CASE REPORT

Interferon alpha-induced non-immune thyrotoxicosis treated by plasmapheresis

Zeynel Abidin Sayiner,¹ Ayten Eraydın,² Taylan Metin,² Mesut Özkaya¹¹Department of Endocrinology and Metabolism, Gaziantep University, Gaziantep, Turkey²Department of Endocrinology and Metabolism, Gaziantep University School of Medicine, Gaziantep, Turkey

Correspondence to

Dr Zeynel Abidin Sayiner, zeynelasayiner@hotmail.com

Accepted 12 September 2017

SUMMARY

Interferon-alpha (IFN- α) is an effective drug used for the treatment of chronic hepatitis C. So far its numerous side effects have been reported in the literature. It may be difficult to always put IFN-induced thyroid diseases into a single classic thyroid disease table. There are numerous atypical thyroid diseases due to IFN usage for hepatitis C virus. Herein, we present a case with a rare clinical table such as thyrotoxicosis observed following IFN- α therapy in a patient with euthyroid nodular thyroid without autoimmune thyroiditis findings and the use of therapeutic apheresis method for the treatment of disease.

BACKGROUND

Interferon-alpha (IFN- α) is an effective drug used for the treatment of chronic hepatitis C. So far its numerous side effects have been reported in the literature. IFN- α has several adverse effects including fever, muscle and joint pain, influenza like symptoms, severe haematological abnormalities and pulmonary complications.¹ In addition, thyroid dysfunction has been found between 5% and 15% and thyroid antibody positivity by 40% in patients with chronic hepatitis C treated with IFN- α .² Thyroid function is divided into two forms as autoimmune, which is more frequent, and non-immune, which is more infrequent. Whereas autoimmune events are characterised by Graves' disease and Hashimoto thyroiditis, non-immune events are seen in the form of destructive thyroiditis and hypothyroidism.³ It may be difficult to always put IFN-induced thyroid diseases into a single classic thyroid disease table. There are numerous atypical thyroid diseases due to IFN usage for hepatitis C virus (HCV).^{4,5} Our case is one of them. Herein, we present a case with a rare clinical table such as thyrotoxicosis observed following IFN- α therapy in a patient with euthyroid nodular thyroid without autoimmune thyroiditis symptoms and the use of therapeutic apheresis method for the treatment of disease.

CASE PRESENTATION

A 61-year-old female patients who had no known systemic chronic disease presented to the endocrinology outpatient clinic with the complaints of fever, flushing, sweating and palpitations. It was learnt from her history that on recognition of HCV positivity in the healthcare centre which the patient had been admitted to due to tooth

extraction, she had been put on treatment with ribavirin 600mg/day and IFN- α -2b. As symptoms of the patient suggested thyrotoxicosis, testing was performed for this purpose. Patient's thyroid-stimulating hormone (TSH) was found as 0.07 uIU/mL (0.34–5.6), FT3 as 27.56 pg/mL (2.5–3.9), FT4 as 4.94 ng/dL (0.61–1.12), antithyroid peroxidase as 1.6 IU/mL (0–9) and antithyroglobulin AB as 1 IU/mL (0–4). TSH receptor antibody was found as negative. Antithyroid therapy was not initiated in the patient with increased aspartate transaminase and alanine transaminase values by about fivefold due to the risk of hepatotoxicity. Thyroid scintigraphy performed revealed toxic nodular thyroid disease on hyperplastic ground (figure 1). It was found in history records of the patient that she had undergone thyroid assessment before initiating IFN therapy. It was observed that the patient who previously had euthyroid nodular thyroid disease was on follow-up, but she had no thyroid dysfunction. The patient was taken to apheresis on the same day. After apheresis was performed two times, the control values were found as FT3: 4.02 pg/mL (2.5–3.9) and FT4: 0.85 ng/dL (0.61–1.12). IFN therapy of the patient was interrupted on consultation with the hepatology department. Active complaints of the patient were regressed. Her thyroid function tests returned to normal within 4 days. The patient was not administered any antithyroid drug. No thyroid dysfunction was found at periodic follow-ups of the patient.

DISCUSSION

IFN-induced thyroiditis (IIT) is a common complication of IFN- α which is used in treatment of chronic hepatitis C infection.³ IIT is clinically divided into two forms as autoimmune and non-immune. Incidence of thyroid dysfunction which is considered to be associated with the use of IFN- α is very variable in the literature.^{6,7} While autoimmune conditions manifest as Hashimoto thyroiditis and Graves' disease, non-immune IIT is seen in the form of destructive thyroiditis or non-immune hypothyroidism. Direct effects of IFN- α on the thyroid are thought to have a part in the development of non-immune thyroiditis.⁸ In addition, HCV itself is likely to trigger immune response in thyrocytes. IFN- α directly induces thyrocyte death and inhibits the production of thyroglobulin (Tg), thyroid peroxidase and sodium iodide symporter proteins.^{9,10} Non-immune IIT is generally presented as destructive thyroiditis. Destructive thyroiditis is a self-limiting inflammatory disease of thyroid glands

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To cite: Sayiner ZA, Eraydın A, Metin T, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-221228

Figure 1 Thyroid scintigraphy: toxic nodular thyroid disease on hyperplastic ground.

which is characterised by early phase due to the release of thyroid hormones and late hypothyroid phase with complete resolution observed.¹¹ The thyroid scintigraphy performed in our patient revealed toxic nodular thyroid disease on hyperplastic ground. There were hyperactivity signs on the ground in the detailed scintigraphic examination, while the nodules were relatively hypoactive. This suggested us a hyperactivity developed on the thyroid ground rather than toxic nodules, but there was no marker positivity that may suggest any autoimmunity. It may be speculated here that there might be a temporary immunity stimulation. Furthermore, the thyrotoxic situation developed might be due to a ground-induced transient immunity stimulus rather than a nodular autonomy and a destructive condition.

New modalities have been developed instead of antithyroid therapy in the case of high values of liver function test in patients with non-immune thyrotoxicosis which is developed with IFN- α , and one of them is therapeutic apheresis which has recently come into prominence. Therapeutic apheresis cleans both free T4 and T3 and those bound to proteins from circulation. Plasma change provides new binding area to free T4 and T3 in the circulation, providing a gradual reduction in free hormone levels which manifest itself as decrease in clinical findings of thyrotoxicosis.¹² Rarely two or three therapeutic apheresis are required for patients to become euthyroid and it tends to persist in those who give no response to this.¹³ In conclusion, although the aetiology of IIT is not clearly understood, immune mechanisms, genetic factors or direct toxic effect on thyroid are the possible options. Herein, it should be kept in mind that HCV itself also contributes to the development of IIT and TSH levels should be monitored every 2–3 months in patients with hepatitis C infection receiving IFN- α therapy.¹⁴

IFN- α -induced non-immune thyrotoxicosis is rare and it should be remembered that IFN-induced immune or

non-immune thyroid cases may be present in a patient who previously had euthyroid nodular thyroid disease. In addition, the use of therapeutic apheresis instead of antithyroid drugs may be an alternative.

Learning points

- It may be difficult to always put interferon (INF)-induced thyroid diseases into a single classic thyroid disease table.
- IFN- α (INF-) induced non-immune thyrotoxicosis is rare and it should be remembered.
- In case of thyrotoxicosis and liver function abnormalities due to IFN- usage and hepatitis C virus infection, therapeutic apheresis instead of antithyroid drugs may be an alternative.

Contributors All authors: shared the responsibilities of the manuscripts writing process. ZAS: planning and conduct; acquisition of data or analysis and interpretation of data. ZAS, AE and TM: reporting. ZAS and MO: conception and design.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- 1 Araújo ES, Campos AF, Yamashiro J, *et al.* Expectoration of large bronchial casts secondary to the treatment of chronic hepatitis C with pegylated interferon and ribavirin. *Clinics* 2010;65:745–8.
- 2 Prummel MF, Laurberg P. Interferon-alpha and autoimmune thyroid disease. *Thyroid* 2003;13:547–51.
- 3 Tomer Y, Blackard JT, Akeno N. Interferon alpha treatment and thyroid dysfunction. *Endocrinol Metab Clin North Am* 2007;36:1051–66.
- 4 Bohbot NL, Young J, Orgiazzi J, *et al.* Interferon-alpha-induced hyperthyroidism: a three-stage evolution from silent thyroiditis towards Graves' disease. *Eur J Endocrinol* 2006;154:367–72.
- 5 Inoue A, Koizumi S, Matsuda A, *et al.* Graves' hyperthyroidism showing transient hypothyroidism during interferon therapy for chronic hepatitis type C. *Endocr J* 2005;52:293–8.
- 6 Fattovich G, Giustina G, Favarato S, *et al.* A survey of adverse events in 11,241 patients with chronic viral hepatitis treated with alfa interferon. *J Hepatol* 1996;24:38–47.
- 7 Preziati D, La Rosa L, Covini G, *et al.* Autoimmunity and thyroid function in patients with chronic active hepatitis treated with recombinant interferon alpha-2a. *Eur J Endocrinol* 1995;132:587–93.
- 8 Tomer Y, Blackard JT, Akeno N. Interferon alpha treatment and thyroid dysfunction. *Endocrinol Metab Clin North Am* 2007;36:1051–66.
- 9 Caraccio N, Giannini R, Cuccato S, *et al.* Type I interferons modulate the expression of thyroid peroxidase, sodium/iodide symporter, and thyroglobulin genes in primary human thyrocyte cultures. *J Clin Endocrinol Metab* 2005;90:1156–62.
- 10 Akeno N, Tomer Y. Dissecting the mechanisms of interferon-induced thyroiditis (IIT): direct effects of interferon alpha on thyroid epithelial cells. In: *89th Annual Meeting of the Endocrine Society*. Toronto, Canada, 2007.
- 11 Mandac JC, Chaudhry S, Sherman KE, *et al.* The clinical and physiological spectrum of interferon-alpha induced thyroiditis: toward a new classification. *Hepatology* 2006;43:661–72.
- 12 Ezer A, Caliskan K, Parlakgumus A, *et al.* Preoperative therapeutic plasma exchange in patients with thyrotoxicosis. *J Clin Apher* 2009;24:111–4.
- 13 Yamamoto J, Dostmohamed H, Schacter I, *et al.* Preoperative therapeutic apheresis for severe medically refractory amiodarone-induced thyrotoxicosis: a case report. *J Clin Apher* 2014;29:168–70.
- 14 Tomer Y, Menconi F. Interferon induced thyroiditis. *Best Pract Res Clin Endocrinol Metab* 2009;23:703–12.

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