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Case Report

PRIMARY THYROID LYMPHOMA (PTL): A RARE CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Primary thyroid lymphoma (PTL) is a rare malignancy of the thyroid, accounting for 5% of all thyroid malignancies and approximately 2% of extranodal lymphomas. PTL occurs mainly in elderly females and diffuse large B-cell lymphoma (DLBCL) is most common. Here we report a case of non-germinal center diffuse large B-cell lymphoma (non - GC DLBCL) occurring in a 62 - year - old female who was admitted to the hospital because of multiple palpable left neck masses. The patient then underwent thyroid ultrasound, detecting multiple nodules in the two lobes and isthmus of the thyroid gland, in which the largest nodule was in the left lobe with TIRADS 5 measuring 47x33 mm, and many cervical lymph nodes. Microscopically, thyroid tissue showed proliferation of tumor cells with large nuclei, coarse chromatin, narrow rims of cytoplasm, and scattered mitoses. There was 01 destructured lymph node, proliferating cells with characteristics similar to those in the thyroid gland; the remaining lymph nodes were chronically inflamed. Immunohistochemically, the tumor cells were positive for CD20, CD79a, Ki67 (40%), and negative for CD10, BCL6, MUM1, CD5, BCL2, c-MYC, CD15, CD30, EBV. Primary thyroid lymphomas are rare with the prognosis of patients depending on the histological classification of the tumor and the stage of the disease. They need to be evaluated and treated individually because there is no unified treatment due to their rarity.

Keywords: *Lymphoma, primary, thyroid.*

I. INTRODUCTION

Primary thyroid lymphoma (PTL) is a rare tumor, defined as lymphoma involving only the thyroid gland or the thyroid gland and regional lymph nodes without contiguity or metastasis of other areas at the time of diagnosis [1]. The disease accounts for only 2.5% to 5% of all thyroid malignancies and 1 - 2% of extranodal lymphomas [2].The female - to - male ratio is 3 - 4/1, and the average age of diagnosis is 65 years, more common in the sixth and seventh decades of life [2,3]. The disease is mostly associated with chronic lymphocytic (Hashimoto) thyroiditis and often presents asamass in the thyroid, with or without cervical lymphadenopathy [3]. Therefore, accurate diagnosis of primary thyroid lymphoma is essential for prognosis and selection of treatment options. This article reports a case of primary thyroid lymphomain a 62 - year - old female patientto showsome clinical and pathological features of primary thyroid lymphomaand review theliterature.

II. CASE REPORT

A62 - year - old woman was admitted to the hospital because of many palpable masses in the left neck region, which grew rapidly within 1.5 months.

Besides that, no other abnormalities were detected. The patient had no history of neck irradiation, chronic lymphocytic (Hashimoto) thyroiditis, or cancer. The patient then underwent thyroid ultrasound, multi-slice computed tomography (MSCT) of the neck, and fine - needle aspiration (FNA) of the nodule in the left lobe (TIRADS 5) and left cervical lymph nodes.

* Thyroid ultrasound:

The thyroid gland: The two lobes hadseveral mixed echoic nodules and cysts clearly demarcated with surrounding tissues, in which the largest nodulein the right lobe measuring11 x 10 mm (TIRADS 2), and the largest nodulein the left lobe measuring 47 x 33 mm, spreading to the isthmus with microcalcification in the solid fraction (TIRADS 5). The thyroid isthmus hadthe largest nodulemeasuring 18 × 6 mm (TIRADS 5), consisting mainly of the solidwithdisruption of the thyroid capsule. The remaining parenchyma wasirregular, with many scattered hyperechoic nodules.

The level II, III, and IV lymph nodes: irregular parenchyma, unclear umbilicuswith fluid in the lymph nodes, andthe largest size of 32x14 mm.

* Multi - slice computed tomography (MSCT) of theneck:

The thyroid gland: The size of the two thyroid lobes was within normal limits.The right lobe had several hypodense nodules with relatively regular margins and some with calcification; the largest nodulemeasured 12x12 mm. The lower third of the left lobe had a hypodense nodule with irregular margins, extending beyond the thyroid capsule, growing to the isthmus of the thyroid gland, measuring 55x43 mm.

The leftlevel Vb, VI lymph nodeslost their normal structure and had poor enhancement aftercontrast injection with the largest lymph node measuring 30x18 mm.

* Fine - needle aspiration (FNA) of the nodule in the left lobe (TIRADS 5): The smear showed proliferation of monomorphic lymphocytes with large nuclei, unknown nucleoli, interspersed withcolloid and clusters of normal follicular cells. The patient was diagnosed with atypia of undetermined significance (AUS - Bethesda III).

* Fine - needle aspiration (FNA) ofleft cervical lymph nodes: The smear showed proliferation of monomorphic lymphocytes with large nuclei, unknownnucleoli. The patient was diagnosed with atypical cytology favoring lymphoma and recommended lymph node dissection for histopathological diagnosis.

* Blood biochemistry: T3 1.91 (1.3 - 3.1) nmol/L, FT4 13.71 (12 - 22) pmol/L, TSH 9.56 (0.27 - 4.2) µIU/mL.

* Other tests (chest X-ray, abdominal X-ray, abdominal ultrasound, gastrointestinal endoscopy, ENT endoscopy): no abnormalities detected.

After that, the patient underwent total thyroidectomy, cervical lymphadenectomy, and specimens are sent to the Department of Pathology for definitive diagnosis. Macroscopically, the first lobe of the thyroid gland was6x4x3.5 cm in size with a uniform gray - white firm appearance on the cross section. The second lobe was 5x3.5x2.5 cm in size and had 2 nodules that measured 1 cm and 2 cm in diameter with a white firm appearance on the cross section. The left cervical lymph node had the largest size of 3.5x1.5x1 cm; the cross section was greyish white and firm.Microscopically, thyroid tissue sectionsshowed areas of diffuse proliferation of tumor cells with large round nuclei, coarse chromatin, prominent nucleoli, eosinophil cytoplasm, and scattered mitoses. The remaining thyroid tissue showed infiltration ofmany lymphocytes in the stroma, sometimes with lymphocytic follicles. One of the left cervical lymph nodes lost itsstructure, proliferating tumor cells with similar characteristics as observed in thyroid tissue. Immunohistochemically, the tumor cells were positive for CD20 (strong, diffuse), CD79a, Ki67(40%), and negative for CD10, BCL6, MUM1, CD5, BCL2, c-MYC, CD15, CD30,
EBV. Histopathology and immunohistochemistry were consistent with primary thyroid diffuse large B-cell lymphoma of non - germinal center type/ chronic lymphocytic (Hashimoto) thyroiditis (Hans' algorithm) [4].

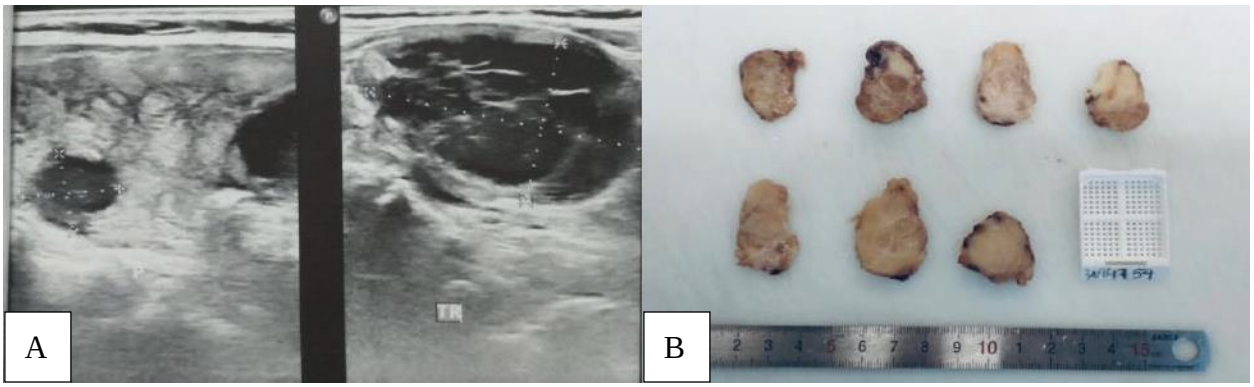

Figure 1. A.Ultrasound image of thethyroid gland: Parenchyma hadseveral mixed echoic nodules and cysts clearly demarcated with surrounding tissues, in which the largest nodulein the right lobe measuring 11 x 10 mm (TIRADS 2), and the largest nodulein the left lobe measuring 47 x 33 mm, spreading to the isthmus with microcalcification in the solid fraction (TIRADS 5).

B. Macroscopic images: The first lobe of the thyroid gland was 6x4x3.5 cm in size with a uniform gray-white firm appearance on cross section. The second lobe was 5x3.5x2.5 cm in size and had 2 nodules that measured 1 cm and 2 cm in diameter with a white firm appearance on cross section.

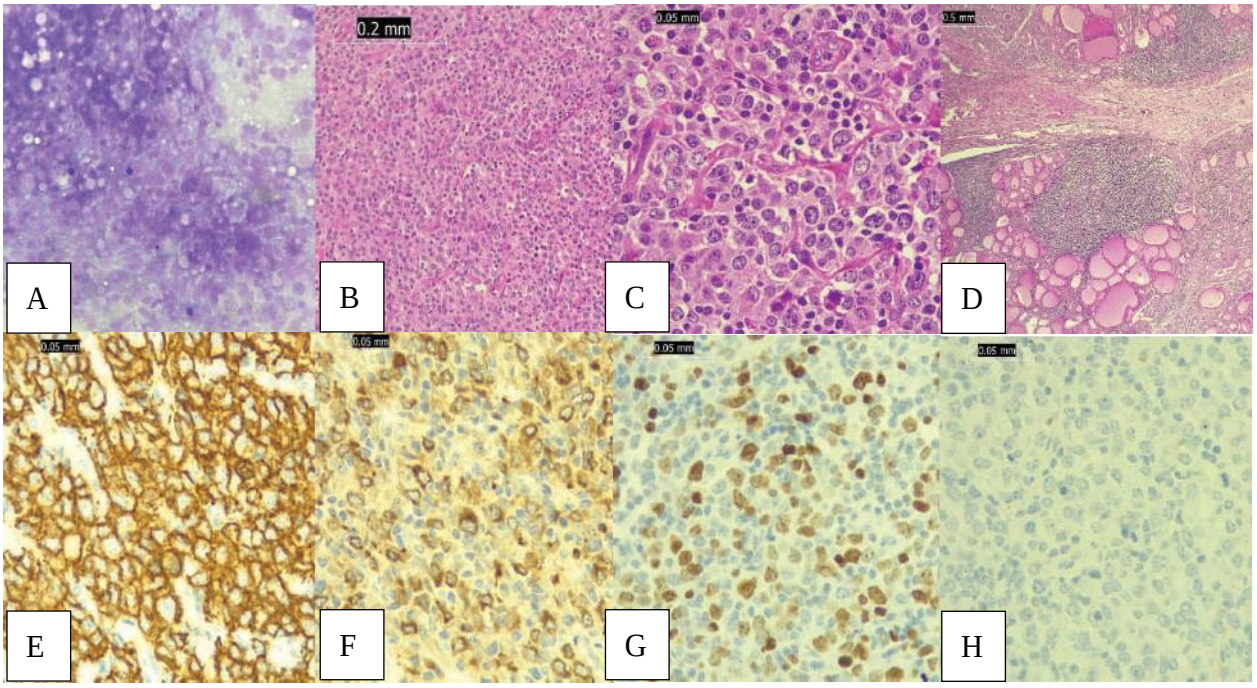

Figure 2. A. Cytological image: The smear showed proliferation of monomorphic lymphocytes with large nuclei, unknownnucleoli (Giemsa, x 400);

B-D. Microscopic images: thyroid tissue sectionsshowed areas of diffuse proliferation of tumor cells with large round nuclei, coarse chromatin, prominent nucleoli, eosinophil cytoplasm, and scattered mitoses (B; HE, x 100) (C; HE, x 400); the remaining thyroid tissue showed infiltration ofmany lymphocytes in the stroma, sometimes with lymphocytic follicles (D; HE, x 400);

E-H. Immunohistochemistry images: the tumor cells were positive for CD20 (strong, diffuse) (E; HMMD, x 400), CD 79a (F; HMMD, x 400), Ki 67 (40%) (G; HMMD, x 400), and negative for CD10 (H; HMMD, x 400).

III. DISCUSSION

Primary thyroid lymphoma (PLT) is a rare malignant disease that affects only the thyroid gland, sometimes the cervical lymph nodes, and infrequently more - distant sites [5]. Primary lymphoma in other sites should be excluded. PLT is more commonly observed in females than males, with a female/male ratio of 4/1. Most patients present with the disease in the 7th decade of life, with a mean age of 67 years [6]. Chronic lymphocytic (Hashimoto) thyroiditisis a well - recognized risk factor for the development of PTL [7]. Patients with Hashimoto's thyroiditis have a significantly higher risk of developing thyroid lymphoma, which is associated with more than 90% of PTL, and according to a study, the risk of PTL of patients with Hashimoto's thyroiditisis 80 times the risk in the general Japanese population [1,3]. This close relationship is probably due to chronic antigenic stimulation leading to malignant transformation [1]. However, it takesa long time (20 - 30 years) to develop PTL after the onset of chronic lymphocytic (Hashimoto) thyroiditis [7]. In our case, although the patient had no history of detecting chronic lymphocytic thyroiditis, pathological results confirmed this pathology's existence.

Most patients present with amassin the thyroid, with or without cervical lymphadenopathy. The tumor enlarges rapidly (usually within 1 to 3 months). Patients may present with hoarseness, dyspnea, and increased serum lactate dehydrogenase, which is more common with aggressive lymphomas than with low - grade cases [3,5]. Due to frequent coexisting with Hashimoto's thyroiditis, circulating antibodies to thyroid peroxidase are positive in a large percentage of patients (60%) [5]. According to Peixoto et al. (2016), 30% of patients arediagnosed with symptoms and signs of compression of adjacent structures such as dyspnea, dysphagia, stridor, hoarseness, coughing, or choking; 10% of patients have hypothyroidism; and 10 - 20% of patients arediagnosed with symptom B (fever, night sweats or weight loss) [1]. In our case, the patient was admitted to the hospital because he palpated many large masses in the left neck region, which grew rapidly within 1.5 months without any other symptoms.

On imaging studies (ultrasound, computed tomography), primary thyroid lymphoma shows diffuse a diffusely enlarged thyroid gland (resembling goiter) or a nodular thyroid gland (solitary or multiple nodules, often cold) that mimics thyroiditis or aprimary thyroid follicular lesion [5]. Fine - needle aspiration (FNA) is now considered a leading tool in diagnosing thyroid diseases. However, according to the literature, FNA has inconsistent rates ofachieving apositive diagnosis, varying from 25% to 90% in the diagnosis of PTL [8,9]. On cytology, the differential diagnosis between thyroid lymphoma, chronic lymphocytic thyroiditis, and even anaplastic thyroid carcinoma is difficultin some cases, presenting a real challenge to the pathologists [1]. Several retrospective studies demonstrated that FNA sensitivity and specificity are increased with other techniques such as flow cytometry, immunohistochemistry, or molecular techniques like PCR amplification [10]. Ultrasound - guided fine-needle aspiration also increases the sensitivity of FNA because it can avoid areas of necrotic tissue and minimize the risk of trauma to adjacent structures. When FNAC is insufficient for diagnosis, core biopsy, incisional biopsy, or even thyroidectomy may be required [11]. Our patient had left cervical lymphadenopathy with a cytologically predisposing finding for lymphoma and lymph node dissection was recommended for histopathological diagnosis. However, the clinicians feared an undifferentiated thyroid carcinoma due to the ultrasound image of the thyroid nodule showing TIRADS 5, then the patient underwent total thyroidectomy and cervical lymph node dissection.

Among primary thyroid lymphomas, diffuse large B-cell lymphoma (DLBCL) is the most common (50 - 80%), followed by extranodal marginal zone B-cell lymphomaof mucosa-associated lymphoid tissue(MALT lymphoma)(20 - 30%) and follicular lymphoma (12%). Some DLBCLs constitute large cell transformation of MALT lymphoma. Other rare lymphomas include T-cell lymphoma, Burkitt lymphoma (4%), small lymphocytic lymphoma (4%), gamma heavy chain disease, and classic Hodgkin lymphoma (7%) [1,3]. DLBCL shows proliferation of tumor cells with large nuclei, prominent nucleoli, and most show a germinal-centre B-cell immunophenotype. In our case, primary thyroid lymphoma belonged to thediffuse large B-cell lymphoma of non - germinal center typewith tumor tissue composed of large round nuclei, coarse chromatin, prominent nucleoli, eosinophil cytoplasm, and scattered mitoses. The remaining thyroid tissue presented with chronic lymphocytic thyroiditis. Immunohistochemical staining revealed tumor cells

positive for CD20, CD 79a, and negative for CD10, BCL6 and MUM1.

In terms of molecular biology, t(3;14)(p14;q32) translocation with *FOXP1-IGH* fusion is found in approximately half of all cases of thyroid MALT lymphoma, whereas other chromosomal translocations characteristic of MALT lymphoma are rarely found. DLBCLs show genetic features similar to those of their nodal and other extranodal counterparts, with some cases having a BCL6 or MYC-related translocation, or 17p11alterations [3].

Primary thyroid lymphoma should be differentiated from primary lymphoma of other sites, which is particularly important given the rarity of PTL. Furthermore, PTL also needs to be differentiated from Hashimoto's thyroiditis and anaplastic thyroid carcinoma because the treatment and prognosis of these diseases are completely different. Supportive techniques such as immunohistochemistry or flow cytometry are of particular importance in the diagnosis of PTL, contributing to the treatment and prognosis of the disease [5]. Secondary thyroid lymphomahas always been a common disease and higher mortality, in contrast to primary thyroid lymphoma in the early stage [1].

The prognosis depends on the histological type of the tumor and the stage of the disease. Patients with localized thyroid lymphoma have a good prognosis, and the 5 - year - survival rate in patients with intrathyroidal disease is 90%, which decreases to 35% in patients with extrathyroid disease. The 5 - year survival rate is 89 - 100% for MALT lymphoma, compared with 75% for DLBCL. Poor prognostic indicators include advanced stage (greater than stage IE), tumor larger than 10 cm, presence of symptoms of local obstruction, rapid tumor growth, advanced age (>60 years), extracapsular extension and vascular invasion, elevated levels of LDH and β2microglobulin [1,3]. The accurate distinction of the germinal center B-cell like (GCB) subtype from the non-GCB subtype is an important predictive factor in DLBCL, NOS since these two subtypes have differences in gene expression, chromosomal aberrations, and repeat mutations [4].

The treatment of primary thyroid lymphoma has varied greatly over time and is controversial because it is a rare disease and, therefore, has not been studied on a large scale. Currently, most authors recommend a multidisciplinary approach: chemotherapy, then radiation therapy, combined with thyroidectomy in case patients have symptoms of tracheal and esophageal compression, severe airway obstruction. However, there are no studies demonstrating that surgery is effective in controlling airway symptoms, while total thyroidectomy may expose patients to unnecessary postoperative risks, including damage to the laryngeal nerve and hyperparathyroidism without increasing overall survival [1,2]. While MALT lymphomais usually detected in the thyroid - localized stage (stage IE), it can therefore be treated with surgerywithout adjuvant treatment [1]. Furthermore, the distinction between the GCB subtype and the non-GCBsubtype should be made for all cases of DLBCL, NOS, at diagnosis because benefits from the addition of bortezomib, lenalidomide, and ibrutinib to R-CHOP is preferentially seen in the non-GCBsubtype [4].

IV. CONCLUSION

We report a case of diffuse large B-cell lymphoma (DLBCL) of non - germinal center type (non-GC)in the thyroid gland in a 62 - year - old female patient. Microscopically, the tumor tissue is composed ofthyroid tissue showed proliferation of tumor cells with large nuclei, coarse chromatin, prominent nucleoli, narrow rims of cytoplasmand scattered mitoses. Immunohistochemically, the tumor cells were positive for CD20, CD 79a, Ki 67 (40%), and negative for CD10, BCL6, MUM1, CD5, BCL2, c-MYC, CD15, CD30, EBV. Primary thyroid lymphoma is a rare tumor that requires apreoperative differential diagnosis from lymphomas of other sites, Hashimoto's thyroiditis, poorly differentiated thyroid carcinomaand anaplastic (undifferentiated) thyroid carcinoma, helping to determine the appropriate treatment.

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REFERENCES

1. Peixoto R, Correia Pinto J, Soares V. Primary thyroid lymphoma: A case report and review of the literature. Ann Med Surg (Lond). 2016.13:29-33.
2. Papadakis G, Tertipi1 A, Papazian M, et al. Case report: primary thyroid lymphoma presenting as a rapidly enlarging thyroid mass. Endocrinol Metab Int J. 2014.1(1):4-6.

3. Lloyd RV, Osamura RY, Kloppel G. WHO classification of tumours of endocrine organs. lyon: International agency for research on cancer (IARC). V10, 4th ed. 2017:137-138.
4. Steven HS, Elias C, Nancy LH. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: International Agency for Research on Cancer. 2017.4(2):293-294.
5. Hedhilia F, Kedousa S, Jbalia S. Primary thyroid lymphoma: Case report and review of the literature. Egyptian Journal of Ear, Nose, Throat and Allied Sciences. 2015.16(2):171-173.
6. Ruggiero FP, Frauenhoffer E, Stack BC. Thyroid lymphoma: a single institution's experience. Otolaryngol Head Neck Surg. 2005.133(6):888-896.
7. Holm LE, Blomgren H, Lowhagen T. Cancer risks in patients with chronic lymphocytic thyroiditis. N Engl J Med. 1985.312(10):601-604.
8. Gupta N, Nijhawan R, Srinivasan R, et al. Fine needle aspiration cytology of primary thyroid lymphoma: a report of ten cases. Cytojournal. 2005.2:21.
9. Nguyen GK, Lee MW, Ginsberg J. Fine-needle aspiration of the thyroid: an overview. Cytojournal. 2005.2(1):12.
10. Walsh S, Lowery AJ. Thyroid lymphoma: recent advances in diagnosis and optimal management strategies. Oncology. 2013.18:994-1003.
11. Sarinah B, Hisham NA. Primary lymphoma of the thyroid: diagnostic and therapeutic considerations. Asian J. Surg. 2010.33:20-24