NOTE

Development of Hyperthyroidism during Long Term Interferon Therapy in a Patient with Chronic Myelogenous Leukemia: Case Report

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Abstract. In this case report a patient with thyroid dysfunction who received chronic treatment with interferon-alpha (INF-α) following a diagnosis of chronic myelogenous leukemia (CML) is described. Generally INF-α induced dysthyroidism develops in the earlier phase of INF-α treatment. This is a case report of thyroid dysfunction which occurred 4 years after the patient began to receive INF-α administration. In addition, INF-α was administered to this patient for a longer period than those reported in the literature.

Key words: Interferon, Leukemia, Hyperthyroidism

THE purpose of interferon-alpha (INF-α) treatment in patients with chronic myelogenous leukemia (CML) is to prolong life expectancy. On the other hand, this treatment results in many undesirable effects. The major side effects are fever, fatigue, depression, articular and muscle pain, loss of appetite, skin reactions and gastrointestinal symptoms. Serious and life threatening effects are fortunately rare. Sometimes INF-α therapy may provoke thyroid dysfunction in patients with or without preexisting thyroid dysfunction.

Clinical Report

A fifty-two-year old female patient with CML was hospitalized with recent onset of symptoms including dispnea on effort, palpitation, anxiety and weight loss on July 27, 1995.

When the patient first applied to our hospital in 1991, she was diagnosed as having CML and was admitted to our clinic. The patient was treated with hydroxyurea and a 6 month course of INF-α (3 million units/m²/day three times weekly). The same therapy was continued 3 million units/m²/day two times week with the addition of hydroxyurea. Hydroxyurea therapy was applied according to the white blood cell count. The patient was in a chronic phase of CML under this treatment for the last 4 years.

Physical examination revealed a pulse rate of 114/min and grade 2/6 systolic heart murmur. An electrocardiogram showed sinus tachycardia. The white blood cell count was 12,000/mm³ and platelet count was 943,000/mm³. Peripheral blood smear confirmed the chronic phase of CML.

The thyroid function tests indicated hyperthyroidism. Free T3 was 15.2 pg/ml (range 2.2–4.7), free T4 5.8 ng/dl (range 0.8–2.67) and thyroid stimulating hormone (TSH) < 0.13 micIU/ml (range < 6.5). The thyroid microsomal antibody level (< 50 IU/ml) and thyroglobuline antibody level (< 50 IU/ml) were found to be within the normal ranges (normal ranges: (negative – < 75)
and, (negative – < 50), respectively). The thyroid gland was found of normal size and character and it was painless. No nodule formation was detected with ultrasonography and scintigraphy. The family history of the patient concerning thyroid disease and preexisting thyroid autoimmunity were negative. These findings were suggestive of probable INF-α induced hyperthyroidism. INF-α and hydroxyurea administrations were withdrawn and antithyroid treatment, propylthiouracil 300 mg/day, was started.

The thyroid hormone levels were reduced after six weeks of antithyroid therapy (September 12, 1995). The patient started to gain weight and the pulse rate returned to normal. Hydroxyurea and INF-α treatment were started again associated with a low dose antithyroid treatment (propylthiouracil 25 mg/day). At present she is still on the same therapy and in a chronic phase of CML. The last free T3 level was 3.5 pg/ml, free T4 1.0 ng/dl and TSH 0.1 micrIU/ml, on January 9, 1997.

Discussion

Thyroid dysfunction is one of the side effects of interferon treatment. Approximately 10% of patients may develop thyroid dysfunction during interferon-alpha (INF-α) treatment with several indications. Half of these thyroid dysfunctions are hypothyroidism, and the remaining are hyperthyroidism (3%) or biphasic (hyperthyroidism followed by hypothyroidism) pattern (2%) [1, 2]. The frequency of thyroid dysfunction increases in female patients and in patients with preexisting thyroid antibodies [2].

The thyroid disorders induced by INF-α are reversible. In many patients, discontinuation of INF-α treatment or specific antithyroid therapy may not be necessary, but in some studies patients required definitive therapy [2–5]. The delay of onset of dysthyroidism in patients treated with INF-α may be as long as 9 months [6]. Data about autoimmune disease (especially thyroid immune dysfunctions) in the hematologic malignancies are fragmentary and chiefly concern case reports. The real incidence of such side effects is unknown [7, 8]. Vallisa et al. reported that the incidence of autoimmune dysfunctions during INF-α therapy in patients with hematologic malignancies is very low and is limited to serological abnormalities. They found thyroid autoimmunity in only 2 of 54 patients and the neither of these patients has presented any clinical symptoms of thyroid disorders [9] but the interferon induced thyroid dysfunction was not only related to thyroid autoimmunity. INF-α treatment can induce a number of changes in thyroid functions, some of which are not clinically evident and are not related to thyroid autoimmunity. The induction of antithyroid autoantibodies or an increase in MHC class I antigen expression on thyrocytes and suppression of the expression of class II antigen may be the reason for the development of thyrotoxicosis [10].

In our case, thyroid dysfunction occurred 4 years after the beginning of the INF-α administration. Upon a diagnosis of hyperthyroidism, INF-α treatment was stopped and antithyroid therapy was started. As soon as the thyroid hormone level returned to normal, INF-α treatment was restarted. The significant point in this particular case is the long term administration (5 years) of INF-α as opposed to those reported in current literature. Our patient is still in a chronic phase of CML without any symptoms of hyperthyroidism.

Since increasing numbers of patients are being treated with interferon alpha, all physicians using this agent in clinical settings should be aware of its undesirable effects. INF-α induced hyperthyroidism may also resemble to blastic phase conversion in patients with CML. For this reason, it is suggested that thyroid function be evaluated before starting treatment with INF-α and be monitored regularly (e.g. every four months) during the therapy. In patients with preexisting thyroid autoantibodies or dysfunction, follow up intervals should not be longer than every two months.

References

1. Tsukada K, Nomura T, Higashi K, Takeuchi T (1994) Thyroid function abnormalities during interferon


