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Case Report

Tocilizumab As Primary Option to The Treatment of Dysthyroid Optic Neuropathy Secondary to Graves' Ophthalmopathy in A Patient Accompanied by Central Serous Chorioretinopathy and Papillary Thyroid Carcinoma

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Abstract

Dysthyroid optic neuropathy (DON) is the most serious classification of Graves'ophthalmopathy (GO). Glucocorticoids is the main treatments of which but not the best choices for all patients. Tocilizumab is used in moderate to severe GO. Here we present a male diagnosed with DON (OS) accompanied by central serous chorioretinopathy (OD) and papillary thyroid carcinoma (left lobe). For that glucocorticoids usage is the risk factor of CSC, intravenous tocilizumab (6 doses of 8mg/kg every 4 weeks) was the primary treatment option for this patient. The severity of the left eye was improved from DON to moderate to severe after tocilizumab infusion. Menwhile, he was received thyroidectomy and pathology verified papillary thyroid carcinoma. This study is the first report about tocilizumab as primary option to the treatment o DON accompanied by central serous chorioretinopathy and papillary thyroid carcinoma.

Keywords: dysthyroid optic neuropathy; central serous chorioretinopathy; papillary thyroid carcinoma; tocilizumab

Introduction

Graves' ophthalmopathy (GO) is an autoimmune and inflammatory disease of orbital tissues which is associated with Graves' disease [1]. Sight-threatening GO, especially dysthyroid optic neuropathy (DON), is the most serious classification of GO [2]. The main treatment choices of DON are intravenous glucocorticoids and orbital decompression. However these two treatments are not the best choices for all patients. Tocilizumab, the monoclonal antibody against IL-6 receptor, is recommended to be used in patients with active moderate to severe steroid-resistant GO [2]. Here we present a case of a male patient who was treated with tocilizumab as the primary treatment of DON accompanied by central serous chorioretinopathy and papillary thyroid carcinoma.

Case Report

A 35-year-old nonsmoking man experienced left eye pain in February 2021 and left exophthalmos with heat intolerance and hidrosis in June 2021. In July 2021, he was diagnosed with Graves' hyperthyroidism and Graves' ophthalmopathy at a local hospital, and ever since he was treated with methimazole. In November 2021, he experienced progressive diplopia with foreign body sensation, and then presented to our hospital in December 2021. He was a programmer with tight competition and always working to late night. The initial eye examination showed corrected visual acuities was 1.0 OD and 1.2 OS (Table 1). The CAS was 0/7 OD and 2/7 OS. The exophthalmometry measurements were 18 mm OD and 24 mm OS. The upper and lower eyelids of both eyes was retracted 1mm above and below the limbus. Corneal ulcer in left eye was observed by front segment photograph (Figure 1). OCT showed papilloedema and choroidal folds in the macular area in the left eye (Figure 1). FFA and ICGA found RPE leakage of the parafoveal macular fovea in the right eye (Figure 2). No vision loss, no pain and no color vision anomalopia, but consistent diplopia were found in both eyes. Enhanced MRI scan of the orbit showed pronounced and circumscribed inflammation of the lateral rectus, superior rectus, medial rectus, superior oblique muscles in the left eye, and inferior rectus muscle in both eyes (Figure 1). Biological test results showed elevated FT3 and FT4, and suppressed TSH levels. Thyrotrophin receptor antibody (TRAb) was much higher than the normal reference range (Table 2). Examination of thyroid ultrasonography showed a single solid hypoechoic nodule in left lobe (10×10mm, ACR TI-RADS 4) (Figure 3), and further FNA demonstrated the hypoechoic nodule was papillary thyroid carcinoma (Figure 3). Therefore, the patient was diagnosed as: [1] Hyperthyroidism, Graves' disease, Graves' ophthalmopathy (DON OS, mild OD; CAS 2/7 OS, 0/7 OD) [2] Central serous chorioretinopathy (OD) [3] Papillary thyroid carcinoma (left lobe). This patient was treated with monthly intravenous tocilizumab (6 doses of 8mg/kg every 4 weeks), besides for methimazole and topical eye treatment. After the second infusion, the papilloedema and

corneal ulcer in the left eye disappeared, and consistent diplopia reduced to intermittent diplopia of both eyes. The clinical activity score dropped from 2 to 0, and the severity was improved from DON to moderate to severe GO in the left eye; no change of clinical activity score and severity of GO was found in the right eye. Then, this patient received bilateral lobectomy of thyroid gland plus central lymph node dissection. Pathological analysis revealed papillary thyroid carcinoma with invasion of the thyroid capsule in left lobe. Immunohistochemical analysis was positive for BRAF (Figure 3). In addition, right central lymph node metastasis of thyroid carcinoma was observed. After the surgery, serum concentration of FT3 and FT4 was immediately dropped below the normal reference range. Meanwhile, TSH elevated much higher than the normal reference range. Then this patient was treated with L-thyroxine. The titer of TRAb markedly dropped and returned to the normal reference range at nearly two months after surgery. Then, he received the remaining four dose of tocilizumab every four weeks. After the six doses of tocilizumab infusion, the exophthalmometry measurements improved from 24 to 21 mm in left eye. The severity of right and left eye was mild and moderate to severe, respectively. The clinical activity score was 0 of both eyes. The corrected visual acuities improved from 1.0 to 1.5 of right eye and remained 1.2 of left eye. MRI after six tocilizumab infusion showed a major reduction of inflammation in all affected muscles (Figure 1). The serum concentration of TRAb, FT3, FT4 maintained within the normal reference range. TSH was suppressed to 0.035 mU/L. The titer of thyroglobulin (HTG) could not be examined (<0.20 ng/mL).

Discussion

In this case, the examination of OCT showed papilloedema and MRI indicated compression of optic nerve in the left eye, and thus DON (OS) was diagnosed. DON is the most severe GO, which can cause impairment of vision or blindness, and thus the treatment of which should be intervened immediately and emergently. Besides the general management including stopping smoking and maintaining normal thyroid function, the mainstay of treatment for DON is high-dose (500 to 1000 mg per day) intravenous methylprednisolone for three consecutive days or on every other day for the first week, which can be repeated for the second week. If this treatment was responseless, orbital decompression surgery is mandatory as the recommendation of 2021 guideline of EUGOGO [2]. Therefore, if there were no contraindications to the use of glucocorticoids to this patient, he would be treated with high-dose intravenous methylprednisolone primarily. Meanwhile, this patient was diagnosed with central serous chorioretinopathy in the right eye. CSC is the fourth common retinopathy, which is more frequently unilateral and mainly affects males aged 25 to 50 years [3,4]. Although the etiology and pathophysiology of CSC have not been completely understood, the potential risk factors include stress burden, personality traits (a competitive drive and a sense of urgency), sleep disorders, glucocorticoid use and infection with Helicobacter (H.) Pylori [4]. This was the case of our patient. It's worth noting that glucocorticoids usage is one of the risk factor of CSC, whereas high-dose intravenous methylprednisolone is the primary treatment of DON.Therefore, DON and CSC comorbidity leads to the contradictory in usage of glucocorticoids in this case. Besides, urgent orbital decompression surgery is not mandatory because of no deterioration in visual acuity or visual fields. Furthermore, there have no specific recommendation of the secondary treatment in the guideline. Then, that which treatment choice is the best one for this case is really a difficult question. Orbital radiotherapy, Cyclosporine, Azathioprine, and biologicals are the secondary treatments of moderate to severe active GOs (2). No matter orbital radiotherapy, Cyclosporine and Azathioprine, a combination of glucocorticoids is required. Teprotumumab, Rituximab and Tocilizumab are the three biologicals recommended for treatment of GO. Teprotumumab is the monoclonal antibody binds to IGF-1R but not yet available in mainland China at that time [5]. Rituximab is the monoclonal antibody against CD20 antigen expressed on B cells. The Chinese guideline mentioned that Rituximab should be avoided for DON [6]. This caution is based on the adverse reactions of Rituximab in previous studies. In a randomized controlled trial concluded moderate to severe active GO patients (Rituximab vs. saline), DON developed in two rituximab-treated patients, while none of saline-treated patients developed DON [7]. Another study reported a severe cytokine release syndrome manifested as obvious periorbital edema and loss of vision in two patients treated with Rituximab [8]. Several successful usages of Rituximab in DON were yet based on the combination with glucocorticoids in the meantime (9,10). Hence Rituximab was not appropriate for our DON patient. Tocilizumab is the monoclonal antibody targeting IL-6 receptors. Although Tocilizumab is recommended to use in patients with moderate to severe active GO, there have a few studies on the treatment of tolizumab for DON reported. A multicenter observational study of 48 glucocorticoid-resistant GO patients, including 7 patients with DON found an obvious improvement after Tocilizumab treatment [11]. Further analysis among the 7 DON patients showed a significant decrease in CAS and intraocular pressure. Moreover, none of these patients experienced a serious adverse reaction. Previous case report described a patient with DON unresponsive to glucocorticoids and orbital radiotherapy but responded well to tocilizumab [12]. Another case report showed Tocilizumab as primary treatment option in a patient with DON and severely uncontrolled diabetes had good clinical results and no adverse effects secondary to Tocilizumab infusion were observed [13]. Finally, we decided to use Tocilizumab to treat DON for this patient after multidisciplinary discussion. The clinical activity score dropped, and the severity was improved. MRI showed a major reduction of inflammation in all affected muscles. Meanwhile, no adverse effects and complications were observed in this patient. Tocilizumab was effective and safe to our DON patient as the previous studies. In addition, this patient had papillary thyroid carcinoma. Several case reports showed newly diagnosed or progressive GO after thyroidectomy and radioactive iodine therapy [14,15,16]. In our patient GO was diagnosed before thyroidectomy, and he did not receive radioactive iodine therapy. There have been no more studies to investigate the association between GO and papillary thyroid carcinoma, but there have studies reported the rate of thyroid cancer is elevated in patients with GD. A cohort study in Taiwan showed GD patients have a higher risk of thyroid cancer after adjusting confounding factors [14]. A retrospective cohort study in Italy reported that the incidence of thyroid carcinoma was much more higher in GD patients [17]. The potential mediator behind this association may be TRAb which activates signal pathway through the TSH receptor, and then results in thyroid gland growth. However, no significant difference was found between the titers of TRAb and PTC development [18]. Meanwhile, the surgical option of PTC and the target of TSH suppression when combined with GO have not been investigated and recommended as well. Hence further studies are need to elucidate these questions. In conclusion, we described a case of DON who was primarily treated with tocilizumab and had good clinical results. Tocilizumab may be proposed as the first-line treatment option in DON patient who had contraindication to glucocorticoids.

Declaration Of Interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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