

Hashimoto's Thyroiditis in HTLV-I Carriers

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We describe two HTLV-I virus carriers who have biopsy-proven Hashimoto's thyroiditis. The first patient, a 64-year-old female, has had goiter and hypothyroidism since the age of 56. The second patient, a 66-year-old male, developed hyperthyroidism and goiter at the age of 44, but at present he is hypothyroid. Both patients are positive for anti-thyroid antibodies and anti-HTLV-I virus antibody. Findings of the thyroid biopsy specimens were consistent with Hashimoto's thyroiditis. These data suggest that Hashimoto's thyroiditis develops in HTLV-I carriers who have no clinical evidence of HAM/TSP. (Internal Medicine 21: 1213-1216, 1992)

Key words: retrovirus, chronic thyroiditis, auto-immune disease, anti-thyroid antibody

Introduction

HTLV-I virus infection, either in asymptomatic carriers or in patients who have developed HTLV-I-associated myelopathy (HAM/TSP) (1, 2), is not infrequently associated with a variety of chronic inflammatory disorders, mostly with autoimmune disease. We previously reported two HAM/TSP patients who also had Hashimoto's thyroiditis (3, 4) and suggested a possible role of HTLV-I virus infection in the pathogenesis of Hashimoto's thyroiditis.

We report here two HTLV-I carriers who have no clinical evidence of HAM/TSP but developed biopsy-proven Hashimoto's thyroiditis, and emphasize the relationship between HTLV-I infection and Hashimoto's thyroiditis.

Case Reports

Case 1

A 64-year-old female, born in Shimizu, Kochi Prefecture, Japan, first noted weight loss and goiter at the age of 56. Initial evaluation showed hypothyroidism but treatment was not instituted. At the age of 63, she noted further enlargement of the thyroid and was diagnosed as having Hashimoto's thyroiditis. Replacement therapy was started with subsequent normalization of thyroid function and a decrease in the size of goiter. She was referred to this hospital because of the presence of anti-

HTLV-I virus antibody in her serum. Her family history was unremarkable.

She was well nourished. Her pulse rate was 84/min, and blood pressure was 146/90 mmHg. The thyroid gland was elastic, hard and enlarged: right lobe, 7.5 × 3.0 cm; left lobe, 7.0 × 3.4 cm.

Her chest and abdomen were normal. Neurologic examination showed no abnormalities.

The erythrocyte sedimentation rate was 20 mm/hr. The hemoglobin content was 13.0 g/dl, the red blood cell count $390 \times 10^4/\mu\text{l}$, the white blood cell count 4,000/ μl , and the platelet count $19 \times 10^4/\mu\text{l}$. The differential of the white blood cells revealed bands 5.0%, segmented neutrophils 54.0%, eosinophils 1.0%, monocytes 3.0%, lymphocytes 34.0% and atypical lymphocytes 3.0%. Surface marker studies of peripheral lymphocytes showed CD3(+), 73.6% (normal, 58-84%); CD4(+), 57.9% (25-56%); CD8(+), 17.4% (17-44%); Leu7(+), 9.5% (6-43%); Leu 11(+), 6.4% (5-37%); and B-1 (+), 16.1% (5-20%). The electrophoretic pattern of serum proteins was normal and immunoglobulin levels were also normal: IgG 1,516 mg/dl, IgA 175 mg/dl, and IgM 74 mg/dl.

The serum free T4 level was 0.49 ng/dl (normal, 0.85-2.15 ng/ml), free T3 level 3.43 pg/ml (normal, 3.0-5.8 pg/ml) and TSH level 11.12 $\mu\text{U}/\text{ml}$ (normal, 0.4-5.3 $\mu\text{U}/\text{ml}$). These values indicate hypothyroidism. The value in a thyroid test was less than 1:100 (normal, <1:100) but that in a microsome test was 1:102,400

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(normal, <1:100). The level of thyroid stimulating antibody (TSAb) was 100% (normal, <145%), anti-thyroglobulin antibody 19.9 ng/ml (normal, <40.0 ng/ml), and TBII 5.6% (normal, <15%). The serum anti-HTLV-I antibody titer measured by a particle agglutination method was 1:512 (normal, <1:100). Western blot analysis revealed p19 and p24 bands of HTLV-I virus antibody. A lymphocyte blast formation test showed 253 S.I. (positive, <200 S.I.) for Con-A, 253 S.I. (positive, <200 S.I.) for PHA, and 187 S.I. (positive, <200 S.I.) for PWM.

Ultrasonography of the thyroid showed generalized low echogenicity and three echogenic nodules (2 in the right lobe and 1 in the left lobe) each of which was surrounded by a hypoechoic halo. A biopsy specimen of the thyroid revealed marked lymphocytic infiltration, atrophy of thyroid follicles and interstitial fibrosis. These findings indicate Hashimoto's thyroiditis (Fig. 1a). Surface markers of infiltrating lymphocytes were studied with a panel of anti-sera (DAKO PATS) and found to be positive for the following markers: L-26, MB-1, LN1, and LN2 of B-cell lineage; UCHL-1, CD3, CD4, CD8, and MT-1 of T-cell lineage.

This case was diagnosed as Hashimoto's thyroiditis on the basis of positive antithyroid antibodies, hypothyroidism and thyroid histology.

Case 2

A 66-year-old male, born in Naruto City, Tokushima Prefecture, Japan, suffered from palpitations and increased sweating, and was found to have goiter and hyperthyroidism at the age of 44. Radioisotope therapy improved his symptoms and decreased the size of the thyroid. At the age of 58, hyperlipidemia was noted. At the age of 66, he was found to be positive for serum anti-HTLV-I antibody and was referred to our hospital. His family history was unremarkable. He had suffered a fracture of the right foot at the age of 41, and received a transfusion of 600 ml of whole blood.

His vital signs were normal. His thyroid was slightly enlarged, but no obvious nodules were noted. Neurological examination showed no abnormality.

His hemoglobin was 16.1 g/dl, red blood cell count $475 \times 10^4/\mu\text{l}$, and white blood cell count $4,300/\mu\text{l}$ with a normal differential, and his platelet count was $23.7 \times 10^4/\mu\text{l}$. His lymphocyte subpopulations consisted of 76.6% CD3(+), 40.3% CD4(+), and 36.4% CD8(+) with a CD4/CD8 ratio of 1.10. His serum cholesterol level was 208 mg/dl, triglyceride level 87 mg/dl and glucose level 87 mg/dl. Serum protein and immunoglobulin levels were normal. His serum TSH level was 6.97 $\mu\text{U/ml}$, T4 8.5 $\mu\text{g/dl}$, T3 1.17 ng/ml, free T4 0.78 ng/dl, and free T3 3.47 pg/ml. A thyroid test gave a value of 1:100, and a microsome test a value of 1:200. No TSAb, TBII, or antibodies against T3 and T4 were detected. Ultrasonography of the thyroid revealed no apparent enlargement,

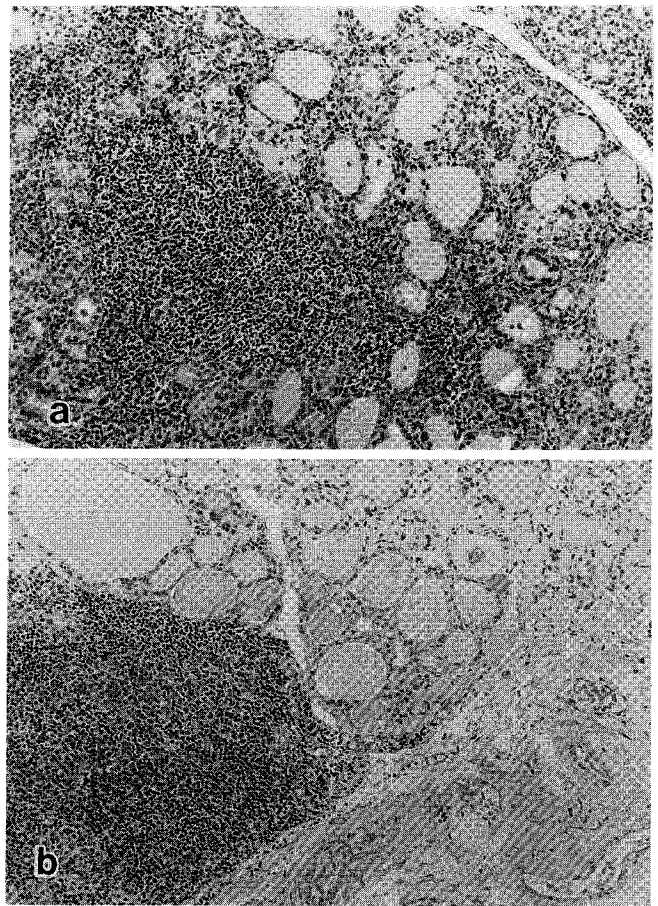


Fig. 1. Pathology of the thyroid. a) Marked lymphocyte infiltration, atrophy of the follicles and destruction of the epithelial cells are seen (case 1). b) Formation of lymphoid follicles, destruction of thyroid follicles, and marked interstitial fibrosis are seen (case 2) (a, b: HE stain, $\times 150$)

but showed an irregular surface, non homogeneous echogenicity inside the gland, and a tiny hypoechoic region. The CT and radioscintigram of the thyroid and results on ^{131}I uptake by the thyroid were normal. The serum anti-HTLV-I antibody titer was 1:512. Western blot analysis revealed bands of p19, p24, gp46, and p53. Lymphocyte blast formation was normal with PHA, Con-A, and PWM. A biopsy specimen of the right lobe of the thyroid revealed lymphoid follicles with a germinal center, epithelial cells with large nuclei and granular oxyphilic cytoplasm, degenerative follicles, fibrosis and lymphocyte infiltration into the interstitium (Fig. 1b). These lymphocytes were positive for L-26, MB-1, LN1, LN2, UCHL-2, CD3, CD4, CD8, and MT-1.

The patient was previously treated with radioisotope for hyperthyroidism, but at present he is diagnosed as having Hashimoto's thyroiditis, because of negative TBII and TSAb and thyroid pathology compatible with Hashimoto's thyroiditis.

The polymerase chain reaction (PCR) (5) to detect HTLV-I proviral DNA in peripheral blood leukocytes

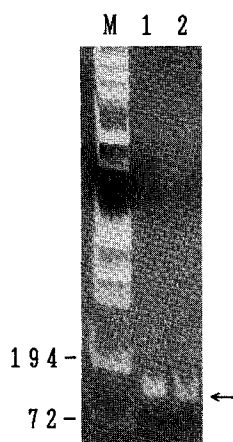


Fig. 2. Amplification of HTLV-I proviral DNA by PCR. PCR-amplified DNAs of 119bp (arrow) were obtained from both patients. Primers corresponding to nucleotide numbers 3365–3384 and complementary to 3465–3483 were used for the pol region of HTLV-I proviral DNA. M: markers; \emptyset X174/Hae III digest, lane 1: case 1, lane 2: case 2.

from both patients revealed amplified PCR products of 119 bp (Fig. 2).

Discussion

HTLV-I virus is not only the cause of human T cell leukemia/lymphoma, but is also etiologically related to the development of HAM/TSP (1, 2). Moreover, chronic inflammatory disorders such as chronic inflammatory arthropathy (6) and pulmonary alveolitis (7–9), and autoimmune disorders including uveitis (10, 11), Sjögren's syndrome (12), Harada's disease (13) and polymyositis (14–16) have been shown to be associated with HTLV-I infection.

Hashimoto's thyroiditis, an autoimmune chronic thyroiditis, has been documented previously in three patients with HAM/TSP: one patient by Fukazawa et al (17) and two by us (3). Another patient reported by Tanaka et al (16) may also have Hashimoto's thyroiditis because this patient has a goiter with fibrosis demonstrated by biopsy. If there is a causal relationship between HTLV-I virus infection and Hashimoto's thyroiditis, as suggested by these previous case reports, one would expect that some HTLV-I carriers should also develop Hashimoto's thyroiditis. To our knowledge, this is the first report of such cases.

Although there is no direct evidence, several indirect lines of evidence indicate a causal relationship between HTLV-I infection and Hashimoto's thyroiditis. First, HTLV-I infection results in predisposition to autoimmune disorders: 1) HAM/TSP is presumably an autoimmune disorder triggered by HTLV-I infection, 2) association of autoimmune disorders with HTLV-I

infection is apparently not infrequent (3, 6–16), and 3) in animal experiments, Sjögren's syndrome-like histology was found in the salivary gland of HTLV-I tax transgenic mice (18), suggesting a relation between HTLV-I infection and this particular autoimmune disorder. Second, a high frequency of Hashimoto's thyroiditis is found in HTLV-I-infected individuals (19). Third, HTLV-I virus may infect thyroid cells: 1) HTLV-I virus has been demonstrated in cells other than lymphocytes; i.e., synovial cells of patients with HTLV-I associated arthropathy (20) and in brain tissue of patients with HAM/TSP (21), 2) an HIV-related gene was found in thyroid follicular cells of patients with Graves' disease (22), 3) retrovirus oncogene can transform thyroid epithelial cells (23), and 4) a retrovirus was found in chickens with spontaneous autoimmune thyroiditis (24).

From these findings, it is possible that HTLV-I virus may infect thyroid epithelial cells, modify the antigenicity of cell proteins, and eventually elicit an autoimmune response against the thyroid. Cross-reaction of anti-HTLV-I antibody with thyroid proteins, class II antigen expression induced by cytokines, dysfunction of the host immune system, genetically determined susceptibility such as that of the HLA type (25), or a combination of these may also be involved in the development of Hashimoto's thyroiditis. However, HTLV-I virus is obviously not the sole cause of Hashimoto's thyroiditis, because HTLV-I antibody is not found in most cases. In HTLV-I sero-negative patients, chronic infection of the thyroid with some other virus(es) may trigger the autoimmune response.

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