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Primary Thyroid Lymphoma: Clinicopathologic Characteristics and Therapeutic Outcomes of Six Cases in Morocco

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Abstract

Background

Primary non–Hodgkin lymphomas of the thyroid are uncommon and account for 1–5% of all thyroid malignancies and less than 2% of extranodal lymphomas. The aim of the present study was to review our experience and management of primary thyroid lymphoma and to discuss the diagnostic and therapeutic considerations.

Methods

All non–Hodgkin lymphoma diagnosed at our institution between 2007 and 2011 were reviewed, six cases of primary thyroid lymphoma were identified. The clinical and pathological features of these patients were analyzed.

Results

There were five females and one male and their mean age was 67.5 years. All patients presented with an enlarging anterior neck mass and two patients also have compressive symptoms. Five patients have a history of pre–existing goiter, four have ‘B’ symptoms and one was hypothyroid. All patients have B–cell Non Hodgkin Lymphoma. Four patients have stage II disease, while two patients have disseminated disease. All patients underwent thyroid resection. One patient died after surgery. The five others were treated postoperatively with 3–weekly cycles of combination chemotherapy. One patient in stage II received consolidation radiotherapy after chemotherapy. Complete remission was achieved in four patients and one patient had partial response to the treatment. After a median follow–up of 26 months (2–51), three patients are still alive without any relapse, one died and the last was lost to follow up.

Conclusion

Primary thyroid lymphomas are rare. Treatment depends on the histological subtype and stage of the disease, including radiotherapy and chemotherapy. The prognosis usually is favorable with proper treatment.

Keys Words

Primary thyroid lymphoma, treatment, prognostic, Morocco.

Introduction

Primary thyroid lymphoma (PTL) is a rare disease, representing approximately 1–5% of all thyroid malignancies, 2.5% of all malignant lymphomas, and 1–2% of all extranodal lymphomas (1, 2). Thyroid lymphoma is a heterogeneous disease, which typically occurs in middle– aged to elderly women (3) and known to be associated with Hashimoto’s thyroiditis (4,5). Most cases of thyroid lymphomas are non–Hodgkin’s lymphomas (NHLs) with B–cell origin (4,6). Hodgkin’s and T–cell thyroid lymphomas are extremely rare (4, 7). Diffuse large B–cell lymphoma (DLBCL) and extranodal marginal zone B cell lymphoma of mucosa–associated lymphoid tissue (MALT) lymphoma are the common subtypes (5). In contrast to the usual presentation of a benign thyroid swelling, patients with PTL are more likely to present with a rapidly enlarging neck mass that is frequently associated with compressive symptoms (6). Diagnosis of PTL can be accomplished using fine needle aspiration biopsy (FNAB) or by core or open biopsy (8). The optimal strategy for managing PTL remains somewhat controversial (8, 9). Management modalities included surgery, chemotherapy, and radiotherapy or combination treatment.

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Primary Thyroid Lymphoma in Moroccan Patients, A. Adani–Ifè, et. al.

Herein, we review the clinicopathological features and treatment outcomes of patients with primary thyroid lymphoma at the National Institute of Oncology in Morocco.

Patients and Methods

All non–Hodgkin’s lymphomas diagnosed or referred to our department between January 2007 and December 2011 were reviewed, six cases of primary thyroid lymphoma were identified. The term primary designated patients with lymphomatous involvement of the thyroid at diagnosis, the disease being localized or disseminated to nodal or extranodal sites. The clinicopathological characteristics and treatment outcomes of these patients were retrospectively analyzed.

All patients were diagnosed on partial or total thyroidectomy specimens. Routine histopathological evaluation and immunohistochemistry using a panel of monoclonal antibodies were performed. Initial staging procedures included complete physical examination; thyroid or cervical ultrasonography; computed tomography of the neck, thorax, abdomen, and pelvis; bone marrow biopsy. Serum lactic dehydrogenase (LDH), blood counts, chemistry, thyroid function tests were systematically performed.

Performance status (PS) was evaluated according to the Eastern Cooperative Oncology Group scale. Symptoms related to lymphoma, including fever, weight loss of 10% or more, and nocturnal sweating (B symptoms), were specifically collected. Patients were staged according to the Ann Arbor classification: stage IIE disease corresponds to disease confined to the thyroid and lymph nodes on the same side of the diaphragm, stage IIIE corresponds to disease confined to the thyroid and lymph nodes on both sides of the diaphragm and/or spleen; and stage IV corresponds to a disseminated nodal and/or additional extranodal involvement. Localized disease was defined as IE and IIE disease, and disseminated disease as stage IIIE and stage IV.

Patients underwent surgery and were treated with chemotherapy according to the stage and histological subtype of the disease. Radiotherapy was delivered after chemotherapy. The radiation dose was 40 Gy which was delivered at a dose rate of 2 Gy per day.

Toxicities were graded according to NCI–CTC–AEv3 (National Cancer Institute–Common Terminology Criteria for Adverse Events version 3) and the response rate to the treatment was evaluated according to Cheson and al criteria.

Consent and statement of ethical approval

The treatment of each patient was decided by the medical staff of the center, oral consent was obtained from the subjects and this study was approved by the institutional review boards of National Institute of Oncology, in Rabat.

Results

Primary thyroid lymphoma accounted for 1.03% of all non–Hodgkin’s lymphomas and approximately 2% of all extranodal lymphomas during the study period.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Clinical presentation</th>
<th>Thyroid function</th>
<th>B symptoms</th>
<th>Histological subtype</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>F</td>
<td>Rapid enlargement of goiter</td>
<td>Euthyroid</td>
<td>Absent</td>
<td>MALT lymphoma</td>
<td>IIE</td>
</tr>
<tr>
<td>2</td>
<td>74</td>
<td>F</td>
<td>Growing anterior neck mass</td>
<td>Euthyroid</td>
<td>Present</td>
<td>MALT lymphoma</td>
<td>IIE</td>
</tr>
<tr>
<td>3</td>
<td>87</td>
<td>F</td>
<td>Rapid enlargement of goiter, dyspnea, dysphagia</td>
<td>Euthyroid</td>
<td>Present</td>
<td>DLBCL</td>
<td>IIIE</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>F</td>
<td>Rapid enlargement of goiter, dyspnea, dysphagia</td>
<td>Euthyroid</td>
<td>Present</td>
<td>DLBCL</td>
<td>IVE</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>M</td>
<td>Growing neck mass</td>
<td>Euthyroid</td>
<td>Absent</td>
<td>MALT lymphoma</td>
<td>IIE</td>
</tr>
<tr>
<td>6</td>
<td>61</td>
<td>F</td>
<td>Rapid enlargement of goiter</td>
<td>Hypothyroid</td>
<td>Present</td>
<td>DLBCL+ MALT lymphoma</td>
<td>IIE</td>
</tr>
</tbody>
</table>

Table 1: Clinicopathologic features of patients
Legend: DLBCL: Diffuse Large B Cell Lymphoma, MALT: Mucosa–Associated Lymphoid Tissue
Patient’s characteristics

Of the six patients with primary thyroid lymphoma, there were five females and one male. The mean age at the time of diagnosis was 67.5 years, with a range of 46 to 87 years. The clinical characteristics of the patients are shown in Table 1.

All patients presented with an enlarging anterior neck mass and two patients had also compressive symptoms including dysphagia, hoarseness of voice and dyspnea. Five patients have a history of pre-existing goiter and four have ‘B’ symptoms. Four patients have associated cervical lymphadenopathy. Five patients have normal levels of thyroid hormones, one was hypothyroid; but Anti-thyroglobulin antibodies and anti-microsomal antibodies were not determined in any case. An elevated LDH level was observed in two patients. At diagnosis, all patients have a performance status less than 2. Surgery was carried out primarily for diagnosis in five cases and in one case for emergency debulking of the tumor for acute airway obstruction. Histologically, all patients had B-cell NHL; histological sub-type was diffuse large B-cell lymphoma (DLBCL) in three patients, mucosa-associated lymphoid tissue (MALT) lymphoma in two patients and combination in one.

After surgery, staging work-up was done, which included a computed tomography scan (neck, chest, abdomen, and pelvis), a bone marrow examination. Four patients have stage II disease; one patient had stage III disease, and the last stage IV disease.

Treatment outcomes

All patients underwent thyroid resection, in one case with neck lymph node dissection (Table 2). One patient died two months after surgery from ischemic cardiomyopathy. The five others were treated postoperatively with 3–weekly cycles of combination chemotherapy: 4 were treated with the CHOP regimen (cyclophosphamide, vincristine, Adriamycin and prednisolone) and one with CHOP and rituximab. The median number of chemotherapy cycles was six (range 4–8). Chemotherapy was well tolerated apart from transient grade II WHO neutropenia, vomiting and mucositis successfully managed with symptomatic treatment. One patient in stage II received consolidation radiotherapy after chemotherapy. Complete remission was achieved in four patients and one patient had partial response.

After a median follow-up of 26 months (2–51 months), three patients were still alive without any relapse, one died and the last was lost to follow up after 17 months.

Discussion

We reported 6 cases of PTL representing 1% of all NHL and approximately 2% of all extranodal lymphomas, over 5 years. Larger series have been reported in the literature (11–13) but the patients were recruited over decades. The majority of patients with PTL are middle to old aged women. Despite the small number of our patients, we observed a female predominance and only one patient had less than sixty years.

<table>
<thead>
<tr>
<th>Case</th>
<th>Surgery</th>
<th>Chemotherapy/number of cycle</th>
<th>Radiotherapy</th>
<th>Outcome/Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Total thyroidectomy</td>
<td>CHOP/5</td>
<td>NR</td>
<td>Complete response. Disease free for 5.8 years</td>
</tr>
<tr>
<td>2</td>
<td>Lobectomy</td>
<td>CHOP/5</td>
<td>RT 40 Gy</td>
<td>Partial response. Disease free for 5 years</td>
</tr>
<tr>
<td>3</td>
<td>Total thyroidectomy and neck lymph node dissection</td>
<td>No Chemotherapy</td>
<td>NR</td>
<td>Died for heart Failure two months after surgery</td>
</tr>
<tr>
<td>4</td>
<td>Isthmectomy</td>
<td>CHOP/8</td>
<td>NR</td>
<td>Complete response. Died for unknown cause after 3years free disease</td>
</tr>
<tr>
<td>5</td>
<td>Total thyroidectomy</td>
<td>CHOP/4</td>
<td>NR</td>
<td>Complete response. Lost to follow up after 17 months</td>
</tr>
<tr>
<td>6</td>
<td>Subtotal thyroidectomy</td>
<td>RCHOP/4</td>
<td>NR</td>
<td>Complete response. Disease free for 2.3 years</td>
</tr>
</tbody>
</table>

Table 2: Treatment modalities and outcomes

NR: No radiation
Primary Thyroid Lymphoma in Moroccan Patients, A. Adani-Ifè, et al.

Primary Thyroid Lymphoma in Moroccan Patients, A. Adani-Ifè, et al.

PTL typically arises in the setting of autoimmune thyroiditis. The relative risk of developing thyroid lymphoma in patients with Hashimoto’s thyroiditis has been reported to be 40 to 80 times greater than in general population (14). Hashimoto’s thyroiditis induces reactive lymphoid proliferation leading to the development of MALT lymphoma, which itself can eventually lead to an aggressive lymphoma through accumulation of genetic abnormalities (15). It takes 20 to 30 years to develop thyroid lymphoma after the onset of Hashimoto’s thyroiditis (4). Five patients in our study have a previous history of goiter evolving for years but diagnosis of Hashimoto’s thyroiditis had been made in any of them. The presenting symptoms in our patients were similar to those previously reported (2–16) but two-thirds of them had classic B-type symptoms of fever, night sweats and weight loss which are less common (7).

Fine needle aspirations guided by the ultrasound, thyroid biopsy, or thyroidectomy are the three diagnostic tools (15). Fine needle aspiration cytology (FNAC) has an established role in the management of thyroid nodules and goiters. However, its role in diagnosing thyroid lymphoma is limited because the small yield from FNAC makes the cytological differentiation of thyroid lymphoma from lymphocytic thyroiditis and anaplastic carcinoma difficult (17). Therefore the results of FNAC for diagnosis of thyroid lymphoma are inconsistent and its diagnostic accuracy varies widely (16, 18–20); but these results can be improved by adjunctive techniques such as immunohistochemical staining, molecular techniques, flow cytometry, or polymerase chain reaction (21). Nevertheless, procedures such as tissue biopsy or surgery are still required in many cases (17, 22). For our patients, pathological specimens were obtained by total thyroidectomy in three cases, subtotal thyroidectomy, isthmectomy and lobectomy in each of other cases.

Thyroid lymphoma is a heterogeneous disease, different histological types can be described (6, 15), but most thyroid lymphomas are of B–cell origin with two predominant subtypes: the pure MALT thyroid lymphomas which tend to have an indolent clinical course with an excellent prognosis and the diffuse large cell types alone or mixed which have a more aggressive clinical course (3, 6). In this study, pure MALT lymphoma have been observed in only two patients. Poor prognostic factors in this disease include advanced stage of the tumor (> stage IE), size greater than 10 cm, mediastinal involvement, rapid clinical growth, and the presence of dysphagia or stridor (6, 7).

The treatment for thyroid lymphoma has evolved during the last few decades (1, 23). Surgery, radiotherapy (RT) and chemotherapy can be used in the management of this disease but because of the rarity of PTL, no randomized controlled trials have compared the efficacy of multimodality versus single modality treatment (6, 9).

Previously, surgery occupied a pre–eminent place in management and most patients underwent extensive resections. With the use of FNA for diagnosis and the discovery that these tumors are radiosensitive and chemo sensitive, the role of surgery for these tumors has declined (23). However, surgery still played a major role in the palliation of symptoms secondary to obstructive thyroid lymphoma (6, 9).

There is no randomized, controlled trials evaluating the efficacy of chemotherapy in PTL, but outcomes have been extrapolated from studies of extranodal non–Hodgkin’s lymphoma. These studies suggest that the use of chemotherapy, most commonly CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) in patients with extranodal lymphomas is both well tolerated and efficacious (1, 9). Since the U.S. Food and Drug Administration approval of rituximab for non–Hodgkin’s lymphoma many centers now treat DLBCL PTL patients with rituximab when appropriate (1).

Currently, there are two regimens of radiotherapy that can be administered to patients with PTL. Firstly, the “Involved field radiotherapy (IFRT)” which includes the thyroid bed and cervical lymph nodes only; and on the other hand the “extended field radiotherapy (EFRT)” which also includes the mediastinal nodes and sometimes the axillary lymph nodes (9). According to the Royal Marsden Hospital experience, extended field RT (EFRT) should be considered as the standard RT technique (24). However, the optimal RT dose varies among different institutions (12, 21, 24).

In general, the choice of treatment in thyroid lymphoma depends on the histological subtype and the stage of the disease (1, 9). For patients with localized aggressive lymphoma, studies demonstrated a benefit of combined chemotherapy and radiotherapy while surgery and/or radiotherapy are used for localized thyroid MALT lymphoma. Chemotherapy is usually indicated for patients with disseminated disease (6, 15). The overall survival ranges from 35% to 79% (3, 4, 25–27). The overall 5-year survival for each stage is stage IE 80%, stage IIE 50% and less than 36% for stage IIIIE and IVE (25). Most recurrences develop within the first 4 years (23).

In our study, all patients with either localized or disseminated PTL, whatever the histological subtype received multidrug regimens, CHOP or R CHOP with good response rate. No relapse was observed.
Conclusion

In summary, clinical features in Moroccan patients with primary thyroid lymphomas are similar to those describe in the literature. Our study demonstrated that PLT showed good response to chemotherapy and had a favorable prognosis.

References


