

Case Report

Primary thyroid T-lymphoblastic lymphoma: a case report and review of the literature

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Abstract: Most thyroid lymphomas are B-lineage, and T-cell lymphomas are rare. Here, we report a case of primary T-cell lymphoblastic lymphoma (T-LBL) of the thyroid gland. A 15-year-old boy presented with a painless thyroid mass. Ultrasonographic examination revealed a hypoechoic thyroid nodule measuring 4.6 cm × 1.9 cm × 3.4 cm. The thyroid function and antibodies were normal. Hemithyroidectomy was performed. Intraoperative frozen section was suggestive of malignant lymphoma. Histological examination showed diffuse round to oval medium sized cells with high nuclear/cytoplasmic ratio, finely dispersed chromatin, scanty cytoplasm, and numerous mitoses. Immunohistochemical studies revealed malignant cells were positive for terminal deoxynucleotidyltransferase, CD5, CD7, CD8, CD10, CD45RO, CD99, CD79a, CD3, CD1a and Ki-67 (>40%) and negative for CD34, CD20, BCL6, CD23, BCL2, Pax5 and EBV. A diagnosis of thyroid T-LBL was made. The patient was treated by intensive chemotherapy followed by allogeneic hematopoietic stem cell transplantation and has been in event-free survival for 65 months. The patient was unique because no cases of thyroid T-LBL have been previously reported, to our knowledge. Moreover, intensive chemotherapy followed by alloHSCT might be one of the adoptive options in therapy for this aggressive disease.

Keywords: Thyroid, lymphoma, T-cell, lymphoblastic lymphoma, allogeneic hematopoietic stem cell transplantation

Introduction

Malignant lymphoma of the thyroid gland is uncommon, accounting for only 2-5% of all thyroid malignancies and less than 2% of extranodal lymphomas [1]. It typically occurs in middle aged to old individuals, with a predilection for females with a previous history of Hashimoto's thyroiditis. Most reported cases are classified as B-cell lymphomas, which include diffuse large B-cell lymphoma (DLBCL) and mucosa-associated lymphoid tissue (MALT) lymphoma, whereas T-cell lineage lymphomas originating in the thyroid are extremely rare with less than 20 cases reported in the English literature so far [2-19]. We hereby report an unusual case of primary T lymphoblastic lymphoma (T-LBL) presenting as a thyroid mass in a Chinese boy. To our knowledge, this is the first report of primary

thyroid T-LBL in literature. Our patient was treated by intensive chemotherapy followed by allogeneic hematopoietic stem cell transplantation (alloHSCT). The patient has been in event-free survival for 65 months.

Case report

In July 2007, a 15-year-old boy was referred to our hospital with one month history of painless thyroid mass. No hoarseness, dysphagia, dyspnea, shakiness, weight loss, or emotional change presented. He had neither previous nor family history of thyroid disease. Physical examination revealed a firm 4 cm × 3 cm non-tender nodule was palpable in the right lobe of thyroid gland which moved with deglutition, with no cervical or other lymphadenopathy. Laboratory tests were as follows: WBC count $4.9 \times 10^9/L$

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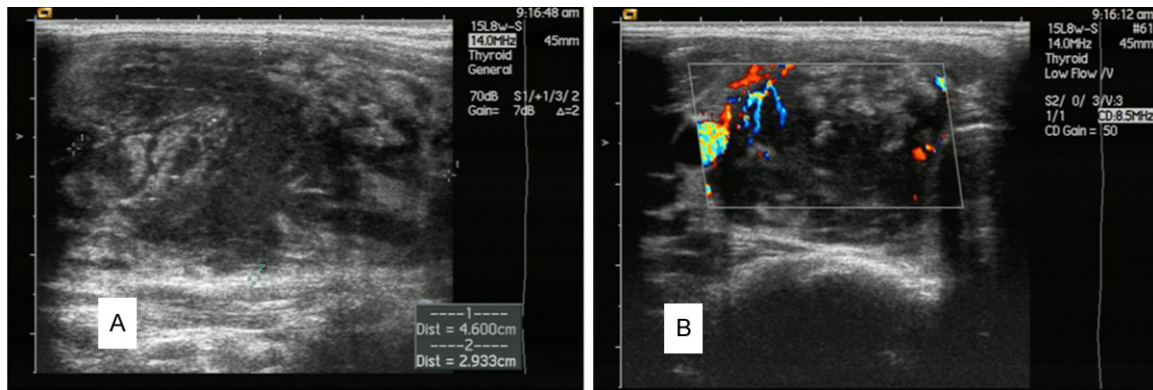


Figure 1. Thyroid ultrasonography (A) A hypoechoic nodule measuring 4.6 cm × 1.9 cm × 3.4 cm in the right lobe of the thyroid gland was noted. (B) Increased peripheral vascularity on color Doppler was noted in the tumor.

(45% neutrophils, 41.2% lymphocytes, 11.9% monocytes, 1.5% eosinophils and 0.4% basophils), hemoglobin concentration 130 g/L, platelet count $280 \times 10^9/L$, hematocrit 38.7%. Thyroid function was normal (free T4 4.9 pmmol/L, free T3 12.5 pmmol/L, thyroid-stimulating hormone (TSH) 3.39 mIU/L). Thyroglobulin (Tg) and thyroid autoantibodies (antithyroid peroxidase, antithyroglobulin) were also within normal limits. The lactate dehydrogenase and serum $\beta 2$ -microglobulin were normal. Thyroid ultrasonography revealed a hypoechoic nodule measuring 4.6 cm × 1.9 cm × 3.4 cm with microcalcifications and increased vascularity on color Doppler in the right lobe of the thyroid gland (**Figure 1A** and **1B**). A chest x-ray, abdominal ultrasonography and abdominopelvic computed tomography were normal. Based on clinical and radiological data, we considered the possibility of papillary thyroid carcinoma. A hemithyroidectomy was performed to obtain a definite diagnosis. We found the trachea, esophagus and the right recurrent laryngeal nerve to be involved by the tumor which fortunately could be separated without injuring those structures. Intraoperative frozen section was suggestive of malignant lymphoma of small cells.

Macroscopically, his thyroid mass showed the white cut surface with obscure boundary and calcification. Histological examination of the tumor revealed diffuse round to oval medium sized cells with a high nuclear/cytoplasmic ratio, finely dispersed chromatin, scanty cytoplasm, and numerous mitoses (**Figure 2A** original magnification × 200). No histological changes characteristic of autoimmune thyroiditis

were found. Immunohistochemical studies were performed on formalin-fixed, paraffin-embedded specimens, using avidin-biotin-peroxidase complex technique. Malignant cells were positive for terminal deoxynucleotidyl-transferase (TdT) (**Figure 2B** original magnification × 400), CD5 (**Figure 2C** original magnification × 400), CD7 (**Figure 2D** original magnification × 400), CD8, CD10, CD45RO, CD99, CD79a, CD3, CD1a and Ki-67 (>40%) and negative for CD34, CD20, BCL6, CD23, BCL2, Pax5 and EBV. A final diagnosis of thyroid T-LBL was made. Staging procedures did not reveal any other involvement except minimal bone marrow invasion (stage IVE). He was treated according to CALGB 9111 protocol, but discontinued when he developed allergy to L-asparaginase and severe complication of intestinal obstruction during course IIB of the protocol. We therefore changed the chemotherapy protocol. He was given one course of methotrexate (MTX), dexamethasone (DXM), one course of teniposide, cytarabine, vincristine (VCR), prednisone (EOAP), and one course of cyclophosphamide (CTX), VCR, daunorubicin, DXM (VDCP). Meanwhile intrathecal chemotherapy with MTX and DXM was given. Bone marrow examination was negative and complete remission (CR) was achieved when he finished the chemotherapy. Since the tumor was highly aggressive, we decided to perform the alloHSCT using his brother, who had 6 of 6 totally matched HLA loci, as a donor. The conditioning regimen consisted of CTX, total body irradiation and meCCNU. Graft-versus-host disease (GVHD) prophylaxis consisted of MTX and cyclosporine A. The patient tolerated the regimen well with no GVHD or readmissions after his engraftment

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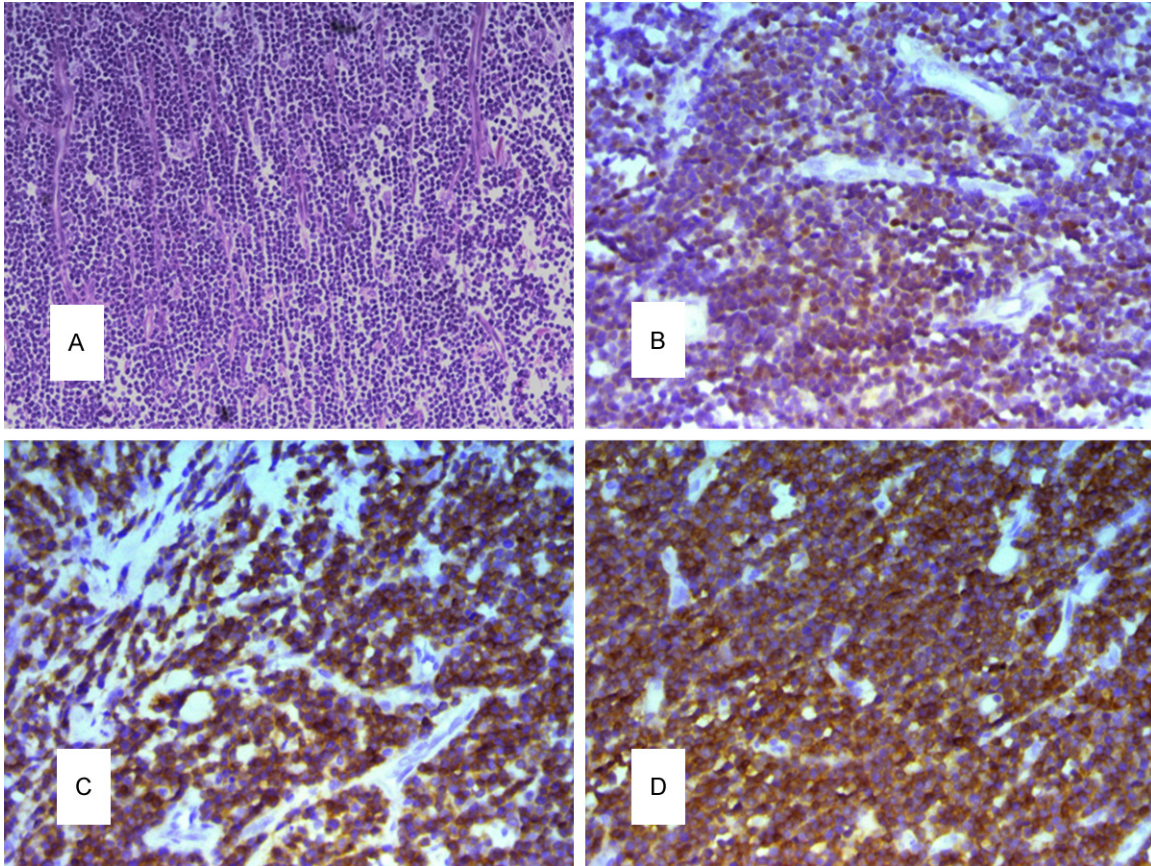


Figure 2. Microscopic findings and immunohistochemical staining. A: Histological examinations stained with hematoxylin and eosin revealed diffuse round to oval medium sized cells with high nuclear/cytoplasmic ratio, finely dispersed chromatin, scanty cytoplasm, prominent nucleoli, and numerous mitoses, $\times 200$. B: Immunohistochemical staining showed that tumor cells was positive for TdT, $\times 400$; C: Immunohistochemical staining showed that tumor cells was positive for CD5, $\times 400$. D: Immunohistochemical staining showed that tumor cells was positive for CD7, $\times 400$.

and discharge. He is now 65 months out from transplantation without relapse or complaints.

Discussion

Primary thyroid lymphoma is a heterogeneous disease with a wide spectrum of histological subtypes. The term “primary” designated patients with lymphomatous involvement of the thyroid at diagnosis, with either localized disease or dissemination to nodal or extranodal sites [20]. Most reported cases are classified as B-cell lymphomas, including diffuse large B-cell lymphoma (DLBCL) and mucosa-associated lymphoid tissue (MALT) lymphoma. Primary T-cell lymphomas of the thyroid gland are extremely rare. We diagnosed precursor T-lymphoblastic lymphoma (T-LBL) of the thyroid gland according to the 2008 World Health Organization (WHO) classification [21]. Except

for minimal bone marrow invasion, no other organ involvement by lymphoma was demonstrated. Therefore, we considered this case to be a rare primary T-cell lymphoma of the thyroid gland, clinical stage IVE-A with bulky mass. To our knowledge, this is the first case of primary thyroid T-LBL in English literature.

A review of the English literature, including our patient, provided 20 cases of thyroid T-cell lymphoma (**Table 1**). The male/female ratio was 8/12. Median age at presentation was 60.2 years (range, 15-86). Most patients had a past history of Hashimoto’s thyroiditis (12/19), which affected females (9/11) more than males (3/8). Of them, thyroid function tests were normal or indicative of hypothyroidism. Most patients also presented a history of rapid thyroid enlargement, sometimes accompanied by nonspecific symptoms related to compression

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Table 1. Lists of reported thyroid T-cell lymphoma

Reference	Age/ gender	Presentation	Thyroid function	Chronic thyroiditis	Imaging	Histologic and molecular diagnosis	stage	Diagnostic intervention	Therapy	Prognosis
(Dunbar et al. 1977) [2]	73/F	Nodular non-tender swelling in the left lobe	normal	-	N/A	N/A	N/A	Left hemithyroidectomy	S+R	24M/alive
(Mizukami et al. 1987) [3]	79/F	Goiter increase in size	Normal	+	N/A	Diffuse small cleaved, OKT4+, OKT11+	IE	Total thyroidectomy	S+R	36M/DUC
(Mizukami et al. 1990) [4]	80/M	Goiter increase in size	N/A	-	N/A	Diffuse small cleaved	N/A	Open biopsy	C+R	48M/alive
(Ohsawa et al. 1995) [5]	59/F	Huge goiter	N/A	N/A	N/A	CD3+, CD4+, CD8-, CD20-, CD22-, CD45RA-, CD45RO+/-, L22-, L24-, L28-	IIIE	N/A	N/A	N/A
(Abdul-Rahman et al. 1996) [6]	64/F	Thyroid mass	hypo	+	Enlargement of both lobes, mass in right lobe	CD2+, CD3+, CD5+, CD4+, CD25+, TCR-β, TCR-γ rearrangement	IE	Total thyroidectomy	S+C+R	9M/alive
(Yamaguchi et al. 1997) [7]	59/F	Goiter	hypo	+	N/A	CD3+, CD4-, CD8-, CD19-, CD20-, CD56-, TCR-δ rearrangement	IIIE	Open biopsy	C+R	22M/alive
(Coltrera 1999) [8]	65/M	Thyroid mass, Hoarseness, Dysphasia	normal	-	Left lobe mass	CD45RO+, CD45-, vimentin+	IE	Open biopsy	C+R	11M/dead
(Forconi et al. 1999) [9]	39/F	Goiter, fever, dysphonia	normal	+	Bilateral Enlargement nodule in isthmus	CD30+, CD45RO+, CD3-, CD20-, CD79a-, CD21-, BCL2-, CD43-	IIIE	Open biopsy	C+R	12M/alive
(Freeman 2000) [10]	66/F	Diffuse enlarged thyroid	hypo	+	N/A	CD3+	N/A	Open biopsy	None	2W/DUC
(Hacıyanli et al. 2000) [11]	63/F	Thyroid mass, Hoarseness, dyspnea	hypo	+	Right lobe nodule	CD45RO+, CD43+, CD20-	IIIE	Total thyroidectomy	S+C+R	36M/alive
(Raftopoulos et al. 2001) [12]	72/M	Thyroid mass, neck pressure, difficulty swallowing, voice change	Normal	+	Bilateral thyroid enlargement, tumor of right robe	CD4+	IE	Right thyroidectomy	C+R	12M/alive
(Motoi and Ozawa 2005) [13]	71/F	neck swelling, hoarseness, goiter	Hypo	+	Thyroid enlargement with decreased internal density	CD3+, CD45RO+, CD4+, TCR-β, TCR-γ rearrangement	IE	Total thyroidectomy	S	25M/alive
(Okamoto et al. 2005) [14]	86/F	Swelling of neck	Normal	-	Homogenous solitary nodule left lobe	CD3e+, CD5+, TIA-1+, CD20-, CD56-, TCR-Cβ rearrangement	IE	Left hemithyroidectomy	S	24M/alive
(Colovic et al. 2007) [15]	34/M	N/A	N/A	-	N/A	CD3+, CD5+, CD7-, CD43+, CD45RO+, CD20-, CD79a-	IE	Subtotal hemithyroidectomy	S+C+R	13M/dead
(Koida et al. 2007) [16]	61/M	Thyroid mass	normal	+	Bilateral thyroid enlargement	CD3+, CD4+, CD8-, CD20-, CD56-, CXCR3+, CCR5+, ST-2-, TCR-Cβ rearrangement	IV	Open biopsy	C	28M/alive
(Koida et al. 2007) [16]	68/M	Thyroid mass, dyspnea	hypo	+	Bilateral thyroid enlargement	CD3+, CD4+, CD8-, CD20-, CD25-, CD56-, TCR-αβ+, DR-	IIIE	Open biopsy	C	5M/dead

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(Yang et al. 2008) [17]	32/M	Swelling of neck, goiter, fatigue, shortness of breath/Goiter, subcutaneous nodules	Hypo	-	Bilateral thyroid enlargement	CD3+, CD20-, TCR-γ rearrangement	IVB	FNA	C	12M/alive
(Kim et al. 2010) [18]	48/F	Neck mass	Normal	+	Right lobe mass	CD3+, CD8+, βF-1+, TIA+	IE	Right hemithyroidectomy	S+C	28M/alive
(Yokoyama et al. 2012) [19]	70/F	Neck swelling	Normal	+	Bilateral thyroid enlargement	CD3+, CD45RO+	IE	Total thyroidectomy	S	20M/alive
present	15/M	Thyroid mass	normal	-	Right lobe mass	TdT, CD5, CD7, CD8, CD10, CD45RO, CD99, CD79a, CD3, CD1a	IVE	Right hemithyroidectomy	S+R+T	65M/alive

N/A, not available; C, chemotherapy; DUC, died of unrelated cause; R, radiation therapy; S, surgery; T, alloHSCT; TCR, T-cell receptor; FNA, fine-needle aspiration.

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of the neck, including hoarseness, dysphasia, and dyspnea. Imaging findings include unilateral nodule or mass (5/13), nodule with bilateral thyroid enlargement (3/13), and diffuse thyroid enlargement (5/13), which are indistinguishable from a broad spectrum of disorders. Open biopsy or surgery was the most common method for diagnosis. A definite diagnosis depends on histological and immunohistochemical examination. New techniques, such as flow cytometry and gene rearrangement studies, have enhanced the diagnostic efficacy. Of these patients, peripheral T-cell lymphoma was the most common pathologic type, while our patient was T-LBL that derived from immature T lymphocytes. Treatment of thyroid T-cell lymphoma has focused on a combination of chemoradiotherapy and surgery, but no consensus has been reached. No survival statistics exist for thyroid T-cell lymphoma. It is generally considered that T-cell lymphomas have worse prognoses than B-cell lymphomas. Whereas only three reported patients died from the disease. Although many clinical features closely resembled those of the usual thyroid T-cell lymphoma, our patient was special in many aspects.

T-LBL is a neoplasm of lymphoblasts that are committed to the T-cell lineage with a proposed normal counterpart of T-cell progenitor cells or thymic lymphocytes, and it has been reported in a limited number of anatomical sites, such as mediastinal, lymph nodes, soft tissue, skin, tonsil, liver, spleen, central nervous system, and testes [21]. Our patient did not present with any of these features, but with a mass of the thyroid gland. T-LBL accounts for one third of cases of non-Hodgkin lymphoma in childhood, with adolescent males being the most frequently affected. The World Health Organization classification groups T-lymphoblastic leukemia (T-ALL) and T-LBL together as T-lymphoblastic leukemia/lymphoma (T-ALL/LBL) [22]. Arbitrarily, 25% bone marrow involvement has been considered the cut-off in differentiating between LBL and ALL. Morphology of T-LBL is generally composed of medium-sized cells with high nuclear/cytoplasmic ratios, round to irregular nuclear contours, fine chromatin, prominent nucleoli, and numerous mitotic figures. The immunophenotype of cells in T-LBL usually includes positivity for TdT with variable expression of CD45, CD34, CD1a,

CD10, CD2, cCD3 (lineage specific), CD4, CD5, CD7, and CD8. More reliable markers to confirm an immature phenotype include TdT, CD1a, CD99, CD34. In our patient, expression of TdT, CD5, CD7, CD8, CD10, CD45RO, CD99, CD79a, CD3, CD1a confirmed the diagnosis of T-LBL. T-LBL is a clinically aggressive disease. The diagnosis of T-LBL predicted a high risk of induction failure, early relapse, and poor event-free survival. Because of the high risk of relapse, high-dose chemotherapy followed by hematopoietic stem-cell transplant has been used to consolidate remission [23, 24]. Several studies have included alloH SCT in their protocols and report good outcomes where alloH SCT was used as part of therapy. Some patients with bone marrow involvement and/or younger age proceeded to allogeneic transplant and did not demonstrate disease relapse at 38-141 months since time of diagnosis [25]. In a study of H SCT in T-ALL, which assessed the role of sibling allograft, OS at 5 years was 61% for the patients who had received alloH SCT and 46% for the patients who didn't; a difference maintained at 10 years suggesting the application of alloH SCT to unselected patients with T-ALL of appropriate age who have a sibling donor is a possible therapeutic strategy [26]. Therefore, the use of intensive treatment regimens followed by alloH SCT may be superior to the use of chemotherapy alone. Planned SCT is a reasonable treatment option for newly diagnosed T-LBL and can be expected to cure the patients. In the present case, intensive chemotherapy regimens were used and subsequently alloH SCT was performed using his brother as a donor. He is doing well for more than five years without relapse.

In summary, we report a case of T-LBL presenting as a thyroid mass that was successfully treated with intensive chemotherapy and alloH SCT. Our patient was unique because no cases of thyroid T-LBL have been previously reported, to our knowledge. We hope that awareness of this entity will help oncologists achieve timely diagnosis and intervention. What's more, intensive chemotherapy followed by alloH SCT might be one of the adoptive options in therapy for this aggressive disease.

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Disclosure of conflict of interest

None.

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