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Methotrexate Use In Thyroid Eye Disease That Does Not Respond To Corticosteroid Therapy

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Abstract:

A 67-year-old man came to the clinic with moderate to severe bilateral active phase TED by complaining the decreased vision and the worse condition of double vision. The patient had previously received several cycles of intravenous corticosteroid therapy from an ophthalmologist; however it did not have a good respond. The patient was treated and showed significant improvement with methotrexate after several months of use. This case indicated the highlights on the use of methotrexate as an alternative therapy in the cases of TED that did not respond to conventional therapy. Based on the case description, the patient was treated with methotrexate after being evaluated post 16 weeks of administration, it turned out that the patient's condition had a very significant improvement.

Keywords: thyroid eye disease; methotrexate; corticosteroid

1. Introduction

Graves' patient that accompanied by other symptoms and signs of eye disorders called as Graves' ophthalmopathy (OG) which has a bad impact because it causes a decrease in patient's quality of life. OG, also known as thyroid eye disease (TED) is the most common extra thyroid disorder in Graves' disease, from mild (40 - 50%) to severe (3 - 5%) (Stan & Bahn, 2010). TED is an autoimmune inflammatory disorder that results in expansion of extra ocular muscle and orbital fat. Edema, the accumulation of glycosaminoglycan and collagen, and Adipogenesis is the major cause of patients to have enlarged extra ocular muscles and orbital adipose tissue, with one dominant case in several patients (R. S. Bahn, 2010; Dolman, 2012)

Patients with TED experience OG in various forms such as eye pain, gritty eyes, retro bulbar pain, diplopia, loss of vision, which ultimately leads to a decrease in patient's quality of life. TED has a negative impact on the patient's lifestyle, work and psychosocial functioning; therefore TED requires a holistic approach. Generally, TED occurs in patients with

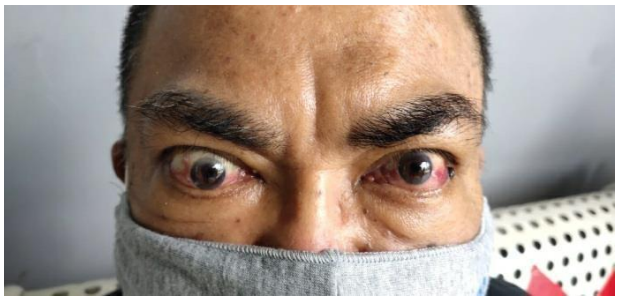
hyperthyroidism or the patient with a history of hyperthyroidism due to Graves' disease. TED is a thyroid disease with relative limited therapeutic modalities with treatment result that have not been fulfill the patient satisfaction (R. Bahn et al., 2007). By writing this case, it is expected that methotrexate can be one of the therapeutic considerations when corticosteroids could not provide the expected results.

2. Case Illustration

A 67-year-old man has consultation for the first time by an ophthalmologist to Endocrine polyclinic Department of Internal Medicine with TED + hyperthyroidism + type 2 diabetes mellitus and should be treated at the same time.

The patient stated that he experience a decrease on vision and accompanied by double vision in both eyes. This complaint began about a year ago. It is also accompanied by protruding eyes, a gritty sensation in the eyes, accompanied by pain, and redness in both of his eyes.

Figure 1. TED on patient (CAS 7/10)



About a year ago, the complaint of unclear vision was felt only in left eye, but over time it was followed by the same complaint in the right eye. The patient then came to hospital's Eye polyclinic for further treatment. Subsequently, the patient was consulted to an Internal Medicine Endocrine polyclinic and received routine therapy with thiamazole 5 mg tablets, propranolol 10 mg tablets, and gliclazide 60 mg tablets every 24 hours. The patient was then re-consulted from an ophthalmologist regarding further treatment of TED that resistant to corticosteroid. The ophthalmologist gave him a high dose of intravenous methylprednisolone within a gram dose for 3 consecutive days. Several months later followed by 500 mg intravenously for up to 6 cycles. After series of treatments, the patient feels that there has no improvement in vision, according to the patient, the symptoms have actually increased. Ophthalmologist stated that there is no improvement on the patient condition.

Physical examination revealed compos mentis consciousness, blood pressure 136/89 mmHg, pulse 92 times per minute, respiration 20 times per minute, body temperature 36.9°C,

SpO2 99% (free air), BMI 25.8 kg/m^2. VAS 3. On eye examination, there is an ODS proptosis, ODS hyperemia while other examinations did not reveal any abnormalities.

The results of threshold test concluded that the right eye was within normal limits and the left eye could not be interpreted (because the patient condition was out of focus); the visual evaluation of left eye 1/60; right eye 5/8. The results of the first evaluation on clinical activity score (CAS) is 7. The first thyroid function examination revealed FT4 2.00 ng/dL (0.89 - 1.76 ng/dl), TSH 0.002 uIU/mL (0.55 - 4.78 uIU/mL), HbA1C 6.5%, FBG 121 mg/dL, 2PPBG 268 mg/dL, triglycerides 150 mg/dL, HDL 53 mg/dL, and LDL 89 mg/dL. Furthermore, the patient was regularly controlled and at the last evaluation, it is obtain the FT4 value of 0.9 ng/dL, TSH 4.473 uIU/mL, FBG 87 mg/dL, HbA1C 5.5%. On the examination of AP chest X-ray within the results of heart and lung impression, there is no abnormalities were seen. Neck ultrasound indicated a bilateral benign thyroid mass TR1 (according to TIRADS). The previous MSCT examination of the head of the orbital focus from a Ophthalmologist obtained a conclusion that the description of thyroid associated orbitopathy (TAO) ODS by figure forming coca cola bottle sign on the right and left of medial rectus muscles (figure 2). The examination of TSH receptor antibodies (TRAb) obtained a value of 2 IU/L (reference value 1.75 IU/L).

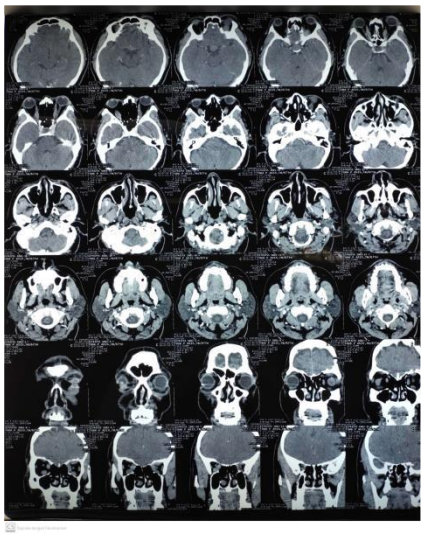


Figure 2. *Coca cola bottle sign* on the medial rectus muscle bilateral

The patient diagnosed with moderate to severe active phase of ODS TED + ODS secondary glaucoma + exposure keratitis + controlled type 2 diabetes mellitus.

The therapy of thiamazole 5 mg tablets every 24 hours, propranolol 10 mg tablets every 24 hours, gliclazide 60 mg tablets every 24 hours keep being implemented, within the additional methotrexate 10 mg tablets once a week, folic acid 1 mg tablets every 24 hours (except on the day that methotrexate was given). and artificial tears a drop every 4 hours ODS,

timolol 0.5% eye drops with a dosage of a drop every 12 hours ODS, and gentamicin eye ointment every 8 hours ODS. The evaluation plan that carried out was CAS, TRAb evaluation and methotrexate side effects.

Treatment week I:

- Symptoms: double vision, feels blurry and gritty, painful, however there is an improvement on the eye that feels a bit light.

Treatment week VI:

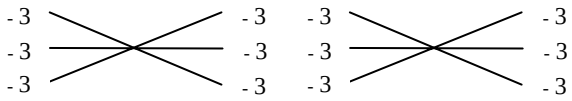
- Symptoms: double vision has not reduced, blurred eyes reduced, there are no more symptoms that the eyes feels like there is sand inside, the pain is still can be felt.

Evaluation result:

VAS: 1

VOD 5/60; TIOD: N+ 2 palpations (on therapy)

VOS 3/60; TIOS: N+ 2 palpations (on therapy)



ODS proptosis (Hertel examination: 22-120-24)

ODS Anterior Segment:

Palpebra : edema +/+, spasm -/-

Conjunctiva: hyperemia +/+, ciliary injection +/+, conjunctival injection +/+, lateral and medial chemosis +/+

Cornea : clear/clear

BMD : shallow/shallow impression, VH II/II

Iris : radier/radier

Pupil : round/round, size 3mm/3mm

Lens : minimal/ minimum blurry

ODS fundoscopy: no evaluation was done

CAS: 6/10 (spontaneous orbital pain, eyelid swelling, conjungtival redness, chemosis, inflammation of caruncle, decrease visual acuity)

Evaluation laboratory:

Hb 12.9 g/dL, WBC 7140 uL, neutrophil 77.5%, lymphocytes 11.9%, platelets 232000 uL,FT4 1.06 ng/dl, TSH 1.232 uIU/mL, FBG 82 mg/dL, 2PPBG 112 mg/dL, SGOT/SGPT 16/26 U/L, albumin 4.1 g/dL, direct/total bilirubin 0.3/1.4 mg/dL, BUN 10 mg/dL, creatinine serum 1.1 mg/dL

- Diagnose: TED ODS active phase moderate - severe + ODS secondary glaucoma + exposure keratitis + controlled type 2 diabetes mellitus

Treatment week XVI:

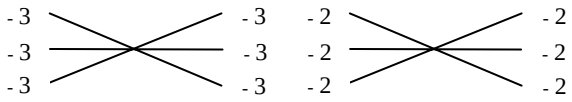
- Symptoms: reduced double vision, no more symptoms of blurred eyes, gritty or painful feeling.
- Evaluation result:

VAS: 0

VOD 5/15 f – 2; TIOD: N+1 (palpation)

VOS 5/10 f – 1; TIOS: N+1 (palpation)

Ocular motility:



ODS Anterior Segment:

Palpebrae : edema +/+, spasm -/-, hyperemia -/-

Conjunctiva: hyperemia +/+, caruncular edema +/+, lateral and medial chemosis +/+ (improved)

Cornea : Clear/Clear

BMD : shallow/shallow impression VH II-III/II-III

Iris : radier/radier

Pupil : round/round, size 3 mm/3 mm

Lens : blurry minimum/minimum

ODS Posterior Segment:

ODS fundal reflex: +/+

CAS: 2/10 (chemosis**,** swollen caruncle)

Laboratory evaluation:

- Hb 13.8 g/dL, WBC 5870 L, neutrophils 61.4%, lymphocytes 30.8%, platelets 283000 L, FT4 0.9 ng/dl, TSH 4.473 uIU/mL, FBG 82 mg/dL, SGOT/SGPT 25/37 U/L, Na 145 mmol/L, K 3.7 mmol/L, Cl 104 mmol/L, BUN 12 mg/dL, creatinine serum 1.0 mg/dL
- Diagnoses: inactive phase of TED ODS + secondary glaucoma ODS + exposure keratitis + controlled type 2 diabetes mellitus.

Treatment week XXIII:

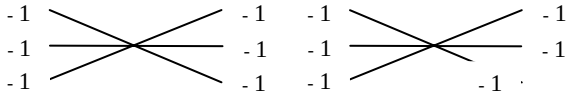
- Symptoms: reduced double vision, no more symptoms of blurred eyes, gritty or painful feeling
- Evaluation result:

VAS: 0

VOD 6/40; TIOD: Normal (palpasi)

VOS 6/12; TIOS: Normal (palpasi)

Ocular motility:



ODS Anterior Segment:

Palpebra : edema -/-, spasm -/-, hyperemia -/-

Conjunctiva : hyperemia +/+, caruncular edema +/+, lateral and medial chemosis +/+ (improved)

Cornea : clear/clear

BMD : deep impression/deep

Iris : radier/radier

Pupil : round/round, 3 mm/3 mm

Lens : clear/clear

ODS Posterior Segment:

ODS fundal reflex: +/+

CAS : 2/10 (chemosis**,** swollen caruncle)

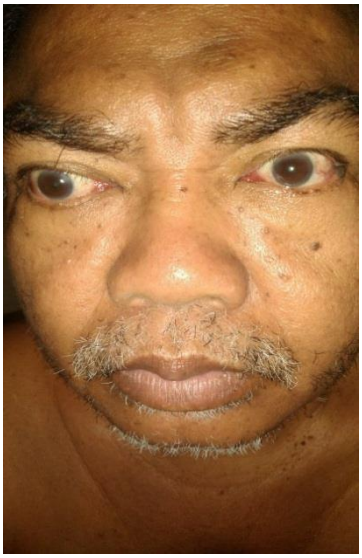


Figure 3. Post-treatment evaluation (CAS 2/10)

Laboratory Evaluation:

TRAb evaluation results obtained 2.0 IU/L (reference value ≤ 1.75 IU/L)

- Diagnose: TED ODS inactive phase + secondary glaucoma ODS + controlled type 2

diabetes mellitus.

3. Discussion

The diagnosis of TED in this patient was made according to the American Academy of Ophthalmology 2014 criteria (Basic and Clinical Science Course, 2014). It is found that the patient has thyroid gland dysfunction that currently being treated, there are specific signs such as eyelid retraction, conjunctival edema, proptosis accompanied by support in form of MSCT that supports the picture of bilateral TED, therefore the diagnosis of TED can be made.

Management of patients with TED is highly depend on the activity of the disease. There are several types of classification to assess TED activity, which the most commonly used is the CAS classification by European Group of Graves Orbitopathy (EUGOGO). The EUGOGO classification divides the severity of the disease into several categories which can be helpful in determining the management of OG (Table 1).

Table 1. CAS Criteria by EUGOGO (Barrio-Barrio et al., 2015)

Initial CAS Assessment
1. Spontaneous orbital pain
2. Orbital pain triggered by eye movement
3. Swollen eyelids suspected to be happen due to the active Graves' ophthalmopathy
4. Eyelids Erythema
5. Redness on conjunctiva happen due to the active Graves' ophthalmopathy
6. Chemosis
7. Inflammation of the caruncle or plica
CAS assessment after re-examination (1-3 months) by adding more score of 8-10
8. Proptosis increases more than 2 mm
9. Reduction of more than 8° the ability to move the eyeball in a direction
10. Decreased visual acuity equivalent to a Snellen line

Each positive symptom was given a score of 1. Ophthalmopathy can be said to be active if the score on early examination is > 3/7 or > 4/10 on re-examination

Severity is classified into three sections based on disturbances in daily activities and treatment plan. OG with minimal impact on daily life, characterized by several factor such as (1) minor lid retraction (less than 2 mm), (2) minimal involvement of soft tissue, (3) exophthalmos less than 3 mm, (4) no diplopia was found or transient diplopia, or (4) corneal involvement that is still responsive to lubricants. it is said that the condition is severe if there is

an interference in visual condition on their daily activities. In this condition, immunosuppressant is given in active conditions or surgery of inactive conditions. The symptom included (1) more than 2 mm lid retraction, (2) soft tissue involvement, (3) exophthalmos bigger than 3 mm, or (4) constant or non-constant diplopia. It can be said that the vision is threatened if there is optic neuropathy or corneal damage due to the prolonged exposure. It should get an immediate treatment (Bartalena et al., 2016).

The level of the disease in this patient was moderate to severe because there is an exophthalmos, diplopia, and soft tissue involvement of eye, therefore the appropriate treatment for this patient is the administration of high-dose intravenous methylprednisolone.

At the initial assessment (before receiving high dose intravenous methylprednisolone therapy), a score of 7/7 was obtained, which means the disease is active. Furthermore, after being reassessed post high dose of intravenous methylprednisolone, it turned out that the results of CAS evaluation have not much different, only 6/7. Then, the patient was treated by methotrexate for 16 weeks and the CAS score was reassessed and score was significantly decreased by 2/10 (chemosis and inflammation of the caruncle) or in the other words the disease became inactive.

Table 2. CAS Patient Improvement

CAS Patient Assessment		
Early condition	After high dosage of Methylprednisolone Intravena	After Methotrexate
1. Spontaneous orbital pain	1. Spontaneous orbital pain	1. Chemosis
2. Orbital pain triggered by eye movement	2. Eyelids swollen due to the active Graves' ophthalmopathy	2. Inflammation of the caruncle or plica
3. Eyelids swollen due to the active Graves' ophthalmopathy	3. Erythema on the eyelids	
4. Erythema on eyelids	4. Redness on conjunctiva happen due to the active Graves' ophthalmopathy	
5. Conjunctiva redness happen due to the active Graves' ophthalmopathy	5. Chemosis	

6. Chemosis	6. Inflammation of the caruncle or plica	
7. Inflammation of the caruncle or plica		
CAS : 7/7	CAS : 6/10	CAS : 2/10

Glucocorticoids are still the most widely used immunosuppressive agents for TED treatment and appear to be most effective for soft tissue inflammation, optic neuropathy, and extra ocular muscle disorders (Bartalena, Marcocci, et al., 2002; Krassas & Heufelder, 2001). The main disadvantages of glucocorticoid therapy are potential for disease recurrence after discontinuation and side effects in long-term treatment. Several alternative therapies have been proposed in the management of glucocorticoid-resistant TED. However, the effectiveness is still being debated in literature.

One of the adverse effects of using corticosteroids is the potential for glaucoma. A steroid is well known to cause ocular hypertension through topical, periocular, systemic and inhalation process. The exact mechanism for the increase in IOP after steroid administration is not clear, it is mainly happen due to the reduced aqueous outflow (Phulke et al., 2017). Discontinuation of steroid use is the first line of management. In majority of cases, the acute increase of IOP which induced with steroid will be normal in few days after discontinuation of steroid and chronically needs a week to four week. Therefore, the choice of therapy should be decided multidisciplinary by considering the advantages and disadvantages of various aspects (Phulke et al., 2017).

In this patient, there was a side effect of glaucoma secondary due to the steroid use, which require the discontinuation of high-dose corticosteroids, beside, the use of corticosteroids did not give any good results on changes in CAS related to TED conditions of patients.

High-dose intravenous corticosteroids are considered first-line treatment for moderate-to-severe and active GO. This therapy should be performed by an experienced medical center therefore it can safely manage the potential for serious side effects. Corticosteroids were given for 6 weeks and if there is no significant improvement then immunosuppressant therapy can be considered as an alternative therapy. For moderate-to-severe GO and inactive state, it can be immediately considered to rehabilitative action. high doses of intravenous corticosteroids for 3 consecutive days are the first-line treatment for sight-threatening cases. It is effective for about 40% of patients, with restoration of vision to normal or near normal (Currò et al., 2014).

If the response is poor, or there is a rapid decline in visual function, immediate decompression should be performed.

Methotrexate is an alternative in a case of glucocorticoid side effects, within a dose of 7.5 - 15 mg/week or 20 mg subcutaneous injection (Bartalena, Tanda, et al., 2002; Stan & Bahn, 2010). The effects of methotrexate have been reported for many autoimmune diseases that require long-term maintenance therapy. Methotrexate is an immunosuppressive agent that inhibits the enzyme dihydrofolate reductase, which leads to inhibition of DNA, RNA, and protein synthesis (Bartalena, Tanda, et al., 2002; Le Moli et al., 2007). Cytotoxic and anti-proliferative effects can be seen at high doses, while anti-inflammatory and immunomodulatory effects can be observed by low-dose chronic treatment (Rampton, 2001).

The use of methotrexate was proposed based on the autoimmune nature of TED (Bartalena 2002b). The reason for using methotrexate in TED is because of its immunosuppressive characteristic. Methotrexate is a folate antagonist that inhibits the enzyme dihydrofolate reductase, thereby it can increase the release of extracellular adenosine. Adenosine acts on a number of leukocyte subtypes through at least four receptors, therefore it has some anti-inflammatory effects (Smith, 2001). Methotrexate also has metabolic effects that have potential to contribute on the success of TED treatment. Methotrexate has been postulated to protect against metabolic risk factors that related to the diabetes mellitus type 2, although the exact mechanism still remain unknown (Pirkmajer et al., 2015). The suppression of chronic inflammation, expected to arise from the release of methotrexate-stimulated adenosine, and it may ultimately and indirectly increase glucose homeostasis (Pirkmajer et al., 2015).

Methotrexate, although not commonly used, it is effective as a single treatment in patients who have failed steroid therapy. A study was conducted in 36 patients with an active TED, who were previously treated with corticosteroids and discontinued due to adverse events, then they started on methotrexate therapy. Different weekly doses are given depends on the patient's weight (7.5 mg or 10 mg). CAS 7, visual acuity, ocular motility, exophthalmos, and eyelid position were retrospectively evaluated at 3, 6, and 12 months and compared with baseline data. The result stated that there was a significant increase in CAS at 3, 6, and 12 months after treatment ($p < 0.0001$) (Strianese et al., 2014). Another study also gave excellent results, 91% achieved an inflammation score of less than 3 in an average 189 days, 29% of patients experienced a rapid decrease in inflammation less than 3 in 90 days, and only 5% experienced side effects that required treatment. It needs a discontinuation of treatment (however the liver function is returning to normal). No major side effects were found (Rubinov et al., 2018).

Specific benefits of methotrexate therapy include minimal hematological toxicity, low risk of opportunistic infections and secondary malignancies, ease of administration (once a week), and relative lower costs (Smith, 2001). Methotrexate was also reported to have minimal adverse effect which reported after a year of continuous treatment with methotrexate in active GO patients (Strianese et al., 2014).

In these patients, the treatment option that given was methotrexate. The use of corticosteroids finally stopped because there is a side effect that was found. Methotrexate is the treatment of choice in this case because methotrexate is known to be effective as a single treatment in patients who have failed on the therapy of corticosteroid. Methotrexate also has a good effect on diabetes mellitus type 2 to reduce the toxicity of methotrexate; the patient was given 6 mg folic acid per week.

The treatment of TED rehabilitation i.e. orbital decompression, squint surgery, and eyelid surgery is required in most patients when TED is already inactivated by immunosuppressive treatment. Surgical rehabilitation in patients with TED is important because it is associated with a significant impact on visual function or quality of life after disease has been inactive for at least 6 months. Surgical rehabilitation in patients with TED is important because it is related to a significant impact on visual function or quality of life after the disease has been inactive for at least 6 months (Bartalena et al., 2016).

The patient was planned for decompression program with lateral tarsorrhaphy as rehabilitation measure, however, until now the action plan still being postponed because according to the EUGOGO recommendations, this action should be carried out at least 6 months after the disease becomes inactive.

4. Conclusion

It is reported that there is a case of 67-year-old man with TED, which is the most common extra thyroid manifestation of Graves' disease. The patient was diagnosed with TED according to the criteria of American Academy of Ophthalmology in 2014. Conventional management is the administration of high-dose intravenous methylprednisolone. However, along with the evaluation, it turned out that the patient did not respond to the therapy. Furthermore, the patient was treated with methotrexate after being evaluated post 16 weeks of administration, it turned out that the patient's condition had a very significant improvement.

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