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ORIGINAL PAPER

MALT Type Lymphoma Demonstrating Prominent Plasma Cell Differentiation Resembling Fibrous Variant of Hashimoto's Thyroiditis: a Three Case Report

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Abstract Fibrous variant of Hashimoto's thyroiditis (HT) is characterized by marked fibrous replacement of one third or more of the thyroid parenchyma. We present here three cases of mucosa associated lymphoid tissue (MALT) type lymphoma demonstrating prominent plasma cell differentiation resembling fibrous variant of HT. Histologically, thyroid structures were disturbed by a diffuse and focally nodular infiltration by mature plasma cells and cells with plasma cell differentiation against a background of prominent hyalinosis. In addition, scattered centrocyte-like (CCL) cells and lymphoepithelial lesions were observed in all three lesions. A portion of the resected specimens in all three cases exhibited HT. However, immunohistochemical study demonstrated that the plasma cells and CCL-cells of these three lesions had monotypic intracytoplasmic kappa light chain. Moreover, these three lesions demonstrated a clonal band on polymerase chain reaction assay for the immunoglobulin heavy chain gene. To avoid underdiagnosis, we emphasize that careful attention should be paid to these immunological features as well as to morphological findings.

Keywords MALT type lymphoma · Thyroid gland · Fibrous variant · Hashimoto's thyroiditis · Immunohistochemistry

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Introduction

In common with other sites where marginal zone B-cell lymphoma (MZBL) of mucosa-associated lymphoid tissue (MALT) type, the thyroid gland is devoid of native lymphoid tissue. Lymphoid tissue acquired in the course of Hashimoto's thyroiditis (HT) [1, 2].

Histologically, HT is characterized by the presence of B-cell follicles, infiltration of thyroid epithelium by B-cells and plasma cell differentiation [2]. These histological characteristics of HT are similar to thyroid gland MALT lymphoma including follicular colonization and lymphoepithelial lesions (LeLs) [1, 2]. Moreover, in comparison with other MALT type lymphomas, plasma cell differentiation is more prominent in thyroid MALT type lymphoma [2]. As a result, CCL-cells were obscured by numerous mature plasma cells. Fibrous variant of HT is characterized by a marked fibrous replacement of one third or more of the thyroid parenchyma [3, 4]. Occasionally, prominent fibrosis, which is one of the characteristic morphological findings of the fibrous variant of HT, is associated with thyroid gland MALT lymphoma [3–5]. We present here three cases of MALT type lymphoma resembling fibrous variant of HT.

Materials and Methods

Three cases were collected from 53 cases of surgically treated HT managed by one of the authors (M.K) between 1983 and 2007. Both the clinical findings and paraffin blocks were available for all three cases. The tissue specimens were fixed in formalin solution, routinely processed and embedded in paraffin. For light microscopic examination, the sections were stained with hematoxylin-eosin (HE).

Immunohistochemical studies were performed using the Ventana automated (BenchMarkTM) stainer according to the manufacturer's instructions. The panel of antibodies included human immunoglobulin light chains (kappa and lambda) (Novocastra, Newcastle, UK), PS-1 (CD3; Immunotech, Marseille, France), 4C7 (CD5; Novocastra), 56C6 (CD10; Novocastra), L26 (CD20; Dako A/S, Glostrup, Denmark), 1B12 (CD 23; Novocastra), DFT-1 (CD43; Novocastra), 1B16 (CD56; Novocastra), 5A4 (p80; Novocastra), SP4 (Cyclin D1; Nichirei Co., Tokyo, Japan), 124 (bcl-2; Dako), AE1/3 (cytokeratin; Dako), HHF35 (muscle actin antibody; Nichirei) and 137B1 (human herpes virus type-8, Novocastra). Sections with known reactivity for the antibodies assayed served as positive controls and the sections treated with normal rabbit- and mouse serum served as negative controls.

In situ hybridization (ISH) with Epstein-Barr virus (EBV)-encoded small RNA (EBER) oligonucleotides was performed to test for the presence of EBV small RNA in formalin-fixed paraffin-embedded sections using a Ventana automated (BenchMarkTM) stainer.

Paraffin-embedded tissues from the operatively resected specimen were prepared for polymerase chain reaction (PCR), and the rearranged immunoglobulin heavy-chain (IgH) genes were amplified using the seminested PCR method as described by Wan et al. [6].

Results

Clinical Findings

Clinical findings were summarized in the Table 1. There was no M-protein in any of the three cases during the course of disease. All three cases underwent thyroidectomy because an association with malignant tumor was suspected.

Pathological, Immunohistological and EBV Findings

The three patients showed essentially similar macroscopic, histological, immunohistochemical and EBV findings. The cut surface showed a fleshy and nodular appearance (Fig. 1a). Histogically, on low power field, there was extensive replacement of the thyroid parenchyma by fibrous tissue, with a broad band of connective tissue, often hyalinized, sparing zone of degenerative thyroid parenchyma (Fig. 1b). A few remnants of residual lymphoid follicles were also noted (Fig. 1b).

On high power field, thyroid structures were disturbed by a diffuse and focally nodular infiltration of mature plasma cells and cells with plasma cell differentiation against a background of prominent hyalinosis (Fig. 1c). However, there were no intranuclear pseudoinclusions (Dutcher bodies) observed in the plasma cells. Scattered small- to- medium lymphocytes and histiocytes were also intermingled with plasma cells. In all three lesions, medium-sized lymphocytes had round or slightly indented nuclei with small conspicuous nucleoli and a moderate amount of clear cytoplasm (centrocyte-like cells; CCL-cells) (Fig. 1d). In all three cases, CCL-cells, cells with plasma cell differentiation and mature plasma cells in variably sized nests infiltrated within the thyroid follicles (LeLs) (Fig. 1d). A portion of the resected specimens in all three cases exhibited HT including lymphoplasmacytic infiltration with the formation of germinal centers, destruction of the normal thyroid follicular architecture, Hürthle cell changes and squamous metaplasia.

Immunohistochemical study demonstrated that the plasma cells were CD20− and had a monotypic nature of the intracytoplasmic immunoglobulin in all three cases (cytoplasmic kappa/lambda ratio of more than 10:1) (Figs. 2a and b) [7]. Moreover, a portion of the CCL-cells had monotypic intracytoplasmic kappa light chain (Figs. 2a and b). CCL-cells were CD5−, CD10−, CD20+, CD23−, CD43−, Cyclin D1−. There were no human herpes virus type 8+ B-cells in any of the three lesions. There were no CD56+ plasma cells in any of the three lesions. CD23 immunostain demonstrated a few residual follicular

Table 1 Summary of clinical findings

	Age/ gender	Presenting symptom	Duration (months)	Thyroid function	Antithyroid antibody	Size (cm)	Initial therapy	Lymph node	Follow-up
1	50/F	Diffuse goiter	8	Euthyroid	Positive	9	Total thyroidectomy	Negative	180 months alive
2	46/F	Diffuse goitor	264	Hypothyroid	Positive	10	Right thyroidectomy	Negative	84 months alive
3	66/F	Diffuse goitor	81	Euthyroid	Positive	5.9	Left thyroidectomy	Not available	3 months alive

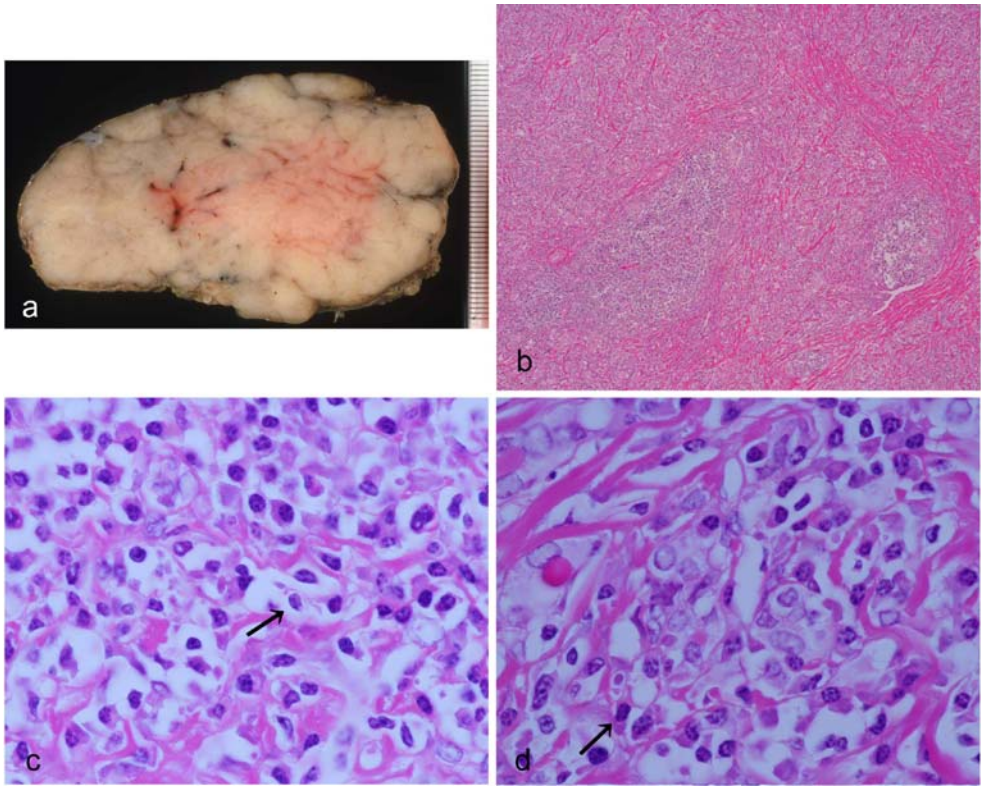

Fig. 1 **a** The cut surface was fleshy and had a nodular appearance. Case 2. **b** Low-power field of the resected specimen demonstrated that there was extensive replacement of the thyroid parenchyma by fibrous tissue, with a broad band of connective tissue, often hyalinized, and a sparing zone of degenerative thyroid parenchyma. A few remnants of residual lymphoid follicles were also noted. Case 2. HE×10. **c** High-power field of the resected specimen demonstrated diffuse infiltration by mature plasma cells and cells with plasma cell differentiation and a few CCL-cells (*arrow*) against a background of prominent hyalinosis. Case 2. HE×250. **d** High-power field of the resected specimen demonstrated numerous mature plasma cells and a few CCL-cells (*arrow*) infiltrated the thyroid gland acini forming a LeL of MALT ball pattern. Case 2. HE×250

dendritic cell networks colonized by the neoplastic plasma cells and CCL-cells (Fig. 2c). LeLs were also highlighted by cytokeratin immunostaining (Fig. 2d). There were no muscle actin and p80+ spindle cells in any of the three lesions.

There was no Epstein-Barr virus (EBV)-encoded small RNA (EBER) positive cells in any of the three lesions.

Genotypic Findings

PCR assay for IgH gene demonstrated a clonal band in all three cases.

Discussion

It has been said that in comparison with other MALT type lymphomas, plasma cell differentiation is more prominent in thyroid MALT type lymphoma [2]. In the three lesions reported here, a few CCL-cells contained monotypic intracytoplasmic kappa light chain. Moreover, immunostain highlighted LeLs and remnants of the follicular dendritic cell network colonized by neoplastic plasma cells and CCL-cells. The present three cases under discussion may be MZBCL of the MALT type showing prominent plasma cell differentiation [2, 8].

The present three lesions should be differentiated from various benign and malignant lymphoproliferative lesions containing numerous plasma cells that affect the thyroid gland [9]. Among these, the fibrous variant of HT appears to be the most important lesion in the differential diagnosis [3, 4]. Occasionally, the fibrous variant of HT contained numerous mature plasma cells [4]. Moreover, kappa-light chain-positive plasma cells were dominant in the fibrous variant of HT as well as in these three lesions [4]. Indeed, the initial diagnosis of all three of the present cases was HT with heavy lymphoplasmacytic infiltration and prominent sclerosis.

Inflammatory pseudotumor of plasma cell variant (plasma cell granuloma; PCG appears to be the most important lesion in the differential diagnosis [9–13]. PCG is a non-neoplastic proliferation of plasma cells within a fibrous stroma with unknown etiology. PCG of the thyroid gland is very rare [9, 12, 13]. However, PCG of the thyroid gland is occasionally associated with HT [12, 13]. Histologically, there is a diffuse and focally nodular infiltration of numerous mature plasma cells intermixed with lymphocytes and surrounded by fibrous tissue [12, 13]. Moreover, squamous metaplasia with lymphoplasmacytic infiltration somewhat resembling LeL in MALT type lymphoma was noted. Histomorphological findings of the present three cases were similar to those of PCG associated with HT. However, there were no muscle actin and p80+ cells in any of the three lesions [10, 11].

Immunohistochemical study demonstrated the polytypic nature of plasma cells in fibrous variant of HT and PCG.

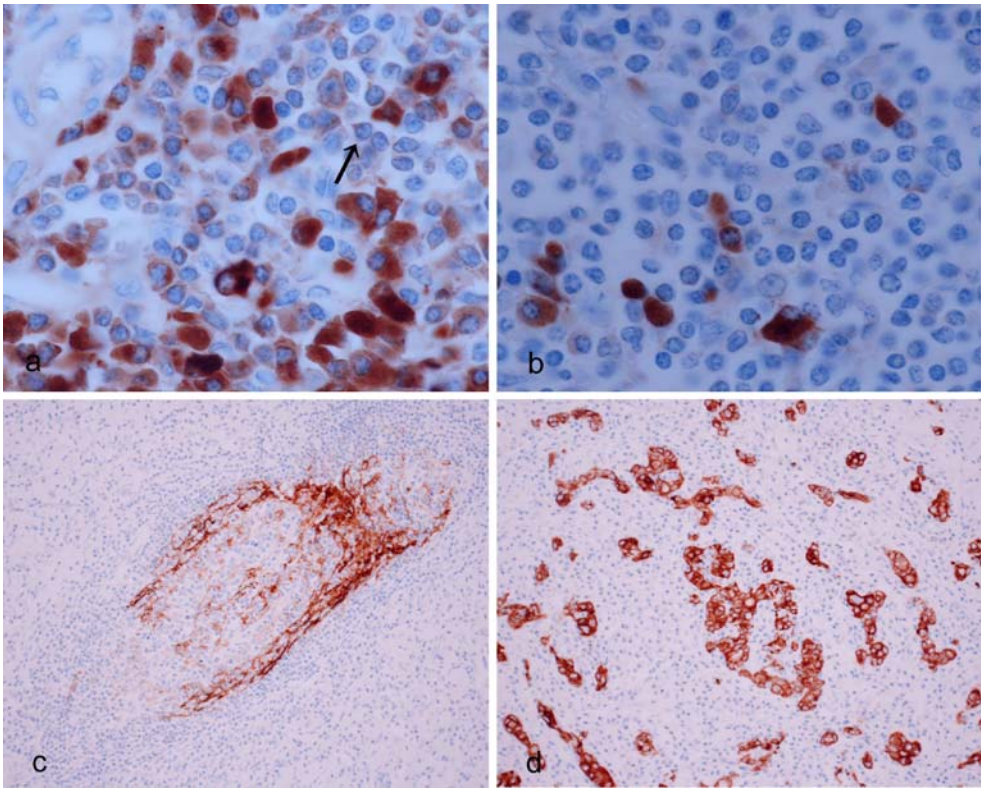

Fig. 2 **a** Immunohistochemical study demonstrated that numerous plasma cells and a portion of CCL-cells (arrow) were kappa light chain positive. Case 2×250. **b** Cytoplasmic Immunohistochemical study demonstrated that a few plasma cells were lambda light chain positive, but CCL-cells were lambda light chain negative. Case 2×250. **c** CD23 immunostain demonstrated a few residual follicular dendritic cell network colonized by the neoplastic plasma cells and CCL-cells. Case 2×50. **d** LeLs were highlighted by cytokeratin immunostaining. Case 1×50

However, plasma cells and CCL-cells of all three lesions reported here demonstrated monotypic intracytoplasmic kappa light chain. Moreover, all three lesions demonstrated a clonal band on PCR assay for the IgH gene.

Thyroid gland involvement of multiple myeloma is ruled out by laboratory and clinical examination [9]. Moreover, there were no CD56+ plasma cells in any of the three lesions [14].

Extramedullary plasmacytoma is another differential diagnostic problem. However, there were no CD20+ tumor cells in the extramedullary plasmacytoma, whereas present three lesions contained a few CD20+ CCL-cells [14].

Rarely, low-grade B-cell lymphoma including small lymphocytic lymphoma, follicular center cell lymphoma and mantle cell lymphoma show prominent plasma cell differentiation [15, 16]. Tumor cells of small lymphocytic B-cell lymphoma express CD5 and CD23 antigens [15]. Follicular center cell lymphoma of Grade 1 or Grade 2 usually CD10+ [15]. Most of the mantle cell lymphomas were positive for CD5 and cyclinD1 [16]. However, CCL-cells were CD5−, CD10−, CD23−, Cyclin D1− in all three lesions.

Unfortunately, information on staging was incomplete in the present series because the initial pathological diagnosis was fibrous variant of HT. However, in the two cases (nos. 1 and 2) in which adequate follow-up was available, there were no evidence of recurrence 180 and 84 months after simple thyroidectomy, respectively. The reason for the excellent prognosis in these cases appears related to the absence of spread beyond the thyroid gland and low-grade morphology as previous reported [1, 2, 5].

In conclusion, we report here, surgically resected specimens of three thyroid gland MALT type lymphomas that resembled fibrous variant of HT. Recognition of the monotypic intracytoplasmic globulin positive CCL-cells appear to the diagnostic clue of these three cases. To avoid underdiagnosis, we emphasize that careful attention should be paid to the immunological features as well as to morphological findings.

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