

## Case Report

# Primary thyroid lymphoma: a comprehensive summary of two cases

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### ABSTRACT

Thyroid lymphoma occurs rarely; constituting approximately 1-5% of all thyroid malignancies. Two cases of thyroid lymphoma are presented herewith. Both the patients were elderly females who presented with a rapidly enlarging anterior neck mass without cervical lymphadenopathy, leading to compressive symptoms like dysphagia, stridor and dyspnoea. Thyroid lymphoma is a great diagnostic and therapeutic challenge which requires high clinical suspicion with rapid and accurate diagnostic modalities to detect it as early recognition of this rare malignancy can lead to timely intervention and avoid morbidity associated with extensive surgery as chemotherapy and radiation are the mainstays of its treatment.

**Keywords:** Thyroid, Lymphoma, FNAC, Immunocytochemistry, Therapy

## INTRODUCTION

NHLs (Non-Hodgkin's Lymphoma) can be aggressive and indolent cell types. Aggressive NHLs comprise a large number of cell types, the most common of which is large-cell lymphoma among which Diffuse Large B-Cell Lymphoma (DLBCL) is the commonest. Although they most frequently arise from lymph nodes, but in approximately 30% of cases they are extranodal in origin. Thyroid gland is among the most common of these extranodal sites. Thyroid lymphoma represents approximately 1 to 2% of all NHLs and are mostly B-cell type NHL, Hodgkin's and T-cell lymphomas are extremely rare.<sup>1</sup> Among the B-cell type NHLs, the most common type is DLBCL, either associated or unassociated with Mucosa-Associated Lymphoid Tissue (MALT) lymphoma (MALToma), Follicular lymphoma, Burkitt lymphoma (rare).<sup>2</sup> It usually occurs in elderly females and has been associated with Hashimoto's Thyroiditis (HT) and prior therapeutic irradiation of the thyroid bed. Here, we discuss these two rare cases of Primary Thyroid Lymphoma (PTL) recognized on Fine Needle Aspiration Cytology (FNAC) and

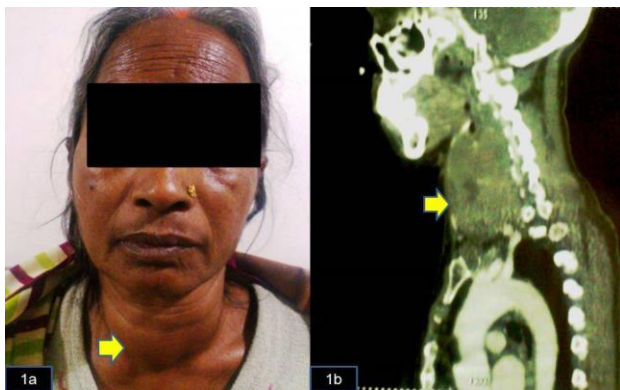
immunocytochemistry which not only helped in timely but also accurate diagnosis of this disease as the prognosis and therapeutic protocol for these patients largely depends on the stage of the lymphoma so early diagnosis and accurate staging are vitally important.

## CASE REPORT

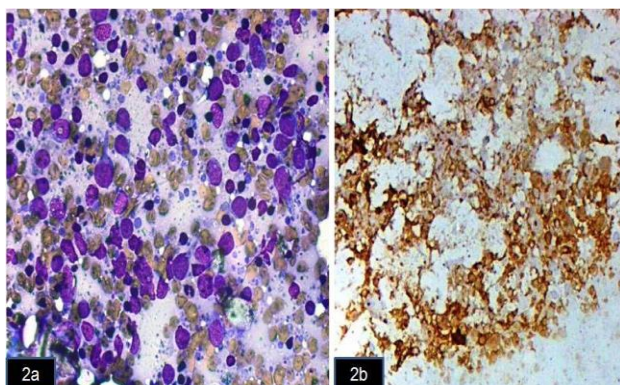
### Case 1

A 60 year old female presented with a thyroid swelling of one year duration, which rapidly increased in size since past 2 months. There was also history of recent change in voice, dysphagia and breathlessness. No history of previous radiation therapy was present. Local examination revealed a 10x10 cm thyroid swelling diffusely involving both lobes, with nodular surface and firm to hard consistency (Figure 1a). There was no cervical lymphadenopathy. Clinical diagnosis of a thyroid malignancy was made. There were no signs of thyrotoxicosis and systemic examination was unremarkable. Ultrasonography (USG) revealed hypoechoic areas in both lobes but no cysts. The

Contrast-Enhanced Computed Tomography (CECT) of neck showed heterogeneous mass in the neck with no other lymphadenopathy (Figure 1b). Her CECT abdomen was unremarkable. T<sub>3</sub>, T<sub>4</sub> and TSH levels were within normal limits. The anti-thyroglobulin and thyroid peroxidase (anti-TPO) antibodies were normal. Fine needle aspiration smears from the thyroid (Figure 2a) were highly cellular comprising predominantly of monomorphic population of medium to large sized lymphoid cells with high nuclear/cytoplasmic (N/C) ratio and scant cytoplasm. Nuclei were round to oval with fine chromatin and prominent nucleoli in some. Few scattered follicular epithelial cells were also identified in between the lymphoid cells. Lymphoglandular bodies were also seen. No Hurthle cells, granuloma, giant cells or colloid was seen. Based on the morphology findings possibility of thyroid lymphoma was made. To confirm the diagnosis immunocytochemistry was done on these smears which revealed these cells to be positive for LCA, CD-20 and Bcl-2 and negative for CK, EMA, CD-15, CD-30 (Figure 2b). Thus, a final diagnosis of DLBCL was made. Core needle biopsy of thyroid was performed but it was inadequate and non-contributory.



**Figure 1: a) Midline neck mass on clinical inspection. b) CECT neck revealing heterogeneously enhancing, infiltrating mass involving the left lobe.**

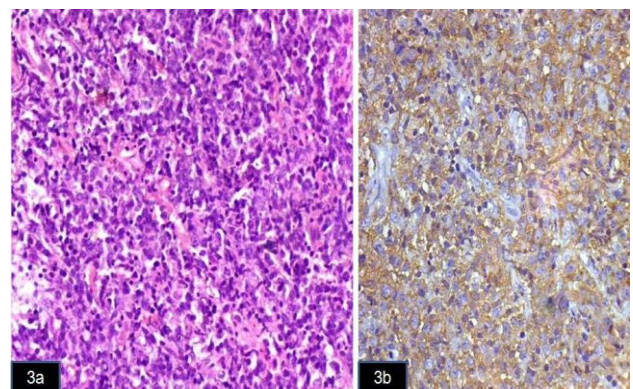


**Figure 2: a) Photomicrograph shows cytological smears showing medium to large lymphoid cells with vesicular nucleus and prominent nucleoli (Giemsa, 40x). b) Immunocytochemistry, the cells are positive for LCA (IHC, 10x).**

## Case 2

A 72 year old female presented with dysphagia, stridor, dysnoea secondary to anterior neck swelling. The swelling had been present since last 5 years and it recently increased in size. Local examination revealed diffuse, firm, non-tender thyroid swelling measuring 9x9 cm which involved both the lobes and moved well with deglutition. No other cervical lymphadenopathy was seen. The X-ray neck showed deviation and compression of the trachea while indirect laryngoscopy showed mobile vocal cords. USG neck showed diffuse enlargement of the thyroid with increased vascularity. The CECT neck revealed an enlarged and homogeneously enhancing left and right thyroid lobe which compressed the trachea. Her CECT abdomen was unremarkable. A clinico-radiological diagnosis of anaplastic carcinoma thyroid was made. The patient was referred to our institution with a previous FNAC diagnosis of Hashimoto's thyroiditis (6 months back). But, currently her thyroid hormone levels were normal. The anti-TPO antibodies were negative in blood. Serum lactate dehydrogenase (LDH) levels and  $\beta$ -2 microglobulin was normal. FNAC was performed and smears revealed morphology as described in case 1. Core needle biopsy of thyroid proved to be confirmatory in this case and predominantly showed monomorphic medium to large sized lymphoid cells with increased N/C ratio and scant cytoplasm, round to oval nuclei with irregular nuclear membrane, open chromatin with prominent nucleoli in some (Figure 3a).

Few thyroid follicles were also seen in between this lymphoid infiltrate. No follicular destruction, hurthle cell change, granuloma or giant cells were appreciated. Based on these features a diagnosis of DLBCL was given which on further immunohistochemistry showed these cells to be positive for LCA, CD-20 and Bcl-2 (Figure 3b). Bone marrow aspirate and biopsy did not show any evidence of lymphoma.



**Figure 3: a) Photomicrograph shows histopathological section exhibiting monomorphic population of lymphoid cells with vesicular nucleus and prominent nucleoli with frequent mitosis (H&E, 40x). b) Immunohistochemistry, the cells show Bcl-2 positivity (IHC, 40x).**

## Follow-up

These patients were started on chemotherapy which was a multidrug regimen consisting of cyclophosphamide, doxorubicin, vincristin, and prednisone (CHOP), to which they responded well followed by regression of these thyroid masses. Case 1 is tumor free after 6 months of therapy while case 2 was lost to follow up.

## DISCUSSION

Primary Thyroid Lymphoma (PTL) is an unusual malignancy, comprising of around 5% of all thyroid malignancies, 1-3% of lymphomas and 2.5-7% of extranodal lymphomas.<sup>4</sup> PTL is a lymphomatous process involving the thyroid gland without contiguous spread or distant metastases from other areas of involvement at diagnosis.<sup>3,5</sup> It is important to distinguish it from secondary thyroid lymphoma. PTL usually occurs in elderly females, is limited to thyroid and usually originates in a setting of autoimmune thyroiditis. On the contrary, secondary thyroid lymphoma (i.e., the thyroid being secondarily involved by lymphoma) affects mainly middle-aged population, presents with disseminated disease and is not associated with thyroiditis.<sup>6</sup>

Among PTL subtypes, DLBCL constitutes 70% of cases and appears to have the most aggressive clinical course with almost 60% of these tumors diagnosed with disseminated disease whereas the other subtype MALT lymphomas (6% to 27% of cases) have a relatively indolent course.<sup>3</sup> They are considered to be of similar endodermal origin, whether in Waldeyer's ring, the thyroid, or the gastrointestinal tract. MALT lymphomas are characterized by the presence of lymphoepithelial lesions, lymphocytes "stuffing" glandular lumina, representing colonization of the thyroid follicles by the lymphoma cells. Other rare subtypes are follicular lymphoma and Burkitt's lymphoma.<sup>2</sup>

The underlying pathogenesis of primary thyroid lymphoma remains obscure. The thyroid gland contains no native lymphoid tissue. Intrathyroid lymphoid tissue is accrued in various pathological conditions, but more evidently in the course of autoimmune thyroid disease, notably chronic autoimmune thyroiditis (Hashimoto's thyroiditis). The association between lymphoma and Hashimoto's thyroiditis has been reported between 30% and 70%. Among patients with Hashimoto's thyroiditis, the risk of thyroid lymphoma is at least 60 times higher than in patients without thyroiditis.<sup>7</sup> Such lesions are an aggressive or high-grade variant. Histologically, this acquired lymphoid tissue can evolve to lymphoma, including MALT type. It is thought that lymphomas originating in this wide variety of primary sites represent a malignant transformation of acquired lymphocytic tissue during the course of a chronic inflammatory or an autoimmune process. Clinically it is characterized by an indolent course and a prognosis better than that of non-MALT lymphomas.<sup>8</sup>

The majority of patients affected are middle to elderly women. PTL typically arises in autoimmune thyroiditis and it takes around many years to develop after the onset of lymphocytic thyroiditis in most of the cases. A history of a rapidly enlarging neck mass with dyspnoea, dysphagia, or change in voice is the typical presentation of thyroid lymphoma.<sup>3</sup> Our patients also presented with similar symptoms.

Hypothyroidism at the time of diagnosis is documented in 30-40% of patients due to replacement of thyroid parenchyma by the lymphomatous process or due to underlying Hashimoto's thyroiditis. Thyrotoxicosis is exceedingly rare.<sup>3,6</sup> Our patients at presentation were euthyroid and antibodies to thyroid peroxidase were negative in both the cases.

High LDH or  $\beta$ -2 microglobulin levels are usually associated with aggressive lymphomas and poor prognosis, and at this stage of the disease, histological diagnosis is usually not difficult.

FNAC has become a routine procedure for the pathological diagnosis of thyroid swellings. In both our cases, this procedure was quite helpful in the diagnosis of this tumor as reported previously.<sup>3</sup> However, studies have also shown that FNAC is unreliable procedure in the diagnosis of thyroid lymphoma. Hypocellularity and the difficulty in distinguishing a lymphoma from the lymphoid infiltrate found in Hashimoto's thyroiditis are the main diagnostic pitfalls which raise a doubt about the reliability of FNAC for its diagnosis, occasionally even thyroidectomy or open biopsy is required. Another important differential diagnosis of DLBCL thyroid is anaplastic carcinoma that shows pleomorphic, round, oval or spindle-shaped cells. Lack of cohesion and absence of lymphoglandular bodies with CK and EMA negativity goes against anaplastic carcinoma.<sup>10</sup> Immunocytochemistry is extremely helpful in confirmation of diagnosis of these cases which was also seen in our cases. By contrast, cytological diagnosis of MALT lymphomas is difficult, because of heterogeneous appearance of the neoplastic infiltrate.<sup>3,9</sup>

Early recognition and correct treatment of this malignancy is vital. The best treatment results for primary thyroid large-cell lymphoma are with combined-modality therapy; which includes chemotherapy and radiotherapy but for primary thyroid MALToma, radiation therapy alone is probably adequate. Obstruction or compression of the trachea may require isthmectomy or thyroidectomy.<sup>1</sup>

The most important prognostic factors influencing the outcome are age, stage, histopathological subtype, grade, elevated LDH and  $\beta$ -2 microglobulin.<sup>3</sup> Local recurrences and distant metastases may develop long after the initial treatment, sometimes after several years, underlining the need for long term follow up.



## CONCLUSION

We present two cases of PTL diagnosed on fine needle aspiration cytology. All preexisting cases of Hashimoto's thyroiditis should be kept under follow-up and PTL has to be ruled out especially if there is sudden increase in size, dysphagia, dysphagia, stridor, and change in voice. In both our cases, since PTL was diagnosed by FNAC and immunocytochemistry which was later confirmed by trucut biopsy; the patient received chemotherapy instead of unnecessary extensive surgery which avoided any morbidity and showed good clinical response.

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