and there was a female preponderance.[6,4]

In our series, the median age was 65-year with all being females. Most patients present without B symptoms as also seen in our study where 6 out of 7 had no B symptoms.[9] The risk of PTL is higher in those with preexisting Hashimoto’s thyroiditis.[8] In our study, 3 out of 7 (42.8%) patients had a diagnosis of hashimoto’s thyroiditis prior to developing PTL. Though, mucosa associated lymphoid tissue (MALT) is the most common lymphoma accounting in patients with hashimotos thyroiditis, in our series all three patients were cases of DLBCL thyroid. Around two-third of patients with PTL have antithyroid antibodies.[6]

Three fourths of thyroid lymphomas are B-cell NHL. Hodgkin’s and T-cell lymphomas are unusual.[10,11] Among the B-cell lymphomas, DLBCL accounts for more than three fourths of the cases, others being MALT and follicular lymphoma.[12] Wang et al. reported five cases of Hodgkin’s lymphoma who were treated with combination chemotherapy and surgery.[12,13] The most common presenting symptoms in our series was thyroid enlargement with cervical lymphadenopathy (100%). However, three patients (42.8%) presented with compressive symptoms—hoarseness, dyspnea and dysphagia. This is in par with other studies including an Indian study published recently by Kumar et al. who also made a similar observation.[9,4]

Table 1: Summarizing the patient characteristics of our study on thyroid DLBCL

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Histology</th>
<th>Stage</th>
<th>PS</th>
<th>IPI score</th>
<th>IPI risk score</th>
<th>Chemo</th>
<th>RT</th>
<th>Surgery</th>
<th>Response</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>72/F</td>
<td>DLBCL</td>
<td>IVAE (thyroid/ stomach involved)</td>
<td>1</td>
<td>4/5</td>
<td>High</td>
<td>CHOP×5 cycles</td>
<td>-</td>
<td>-</td>
<td>uCR</td>
<td>Lost to follow up PFS- 3 months OS- 3 months</td>
</tr>
<tr>
<td>65/F</td>
<td>DLBCL</td>
<td>II AE</td>
<td>1</td>
<td>1/5</td>
<td>Low</td>
<td>CHOP×6 cycles</td>
<td>+</td>
<td>-</td>
<td>CR after 6 cycles of chemo</td>
<td>32 months follow up, Alive with NED DFS- 32 months</td>
</tr>
<tr>
<td>68/F</td>
<td>DLBCL</td>
<td>II AE</td>
<td>2</td>
<td>3/5</td>
<td>High intermediate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>PFS- 8 months OS- 8 months</td>
</tr>
<tr>
<td>64/F</td>
<td>DLBCL</td>
<td>II AE</td>
<td>1</td>
<td>1/5</td>
<td>Low Intermediate</td>
<td>CHOP×6 cycles</td>
<td>+</td>
<td>-</td>
<td>PR after 6 cycles</td>
<td>PFS- 4 months Lost to follow up OS- 3 months</td>
</tr>
<tr>
<td>50/F</td>
<td>DLBCL</td>
<td>II AE</td>
<td>2</td>
<td>3/5</td>
<td>High Intermediate</td>
<td>COP×6 cycles</td>
<td>+</td>
<td>Sub total thyroidectomy</td>
<td>PR</td>
<td>OS- 18 months</td>
</tr>
<tr>
<td>56/F</td>
<td>DLBCL</td>
<td>II AE</td>
<td>1</td>
<td>1/5</td>
<td>Low</td>
<td>CHOP×6 cycle</td>
<td>+</td>
<td>-</td>
<td>CR</td>
<td>15 m</td>
</tr>
<tr>
<td>55/F</td>
<td>DLBCL</td>
<td>II AE</td>
<td>1</td>
<td>1/5</td>
<td>Low</td>
<td>CHOP×6 cycle</td>
<td>+</td>
<td>Sub total thyroidectomy</td>
<td>CR</td>
<td>16 m</td>
</tr>
</tbody>
</table>

Table 2: Summarizing the various studies and in comparison with the current study

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Histology</th>
<th>Stage</th>
<th>Chemotherapy</th>
<th>Surgery</th>
<th>Radiotherapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>7</td>
<td>DLBCL</td>
<td>6- II AE</td>
<td>CHOP-5</td>
<td>2- Sub total thyroidectomy</td>
<td>5</td>
<td>OS- 15 m (3-32 months)</td>
</tr>
<tr>
<td>Nitin et al. (2013)</td>
<td>2</td>
<td>DLBCL</td>
<td>1- IV AE</td>
<td>COP-1</td>
<td>Near total thyroidectomy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ritesh et al. (2013)</td>
<td>16</td>
<td>DLBCL 14 (87.5%)</td>
<td>I AE</td>
<td>R- CHOP x 6 cycles</td>
<td>-</td>
<td>14 (87.5%)</td>
<td>5-year DFS was 40.0% and median DFS was 47 m. The 5-year OS was 41.0% and median OS was 51 m</td>
</tr>
<tr>
<td>Onal et al. (2010)</td>
<td>87</td>
<td>56 (DLBCL) 2 (lymphoblastic lymphoma) 1 (T-cell lymphoma) 1 (mantle cell lymphoma) 27 (31%) had indolent lymphoma, either MALT lymphoma (18 patients; 21%) or follicular lymphoma (9 patients; 10%)</td>
<td>53 stage I and 34 stage II</td>
<td>(31 with chemotherapy alone) 35 received chemo+RT</td>
<td>Fifty-five patients (64%) underwent thyroid resection: 42 (48%) hemithyroidectomy and 13 (16%) total thyroidectomy</td>
<td>21 with radiotherapy alone</td>
<td>5- and 10-year overall survival (OS) rates were 74% and 71%, respectively, and the disease-free survival (DFS) rates were 68% and 64%</td>
</tr>
<tr>
<td>Baker et al. (2009)</td>
<td>1408</td>
<td>68% DLBCL 10% FL, 10% marginal zone, and 3% small lymphocytic</td>
<td>88% had stage I-II disease</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>OS 9.3 years</td>
</tr>
<tr>
<td>Niitsu et al. (2007)</td>
<td>32</td>
<td>DLBCL</td>
<td>I E- 18</td>
<td>CHOP</td>
<td>-</td>
<td>RT given (number N.A.)</td>
<td>5-year OS - 90% 5-year PFS was 84%</td>
</tr>
</tbody>
</table>


The treatment of thyroid lymphomas has been an area of intense interest with no consensus. For diagnosis, fine-needle aspiration biopsy or core open biopsy is used. It has the capability of masquerading as thyroid carcinoma, especially anaplastic histopathology. Treatment for aggressive lymphomas involves a multi-modality approach involving chemotherapy and IFRT. As this entity is quite uncommon, very few studies are found on the literature search [Table 2]. The largest study so far was the one reported by Graff-Baker et al. in 2009, where PTL patients were identified in the SEER database. Of the 1408 patients who were identified over 32-year of follow-up, median age was 66-year with three fourths being females and 68% with DLBCL histology. In this study, advanced age, stage, DLBCL histology and no radiation/surgery were adverse prognostic factors. Aggressive lymphomas of the thyroid like DLBCL require a multimodality treatment strategy involving chemotherapy, ± surgery and radiation therapy as also seen in the Indian study by Ritesh et al.[13] who reported a 5-year OS of 41%, which was probably less compared to other studies. The reasons cited by the authors were advanced stage and age. Various other studies have reported superior efficacy of chemotherapy with radiation therapy. Matsuzuka et al.[18] reported a 100% OS rate at 8-year. Ha et al. in 2001 showed 5-year OS and disease free survival (DFS) of 64% and 76% with combined modality.[19] Niitsu et al. in 2007 reported 32 cases of DLBCL thyroid and their results showed a 5-year OS was 90.3% and the 5-year DFS was 84.3% (18 had stage IE and 14 IIIe).[17] In our study, five patients received combined chemotherapy and radiation therapy and hence had a better survival compared to others [Table 1].

To conclude PTL is more common in elderly age group and in females. The index of suspicion with appropriate biopsy with immunohistochemistry is required for early diagnosis. The treatment with multimodality treatment with anthracycline based chemotherapy, with/or surgery with radiotherapy may improve the survival.

We have compared our study with a large study by Baker et al. of >1400 patients.[14] The strengths of our study include one of the few reports from India and limitations include a short follow-up and rather small case series. This study per say does suggest that more studies on this entity are required, and a multi-modality approach is required to treat this condition. Moreover, a high index of suspicion is required to diagnose this PTL when a thyromegaly is observed.

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