Autoimmune Polyglandular Syndrome Type 2 Induced by Treatment With Interferon Alpha

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Abstract: Interferon α therapy has been reported to result in a variety of autoimmune side effects and to increase the risk of thyroid dysfunction. Autoimmune polyglandular syndromes are rarely described conditions characterized by the combination of at least 2 autoimmune endocrinopathies and nonendocrine autoimmunopathies, differing in the immunologic features of their pathogenesis. In light of research carried out in recent years, it seems that autoimmune polyendocrine syndromes occur much more frequently than previously estimated. In this article, the authors describe autoimmune polyglandular syndrome type 2 composed of autoimmune thyroid disease, Addison's disease and premature ovarian failure in a 37-year old woman after treatment of hairy cell leukemia with interferon α. Because of the underlying disorder, interferon α treatment had to be continued, and therefore the patient was prescribed with levothyroxine, hydrocortisone, fludrocortisone and oral contraceptives. Termination of interferon α therapy was associated with a spontaneous normalization of thyroid and adrenal functions, and therefore levothyroxine, hydrocortisone and fludrocortisone treatment was withdrawn.

Key Indexing Terms: Autoimmune polyglandular syndromes; Hypothyroidism; Adrenal cortex insufficiency; Premature ovarian failure; Interferon α. **[Am J Med Sci 2011;341(6):504–507.]**

Autoimmune polyglandular syndromes (APS) are conditions characterized by the association of 2 or more organ-specific autoimmune endocrine disorders and nonendocrine autoimmunopathies.[1–3] In light of research carried out in recent years, it seems that APS occur much more frequently than previously estimated. Based on their clinical manifestations, APS are divided into several types. APS type 2 (APS2) is composed of autoimmune adrenal insufficiency coexisting with autoimmune thyroid disease and/or type 1 diabetes mellitus.[4,5] Although it may manifest for the first time in different age groups, its onset is the most frequently observed in the third or fourth decade of life.[6] There are some differences in the assessment of prevalence of this clinical entity. Depending on the authors, the prevalence varies from 1.4 to 4.5 cases per million to 4 to 5 cases per 100,000 persons.[2,3] The syndrome occurs at least 3 times more frequently in females than males and sometimes is present in several generations of the same family.[4,5] Interestingly, despite an established relationship between interferon α treatment and thyroid dysfunction, particularly in patients with chronic C hepatitis,[7,8] to the best of our knowledge, only 2 articles to date have reported the development of APS in patients receiving interferon α. In the study by Sasso et al,[9] treatment of chronic C hepatitis with this agent resulted in the development of thyroid autoimmunity coexisting with type 1 diabetes. In turn in the study by Fujioka et al,[10] combined therapy with interferon α and ribavirin led to the recurrence of Graves disease and the development of type 1 diabetes mellitus. Both patients were diagnosed with APS type 3. In our article, we describe for the first time the case of a female patient who developed APS2 after the administration of interferon α because of hairy cell leukemia. We describe dilemmas associated with discovering and management of this disorder during treatment with interferon α and its natural course after termination of this therapy.

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Submitted October 26, 2010; accepted in revised form January 12, 2011.

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CASE REPORT

A 37-year-old woman started the treatment with pegylated interferon α because of hairy cell leukemia. Before this treatment, the patient had received cladribine and pentostatin, but their administration had resulted in serious adverse effects. The induction dose of interferon α was 3 mIU daily for 24 weeks, administered as a subcutaneous injection, which was followed by a maintenance dose of 3 mIU 3 times a week. Because the presence of thyroid antibodies before the initiation of interferon α therapy is considered a significant risk factor for the development of autoimmune thyroid disorder,[7,8] our patient was screened for thyroid autoimmunity and function. However, thyroid peroxidase antibodies were absent and thyroid-stimulating hormone (TSH) and free thyroid hormone levels were within normal limits (Figure 1). Three months after the onset of the therapy, the patient noticed fatigue, intermittent muscle cramping, cold intolerance, dyspnea, weight gain, constipation, hair loss, dry skin and menstrual irregularities. Physical examination showed nonpitting bilateral edema of the lower extremities, slightly puffy and swollen eyelids, dry skin, hoarseness and low body temperature (35.9°C). Her thyroid profile showed features of hypothyroidism (TSH, 25.2 mIU/L, reference values: 0.45–4.5 mIU/L; free thyroxine, 0.62 ng/mL, reference values: 0.90–1.7 ng/dL; free triiodothyronine, 2.39 pg/mL, reference values: 2.77–5.27 pg/mL) and autoimmune thyroid disease (positive thyroid peroxidase antibodies; Figure 1) and therefore the patient started treatment with levothyroxine. The initial dose of this hormone (50 μg daily) was gradually (during following 4 months) titrated up to 100 μg daily. Only using the last dose of levothyroxine was her thyroid function normal (TSH, 1.25 mIU/L). Administration of levothyroxine improved the clinical status of the patient, but 10 months after the beginning of the therapy with interferon α, she required admission to hospital due to abdominal pain, persistent nausea and vomiting and body weight loss (12 kg within 2 months). Her skin darkened gradually, and on admission, bronze color skin was observed on the face, neck, back of the hands, the palmar folds and the areola of the nipples. On admission the patient was thin, weighting 56 kg, whereas her height was 170 cm (body mass index, 19.4). On physical examination, she presented low blood pressure (80/40 mm Hg), tachycardia (110 beats per minute) and marked dehydration. Plasma adrenocorticotropic hormone levels were high (312 pg/mL, reference

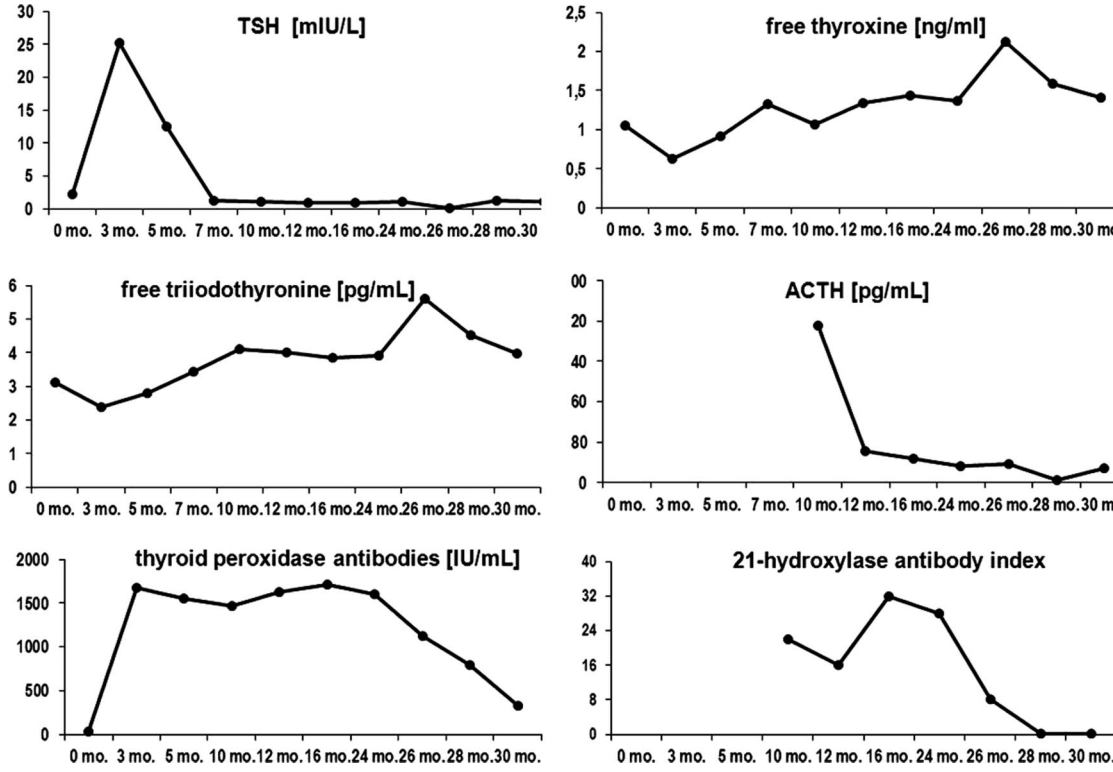

FIGURE 1. Thyroid and adrenal cortex function in the case patient. The *x* axis represents the time (in months) from the beginning of interferon α treatment, which lasted 24 months.

values: 20.0–60.0 pg/mL), whereas morning plasma cortisol (2.9 μg/dL; Figure 1) and dehydroepiandrosterone sulphate (69.2 μg/dL, reference values: 80.0–450.0 μg/dL) were reduced. 17-Hydroxyprogesterone levels were normal (0.5 ng/mL, reference values: 0.2–1.0 ng/mL). Once adrenal function was brought under control, the patient underwent further detailed endocrinological investigation. A 250-μg cosyntropin stimulation test confirmed cortisol insufficiency with a peak cortisol level of 7.2 μg/dL (reference values, >19.6 μg/dL). Supine plasma renin activity was markedly enhanced (30.2 ng/mL/hr; reference values: 0.3–2.8 ng/mL/hr), whereas supine plasma aldosterone was reduced (10.8 pg/mL, reference values: 30–150 pg/mL). After standing for 4 hours, her plasma aldosterone level remained at the similar level (11.2 pg/mL). These results suggested the presence of adrenal cortex failure. The findings that the patient was seropositive for 21-hydroxylase and 17α-hydroxylase antibodies indicated the autoimmune nature of this disorder. Normal levels of catecholamines and their metabolites in urine excluded the presence of coexisting impaired adrenomedullary function. Because of diagnosis of primary adrenal insufficiency, the patient was prescribed with hydrocortisone administered at the daily dose of 15 mg 2 times a day (10 mg in the morning and 5 mg at 4 PM) and fludrocortisone (0.1 mg daily). Sixteen months after beginning of interferon α therapy, the patient contacted our department again because of secondary amenorrhoea, which was accompanied by symptoms of sex steroid deficiency (hot flashes, vaginal dryness and dyspareunia). A gynecological examination revealed that the adnexa on both sides were impalpable and painless in examination. Laboratory examination results revealed high levels of both follicle-stimulating hormone (84.6 IU/L) and leuteinizing hormone (21.2 IU/L) and low plasma estradiol levels (25.8 pg/mL). The concentrations of prolactin, testosterone and androstenedione were within normal limits. Clinical picture and laboratory results indicated the presence of premature ovarian failure, and because of young age, she was started on oestrogen replacement therapy. We decided on the molecular typing of class II major histocompatibility complex alleles, which revealed the presence of the APS2-associated DR3 (DQB*0201)/DR4 (DQB1*0302) genotype.

After 24 months, interferon α treatment was terminated because of achieving a sustained clinical remission. Thyroid, adrenal and ovarian functions were monitored regularly, and 2 months after cessation of the treatment, TSH levels fell to 0.07 mIU/L (Figure 1). This finding and clinical symptoms of hyperthyroidism suggested the excess of thyroid hormones, and therefore the dose of levothyroxine was gradually reduced. Four months after termination of interferon α treatment, we also started to reduce the doses of hydrocortisone and fludrocortisone, because of an increase in plasma morning cortisol (28.5 μg/dL), low adrenocorticotropic hormone levels (5 pg/mL), clinical manifestations of glucocorticosteroid excess, an increase in body weight and hypokalemia, suggesting the excess of mineralocorticoids, and disappearance of 21-hydroxylase and 17α-hydroxylase antibodies. In turn, follicle-stimulating hormone levels remained elevated, and the undertaken trial of estrogen replacement therapy withdrawal was unsuccessful. This therapy was continued for the following 8 years and terminated at the age of 47 years.

Presently, 10 years after treatment with interferon α, the patient feels well. Bone marrow cytology and histology show a complete remission with no evidence of leukemia relapse. She does not experience any endocrinological symptoms. The only