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Case Report

Primary Thyroid Lymphoma – Case Report

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Abstract

Primary thyroid Lymphoma (PTL) is a rare tumor involving thyroid gland with or without adjacent nodes. It usually presents as a rapidly enlarging mass in neck with compressive symptoms, in the background of long-standing hypothyroidism. FNAC may not be diagnostic and a core biopsy or rarely open biopsy might be required to establish the diagnosis. It might mimic anaplastic carcinoma in a clinical setting. Therapeutic strategy will include chemo radiation therapy with high potential of complete cure. Surgical resection has limited role & the plan of treatment need to be tailored to the given situation. High degree of suspicion in clinical setting with optimal interaction in multidisciplinary team is essential for the management of these rare situation.

Categories – Surgery, Oncology

***Key words**- Primary thyroid lymphoma, DLBCL- Diffuse large B cell lymphoma, core biopsy, immunohistochemistry.*

Introduction

Primary thyroid lymphoma (PTL) is defined as a lymphoma involving only the thyroid gland or the thyroid gland and adjacent (regional) neck lymph nodes, without contiguous spread or distant metastases from other areas of involvement at diagnosis [1,2]. In this article, we have discussed about 2 cases of primary thyroid lymphoma recently treated in our hospital. The aim of this article is to highlight the rarity of the situation, importance of early detection due to high index of clinical suspicion.

Case Presentation:

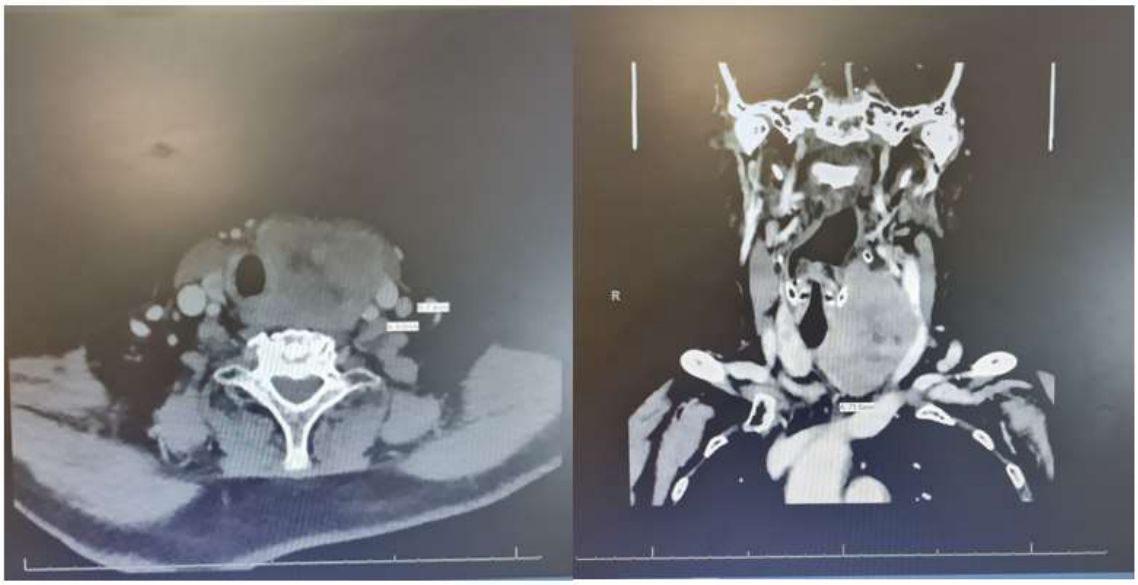
Case 1:

An 80-year-old female patient presented with recently noticed goiter in December 2021. She is a known hypothyroid on medication for the past 8 years. Clinically, the left lobe was enlarged. Her voice was normal. Initial blood test showed normal thyroid function on medication. Ultrasound scan revealed a large lobulated

nodular lesion involving the whole of left lobe measuring about 5.4 x 4.2 x 3.2 cm TR4, corresponding to palpable lesion. In the Right lobe there were two nodules measuring 1.8 and 1.6 cm respectively TR3. USG guided FNAC from the left lobe nodule was reported as Bethesda category II- benign thyroid nodule/ lymphocytic thyroiditis. Patient preferred to be on follow up an was kept on eltroxine for hypothyroidism as she was asymptomatic otherwise. However, 3 months later, she presented with hoarseness of voice and mild dysphagia. Re-evaluation showed almost the same clinical and radiological findings. Laryngoscopy showed left vocal cord palsy. CT scan of the neck was done which showed multinodular goiter as in ultrasound scan. Picture 1 – CT scan axial and coronal section. Additionally, a few lymph nodes were seen in the left paratracheal region below the left lobe nodule as well as the internal jugular vein was partially encased by left lobe nodule. Repeat FNAC from the left lobe nodule was reported again as Bethesda category II - benign thyroid nodule/ lymphocytic thyroiditis. Core biopsy was not considered due to its close proximity to the Internal jugular vein. Considering the age, with progressive worsening of symptoms, it was decided to go ahead with surgery. She was scheduled for total thyroidectomy under general anesthesia. During surgery, Gross extrathyroidal spread from the left lobe involving the strap muscles, left side internal jugular vein, recurrent laryngeal nerve was noted. Total thyroidectomy with paratracheal nodal dissection was done taking care not to leave gross residue behind (Picture 2). She recovered well. Histopathology showed high grade B-cell lymphoma (Picture 3). Immunohistochemistry reported as diffusely positive cells for CD45, CD20 and BCL-2. CD3, CD5 highlights background reactive T cells. CD23 demonstrated residual follicular dendritic meshwork. Pan CK, BCL 6, cyclin D1 and CD10 were negative. Ki-67: 70-75%. 5 paratracheal nodes showed only reactive changes & no malignancy.

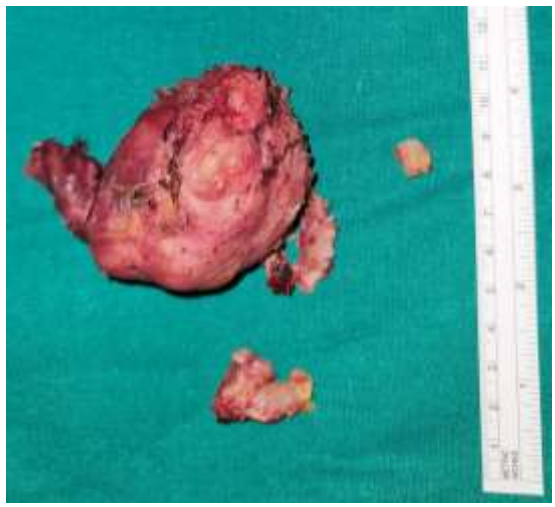
The case was discussed in the multi-disciplinary tumor board. PET scan did not reveal any distant metastases. She was staged as primary thyroid lymphoma stage-1E. Her cardiac and liver status was found to be normal and satisfactory. She received chemotherapy as per RAPID protocol. She received three cycles of RCHOP. Rituximab 375 mg/m2, CHOP -cyclophosphamide 750 mg/m2, adriamycin 50 mg/m2, vincristine 1.4 mg/m2, and prednisolone 100 mg/day.

Patient tolerated the chemotherapy well. Follow up PET CT was done which showed no active disease. One more cycle of RCHOP was given and was kept under observation. One year follow up evaluation confirmed disease-free status.

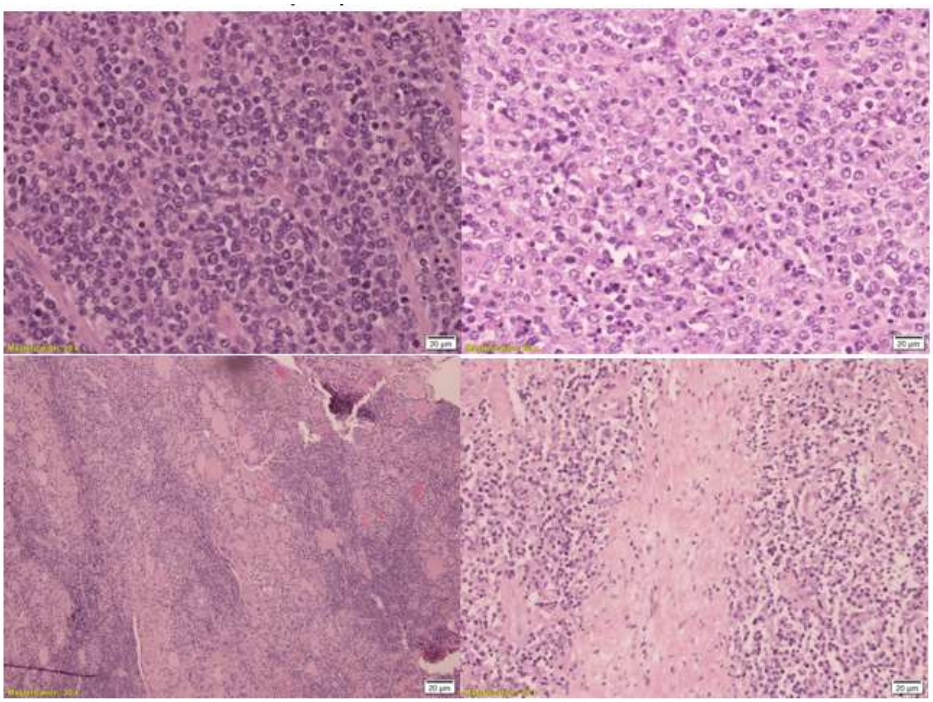


Axial section Coronal Section

Picture 1 – CT Scan



Picture 2 – Macroscopic specimen



Picture 3 – Microscopic Picture

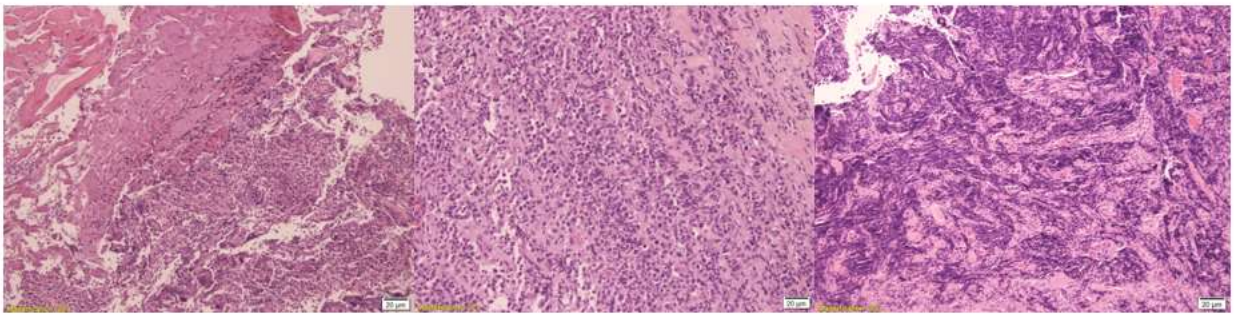
Left thyroid lobe totally obliterated by tumor composed of large cells with vesicular nuclei, distinct nucleoli & amorphous cytoplasm, with areas of necrosis & fibrosis. Focal area of preserved thyroid tissue with lymphocytic thyroiditis.

Case 2:

A 41-year-old male presented with left sided neck swelling for the past one month. Clinical evaluation showed a large thyroid nodule involving the left lobe measuring about 6 cm. Multiple hard nodes were felt in level 2, 3 and 4. Ultrasound scan showed an mildly enlarged right lobe of thyroid gland, mild coarsening of echotexture with tiny scattered nodularity. No discrete focal lesion could be made out. Left lobe of thyroid gland appears enlarged and completely replaced by a poorly enhancing lesion which is also extending into left side of isthmus. Multiple bulky and enlarged lymph nodes in the left side level 2, level 3 and level 4 as well as in the left paratracheal region just inferior to thyroid gland. Radiologically it was suspected to be Thyroid Neoplasm with left side neck lymphadenopathy. US guided FNAC from the thyroid nodule as well as left level 3 node was done. It was reported as atypical lymphoid proliferation. CT neck showed enlarged Left lobe of thyroid gland replaced by a poorly enhancing lesion which is also extending into left side of

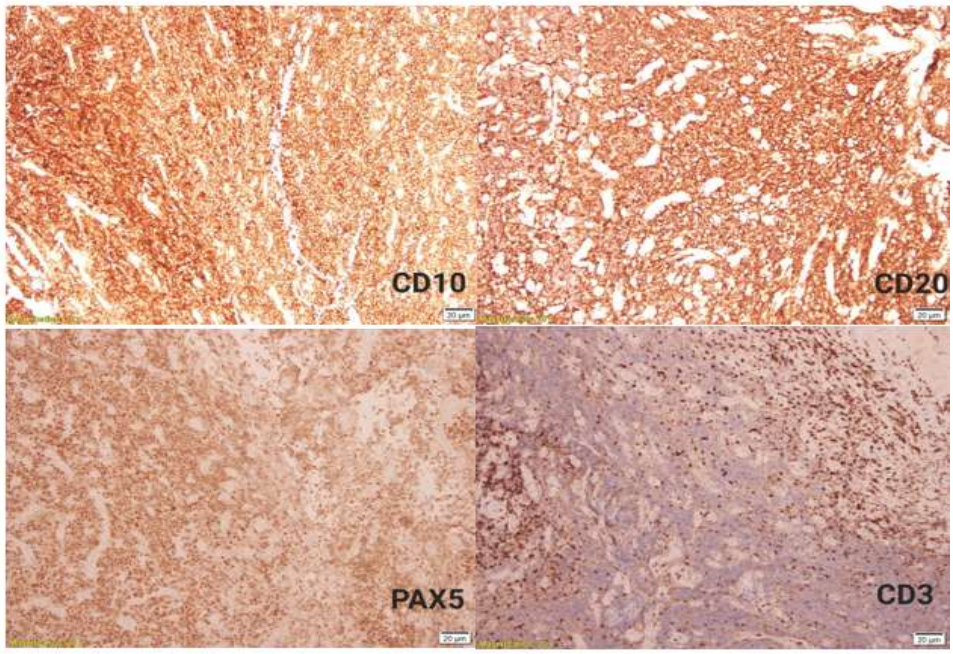
isthmus. Multiple bulky and enlarged lymph nodes in the left side level 2, level 3 and level 4 as well as in left paratracheal region just inferior to thyroid gland. Significant compression of left side IJV by nodal masses, and just below the level of left submandibular gland region. left IJV is almost obliterated by external compression.

Clinico-radiologically, at this juncture, thyroid neoplasm and possible lymphoma were strongly suspected. There were no B symptoms. Patient underwent excision biopsy of the left level 3 node. HPE showed Compatible with Lymphoproliferative Disorder Infiltrating Adjacent Skeletal Muscle cells: Diffuse Large Non-Hodgkin B Cell Lymphoma with High Grade Features (Picture 4). Immunohistochemistry (Picture 5) was done which confirmed the diagnosis of DLBCL/ High Grade B-cell lymphoma with MYC and BCL2 rearrangements. IHC included Cytokeratin (AE1/AE3): Negative, CD3 (LN10):Positive for few reactive T lymphocytes, CD20cy (L26):Strongly diffuse positive for neoplastic B lymphocytes, Vimentin (V9):Negative, CD10 (56C6):Diffuse positive for neoplastic B lymphocytes, BCL2 (bcl-2/100/D5):25% of neoplastic cells, BCL6 Protein (PG-B6p):Diffuse mild to moderate nuclear positivity for neoplastic lymphoid cells, PAX-5 (1EW): Diffuse nuclear positivity for neoplastic lymphoid cells, CD30 (JCM182): Negative for neoplastic lymphoid cells, CD5 (4C7): Positive for some reactive lymphocytes, ki-67 (MIB-1): 100%, MUM 1 : Negative, C-MYC :Focal Faintly nuclear staining (30%), CD34 Class II (Qbend 10): Negative. Bone marrow biopsy and PET CT did not show distant metastases. He received chemotherapy and had complete response. Subsequently he had radiation to neck and is found to be free of disease.



Picture 4 Microscopic Picture

Lymph node showing features compatible with lymphoproliferative disorder infiltrating skeletal muscles – diffuse large Non-Hodgkin's B cell lymphoma.



Picture 5 - Immunohistochemistry

Discussion

Epidemiology - Primary thyroid lymphoma (PTL) is a rare malignancy affecting the thyroid gland. It accounts for only less than 5% of thyroid malignancies and 1-2% of extra nodal lymphoma [3]. Most cases of NHL (Non-Hodgkin's Lymphoma) affecting the thyroid are derived from the B-cells. They are mostly diffuse large B-cell lymphoma (DLBCL) followed in frequency by MALToma. Other subtypes are very rare. It is commonly encountered in female gender affecting the 6th decade and above. The Male:Female ratio is 1:4 and the mean age is about 65 years at the time of diagnosis [4].

Associated factors

Hashimoto's autoimmune thyroiditis has been implicated as the single most important risk factor for lymphoma of thyroid gland [5]. 78% of the primary thyroid lymphomas had evidence of Hashimoto's thyroiditis [6]. The risk is almost 60 times higher for those with Hashimoto's thyroiditis when compared to those without Hashimoto's thyroiditis [7]. There is no association with any other common thyroid problems like colloid goiter, thyrotoxicosis, previous exposure to radiation or any genetic abnormality. Rarely, PTL can coexist with grave's disease [8] or papillary carcinoma thyroid [9,10].

Clinical Features

The tumor usually present with a painless neck mass that rapidly increases in size [11]. Other symptoms include dyspnea, dysphagia, and change in voice. The age at presentation for male patients is almost a decade earlier than for females. Most patients present with early-stage disease

In our report, the first patient was a known case of hypothyroidism, possibly due to Hashimoto's thyroiditis for the past 10 years. She recently had noticed an enlarging mass in the neck arising from the thyroid gland. Repeated FNACs did not prove malignancy. It would be prudent to check for the possibility of a lymphoma in the backdrop of Hashimoto's thyroiditis when there is an enlarging mass causing symptoms. Although initially asymptomatic, she presented with left vocal cord palsy in 3 months. While the 2nd case presented with large asymptomatic neck mass.

The most common symptom is rapidly enlarging goiter with obstructive symptoms which includes dyspnea, stridor due to tracheal compression, dysphagia due to esophageal compression or local neck pain. In case 1, the patient had left sided vocal cord palsy with difficulty in swallowing. Usually patients are hypothyroid but there it may occasionally be seen in hyperthyroid cases as well [8]. In both our case, there were no B symptoms. Clinical examination usually reveals a firm to hard, diffusely enlarged, immobile thyroid gland with adjacent lymphadenopathy. In our first case, a few nodes were identified in the paratracheal region by CT scan, while second patient had significant nodal disease in left side neck.

Imaging

Ultrasound is the initial diagnostic modality in investigation of thyroid masses. However, the diverse imaging characteristics of PTL make it difficult to distinguish from other thyroid disorders [11]. Certain Ultrasound scan features such as enhanced posterior echoes can suggest the diagnosis but biopsy is required [12]. CT scan of the neck will give the details of the extrathyroidal spread like tracheal invasion, nodal involvement. In our first case, jugular vein was suspected to be involved in the CT scan, while during surgery, it was found to be infiltrating the internal jugular vein, which was excised. Imaging by ultrasound or CT scan does not show classical features of a lymphoma, but a core biopsy can be considered if there is a high clinical suspicion. For definite subtyping, an open biopsy can be considered; rarely thyroidectomy is done to prove diagnosis of a lymphoma.

Role of PET CT scan

A recent study has described positron emission tomography – computed tomography as a useful imaging technique for differentiating between PTL and chronic thyroiditis [13]. In our cases, PET CT was done in the post-operative situation to assess the extent of the disease as well response to treatment.

Histopathology

Ultimately, histopathological examination is the gold standard in diagnosis lymphoma. Nearly 98% of primary thyroid lymphomas are B-cell lymphoma [4]. Among the B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL) is the most common subtype. Extra nodal marginal zone lymphoma is the next common subtype. Other less common subtypes include Follicular Lymphoma, small lymphocytic lymphoma, Burkitt's lymphoma, mantle cell lymphoma, T-cell lymphoma and Hodgkin's Lymphoma. Only a few cases of T cell lymphoma of thyroid gland are reported [14]. With regards to obtaining the pathology, FNAC is the initial diagnostic procedure. Usually, FNAC has low sensitivity and is likely to give a clue regarding lymphoma [15]. Core biopsy is more sensitive as it yields more tissue and the architecture. In our first case, core biopsy was not done due to location and close proximity to major vasculature of neck. Thyroidectomy was diagnostic in clinching the diagnosis along with subtype to plan further treatment. In the second case, node biopsy confirmed the diagnosis with subtyping. Rare cases of synchronous double primary of thyroid cancer coexisting with lymphoma were also documented [9,10]. These cases were suspected on the basis of radiological finding. Final histopathology showed lymphoma coexisting with papillary cancers.

Treatment and management - Primary thyroid lymphoma is a rare disease that continues to be a diagnostic and therapeutic dilemma. There was great difficulty in distinguishing thyroid lymphoma from anaplastic thyroid carcinoma but, because of new immunocytochemical staining techniques, our ability to diagnose thyroid lymphoma has improved drastically over the past decade. Surgery that was once the mainstay of treatment for this disease, now plays a minimal role [16]. Surgery is usually not recommended, except for a diagnostic biopsy, due to the potential surgical risk and no additional benefit compared to chemo-radiation therapy. Surgery is also considered as a palliative measure to relieve obstruction in specific situations. The primary treatment includes a combination of chemotherapy and/or radiotherapy. Case series on patients of

primary DLBCL recommend a combination of chemotherapy and radiotherapy for better results. Relapse rates were 7.7 % for combined chemo and radiotherapy, 37.1 % for only radiation therapy and 43 % for just chemotherapy [17,18].

Chemotherapy alone is the therapy of choice for advance stage diffuse large B-cell lymphoma. The chemotherapy regimen used is usually is RCHOP regimen. Radiotherapy alone is an option for early stage disease [19,20]. The usual differential diagnosis is anaplastic carcinoma and sometimes, it can clinically resemble a thyroid lymphoma due to a rapidly enlarging/growing thyroid mass which is involving adjacent structures. Modified Ann-Arbor staging classification is the means for staging primary thyroid lymphoma. In this case report, case 1 was in stage 1E, and case 2 was in stage 2E, the disease was involving the thyroid gland along with regional lymph nodes.

Prognosis - 80% patients are likely to be in stage 1E or 2E. The Prognosis is excellent with a 5-year survival rate for patients in stage 1E or 2E who have received complete treatment is about 91% [19].

Conclusion

Primary thyroid lymphoma is a rare condition with DLBCL being the most common type. The key to diagnose is to have a high degree of clinical suspicion and whenever appropriate, a core biopsy from thyroid gland or a node biopsy can be done to diagnose a lymphoma. An early diagnosis and early initiation of treatment might result in good symptomatic relief and a complete cure from the disease. The way ahead in management of primary thyroid lymphoma is a multidisciplinary approach, including specialists from different specialities including surgery, medical oncology and radiation oncology to optimize the treatment to achieve the best possible result.

References

1. Ruggiero FP, Frauenhoffer E, Stack BC Jr. Thyroid lymphoma: a single institution's experience. Otolaryngol Head Neck Surg. 2005 Dec;133(6):888-96. doi: 10.1016/j.otohns.2005.07.040. PMID: 16360509.

2. Thieblemont C, Mayer A, Dumontet C, Barbier Y, Callet-Bauchu E, Felman P, Berger F, Ducottet X, Martin C, Salles G, Orgiazzi J, Coiffier B. Primary thyroid lymphoma is a heterogeneous disease. J Clin

Endocrinol Metab. 2002;87:105–111.

3. Ansell SM, Grant CS, Habermann TM. Primary thyroid lymphoma. Semin Oncol. 1999 Jun;26(3):316-23. PMID: 10375088.

4. Pedersen RK, Pedersen NT. Primary non-Hodgkin's lymphoma of the thyroid gland: a population based study. Histopathology. 1996 Jan;28(1):25-32

5. Pavlidis ET, Pavlidis TE. A Review of Primary Thyroid Lymphoma: Molecular Factors, Diagnosis and Management. J Invest Surg. 2019 Mar;32(2):137-142. doi: 10.1080/08941939.2017.1383536. Epub 2017 Oct 23. PMID: 29058491.

6. Travaglino A, Pace M, Varricchio S, Insabato L, Giordano C, Picardi M, Pane F, Staibano S, Mascolo M. Hashimoto Thyroiditis in Primary Thyroid Non-Hodgkin Lymphoma. Am J Clin Pathol. 2020 Jan 2;153(2):156-164. doi: 10.1093/ajcp/aqz145. PMID: 31584614.

7. Kesireddy M, Lasrado S. Thyroid Lymphoma. 2023 Mar 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 31335002.

8. Doi Y, Goto A, Murakami T, Yamashita H, Yamashita H, Noguchi S. Primary thyroid lymphoma associated with Graves' disease. Thyroid. 2004 Sep;14(9):772-6. doi: 10.1089/thy.2004.14.772. PMID: 15361265.

9. Li Q, Zhu F, Xiao Y, Liu T, Liu X, Zhang L, Wu G. Synchronous double primary lymphoma and thyroid cancer: A single-institution retrospective study. Medicine (Baltimore). 2021 Oct 1;100(39):e27061. doi: 10.1097/MD.0000000000027061. PMID: 34596109; PMCID: PMC8483851.

10. Chen L, Liu Y, Dong C. Coexistence of primary thyroid diffuse large B cell lymphoma and papillary thyroid carcinoma: a case report and literature review. J Int Med Res. 2019 Oct;47(10):5289-5293. doi: 10.1177/0300060519869133. Epub 2019 Aug 28. PMID: 31456463; PMCID: PMC6833368.

11. Kakkar A, Purkait S, Agarwal S, Mallick S, Gogia A, Karak AK, Sharma MC, Julka PK. Primary thyroid lymphoma: A series from a tertiary care center in Northern India. J Cancer Res Ther. 2019 Jul-Sep;15(3):669-675. doi: 10.4103/jcrt.JCRT_135_17. PMID: 31169238.

12. Stein SA, Wartofsky L. Primary thyroid lymphoma: a clinical review. J Clin Endocrinol Metab. 2013 Aug;98(8):3131-8. doi: 10.1210/jc.2013-1428. Epub 2013 May 28. PMID: 23714679.

13. Nakadate M, Yoshida K, Ishii A, Koizumi M, Tochigi N, Suzuki Y, et al Is 18F-FDG PET/CT useful for distinguishing between primary thyroid lymphoma and chronic thyroiditis? Clin Nucl Med. 2013;38:709–14

14. Chen C, Yang Y, Jin L, Dong L, Zhang X, Xiang Y. Primary thyroid T-lymphoblastic lymphoma: a case report and review of the literature. Int J Clin Exp Pathol. 2013 Dec 15;7(1):443-50. PMID: 24427370; PMCID: PMC3885504.

15. Sharma A, Jasim S, Reading CC, Ristow KM, Villasboas Bisneto JC, Habermann TM, Fatourechi V, Stan M. Clinical Presentation and Diagnostic Challenges of Thyroid Lymphoma: A Cohort Study. Thyroid. 2016 Aug;26(8):1061-7

16. Widder S, Pasieka JL. Primary thyroid lymphomas. Curr Treat Options Oncol. 2004 Aug;5(4):307-13. doi: 10.1007/s11864-004-0021-7. PMID: 15233907.

17. Mack LA, Pasieka JL. An evidence-based approach to the treatment of thyroid lymphoma. World J Surg 2007;31:978-86. doi: 10.1007/ s00268-005-0768-z

18. Khan SA, Ali D, Aziz A, Islam N. Primary thyroid lymphoma: Case series of patients from a developing country. J Pak Med Assoc. 2022 Sep;72(9):1858-1861. doi: 10.47391/JPMA.4281. PMID: 36280993.

19. Ha CS, Shadle KM, Medeiros LJ, Wilder RB, Hess MA, Cabanillas F, Cox JD. Localized non-Hodgkin lymphoma involving the thyroid gland. Cancer. 2001 Feb 15;91(4):629-35

20. Cha H, Kim JW, Suh CO, Kim JS, Cheong JW, Lee J, Keum KC, Lee CG, Cho J. Patterns of care and treatment outcomes for primary thyroid lymphoma: a single institution study. Radiat Oncol J. 2013 Dec;31(4):177-84.