

Hashimoto's disease during interferon-alpha therapy in a patient with pre-treatment negative anti-thyroid autoantibodies and with the specific genetic susceptibility to the thyroid disease

Antonio Martocchia,¹ Giancarlo Labbadia,² Vincenzo Paoletti,² Serena Gargano,¹ Antonio Grossi,¹ Simonetta Trabace,³ Antonino Musca² & Paolo Falaschi¹

1. Chair of Internal Medicine – II Faculty of Medicine
2. Department of Medical Therapy
3. Chair of Medical Genetics, University of Rome “La Sapienza”, Italy.

Correspondence to: Dott. Antonio Martocchia, Via della Magnetite 42, 00158 Rome, Italy.
TEL./FAX: +39 064501245

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Abstract

OBJECTIVES: The authors described a case of Hashimoto's disease during interferon-alpha (IFN- α) treatment for chronic viral C hepatitis in a patient with the specific genetic susceptibility associated with the thyroid disease.

RESULTS: A 60-year-old woman with chronic active viral C hepatitis (HCV genotype = 3a) started IFN- α therapy in November '96. Before treatment thyroid function tests were normal and anti-thyroid (anti-thyroglobulin and anti-thyroid peroxidase) Abs were negative. During IFN therapy, serum aminotransferases fell within the normal range and viremia (serum HCV-RNA) became negative after one year. After 20 months, the patient presented clinical features of primary hypothyroidism. Anti-thyroid Abs were found positive. Hormonal, ultrasonographic, radioiodine scanning and fine needle aspiration findings were consistent with the diagnosis of Hashimoto's thyroiditis. The tissutal typing of the patient showed the presence of Human Leukocyte Antigen (HLA) DRB1*11 gene (corresponding to DR5 antigen). IFN- α therapy was suspended and a treatment with l-T4 started. Chronic viral infection relapsed after the suspension of the IFN- α therapy.

CONCLUSIONS: This case report showed that the clinical appearance of Hashimoto's disease after IFN- α therapy for chronic C hepatitis in our patient was associated with a specific genetic predisposition (DR5) for this pathology. Further studies are necessary to evaluate whether the study of HLA antigens may be a very useful tool to detect the patients with a predisposition to develop autoimmune thyroiditis, in order to make a early diagnosis of thyroid disorders during the IFN- α treatment.

ABBREVIATIONS AND UNITS

IFN- α :	interferon alpha
HCV:	hepatitis C virus
HLA:	human leukocyte antigen
Abs:	autoantibodies
l-T4:	levo-thyroxine
AST:	aspartate aminotransferase
ALT:	alanine aminotransferase
IU:	international unit
i.m.:	intra muscular
TT3:	total triiodothyronine
TT4:	total thyroxine
FT3:	free triiodothyronine
FT4:	free thyroxine
TSH:	thyrotropin
RIA:	radio-immuno assay
IRMA:	immuno-radiometric assay
AntiTG:	anti-thyroglobulin
AntiTPO:	anti-thyroperoxidase
Anti-TSHr Abs:	anti thyrotropin receptor antibodies
PCR:	Polymerase Chain Reaction
FNA:	fine needle aspiration

Introduction

It has been recently shown that interferon- α (IFN- α) therapy for chronic C active viral hepatitis may induce autoimmune thyroid diseases and thyroid dysfunctions with clinical features of both hypo- and hyper-thyroidism [1-8].

The clinical exacerbation of thyroid disorders during IFN- α treatment occurred more frequently in patients with pre-existing clinical signs of thyroid autoimmunity, like the presence of anti-thyroid autoantibodies (Abs) [1].

Environmental (viral agents) and genetic (genic susceptibility) factors are invoked to explain the thyroid autoimmune pathogenesis [9].

We now present a case of Hashimoto's disease in a patient receiving IFN- α therapy for chronic hepatitis C, with normal thyroid function and negative anti-thyroid Abs before treatment, and with a genetic susceptibility to develop autoimmune thyroid disease.

Case report

A 60-year-old woman occasionally found high serum AST and ALT in 1993, with recurrent elevations in the following years. No apparent way of HCV infection was notable.

Positive serum anti-HCV Abs and HCV-RNA were detected in 1996. Serum anti-HCV Abs were determined by a recombinant immunoblot assay (Ortho Diagnostic System, New Jersey, USA); HCV RNA was carried out by PCR analysis, with type specific primers within the core region of HCV genome, as

described by Okamoto et al. [10]. The genotype of the virus was 3a, according to Simmonds classification [11].

In the same period, a liver needle biopsy revealed a chronic hepatitis with moderate inflammatory activity (Knodell's score =5+1) [12].

IFN- α therapy was started in November 1996 (3 million IU im of recombinant human IFN- α , Roferon A, three times a week). Before treatment, thyroid function and anti-thyroid auto-antibodies were within the normal range (table 1).

TT3 and FT3, TT4 and FT4 have been measured by RIA (commercial kit by Ares-Serono, Italy), TSH has been detected by IRMA (Ares-Serono, Italy); anti-Tg and anti-TPO has been performed by RIA (Bioline, Belgium).

During IFN therapy, serum AST and ALT fell within the normal range and viremia (serum HCV-RNA) became negative after one year.

After 20 months, the patient presented clinical features primary hypothyroidism, with a symptomatology characterized by a pronounced fatigue.

Thyroid function test showed reduced FT3 and FT4 and increased TSH blood levels. Anti-thyroid Abs (excluding anti-TSHr Abs) were found positive (table 1).

A thyroid scan evidenced an irregular distribution of radioiodine.

Ultrasound examination showed a remarkably dishomogeneous structure and a low echoic pattern. Multiple, partially confluent, pseudo-nodular areas, with a maximum diameter of 1 cm, were present, particularly in the right lobe, as commonly observed in thyroid inflammatory processes.

FNA of the thyroid showed the presence of numerous thyrocytes (isolated and aggregated in follicles, with anisonucleosis), abundant colloid and a great number of infiltrating lymphocytes, consistent with the diagnosis of Hashimoto's thyroiditis.

The patient's HLA type was examined, evaluating antigens of locus A, B and Cw and alleles of locus DRB1* and DQB1*. HLA antigens were determined by the complement-dependent lymphocyte cytotoxicity test and HLA genes were determined by PCR method with the technique of sequence-specific priming (SSP). The tissutal typing of the patient resulted: A1, A2 | B18, B70 | Cw7, - | DRB1*03, DRB1*11 (corresponding to DR3, DR5).

IFN- α therapy was suspended and a treatment with l-T4 (100 mcg/die, the patient's weight being 68 kg) was started. During the treatment with l-T4, her symptomatology improved, thyroid hormone levels normalized and thyrotropin concentrations progressively decreased. Anti-Tg and Anti-TPO levels remained high. Anti-TSH-r Abs were examined twice

Table 1. Thyroid and liver function tests and anti-thyroid autoantibodies during the clinical course.

Test (normal range)	04/96	04/98	09/98	06/99	06/00
T3 (0.8-2 ng/ml)	1.6	-	0.91	-	-
T4 (45-120 ng/ml)	64	-	112.3	-	-
FT3 (2.7-5.2 pg/ml)	-	2.6	2.6	4.4	3.1
FT4 (10-19 pg/ml)	-	5.9	12.2	19.4	15.1
TSH (0.4-3.8 mU/ml)	1.85	36.3	0.69	0.04	0.09
Anti-TG Abs (<150 U/ml)	<150	3400	2400	5000	3400
Anti-TPO Abs (<100 U/ml)	<100	1200	236	372	283
AST (<40 U/ml)	73	19	57	78	88
ALT (<40 U/ml)	121	19	89	144	127

IFN-α [04/98 - 06/99]

 levo-Thyroxine 100mcg/die [04/98 - 06/00]

and were absent. The repeated ultrasonography showed findings similar to those previously reported with thyroid lobes increased in dimensions.

Chronic viral infection relapsed after the suspension of the IFN- α therapy, as shown by the raising of the serum aminotransferases (table 1) and positivity of serum HCV-RNA.

Discussion

The development or the exacerbation of thyroid disorders, like autoimmune thyroid dysfunction (hyper- and hypo-thyroidism) have been described during IFN- α treatment for chronic active C hepatitis, above all in the subgroup of patients with pre-existing positive anti-thyroid Abs [1-8]. Evidence in the literature suggests that thyroid autoimmunity may occur in the clinical history of HCV patients, with a high incidence, both in treated and untreated subjects [4, 8].

The incidence of thyroid alterations is highly variable, probably depending by several factors, such as age, geographic origin, race, sex, iodine intake, viral load and genotype, and type of IFN- α used for the therapy (leukocyte-derived, lymphoblastoid, recombinant alpha 2a/2b) [1, 6, 9, 13, 14].

In autoimmunity disorders the dendritic cells process autoantigens and express the processed peptide to lymphocytes, in association with the specific, genetically determined, molecules of the HLA [15]. A recently emerging hypothesis is that HCV may have direct extrahepatic effects, both on the immune system and on the thyroid cells [7, 9], interfering with their functions and with the fundamental mechanism of self recognition. In fact, it has been reported that HCV shares a partial sequence of peptides with thyroid tissue antigens (like amino acid sequence 647-653, 1047-1054 of thyroglobulin and amino acid sequence 471-476 of thyroid microsomes) [7]. Therefore, HCV may start autoimmune thyroid diseases by directly destroying thyroid tissue or mimicking the structure of some component of thyroid gland.

We previously described a case of De Quervain's thyroiditis, during IFN- α therapy for chronic active C hepatitis [16]. In such case, the study of HLA antigens revealed the presence of B35 antigen, predisposing to subacute thyroiditis [17]. In another study from Japan, the incidence of HLA-A2, B46 and Cw7 was increased in patients with interferon-alpha-induced autoimmune disorders [18]. In that country, patients with Hashimoto's thyroiditis were frequently associated with HLA-A2 antigen [19].

During IFN- α treatment, our euthyroid patient, with negative anti-thyroid Abs before IFN- α treatment, developed clinical, hormonal, ultrasonographic, radioiodine scanning and fine needle aspiration findings consistent with the diagnosis of Hashimoto's disease. The study of HLA antigen showed the typical association for Hashimoto's disease (DR5) in Caucasians [20].

This is the second case report of our group, in which an autoimmune thyroiditis (in particular, Hashimoto's disease) developed in a patient with the specific associated HLA haplotype. Such evidence suggests that HLA predisposition may be another important factor to be considered in the evaluation of autoimmune thyroid disorders induced by IFN- α therapy.

IFN- α therapy, acting as an immunomodulatory agent, may accelerate a clinical course, already present in the genetic background of the patient, inducing or exacerbating thyroid dysfunctions in susceptible patients [7].

In conclusion, this case report suggests that the clinical appearance of Hashimoto's disease after IFN- α therapy for chronic C hepatitis is associated with the specific genetic predisposition (DR5) for this pathology.

The study of HLA antigens may be a very useful tool to detect the patients with a predisposition to develop autoimmune thyroiditis. The presence of DR5 HLA antigen in a selected number of patients could suggest, rather than an alternative therapeutic option, a careful monitoring of thyroid function in such patients in order to make an early diagnosis of thyroid disorders during the IFN- α treatment. Further studies in a large group of patients are necessary to confirm the results obtained in our case report.

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