ABSTRACT We describe the first case of Graves’ disease occurring at Sultan Qaboos University Hospital, Oman, in a patient who was under treatment with interferon alfa for HCV infection. INF-α is now being widely used to treat patients with a variety of disorders including infection with hepatitis C virus. Clinical thyroid disease, hypo and hyperthyroidism can occur in up to 15% of patients. We emphasize the need for thyroid function screening before and during therapy to identify patients early in the course of their disease.

Key words: Interferon; Thyroid function test; Thyrotoxicosis; Antibodies, thyroid; Case Report, Oman.

CASE REPORT

Graves’ Disease following Interferon Therapy for Chronic Hepatitis C Infection

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Graves’ disease following interferon therapy for chronic hepatitis C infection

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TSH) and thyroid antibody studies (antimicrosomal and antithyroglobulin negative) were normal.

Twelve weeks after initiation of IFN-α therapy, she complained of palpitations and fatigue and was admitted to the hospital. Physical examination revealed tachycardia, finger tremor, eyelid oedema and a soft thyroid gland with diffuse enlargement: FT4 was 30 (7.9-14.4 pmol/L), TSH <0.005 - (0.34-5.6 mIU/L). IFN-α therapy was discontinued and the patient was started on carbimazole (CB) 45 mg and propanolol 40 mg twice daily. After three months treatment she was euthyroid and was referred to Sultan Qaboos University Hospital for radio-active iodine therapy [Table 1]. Her Tc99m thyroid scan showed a diffuse uptake consistent with Graves’ Disease [Figure 1], having been on carbimazole for 3 months, with FT4: 8.3 (7.9-14), TSH: 0.34 (0.34-5.6). The TSH receptor antibodies were raised 4.5 (-ve < 1 u/L) as were her thyroid antibodies at 420 iu/ml (n 0 - 100).

She received I-131 therapy 653 MBq on 22 April 2007 and it was planned to have a repeat thyroid function tests after 2 months.

**DISCUSSION**

This patient developed thyrotoxicosis while taking IFN-α therapy. A diagnosis of Graves’ disease was made as the patient showed: 1) clinical signs of thyrotoxicosis with a diffuse goiter and periorbital oedema; 2) elevated levels of thyroid hormones and undetectable levels of TSH; 3) diffuse high uptake on Tc99m Scan and 4) a raised TSH receptor antibody titer.

It has been well documented that treatment of chronic hepatitis B and C infections with IFN-α can lead to induction of thyroid antibodies with hypothyroidism or thyrotoxicosis.\(^1\)\(^8\)

The mechanism by which IFN-α induces thyroid dysfunction remains unclear, but the autoimmune mechanism is thought to play an important role. IFN-α enhances the surface expression of major histocompatibility complex (MHC) Class I antigens, which activate cytotoxic T cell function. IFN-α also induces MHC Class II antigens on thyroid cells in patients with autoimmune thyroid diseases. The aberrant expression of MHC antigens on the cell surface, in association with cellular antigens, may be sufficient to interrupt the tolerance and induce autoantibody production. Cytokines (TNFα, IL-1β) that are induced by IFN-α may directly or indirectly disturb the thyroid function by their immunomodulatory effects.\(^2\)

Interferon-associated thyroid disease was first reported in 1985 when three cases of hypothyroidism were seen following IFN-α treatment of breast cancer.\(^2\) Since then, many more cases of thyroid disease induced by IFN-α have been published.\(^1\)\(^-\)\(^8\) IFN-α may provoke two different forms of thyrotoxicosis: a Graves’ disease picture or thyroiditis. The two forms of thyrotoxicosis should be differentiated as they have different implications for therapy.\(^3\) The two forms can readily be distinguished by TSH serology and thyroid scintigraphy. The bi-phasic thyroiditis would not require specific anti-thyroid medications, and the thyrotoxicosis would resolve spontaneously. If the clinical picture is severe, the use of corticosteroids may be appropriate for an anti-inflammatory effect. More important, the risk of subsequent hypothyroidism is high and this requires close monitoring. By contrast, Graves’ disease requires standard and prolonged anti-thyroid drugs. Long term follow up of this group of patients will be interesting as their risk of recurrent thyrotoxicosis or subsequent hypothyroidism is unknown. Radioactive iodine therapy may be necessary for some patients.

Early detection and therapy of these conditions is

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**Table 1: Thyroid hormones and thyroid antibodies before, during, after discontinuation of IFN**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>FT4 (pmol/L)</th>
<th>TSH (mIU/L)</th>
<th>Thyroid Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before IFN</td>
<td>12</td>
<td>2.4</td>
<td>- ve</td>
</tr>
<tr>
<td>On IFN (3/12)</td>
<td>30</td>
<td>&lt;0.005</td>
<td>+ ve</td>
</tr>
<tr>
<td>On CB (1/12)</td>
<td>18</td>
<td>0.005</td>
<td>+ ve</td>
</tr>
<tr>
<td>On CB (3/12)</td>
<td>12</td>
<td>0.005</td>
<td>+ ve</td>
</tr>
<tr>
<td>After I-131 (1/12)</td>
<td>8.3</td>
<td>0.34</td>
<td>+ ve</td>
</tr>
</tbody>
</table>

Normal values: FT4 (7.9-14.4) pmol/L, TSH (0.34 – 5.6) mIU/L.

IFN: Interferon; CB: Carbimazole; FT4: free thyroxine; TSH: thyroid stimulating hormone.
important in order to avoid the complications of thyroid disease such as life threatening cardiac arrhythmias. While it is not clear which factors contribute to susceptibility to interferon induced thyroiditis (IIT), recent evidence suggests that genetic factors, gender and hepatitis C infection may play a role. Viral genotype and therapeutic regimen do not influence susceptibility to IIT. The etiology of IIT is unknown and may be secondary to immune modulation by IFN-α and/or direct effects of interferon on the thyroid.

Our patient, in view of old age, was treated with I-131 therapy, and our plan is to repeat thyroid function tests after two months. If she becomes hypothyroid, she will require lifelong thyroxine.

CONCLUSION

Clinical thyroid disease occurs in up to 15% of patients with interferon-α therapy. We therefore recommend measuring the thyroid function tests and thyroid antibodies before, during, and after interferon therapy to avoid any associated complications such as life threatening cardiac arrhythmias.

REFERENCES


