Primary T-cell lymphoma of the thyroid gland with chemokine receptors of Th1 phenotype complicating autoimmune thyroiditis

Lymphoma of the thyroid is almost exclusively derived from B cells of mucosa-associated lymphoid tissue (MALT), and frequently co-exist with autoimmune thyroiditis in which most infiltrating cells are of Th1 cell origin. We present here two rare cases of peripheral T-cell lymphoma (PTCL) based on chronic thyroiditis with the phenotype CD3$^+$, CD4$^+$, CD8$^-$, TCRαβ$^+$. Furthermore, lymphoma cells in both cases were CXCR3$^+$, CCR5$^+$ and ST2(L)$^-$, suggesting a Th1 cell origin. Eight of 11 cases of PTCL of the thyroid in the literature, including our cases, were associated with thyroiditis. Except for one tumor of γδT-cell type, all of the five lymphomas analyzed for CD4 expression were positive for the antigen. Among them, both those examined for chemokine receptors were phenotypically of Th1-cell origin with a background of thyroiditis, suggesting that Th1 activation induced by chronic inflammation could lead to PTCL of themselves as well as MALT-lymphoma of B cells.

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Introduction

Primary lymphoma of the thyroid accounts for only 2% to 4% of thyroid malignancies and less than 2% of extranodal lymphomas.[1] Primary thyroid lymphoma is frequently associated with chronic thyroiditis in which most infiltrating cells are Th1 cells.[2] In contrast, lymphoma cells of the thyroid are exclusively of B-cell phenotype.[1,2] The majority are aggressive diffuse large B-cell lymphomas and the second most common histologic type is mucosa-associated lymphoid tissue (MALT)-B-lymphoma.[1] There is evidence that large-cell lymphomas probably evolve from persistent low-grade MALT -B-lymphomas, suggesting a morphologic progression from chronic lymphocytic thyroiditis to low-grade MALT lymphoma and subsequently to high-grade large-cell lymphoma.[1,3] In contrast, primary T-cell lymphoma of the thyroid is extremely rare, and little is known about the origin or phenotype of the T-cells. [4-12] We report here two rare cases of T-cell lymphoma of the thyroid gland with chemokine receptors of Th1 phenotype complicating autoimmune thyroiditis.

Case report

Case 1. A 61-year-old man was referred to our hospital with a 16-month history of a progressively enlarging thyroid mass without symptoms. Physical examination revealed only diffuse thyroid enlargement. Laboratory data were as follows: leukocyte count 10300 (stab 10%, seg 41%, mono 1%, eosino 2%, lymphocytes 19%, abnormal lymphocytes 27%)/μL, RBC 4.83x10^6/μL, hemoglobin 15.0g/dl, platelets 26.5x10^4/μL, lactate dehydrogenase (LDH) 148 IU/l (normal range; 119-229) and soluble interleukin-2 receptor (sIL2R) 2048 U/mL (normal range; 145-518). Small to medium-sized abnormal lymphocytes with convoluted nucleoli, and relatively condensed chromatin were observed in peripheral blood (Figure 1A). Ultrastructual examination revealed that nuclei had some lobulation, but less than that of cerebriformed nuclei in typical Sezary cells (Figure 1B).1) A flow cytometric analysis of peripheral blood mononuclear cells (PBMNC) showed that the neoplastic cells were positive for mature helper T-cell markers (CD3, CD4, CD5, CD7, CD45RO and TCRαβ) but negative for B cell markers (CD19 and CD20), NK cell markers (CD16 and CD56) and activation markers (CD25 and DR). Bone marrow (BM) aspiration demonstrated no neoplastic cell infiltration. Serum-test results were negative for human T-lymphotropic virus type-1 (HTLV-1). Southern blotting revealed PBMNC to be positive for clonal rearrangement of the T-cell receptor Cβ-chain gene, but negative for integration of the HTLV-1 provirus or Epstein Barr virus. Thyroid functions (fT3, fT4 and TSH) were within the normal range, but serum-test results were positive for anti-thyroglobulin antibody and anti-microsome antibody. A magnetic resonance image scan of revealed bilateral thyroid enlargement without lymphadenopathy. An open biopsy of the thyroid showed diffuse infiltration of small to medium-sized atypical lymphocytes in thyroid follicles associated with lymphoepithelial lesions (Figures 1C, 1D). Immunohistochemistry revealed that lymphoma cells were mature T-cells with the phenotype CD3$^+$, CD4$^+$, CD8$^-$, CD20$^-$, CD56$^-$ (Figures 1E, 1F). Furthermore, analysis of chemokine receptors revealed that lymphoma cells were CXCR3$^+$, CCR5$^+$ and ST-2$^-$, suggesting a Th1 cell origin (Figures 1G, 1H, 1I).[13] Results of flow cytometric analysis of a cell suspension from the thyroid were similar to those of PBMNC. Furthermore, the analysis revealed that leukemic cells were CCR7$^+$ and CCR4$^-$, supporting a Th1 cell origin. The patient was diagnosed as having peripheral T-cell lymphoma (PTCL) of the thyroid gland with leukemic manifestation, and started on CVP (cyclophosphamide, vincristine and prednisolone) chemotherapy. After 3 cycles of CVP, partial remission of the lymphoma was achieved and the therapy was discontinued because of peripheral numbness associated with vincristine. He is still alive with a residual thyroid mass and leukemic-manifestation confirmed by TCR-Southern blotting for more than four years.

Case 2. A 68-year-old man, who had been treated for Hashimoto's thyroiditis and hypertension for 10 years, presented with a 3-week history of a progressively enlarging thyroid mass with dyspnea. Physical examination revealed diffuse thyroid enlargement with cervical lymphadenopathy. Laboratory data were as follows: WBC 5200/uL, Hb 13.0 g/dL, platelet 26.6X10^4/uL, LDH 398 IU/L, sIL2R 1534 U/mL and negative for HTLV-1 antibody. Abnormal lymphocytes were not detected in PB and BM. Computed tomography revealed bilateral thyroid enlargement with lymphadenopathy. An open biopsy of the thyroid showed diffuse infiltration of large atypical lymphocytes (Figures 2A, 2B). Immunostaining of thyroid tissue and cell suspension revealed that lymphoma cells were mature helper T-cells with the phenotype CD3$^+$, CD4$^+$, CD8$^-$, CD20$^-$, CD25$^-$, CD56$^-$, TCRαβ$^+$, DR$^-$ (Figures 2C, 2D). Furthermore, an analysis of chemokine receptors revealed that lymphoma cells were CXCR3$^+$, CCR5$^+$ and ST-2$^-$, suggesting a Th1 cell origin (Figures 2E, 2F, 2G).[13] After 5 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), complete remission of the PTCL was acheived. However, the patient died of lymphoma relapsing at the meninx five months after onset.

Discussion

Most extranodal lymphomas are of B-cell origin and frequently follow chronic inflammation.[3] PTCL of the thyroid is extremely rare, with only 11 cases, including our two cases, reported in the literature (Table 1).[4-12] Eight of them were associated with hypothyroidism or

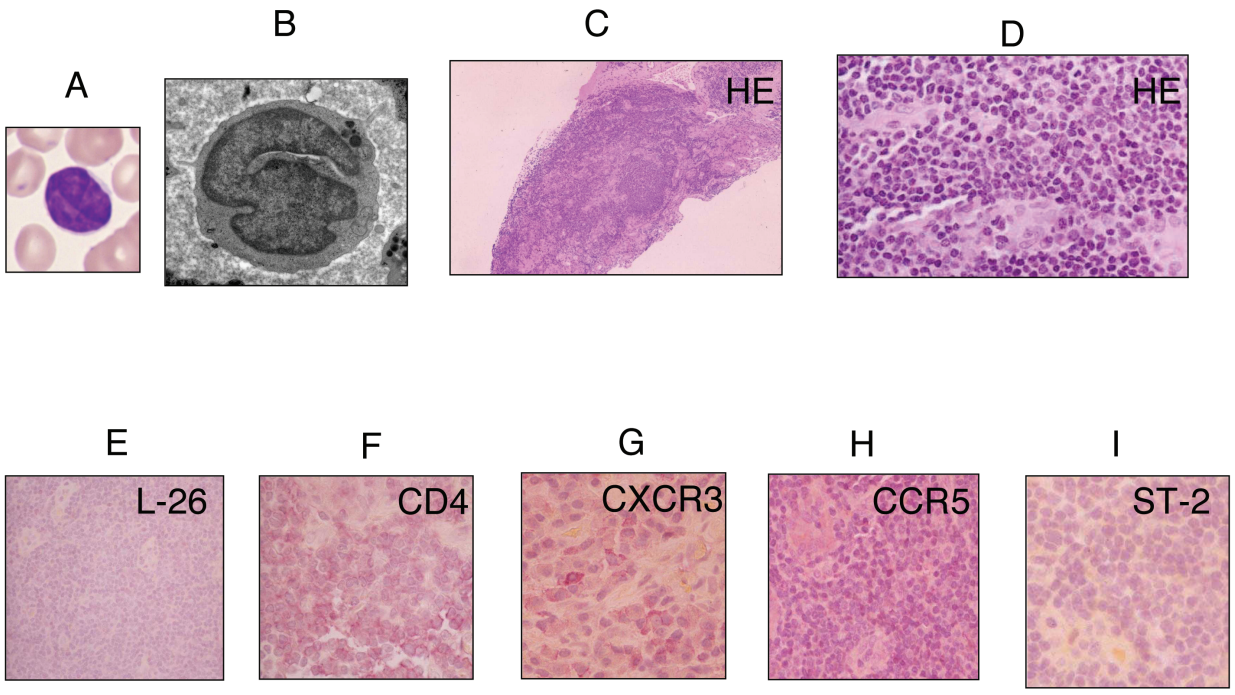

Figure 1. Histological analysis of a thyroid-gland biopsy sample and cytological analysis of peripheral blood from patient 1 with primary T-cell lymphoma of the thyroid gland with leukemic manifestation. (A) Cytomorphology of the lymphoma cell in the peripheral blood (Wright-Giemsa, original magnification x1000). (B) Ultrastructural morphology of the lymphoma cell in the peripheral blood. (C) The tumor cells surround and partially infiltrate thyroid follicles (stained with hematoxylin and eosin; x40). (D) Small to medium-sized lymphoma cells showing marked nuclear irregularity and rare mitoses associated with lymphoepithelial lesions in thyroid follicles. The lymphoma cells strongly express CD4 (x400) (E), CXCR3 (x200) (F) and CCR5 (x400) (G), but not L26 (x200) (H) and ST1 (x400) (I).

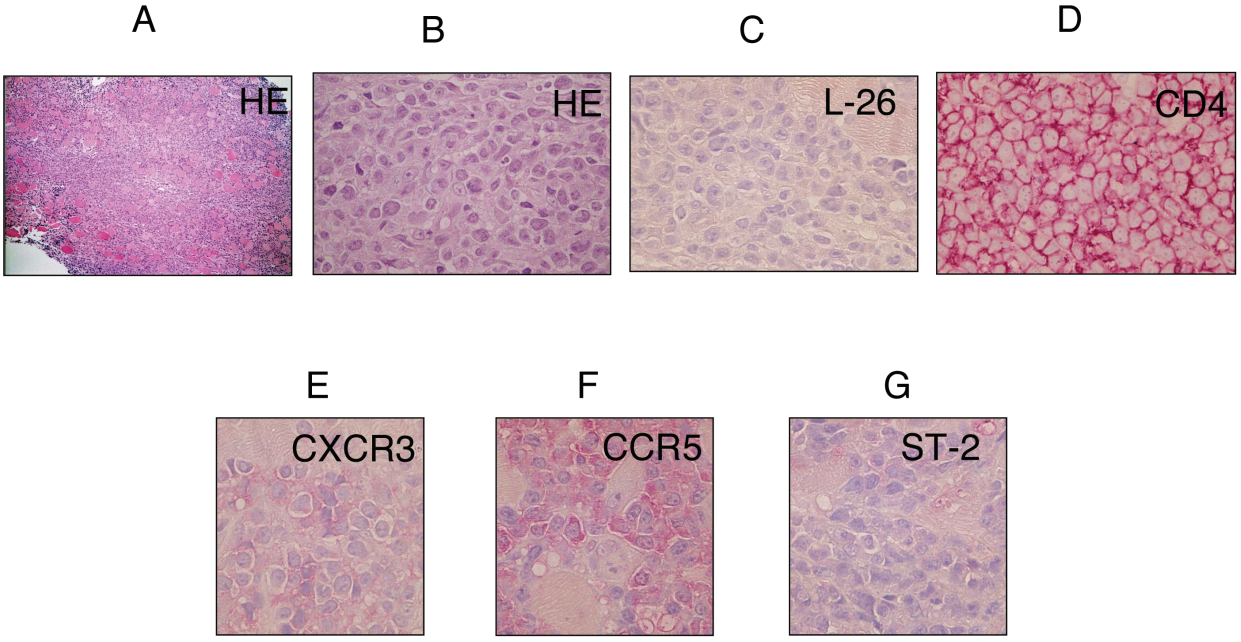

Figure 2. Histological analysis of a thyroid-gland biopsy sample and cytological analysis of peripheral blood from patient 2 with primary T-cell lymphoma of the thyroid gland. (A) The tumor cells infiltrate muscle without thyroid a structure (stained with hematoxylin and eosin; x40). (B) Large lymphoma cells showing some nuclear irregularity and occasional mitoses. The lymphoma cells strongly express CD4 (x400) (D), CXCR3 (x400) (E) and CCR5 (x400) (F), but not L26 (x400) (C) and ST1 (x400) (G).

anti-thyroid antibody. Pathology and stage of the lymphoma, and disease course varied. Immunophenotyping revealed that in one case, the lymphoma was of γδT-cell type.[7] Phenotypical findings in the other cases were distinct especially for CD4. All of the five patients analyzed for CD4 expression were positive for the antigen, irrespective of cell size or clinical course. Interestingly, both of the cases with $CD4^+$ small cell infiltration, including case 1 in this study, showed a lymphoepithelial lesion, resembling MALT-B lymphoma. Among five $CD4^+$ thyroid T-cell lymphomas, two examined for chemokine receptors had an apparent Th1 phenotype with $CXCR3^+$, $CCR5^+$ and ST-2^-.[13] In one case with leukemic manifestation, the cells were $CCR7^+$, $CCR4^-$, further supporting the phenotype. These findings in rare PTCL of the thyroid raise the possibility of a distinct clinicopathlogical disease entity, that is, primary T-cell lymphoma of the thyroid gland with chemokine receptors of Th1 phenotype complicating autoimmune thyroiditis.

The classification of peripheral T-cell lymphoma remains to be clarified.[1] Particularly, the unspecified type is considered a heterogeneous category. Recently, using the expression pattern of chemokine receptors, Th1-associated CXCR3 and CCR5 and the Th2-associated marker ST2(L), the PTCL lymphoma, unspecified, could be classified as functional (Th1/ Th2 phenotype; positive for at least one antigen) or non-functional (Th0 phenotype; all negative) with prognostic significance.[13] All cases excluding one γδT-cell lymphoma in Table 1 could be classified as PTCL lymphoma, unspecified.[1] Among them the disease course was diverse as mentioned above, and was apparently associated with the size of the lymphoma cells. Chronic inflammation at various extranodal sites could cause MALT lymphoma of B-cell type.[3] However, T-cell lymphoma has been reportedly rare at each site. Further phenotypical studies on chemokine receptors are necessary for extranodal lymphomas not only at the thyroid but also at other sites to evaluate the possible disease entity of MALT Th1-lymphoma associated with chronic inflammation.

Autoimmune thyroiditis is associated with a dysfunction of suppressor T cells. This defect allows the overgrowth of Th1 cells, which in turn activate the B cells in the thyroid to produce anti-thyroid antibodies.[2] Recent studies have implicated different chemokines and their receptors in the pathogenesis, including migration pattern of lymphocytes, of different inflammatory diseases including autoimmune thyroid diseases (AITDs).[2] Most infiltrating cells in AITDs are $CD3^+$, $CD4^+$ T cells with Th1-type chemokine receptors such as CXCR3 and CCR5.[2,14] It is possible that chronic stimulation of the CD4 Th1 cells might lead to the development of malignant clones of themselves like MALT-B-lymphoma. This may explain the development of the PTCL with Th1 phenotype in our cases. However, in the present study, a functional analysis such as the measurement of cytokine levels in each case was difficult. Furthermore, the reason for the much higher frequency of MALT-B-lymphomas than PTCL as extranodal lymphomas following chronic inflamation remains unknown.

To our knowledge, the two cases in our study are the first report of primary T-cell lymphoma of the thyroid gland with chemokine receptors of Th1 phenotype complicating autoimmune thyroiditis.

Table 1. Cases with primary T-cell lymphoma of the thyroid gland

patient No.	age/gender	thyroid function	anty-thyroid antibody	pathology	phenotype	stage	survival	reference
1	72/M	normal	+	small to medium, LE (+)	CD4+, 7-	IE	12M/alive	12
2	63/F	hypo	+	diffuse large	CD45RO+, 20-	IIE	36M/alive	11
3	66/F	hypo	+	diffuse	CD3+	unknown	2week/dead*	10
4	39/F	no_mal	-	small to large	CD30+, 3-, 4 5 RO+	IIA	12M.alive	8
5	65/M	norma	unknown	small	CD45RO+, 30-, 20-	IE	11M/dead	9
6	59/F	hypo	unknown	diffuse large	CD3+, 4-, 8-, TCR γ δ +	IIA	20M/alive	7
7	64/F	hypo	unknown	diffuse medium to large	CD3+, 4+,8-, 25+, TCR α β +	unknown	2M/alive	6
8	57/F	normal	+	unknown	CD4+, 8-, 25-, TCR α β +	IV	unknown	5
9	79/F	normal	-	diffuse medium to large	CD2+, CD4+	unknown	on therapy	4
10	61/M	norma	+	small to mediuium, LE (+)	CD4+, 8-, 25-, TCR α β +	IV	28M/alive	case 1 in this sutudy
11	69/M	hypo	+	diffuse large	CD4+, 8-, 25-, TCR α β +	IIE	5M/dead	case 2 in this sutudy

LE indicates lymphoepithelial lesion.
**: because of acute myocardial infarction not associated with lymphoma*

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Masao Tomonaga: Provided guidance for the study design, edited the manuscript

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