Chapter 5
Interferon-Induced Hyperthyroidism

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Objectives

Interferon-alpha (IFN-α) treatment for hepatitis C virus (HCV) and other disorders has been associated with an increased risk for thyroid dysfunction and autoimmunity. Here, we report the case of a 50-year-old woman who developed Graves' disease in the setting of IFN-α therapy for HCV. We discuss potential mechanisms of thyroid disease induction, recommendations for screening, and clinical strategies for the management of patients who develop IFN-related thyroid disease.

Case Presentation

Ms. M.B. is a 50-year old woman with hepatitis C and no history of thyroid disease. She was referred to the endocrine clinic for evaluation of abnormal serum thyroid function tests (TFTs) in the setting of interferon alfa-2b (IFN-α-2b) therapy for HCV. Three months after starting her treatment, she began experiencing insomnia, weight loss, weakness, palpitations, and shortness of breath. She denied heat intolerance, nervousness or tremor, bowel changes, dysphagia, neck discomfort, or visual disturbances.

On physical examination, the blood pressure was 120/80 and the pulse was 78 and regular. There was no exophthalmos. The thyroid was not palpable, nontender, and there was no bruit audible her skin was warm and moist. There was no tremor of the outstretched hands.

Prior to starting IFN-α, her TSH had been 1.5 mU/L (normal 0.5–5.0). TFTs drawn after the onset of her symptoms showed a thyroid-stimulating hormone (TSH) of 0.02 mU/L (normal 0.5–5.0), a total thyroxine (TT_4) of 15.6 g/dL (normal 4.6–12), a triiodothyronine resin uptake (T_3RU) of 28%, and a free thyroxine index (FTI) of 4.4 (normal 1.6–3.7). She also had markedly positive antithyroid peroxidase antibodies, and a 24–hour radioiodine uptake of 58% (normal 10–30%).

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Background

Interferons (IFNs) are naturally occurring proteins secreted by cells in response to viral infections that play a major role in modulating immune function. Thyroid dysfunction is a known complication of interferon therapy in the treatment of hepatitis B or C or during therapy for certain malignancies [1]. Thyroid dysfunction occurs in up to 15% to 20% of patients treated with IFN-α for chronic HCV [2], but others have reported numbers as high as 34%, with induction of antithyroid antibodies occurring in up to 40% of patients with negative antibodies at baseline [3]. A recent literature review found that of those who developed thyroid dysfunction with IFN-α, 60% became hypothyroid and about 40% developed hyperthyroidism [4]. Risk factors for the development of thyroid disease with interferon therapy include female sex, combination immunotherapy (especially IL-2), and preexisting thyroid autoantibodies [5].

The mechanisms by which IFN-α leads to thyroid dysfunction be divided into immune and nonimmune (i.e., direct effects of IFN on the thyroid) mediated effects.

Immune-Mediated Effects

Immune system effects of IFN-α that could potentially mediate the development of autoimmune thyroid disease include the enhancement of major histocompatibility complex (MHC) class I antigen expression, a generalized shift toward cell-mediated immunity, as well as increases in circulating interleukin-6 (IL-6) levels [2]. IL-6 may be important for the development of thyroid autoimmunity, and may also directly inhibit thyroidal iodide uptake and thyroid hormone release[6].

Nonimmune Effects

Direct effects of IFN-α on the thyroid include inhibition of thyroid hormone synthesis, release, and metabolism, and disruption of thyroidal iodine organification [2, 7]. In primary human thyrocyte cultures, IFN-α has been shown to inhibit TSH-induced gene expression of thyroglobulin, thyroperoxidase (TPO), and sodium iodide symporter (NIS) [8].

Based on the dual mechanisms by which IFN-α may induce thyroid dysfunction, Mandac et al [1] proposed a new classification of interferon-induced thyroid disease (IITD), in which thyroid abnormalities are considered to be either autoimmune- or nonautoimmune in nature,. While this classification may have some validity, it does not account for all of the features of IITD that are observed clinically (see below). Specifically, this classification categorizes destructive thyroiditis as nonautoimmune, whereas this may not be the case in some or even most patients. Our classification of IITD will be as follows:

Autoimmune IITD:

1. Increase in the titer of preexisting autoantibodies or de novo induction of autoantibodies, without clinical evidence of thyroid disease
2. Destructive thyroiditis
3. Hashimoto's thyroiditis (autoimmune hypothyroidism)
4. Graves' disease

Nonautoimmune IITD:

1. Destructive thyroiditis without thyroid autoantibodies
2. Nonautoimmune hypothyroidism

Autoimmune IITD

The most common immune manifestation occurring with IFN-α therapy is the presence of thyroid autoantibodies in the absence of clinical thyroid dysfunction [9]. In this situation, there may either be an increase in the titer of preexisting thyroid autoantibodies or the *de novo* induction of thyroid autoantibodies [10].

Preexisting Thyroid Autoantibodies

About 18% of the thyroid disease–free population have detectable serum antithyroperoxidase (TPO-Ab) and antithyroglobulin (Tg-Ab) antibodies [11]. In one prospective study, Carella et al [12] monitored changes in thyroid autoantibodies titers in patients with HCV treated with IFN-α. Tg-Ab levels increased from a median of 29 U/mL to 35.0 and 73.0 U/mL before, at 6 months after, and at 12 months after starting IFN treatment, respectively; and titers of TPO-Abs also increased from a median baseline of 1.0 U/mL before IFN therapy to 3.0 and 6.0 U/mL at 6 and 12 months into treatment, respectively.

De Novo Thyroid Autoantibodies

The prevalence of de novo induction of thyroid autoantibodies by IFN-α has varied among different studies ranging from 1.9% [13] to 40% [3]. In the study by Carella et al [12], the number of patients positive for one or both thyroid autoantibodies increased from eight of 75 (10.7%) before starting IFN-α treatment to 34 of 75 (45.3%) at 12 months into therapy, with only five of the antibody-positive patients developing thyroid dysfunction. Similar findings of de novo thyroid autoantibodies production without clinical evidence of thyroid disease were also reported by Imagawa et al [14] and Preziati et al [3].

Destructive Thyroiditis

In those patients who develop hyperthyroidism, destructive thyrotoxicosis is often the cause (5,15). Destructive thyroiditis is an inflammatory condition of the thyroid gland that usually occurs in the first weeks of IFN treatment [15]. Since some cases may occur in the absence of detectable thyroid autoantibodies, suggesting a nonautoimmune etiology [1], this issue remains unsettled. Mazziotti et al [16] prospectively monitored patients with hepatitis C for the development of thyroid dysfunction or thyroid autoimmunity during IFN-α therapy. The authors noted that the appearance of thyroid autoantibodies always preceded the development of destructive thyrotoxicosis, suggesting that the thyroid dysfunction was in fact immune-mediated. On the other hand, it could still be argued that the appearance of antithyroid antibodies was an early marker of thyroid follicular disruption, and was not truly etiologic in the development of thyroid dysfunction.

The diagnosis of destructive thyrotoxicosis is supported by a low radioiodine uptake (RAIU), negative anti-TSH receptor antibodies, diffuse hypoechogenicity on ultrasound, and, if performed, reduced thyroid vascularity on color flow Doppler [15]. Destructive thyrotoxicosis is frequently mild (subclinical) but in some cases it is more extensive and leads to overt thyrotoxicosis [15]. As is true for most types of destructive thyroiditis, hypothyroidism subsequently develops in most patients after several months [15].

Hashimoto's Thyroiditis

The prevalence of hypothyroidism among HCV patients treated with IFN-α ranges from 2.4% to 19% [15], with over two thirds exhibiting thyroid autoantibody positivity [4]. Hypothyroidism is often mild or subclinical, and is more likely to be overt in patients with preexisting thyroid autoantibody positivity [15].

Graves' Disease

The overall frequency of Graves' disease among patients who develop IFN-α–related thyrotoxicosis is uncertain. Carella et al [15] and Koh et al [5] suggest that it is less common than destructive thyrotoxicosis, whereas Prummel and Laurberg [4] believe that it is the most common etiology [16]. In addition to developing de novo, Graves' hyperthyroidism may occur after a transient phase of destructive thyrotoxicosis, following a period of hypothyroidism [15], and persist after cessation of IFN-α therapy [17]. Wong et al [17] reviewed the medical records of 321 patients receiving IFN-α for chronic hepatitis B or C between 1996 and March 2001; six out of 10 who were found to have biochemical thyrotoxicosis had other findings consistent with Graves' disease, such as diffuse uptake on thyroid scintigraphy or positive TSAb. In all six patients, the thyrotoxicosis failed to resolve with cessation of IFN-α, and required prolonged treatment with antithyroid medications [17].

Nonautoimmune Interferon-Induced Thyroid Disease (IITD)

The development of thyroid dysfunction in association with IFN-α therapy in the absence of evident thyroid autoimmunity is an important but poorly understood feature of IITD. The two forms of nonautoimmune IITD are destructive thyroiditis and hypothyroidism.

Destructive Thyroiditis

As noted above, one recent review has suggested that destructive thyroiditis is caused mainly by nonimmune mechanisms [1]. However, this interpretation is based on relatively scant clinical data. In one such report, three patients developed hyperthyroidism with biochemical and RAIU values consistent with destructive thyroiditis (low TSH, high free T_4) with negative thyroid autoantibodies (TPO and TSH receptor Abs), and without low RAIU [18].

Hypothyroidism

Non–immune IFN-α hypothyroidism have also been rarely reported [14]. Potential direct mechanisms of IFN-α to impair thyroid function were discussed earlier [2, 7, 8].

Considerations for Baseline Screening

It has been suggested that prior to the initiation of IFN therapy, serum TSH, TgAb, and TPO-Ab concentrations and perhaps thyroid sonography should be carried out to identify preexisting thyroid dysfunction or thyroid autoimmunity [15]. If all studies are normal, we recommend that TSH levels be followed every 3 months until interferon therapy is completed [1]. If TSH levels are normal but thyroid antibodies are positive, the patient is at increased risk for developing clinical thyroid dysfunction with IFN therapy [5], and therefore TSH levels be tested every 2 months [1]. If the patient develops hypo- or hyperthyroidism, a full workup is required [1].

Therapeutic Considerations

Figure 5.1 shows an algorithm highlighting therapeutic approaches for the management of patients with interferon-induced thyroid disease.

Destructive Thyrotoxicosis

In symptomatic patients, treatment with beta-blocking agents is usually sufficient to control the signs and symptoms of thyrotoxicosis [15]. If an asymptomatic patient has biochemical evidence of thyrotoxicosis and concomitant cardiac risk factors, treatment with beta-blocking agents is also reasonable. When the thyrotoxicosis is

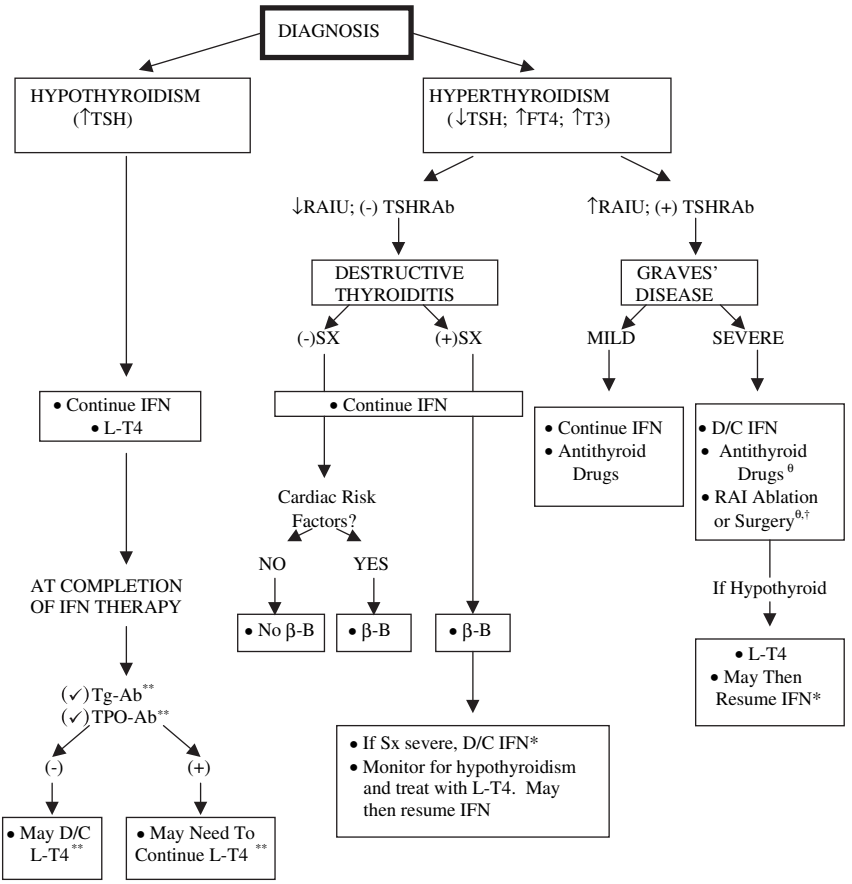

Fig. 5.1 Algorithm for the treatment of interferon-induced thyroiditis. β-B, beta blockers; D/C, discontinue; FT4, Free thyroxine; T3, Triiodothyronine; IFN, interferon; L-T4, levothyroxine; RAI, radioactive iodine; RAIU, RAI uptake; bf Sx, symptomatic; Tg-Ab, thyroglobulin antibody; TPO-Ab, thyroperoxidase Ab; TSH, thyroid stimulating hormone; TSHRAb, TSH receptor Ab
θ Remission of hyperthyroidism with antithyroid drugs is unlikely (*Carella *et al.*, 2004; **Carella *et al.*, 2001).
†Mandac *et al.*, 2006.

more severe and the symptoms are not well controlled by beta-blocking agents, Carella et al [15] suggest that IFN be discontinued. However, it is uncertain that discontinuation of IFN will lead to resolution of the hyperthyroidism any more rapidly.

While corticosteroids are helpful in other forms of destructive thyroiditis such as type 2 amiodarone-induced thyrotoxicosis, they are generally contraindicated in patients with HCV [15]. Furthermore, Minelli et al [19] showed no additional benefit of steroid therapy on the rate of normalization of TFTs 6 months after the discontinuation of IFN therapy in IFN-α–treated hepatitis C patients.

Close monitoring of patients for the development of hypothyroidism following the hyperthyroid phase of destructive thyroiditis is necessary [1]. If hypothyroidism develops, it is usually mild, asymptomatic, and self-limited. If it is more severe [15], levothyroxine therapy, which can be started and continued until the course of IFN treatment is complete. At that point, it can be discontinued and an assessment made about whether the hypothyroidism is permanent or not.

Hypothyroidism

In patients who develop hypothyroidism during IFN-α treatment, supplementation with levothyroxine is usually indicated, without the need to withdraw IFN-α [15]. Levothyroxine is usually discontinued at the completion of IFN-α therapy; however, in patients with positive Tg-Abs and TPO-Abs, hypothyroidism is more likely to be persistent, and levothyroxine therapy may need to be continued or restarted if it had been withdrawn [20]. Antithyroid antibodies may persist for years in euthyroid individuals after a course of IFN therapy, suggesting continual risk for the development of thyroid dysfunction.

Graves' Disease

In patients with mild Graves' hyperthyroidism, IFN-α treatment may be continued, with the addition of an antithyroid drug at low doses to control the excessive thyroid hormone production [14]. If Graves' disease is severe, withdrawal of IFN seems appropriate and large doses of antithyroid drugs may be necessary to control the disease [15]. Although antithyroid drugs have rare idiosyncratic hepatotoxic reactions, underlying liver disease is not a contraindication to antithyroid drug use. However, higher doses of antithyroid drugs may increase the risk for hepatic dysfunction, and some recommend against their use in patients with HCV [1]. Furthermore, since remission of Graves' disease with antithyroid drugs is unlikely in severe hyperthyroidism [21], definitive treatment with radioiodine or, rarely, thyroidectomy followed by supplementation with levothyroxine may be required.

How the Diagnosis Was Made

In the case described above, the TFTs [suppressed TSH of 0.02 mU/L (normal 0.5–5.0), TT_4 of 15.6 g/dL (normal 4.6–12), T_3RU of 28%, and FTI of 4.4 (normal 1.6–3.7)] were consistent with hyperthyroidism. The differential diagnosis included destructive thyroiditis versus Graves' disease. The subsequent laboratory data, which showed an increased 24-hour RAIU (58%) and markedly positive TPO-Ab, were consistent with Graves' disease.

Interferon-α was initially continued and the patient was started on methimazole. However, she remained biochemically hyperthyroid. IFN-α was then discontinued,

but hyperthyroidism did not remit after an additional 6 months of antithyroid drug treatment, and she ultimately received radioiodine therapy. Three months later, she developed postablative hypothyroidism and was started on levothyroxine replacement. Six weeks after starting levothyroxine, her TSH was 1.05 mU/L.

Lessons Learned

1. Up to 20% of patients treated with IFN for HCV develop thyroid dysfunction [2].
2. IFN-α–induced thyroid dysfunction can be immune and nonimmune related.
3. Autoimmune IITD: (1) increase in the titer of preexisting antithyroid antibodies or de novo induction of autoantibodies without clinical evidence of thyroid disease; (2) destructive thyroiditis; (3) Hashimoto's thyroiditis (autoimmune hypothyroidism); (4) Graves' disease.
4. Nonautoimmune IITD: (1) destructive thyroiditis; (2) hypothyroidism.

Destructive Thyroiditis

- ↓ TSH, ↑ free T_4, ↑ free T_3, (–)TSAb, ↓ RAIU, and ↓ vascularity on color flow Doppler.
- Treatment: (1) mild or asymptomatic: no treatment, continue IFN; (2) asymptomatic and cardiac risk factors: beta-blocking agents, continue IFN; (3) symptomatic: beta-blocking agents, continue IFN; if symptoms uncontrolled, discontinue IFN until patient euthyroid; (4) if hypothyroidism develops, it is reasonable to treat with levothyroxine and continue IFN.

Hypothyroidism

- Occurs in about 2.4% to 19% of the patients with HCV receiving IFN-α;
- Can be immune (Hashimoto's) or nonimmune (direct effect of IFN) mediated.

Graves' Disease

- ↓ TSH, ↑ free T_4, ↑ free T_3, (+)TSAb, and high RAIU.
- Treatment: (1) mild: continue IFN-α with low dose antithyroid drugs [15]; (2) severe: discontinue IFN, use larger doses of antithyroid drugs (controversial because of side effects); definitive treatment with radioiodine or thyroidectomy followed by supplementation with levothyroxine, may be required.

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Multiple-Choice Questions

1. 45-year-old woman, was recently started on IFN-α therapy for the treatment of hepatitis C. A few weeks later she developed symptoms of hyperthyroidism. You are suspicious of destructive thyrotoxicosis. To confirm your diagnosis, you order thyroid function tests. Which of the following laboratory sets of data is likely to be seen with destructive thyroiditis? (TSH, thyroid-stimulating hormone; FT_4, serum free thyroxine; TSHR-Abs, TSH receptor antibodies; RAIU, radioactive iodine uptake; color Doppler, color-flow ultrasound Doppler of the thyroid.)

	TSH	FT_4	TSHR-Abs	RAIU	Color Doppler
A	↓	↑	+	↑	↑
B	↓	↑	−	↓	↓
C	↓	↑	+	↓	↓
D	↑	↓	+	↑	↑
E	↑	↓	−	↓	↓

Answer: B. Refer to the text for an explanation.

2. Which of the following is NOT true regarding destructive thyrotoxicosis in the setting of IFN-α therapy?

A. Destructive thyrotoxicosis usually occurs in the first weeks after the initiation of IFN-α therapy.
B. In contrast to patients with subacute thyroiditis, neck pain is rarely present.
C. Thyrotoxicosis is frequently mild and transient.
D. Treatment with beta-blocking agents and antithyroid medications is usually the first-line therapy to control symptoms of thyrotoxicosis.
E. All of the above are true.

Answer: D. Refer to the text for an explanation.

3. 50-year-old man with a history of hepatitis C, is treated with IFN-α. A few weeks after the initiation of IFN-α, the patient returned to his primary care physician complaining of a mild tremor and heat intolerance. He has no weight changes, palpitations, or gastrointestinal symptoms, and he denied any dysphagia or visual disturbances. His thyroid function tests revealed a TSH of 0.04 mU/L (normal 0.5–5), a free T_4 of 2.0 ng/dL (normal 0.8–2.0), and a total T_3 of 220 ng/dL (normal 70–190). He was then referred to the endocrine clinic for the evaluation. You ordered a TSH receptor antibody (TSHR-Ab) assay, which was positive, and a 24–hour radioactive iodine uptake (RAIU) was 46%. The next best step in the management of this patient is:

(A) Continue IFN-α, start low-dose antithyroid medication.
(B) Continue IFN-α, start high-dose antithyroid medication.
(C) Continue IFN-α, start a beta-blocking agent.
(D) Discontinue IFN-α, start low-dose antithyroid medication.
(E) Discontinue IFN-α, start high-dose antithyroid medication.

Answer: A. Thyroid function tests are consistent with mild Graves' hyperthyroidism. Unlike in destructive thyroiditis, which is usually self-limited and treatment with beta-blocking agents is useful in controlling the signs and symptoms of thyrotoxicosis, patients who develop mild Graves' disease require the addition of low doses of antithyroid drugs to control excessive thyroid hormone production .