CASE REPORT

A rare case of Interferon-alpha-Induced Hyperthyroidism in patients with a chronic hepatitis C with granulocytopenia and transaminasemia treated successfully with radioiodine

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Abstract

BACKGROUND: Conventional management of Interferon-α-Induced Hyperthyroidism (IIH) with radioactive iodine (RAI) may be used when treatment with beta blockers or antithyroid drugs (ATD), proves ineffective or is contraindicated. **CASE PRESENTATION:** We present a 38-year-old woman who has been treated with combined pegylated interferon alpha (INF-α) and Ribavirin for chronic hepatitis C. Destructive thyrotoxicosis appeared after four months of continuous IFN-α therapy and a beta blocker was prescribed. Initially, the patient presented normal TSH 2.4 μIU/mL, however during therapy with INF-α, TSH diminished to 0.05 and thyroid hormones were elevated: fT4 23.1 pmol/L, fT3 7.2 pmol/L. Ultrasound examination showed completely irregular and greatly decreased echogenicity of the thyroid gland. The radioiodine uptake (RAIU) was deeply decreased to 2 and 3% at 5 h and 24 h, respectively. The thyroid scintiscan showed lack of isotope accumulation. Hypothyroidism developed and L-thyroxine was prescribed. The following year, hyperthyroidism reoccurred with TSH 0.08 μIU/mL, fT4 26.4 pmol/L, fT3 8.2 pmol/L, positive TSHR-Abs 6.2 (normal <2 IU/L) and mild Graves' Ophthalmopathy (GO). RAIU values were 23% at 5 h

and 46% at 24 h. Thyroid scintiscan showed diffuse goiter. At this point beta blocker was introduced and ATD was started. After three months of therapy an increased level of aminotransferases and granulocytopaenia were observed. Hence, the patient received RAI and glucocorticosteroid, while INF-α therapy was continued. After approximately 4 months, hypothyroidism reappeared with insignificantly raised TSH level. One year later the patient was euthyroid and required no further treatment.

CONCLUSIONS: Our report suggests that: 1. Radioiodine therapy might be an effective and safe method of treatment in cases of IIH with mild GO. 2. IFN-α therapy need not be discontinued in patients with IIH.

Abbrevations:

AST	- Aspartate Aminotransferase
ALT	- Alanine Aminotransferase
ATDs	- antithyroid drugs
CHC	- chronic hepatitis C
GD	- Graves' disease
GO	- Graves Ophthalmopathy
fT4	- free tetraiodothyroxine
fT3	- free triiodothyronine
IIH	- Interferon-α-Induced Hyperthyroidism
RAIU	- radioiodine uptake
RIT	- radioiodine therapy
TNG	- toxic nodular goiter
TSH	- thyrotropin
TSHR-Abs	- autoantibodies to the thyrotropin receptor
Tg-Abs	- thyroglobulin autoantibodies
TPO-Abs	- thyroperoxidase autantibodies

INTRODUCTION

Radioiodine therapy (RIT) is one of the methods used to treat Graves' disease (GD) and toxic nodular goiter (TNG) when antithyroid drugs (ATDs) therapy proves ineffective. Despite frequent hypothyroidism, RIT is an effective method that is a low-cost therapeutic option devoid of major side effects (Antonelli *et al.* 2007). Still, RIT arouses much controversy, particularly in the case of Interferon-α-Induced Hyperthyroidism (IIH) in chronic hepatitis C patients (CHC). IIH is usually transient and in the majority of cases resolves spontaneously. However, in special situations, when ATDs are contraindicated (high levels of aminotransferases, thrombocytopenia, agranulocytosis), RIT is a viable method in these cases.

The aim of this study is to present a rare case of IIH with granulocytopenia and transaminasemia treated successfully with RIT.

CASE PRESENTATION

The paper presents a 38-year-old woman who has been treated with combined pegylated INF-α (Peginterferon alfa-2a; Pegasys) and Ribavirin (Copegus) for CHC since March, 2006. Her family history showed her mother suffered from hypothyroidism, while her father had type 1 diabetes mellitus. During qualification for INF-α therapy, the patient had elevated thyroglobulin autoantibodies (Tg-Abs) titer of 1: 135 (N: 10–115 IU/ml), normal level of antithyroperoxidase autantibodies (TPO-Abs) {titer of 1: 34 (N: <34 IU/ml)}, TSHR-Abs 1.2 (N: <2 IU/L) and leukocytes (5327/μl), while aminotransferase level were slightly elevated: AST 38 U/l (N: 10–31 U/l), ALT 36 U/l (10–31 U/l). Three months later (at the time of admission to our Department) the patient showed typical manifestations of thyrotoxicosis: nervousness, weight loss (5 kg within two months) despite good appetite, heart palpitations (sinus tachycardia at 120 beats per minute). A physical examination detected a blood pressure of 165/70 mm Hg, painless goiter without any palpable nodules. Formerly, the patient had normal TSH: 2.4 (N: 0.27–4.2 μU/mL), free tetraiodothyroxine (fT4): 12.7 (N: 11.5–21.5 pmol/L), free triiodothyronine (fT3): 4.1 (fT3 (N: 3.9–6.8 pmol/L), and, during therapy of INF-α, TSH diminished to 0.05. The thyroid hormones were elevated: fT4: 23.1, fT3: 7.2, respectively. The US examination indicated completely irregular and deeply decreased echogenicity of the thyroid with reduced vascularization. The ^{131}I uptake (RAIU) measured at 5 and 24 h after administration of diagnostic dose was deeply decreased to lower than 2 and 3%, respectively. The thyroid scintiscan performed 30 min. after an i.v. administration of 150 MBq of ^{99m}Tc [Nucline gamma camera (Mediso, Hungary)] showed lack of accumulation of isotope (Figure 1). Destructive thyroiditis was diagnosed and a β-blocker was prescribed. In April, 2007 Pegasys was discontinued. At the end of June, 2008 hypothyroidism developed (TSH: 9.3 μIU/mL, FT4: 8.1 pmol/L, fT3: 3.1 pmol/L). B-blocker was withdrawn and L-thyroxine (L-T4 at 25 μg/day) was started and continued for 10 months. The following year, INF-α [peginterferon alpha-2b (Peg-Intron) with Rybawirin (Rebetol)] was re-introduced due to the increased level of viremia. After three months of the therapy, hyperthyroidism recurred with TSH: 0.08 μIU/mL, FT3: 8.2 pmol/L, and FT4 26.4 pmol/L with positive level of TSHR-Abs 6.2 (N: <2 IU/L) and Graves' disease with mild ophthalmopathy (GO) (CAS = 3 pts, NOSPECS <3 pts) was diagnosed. Thyroid US confirmed intensive hypervascularization of the parenchyma, with overall thyroid volume of 26 ml (N: <18 ml), RAIU values of 23% at 5h, and 46% at 24h after administration of a tracer dose (ca. 2MBq of ^{131}I) and thyroid scintiscan showed diffuse goiter (Figure 2). The β-blocker (20mg/day) therapy was introduced and ATD – thiamazole [(Thyrozol®) 20 mg daily] was started. After three months of therapy an increased level of aminotransferases (AST 112 IU/l, ALT 74 IU/l) and granulocytoenia (1420/μl) were observed. At the time, the patient received RIT [185 MBq (5 mCi)] and glucocorticosteroid (Encorton 30 mg daily) while INF-α therapy was continued until February, 2010. Approximately 4 months later,

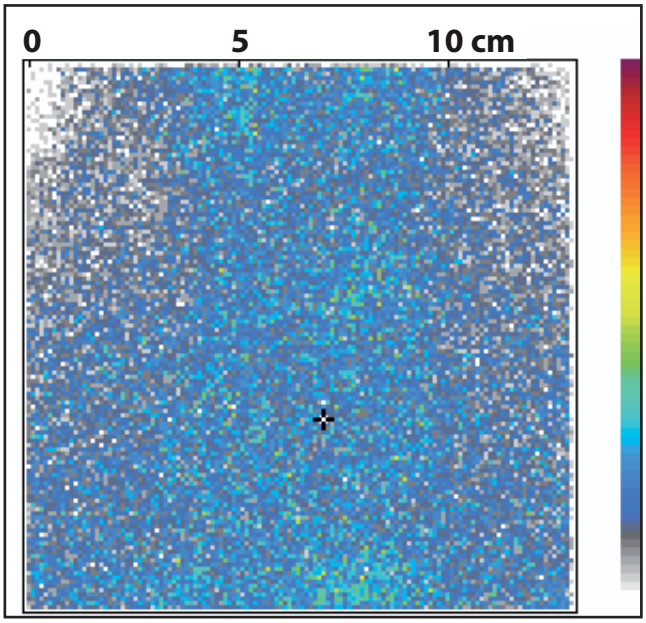

Fig. 1. Thyroid ^{99m}Tc scintygraphy – lack of accumulation of isotope in the thyroid gland.

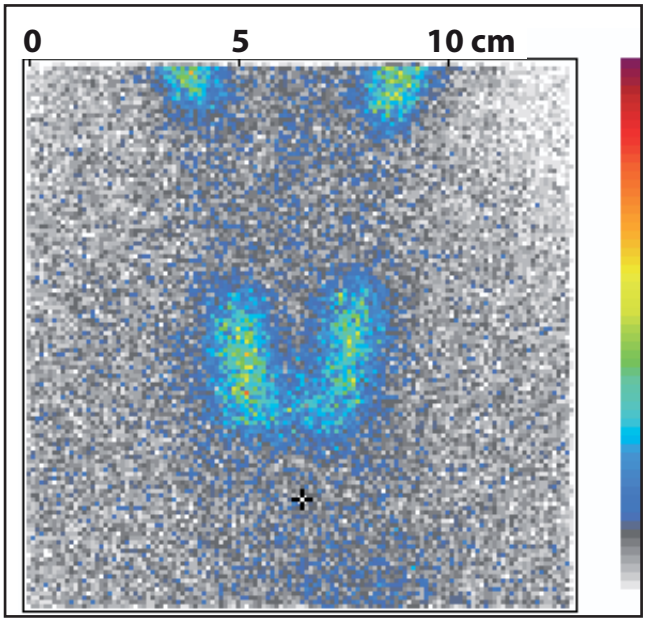

Fig. 2. Thyroid ^{99m}Tc scintygraphy – regular accumulation of isotope in the thyroid gland.

hypothyroidism was reported again with insignificantly raised TSH level (31.2 μIU/mL), and decreased concentration of FT4 (11.2 pmol/L). In this clinical situation LT4 was applied. After about one year the patient was euthyroid and required no further treatment (Figure 3).

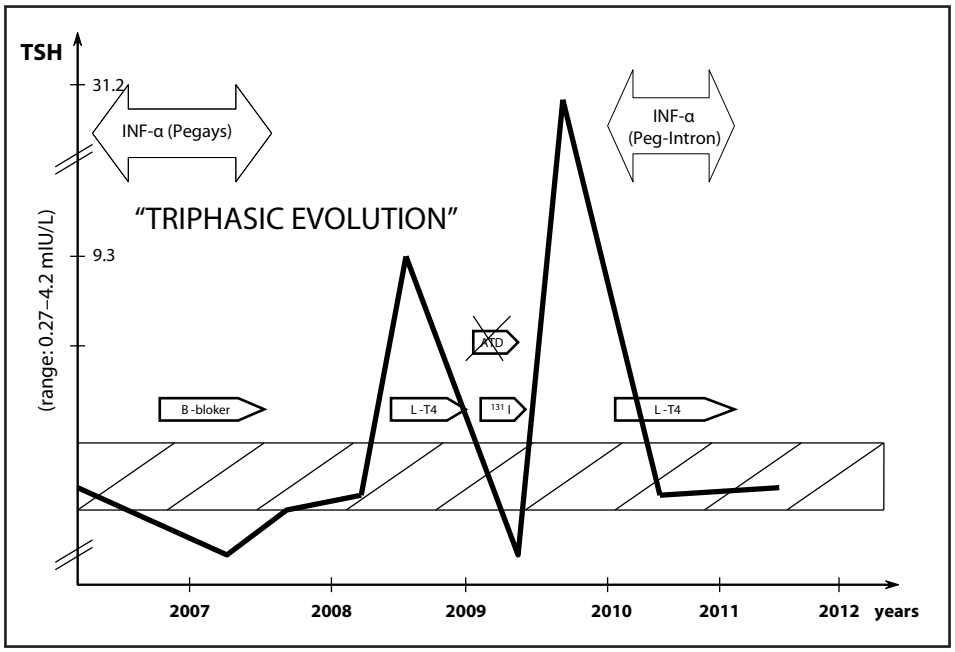

Fig. 3. Evolution from destructive thyroiditis to Graves' disease with mild orbithopathy during INF-α therapy.

DISCUSSION

Interferon Alpha-2a is commonly used as antiviral medication for therapy of CHC infection with varying effects on the thyroid. Patients treated with this drug may present Graves' hyperthyroidism, destructive thyrotoxicosis, hypothyroidism or more than one thyroid ailments occurring concomitantly (Braga-Basaria *et al.* 2003; Csaki *et al.* 2000; Vassilopoulou-Sellin *et al.* 1992; Wong *et al.* 2002). A considerable number of studies on INF-α therapy documents that thyroid disease is diagnosed from three to seven times more often in women than men (Fernandez-Soto *et al.* 1998; Hsieh *et al.* 2000; Koh *et al.* 1997; Okanoue *et al.* 1996; Prummel *et al.* 2003), however dissenting opinions exist (Baudin *et al.* 1993; Floreni *et al.* 1998; Lisker-Melman *et al.* 1992; Tran *et al.* 1993; Watanabe *et al.* 1994). A retrospective literature review by Koh *et al.* (1997) observed that patients with positive TPO-Abs prior to interferon therapy were at ten times higher risk of progressing to thyroid dysfunction, while only 5.4% with negative TPO-Abs developed thyroid disease. Destructive thyrotoxicosis caused follicle destruction and led to clinical symptoms of hyperthyroidism in patients with low RAIU and negative TSHR-Abs, reduced vascularity and hypoechogenicity in Color flow Doppler examination (Wong *et al.* 2002;

Bogazzi *et al.* 1997; Mazziotii *et al.* 2002; Ruchala & Szczepanek 2010). In the presented case report, the first phase of the disease was consistent destructive thyrotoxicosis. Signs and symptoms of thyrotoxicosis were effectively controlled with β-blockers only. However, Graves' hyperthyroidism occurred after several months' therapy of INF-α, which was confirmed by the increase in serum TSHR-Abs, which is a key pathogenetic factor (Braga-Basaria *et al.* 2003; Okanoue *et al.* 1996). The changes of TSHR-Abs may also lead to mild ophthalmopathy. An interesting observation is the change in the RAIU. This test showed extremely reduced uptake when destructive thyrotoxicosis occurred and was significantly elevated during evolution to GD.

When thyrotoxicosis is long lasting and does not respond appropriately to beta-blockers, other therapy is required. Although ATDs (like thiamazole or carbimazole) may be used INF-α and ATDs present many common side effects. Minor side effects (rash, purities, hives, hair loss, nausea, decreased taste and joint pain) can occur, but special attention needs to be paid to severe side-effects of these drugs such as: agranulocytosis, neutropenia or thrombocytopenia, not to mention further consequences that include, e.g. Stevens-Johnson syndrome or cholestatic jaundice. These complications argue strongly in favor of the use of RIT as the preferred method due to its safety and effectiveness.

In the literature we have found publications stating that INF-α should be discontinued during hyperthyroidism (Carella *et al.* 1995; Carella *et al.* 2001; Cooper 2005; Bohbot et al 2006; Roti & Uberti 2002), while our observations demonstrate that there is no important reason to interrupt therapy. However, it requires close collaboration between an endocrinologist and a specialist in infectious diseases. Therefore, we do not advocate temporary cessation of INF-α use during RIT. However, according to Carella's observations (Carella *et al.* 1995; Carella *et al.* 2001), only in cases that involve the exacerbation of hyperthyroidism, therapy may be discontinued for 2 to 3 months and RIT applied.

This case report confirms the occurrence of "triphasic" thyroid dysfunction (Fig. 5), initially described by Bohbot *et al.* (2006) and confirmed by Tran *et al.* (1993). The meticulous details of "tri-phasic" evolution of autoimmune thyroid disease presented by the both authors remain unsurpassed. Hence, admittedly numerous reports exist, analyzing the evolution from thyroiditis to GD during INF-α therapy (Braga-Basaria *et al.* 2003; Eugene *et al.* 1993; Koizumi *et al.* 1995). In this case with granulocytopenia and transaminasemia we used RIT therapy in place of ATDs. Our case seems to be the more interesting, though, as the available literature does not address sufficiently or provide enough details about IIH and the use of RIT.

To summarize, it should be added that IIH causes numerous challenges even for experienced clinicians. A significant number of symptoms may be subclinical, without typical signs of thyroid dysfunction, and can be diagnosed based on laboratory findings. Further complicating diagnosis is that symptoms of both hyperthyroidism and hypothyroidism can be masked by undesired effects of an INF-α therapy (Parana *et al.* 2000; Shen *et al.* 2005; Soultati et al 2007).

CONCLUSIONS

Our report suggests that: 1. Radioiodine therapy might be an effective and safe method of treatment in cases of IIH with mild GO. 2. IFN-α therapy need not be discontinued in patients with IIH.

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