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Review Article

Clinical Advances in the Diagnosis and Treatment of T-Cell Lymphomas of the Thyroid Gland

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Abstract

Malignant lymphoma of the thyroid gland is uncommon, representing only 2–5% of all thyroid malignancies, and is often associated with Hashimoto's thyroiditis. Many reported cases are B-cell lymphomas of the thyroid gland. Primary T-cell lymphomas are extremely rare at less than 2% of all primary lymphomas of the thyroid gland. Given that almost all primary T-cell lymphomas are associated with Hashimoto's thyroiditis and without a reliable immunohistochemical marker of clonality of T-lymphocytes, it can be problematic to diagnose pathologically. As a result, primary T-cell lymphoma of the thyroid gland poses significant diagnostic and therapeutic challenges to pathologists and clinicians. Due to advances in molecular diagnosis, molecular diagnosis is recommended as the most effective method by which to detect the presence of a dominant T-cell clone in a lymphocytic infiltrate. Since the 1990's, primary T-cell lymphomas of the thyroid gland could be accurately detected and slightly more cases were reported than in the 1980's. Monoclonality of the proliferated lymphoid cells was observed on Polymerase chain reaction (PCR). Very rare cases of peripheral T-cell lymphoma of the thyroid gland with Hashimoto's thyroiditis were successfully diagnosed by the gene rearrangement procedure. Given these results, patients with rapid thyroid enlargement accompanied with Hashimoto's thyroiditis should be examined by the gene rearrangement procedure.

Keywords: Peripheral T-cell lymphoma; Thyroid gland; Hashimoto's thyroiditis; Molecular diagnosis; Gene rearrangement

Introduction

Malignant lymphoma of the thyroid gland is uncommon, representing only 2–5% of all thyroid malignancies, and is often associated with Hashimoto's thyroiditis [1]. Many reported cases are B-cell lymphomas of the thyroid, which include marginal zone B cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type (maltoma) and diffuse large B-cell lymphoma. Among of all primary lymphomas of the thyroid gland, primary T-cell lymphomas (TCL) are extremely rare at less than 2%. Examining rare cases of primary TCL of the thyroid gland, we review epidemiology, diagnosis, treatments, and associated problems of TCL of the thyroid gland.

Epidemiology

We reviewed English literature in relation to TCL of the thyroid gland documented from 1977 to 2016. The first reported case of TCL of the thyroid gland was an English lady in 1977. During almost four decades, clinicopathological reports regarding TCL of the thyroid gland have gradually increased to 18 cases. The mean age of these patients is 60.6 years with a wide range spanning from 26 to 86 years. The male to female ratio is 8:10. As the male to female ratio of thyroid B cell lymphoma is reported to be approximately 1:3, the ratio of thyroid TCL differs markedly from the ratio of thyroid B cell lymphoma [2].

The majority of thyroid TCL is associated with Hashimoto's thyroiditis as is the case with B cell lymphoma. Among 16 cases referred to Hashimoto's thyroiditis, 12 cases were found to be associated with Hashimoto's thyroiditis. Since the infiltrated lymphocytes are phenotypically of helper or cytotoxic T-cell origin with a background of Hashimoto's thyroiditis, it suggests that helper or cytotoxic T-cell activation induced by chronic inflammation could lead to peripheral T-cell lymphoma.

Among 9 cases referred to as Human T-cell lymphoma virus type 1(HTLV-1), 9 cases were found not to be associated with HTLV-1. In regard to EBV, the vast majority of published reports do not refer to EVB.

Among 18 cases of thyroid TCL, 8 cases were reported from Japan. Two cases were reported from the UK, with one case reported from Belgium, China, India, Italy, Korea, Turkey and the USA. Consequently, 11 of the 18 cases originated in Asian countries (Japan, China, India and Korea) while 4 of the 18 were reported from European countries (UK, Belgium and Italy). In view of the fact that more than half of the TCL of the thyroid gland cases originated from Asia, especially Japan, it is possible that the etiology of the disease may be associated with regional factors.

Diagnosis

Pathological diagnosis: Histologically, severe and diffuse infiltration of the lymphoid cells was found in the medullary region (Figure 1). Lymph follicle formation with germinal centers was noted in the periphery of the medullary region. Atypical lymphoid infiltrations were also located among the atrophic thyroid follicles. Infiltrated lymphoid cells were relatively uniform, small-to-medium

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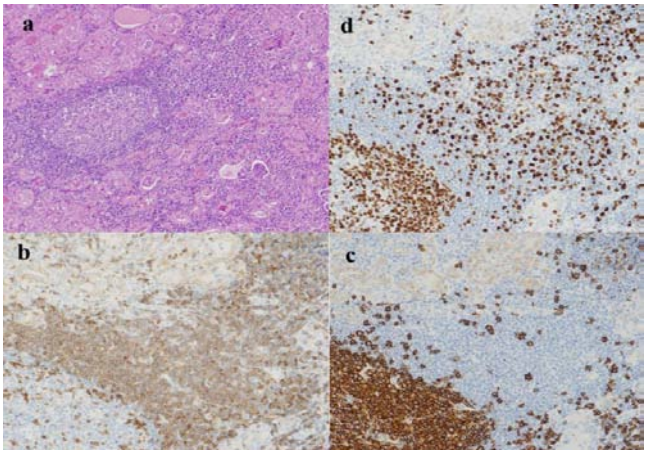

Figure 1: Microscopic findings and Immunohistochemical staining.
a) Low-power view of histological examinations revealed massive infiltration of small lymphocytes. It was difficult to distinguish tumor cells from reactive lymphocytes in Hashimoto's thyroiditis. (Hematoxylin and eosin staining, X100).
b) Immunohistochemical staining showed that tumor cells had T-cell markers for CD3. (X400).
c) Immunohistochemical staining by CD20 showed infiltrated lymphoid cells had B-cell markers. (X400).
d) MIB staining. MIB 1 index was as high as 60% in high-power fields. (X400).

sized, round cells with a high nuclear to cytoplasmic (N/C) ratio. These cells had round nuclei with increased coarse chromatin and small nucleoli. Mitotic figures were often seen as high as 60% in high-power fields. These findings suggested small lymphocytic lymphoma. The atrophic thyroid epithelia showed enlarged and eosinophilic granular cytoplasm with large nuclei, so- called Hürthle cell metaplasia. Around these Hürthle cells there were many plasma cells, lymph follicles with germinal centers, and a few eosinophils (Figure 1). These findings suggest complication associated with Hashimoto's thyroiditis.

Immunohistochemical examinations were performed on formalin-fixed, paraffin-embedded specimens, using an auto staining system according to the manufacturer's protocol. From these results, diffusely infiltrated lymphocytes were positive for T-cell markers (CD3 and CD45RO) and positive for B-cell markers (CD20). However, infiltrated atypical T cells showed CD3 dominancy (Fig.1). In contrast, lymphoid cells of the peripheral area with lymph follicles showed an admixture of T and B cells, mimicking lymph follicles. On the absence of a reliable immunohistochemical marker of clonality of thyroid TCL with Hashimoto's thyroiditis, it is difficult to diagnose thyroid TCL pathologically.

Flow cytometry

Flow cytometry is rapid and appears to be virtually diagnostic of non-Hodgkin B cell lymphoma. In thyroid TCL with Hashimoto's thyroiditis, surface marker analysis of tumors showed T-cell dominancy (CD2+, CD3+, CD4+, CD5+, CD45+). There was also a small population of B-cell lineage, with no dissociation of surface membranous immunoglobulin light chain kappa or lambda. These data suggest the polyclonal nature of infiltrated B lymphocytes associated with Hashimoto's thyroiditis. Even though one case of dominant T-cell population with positive CD4 by flow cytometry was detected, it is challenging to diagnose thyroid TCL with Hashimoto's thyroiditis by flow cytometry.

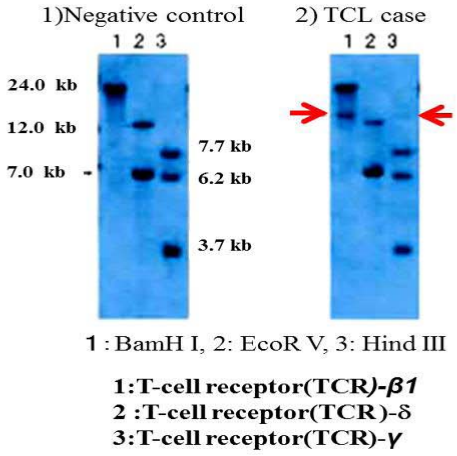

Figure 2: PCR analysis of rearrangement of T-cell receptor (TCR) Rearrangement of T-cell receptor (TCR)- β1 (lane 1) and TCR-γ (lane 3) were found in the case. Rearrangement of TCR- δ (lane 2) was negative in the case. M, molecular weight marker; 1, normal control (human placental DNA); 2, TCL case. 1, BamH I; 2, EcoR V; 3, Hind III.

Molecular analysis

Southern blot analysis was conducted for detection of rearrangement of immunoglobulin heavy chain (IgH) hypervariable region and T-cell receptor (TCR). Polymerase chain reaction (PCR) for detection of rearrangement of IgH hypervariable region and TCR were also performed using fresh specimens as described previously [3]. PCR analysis clearly produced a rearrangement band of *TCR-γ* by *Hin*d III digestion and *TCR-β* by BamH I digestion (Figure 2). However, Southern blot analysis didn't produce a rearrangement band of *TCR-γ* by *Hin*d III digestion and *TCR-β* by BamH I digestion so clearly as PCR analysis. As a result, PCR analysis is recently being used to detect rearrangements of IgH and TCR more frequently than Southern blot analysis. With regard to rearrangement band of *TCR*, the majority of recent thyroid TCL cases since 2007 have been detected by PCR procedure. Among 10 cases detected by means of rearrangements of TCR through using PCR procedure, the number of rearrangements of *TCR-β, TCR-γ* both *TCR-β* and *TCR-γ,* and *TCR-δ* cases were 7, 5, 3 and 1, respectively. There was no rearrangement of the IgH.

Case report

We experienced a very rare case of TCL of the thyroid gland that developed in a 70-year-old Japanese woman with a past history of hypothyroidism due to chronic thyroiditis. The chief complaint was a rapidly growing neck mass. The patient indicated feeling oppression of the neck. CT and ultrasonographic examination revealed a diffuse large thyroid gland without a nodule extending up to 13cm. The patient had a past history of hypothyroidism and enlargement 10 years earlier and took levothyroxine sodium 50 μg daily. Laboratory examination indicated almost normal thyroid function (free T4 1.3 ng/dL, free T3 3.6 ng/dL, thyroid-stimulating hormone (TSH) 0.04 m unit/mL). Although the presence of abnormal lymphoid cells in the peripheral blood was not found, the sIL-2 Receptor antibody and thyroglobulin measured as high as 970 U/ml and 600 ng/mL,

Table 1: Lists of previously reported thyroid T-cell lymphoma
References*, Number in brackets indicate reference numbers and other numbers indicate published year; Age/G: Age/Gender, Chr thyroiditis: Chronic thyroiditis; N/A: not available; C: Chemotherapy; DFS: Ddisease-Free Survival; DUC: Died of Unrelated Cause; IgH: Immunoglobulin Heavy Chain; PCR: Polymerase Chain Reaction; R: Radiation therapy; S: Surgery; TCR: T-cell Receptor.

Ref.	Age/G	Presentation	Chr thyroiditis	HTL V-1	Histology	Molecular Diagnosis	Diagnostic intervention	Therapy	prognosis	country
[4]	73/F		N/A	N/A				S + R	alive at 24 months	UK
[5]	79/M	Goiter	N/A	N/A	Diffuse small cleaved		open biopsy	C + R	alive at 4 years	Japan
[5]	80/F	Goiter	(+)	N/A	Diffuse small cleaved		Hemithyroidectomy	S	DUC	Japan
[6]	64/F	Thyroid mass, Hypothyroidism	(+)	(-)	CD2+, CD3+, CD5+, CD45R0+	TCR-β, TCR-γ rearrangement	Total thyroidectomy	5 + C + R	alive at 9 months	UK
[7]	59/F	Goiter	(+)	(-)	CD3+, CD4-, CD8-, CD19-,	TCR-δ rearrangement	Open biopsy	C + R	alive at 22 months	Japan
[8]	65/M	Thyroid mass, Horseness, dyspasia,	(-)	N/A	CD45RO+, CD45-, vimentin+		Open biopsy	C + R	died at 11 months	USA
[9]	39/F	Goiter, fever, dysphonia	(+)	N/A	CD30+, CD45RO+, CD3-, CD20-, CD79a-, CD21-		Open biopsy	C + R	alive at 1 year	Italy
[10]	63/F	Thyroid mass, Hoarseness, dyspnea	(+)	N/A	CD45RO+, CD43+		Total thyroidectomy	S + C + R	alive at 3 years	Turkey
[11]	72/M	Thyroid mass, pressure, difficulty swallowing	(+)	N/A	CD4+ flow cytometry		Right hemithyroidectomy	C + R	alive at 12 months	Belgium
[12]	71/F	Thyroid swelling, horseness, goiter	(+)	(-)	CD3+, CD45RO+, CD4+	TCR-β, TCR-γ rearrangement	Total thyroidectomy	S	alive at 25 months	Japan
[13]	86/F	Swelling of neck	(-)	(-)	CD3e+, CDS+, T1A-1+ (T-cell restricted antigen)	TCR-β rearrangement	Left hemithyroidectomy	S	alive at 2 years	Japan
[14]	34/M	N/A	(-)	(-)	CD3+, CD5+, CD7-, CD43+, CD45RO+, CD20-		N/A	S+C+R	died at 13 months	Serbia
[15]	61/M	Thyroid mass	(+)	(-)	CD3+, CD4+,	TCR-β rearrangement	Open biopsy	C	alive at 4 years	Japan
[15]	68/M	Thyroid mass, dyspnea	(+)	(-)	CD3+, CD4+, TCR-, ab+	TCR-β rearrangement	Open biopsy	C	died at 5 months	Japan
[16]	32/M	Swelling of neck, fatigue, shortness of breath	(-)	N/A	CD3+,	TCR-γ rearrangement(PCR)	Open biopsy	C	alive at 1 year	China
[17]	48/F	incidentaloma (right lobe)	(+)	(-)	CD3+, CD8+, βF- 1+, TIA+	TCR-γ rearrangement(PCR)	Right hemithyroidectomy	S + C	alive at 25 months	Korea
[I8]	70/F	Neck swelling	(+)	(-)	CD3+, CD45RO+,	TCR-β, TCR-γ rearrangement(PCR)	Total thyroidectomy	S	alive at 82 months	Japan
[19]	26/M	Thyroid mass, Hoarseness, dyspnea	(+)	N/A	CD3+, CD5+, CD2+, CD45+	TCR-β rearrangement(PCR)	Total thyroidectomy	S + C + R	alive	India

respectively. Fine needle aspiration cytology diagnosed chronic thyroiditis.

A preoperative diagnosis of suspicious malignant lymphoma of the thyroid gland accompanied by Hashimoto's thyroiditis was made. A right hemithyroidectomy was performed to confirm the preliminary diagnosis and alleviate local symptoms caused by the enlarged goiter. Histological examination revealed diffuse small lymphocytic infiltration in the thyroid gland associated with Hashimoto's thyroiditis. Immunohistochemical examination showed that the small lymphocytes were positive for T-cell markers with CD3 and CD45RO. However, Immunohistochemical staining by CD20 also showed infiltrated lymphoid cells which had B-cell markers. The final pathological diagnosis was chronic thyroiditis with atypical lymphocytes infiltration. However, PCR analysis of tumor specimens revealed only a monoclonal T-cell receptor gene rearrangement. Finally, peripheral T cell lymphoma was diagnosed. No other organ involvement of lymphoma was detected, including the lymph nodes, the mediastinum and the bone marrow. For these reasons, we considered this case to be a rare primary T-cell lymphoma of the thyroid gland, clinical stage I E-A with bulky mass. Therefore, the left hemithyroidectomy was also performed one month later. No adjuvant

therapy was performed due to the tumor stage and its subtype. The patient is healthy with no recurrence or metastasis 82 months after the surgical removal of the thyroid. As TCL of the thyroid gland with Hashimoto's thyroiditis was difficult to diagnose pathologically, gene rearrangement examination needed to be performed concurrently.

Treatments

Treatment of thyroid T-cell lymphoma has focused on a combination of chemoradiotherapy and surgery, but no consensus has been reached. Based on literature acquired on 18 cases of thyroid TCL, there have been only 4 cases in which chemoradiotherapy and surgery were both performed. The number of chemoradiotherapy cases was 5 while the number of cases in which surgical treatment alone was performed was 4. Surgical treatment including chemotherapy, or radiotherapy numbered 10 cases. On the other hand, non-surgical treatment numbered 8 cases. In our case examined above, as histology of the tumor showed that it was a low-grade lymphoma without extracapsular spread and pathologically no lymph node metastasis, surgical treatment could be one of the most effective treatments for treating thyroid TCL. In 3 of the 18 thyroid TCL cases the patient died from the disease. In 2 of these 3 cases the patients were treated by non-surgical procedures. Though T-cell lymphomas are generally considered to have worse prognoses than B-cell lymphomas, the survival for patients who underwent surgical treatment was 9 out of 10 patients. Based on the literature available, we surmise that adjuvant chemoradiotherapy for Stage IE-A with bulky mass does not appear to contribute to a better prognosis than surgery alone (Table 1). Unlike B cell lymphoma, there is no effective chemotherapy regimen for thyroid TCL.

Discussion

On the absence of a reliable immunohistochemical marker of clonality of T-lymphocytes, thyroid TCL associated with Hashimoto's thyroiditis is difficult to diagnose pathologically. We have examined problems of thyroid TCL resulting from difficulties of diagnosis and treatments. Malignant lymphoma of the thyroid gland is often associated with Hashimoto's thyroiditis [1]. Most thyroid lymphomas are of the B-cell type lymphoma. Thyroid TCL is extremely rare with only 18 cases having been reported in English literature to date (Table 1). Most patients had a past history of Hashimoto's thyroiditis, which affects females more than males. Most patients also had a history of rapid thyroid enlargement, sometimes accompanied with hoarseness or dysphasia. Open biopsy was the most common method of diagnosis, however it is difficult to make a reliable diagnosis of thyroid TCL pathologically. Even a hemithyroidectomy suspecting malignant lymphoma in the thyroid, histological examinations revealed massive infiltration of small monotonous lymphocytes, which were difficult to distinguish from reactive lymphocytes in Hashimoto's thyroiditis. Immunohistochemical examination showed that these lymphocytes had T-cell markers (CD3 and CD45RO). However, pathological diagnosis could not accurately diagnose T-cell lymphomas. There are several reasons for misdiagnosis in the thyroid TCL.

Firstly, Hashimoto's thyroiditis induced complicated massive infiltration of small lymphocytes, which were stained with B cell markers and T cell markers. It is difficult to distinguish tumor cells from reactive lymphocytes in Hashimoto's thyroiditis. Secondly, T-cell lymphomas of the thyroid gland are very rare and cannot be easily referred to as an indicator. Thirdly, present pathology has developed into various subdivisions and pathologists are not always capable of detecting malignant lymphoma disease.

All patients with rapid thyroid enlargement should be examined by standard procedures including blood examinations, images such as echo or CT, and fine needle aspiration. As patients with TCL cannot be diagnosed by these examinations, these patients with Hashimoto's thyroiditis should be examined by not only pathological examinations, but also the gene rearrangement procedure [20,21]. Since the 1990's, advances in molecular diagnosis, primary T-cell lymphomas of the thyroid gland could be detected accurately, and gradually more cases were reported than in the 1980's. T-cell lymphomas are generally considered to have worse prognoses than B-cell lymphomas. However, with the exception of three, all patients with T-cell lymphomas did not die as a result of the disease. Once accurate diagnosis and adequate surgical resection for the thyroid TCL was conducted, prognosis of the thyroid TCL might be improved with minimally invasiveness. However, further investigations are needed to clarify this matter.

Conclusion

Given the absence of a reliable immunohistochemical marker of clonality of thyroid TCL with Hashimoto's thyroiditis, it is difficult to diagnose thyroid TCL pathologically. We recommend that patients with rapid thyroid enlargement accompanied with Hashimoto's thyroiditis should be examined by the gene rearrangement procedure.

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