CASE REPORTS

Sustained hypothyroidism induced by recombinant α interferon in patients with chronic hepatitis C

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Abstract

Thyroid dysfunction has been reported in patients with malignant disease treated with recombinant α interferon. Two cases of hypothyroidism in patients with chronic hepatitis C treated with recombinant α interferon are reported. In one patient, interferon induced hypothyroidism in the absence of pre-existing thyroid dysfunction and in the other it aggravated a pre-existing thyroid dysfunction. Both patients developed a severe, sustained hypothyroidism requiring thyroxine treatment for one year or more after stopping α interferon. Diagnosis of hypothyroidism during treatment can be difficult because of the common side effects of α interferon. Thyroid function should be assessed before and during α interferon therapy in patients with chronic hepatitis C.

Recombinant α interferon treatment returns serum alanine aminotransferase activities to normal in about 40% of patients with chronic hepatitis C.¹⁻³ In most treated patients, the side effects are mild but α interferon has been reported to induce hyperthyroidism.¹⁴ We report two cases of sustained hypothyroidism induced by α interferon in patients with chronic hepatitis C.

Patients

PATIENT 1

A 30 year old woman suffering from post-transfusion chronic hepatitis C received recombinant α interferon (recombinant interferon alfa 2-b, Intron-A, Schering-Plough) (3 MU, thrice weekly) from January to July 1990. At the end of treatment, she complained of chills and increasing fatigue. The patient had no history of thyroid disease and had not received any drugs known to be toxic to the thyroid. Her serum thyroid stimulating hormone (TSH) and serum free thyroxine (FT₄) values were tested when clinical hypothyroidism was observed and a retrospective analysis was performed on frozen serum aliquots collected before and during α interferon therapy. TSH was determined using a IRMA assay (Behring-France, Rueil, France) (normal, 0.3 to 3.5 mU/l) and FT₄ was determined by radioimmunoassay after direct chromatographic separation (Sclavo-Cis, Gif-sur Yvette, France) (normal, 7.5 to 24 pmol/l). Retrospective analysis showed normal thyroid function before interferon therapy (TSH: 0.8 mU/l; FT₄: 17 pmol/l). At the end of treatment, thyroid function tests showed a low FT₄ value (2.7 pmol/l) and a high TSH (50 mU/l) (Figure). Nine days after the end of treatment, antithyroglobulin antibodies were undetectable (passive haemagglutination); antithyroid microsomal antibodies were detectable (1:25600), then disappeared six months later. The patient received 100 μ g thyroxine daily. Five months later the dose of thyroxine was reduced then stopped. Hypothyroidism recurred with an increased TSH value (28 mU/l) and thyroxine was reintroduced. During interferon therapy her alanine aminotransferase activities returned to normal and remained normal after stopping interferon therapy (at six month follow up).

Serum thyroid stimulating hormone and free thyroxine₄ before, during and after recombinant α interferon administration in two patients with chronic hepatitis C.

PATIENT II

A 39 year old woman with von Willebrand disease, suffering from post-transfusion chronic hepatitis C, received three courses of recombinant α interferon (Intron-A) (3 MU thrice weekly) from October 1987 to March 1988, from June to July 1988, and from August 1989 to March 1990. The patient had no history of thyroid disease and had not received any drug known to be toxic to the thyroid. In October 1989, she complained of progressive fatigue, increasing weight and constipation. In March 1990, a small, firm, and painless goitre was obvious at palpation and at ultrasonography. Thyroid scintigraphic examination (^{123}I) showed poor fixation with a 4% thyroid uptake at four hours (normal, 10 to 25%). Her TSH concentration was high (51 mU/l) and her FT_4 value was low (1 pmol/l). Antithyroglobulin and antithyroid microsomal antibodies were 1:640 and 1:50, respectively. Retrospective analysis showed a mildly increased TSH level (11 mU/l) and normal FT_4 level (9 pmol/l) before interferon therapy. During the first course, obvious biochemical hypothyroidism developed (TSH: 40 mU/l, FT_4 : 3 pmol/l). During the second course of interferon, hypothyroidism remained and was aggravated during the third course (TSH: 51 mU/l, FT_4 : 1 pmol/l) (Figure). Interferon was withdrawn and the patient received 200 μg thyroxine. Serum alanine aminotransferase activities remained slightly increased (60 U/l; normal <40 U/l) at the end of the third course of interferon but returned to normal as soon as thyroxine was given (12 months of follow up).

Discussion

Hypothyroidism and hyperthyroidism induced by α interferon have been described in patients suffering from malignant conditions such as carcinoid tumors, breast cancer and leukaemia.⁵⁻⁷ In patients with chronic hepatitis C treated by α interferon, four cases of hyperthyroidism have been reported.¹⁴ In this report, we describe two cases of sustained hypothyroidism induced by α interferon in patients with chronic hepatitis C. In patient 1, retrospective analysis showed that one course of α

interferon induced clinical hypothyroidism in the absence of pre-existing thyroid dysfunction. In patient 2, retrospective analysis showed that the three successive courses of α interferon progressively aggravated a pre-existing thyroid dysfunction, leading to biochemical then clinical hypothyroidism. In both patients, thyroid function did not return to normal after withdrawal of α interferon and permanent substitute treatment was needed.

Diagnosis of hypothyroidism during interferon therapy can be difficult since non-specific symptoms such as fatigue may be considered a side effect of treatment. The presence of high antithyroid microsomal antibody titre in patient 1 and of moderate antithyroglobulin antibody titre in patient 2 suggest that hypothyroidism may be related to an autoimmune thyroiditis, as previously reported.^{5,6} Persistence of mildly increased alanine aminotransferase activities during interferon therapy may be related to hypothyroidism as shown in patient 2 whose alanine aminotransferase activity returned to normal with thyroxine administration.

In conclusion, hypothyroidism is a serious side effect of recombinant α interferon treatment in patients with chronic hepatitis C. We recommend that thyroid function should be assessed before and during administration of α interferon.

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