

## Research Article

# Lymphoma of the thyroid gland: a clinicopathologic study over a period of five years in a tertiary care center

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**Received:** 4 January 2015

**Accepted:** 1 February 2015

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### ABSTRACT

**Background:** Primary Thyroid Lymphoma (PTL) is uncommon, accounting for only 5% of thyroid neoplasms and less than 2.5 to 7% of extranodal lymphomas. The study aims to analyze the histopathological findings and to correlate it with clinical features.

**Methods:** This study includes cases of PTL received in the department of pathology in a tertiary care center, Kerala, south India over a period of 5 years. Patient details and follow up data were obtained by communication with treating doctors and reviewing the hospital records. All cases had a minimum follow up of 6 months.

**Results:** 15 cases of PTL were diagnosed over the five year period. In total 72 cases of extranodal lymphomas were diagnosed, thus forming 20.83% of extra nodal lymphomas. Lymphocytic thyroiditis was present in 93.3%. Most of the cases were Extranodal Marginal Zone B Cell Lymphoma (EMZBCL) and Diffuse Large B Cell Lymphoma (DLBCL).

**Conclusion:** It is important to consider the diagnosis of primary thyroid lymphoma in patients presenting with an enlarging neck mass especially with the history of Hashimoto's thyroiditis. Random microscopic foci of DLBCL or small areas of MZBL could be overlooked examination or missed with limited sampling. The distinction between MZBL and DLBCL in the thyroid is clinically significant.

**Keywords:** Lymphoma, Extra nodal, Immunohistochemistry, FNAC

### INTRODUCTION

A substantial percentage of lymphomas arise from tissues other than lymph nodes and even from sites which normally contain no lymphoid tissue. It has been noticed recently that during the last two decades, incidence of lymphomas has increased at a rate of 4% per year. A relationship between Hashimoto's disease and malignant lymphoma has been well documented.<sup>1</sup>

Primary thyroid lymphoma is uncommon, accounting for only 5% of thyroid neoplasms and less than 2.5 to 7% of extranodal lymphomas.<sup>2-4</sup>

Analysis of the pathogenesis of PTL suggests that both antigenic stimulation in the setting of Hashimoto's thyroiditis and aberrant somatic hypermutation may play a role.

### METHODS

This retrospective clinicopathologic study conducted at the department of pathology aims to analyze the clinical presentation.

This study includes cases of PTL received in department of pathology over a period of 5 years. Patient details and

follow up data were obtained by communication with treating doctors and reviewing the hospital records. Follow up data was included. PTLs were defined as lymphomas that presented primarily as thyroid gland tumors. A minimum follow up of 6 months was available for cases included in the analysis. Cases which turned out to be secondary lymphoma were excluded.

Materials were supplemented by a review of surgical pathology and operative reports, cancer registry records, oral communication with the treating physician(s) lymphoma treatment modalities and the current status of the disease and patient.

The specimens were fixed in 10% Formalin. Gross features like size, weight, margins and parenchymal infiltration were noted. Microscopically features like Lympho-Epithelial Lesions (LEL), centrocyte like cells, monocytoid B cells, and plasma cells were assessed. Reactive Follicles with or without colonization by follicular lymphomas were also assessed. Fibrosis if any was graded semiquantitatively as mild, moderate and severe. Mitotic activity was rated as low (less than 10 mitotic figures/10 HPF) or high (greater than 10 mitotic figures/10 HPF) using the 40 × objective.

Diffuse large cell lymphoma was defined as a lymphoma or areas within a small cell lymphoma that were comprised of large lymphoid cells that “sheeted out” in a diffuse manner.

All cases were looked for the presence of lymphocytic thyroiditis. Additional features like presence or absence of apoptosis, tumor necrosis, perithyroidal extension into adipose tissue and muscle, vascular invasion and were also studied. Immunophenotypic analysis was performed according to the standardized avidin-biotin method using relevant commercially available antibody panels. The lymphomas were classified with the aid of established criteria, recent studies and the REAL and WHO classifications.

## RESULTS

The lymphomas ranged in size from 2 to 13.5 cm in maximum dimension with a mean size of 7.75 cm. The tumors were described grossly as firm to soft, lobulated, multinodular to diffuse, solid or cystic masses. The cut surface was smooth or slightly bulging, pale, tan to white-gray, or red with a “fish-flesh,” uniform, homogeneous to mottled appearance. Foci of hemorrhage and necrosis were frequently noted especially in large tumours.

15 cases of PTL were diagnosed over the five year period. In total there were 72 cases of extranodal lymphomas, thus forming 20.83% of extra nodal lymphomas.

Lymphocytic thyroiditis was present in 93.3% (n=14). Lymphocytic thyroiditis usually contained reactive follicles with an absence of a dense, sheet-like effacement of the thyroid parenchyma and demonstrated both B and T cell areas by immunohistochemistry. Neoplastic cells occasionally colonized the germinal centers of reactive follicles in areas of lymphocytic thyroiditis.

Extranodal Marginal Zone B Cell Lymphoma (EMZBCL) - 6 out of 15 (40%) were classified as Marginal Zone B Cell Lymphoma, consisted of predominantly small lymphoid cells with variable proportions of centrocyte-like cells, plasma cells, lymphoplasmacytoid lymphocytes, monocytoid B cells, and interspersed large LEL were identified in all cases including MALT Balls. Plasma cells were recognized in all cases, but plasmacytoid differentiation was prominent, at least focally in 3 cases. Reactive secondary lymphoid follicles, with or without follicular colonization or a follicular pattern, were found in 2 cases. All cases were associated with Lymphocytic thyroiditis.

Diffuse Large B Cell Lymphoma (DLBCL) - 6 out of 15 (40%) were large cell lymphomas that lacked an associated MZBL. DLBCL was associated with either a transitional zone of increasing numbers of large cells intermixed with smaller neoplastic lymphocytes or occurred as an abrupt proliferation of large lymphoid cells. Variably present in each case, the large cells demonstrated centroblastic like, immunoblastic, monocytoid B cell and plasmacytoid differentiation. One case was not to be seen associated with Lymphocytic Thyroiditis.

Mixed DLBCL and MZBL [Marginal Zone B Cell Lymphoma of MALT - (Type with Large Cell Transformation)] - 3 out of 15 (20%). The MZBL portion had similar histologic features to those described already. The DLBCL was associated single or multifocal areas of large cell transformation surrounded by typical MZBL. Large cells demonstrated centroblastic-like, immunoblastic, monocytoid B cell and plasmacytoid differentiation.

Usually, the DLBCL component represented more than 50% of the entire lymphoma to even 90%. LEL were identified in nearly every case of the mixed DLBCL and MZBL group, though more obvious in the MZBL areas. In the areas of DLBCL, the LEL were usually smaller, more widely separated from one. 48% of mixed DLBCL and MZBL showed reactive secondary follicles with or without colonization by neoplastic cells.

In cases where follicular architecture was noteworthy and caused diagnostic confusion they were correctly classified by the identification of features of lymphomas of MALT-type and immunohistochemical and molecular analysis.

**Table 1: Pathological features in various subtypes of thyroid lymphomas.**

Pathologic feature	MZBL (n=6)	Mixed DLBCL & MZBL (n=3)	DLBCL (n=6)
Maximum size of tumor	5.5 cm	8 cm	13.5 cm
Lymphocytic thyroiditis	100% (6)	100% (3)	83% (5)
Perithyroidal extension	50% (8)	33% (1)	67% (4)
Vascular invasion	0% (0)	33% (1)	50% (3)
Lymphoepithelial lesion	100%	100% (5)	67% (3)
MALT Ball type LEL	67% (4)	33% (1)	17% (1)
Marginal zone / monocytoid B cell differentiation	100% (6)	67% (2)	32% (3)
Plasmacytoid differentiation	100% (6)	67% (2)	17% (1)
Reactive follicles	67% (4)	67% (2)	17% (1)
Colonized follicles	50% (3)	33% (1)	17% (1)
Mitotic rate*	Low	67% (4)	0% (0)
	High	33% (2)	67% (2)

\*Mitotic activity was rated as low (less than 10 mitotic figures/10 HPF) or high (greater than 10 mitotic figures/10 HPF) using the 40 × objective

### Immunohistochemical analysis

The B cell immunophenotype of the lymphomas was confirmed by immunoreactivity with antibodies to CD20 and with CD79a in three cases with extensive plasmacytoid differentiation. Kappa or lambda light chain restriction was demonstrated in 22% of cases. For highlighting LEL antibodies for cytokeratin were particularly especially in areas of DLBCL. CD10 immunohistochemical analysis was performed on those cases that demonstrated a follicular pattern. Immunoreactivity was uneven with weak staining of small clusters or individual cells in the follicular areas, interpreted as residual reactive germinal center cells, or highlighted the germinal centers in areas of lymphocytic thyroiditis. Markers including CD5, CD23 and CD 43 were used to rule out small cell lymphomas and mantle cell lymphomas.

### Clinical - age, gender, signs, and symptoms

The patients included 10 women and 5 men, with a female to male ratio of (2:1). Their ages ranged from 27 to 88 years with a mean of 57.5 years at initial presentation. The difference in mean age at presentation for women (50.7 years) and men (60.5 years) was not statistically significant.

All patients clinically presented with a mass in the thyroid gland. The swelling was rapidly enlarging in 73% (n=11). Rapidly enlarging masses were reported more frequently in DLBCL (83% of DLBCL without MZBL,

67% of mixed DLBCL and MZBL) than in the MZBL (33%), yielding a statistically significant result (P = 0.042). Symptoms associated with compression / infiltration of the neck organs such as dyspnea, dysphagia were reported in 40% of cases (n=6). Pain was also experienced. 4 patients presented with hypothyroidism.

The frequency of associated symptoms resulting from compression/ infiltration of the neck structures was proportionate to large cell component. (16% of MZBL, 33% of mixed DLBCL and MZBL and 50% of DLBCL without MZBL).

### Staging

With the aid of Musshoff's modification of the Ann Arbor staging the PTLs were staged. The majority of patients presented with stage IE disease (n=10, 66%). An additional 3 patients presented with stage IIE, with the remaining 3 patients presenting with stage IIIE (n=2) disease. MZBL patients presented with stage IE (83%) or IIE (17%) disease. All patients who presented with stage IIIE had DLBCL.

### DISCUSSION

PTLs typically occur in middle to old aged individuals in the setting of lymphocytic thyroiditis with a predilection for females. Patients present with a mass in the thyroid, usually progressively enlarging, and often have symptoms related to compression of neck structures.

Fine needle aspiration has become the procedure of choice for the initial pathological diagnosis of thyroid nodule.<sup>5</sup> However, studies have also shown inconsistent results in the diagnosis of lymphoma of the thyroid. In one series, a correct diagnosis with FNAC was made in 70-80% of patients with thyroid lymphoma, but in others, FNA was suggestive but not diagnostic in only 50-60% of patients. Primary thyroid lymphoma should be suspected in patients with a rapidly enlarging neck mass, especially in women with Hashimoto's thyroiditis. Though ultrasound features such as enhanced posterior echoes can suggest the diagnosis, but biopsy for confirmation is ultimately needed. The most common type of primary thyroid lymphoma is diffuse large B cell lymphoma, which behaves in a more aggressive manner than mucosa associated lymphoid tissue lymphoma. Radiation therapy can be employed for treatment of localized mucosa-associated lymphoid tissue lymphoma, but a combination of chemotherapy and radiation is needed for disseminated disease or aggressive histological subtypes. It is important to consider the diagnosis of primary thyroid lymphoma in patients presenting with an enlarging neck mass and a history of Hashimoto's thyroiditis.

Although isolated T-cell PTLs have been reported all cases in this study were B cell lymphomas.<sup>6</sup> The cases in

the study fell into three groups: MZBL, mixed DLBCL and MZBL, and DLBCL without MZBL.

Around 20% of our tumors that contained a DLBCL contained a MZBL, to which the term mixed DLBCL and MZBL. Random microscopic foci of DLBCL or small areas of MZBL could be overlooked examination or missed with limited sampling.

All the histologic features previously described as indicators of poor prognosis were significantly more characteristic of DLBCL (high mitotic activity, frank necrosis, and abundant apoptosis). In our study, only patients with DLBCL presented with advanced stage (stage IIIE). The drawback of this study was that it did not include the long term follow up and outcome could not be commented. All MZBL presented with lower stage disease (most stage IE). Therefore the distinction between MZBL and DLBCL in the thyroid is clinically significant. MZBL and stage 1E tumours have an excellent prognosis, whereas tumours with a large cell component or DLBCL or stage greater than 1E have the greatest potential for a poor outcome.<sup>7</sup>

Whereas large cell transformation of MZBL (mixed DLBCL and MZBL) is recognized and has been reported in the thyroid and studied in other extranodal sites, its characterization, frequency, and effect on clinical behavior remains unclear in the thyroid gland. Long-term clinicopathologic studies of PTLs using the MALT concept and the most recent lymphoma classification are needed.

## CONCLUSIONS

Possibility of primary thyroid lymphoma in patients presenting with an enlarging neck mass especially with the history of Hashimoto's thyroiditis is to be considered important. The distinction between MZBL (lower stage

disease) and DLBCL in the thyroid is clinically significant.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the institutional ethics committee*

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DOI: 10.5455/2320-6012.ijrms20150309

**Cite this article as:** Anjit U, Gopal A. Lymphoma of the thyroid gland: a clinicopathologic study over a period of five years in a tertiary care center. Int J Res Med Sci 2015;3:579-82.