

Caso
clinico

Case
report

Herpes virus associato a tiroidite di Hashimoto

Human herpes virus associated with Hashimoto's thyroiditis

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INTRODUCTION

Hashimoto's thyroiditis (HT), or chronic lymphocytic thyroiditis, is the most common autoimmune disorder, with an increasing prevalence in the last decades, more frequent in the female gender and in adults [1, 2]. This disease is characterized by a large lymphocytic infiltrate of the thyroid gland, with T-helper lymphocytes of the Th1 type, cytotoxic T lymphocytes, natural killer cells (NK), monocytes, plasma cells and lymphoid centers [2]. The pathology features change according to the disease phases [3, 4]. In late phases, the gland exhibits fibrous aspect, with reduced thyroid epithelial cell number and increased presence of fibroblasts [3]. The lymphoid infiltrate is accompanied by the production of auto-antibodies against specific thyroid antigens, including thyroglobulin (TG) and thyroperoxidase (TPO). The pathogenesis of HT is linked to both cellular- and antibody-mediated immunity. Besides anti-thyroid auto-antibodies, the lymphoid infiltrate release in the thyroid various cytokines, including interferon- γ , interleukin-1 and -6 [5-7]. Although different factors have been proposed to trigger HT, the primary etiology is still unknown. The high familiarity and the higher prevalence in the female gender, indicate that genetic factors, along with environmental factors and occurring diseases are important for the development of HT. Within occurring dis-

eases, viral infectious have been charged for triggering a number of autoimmune diseases, including thyroid autoimmunity. Among these, cytomegalovirus, EBV and herpes virus (HSV) infections are those most likely involved [8, 9]. Patients with Graves' disease display a higher frequency of EBV-infected B cells, and patients with anti-thyroid antibodies frequently have also elevated antibody titers against EBV antigens [10, 11]. Here, we present 3 cases of subjects with HT whose onset is concurrent with the first appearance of HSV infection.

PATIENTS AND METHODS

Serum concentrations of FT4, FT3, and TSH were determined by electrochemiluminescent assay using commercially available kits (Roche, Mannheim, Germany). The normal ranges for serum FT4 and FT3 were 0.8-1.9 ng/dl and 1.8-4.2 pg/ml, respectively. The normal range for serum TSH was 0.27-4.0 μ IU/ml. TG-Ab and TPO-Ab were determined by a RIA kit (B.R.A.H.M.S. Diagnostica, Berlin, Germany). TPO-Ab and TG-Ab <60 U/ml were considered negative. A enzyme immunoassay and immunofluorescence kit were used for IgG and IgM were used to quantify anti-HSV IgG and IgM antibodies. Thyroid ultrasonography was performed using a 7.5- to 10-MHz linear transducer (Esaote, Genoa, Italy). All patients showed palpable nodular enlargement of the thyroid and underwent to fine-needle cytology (FNC) for a further confirmation of the HT diagnoses. FNC was performed under US control, as previously described [12-14].

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RESULTS

Patient 1

A 32-year-old woman presented to our attention with rapid heartbeat (80 beats a minute) and slight pain at palpation in the thyroid region. The thyroid gland was slightly enlarged at palpation. She referred weight loss (6 kg in 3 months), anxiety and irritability, and difficulty sleeping. She referred also to have had herpes labialis for the first time 3 months before, accompanied by moderate fever (<38°C). Ultrasound thyroid examination revealed a hypo-echoic micronodular pattern. IgM and IgG antibodies to *Herpes simplex* virus were positive. TSH and thyroid hormones indicated a moderate hyperthyroidism and thyroid auto-antibodies were positive (Table 1).

Patient 2

A 27-year-old woman presented to our attention with tachycardia (85 beats a minute), slight pain at palpation in the thyroid region, the thyroid was moderately enlarged and irregular at palpation. She referred weight loss (4 kg in 3 months), sweating, anxiety and irritability. She referred herpes labialis for the first time 2 months before, accompanied by fever (up to 38°C). Sonographic presentation was characterized by heterogeneous echo-texture with multiple hypo-

echoic micro-spots (<1 cm of diameter). IgM and IgG antibodies to *Herpes simplex* virus were positive. TSH and thyroid hormones indicated a moderate hyperthyroidism and thyroid auto-antibodies were positive (Table 1).

Patient 3

A 57-year-old woman presented to our attention with rapid heartbeat (80 beats a minute), slight pain at palpation in the thyroid region, the thyroid was enlarged and irregular at palpation. She referred sweating, anxiety and irritability. She referred herpes labialis for the first time 6 months before. Sonographic presentation was characterized by multiple hypo-echoic nodules, with a surrounding heterogeneous echo-texture mostly hypo-echoic. Major nodules were 2.3x1.8x1.8 mm and 2.5x2.5x1.8 mm (width x length x thickness). IgG antibodies to *Herpes simplex* virus were positive, while IgM were negative. TSH and thyroid hormones indicated a subclinical hyperthyroidism and thyroid auto-antibodies were positive (Table 1). The patient was affected by type 2 insulin-dependent diabetes diagnosed 18 years before, with retinopathy, cataracts, and initial foot complications [15]. Thyroid nodules were subjected to fine needle aspiration cytology. One nodule was classified as indeterminate lesion, negative for RET/PTC and BRAF mutation and subjected to clinical follow-up [16-18].

Table 1 - Clinical, thyroid ultrasonographic and serological features of patients.

	Patient 1	Patient 2	Patient 3
Age (yrs)	32	27	57
HSV onset (months before observation)	3	2	6
Sonography suggestive for HT	Yes	Yes	Yes in a multinodular goiter pattern
Pain at palpation of the thyroid region	Yes	Yes	Yes
anti-HSV IgM (negative <10)	17.6	21.2	8.3
anti-HSV IgG (negative <0.9)	48.2	57.2	54.4
TSH (IU/mL) 0.27-4.0	0.02	0.03	0.08
FT3 (ng/mL) 2.9-5.8	6.8	7.2	5.7
FT4 (ng/mL) 7.8-14.2	15.4	12.3	9.8
TG-Ab <60	183	329	41
TPO-Ab <60	3455	3041	4685
HT, Hashimoto's thyroiditis; TG, thyroglobulin; TPO, thyroperoxidase.			

DISCUSSION

Usually, HT begins as a gradual enlargement of the thyroid gland with a progressive development of hypothyroidism. It is often discovered by the patient, who finds symptoms of hypo/hyperthyroidism and a vague discomfort in the neck.

Hashitoxicosis is a transient hyperthyroidism caused by inflammation, occurring often at onset of Hashimoto's thyroiditis, characterized by an excessive release of thyroid hormone. Major clinical signs include weight loss, weakness, fatigue, intolerance to heat, sweating, hyperactivity, irritability, anxiety, loss of libido, polyuria, polydipsia, and hair loss.

Possible HT complications include papillary carcinoma (PTC) and, rarely, primary non-Hodgkin lymphoma (PTL) in addition to hypothyroidism [3, 5, 6, 12, 19-22]. Therefore a direct evaluation of diffuse or nodular thyroid enlargement in case of HT may be needed.

Fine-needle cytology (FNC) is widely used in the diagnosis of thyroid nodules, and the application of molecular techniques to FNC has dramatically increased its sensitivity, including in cases of HT with diffuse or nodular enlargement [5, 23-31].

An effective FNC diagnosis avoids useless diagnostic surgery or leads to the proper surgical treatment, when needed [32]. These advantages are enhanced in the case of HT which does not require surgical treatment, especially in elderly patients in which any surgery is generally more burdensome, complex and expensive than younger patients [32, 33].

In some cases, the onset of HT can be recognized by the occurrence of symptoms of hashitoxicosis.

The thyrotoxicosis in HT as well as in subacute thyroiditis or De Quervain's thyroiditis, is induced by leakage of intra-thyroidal hormones into the circulation caused by damage to thyroid epithelial cells from inflammation. Thyroid inflammation can be sustained by an autoimmune process, like in HT, or by a viral infection like in De Quervain's thyroiditis. Hashitoxicosis was diagnosed in the three patients reported in this study.

The presence of anti HSV IgM, the exhibition of a first-episode of cold sores few months before and the tenderness of the thyroid in patient 1

and patient 2, strongly supported an etiological role for HSV infection in the development of HT. In patient 3, a direct correlation between HSV infection and HT was less evident as only the IgG type of anti-HSV were present. However, this was an older subject with concurrent infectious diseases that can make the clinical course more complicated [34]. HSV is among the viruses known to affect the upper aerodigestive tract.

Recurrent herpes labialis is the most common clinical manifestations of first-episode HSV infection. Gingivostomatitis and pharyngitis are also common clinical manifestation of HSV infection. HSV infection has been proposed as etiologic factors of different tumors, including breast cancer, thyroid cancer and lymphomas [35].

Virus infection of thyroid cells in culture were shown to act as antigen presenting cells and therefore might be involved in autoimmunity. Induction of HLA-DR expression was shown on thyroid follicular cells infected *in vitro* by cytomegalovirus [36].

Patients with Graves' disease display a higher frequency of EBV-infected B cells secreting antibody to TSH receptor [11]. Subjects with thyroid autoimmunity have more frequently elevated antibody titers against EBV antigens [12]. Human HSV-6 DNA has been detected in HT tissue specimens, but not in tissues from other thyroid diseases such as multinodular goiter [10]. HSV has occasionally been detected in thyroid tissue of patients with thyroid autoimmunity and other diseases [37-40].

Very recently, experimental evidence supporting a role for HSV in the etiology of HT has been provided. The presence and transcriptional state of HSV-6 was demonstrated in thyroid fine needle aspirates and peripheral blood mononuclear cells from HT patients [41]. Noteworthy, thyrocytes from fine needle aspirates displayed a 100-fold higher HSV-6 DNA load compared to infiltrating lymphocytes, strongly supporting a direct thyroid infection. In conclusion, although the role of HSV in HT etiology is still a debated issue, the three cases presented in this study support the possibility that HSV infection may trigger HT.

Keywords: Hashimoto thyroiditis, autoimmune disease.

SUMMARY

Hashimoto's thyroiditis is the most frequent autoimmune disease with genetic and environmental aetiologies. Viral infections have been postulated as one of the factors that may trigger autoimmune diseases. Many studies suggest that *Herpes simplex* virus infections are involved in a variety of au-

toimmune diseases. We report the case of three patients presenting for the first time herpes labialis a few months before the onset of hashitoxicosis. Serological and clinical exams support the possible role of human herpes viruses in the aetiology of Hashimoto's thyroiditis.

RIASSUNTO

La tiroidite di Hashimoto è la più frequente malattia autoimmune, con un'etiologia genetica e ambientale. Le infezioni virali sono considerate come uno dei possibili fattori scatenanti le malattie autoimmuni. Molti studi indicano che i virus *Herpes simplex* sono coinvolti in diverse malattie autoimmuni. In questo studio

riportiamo i casi di 3 pazienti che presentavano per la prima volta herpes labiale pochi mesi prima della comparsa di hashitossicosi.

Gli esami sierologici e clinici erano in favore di un possibile ruolo degli *Herpes virus* nella eziologia della tiroidite di Hashimoto.

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