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Treatment of glaucoma complicated with nodular scleritis with Cyspin: a case report and literature review

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Introduction

The sclera is an avascular connective tissue compromising collagen, elastin, and extracellular matrix proteoglycan. It is covered by the fascia bulbar posteriorly and the conjunctiva anteriorly. Therefore, people are less vulnerable to sclera problems. The etiology of scleritis remains unclear, although there are many theories, ranging from a primary infection (pathogens: bacteria, viruses, fungi, parasites, or *M. tuberculosis*) to secondary immune responses [1, 2]. Scleritis has been associated with systemic diseases (about 30% of patients), ophthalmic surgery or trauma [3]. Based on the Watson and Hayreh classification [4] scleritis is divided into anterior and posterior forms. Anterior scleritis can be further divided into diffuse, nodular, and necrotizing with or without inflammation. Nodular scleritis is the second most common form of anterior scleritis, accounting for approximately 20% of all scleritis [5]. Nodular scleritis is characterized by a localized inflammatory nodule due to dilated scleral vessels.

There are different methods available for nodular scleritis treatment. Most patients respond well to treatment with nonsteroidal antiinflammatory drugs (NSAIDs) in the early stage. Systemic steroids can be considered if NSAIDs fails to relieve pain. The total response rate for steroid therapy varies tremendously among different scleritis forms: nodular scleritis 4–14%, diffuse scleritis 8–33%, posterior scleritis 83% [6]. About 26–38% patients may receive necessary immunosuppressants, such as Cyspin [7].

Here we report the case of a woman who developed glaucoma complicated with nodular scleritis and summarize the use of corticosteroids/Cyspin. This combination therapy appears to be an effective way to shorten the duration of treatment, reduce scleral inflammation, prevent long-term side effects of corticosteroids, and improve the quality of life.

Case report

A 53-year-old female was transferred to our institution for treatment of right eye pain and a blue-grey bump on her superior conjunctiva. Three months ago, she was admitted to a local hospital complaining of a sudden vision decline and redness in her right eye, nausea and vomitting. Her intraocular pressure (IOP) was 50 mm Hg using a non-contact tonometer. She received Pranoprofen TID, Alphagan P BID, Mikelan BID, oral Methazolamide Tablets 1 tablet/time BID and intravenous mannitol QD. She was discharged from the hospital with an IOP 18–20 mmHg and continued IOP-lowering medication at home. About 15 days ago she underwent subconjunctival injection of dexamethasone+lidocaine 3 times due to vision decline and redness in her right eye. But these procedures did not improve her symptoms of eye redness and pain.

Physical examination found that she had a healthy left eye, her right eye vision was 0.04, IOP 28 mm Hg, no swelling on her right upper eyelid. There was a tender oval blue-grey nodule (6×3×3 mm) on her right sclera due to congested sclera and conjunctiva at 12 o'clock position supranasally. Earthworm-shaped blood vessel shadows were seen with negative light transmission test. Her cornea was transparent and remaining conjunctiva was not red with inferior old KP and positive Tyndall phenomenon, and normal anteriror chamber. There was an irregular shaped and enlarged pupil with posterior synechiae at 5–7 o'clock zone, without direct or indirect light reflex. Pigment spots on the anterior lens capsule, mild lenticular opacity and vitreous opacity (++) were observed. The optic disc appeared collapsed and pale (cup/disc ratio 1.0). Macular reflex was not seen. Her examination findings were summarized as follows: ASO (-), RF (-), CRP (-), ESR CCP (-), TORCH: Rub-IgG 18.77IU/ml, CMV-IgG 373.30AU/ml, HSV-I-IgG 363/14AU/ml.

Ultrasound revealed vitreous opacity accompanied with posterior vitreous detachment. Ultrasound biomicroscopy and optical coherence tomography (OCT) found a synechiae between the base of iris and sclera at 6 o'clock position. The chamber angle was open at 3 and 9 o'clock position, but closed at 6. Iris abnormalities were detected at 8–9 o'clock position. There were thickening of the conjunctiva and sclera tissue, echo reduction with cavities, anterior synechiae at the base of iris at 11–12 o'clock position. VOD

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revealed serious vision loss. Macular OCT suggested a normal macular fovea. Fluorescein fundus angiography and indocyanine green angiography confirmed right optic disc collapse and vitreous opacity. There was no dye leakage. Specular microscope revealed normal size (1800/mm^2) and shape of the corneal endothelium. Ocular contrast-enhanced ultrasound showed a 4×2 mm mixed echo bump in the superficial layers just above the sclera which had clear boundaries and irregular shape. There were 3 bright echogenic foci behind the bump. Enhancement pattern of the lesion suggested poor perfusion, slow in and slow out indicating an avascular angioma. She had a mixed echoic nodule with calcification of the right eye; thus, she was diagnosed with scleritis. Enhancement MRI scan of the orbits reported slight thickening of anterior superior sclerotic ring, and linear enhancement. She had a normal chest X-ray. And she did not have a medical or family history of rheumatic diseases, systemic lupus erythematosus.

These findings suggested a diagnosis of glaucoma complicated with nodular scleritis. The treatment plan was as follows:

Stage I (week 1): Tobradex Q1H, Pranoprofen Q2H, methylprednisolone 60 mg/Cyspin 50 mg oral BID, ibuprofen 1 tablet, Brinzolamide TID and Mikelan BID for lowering IOP. Conjunctival hyperemia significantly improved, while the purplish red bump on the sclera did not change.

Stage II (week 2–4): methylprednisolone 40 mg/Cyspin 25 mg oral BID, Pranoprofen QID, Brinzolamide TID and Mikelan BID. Conjunctival hyperemia further improved, and the purplish red bump on the sclera faded. The IOP of the right eye was 13 mmHg. Her kidney & liver function tests were normal.

Stage III: initial dose: methylprednisolone 40 mg; decrease in 4 mg every 3 days; maintenance dose: 8 mg, Cyspin 25 mg oral BID for 2 months, Bromfenac Ophthalmic Solution BID, IOP-lowering drug discontinuation. Her conjunctival hyperemia and pain completely disappeared. The purplish red bump remained. During 1-year follow-up, she was asymptomatic with normal kidney & liver function tests and IOP.

Discussion

In this case, we hypothesize some possible causes of glaucoma and nodular scleritis. 1) Anterior scleritis is the scleral inflammation anterior to the extraocular recti muscles. A persistent elevated IOP and scleritis may induce a scleral staphyloma. 2) Tissue thickening caused by perivascular inflammation of the sclera may further induce elevated scleral venous pressure. 3) Inflammatory cells infiltration in aqueous humor may obstruct the trabecular meshwork and chamber angle resulting in resistant elevated IOP, which reversely worsen inflammation. 4) In our case, scleral thinning might be attributed to subconjunctival steroid injection (we are uncertain about the reason, steroid carrier, or steroid itself).

Scleritis is a painful ocular disease often associated with an underlying systemic illness. Thus, patients should be carefully evaluated for systemic involvement with complete blood count, uric acid blood test, tuberculin test, syphilis, chest X-ray, antinuclear antibodies, complement, antinuclear factor and soluble immune complex. MRI scan of the orbits or ocular contrast-enhanced ultrasound can be performed to help diagnose orbital masses. The use of biopsy is a controversial issue for clinicians. A study by Watson found that biopsy of sclera is contraindicated because the biopsy induces the exposure of choroid resulting in poor scleral healing. In addition, some scleral bumps have the power of healing and fibrosis due to specific proteins within themselves. Another study by Guan suggested that biopsy is a valuable procedure to remove necrotic tissues, promote collagen growth, and help confirm a diagnosis [8]. Scleritis is a kind of disease with a long course and frequent relapse. It is difficult to control, especially when accompanied with glaucoma. The main principles of treatment include lowering IOP, reducing scleral inflammation, preventing staphyloma growth and scleral perforation to save vision and eyeball. Thereafter, regular follow-up is recommended for the remaining eye.

Cyspin is a potent immunosuppressive agent that specially target lymphocytes to inhibit synthesis and release of IL-2 in lymphocytes. It selectively inhibits immune-mediated HLA-DR expression on inflammatory cells to block the cell cycle of lymphocytes in G0 and early G1 phase. Meanwhile, it has no role in erythropoiesis and phagocyte function. Its metabolites are excreted through the bile and feces (half-life: 10–27 hours).

Conclusion

For those patients with complex scleritis and refractory glaucoma, clinicians should avoid the use of subconjunctival glucocorticoids injection for high drug concentration. Immunosuppressants can reduce the dose of corticosteroids and scleral inflammation, especially when corticosteroid dependence, resistance or side effects occur [9] The case suggests the importance of exploring the trough value of Cyspin in order to

control glaucoma complicated with nodular scleritis. Aoki Haruka also reported systemic cyclosporine therapy for complex scleritis [10]. When scleral inflammation and IOP are lowered successfully, clinicians should assess whether to reduce or quit using Cyspin. Further studies with large sample size and long follow-up are required to understand the efficacy and side effects of Cyspin, in addition, we should further investigate the feasibility of needle biopsy and a large number of experiments to further verify.

Aoki Haruka,Hiraoka Miki,Hashimoto Masato et al. Systemic Cyclosporine Therapy for Scleritis: A Proposal of a Novel System to Assess the Activity of Scleritis.[J] .Case Rep Ophthalmol, 2015, 6: 149-57

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Figure legends

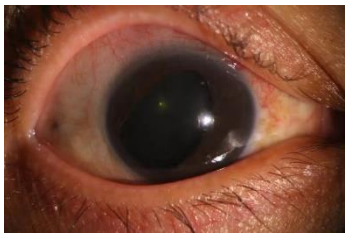

Figure. 1. **It showed an irregular shaped and enlarged pupil with posterior synechiae at 5–7 o'clock zone.**

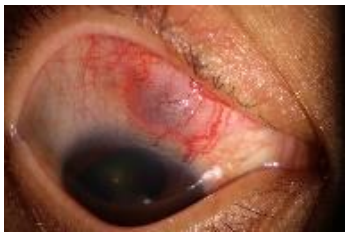

Figure. 2. **There was an oval blue-grey nodule (6×3×3 mm) on sclera due to congested sclera and conjunctiva at 12 o'clock position supranasally. Earthworm-shaped blood vessel shadows were seen with negative light transmission test.**

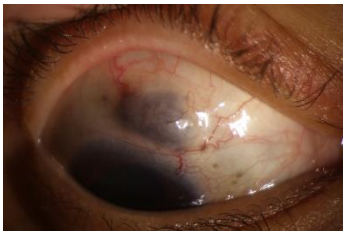

Figure. 3. **Blood vessel shadows disappeared 6 months after treatment.**