Development of Graves’ Ophthalmopathy and Uveitis after Radioiodine Therapy for Graves’ Disease in a Patient with HTLV-I Associated Myelopathy (HAM)

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HTLV-I carriers or patients with HTLV-I associated myelopathy (HAM) are prone to immune-mediated inflammatory disorders. We present a 44-year-old female with HAM who developed Graves’ disease. She developed severe Graves’ ophthalmopathy shortly after 131I therapy, concurrently with a remarkable increase in TSH-receptor antibody titer. Ophthalmopathy was aggravated in spite of prednisolone therapy and euthyroidism being maintained by thyroxine replacement. Uveitis also developed after 131I therapy and iridocyclitis finally required trabeculotomy. This case suggests that HAM patients may have a higher risk of immune-mediated Graves’ ophthalmopathy after 131I therapy.

Key words: 131I therapy, exophthalmos, TSH receptor antibody, hyperthyroidism, autoimmune disease

Introduction

For the hyperthyroidism of Graves’ disease, radioiodine (131I) therapy is popular. About 70% of patients with Graves’ disease are treated by this method in the United States (1), and about 20% and 10% receive such therapy in Europe and Japan, respectively (1–3). Although adverse effects are usually negligible in radioiodine therapy, the development or aggravation of Graves’ ophthalmopathy has been reported (4, 5). We present the case of a patient with HTLV-I associated myelopathy (HAM) who developed severe Graves’ ophthalmopathy and uveitis after 131I therapy for hyperthyroidism. HAM, or tropical spastic paraparesis (TSP), is a spastic spinal paralysis due to HTLV-I infection (6, 7). The geographic distribution of HTLV-I infection is worldwide and the prevalence is strikingly high in southwest Japan, the Caribbean, Central Africa, and Melanesia. The mechanism by which spinal cord degeneration is caused by HTLV-I infection is considered to be immunologic (8, 9). The association of Graves’ disease with HAM is not incidental, because the incidence of many other autoimmune diseases or immune-mediated diseases are high in HAM patients or HTLV-I carriers (10–23). We discuss the various mechanisms by which Graves’ ophthalmopathy and uveitis may have developed or been aggravated after radioiodine therapy in this HAM patient.

Methods

Serum levels of total T4, T3, and TSH were measured by an immunofluorometric assay or immunoradiometric assay using commercially available kits. Free T4 (fT4) and free T3 (fT3) were measured by a one-step analog-tracer-based radioimmunoassay (Amerlex-M Free T4 RIA and Free T3 RIA, Amersham Medical Ltd, Buckinghamshire, UK). The normal ranges of T4, T3, fT4, fT3 and TSH were 80–140 nmol/l (6–11 µg/dl), 1.3–3.1 nmol/l (80–200 ng/dl), 11–28 pmol/l (0.85–2.15 ng/dl), 4.6–8.9 pmol/l (3.0–5.8 pg/ml) and 0.04–4.10 mU/l, respectively. Antithyroglobulin and antimicrosomal antibodies were examined by the particle-agglutination method (Serodia-ATG & Serodia-AMC, Fujirebio Inc., Tokyo, Japan). TSH-binding inhibiting immunoglobulins (TBIH) were measured by their ability to inhibit 125I-TSH binding to solubilized porcine TSH receptors (TRAb Kit, RSR Limited, Cardiff, UK) (normal range: <10%). Both the thyroid stimulating antibody (TSAb) and TSH stimulation-blocking antibody (TSBAb) were measured using cultured porcine thyroid cells (24). Bovine TSH

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Received for publication December 21, 1993; Accepted for publication June 6, 1994
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was used as the standard for thyroid stimulation and TSAb activity was expressed as the percent of cAMP production compared to the control sample (normal: <120%), and as bovine-TSH-equivalent units (normal range: <0.3 mIU/l bovine-TSH-equivalent units). TSAb was expressed as the percent inhibition of bovine-TSH (100 mIU/l)-stimulated cAMP increase (normal range: -16–20%).

Ocular involvement was assessed by physical examination, Hertel exophthalmometry, testing of visual field and acuity, tonometry, slit-lamp examination, and tests of extraocular muscle function with Hess’ chart findings and forced duction test. Additionally, proptosis and extraocular muscle involvements were studied with CT scanning of both horizontal and vertical sections to Reid’s baseline. The degree of proptosis was expressed as the distance from the top of the cornea to the line connecting the frontal edges of the lateral orbit on the CT section which visualized horizontally the center of the lens and the optic nerve. The degree of extraocular muscle enlargement was expressed by the ratio of the maximum cross diameter of the extraocular muscle to that of the optic nerve (normal <1.0).

The degree of ocular involvement was also expressed conventionally according to an ophthalmopathy index (4, 25) based on the American Thyroid Association classification of changes in the eye in Graves’ disease (26).

Case Report

A 44-year-old woman with a 15-year history of HTLV-I associated myelopathy (HAM) was admitted to the hospital for the treatment of Graves’ disease. Her spastic gait developed at age 29 in 1976 and progressed gradually. In 1983, vesicorectal disturbances developed. In 1987, HTLV-I antibody in her serum was examined for the first time and found to be positive, i.e., 8.192 × by the passive agglutination method and 1.280 × by the immunofluorescence method. HTLV-I antibody was also positive in the cerebrospinal fluid (1.280 ×) by passive agglutination. Western blot analysis confirmed that HTLV-I antibody was present in both serum and cerebrospinal fluid. The diagnosis of HAM was thus made. Her HLA type was A24, A31; B51, B52; C blank; DR9, DR14. She began prednisolone (30 mg/day) which was decreased later in a stepwise manner to the dose of 20 mg every other day. Although this therapy, her spastic paraparesis gradually progressed.

In April 1991, she noticed palpitation, diaphoresis and weight loss. She had a diffuse goiter of about 35 g in weight as estimated by palpation. Serum levels of T4, T3, fT4, and fT3 were 360 nmol/l (28.0 μg/dl), 10.3 nmol/l (672 ng/dl), 96 pmol/l (7.43 ng/dl), and >23.0 pmol/l (>15.0 pg/ml), respectively. The serum TSH was suppressed to less than 0.022 mIU/l. Both antimicrosomal and antithyroglobulin antibodies were positive (both 1:2,400). TSH receptor antibodies were positive; TBII, thyroid stimulating and TSH stimulation-blocking antibodies were 37%, 223% and 19%, respectively. Thyroidal radioactive iodine uptake (RAIU) was 62% at 24 hours. She had only minimal eye signs of Graves’ disease, i.e., decreased blinking due to increased sympathetic tone. The Hertel exophthalmometer showed no exophthalmos (15.0 mm, normal: <16 mm in Japanese) for both eyes. She had neither circumscribed myxedema nor achropathy. As treatment for Graves’ disease, 131I therapy was chosen because her gait disturbance seemed to make it difficult for her to visit the hospital at regular intervals for antithyroid drug therapy. 131I therapy (370 MBq, 90 Gy) was performed in May 1991 (Figs. 1 and 2). Treatment by 131I therapy and additional methimazole administration was effective and she became euthyroid and then hypothyroid, as her TSH levels increased markedly. Very soon, however, she relapsed into hyperthyroidism. Serum levels of T4, T3, fT4, and fT3 were 246 nmol/l (19.1 μg/dl), 4.7 nmol/l (303 ng/dl), 47 pmol/l (3.62 ng/dl), and 12.8 pmol/l (8.33 pg/ml), respectively. The RAIU was 40% at 24 hours. 131I therapy (285 MBq, 90 Gy) was performed again in October 1991. Just before the second 131I treatment, the oral prednisolone dose was increased from 20 mg every other day to 20 mg per day to prevent the development of ophthalmopathy. Again, 131I therapy was effective and the thyroid function decreased rather rapidly to the hypothyroid range, and the euthyroid state was maintained by thyroxine supplementation. TSH receptor antibodies increased significantly after 131I therapy as shown in Fig. 2. TBII increased from the pretreatment level of 37% to a peak level of 67%. TSAb increased from the pretreatment level of 223% (2 mIU/l bovine-TSH-equivalent) to a peak level of 3304% (26 mIU/l bovine-TSH-equivalent) after 131I therapy. The change in TSAb titer was not significant (from 19% to 8%). The titers of antimicrosomal and antithyroglobulin antibodies did not change significantly after 131I therapy.

Although these therapies were successful in achieving euthyroidism rather quickly, eye symptoms developed after the 131I therapies. After the first 131I treatment, she noticed right myodesopsia. A detailed ophthalmological examination revealed iridocyclitis which disappeared spontaneously in one month. However, two weeks after the second 131I treatment, she suffered from eye irritation and epiphora. Shortly afterward, exophthalmos, chemosis, conjunctival injection and swelling of the eyelids, which are typical of acute Graves’ ophthalmopathy, developed. The Hertel exophthalmometer showed 21 mm on the right and 22 mm on the left. The oral prednisolone dose was increased from a daily dose of 20 mg to 40 mg. In spite of the prednisolone therapy and maintaining euthyroidism, soft tissue involvement (pain, epiphora, chemosis, conjunctival injection and eye lid swelling) and exophthalmos progressed. She developed diplopia on upward and downward gaze in January 1992. She suffered from a painful, oppressive feeling behind the globes, and had pain on attempted upward and downward gaze. The Hertel exophthalmometer showed proptosis of 23 mm on the right and 24 mm on the left. The forced duction test was negative. CT scanning revealed proptosis (25 mm on the right, 26 mm on the left), swelling of the eye lids, increased retrobulbar tissue volume, and swelling of external ocular muscles (superior rectus: 1.25, inferior rectus: 2.0, medial rectus: 1.5, lateral rectus: 1.25). The ophthalmopathy index was 6; 2 for soft tissue involvement, 2 for proptosis, 2 for extraocular muscle involvement, 0 for corneal involvement, and 0 for visual

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Internal Medicine Vol. 33, No. 9 (September 1994)
Fig. 1. The clinical course of Graves' ophthalmopathy and uveitis which developed after radioiodine therapy for hyperthyroidism in a patient with a 15-year history of HTLV-I associated myelopathy (HAM). MMI: 1-methyl-2-mercaptoimidazole (methimazole), \(^{131}\text{I}\): \(^{131}\text{I}\) treatment (90 Gy), x-rays (r.o.): retro-ocular irradiation with 4 MV photons (20 Gy), e.o.d.: every other day.

disturbance. For the rapid aggravation of Graves' ophthalmopathy, the retrobulbar tissue was irradiated with 4 MV photons (20 Gy). With this treatment, the soft tissue involvement and proptosis improved slightly (proptosis 23 mm on the right and 24 mm on the left). The dose of prednisolone was decreased because of the development of iatrogenic Cushing's syndrome. After the decrease in the dose of prednisolone, the soft tissue involvement and proptosis was aggravated again (proptosis 24 mm on the right, 25 mm on the left) and severe uveitis developed in both eyes. The development of uveitis required another increase in the dose of prednisolone. On a large dose of prednisolone, the uveitis subsided gradually. However, the intraocular pressure increased in both eyes (56 mmHg on the right, 44 mmHg on the left) in a manner typical of secondary glaucoma. Various conservative ophthalmological treatments did not protect sufficiently the visual acuity and visual fields and, finally, trabeculotomy was performed for both eyes.

Fig. 2. Alterations in thyroid function and TSH-receptor antibody titers. After radioiodine therapy, a marked increase in TSH-receptor antibody titer was observed concurrently with the development of Graves' ophthalmopathy. TBII: TSH-binding inhibiting immunoglobulins, TSAb: thyroid stimulating antibody.
Discussion

The mechanism by which myelopathy develops in HTLV-I infection has been studied intensively and several lines of evidence suggest that some immune-mediated mechanism damages the central nervous system (8, 9). The characteristics of immunological findings in HAM patients mimic those observed in autoimmune diseases. They include the activation of polyclonal B lymphocytes (27), the increase in activated T cells (28, 29), the increased spontaneous proliferation of the peripheral blood lymphocytes (30–34), HLA-haplotype-linked high immune responsiveness against HTLV-I (35), and increased adherence of T cells to endothelial cells (36). Further, the development of a wide variety of inflammatory lesions in organs other than the central nervous system in HAM patients or HTLV-I carriers has been reported. These include bronchopneumopathy (10–12), polyarthritis (13–15), Sjögren’s syndrome (16), polymyositis (17, 18), uveitis (19–21), and chronic lymphocytic thyroiditis (22, 23). Since a wide spectrum of multiorgan disorders may result, Maruyama et al proposed designating HTLV-I associated complex (HAC) as a new clinical entity (37). Many of these disorders are considered to be autoimmune. Therefore, it is speculated that HTLV-I infection may be involved in the development of autoimmune diseases. Therefore, the association of Graves’ disease with HAM in the present patient is not considered to be incidental. Kawai et al reported that the incidence of HTLV-I infection in patients with chronic lymphocytic thyroiditis is higher than in the general population in an area endemic for HTLV-I infection (23). The involvement of HTLV-I infection in the development of autoimmune disease can be explained by several hypotheses. HTLV-I infected T cells may injure tissue directly or by disregulating the immune system. Alternatively, cytokines produced in the HTLV-I infected tissue cells, for example, synovial cells or alveolar cells, may play an important role in provoking inflammation. Third, anti-HTLV-I antibodies may be involved in the development of inflammation by cross-reacting with tissue antigens. Finally, HTLV-I infection may modify a preexisting autoimmune disease.

In the present patient, severe Graves’ ophthalmopathy developed after 131I therapy. Although aggravation of Graves’ ophthalmopathy after radiiodine therapy is known (4, 5), severe ophthalmopathy is rare in Japan even after radiiodine therapy (38, 39). Therefore, the development of severe ophthalmopathy after radiiodine therapy in the present patient deserves special mention. Graves’ ophthalmopathy is also an immune-mediated disorder of extraocular muscles and retrobulbar connective tissue. Although the precise immunological relationship between retrobulbar inflammation and thyroiditis is unclear, it has been hypothesized that the release of antigens from the thyroid gland causes an immune response which also provokes the inflammation of orbital tissue, probably because there is antigen similarity between the tissues. Thus, the destruction of thyroid follicles by radiiodine has the potential risk of exposing antigens to the immune system and provoking an autoimmune reaction. In fact, the increase in TSH receptor antibody after radiiodine therapy, which was also seen in the present patient (Fig. 2), is a well known phenomenon (40, 41). Bartalena and colleagues reported that prednisolone treatment is useful as a prophylaxis against the aggravation of Graves’ ophthalmopathy after 131I therapy (4). The present patient had been taking a daily dose of 20 mg of prednisolone when she developed Graves’ ophthalmopathy.

Hypothyroidism produced by treatment for hyperthyroidism is also known to aggravate Graves’ ophthalmopathy (42). It is speculated that the increased TSH stimulates the thyroid gland to express and release antigens which provoke autoimmune reactions against retrobulbar tissue. In the present patient, TSH was increased after both 131I therapies. The increase in TSH after the first 131I treatment was very transient and was followed by the relapse of thyrotoxicosis. TSH was increased again after the second 131I treatment and then normalized by thyroxine replacement. It was difficult to prevent the TSH increase in the present case because it increased very rapidly after the 131I therapies. These episodes of increase in TSH may have aggravated the Graves’ ophthalmopathy in the present patient.

The development of severe Graves’ ophthalmopathy in the present HAM patient suggests that hyperthyroidism should be treated carefully so as not to stimulate the autoimmune mechanism of Graves’ disease, particularly in HAM patients or HTLV-I carriers, because these patients may have a higher risk for autoimmune-mediated provocation of ophthalmopathy.

The uveitis which also developed after radiiodine therapy in the present patient may not have been influenced by radiiodine therapy because uveitis is not a rare disease in the HTLV-I associated complex (19–21). However, it is probable that the underlying uveitis was affected adversely by the severe Graves’ ophthalmopathy. In the present patient, refractory iridocyclitis and large dose prednisolone therapy finally induced bilateral glaucoma that required trabeculotomy.

References