Successful Treatment of Hypothyroid Graves’ Disease with a Combination of Levothyroxine Replacement, Intravenous High-Dose Steroid and Irradiation to the Orbit

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A 46-year-old woman with hypothyroid Graves’ disease (EMO syndrome) is reported. The patient had bilateral exophthalmos, conjunctival chemosis, periorbital edema and limitation of lateral gaze. Laboratory examination revealed the presence of primary hypothyroidism with positive thyroid-stimulating hormone (TSH) binding inhibitory immunoglobulin and thyroid stimulation antibody. These findings indicated a diagnosis of hypothyroid Graves’ disease or EMO syndrome. She received levothyroxine replacement and steroid pulse therapy followed by radiotherapy. Her visual symptoms showed marked improvement and pretibial myxedema disappeared. Although several studies indicate that hypothyroid Graves’ disease is a different entity from hyperthyroid Graves’ disease, this report suggests that steroid pulse therapy combined with radiotherapy may be effective to treat ophthalmopathy in both diseases.

(Key words: EMO syndrome, ophthalmopathy, pulse therapy, supervoltage radiotherapy)

Introduction

Graves’ disease is characterized by hyperthyroidism with diffuse goiter, infiltrative ophthalmopathy and pretibial myxedema (1). A subgroup of Graves’ disease presenting with hypothyroidism has been reported and is called hypothyroid Graves’ disease (2) or Exophthalmos-myxoedema circumscrip- tum praetibiale-osteoarthropathia hypertrophicans (EMO) syndrome (3).

Here, we report a case of hypothyroid Graves’ disease (EMO syndrome) which responded very well to the combined therapy with levothyroxine, steroid pulse therapy and high energy X-ray irradiation to the orbit. Although there is increasing evidence suggesting that hypothyroid Graves’ disease is a different entity from “hyperthyroid” Graves’ disease, the combination of steroid pulse therapy and irradiation to the orbit may be effective in treating the ophthalmopathy of hypothyroid Graves’ disease as well as “hyperthyroid” Graves’ ophthalmopathy.

Case Report

A 46-year-old woman presented with diplopia and pain on gazing in the left direction. She was diagnosed as having Graves’ disease in her twenties, although she had never received any therapy. She began to develop memory loss and general malaise in 1988, and was diagnosed to have hypothyroidism at a local hospital. Although levothyroxine (200 µg day) was prescribed, she took it only irregularly. She visited our hospital for further evaluation in November 1991. Her height was 150 cm, weight 57 kg. She had bilateral exophthalmos, conjunctival chemosis, periorbital edema, excessive lacrimation and a limitation of the left lateral gaze. Proptosis was 22 mm in each eye as measured with a Hertel’s ophthalmometer (normal Japanese, less than 18 mm). The ophthalmopathy index, based on the American Thyroid Association’s classification of the eye change in Graves’ disease (4), was therefore calculated as four. Goiter was not palpable. She developed pretibial myxedema after admission. Ocular magnetic resonance imaging (MRI) and computed tomography revealed slight hypertrophy of the bilateral medial rectus muscles. Plasma thyroid-stimulating hormone (TSH) was measured by immunoradiometric assay using a commercially available kit (TSH-RIABEAD II, Dinabott, Tokyo). Anti-thyroglobulin and antithyroid microsomal antibodies were determined by commercially available hemagglutination methods (TGHA: Thyroid test and MCHA: Microsome test, Fuji Rebio, Tokyo). Serum TSH binding inhibitory immunoglobulin (TBI) activity was measured with a commercially available RIA kit.

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(TRab, Baxter, normal range less than 10%). Thyroid stimulation antibody (TSAb) and thyroid-stimulation blocking antibody (TSBAb) were assayed in FRTL-5 thyroid cells as previously described (5). The thyroid function test revealed the presence of primary hypothyroidism (free T4 0.6 ng/dl and TSH 67.3 µU/ml). TBII and TSAb were positive (34.0% and 200%, respectively), but TSBAb was negative. Anti-thyroid microsomal antibody was positive (×40²), and antithyroglobulin antibody was negative. Treatment with levothyroxine (200 µg/day) was initiated. ³⁹⁹Tc uptake ratio (30 min) was not decreased (1.22%) even after the normalization of TSH levels by replacement therapy, suggesting nonsuppressibility of the thyroid. These findings indicated a diagnosis of hypothyroid Graves' disease (EMO syndrome).

Since the ophthalmopathy improved after administration of prednisolone (25 mg/day for 10 days), steroid pulse therapy (methylprednisolone 1,000 mg, iv for 3 days) was given, followed by radiation to the orbit with high energy X-ray (20Gy) generated by a linear accelerator, as described previously (6) (Fig. 1). Prednisolone was administered orally (40 mg/day for 10 days) and tapered. Visual symptoms such as lacrimation and double vision completely disappeared, which was in accordance with improvement of muscle hypertrophy on MRI. Conjunctival chemosis and preorbital edema also disappeared. Proposis decreased to 18 mm in each eye. Therefore, the ophthalmopathy index was decreased to zero. TBII, TSAb and antithyroid microsomal antibody were also decreased to 6.3%, 108% and 200², respectively. Her pretibial myxedema disappeared. The amount of levothyroxine required to maintain a normal TSH value decreased to 150 µg/day. The patient showed no sign or symptom suggesting recurrence of ophthalmopathy four months after steroid pulse therapy and irradiation.

**Discussion**

Christy and Morse (2) defined hypothyroid Graves' disease as a subgroup of Graves' disease with ophthalmopathy and/or pretibial edema, which presents as hypothyroidism without any antithyroid treatment. It has been reported that spontaneous hypothyroidism develops in some patients with Graves' disease who were previously treated with antithyroid drugs, and that about one-third of such patients are thought to be hypothyroid because of the presence of TSBAb (5). In contrast, in a very recent study, none of the patients with hypothyroid Graves' disease had positive TSBAb (7). These findings suggest that the pathogenesis of hypothyroid Graves' disease may differ from that of "hyperthyroid" Graves' disease.

There is still considerable disagreement concerning the management of Graves' ophthalmopathy (8). It was reported that orbital cobalt irradiation combined with systemic corticosteroid therapy may be more effective than either therapy alone in the treatment of Graves' ophthalmopathy (9). Kendall-Taylor et al advocated the use of high-dose bolus intravenous methylprednisolone (10). We recently reported, in a preliminary form (11), that a combination of high-dose methylprednisolone and supervoltage orbital radiotherapy yielded good results in Graves' ophthalmopathy.

There are few reports concerning the treatment of ophthalmopathy in hypothyroid Graves' disease. It was recently reported that the ophthalmopathy of cases with hypothyroid Graves' disease improved following levothyroxine replacement (12). However, the improvement of ophthalmopathy in the present case cannot be attributed solely to the effect of levothyroxine, because her ophthalmopathy showed further improvement following the combination of steroid pulse therapy and irradiation, which was performed after the normalization of elevated TSH.

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**Fig. 1.** Clinical course after admission. The effects of treatment on ophthalmopathy and the results of thyroid function test are shown.
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with levothyroxine.

In summary, the present case suggests that the combination of high-dose steroid and irradiation to the orbit may be effective in the treatment of ophthalmopathy in hypothyroid Graves' disease, as well as in "hyperthyroid" Graves' ophthalmopathy.

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