Primary thyroid lymphoma with Hashimoto's thyroiditis: A case report and literature review

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Abstract. Primary thyroid diffuse large B-cell lymphoma (DLBCL) represents a rare and diagnostically challenging malignancy, particularly when arising in the setting of pre-existing Hashimoto's thyroiditis (HT). The present case report describes the case of an 86-year-old female patient with primary thyroid lymphoma (PTL) who presented with life-threatening tracheal compression. The aim of this report is to emphasize the diagnostic challenges due to overlapping clinical features with thyroid carcinoma and the absence of consensus management guidelines. Following ultrasound-guided biopsy and immunohistochemical analysis, germinal center-originated DLBCL was confirmed. The patient received four cycles of zuberitamab (a novel anti-CD20 monoclonal antibody) plus mini-CHOP therapy, with CT imaging demonstrating notable tracheal re-expansion after the first cycle. Successful disease control and quality of life were maintained throughout the follow-up. Furthermore, a comprehensive literature review was performed to elucidate the clinical manifestations and therapeutic approaches of PTL. In conclusion, the present case exemplifies that elderly patients with rapidly enlarging neck masses require urgent evaluation to distinguish between thyroid lymphoma and carcinoma. While individual case results cannot be generalized to all clinical scenarios, prompt diagnosis followed by appropriate treatment remains critical for favorable outcomes

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Introduction

Primary thyroid lymphoma (PTL), an uncommon malignancy accounting for 1-5% of thyroid neoplasms and <2.5-7% of extranodal lymphoma, typically manifests as a rapidly enlarging neck mass that causes compressive symptoms such as dysphagia, dyspnea and hoarseness in >70% of patients at diagnosis (1-5).

The predominant histopathological subtypes of thyroid lymphoma include diffuse large B-cell lymphoma (DLBCL) and mucosa-associated lymphoid tissue (MALT) lymphoma (6). Other subtypes, such as follicular lymphoma, small lymphocytic lymphoma and Burkitt lymphoma, are infrequently observed, whilst mantle cell lymphoma, T-cell lymphoma and Hodgkin's lymphoma constitute rare exceptions (7).

Hashimoto's thyroiditis (HT), the most prevalent autoimmune thyroid disorder, affects 1-2% of the global population with a 10:1 female predominance (8,9). A triad of features pathologically defines HT: Diffuse lymphoplasmacytic infiltration with germinal center formation, progressive thyroid parenchymal destruction leading to hypothyroidism and detectable serum antibodies against thyroid peroxidase (sensitivity, ~95%) and thyroglobulin (specificity, ~80%) (10).

PTL has a pathophysiological association with autoimmune thyroid disorders, most notably HT (11). Patients with HT demonstrate an increased risk of developing PTL (12). The low incidence of PTL contributes to a lack of standardized diagnostic and therapeutic guidelines. This results in a lack of consensus regarding the diagnosis and treatment of affected individuals, primarily due to its low prevalence. Furthermore, the coexistence of PTL and HT is exceedingly rare. A case of concurrent primary thyroid PTL lymphoma and HT is described in the present report.

Case report

An 86-year-old female patient with no prior medical history was admitted to the Department of Cervicothoracic Surgery at the 331 Hospital (Zhuzhou, China) in October 2024, presenting with a recurrent cough, shortness of breath, stridor and neck swelling persisting for ~2 months. Contrast-enhanced

CT demonstrated suspected thyroid malignancy with invasion into the strap muscles, trachea and right jugular vein, accompanied by tracheal stenosis, tumor thrombus in the right jugular vein and bilateral metastatic lymphadenopathy in the central and lateral cervical regions (predominantly on the right side) (Fig. 1A). A clinical exam confirmed a palpable, large nodule on the neck. Blood analysis revealed normal free triiodothyronine (3.56 pmol/l; normal range, 3.10-6.80 pmol/l) and free thyroxine levels (15.6 pmol/l; normal range, 12.00-22.00 pmol/l). Both anti-thyroglobulin antibodies (915 IU/ml; normal range, 0-115 IU/ml) and thyroid peroxidase antibodies (73.6 IU/ml; normal range, 0-34 IU/ml) were elevated, as was thyroid stimulating hormone (12.2 μIU/ml; normal range, 0.27-4.20 μIU/ml). Ultrasonography of the thyroid gland exhibited a reduced volume with diffuse parenchymal alterations, suggestive of HT and potential atrophy. In the right lobe, a hypoechoic lesion exhibited ill-defined borders with the trachea, disruption of tracheal rings and associated right cervical lymphadenopathy with soft tissue edema (Fig. 1B-D).

The diagnostic challenges in this case primarily stemmed from the clinical and radiological mimicry of a far more common aggressive malignancy, anaplastic thyroid carcinoma, compounded by the underlying background of HT. Due to diagnostic challenges, a needle biopsy was performed, and the diagnosis was confirmed by histological examination. The harvested thyroid tissue was fixed in 10% neutral buffered formalin at room temperature for 24 h and subsequently embedded in paraffin. Sections were cut at a thickness of 4 μm. For hematoxylin and eosin (H&E) staining, sections were stained with Mayer's haematoxylin for 5 min and eosin for 2 min at room temperature. For immunohistochemistry (IHC), heat-induced antigen retrieval was performed using EDTA buffer (pH 9.0) in a pressure cooker (120˚C for 3 min). Endogenous peroxidase activity was blocked with 3% hydrogen peroxide for 10 min. Following incubation with primary antibodies [including CD20 (cat. no. ZM-0039; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.), CD10 (cat. no. MAB-0668; Fuzhou Maixin Biotechnology Development Co., Ltd.), BCL-6 (cat. no. ZM-0011; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.), MYC (cat. no. ZA-0555; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.) and Ki-67 (cat. no. (10) N17369; Roche Diagnostics GmbH)] at 4˚C overnight and an enzyme-labeled goat anti-mouse/rabbit IgG conjugate (cat. no. PV-9000; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd.) system, chromogen detection was performed using DAB. Sections were counterstained with haematoxylin and examined under a light microscope at x400 magnification. The results of the histopathological analysis of the thyroid lesion biopsy, combined with immunophenotypic profiling, were consistent with high-grade B-cell lymphoma, most suggestive of DLBCL of germinal center origin. The immunophenotypic profile showed the following negative markers: Thyroglobulin, cytokeratin, thyroid transcription factor-1, Vimentin, CD3, CD5, Cyclin D1, BCL-2, anaplastic lymphoma kinase, CD21 and CD30, and the following positive markers: CD20 (strong/diffuse), Ki-67 (proliferation index, ~90%), CD10, BCL-6 and MYC (~20% nuclear positivity) (Fig. 2). The diagnosis of DLBCL with a germinal center B-cell lineage per the Hans classification (13)] was conclusively established by combined morphological assessment, immunophenotypic profiling and molecular studies (14).

The treatment strategy prioritized the zuberitamab plus mini-CHOP regimen based on a comprehensive geriatric assessment, given the patient's advanced age and anticipated treatment tolerance. zuberitamab (also known as Anruixi®) is a novel, humanized anti-CD20 monoclonal antibody independently developed in China (15). It was approved by the National Medical Products Administration (NMPA) for the treatment of CD20-positive diffuse large B-cell lymphoma in combination with chemotherapy, providing a new treatment option in clinical practice. The patient received four cycles of targeted therapy for DLBCL, including zuberitamab plus mini-CHOP. In November 2024, the patient received the first cycle of the zuberitamab plus mini-CHOP regimen. The specific doses were as follows: 500 mg zuberitamab on day 0; 600 mg cyclophosphamide on day 1; 20 mg doxorubicin hydrochloride liposome on day 1; 1.3 mg vincristine (Oncovin) on day 1; and 50 mg prednisone orally on days 1-5. The chemotherapy course proceeded smoothly without any specific discomfort and the patient requested discharge. A total of 24 days after the beginning the first cycle of the zuberitamab plus mini-CHOP regimen, the patient began the second cycle. The specific doses were as follows: 500 mg zuberitamab on day 0; 600 mg cyclophosphamide on day 1; 20 mg doxorubicin hydrochloride liposome on day 1; 1.3 mg vincristine on day 1; and 50 mg prednisone tablets orally on days 1-5. This chemotherapy course proceeded smoothly without any specific discomfort and the patient requested discharge.

After two treatment cycles, a repeat neck CT scan revealed tracheal reopening compared to prior imaging (Fig. 3A). Although the patient experienced a treatment delay for personal reasons, consolidation therapy with zuberitamab plus mini-CHOP was subsequently administered in January and February 2025 at the same doses. A follow-up CT scan in February 2025 showed mild residual tracheal narrowing (Fig. 3B). The patient is currently undergoing regular follow-up examinations every 3 months. The follow-up protocol includes outpatient physical examinations and neck/chest CT scans to monitor the local and systemic response, supplemented by monthly telephone consultations to assess the patient's general well-being. The condition has remained stable without any further progression.

Discussion

PTL is a rare malignancy, representing 1-5% of thyroid neoplasms (16). HT, characterized by lymphocytic infiltration and elevated thyroid autoantibodies, creates a pro-inflammatory microenvironment conducive to B-cell clonal expansion (9).

The development of PTL within the inflammatory milieu of HT is a paradigmatic example of lymphomagenesis driven by chronic antigenic stimulation. Clinical data underscore this strong association; studies indicate that HT is present in ~40 to 90% of PTL cases, who have a nearly 40- to 80-fold increased risk of developing thyroid lymphoma compared to the general population (12,14). The present case reinforces the critical need to consider PTL in patients with HT presenting with a rapidly enlarging neck mass. A prompt and definitive diagnosis via ultrasound-guided core needle biopsy (CNB)

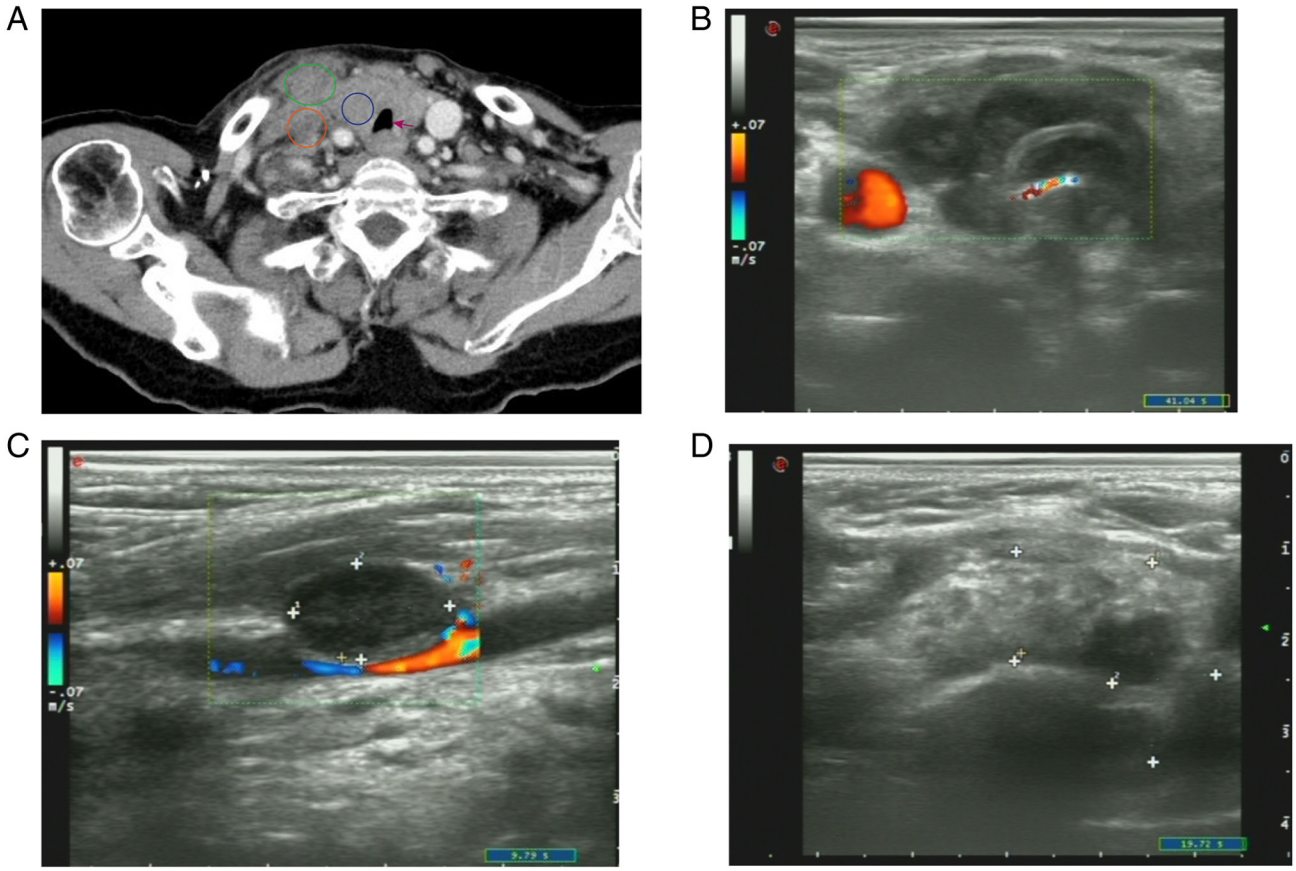

Figure 1. Preoperative imaging. (A) Axial CT image demonstrates diffuse enlargement of the residual thyroid tissue (blue circle) with marked compression and rightward displacement of the trachea (red arrow). An intraluminal tumor thrombus is visible in the right internal jugular vein (orange circle). Enlarged metastatic lymph nodes are present in the cervical regions (green circles). (B) Color Doppler ultrasonography of the thyroid isthmus revealing a 12-mm thick irregular hyperechoic area (rectangle); normal thyroid parenchyma is not observed. (C) Ultrasonography of the right lobe showing an irregular hypoechoic lesion (white plus sign) exhibiting ill-defined borders with the trachea. (D) Ultrasonography of the right neck demonstrating multiple hypoechoic masses (white plus signs) representing lymphadenopathy, the largest measuring 13x8 mm.

with immunohistochemistry is essential to distinguish PTL from thyroid carcinoma. This distinction is clinically paramount as it dictates the entire management strategy: While thyroid carcinoma often necessitates aggressive surgical intervention, PTL is primarily a systemic disease that responds remarkably well to immunochemotherapy. Relying solely on clinical presentation or suboptimal sampling may lead to unnecessary radical surgery for a condition that could be effectively managed with systemic agents. As demonstrated in the present case, the rapid initiation of systemic therapy post-CNB diagnosis can provide immediate relief of compressive symptoms and avoid the morbidity associated with high-risk thyroidectomy in elderly patients. A persistent autoimmune attack leads to the accumulation of lymphoid tissue and the formation of acquired MALT within the thyroid gland (17,18). Chronic antigenic stimulation leads to the accumulation of acquired MALT and potential transformation into aggressive DLBCL, often driven by MYC or BCL2/BCL6 alterations (19). The immunophenotype of the case in the present report (germinal center B-cell origin with high Ki-67) underscores this aggressive potential.

While R-CHOP remains the standard of care for DLBCL-PTL, the choice of anti-CD20 antibody is evolving. Zuberitamab, a novel fully humanized anti-CD20 antibody, demonstrated non-inferiority and superior complete response (CR) rates in GCB-subtype patients in the Hi-CHOP trial (20). In this study, the zuberitamab plus CHOP regimen demonstrated non-inferiority to rituximab plus CHOP in terms of tumor response, with superiority in the CR rate as assessed by blinded independent central review in the per-protocol set. With a median follow-up of 29.6 months (range, 0.07-39.1 months), patients treated with the Hi-CHOP regimen showed marginally improved survival. Notably, patients with the germinal center B-cell (GCB) subtype appeared to benefit more from Hi-CHOP compared with those with the non-GCB subtype. The Hi-CHOP regimen was well tolerated, with no new significant safety signals detected. Based on these efficacy and safety data, the NMPA of China approved zuberitamab as an initial therapy for CD20-positive DLBCL on May 17, 2023. Additionally, a phase 2 study has shown its activity in primary immune thrombocytopenia, another B-cell-mediated disorder (15).

However, PTL, a rare extranodal presentation of DLBCL, has not been specifically evaluated in these trials, and to date, no dedicated studies or case reports have documented the use of zuberitamab in PTL. Compared to the traditional Rituximab-based regimens used in historical cases, zuberitamab offers distinct clinical advantages and specific limitations. The primary advantages include its potentially superior response rates in GCB-subtype patients and its

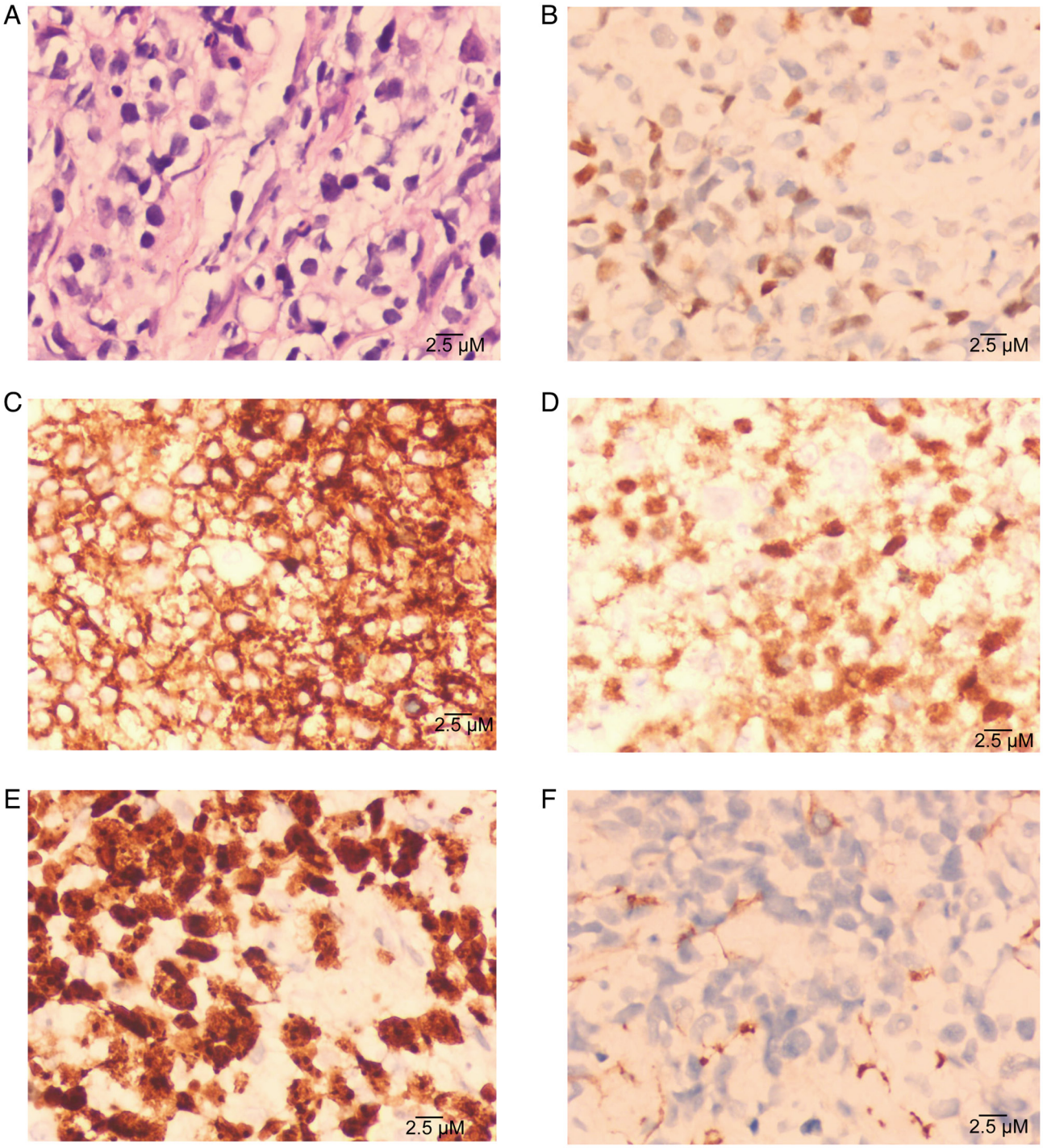

Figure 2. Histopathology of DLBCL. (A) Histopathological examination of the thyroid biopsy showing diffuse infiltration of large lymphoid cells (H&E staining; magnification, x400). (B) C-MYC expression in a tissue core of DLBCL. (C) CD20 expression in a tissue core of DLBCL. (D) BCL6 expression in a tissue core of DLBCL (magnification, x400; scale bar, 2.5 μm). (E) Ki-67 expression in a tissue core of DLBCL (magnification, x400). (F) CD10 expression in a tissue core of DLBCL (magnification, x400). DLBCL, diffuse large B cell lymphoma.

reduced immunogenicity as a fully humanized antibody, which may minimize infusion-related reactions in patients with autoimmune dysregulation such as HT (15,20). Furthermore, the present case demonstrates the feasibility of combining zuberitamab with dose-adjusted 'mini-CHOP' to achieve rapid tracheal re-expansion in an 86-year-old patient. However, a notable disadvantage is that zuberitamab, approved in 2023, currently lacks the extensive decades-long longitudinal data and global clinical footprint that support the use of Rituximab. The present case therefore represents, to the best of our knowledge, the first reported clinical application of zuberitamab in primary thyroid DLBCL arising from HT. Given that the present patient's disease falls within the approved indication for zuberitamab and that the patient's immunophenotype was of GCB origin-a subgroup that appeared to derive enhanced benefit in the Hi-CHOP trial-its use is both clinically justified and biologically rational (20). In this frail, elderly patient with life-threatening tracheal

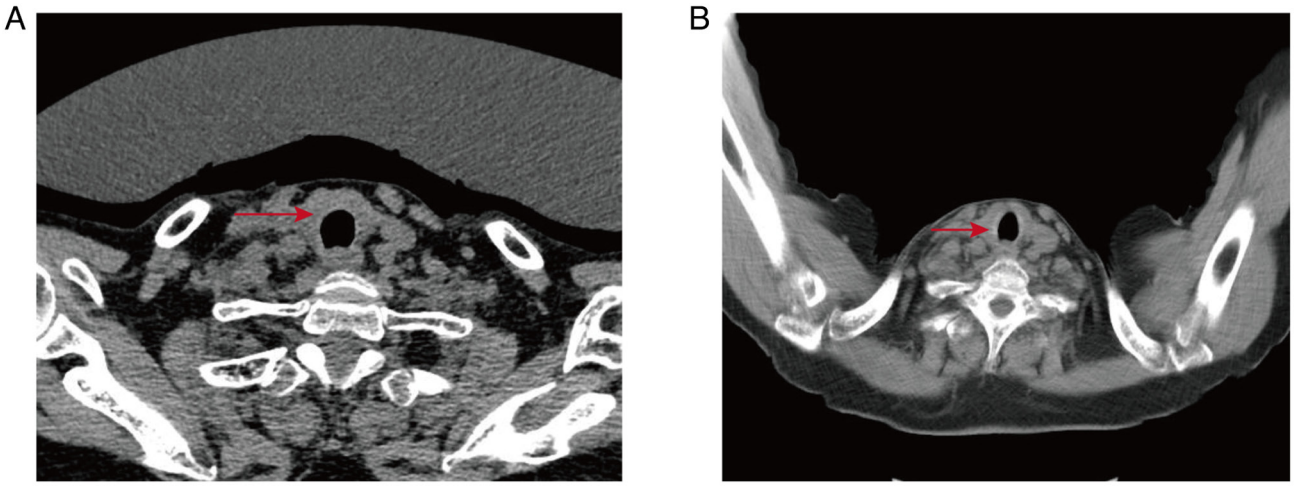

Figure 3. Imaging after chemotherapy. (A) CT scan in December 2024. (B) CT scan in February 2025. The red arrow indicates the restored trachea.

compression, the zuberitamab plus mini-CHOP regimen achieved rapid symptomatic relief and sustained disease control without significant adverse events, providing preliminary real-world evidence supporting the feasibility and effectiveness of this novel agent in the dose-adjusted management of high-risk PTL. Beyond the selection of specific anti-CD20 antibodies, the therapeutic landscape for DLBCL is rapidly evolving. Novel agents such as Bruton's tyrosine kinase inhibitors, BCL-2 antagonists and immunomodulatory drugs are expanding options for relapsed/refractory disease (21-23). Furthermore, breakthrough immunotherapies, including bispecific T-cell engagers (e.g., glofitamab) and chimeric antigen receptor T-cell therapy, are reshaping outcomes in aggressive B-cell lymphomas and warrant exploration in PTL (24,25). Future management will increasingly rely on molecular profiling for risk stratification and precision-based approaches.

The present case reinforces the need to consider PTL in patients with HT presenting with a rapidly enlarging neck mass. Prompt diagnosis via core needle biopsy with immunohistochemistry is critical for distinguishing it from carcinoma and initiate appropriate, potentially life-saving systemic therapy. In addition, the present case highlights several clinically significant aspects of primary thyroid DLBCL in elderly patients, particularly its diagnostic challenges, therapeutic considerations in geriatric oncology and the importance of multimodal management. Bergsma *et al* (26) evaluated a 70-year-old female with PTL and HT who achieved confirmed complete remission after 6 cycles of standard R-CHOP chemotherapy. In a single-center study of 171 patients with PTL, 90% had concurrent HT, with CHOP-based regimens yielding a 5-year overall survival rate of 85% (27). Similarly, in a multi-center study, 48.4% of PTL patients had HT, with an OS rate of ~84% following CHOP-based therapy and/or radiation (28). Furthermore, Gu *et al* (29) reported the case of a 48-year-old woman admitted with dyspnea and diagnosed with thyroid lymphoma via fine-needle aspiration (FNA), whose respiratory distress resolved after 1 day of chemotherapy. Sharma *et al* (30) evaluated 75 patients with thyroid lymphoma, whose main symptoms included neck mass (88.0%), dysphagia (45.3%) and hoarseness (37.3%), with 70.7% showing abnormal FNA biopsy results. Finally, Karabachev *et al* (31) evaluated three cases of symptomatic thyroid masses and demonstrated that FNA cytology was a viable diagnostic modality for PTL. The novelty and new knowledge contributed by the present case are threefold: i) It is the first reported use of Zuberitamab, a novel anti-CD20 monoclonal antibody approved in China for DLBCL, in primary thyroid DLBCL arising from HT; ii) it demonstrates successful treatment with dose-adjusted mini-CHOP plus zuberitamab in an advanced-age patient (86 years), proving feasibility and tolerability in frail, high-risk individuals; and iii) this case serves as a translation of pivotal trial data into an ultra-rare extranodal DLBCL subset, offering the first real-world evidence for this novel agent in the specific context of PTL with HT. These elements collectively distinguish the present case from prior reports and advance the literature by introducing a new treatment option, demonstrating its applicability in a geriatric GCB-subtype patient and providing a framework for future investigation.

In conclusion, whilst a limitation of the present study is that, as a case report, it is inherently biased, it overall demonstrates that thyroid lymphoma is associated with HT. As HT is a well-established risk factor for lymphoma development, close monitoring of affected patients is essential, particularly for those presenting with a rapidly enlarging neck mass, dysphagia and/or hoarseness. In such cases, an urgent ultrasound-guided core needle biopsy should be performed to confirm the diagnosis of thyroid lymphoma and to maximize diagnostic accuracy and facilitate the timely initiation of appropriate therapy. In this elderly, high-risk patient, the zuberitamab plus mini-CHOP regimen demonstrated notable efficacy and tolerability, underscoring the clinical relevance of this novel anti-CD20 monoclonal antibody as a valuable component of first-line immunochemotherapy in such challenging presentations. With prompt diagnosis and tailored treatment, patients with PTL can achieve favorable therapeutic outcomes and encouraging survival rates.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

FSL conceived the study, performed the primary clinical data acquisition, and was responsible for the initial drafting of the manuscript. XYX and KT performed the comprehensive analysis and interpretation of the patient's clinical course and conducted the systematic literature review to establish the case's novelty. XNC provided critical diagnostic resources, specifically in the acquisition and professional interpretation of the histopathological and immunohistochemical findings essential for the definitive diagnosis of primary thyroid lymphoma. CJS and QHY provided expert clinical guidance, supervised the patient's diagnostic and treatment strategy, and critically revised the manuscript for important intellectual content. QHY and CJS confirm the authenticity of all the raw data and performed the final verification of clinical records. All authors have read and approved the final manuscript, and agree to be accountable for all aspects of the work, ensuring its accuracy and integrity.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of their clinical data and any associated medical images.

Competing interests

The authors declare that they have no competing interests.

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