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CASE REPORT

Graves' Disease following Interferon Therapy for Chronic Hepatitis C Infection

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مرض جريفيز الناتج عن علاج التهاب الكبد المزمن نوع (ج) بالانترفيرون

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الملخص: تقرير عن أول حالة لمريضة اصيبت بمرض جريفز في مستشفى جامعة السلطان قابوس (سلطنة عمان) نتيجة علاجها بعقار الانترفيرون ألفا . لأنها كانت تعاني من التهاب الكبد نوع (ج (. هذا العقار يستخدم في علاج اضطرابات عديدة منها التهاب الكبد الفيروسي نوع (ج) . قد يؤدي هذا العقار إلى اضطراب عمل الغدة الدرقية مما يتسبب في ارتفاع أو انخفاض افراز هرمون الغدة الدرقية بنسبة 15% من المرضى . ولذا ننصح بفحص هرمون الغدة الدرقية قبل وأثناء استعمال هذا العقار للتعرف المبكر على حصول الاضطراب المذكور .

مفتاح الكلمات: انترفيرون . فحص الغدة الدرقية . التسمم الدرقي . الأجسام المضادة . الدرقية . تقرير حالة . عمان .

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.

Interferon α IFN-α is a major therapeutic modality for patients with severe malignant and non-malignant disease including hepatitis C, the latter being fairly common in Oman.[1-4] Prospective studies have shown that up to 15% of those treated with interferon for hepatitis C virus (HCV) will develop clinical thyroid disease and 40% thyroid antibodies. IFN-α induced thyroiditis is of 2 types, autoimmune or non-autoimmune. The former is characterised by the development of thyroid antibodies, with or without clinical disease. These can either block the thyroid stimulating hormone receptor (TSH-R) causing hypothyroidism or stimulate it causing Graves' disease. Non-autoimmune disease can present as destructive thyroiditis and sometimes transient thyrotoxicosis followed by hypothyroidism with negative thyroid antibodies.[1] In this paper, we report the first case of IFN-α induced Graves' disease in Oman. With increasing use of INFα in patients with HCV infections we should screen every patient for thyroid disease before and during therapy.

CASE REPORT

A 60-year old Indian female was diagnosed as having had chronic hepatitis C infection for many years. She had undergone a hysterectomy for carcinoma of the uterus 17 years previously and received a blood transfusion. The patient had no history of thyroid disease and no relevant family history. The genotype of the virus being Type IV, the patient was treated with peginterferon alfa-2a (IFN-α) (180 μg once weekly by subcutaneous administration) from September 2006 through February 2007. Before treatment was started her thyroid function tests: free thyroxine, triiodothyronine and thyroid stimulating hormone (FT_4, FT_3 and

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Table1: ***Thyroid hormones and thyroid antibodies before, during, after discontinuation of IFN***

Treatment	FT4	TSH	Thyroid Antibodies
Before IFN	12	2.4	- ve
On IFN (3/12)	30	<0.005	+ ve
On CB (1/12)	18	0.005	+ ve
On CB (3/12)	12	0.005	+ ve
After I-131 (1/12)	8.3	0.34	+ ve

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

IFN: Interferon; CB: Carbimazole; FT4: free thyroxine; TSH: thyroid stimulating hormone

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

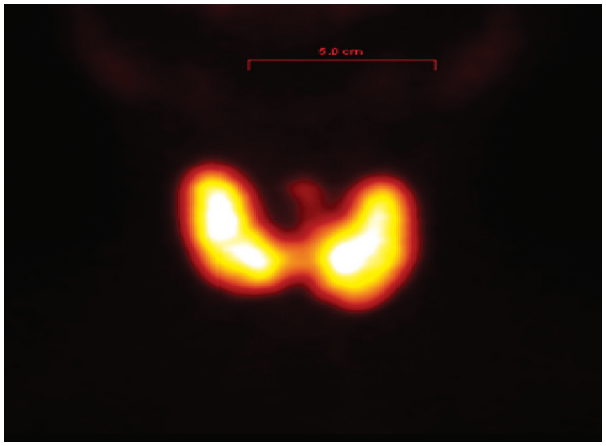

Figure 1: ***Tc-99m thyroid scan with diffuse uptake 3.5% (n 1.0 – 4.0)***

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.[1]

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.

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