Development Of Hashimoto’s Thyroiditis After Subacute Thyroiditis: An Unusual Patient

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Dear Editor:

De Quervain’s thyroiditis (subacute thyroiditis [SAT]) is an inflammatory disorder of the thyroid that is thought to be induced by viruses in genetically predisposed individuals (1). Evidence that viral infections may cause SAT is strong, because SAT is often preceded by an upper respiratory tract infection caused by viruses such as influenza, adenovirus, Coxsackie, or less frequently Epstein-Barr and cytomegalovirus (CMV) (1). However, genetic factors, including human leukocyte antigen (HLA) haplotype, play an important role in the onset of SAT. A strong association between SAT and HLA-B35 has been found in all genetic groups (2). Reports of the development of SAT in identical twins were both heterozygous for HLA-B35, and familial occurrence of SAT in family members heterozygous for HLA-B35 provided additional evidence that this haplotype confer genetic susceptibility for the disease (3,4).

Of interest, only a few cases of an association between SAT and autoimmune thyroid disease (AITD) have been reported. Particularly, in the last two decades, five papers described seven cases of Graves’ disease (GD) occurring 4 months to 8 years after SAT (5–9). We have recently seen a patient with SAT who developed autoimmune thyroiditis (ATD) within 4 years after SAT. Roti et al. (11) reported that patients with a previous history of SAT are prone to develop iodide-induced hypothyroidism, suggesting that a persistent subtle defect in thyroid function may persist years after resolving SAT (11). In our case, however, the subclinical hypothyroidism was determined by ultrasonography (US) and fine-needle aspiration cytology (FNAC) to be evidence of HT, indicating an autoimmune etiology of the thyroid dysfunction.

A 30-year-old woman with no history of thyroid disease was seen in our out-patient clinic in September 2003 because of pain and tenderness in the anterior cervical region, low-grade fever, fatigue, and palpitations of 1 month’s duration. The neck pain was severe, aggravated by swallowing, and poorly responsive to nonsteroidal anti-inflammatory drugs (NSAIDs). Familial history revealed that HT had been diagnosed in her mother and one maternal aunt, and rheumatoid arthritis in her mother. Physical examination revealed mild tremors of the extremities, a diffuse painful goiter, and enlarged and tender cervical and submandibular lymph nodes.

Serum markers of acute inflammations were positive (erythrocyte sedimentation rate, 106 mm [normal, 0–15 mm]; C reactive protein [CRP], 17.25 mg/L [normal, 0–5 mg/L]; fibrinogen, 548 mg/L [normal, 150–350 mg/L]). Baseline chemistry, blood count, white blood cell differential, and hepatic and renal function were all within normal ranges. Serum thyrotropin (TSH) was 0.22 μIU/mL (normal range, 0.27–4.2 μIU/mL), and serum free triiodothyronine (FT3) and free thyroxine (FT4) levels were in the upper part of their normal range (FT3, 6.3 pmol/L [normal, 3.0–6.7 pmol/L]; FT4, 18.50 pmol/L [normal, 12.0–22.0 pmol/L]). Serum thyroglobulin (Tg) was markedly increased (151.2 pg/mL; normal, 0–70 pg/mL), whereas anti-thyroglobulin antibodies (TgAb), anti-peroxidase antibodies (TPOAb), and anti-microsomal antibodies (TMAb) were undetectable. The patient was found to have both IgM (40 IU/mL; normal, <15 IU/mL) and IgG (0.73 IU/mL; normal, <0.4 IU/mL) antibodies to CMV, suggesting that CMV might have caused the thyroiditis. US of the thyroid showed a diffuse enlargement and hypoechogenic structure of the gland. Thyroidal radioactive iodine uptake was markedly decreased (Fig. 1). All findings were consistent with SAT, and treatment with oral deflazacort (30 mg/d as the starting dose, gradually tapered) was prescribed. Under the corticosteroid therapy, there was a progressive resolution of symptoms and signs. Within 4 weeks, serum inflammatory indexes, TSH, FT3, and FT4 values normalized (TSH, 1.23 μIU/mL; FT3, 13.9 pmol/L; FT4, 4.5 pmol/L).

The patient returned 4 years later, complaining of fatigue and mental impairment. Serum TSH was 5.73 μIU/mL; FT3 5.02 pmol/L, and FT4 13.9 pmol/L (corresponding normal values as above). TgAb and TPOAb were negative. Thyroid US displayed the typical echographic features of the atrophic variant of HT: a decreased volume of the whole gland with a

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FIG. 1. Iodine 131 thyroid scintigraphy showing a markedly decrease uptake of the tracer throughout the gland.

diffusely, nonhomogeneous and hypoechoic pattern, with pseudo-nodular areas and an increased vascularization. FNAC of pseudo-nodular areas from both lobes demonstrated the classic features of HT (lymphocytic infiltrate and oncocytic metaplasia of the follicular cells).

HLA genotyping disclosed the following haplotype: A* 2309, A* 2909, B* 0705, B* 3508, C* 0417, C* 1502, DQA1* 0105, DQB1* 0201, DQB1* 0303, DQB1* 0501, DRB1* 0701, DRB1* 1001, DRB4* 0101. Of note, HLA B35 and HLA DR4 confer predisposing risk for SAT (2–4) and HT (10), respectively.

HT with subclinical hypothyroidism was diagnosed and levothyroxine treatment (100 µg/d) was started.

The appearance of an AITD following SAT represents a quite rare condition. Until now, only one patient with HT following SAT has been reported (10), as opposed to five cases of GD (5–9). The patient described by Papi and Ezzat (10) was a 59-year-old man who became overtly hypothyroid (TSH, 62 mUI/L) approximately 5 months after the onset of SAT. Both serum TgAb and TPOAb were present at high levels when hypothyroid, whereas they had been within normal limits during the hyperthyroid phase of SAT. Neither viral etiology of AT nor HLA studies were conducted in this patient (10).

In the five GD patients, the lag time was 4 months to 8 years (5–9). In the four patients in whom HLA typing was performed, three patients displayed a genetic predisposition to hyperthyroid GD as well as subacute thyroiditis (6–9). One patient had the HLA locus typical of SAT (B35) and one HLA locus frequent in HT (DR4). SAT preceded HT by 4 years and was probably due to a CMV infection.

Although no data are available on a direct effect of CMV on thyroid epithelial cells, it may be possible that an aberrant immune response against the thyroid gland is initiated and propagated through CMV infection in genetically predisposed individuals. This is similar to other autoimmune diseases (e.g., insulin-dependent diabetes) in which a viral infection represents an environmental contribution for triggering the clinical onset of the autoimmune disease. It has been postulated that infectious agents, like viruses, may cause autoimmunity via tissue damage, polyclonal T cell activation, and/or molecular mimicry also in AITD (12–13).

Moreover, our group has demonstrated that the Na+/I– symporter has local amino acid sequence homologies with proteins of viral origin, including human CMV (14), thus reinforcing the view that, indeed, viral infections may trigger AITD.

References


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