Malignant Exophthalmos Associated with Multiple Myeloma

Akira Seya, Takashi Terano, Yoko Hattori, Takuya Tomizuka, Hiroshi Morio, Tomoshige Kino, Aizan Hirai, Tetsuo Nishikawa*, Yasushi Tamura and Sho Yoshida

We report a patient with malignant exophthalmos associated with multiple myeloma which showed no evidence of direct orbital involvement of plasma cells. This exophthalmos had similarities with Graves' ophthalmopathy, but the patient had no detectable autoimmune thyroid diseases. Plasmapheresis was effective not only for the treatment of heart and renal failure due to the myeloma kidney but also for the malignant exophthalmos. As the serum monoclonal IgG level was decreased by plasmapheresis, the improvement of proptosis, visual acuity, and hypertrophy of the extraocular muscle as measured by magnetic resonance imaging were observed. It is suggested that humoral factors removed by plasmapheresis might be involved in the pathogenesis of this nonendocrine exophthalmos.

(International Medicine 32: 875-878, 1993)

Key words: plasmapheresis, Graves' ophthalmopathy

Introduction

The association between Graves' disease and ocular abnormalities, especially exophthalmos, has been recognized since the observation of von Basedow. Although Graves' ophthalmopathy is thought to be immunologically mediated (1), neither the precise mechanism producing eye tissue damage nor the target of the autoimmune reaction is understood. The eye muscle appears to be the best candidate as an initial target (2). However, few patients with ophthalmopathy are assumed to have any associated thyroid disease (3, 4). In such cases, the pathogenesis of exophthalmos remains unclarified. Although we couldn't point out any evidence of the existence of autoimmune thyroid diseases, the present exophthalmos showed similarities with Graves' ophthalmopathy (GO). Several therapeutic modalities designed to modify immune responses have been proposed for severe forms of GO, such as corticosteroid and other immunosuppressive drugs, orbital irradiation, and more recently, plasmapheresis (5). Plasmapheresis acts directly by extracting a pathogenic immunoglobulin, thereby reducing secondary events induced by abnormal substances. According to Glinoer and colleagues, the most marked effects of plasmapheresis were on soft tissue involvement, proptosis, intraocular pressure and visual acuity (5). Plasmapheresis was quite effective for the present exophthalmos, suggesting that the humoral factors which might relate to multiple myeloma, but were removed by plasmapheresis, might play an important role in the pathogenesis of the present exophthalmos.

Patient and Methods

A 69-year-old woman was admitted to Chiba University Hospital in June 1990 with the chief complaint of dyspnea and disturbance of visual acuity. She had been suffering from heart failure, renal insufficiency (serum creatine 2.0 mg/dl), diabetes mellitus (FPG 128mg/dl, HbA1c 7.1%) and hypertension since 1988 and was being treated at another out-patient clinic. She was taking medications prescribed by that clinic, and still experiencing dyspnea occasionally. In December 1989, she developed discomfort in both eyes. As she complained of edema of both eyelids, exophthalmos and decreased visual acuity, she was referred to the Department of Ophthalmology of Chiba University Hospital, where she was diagnosed as having GO, and then referred to the Second Department of Internal Medicine. Her visual acuity had been progressively worsening and she developed orthopnea ten days before admission.

A physical examination on admission revealed the patient to be emaciated, chronically ill and bedridden. Her height was 152 cm, body weight 45 kg, blood pressure 170/80 mmHg, pulse rate 112/min, body temperature 36.3°C, respiratory rate 24/ min. She had bilateral peri orbital and conjunctival edema. The patient's Hertel measurements were 25mm (right) and 24mm...
On her cornea, bilateral superficial keratitis was present, and the convergence was disturbed. Von Graefe's sign was bilaterally observed, and extraocular movements were disturbed in her left eye when she looked down. Visual acuity of the left and right eyes was 0.06 and 0.08, respectively. A fundoscopic examination showed early diabetic retinopathy (Scott 2). A very small diffuse soft goiter was palpable. Dilated vessels were audible in the bilateral lung base. Edema on bilateral lower extremities was recognized.

**Laboratory findings**

Routine blood studies showed the following: white blood cell count 10,700/mm³; red blood cell count 270 x 10⁶/mm³; hemoglobin 8.0 g/dl; serum GOT 18 IU/l; GPT 11 IU/l; ALP 123 IU/l; LDH 679 IU/l; BUN 49 mg/dl; creatinine 5.27 mg/dl; uric acid 7.6 mg/dl and serum β₂-microglobulin 21,800 g/l. The erythrocyte sedimentation rate was 151 mm/hr. The total protein was 6.7 g/dl. Distribution of the protein fraction was: albumin 41%, α₁ 4.1%, α₂ 18.3%, β 0.6%, γ 29.8%. Serum immunoglobulins were: IgG 2,896 mg/dl; IgA 85 mg/dl and IgM 78 mg/dl. Serum immunoelectrophoresis revealed positive IgG type M-protein. Antinuclear antibody and anti-DNA antibody were both negative. C3 and C4 were within normal range. Fasting plasma glucose was 140 mg/dl. The urinalysis revealed proteinuria (4.5 g/day) with unremarkable sediment. A concentrated (15 times) urinary sample using immunoelectrophoresis showed positive IgG type M-protein without Bence-Jones protein. An electrocardiogram showed left ventricular hypertrophy with inferolateral ischemia. A chest roentgenogram revealed marked cardiomegaly (CTR 74%), bilateral pleural effusion and pulmonary congestion.

Thyroid function tests were: Free T3 1.84 pg/ml; Free T4 0.70 ng/dl; TSH 3.82 µU/ml; thyroglobulin 110 ng/ml; suggesting low T3 syndrome. Thyrotropin binding inhibitor immunoglobulin (TIIB), thyroid stimulating antibody (TSAb), thyroid stimulation blocking antibody (TSBAb), microsome hemagglutination (MCHA) and thyroglobulin hemagglutination (TGHA) were all negative. ¹²³I uptake was 30%/24 hr. In a bone marrow aspiration specimen, 10% of mildly atypical plasma cells were noted. In a rectal biopsy specimen, no amyloid deposition was observed. An eye muscle biopsy specimen revealed the marked infiltration of lymphocytes between eye muscle cells (Fig. 1) but no plasma cell infiltration and no amyloid deposition. Immunohistochemical staining revealed that infiltrated lymphocytes were mainly CD4 positive helper T cells. IgG, IgA and IgM were not stained in the eye muscle cells. Magnetic resonance imaging (MRI) of the orbits showed no orbital tumor but profound swelling of extraocular muscles, especially in the medial rectus muscle (Fig. 2a). Ultrasonography of the thyroid gland showed very small diffuse struma with small cysts. Aspiration biopsy cytology of the thyroid revealed benign follicular epithelial cells and no lymphocyte infiltration. Ultrasonography of the abdomen revealed cholecystolithiasis. The longitudinal kidney size was 7 cm (right) and 10 cm (left) without ultrasonographic finding of amyloidosis. An echocardiogram revealed dilatation of the left ventricle and left atrium with generalized hypertrophy of the cardiac muscle wall. In a skull x-ray, “punched-out” lesions were recognized. A bone mineral scan revealed no abnormal accumulation.

The tentative diagnosis was congestive heart failure and renal failure probably due to multiple myeloma (IgG k type) associated with malignant exophthalmos of an unknown origin, although we could not rule out the possibility of diabetic nephropathy and nephrosclerosis due to hypertension as the cause for the renal failure. As for the exophthalmos, we excluded the possibilities of orbital tumor and plasma cell invasion of the orbit by a biopsy of eye muscle cells. As renal failure and congestive heart failure progressed rapidly after admission, hemodialysis followed by plasmapheresis five times (using double filtration membrane, 1,000–1,200 ml/2 hr) was performed. As the serum IgG level decreased by plasmapheresis, the improvement of not only heart and renal failure but also proptosis, visual acuity, and hypertrophy of extraocular muscle as measured by MRI were recognized almost simultaneously (Fig. 2b). Then, by using prednisolone and melphalan, improvement of these clinical parameters were maintained (Fig. 3).

**Discussion**

A 69-year-old patient presented with malignant exophthalmos associated with multiple myeloma which was not due to plasma cell infiltration and amyloid deposition to the orbit. However, it showed a similarity with Graves' ophthalmopathy based on the characteristic orbital MRI which exhibited swelling of extraocular muscles and also on the evidence of the extraocular muscle biopsy which exhibited lymphocyte infiltration. However, laboratory findings showed no detectable autoantibodies to the thyroid. The thyroid aspiration biopsy cytology specimen showed very little benign follicular cells without lymphocyte infiltration. These laboratory findings combined with the patient's past history does not support the existence of an auto-
Exophthalmos with Multiple Myeloma

Fig. 2. Magnetic resonance imaging (MRI) of the orbit before (a) and after (b) plasmapheresis. In the T1 weighted axial (upper panel) and the coronal view (lower panel), all the extraocular muscles, especially the medial rectus muscle, were swollen before plasmapheresis (a). Marked improvement of the swelling of the extraocular muscle was noted after five plasmaphereses (b).

A case of multiple myeloma in which the bilateral exophthalmos was due to plasma cell infiltration of the orbit has been reported (6). A literature search did not reveal any reported cases of malignant exophthalmos with multiple myeloma without plasma cell infiltration to the orbit.

In the present case, we dealt with not only heart and renal failure, thought to be due to a myeloma kidney, but also malignant exophthalmos, which was not associated with Graves’ disease. The exophthalmos was improved after five plasmaphereses. Plasmapheresis effectively improved the exophthalmos, visual acuity, and swelling of the extraocular muscles as confirmed by MRI of the orbits. It might be suggested that humoral factors removed by plasmapheresis were involved in the pathogenesis of this nonendocrine exophthalmos.

Although few cases of ophthalmopathy are assumed to have any thyroid disease association (3), some immunologically-mediated mechanisms were believed to be working as pathogenic factors in those patients. These factors, including responsible immunoglobulin, have not yet been clarified. In addition to GO, Bankhurst and colleagues reported three patients with exophthalmos secondary to systemic lupus erythematosus, an autoimmune disease (4). In these cases some autoantibody against the eye muscle might be responsible for the exophthalmos. In the present case, the eye muscle biopsy specimen revealed the infiltration of lymphocytes, mainly CD4 positive helper T-lymphocytes between the eye muscles. This might suggest the possibility of the existence of autoimmune mechanism-mediated inflammation, although CD4 positive T cells were also observed to be reactive to inflammation. This inflammation might have caused the swelling of the eye muscles in the present case because other causes of inflammation were not observed. Further study will be necessary to clarify the humoral factors against eye muscles and soft tissues which might be

Immune thyroid disease.
Fig. 3. Clinical course of the patient. Plasmapheresis was effective in decreasing serum IgG, serum creatinine and proptosis. It was also effective in improving visual acuity and subjective complaints. By using both prednisolone and melphalan, improvement of these clinical parameters were maintained. * means the decrease in IgG level just after plasmapheresis.

responsible for the present unknown exophthalmos.

This report describes the first known patient with malignant exophthalmos associated with multiple myeloma who had neither evidence of plasma cell infiltration of the orbit nor detectable autoimmune thyroid disorders.

References