


Original Article

# Primary Thyroid Non-Hodgkin B-Cell Lymphoma: A Case Series

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## Abstract

### Introduction

Non-Hodgkin lymphoma (NHL) of the thyroid, a rare malignancy linked to autoimmune disorders, is poorly understood in terms of its pathogenesis and treatment outcomes. This study aims to review a single-center experience in managing primary thyroid non-Hodgkin B-cell lymphoma cases.

### Methods

This retrospective case series was conducted at a single center from January 2020 to November 2024, including patients diagnosed with B-cell NHL of the thyroid who underwent surgical intervention. Data, including clinical, demographic, laboratory, and imaging information, were extracted from medical records. Diagnostic procedures involved core needle or surgical biopsy with immunohistochemistry analysis. Treatment included excisional biopsy, thyroidectomy, lobectomy, and chemotherapy. Quantitative data is presented as means and standard deviations, and qualitative data as frequencies and percentages.

### Results

Among nine NHL cases, seven (77.8%) were female, with a mean age of 60.78 ± 12.53 years. Anterior neck swelling was the most common presentation in 6(66.7%) cases. Seven patients (77.8%) received R-CHOP chemotherapy; histopathology confirmed B-cell lymphoma in eight cases (88.9%). Thyroid function was euthyroid in four cases (44.4%), hypothyroid in three (33.3%), and hyperthyroid in one (11.1%). TI-RADS (Thyroid Imaging Reporting and Data Systems) classification showed five cases (55.6%) as TI-RADS 5. Follow-up revealed no recurrence in four cases (44.4%), and two deaths (22.2%).

### Conclusion

Primary thyroid NHL is a rare condition requiring early diagnosis and personalized treatment. The variability in treatment responses highlights the need for individualized approaches to optimize patient outcomes.

## 1. Introduction

Non-Hodgkin lymphomas (NHLs) represent a heterogeneous group of lymphoid malignancies from lymphocytes,

predominantly of B-cell origin. While many NHLs develop within lymph nodes, approximately 30-40% originate in extra-

nodal sites [1]. Primary thyroid lymphoma is defined as a lymphoma that arises from the thyroid gland, excluding those that invade the thyroid due to either metastasis or direct extension. This rare malignancy accounts for approximately 5% of all thyroid malignancies and only 1-2% of all extra-nodal lymphomas, with an estimated annual incidence of 2 cases per million population [2].

The precise pathogenesis of primary thyroid lymphoma remains unclear. However, associations between autoimmune diseases, chronic antigenic stimulation, and the development of primary thyroid lymphoma have been identified. The most significant risk factor for primary thyroid lymphoma is the presence of hashimoto's thyroiditis, with patients affected having a risk of developing primary thyroid lymphoma that is 40 to 80 times higher. Notably, the incidence of hashimoto's thyroiditis among primary thyroid lymphoma patients is nearly 80% [3, 4]. The proposed pathogenesis involves chronic antigenic stimulation from autoimmune processes leading to persistent lymphoid proliferation, eventually undergoing malignant transformation. Recent research has also implicated mutations in regulatory pathways, particularly the NF- $\kappa$ B signaling pathway through A20 gene mutations or deletions, in the development of certain thyroid B-cell lymphomas [5]

Primary thyroid lymphomas are almost exclusively NHL, with B-cell phenotype representing over 95% of cases [6]. Histologically, diffuse large B-cell lymphoma is the most common subtype, accounting for approximately 60-70% of cases. Meanwhile, mucosa-associated lymphoid tissue lymphoma represents the second most common subtype, comprising about 20-30% of cases. Other less common variants include Burkitt lymphoma [7]. These subtypes exhibit varying clinical behaviors and prognoses, necessitating accurate diagnosis for appropriate management.

Despite advances in understanding the pathophysiology and management of primary thyroid lymphoma, several knowledge gaps persist regarding optimal therapeutic strategies and long-term outcomes. This study aims to review a single-center experience in managing primary thyroid non-Hodgkin B-cell lymphoma cases. The eligibility of the references has been verified [8].

## 2. Methods

### 2.1. Study design and setting

This retrospective case series study was conducted at Smart Health Tower. It included patients diagnosed with NHL of B-cell origin in the thyroid gland based on pathological diagnosis who underwent surgical intervention, excisional biopsy, or thyroidectomy for definitive diagnosis. The study spanned from January 2020 to November 2024, with an average follow-up time of one year.

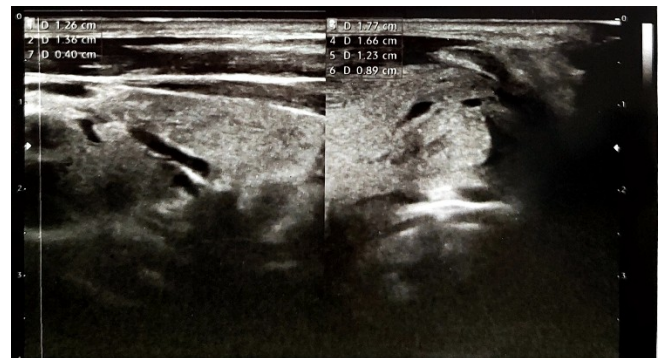
### 2.2. Data Collection

Data collection was performed over one month. Medical information, including demographic, clinical, and laboratory data, was retrospectively extracted from electronic medical

records. Variables collected included past medical history, surgical history, clinical presentation, thyroid status, thyroid function tests, autoimmune markers, fine needle aspiration findings, imaging studies, and treatment modalities. Pathological data were independently reviewed by an expert pathologist using specimen slides.

### 2.3. Laboratory and Imaging Assessments

Comprehensive laboratory evaluations were conducted to assess thyroid function, autoimmune markers, and general health status. Thyroid function tests included thyroid-stimulating hormone and free thyroxine. Autoimmune markers measured included thyroid peroxidase antibodies and thyroglobulin antibodies. Additional tests included viral screenings and hemoglobin levels (complete blood count). Imaging studies included preoperative ultrasound to evaluate thyroid morphology, with hypoechoic lesions defined as having reduced echogenicity relative to normal thyroid tissue, while very hypoechoic lesions exhibited even lower echogenicity compared to adjacent musculature (Figure 1). Computed tomography (CT) and positron emission tomography (PET) scans were performed to assess disease extent in selected cases.



**Figure 1.** Ultrasound image of a 46x47x18 mm solid hypoechoic nodule in the thyroid isthmus, demonstrating mild vascularity and no micro or macrocalcifications. The nodule is classified as TIRADS-IV, indicating moderate suspicion for malignancy.

### 2.4. Diagnostic Biopsy Procedures

A core needle biopsy was performed using a spring-loaded Tru-Cut biopsy needle (18G). All patients underwent core needle or surgical biopsy for accurate diagnosis and immunohistochemistry analysis for markers.

### 2.5. Treatment Modalities

Surgical intervention primarily served a diagnostic role rather than a curative approach, with excisional biopsy, thyroidectomy, or lobectomy performed for tissue diagnosis. Chemotherapy protocols included the CHOP regimen, consisting of cyclophosphamide (750 mg/m<sup>2</sup>), adriamycin (50 mg/m<sup>2</sup>), vincristine (1.4 mg/m<sup>2</sup>), and prednisolone (100 mg/day), often combined with rituximab (375 mg/m<sup>2</sup>) to enhance therapeutic efficacy.

## 2.6. Ethical Considerations

The study was approved by the ethical committee of the Kscien organization. The study adhered to the principles of the Declaration of Helsinki. Due to its retrospective nature, neither patient approval nor informed consent was required.

## 2.7. Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 27.0. Quantitative data were presented as means and standard deviations. Qualitative data were expressed as frequency and percentages.

## 3. Results

Among the nine cases, seven (77.8%) were female and two (22.2%) were male, with male-female ratio was 1:3.5. The mean age of patients was  $60.78 \pm 12.53$  years. Clinically, anterior neck swelling was the most common presentation, observed in six cases (66.7%), while one case (11.1%) was on follow-up for preexisting thyroid conditions. The CT imaging revealed locally invasive thyroid masses involving the trachea, retrosternal space, or esophagus in three cases (33.3%), three cases (33.3%) had no available CT data. A history of prior thyroid surgery was noted in only one case (11.1%) (Table 1).

Seven (77.8%) cases received R-CHOP chemotherapy, with six (66.7%) completing six or more sessions. Total thyroidectomy was performed in one case (11.1%). Histopathological examination confirmed B-cell lymphoma in eight cases (88.9%) and marginal zone lymphoma in one case (11.1%). Thyroid function testing revealed TSH abnormalities in four cases (44.4%), with one (11.1%) presenting significantly elevated TSH levels (100.0 mIU/L) (Table 2).

Thyroid function status was euthyroid in four cases (44.4%), hypothyroid in three cases (33.3%), and hyperthyroid in one case (11.1%). Nodule location based on ultrasound was left-sided in four cases (44.4%), right-sided in three cases (33.3%), and bilateral in two cases (22.2%). The TI-RADS (Thyroid Imaging Reporting and Data Systems) classification showed that five cases (55.6%) were TI-RADS 5, while two (22.2%) were TI-RADS 4. The mean Free T4 and TSH levels were  $11.93 \pm 6.02$  ng/dL and  $19.31 \pm 36.36$  mIU/L, respectively. Regarding follow-up outcomes, four cases (44.4%) showed no recurrence, and two (22.2%) resulted in mortality (Table 3).

## 4. Discussion

Primary thyroid lymphoma is confined to the thyroid gland, with or without local lymph node involvement in the neck. There is no evidence of distant metastasis at the time of initial diagnosis. Epidemiological studies have consistently shown a higher prevalence of primary thyroid lymphoma (including NHL) in females compared to males, with a female-to-male ratio ranging from 1.8 to 4.4:1, predominantly affecting individuals in their fifth to eighth decades of life [9, 10]. In line with these findings,

the present study also noted a female predominance, a female-to-male ratio of 3.5:1, and an average age of 60.78 years.

The primary risk factor for primary thyroid lymphoma, including NHL, is Hashimoto's thyroiditis, which significantly increases the likelihood of developing it by 40 to 80 times. Despite this elevated risk, only 0.6% of individuals with Hashimoto's thyroiditis go on to develop primary thyroid lymphoma [11, 12]. The condition is predominantly associated with hypothyroidism, especially in the context of Hashimoto's thyroiditis, whereas cases of primary thyroid lymphoma occurring in hyperthyroid or euthyroid states are rare. This association is thought to arise due to the thyroid's lack of native lymphoid tissue, which may accumulate due to chronic antigenic stimulation in Hashimoto's thyroiditis, leading to lymphoid infiltration and the subsequent risk of lymphoma [10]. In the present study, of the nine cases of NHL, 5(55.6%) were euthyroid or hyperthyroid, with four patients being euthyroid and one hypothyroid. This supports the notion that while hypothyroidism is commonly associated with NHL, other thyroid states, including euthyroid and hyperthyroid, can also occur in these cases.

Patients with thyroid NHL typically present with a rapidly enlarging cervical mass that remains mobile during swallowing. This thyroid enlargement may result in compressive symptoms, including dysphagia, dyspnea, and hoarseness [13,14]. The mass can sometimes exert pressure on venous structures, leading to facial puffiness or swelling. Furthermore, lymphoma infiltration of the thyroid can induce hypothyroidism, manifesting as fatigue, cold intolerance, and dry skin. Additionally, systemic symptoms commonly associated with lymphoma, such as fever, night sweats, unexplained weight loss, and generalized pruritus, may also be observed [15]. In the current study, anterior neck swelling was the most common presentation, observed in six cases (66.7%). The high prevalence of anterior neck swelling in this study likely reflects the tumor's location in the thyroid, causing significant local enlargement and compressive effects.

Diagnosis of NHL of the thyroid necessitates a multifaceted approach, integrating clinical findings, advanced imaging techniques, and definitive tissue sampling. Imaging modalities such as ultrasound and CT scans are crucial in identifying thyroid abnormalities and associated lymphadenopathy [16]. Diagnosis is typically confirmed through histological examination and immunohistochemical results [10]. Identifying immunoglobulin clonal gene rearrangements is essential for the differential diagnosis in patients with Hashimoto thyroiditis and a histologically benign lymphoepithelial lesion. Core needle biopsy or surgical excision is required to obtain sufficient tissue for accurate diagnosis and subtyping [17]. The present study used a comprehensive diagnostic approach, including ultrasound, CT scans, positron emission tomography scans, and fine needle aspiration cytology to detect thyroid abnormalities and associated lymphadenopathy. Core needle biopsy was performed when fine needle aspiration cytology alone was

**Table 1.** Clinical, Diagnostic, and Imaging Features of Patients

Cases	Age (year)	Gender	PMH	PSH	Presentation	Thyroid status	Nodule location (Ultrasound)	TI-RADS score	CT scan	PET scan
Case 1	70	Female	Hypothyroidism, Hypertension	Thyroid surgery	Follow Up	Hypothyroid	Right nodule	TI-RADS 5	Right thyroid mass with tracheal invasion	No abnormal metabolic activity, except in the thyroid gland
Case 2	67	Male	Type 2 diabetes mellitus, Colon cancer	None	Anterior neck swelling	Euthyroid	Bilateral nodule	TI-RADS 5	Right thyroid mass with retrosternal extension, Suspicious left thyroid lesion	No abnormal metabolically active lesion
Case 3	79	Female	Hypothyroidism, Atherosclerosis	None	Anterior neck swelling	Hypothyroid	Right nodule	TI-RADS 5	Right thyroid mass with esophagus invasion	No abnormal metabolically active lesion
Case 4	62	Female	Heart failure	None	Anterior neck swelling	Euthyroid	Bilateral nodule	TI-RADS 3	Left lung focal ground glass appearance	No abnormal metabolically active lesion
Case 5	52	Female	Hypertension	None	Anterior neck swelling	Euthyroid	Left nodule	TI-RADS 4	NA	No abnormal metabolically active lesion
Case 6	47	Female	Cerebrovascular accident	None	Anterior neck swelling	Hyperthyroid	Left nodule	TI-RADS 5	Right thyroid mass	NA
Case 7	41	Female	Systemic lupus erythematosus	None	Thyroid problem	Hypothyroid	Left nodule	TI-RADS 2	NA	No abnormal metabolically active lesion
Case 8	72	Female	Hydatid cyst	None	Thyroid problem	Euthyroid	Left nodule	TI-RADS 5	Left thyroid nodule	No abnormal metabolically active lesion
Case 9	57	Male	Negative	None	Anterior neck swelling	NA	Right nodule	TI-RADS 4	NA	No abnormal metabolically active lesion

PMH: Past medical history. PSH: Past surgical history. NA: Not applicable, TI-RADS: Thyroid Imaging Reporting and Data Systems, CT: Computed tomography, PET: positron emission tomography

insufficient for diagnosis. Histopathological and immunohistochemical evaluations confirmed the presence of lymphoma.

Management of NHL of the thyroid typically involves a combination of approaches, including chemotherapy, radiation therapy, and, in some cases, surgery. The choice of treatment depends on the stage and grade of the lymphoma and the patient's overall health. In current practice, surgery mainly serves the purpose of obtaining tissue for diagnosis [2]. Radiotherapy, being highly effective for local disease control, is often utilized due to the radiosensitive nature of thyroid NHL. In contrast, chemotherapy targets occult or systemic disease, thereby enhancing long-term outcomes. The conventional CHOP regimen, comprising Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone, remains the standard treatment approach for systemic disease management [15,18]. Following three to six cycles of chemotherapy, radiation therapy is commonly administered to enhance disease control. The introduction of Rituximab has shown promising efficacy, particularly in elderly patients with diffuse large B-cell lymphoma. However, the role of surgical intervention remains debated [19]. Several factors influence prognosis, including patient age, tumor grade, and disease stage. Notably, mucosa-associated lymphoid tissue lymphoma generally exhibits a more favorable prognosis than large B-cell lymphoma, and outcomes are typically better in pediatric and young adult patients [20].

Recent studies on outcomes of primary thyroid lymphoma underscore substantial prognostic heterogeneity influenced by histopathological classification, therapeutic approach, and clinical factors. A population-based study of 1,408 primary thyroid lymphoma (including NHL) patients reported a median survival of 9.3 years, with multivariate analysis identifying advanced age, disease stage, histological subtype, and treatment modality as independent prognostic determinants [3]. Diffuse large B-cell lymphoma, the most prevalent subtype comprising approximately 68% of cases, exhibits variable 5-year survival rates between 45% and 90%, contingent on treatment protocols [4]. Notably, combined-modality therapy, particularly rituximab-based immunochemotherapy with radiation, has significantly enhanced prognosis, achieving 5-year overall and progression-free survival rates of 81.2% and 77.8%, respectively, compared to monotherapy approaches. In contrast, indolent subtypes such as mucosa-associated lymphoid tissue lymphoma demonstrate intermediate 5-year survival rates of approximately 62%, though they remain susceptible to persistent recurrence, unlike aggressive variants, which exhibit cure probabilities exceeding 90% after three years of remission [9]. Molecular analyses have further elucidated distinct evolutionary pathways underlying thyroid lymphoma relapse, providing insight into the observed variations in treatment response and clinical outcomes [21]. These findings collectively support the development of risk-adapted treatment algorithms, highlighting the necessity of histology-directed, multimodal therapeutic strategies to optimize survival while mitigating treatment-associated morbidity in this rare lymphoproliferative malignancy [22].

This retrospective case series of primary thyroid B-cell NHL is subject to several limitations. The short follow-up period of one

**Table 2.** Thyroid Function Tests, Treatment, and Outcomes in Patients with Thyroid Non-Hodgkin Lymphoma

Cases	TSH (mIU/L)	Free T4 (ng/dL)	TPO Ab (IU/mL)	TG (ng/mL)	CATN (pg/mL)	Surgical management	Chemotherapy	Histopathological examination type	Histopathological examination sub-type	Follow-up
Case 1	7.01	11.7	NA	169	0.5	NA	R-CHOP 6 session	NHL	B-cell lymphoma	No Recurrence
Case 2	NA	NA	NA	NA	0.5	NA	R-CHOP 6 session	NHL	B-cell lymphoma	No Recurrence
Case 3	100	0.97	372.6	0.04	0.5	NA	R-CHOP 5 session	NHL	B-cell lymphoma	Dead
Case 4	0.57	15.2	NA	NA	NA	NA	R-CHOP	NHL	B-cell lymphoma	NA
Case 5	2.93	NA	499	134	0.6	NA	R-CHOP 6 session	NHL	B-cell lymphoma	No Recurrence
Case 6	0.039	18.54	NA	NA	NA	NA	Not take chemotherapy	NHL	B-cell lymphoma	Dead
Case 7	21.8	9.66	600	NA	NA	Total thyroidectomy	R-CHOP 8 session	NHL	B-cell lymphoma	No Recurrence
Case 8	2.81	15.5	52.7	NA	0.9	NA	R-CHOP 9 session	NHL	B-cell lymphoma	NA
Case 9	NA	NA	NA	NA	NA	NA	5 biology + 15 radiotherapy	NHL	Marginal zone lymphoma	NA

TSH: Thyroid stimulating hormone, TPO Ab: Thyroid Peroxidase Antibodies, TG: Thyroglobulin, CATN: Calcitonin, NHL: Non-Hodgkin Lymphoma, R-CHOP: Rituximab-Cyclophosphamide Doxorubicin Vincristine Prednisone, NA: Not Available

year restricts the ability to evaluate long-term outcomes, recurrence patterns, and survival rates. Additionally, as a single-

**Table 3.** Demographic and Clinical Characteristics of Patients

Variables	Frequency (%)
Age (Mean ± SD)	60.78 ± 12.53
<b>Gender</b>	
Male	2 (22.2)
Female	7 (77.8)
<b>Thyroid status</b>	
Euthyroid	4 (44.4)
Hypothyroid	3 (33.3)
Hyperthyroid	1 (11.1)
NA	1 (11.1)
<b>TI-RADS score</b>	
TI-RADS 2	1 (11.1)
TI-RADS 3	1 (11.1)
TI-RADS 4	2 (22.2)
TI-RADS 5	5 (55.6)
Free T4 (Mean ± SD)	11.93 ± 6.02
TSH level (Mean ± SD)	19.31 ± 36.36
TPO Ab (Mean ± SD)	381.08 ± 237.86
CATN (Mean ± SD)	0.60 ± 0.17
<b>Follow-up</b>	
No Recurrence	4 (44.4)
Dead	2 (22.2)
NA	3 (33.3)
<b>Nodule location (Ultrasound)</b>	
Right nodule	3 (33.3)
Left nodule	4 (44.4)
Bilateral nodule	2 (22.2)
<b>PET scan findings</b>	
Thyroid gland lesion	1 (11.1)
No abnormal active lesion	7 (77.8)
NA	1 (11.1)

TI-RADS: Thyroid Imaging Reporting and Data System, TSH: Thyroid stimulating hormone, TPO: Thyroid Peroxidase, CATN: Calcitonin, SD: Standard deviation, NA: Not available

center study, the findings may lack broader applicability across different healthcare settings. The heterogeneity in treatment modalities, coupled with the absence of molecular and genetic analyses, further limits insights into the pathophysiology of the disease and optimal therapeutic strategies.

## 5. Conclusion

This study underscores the significance of early diagnosis and tailored treatment for primary thyroid NHL. The findings highlight the variable thyroid function and treatment responses, underscoring the need for personalized approaches to optimize patient outcomes.

## Declarations

**Conflicts of interest:** The author(s) have no conflicts of interest to disclose.

**Ethical approval:** The study was approved by the ethical committee of the Kscien organization (No.32).

**Patient consent (participation and publication):** Written informed consent was obtained from patients for publication.

**Source of Funding:** Smart Health Tower.

**Role of Funder:** The funder remained independent, refraining from involvement in data collection, analysis, or result formulation, ensuring unbiased research free from external influence.

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**Authors' contributions:** AMS and SFA were significant contributors to the conception of the study and the literature search for related studies. RMA, HOB, IJH, DOK, ROM and SHH were involved in the literature review, the study's design, the critical revision of the manuscript, they participated in data collection. AMM, HAA, and AAQ were involved in the literature review, study design, and manuscript writing. AJQ was the radiologists who performed the assessment of the cases. AMA was the pathologist who performed the histopathological diagnosis. AMS and SHH confirm the authenticity of all the raw data. All authors approved the final version of the manuscript.

**Use of AI:** AI was not used in the drafting of the manuscript, the production of graphical elements, or the collection and analysis of data.

**Data availability statement:** Not applicable.

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