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Case History

Familial Occurrence of Subacute Thyroiditis Associated with Human Leukocyte Antigen-B35

Andrea B. Kramer,^{1,2} Caroline Roozendaal,² and Robin P.F. Dullaart¹

Subacute thyroiditis (SAT) is a spontaneously remitting inflammatory disorder of the thyroid, associated with human leukocyte antigen (HLA)-B35, and may be virally induced in genetically predisposed individuals. A 57-year-old Caucasian man presented with symptoms of hyperthyroidism as well as enlargement and tenderness of the thyroid. The patient had an elevated erythrocyte sedimentation rate, low thyrotropin (TSH) and elevated thyroxine and triiodothyronine levels with suppressed ¹³¹I thyroidal uptake. He was diagnosed to have SAT. In the patient's family three sisters and one brother also had had SAT, as probably did the deceased father. Because of the familial occurrence HLA-typing was performed. All affected family members were heterozygous for HLA-B35. The family members lived more than 50 miles apart in different regions of The Netherlands and had SAT at different time points between 1986 and 2002, which in combination with HLA-B35 seems to highlight the importance of genetic influences as a risk factor for the development of SAT in this family. In conclusion, the case described here represents the second familial incidence and largest family reported so far with occurrence of SAT in association with HLA-B35.

Introduction

SUBACUTE THYROIDITIS (SAT), also referred to as granulomatous or De Quervain's thyroiditis, is a spontaneously remitting inflammatory disorder of the thyroid gland (1). It is characterized by infiltration with lymphocytes and giant cells into the thyroid gland, accompanied by parenchymal destruction. Patients with subacute thyroiditis usually present with tenderness and enlargement of the thyroid gland, and hyperthyroidism sometimes followed by hypothyroidism. The disease is self-limiting and often does not require treatment. Subacute thyroiditis is an uncommon cause of permanent hypothyroidism and affects women four times more frequently than men (1).

Subacute thyroiditis is thought to be caused by a viral infection or a postviral inflammatory process. The majority of patients have a history of an upper respiratory infection shortly preceding the onset of thyroiditis. Many cases have been reported in association with Coxsackie virus, mumps, measles, adenovirus, and other viral infections (1). Thyroid autoimmunity does not appear to play a role in the disorder, but the condition is strongly associated with human leukocyte antigen (HLA)-B35 in many ethnic groups (2–5). Whatever factors initiate subacute thyroiditis, the resulting thyroid inflammation damages thyroid follicles and activates proteolysis of the thyroglobulin stored within the follicles

that results in unregulated release of large amounts of thyroxine (T₄) and triiodothyronine (T₃) into the circulation (6).

Here we describe the familial occurrence of SAT in association with HLA-B35.

Case Report

A 57-year-old Caucasian man presented with complaints of enlargement and tenderness of the thyroid gland. There was a history of tiredness, general ill feeling, nervousness, and weight loss amounting to 20 kg over a 4-week period. Physical examination revealed a body temperature of 39°C and a heart rate of 110 beats per minute. The thyroid gland was diffusely enlarged to approximately twice the normal size. The erythrocyte sedimentation rate was 58 mm/hr (normal, < 20 mm/hr) and C-reactive protein was found to be 156 mg/L (normal, < 5 mg/L). Thyrotropin (TSH) was suppressed with 0.02 mU/L (normal range, 0.3–5.0), whereas free thyroxine (FT₄) and free triiodothyronine (FT₃) levels were elevated with 75.0 (normal range, 6.3–18.2) pmol/L and 36.5 (normal range, 2.4–6.7) pmol/L, respectively. Thyroidal uptake of ¹³¹I was minimal with 1.5% after 4 hours, and thyroid autoantibodies were absent. On the basis of these signs and symptoms he was diagnosed to have SAT. HLA typing revealed that the patient had HLA-B35.

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In the patient's family, three sisters, one brother, and his deceased father had had from the same signs and symptoms as the index case, whereas another brother and the mother had remained unaffected. Because of the familial occurrence, we decided to chart the family.

Methods

After an explanation for the purpose of the study the three affected sisters, the affected brother, and the unaffected brother and mother provided written informed consent and participated in the study. Medical data concerning clinical symptoms, thyroid hormone levels, and inflammation parameters at the time of presentation of the disease were provided by the general practitioner of the family members. All agreed to donate blood for determination of HLA typing, thyroid hormones and thyroid autoantibodies.

HLA typing was performed by the standard complement-dependent cytotoxicity assay (National Institute of Health [NIH]) for HLA class I typing and two-color fluorescence (TCF) for HLA class II typing. Serum TSH and thyroid hormones in were determined by time-resolved fluoroimmunoassay using an automated AutoDELFIA analyzer (Perkin Elmer, Turku, Finland). Thyroid autoantibodies (antithyroid peroxidase and antithyroglobulin) in serum were measured on a UniCAP system (Pharmacia, Freiburg, Germany).

Results

The clinical and laboratory characteristics of the family members at presentation of the disease are summarized in Table 1. Clinical signs and symptoms as well as laboratory abnormalities were consistent with SAT in the affected family members. In all of them the disease had remitted spontaneously and they were euthyroid during the evaluation (Table 1). None of the family members had positive thyroid autoantibodies at the time of review, thyroid autoantibodies at the time of SAT were available for two patients, both were negative. No viral titres were available at the time of SAT or review. In Figure 1 the pedigree of the family with their HLA haplotypes is presented, showing that all affected family members are heterozygous for HLA-B35 in combination with HLA-B7 except one family member having a combination with HLA-B44. The unaffected brother was carrying the same HLA-B35-positive haplotype as the affected family members. From the pedigree it can be deduced that the HLA-B35-positive haplotype was inherited from the deceased father, who possibly also had suffered from SAT, while the other paternal haplotype remains unknown.

Discussion

An association between HLA-B35 and SAT has been described since 1975 (5,6), however, to our knowledge, famil-

TABLE 1. CHARACTERISTICS OF THE FAMILY

<i>Family members</i>		<i>A</i>	<i>B</i>	<i>C</i>	<i>D</i>	<i>E^a</i>	<i>F</i>	<i>G</i>
Disease manifestation	Gender	F	F	M	M	M	F	F
	Current age (yrs)	88	65	63	62	57	54	54
	Age at disease (yrs)	—	58	—	45	56	53	43
	Year at diagnosis	—	1996	—	1986	2002	2002	1992
	Major complaints	—	Tiredness, goiter, painful throat	—	Tiredness, fever, painful thyroid	Tired, nervousness, 20-kg weight loss	Tiredness, painful throat, 5-kg weight loss	Painful thyroid
	ESR	—	93 (↑)	—	68 (↑)	58 (↑)	89 (↑)	78 (↑)
	TSH (mU/L)	—	0.09 (↓)	—	—	0.02 (↓)	0.15 (↓)	<0.1 (↓)
	FT ₄ (pmol/L)	—	21 (↑)	—	—	75.0 (↑)	14.2	26.8 (↑)
	Total T ₄	—	—	—	208 (↑)	—	—	161 (↑)
	FT ₃ (pmol/L)	—	—	—	—	36.5 (↑)	—	—
After 1 month	ESR	—	22 (↑)	—	—	16	31 (↑)	23 (↑)
	TSH (mU/L)	—	3.91	—	0.8	4.1	<0.03 (↓)	<0.1 (↓)
	FT ₄ (pmol/L)	—	10	—	—	6.4	15.2	—
	Total T ₄	—	—	—	95	—	—	130 (↑)
	FT ₃ (pmol/L)	—	—	—	—	3.8	1.9	—
After 2 months	ESR	—	—	—	5	5	6	6
	TSH (mU/L)	—	1.70	—	0.4	1.20	6.7	2.1
	FT ₄ (pmol/L)	—	12	—	—	10.5	10.7	12.5
	Total T ₄	—	—	—	109	—	—	80
	FT ₃ (pmol/L)	—	—	—	—	5.2	2.0	—
2003	TSH (mU/L)	0.57	1.43	0.90	1.72	2.60	3.24	1.11
	FT ₄ (pmol/L)	18	10.7	14.4	11.6	11.7	14.4	10.2

^aIndex case. Family members A and C are unaffected. Abnormal laboratory values are indicated by arrows. Note that thyroid hormones were determined in various laboratories and that reference values may differ between laboratories as well as in time.

ESR, erythrocyte sedimentation rate; TSH, thyrotropin; FT₄, free thyroxine; T₄, thyroxine; FT₃, free triiodothyronine.

FIG. 1. Family tree of index case with human leukocyte antigen (HLA)-haplotypes. Case E is index case. Square refers to a male, circle to a female. Closed figures are affected family members, open are not-affected. Case F and G are twins. The black haplotype of the deceased father was deduced from the family tree; the other paternal haplotype remains unknown.

ial occurrence of SAT has only been reported twice. The first report described SAT in identical twins, both heterozygous for HLA-B35, who lived 2 miles apart and developed symptoms in the same week. The week before they had gone on a hunting trip, shot a deer, and ate well-cooked parts of it. A friend who also went on that trip did not develop symptoms, nor did the other family members who shared meals with the twins. HLA typing of the other family members was not performed (3). The second report concerned two sisters of whom the older sister was affected first. Her younger sister cared for her and she developed SAT 3 weeks later. Unfortunately, HLA typing of these sisters was not performed (7).

The cases described in this report represent the second example of familial occurrence of SAT in association with the HLA-B35 allele. The family members we described all lived more than 50 miles apart in different regions of The Netherlands, and had from SAT at different time points between 1986 and 2002. Together with the observation that all affected family members were positive for the HLA-A26, HLA-B35, HLA-DR7 haplotype, this seems to highlight the importance of this HLA haplotype (probably the HLA-B35 allele) as major a risk factor for the development of SAT in this family.

There are several explanations for the predisposition of a certain HLA allele to disease susceptibility. Because it has been suggested that the development of SAT is associated with viral infection, a direct role for HLA-B35-restricted viral antigen presentation is likely. This may involve molecular mimicry: a cross-reactive immune response is raised toward an environmental agent that shows homology with a host antigen, resulting in disease (8). Certain specific viral amino acid sequences may, for example, resemble autologous thyroid peptides that are present in the groove of the HLA-B35 molecule. An antiviral immune response may be a sufficient stimulus to break tolerance towards the autolo-

gous peptides and generate autoreactive T-cell clones, which may cause an autoimmune response towards thyroid tissue. Another trigger for the development of an HLA-B35-restricted autoimmune process may be the alterations in tissue components that occur during infection, as a result of release of viral products, expression of viral antigens on host cells, or tissue injury caused by the accompanying inflammatory response. Modified proteins in the thyroid, that are presented in the groove of HLA-B35, may be recognized as foreign, which leads to the development of an autoimmune process and thus to tissue damage (9).

Goto et al. (10) suggested that homozygotes for HLA-B35 are at higher risk for the development of subacute thyroiditis compared to heterozygous subjects. The present index patient and his family members are heterozygous for HLA-B35. Interestingly, the only sibling that was unaffected until now is also heterozygous for HLA-B35. It is clear that this sibling is still at risk for developing SAT.

In conclusion, the case described here represents the second familial incidence and largest family reported so far with occurrence of SAT in association with HLA-B35.

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