Intravenous Cyclophosphamide Pulse Therapy Is Effective for Refractory Graves’ Ophthalmopathy

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Abstract: Graves’ ophthalmopathy is the most frequent extrathyroidal manifestation of Graves’ disease. Although glucocorticoids and orbital radiotherapy have been used and are effective for the disease, we often experience cases refractory to either therapy. We report here a case that did not respond satisfactorily to either therapy and was later successfully treated by intravenous cyclophosphamide (IV-CY) pulse therapy. A 31 year old woman presented with typical Graves’ disease and ophthalmopathy. After establishing a euthyroid state, she received intravenous glucocorticoid pulse therapy and orbital radiotherapy. Although this induced the resolution of the ophthalmopathy, it was temporary and thyroid-stimulating antibody (TSAb) increased to high titers, associated with relapse of ophthalmopathy 2 months after the treatment. Four courses of IV-CY pulse therapy were administered, which resulted in complete improvement of the symptoms and normalization of the TSAb titers. We suggest that IV-CY pulse therapy might be useful for Graves’ ophthalmopathy, especially for patients refractory to glucocorticoid pulse therapy.

Key words: Graves’ disease, ophthalmopathy, intravenous cyclophosphamide pulse therapy.

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Introduction

Graves’ ophthalmopathy is the most frequent extrathyroidal manifestation of Graves’ disease and remains a pathogenic enigma and a therapeutic dilemma [1]. In its severe expression, it is a disfiguring and invalidating disease that profoundly influences and impairs the quality of life of affected individuals. Glucocorticoids and orbital radiotherapy have been used for many years [2, 3]. The reported average response rate to treatment with intravenous glucocorticoids is 77% [4]. On the other hand, the reported beneficial effect of orbital radiotherapy is 65% [4]. Furthermore, orbital radiotherapy has been used in combination with high-dose glucocorticoids so as to combine the more rapid action of glucocorticoids and the more persistent effect of irradiation [5]. However, although some patients do not respond well to the combined therapy, there are no established therapies for such cases. On
the other hand, intravenous cyclophosphamide (IV-CY) pulse therapy has been used for the treatment of a wide variety of autoimmune disorders, such as Wegener’s granulomatosis [6], rheumatoid vasculitis [7] and systemic lupus erythematosus [8]. Durrani et al. [9] reported the efficacy and short-term safety of IV-CY in the treatment of patients with severe ocular inflammatory diseases.

Here we report a patient with severe Graves’ ophthalmopathy treated successfully with IV-CY, and suggest that IV-CY therapy may be potentially useful for the management of Graves’ ophthalmopathy refractory to steroid therapy.

**Case Report**

A 31 year old woman first noted symptoms of palpitation, finger tremor and heat intolerance in June 2000. Laboratory tests were consistent with hyperthyroidism including TSH <0.03 μU/ml, free T3 17.5 pg/ml, and free T4 7.3 ng/dl. Based on the presence of diffuse goiter and a positive TSH receptor antibody (TRAb: 77.5%), she was diagnosed with Graves’ disease and treated with metimazole (20 mg/day). The treatment resulted in the resolution of clinical symptoms one month later. Although she became euthyroid state, bulging of both eyes was noted, together with diplopia, pain and overflow of tears from both eyes. In December 2000, she was referred to our hospital for treatment of ophthalmopathy. Physical examination showed a positive Grafe’s sign, lid retraction and disturbance of right eyeball movement in the right lateral view. The proptosis was 23 mm for the left eye and 24 mm for the right. Laboratory studies revealed mild hypercholesterolemia but no abnormality on urinalysis. Magnetic resonance imaging (MRI) demonstrated exophthalmos and thickening of extraocular muscles bilaterally (Fig. 1A), confirming the diagnosis of Graves’ ophthalmopathy. Marked enlargement of superior, inferior and medial rectus muscles were observed. The clinical activity score (CAS) was 6 and NOSPECS (N: no signs, no symptoms, O: only signs, no symptoms, S: soft tissue involvement, P: proptosis, E: extraocular muscle involvement, C: cornea involvement, S: sight loss) was class V. Thyroid-stimulating antibody (TSAb) was highly positive (2430%).

Glucocorticoid pulse therapy (500 mg/day methylprednisolone intravenously) was administered for 3 days, and the course was repeated twice within 3 weeks. Orbital radiotherapy (20 Gy in 10 fractions over 14 days) was also applied during the steroid therapy. The combined treatment resulted in the resolution of the eye symptoms, and the patient was maintained on 5 mg/day oral prednisolone. In May 2001, oral prednisolone was discontinued, since both eyes showed full movement. The proptosis was 19 mm for the left eye and 21 mm for the right, and the CAS was 1, and NOSPECS improved to class III. Although the euthyroid state was maintained with metimazole (5 mg/day), the TSAb titers remained high. In October, the eye symptoms worsened again, including pain, overflow of tears and diplopia again. The disturbance of right eyeball movement in the right lateral view also ap-
Fig. 1.  A: Head magnetic resonance imaging demonstrated exophthalmos and thickening of extraocular muscles of both eyes. Marked enlargement of superior, inferior and medial rectus muscles were observed (December 2000).  
B: Magnetic resonance imaging demonstrated reduced thickening of the extraocular muscles after four courses of IV-CY pulse therapy (June 2002).

peared. Although she was administered oral prednisolone (5 mg/day) again, her symptoms did not improve. In January, 2002, NOSPECS became class IV, and the proptosis was 22 mm for the left eye and 23 mm for the right, and the CAS increased to 4. At that stage, we considered the use of other immunosuppressive therapies for the following reasons: 1. relapse of ophthalmopathy soon after glucocorticoid pulse therapy and orbital radiotherapy, 2. oral prednisolone failed to control the symptoms, 3. hypercholesterolemia, and 4. the patient was a mother of three children. After obtaining informed consent, the patient received intravenous pulse cyclophosphamide therapy (750 mg). This treatment was repeated four times every 4 weeks. In May 2002, all symptoms disappeared, and both eyes showed full movement. The proptosis was improved (19 mm for the left and 21 mm for the right eye). The CAS diminished to 1, and TSAb decreased after four courses of treatment. MRI demonstrated bilateral reduction of extraocular muscle thickening (Fig. 1B). Since the symptoms have not worsened since the treatment, oral prednisolone was discontinued in October 2003. The clinical symptoms continue to show sustained improvement at the time of writing of this report. No adverse effects associated with cyclophosphamide therapy were seen. The clinical course is illustrated in Fig. 2.

Discussion

Graves’ ophthalmopathy is an inflammatory condition of the orbits and the most frequent extrathyroidal complication of Graves’ disease [1]. It is an organ-specific autoim-
mune disease characterized by enlargement of the extraocular muscles and increased retrobulbar connective tissues, which cause exophthalmos, periorbital swelling and venous congestion, the main clinical manifestations of the disease. The symptoms include blurring of vision, proptosis, extraocular muscle dysfunction, eyelid swelling, chemosis, redness of conjunctiva, pain, lid lag and retraction. Glucocorticoid and/or orbital radiotherapy have been used in severe and active ophthalmopathy [2, 3]. The beneficial effects of intravenous glucocorticoid therapy were noted in 77% of the cases, while those of orbital radiotherapy were noted in 65% of the cases [4]. Others have suggested that the combination of orbital radiotherapy and high-dose intravenous glucocorticoid pulse therapy provided better results than either therapy alone [5].

However, some patients do not respond to the combination therapy. The use of other immunosuppressive therapies was reported previously for such patients [10, 11], however, none of these approaches showed consistently satisfactory results. In our case, the combination of orbital radiotherapy with intravenous glucocorticoid pulse therapy showed a temporary relief, but the ophthalmopathy relapsed soon after discontinuation of the therapy. Because the symptoms did not improve by oral prednisolone and the patient refused glucocorticoid pulse therapy, we tried intravenous cyclophosphamide (IV-CY) pulse therapy for the refractory Graves' ophthalmopathy after obtaining informed consent. IV-CY pulse ther-
apy has been widely used recently in the management of autoimmune connective tissue diseases, and has resulted in marked improvement in patient outcome [6, 7]. The therapy is especially well established for the treatment of lupus nephritis, where it reduces the risk of end-stage renal failure [8]. Durrani et al. [9] reported the efficacy and short-term safety of the therapy in the treatment of patients with severe ocular inflammatory disease, such as rheumatoid arthritis, systemic lupus erythematosus, Behçet’s disease and idiopathic ocular inflammation. Although the use of cyclophosphamide pulse therapy has been documented in a single case report [12], it was combined with doxorubicin.

Cyclophosphamide is a potent immunosuppressive agent acting on T and B lymphocytes, and the numbers of T and B lymphocytes are known to decrease during the cyclophosphamide therapy [13]. Furthermore, cyclophosphamide suppresses the activation of CD2 on T lymphocytes [14] and the secretion of immunoglobulin by B lymphocytes [15]. In Graves’ ophthalmopathy, autoreactive T lymphocytes recognizing an antigen shared by the thyroid and the orbit infiltrate the orbital tissue [1]. After infiltration of the orbit by T lymphocytes, the shared antigen could be recognized by a T cell receptor on CD4⁺ T lymphocytes. After antigen recognition, CD4⁺ T lymphocytes secrete cytokines that amplify the immune reaction by either activating CD8⁺ T lymphocytes or B lymphocytes, producing autoantibodies [4]. The shared antigen is probably the TSH receptor. In a sample of orbital fat from a Graves’ ophthalmopathy patient, the major TSH receptor transcripts were demonstrated by Northern blot analysis [16]. In fact, TSAb is a sensitive marker of activity of Graves’ ophthalmopathy [17]. In our case, the ophthalmopathy did not improve, while TSAb showed a persistent high titer. TSAb titers markedly decreased, and the activity of ophthalmopathy improved after IV-CY pulse therapy. Thus, we suspect that the effects of cyclophosphamide on inhibition of both T and B lymphocyte function result in reduced production of TSAb.

Finally, four courses of IV-CY pulse therapy were used in our case. The treatment was terminated upon resolution of the symptoms and reduction of TSAb titer to an almost normal level. Fortunately, no adverse effects were seen during the therapy. IV-CY pulse therapy may be useful for Graves’ ophthalmopathy, especially for patients refractory to glucocorticoid pulse therapy. However, further studies are needed to determine the dose and duration of the IV-CY pulse therapy and to assess its safety.

Reference
シクロフォスファミドパルス療法が有効であった難治性甲状腺眼症の1例

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要旨：甲状腺眼症はパセドウ病でよく認められる病態の一つである。グルココルチコイド療法と放射線療法はよく用いられ、最も有効な治療であるが両方の治療に抵抗性の症例もしばしば経験する。我々はこのような難治性の甲状腺眼症にシクロフォスファミドパルス療法が有効であった症例を経験したので報告する。症例は31歳の女性でパセドウ病発症時に眼症を伴っており、甲状腺ホルモンが正常化した後にも症状が持続していたため、グルココルチコイドパルス療法と放射線療法を行った。一旦は改善したが甲状腺刺激型受容体抗体の抗体価が高値となり、2ヶ月後には眼症は再度、悪化したため、シクロフォスファミドパルス療法を4回行ったところ症状は改善し、抗体価も正常化した。

キーワード： パセドウ病，甲状腺眼症，シクロフォスファミドパルス療法。

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