Clinical characterization of refractory virus-related inflammation inside aqueous outflow pathways in Chinese immunocompetent patients

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To the Editor: Posner-Schlossmann syndrome (PSS), also known as glaucomatocyclitic crisis, is characterized by acute, unilateral, recurrent attacks of ocular hypertension, mild non-granulomatous anterior uveitis (AU), and spontaneous recovery. However, the etiology of this disease is unknown. Many mechanisms have been proposed including viral infection, autoimmune, autonomic dysregulation, allergic conditions and vascular endothelial dysfunction. Topical anti-hypertensives and anti-inflammatory medications are typically prescribed to combat this disease. Repeated attacks may lead to long-term glaucomatous optic nerve damage over 5–10 years after the first episode. Because the pathophysiology is not completely understood, treatment and prevention of recurrences has proven to be difficult.

While PSS is generally considered a self-limiting disease, we have encountered many refractory cases in Zhongshan Ophthalmic Center. After multiple recurrences despite treatment with anti-inflammatory and anti-hypertensive medications, these refractory cases tend to develop progressive aqueous outflow dysfunction. Some refractory cases require life-long use of intraocular pressure (IOP)-lowering medications while others require filtration surgery to control the IOP. We hypothesized that these refractory cases have features and pathophysiology different from PSS. This disease may be a new clinical entity whose clinical characterization and treatment have not been fully evaluated.

To investigate this entity of “refractive PSS”, we systemically reviewed medical records of “extreme” cases over the past decade. The first group of patients included 21 patients who received filtration surgery (trabeculectomy, Ex-PRESS implant surgery or Ahmed tube implant surgery) due to uncontrolled IOP despite maximal anti-hypertensive medications. Because these patients did not respond to classic steroid treatment, we proposed that autoimmune inflammation is not the principal underlying pathology. The presenting clinical features, disease course, and poor response to classic treatment suggested a clinical diagnosis of refractive viral infection inside the trabecular meshwork (TM) and uveal scleral outflow pathway.

After in-depth analysis, we summarized the common clinical features of these 21 patients as follows: (1) The disease course was prolonged for at least 1 month or frequent relapses; (2) The inflammation and IOP were increasingly refractory to corticosteroids and IOP control medicines; (3) Patients had one or more additional traits: non-mutton fat keratoprecipitates (KP), endothelium cell lesion/loss, or iris atrophy/heterochromia. We hypothesized that patients with these features demonstrated refractory virus-related inflammation inside aqueous outflow pathways and should be systemically treated with anti-viral medications immediately. To evaluate this hypothesis, we conducted the retrospective study of second group.

The 17 patients (including 18 eyes) from April 2016 to July 2017 in second group were retrospectively reviewed. The inclusion criteria were as follows: (1) Patients with a primary diagnosis of PSS and a revised diagnosis of refractory virus-related inflammation inside aqueous outflow pathways; (2) The disease course was prolonged for at least 1 month or had at least 3 recurrences per 6 months or 5 recurrences per year; (3) The inflammation and IOP were increasingly refractory to corticosteroids.

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and IOP lowering medications; (4) Patients had one or more additional traits: non-mutton fat KPs, corneal endothelial cell lesion/loss, or iris atrophy/heterochromia; (5) Patients whose disease course resolved without relapse after receiving oral ganciclovir together with anti-hypertensive medications and anti-inflammation medications. Exclusion criteria were as follows: (1) Immunodeficient patients; (2) Patients with other systemic diseases such as diabetes, or with other eye diseases such as Harada syndrome, Behcet disease, eye trauma or tumor. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Zhongshan Ophthalmic Center. The data was all from the medical database of Zhongshan Ophthalmic Center with informed consent.

The second group included 6 females and 11 males with a mean age of 40.4 ± 14.2 years (ranging from 24 years to 75 years). Mean follow-up time was 10.8 months. All 17 patients experienced multiple acute IOP elevations prior to referral to our clinic. In 9 eyes, the mean presenting IOP was 32.4 mmHg (ranging from 22.7 mmHg to 68.0 mmHg), displayed with high IOP (higher than 21.0 mmHg) despite maximal IOP-lowering and corticosteroid medications. There were only one or a few KPs detected in each affected eye. Most of these KPs were round, thin, white, non-mutton fat, and some with pseudopods or space gaps inside the KP. Stellate KPs were also detected. KPs were mostly identified in the inferior cornea in all the patients, while gonioscope KPs were sometimes detected. The ocular angle was open for all the patients with no neovascular membrane or inflammation detected. Anterior ocular inflammation was mild to moderate for all the patients. Four eyes with severe corneal endothelial cell lesions developed corneal edema. Endothelium cells morphology was distorted with blurred cell margins. Six of the affected eyes had iris atrophy, among which heterochromia was detected in 2 eyes. Cataract was detected in 4 eyes. No patient underwent cataract surgery during our follow-up period. No posterior iris synchiae were detected in any of our patients, either. Additional details of the 17 PSS patients are illustrated in Table 1.

Systemic anti-viral treatments were administered for these 17 patients in addition to IOP lowering and anti-inflammatory medications. One gram of oral ganciclovir three times per day was prescribed within the first 2 or 3 weeks to control the corneal endothelial cell lesions. The dosage was slowly tapered to 0.5 g, twice daily and maintained for at least 3 months. At last follow-up, all patients had fully recovered without relapse.

Inflammation within the aqueous outflow pathways is very common in many kinds of anterior segment disease, such as PSS, Fuch heterochromatic iridocyclitis, and anterior uveitis. An acute IOP elevation generally occurs at the beginning of the disease without signs of glaucomatous damage. Clinically, an acute elevation of IOP in a patient with open-angle glaucoma but without glaucomatous optic neuropathy strongly suggests a secondary etiology. Clinicians should search for common signs of viral infection in the anterior chamber if other secondary signs such as neovascularization or ICE pathology within the angle is missing. For patients with virus-related inflammation in the aqueous outflow pathways, corticosteroids may work during the initial stage. However, as the pathological changes to the aqueous outflow pathway evolve from edema to scarring, its effect diminishes. In some cases, the management of elevated IOP may be further complicated by corticosteroid-induced IOP elevations.

We proposed that the pathogenesis of such refractory cases could be chronic virus infection inside aqueous outflow pathways. We suspected that in the initial 21 patients we reviewed in the first group, the pathology involved trabecular cell damage, which progressed from cell edema and inflammatory debris blockage to trabecular cell death, cirrhosis, scarring and complete loss of trabecular aqueous outflow function. Considering this pathological process,

Table 1: Clinical characteristics of the 17 refractory virus-related PSS patients receiving systemic anti-viral treatments

| Patient No. | Age (years) | Gender | KP | Anterior segment inflammation | Corneal change | Endotheliitis | Iris atrophy | Heterochromia | Cataract | Max IOP (mmHg) | Follow-up (months) |
|------------|-------------|--------|----|-------------------------------|----------------|--------------|-------------|-------------|---------|-------------|------------------|
| 1          | 29          | Female | +  | fl (+), cell (++)            | Edema          | +            | –           | –           | –       | 20.3         | 14               |
| 2          | 73          | Male   | +  | fl (+)                        | –              | +            | –           | –           | –       | 33.7         | 9                |
| 3          | 61          | Male   | +  | fl (+)                        | –              | +            | –           | –           | –       | 11.2         | 10               |
| 4          | 42          | Male   | +  | fl (+)                        | –              | +            | –           | –           | –       | 68.0         | 15               |
| 5          | 29          | Female | +  | cell (++)                     | –              | +            | –           | –           | –       | 29.0         | 14               |
| 6          | 27          | Male   | +  | cell (+)                      | –              | +            | –           | –           | –       | 10.3         | 10               |
| 7          | 52          | Male   | +  | cell, mutton-like             | –              | +            | –           | –           | –       | 42.7         | 12               |
| 8          | 57          | Male   | +  | cell (++)                     | Edema          | +            | –           | –           | –       | 22.7         | 12               |
| 9          | 24          | Female | +  | cell (+)                      | –              | –            | –           | –           | +       | 17.7         | 15               |
| 10         | 36          | Male   | +  | cell (+)                      | –              | –            | –           | –           | –       | 11.6         | 12               |
| 11         | 27          | Male   | +  | fl (+)                        | –              | –            | –           | –           | –       | 23.0         | 12               |
| 12         | 28          | Male   | +  | fl (+)                        | Partial edema  | +            | –           | –           | –       | 34.2         | 14               |
| 13         | 42          | Female | +  | fl (+)                        | –              | +            | –           | –           | –       | 22.7         | 14               |
| 14         | 45          | Male   | +  | fl (+), cell (+)              | –              | +            | –           | –           | –       | 34.0         | 12               |
| 15         | 38          | Male   | +  | fl (+), cell (+)              | +              | –            | –           | –           | –       | 12.0         | 3                |
| 16         | 44          | Female | +  | fl (+), cell (+)              | Edema          | +            | –           | –           | –       | 29.0         | 3                |
| 17         | 31          | Female | +  | cell (+) for both eyes        | –              | –            | +           | –           | –       | 23.0 for both right eye; 26.3 for left eye | 3 for both eyes |

*Two eyes involved in this patient. –: negative; +: positive; fl: flare; IOP: intraocular pressure; KP: keratic precipitate; PSS: Posner-Schlossmann syndrome.

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traditional anti-inflammatory treatment is beneficial only when trabecular damage is at the reversible edematous stage. If the viral infection is self-limiting, traditional treatment works well, and patients get complete recovery. However, if patients present with the clinical features of refractory disease as outlined earlier, the outcome likely results in complete loss of trabecular cells. Considering this dynamic pathological process of refractory virus-related PSS, clinicians should promptly identify these patients aiming to treat these patients while during the early reversible stage.

Besides virus damage to the aqueous outflow pathways, corneal endothelial cells are also commonly affected. We believed that untreated viral endothelitis causes endothelial cells to undergo morphological changes culminating in endothelial decompensation.[3] Of the 21 refractory PSS cases we described in the first group, 2 developed corneal endothelial decompensation requiring PKP surgery. Unfortunately, corneal edema recurred following corneal transplantation, most likely due to the persistent viral infection. An aqueous humor paracentesis with PCR analysis was performed for these 2 patients, confirming the diagnosis of a viral infection. After systemic anti-viral treatment was initiated, the corneal edema resolved and did not recur. Endothelial cell loss, distorted endothelial cell morphology, or blurred endothelial cell margins suggested that a refractory virus infection could be the cause.

The mean age of second group was 40.4 ± 14.2 years, which was slightly older than the common onset age of classic PSS. For patients over 50 years old, the diagnosis of PSS should be approached with caution. Immunological inflammation is generally less common in this subset of patients, and a viral etiology should be considered. Additionally, older patients are more prone to viral infections. We frequently noted that older PSS patients with self-limited or refractory disease often reported a recent history of a cold. In these older patients, close follow-up is advised. If the pathology persists for more than 1 month, or recurrences are encountered, refractory viral infections should be considered on the differential.

KPs are observed in all patients in this study, ranging from + to ++. Most of the KPs were round and white, located in the inferior area of the cornea. Pigment was also detected in the KPs. Pigmented KPs were observed in one patient whose disease persisted over 7 years. Stellate KPs were also found in one of the patients. CMV positive patients demonstrated small round and white KPs with pseudopods. HSV positive patient had larger KPs compared to CMV positive patients. The classic mutton-fat KP is not common in the refractory virus-related patients because viral infection primarily signals lymphocyte and monocyte infiltration, resulting in distinct smaller KPs, sometimes with pseudopods or space gaps. However, we did occasionally see slightly bigger mutton-like KPs in patients with a long protracted disease course, presumably due to chronic inflammation and immune response.

This study observed iris atrophy in 6 out of 18 eyes. It was likely that virus infection infiltrated the iris, leading to the ischemic necrosis of the iris stroma. Previous studies reported that CMV was identified in the smooth muscle cells of the iris.[4] The patients of this study demonstrated diffuse, sectoral or patchy iris atrophy patterns. Virus infection can also cause depigmentation of iris. We observed heterochromia in 2 of the 18 eyes in addition to iris atrophy. Because iris pigmentation is relatively thick in Chinese people, detailed examination of subtle color disparities should be performed in clinically suspicious cases of retracted virus-related PSS. No posterior segment involvement was detected in any of our case series, which was consistent with previous PSS related studies.

In conclusion, clinicians should differentiate classic PSS from refractory virus related inflammation inside aqueous outflow pathways. For the 17 refractory patients we reviewed in the second group, oral ganciclovir given at a relatively early disease stage in addition to traditional ocular treatment achieved complete recovery without recurrence. This benign clinical course was in sharp contrast to poor outcomes found in the 21 refractory cases in the first group. These patients experienced sustained uncontrolled IOP resulting in filtration surgery. This substantial difference in clinical outcomes endorsed our hypothesis that clinical diagnosis of refractory virus-related inflammation of aqueous outflow pathways was correct. It should be noted that positive detection rates for suspected virus infection in the aqueous humor vary significantly among various previous studies.[1][5] Virus pathogen tests are a technological challenge for most Chinese ophthalmic practices. Therefore, we recommended diagnosing refractory virus-related inflammation inside the aqueous outflow pathway based on specific groups of clinical signs rather than laboratory results. Lack of laboratory test is a weakness of this study. In the future, building a powerful eye-specific platform of aqueous humor analysis at the microliter level and conducting corresponding basic experiments and animal experiments are needed to support our hypothesis. When the refractory virus-related inflammation inside the aqueous outflow pathway is suspected in patients presenting with a primary diagnosis of PSS, the following features may help distinguish the correct diagnosis: (1) The disease course is prolonged and refractory; (2) The inflammation and IOP are increasingly resistant to corticosteroids and IOP lowering medicines; and (3) Patients have one or more additional traits, including non-mutton fat KPs, corneal endothelial cell lesion/loss, or iris atrophy/heterochromia. If present, then anti-viral treatment should be considered to improve prognosis.

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Conflicts of interest
None.
Author contributions

Zhang DD and Le C: provision of study, collection and assembly of data, data analysis and interpretation, manuscript writing; Liu JF and Guo CC: provision of study, collection and assembly of data, data analysis and interpretation; Li JL, Zhang JM, Li ZW, Zhao ZN, Chen DH, Zhang M, and Sun NN: provision of study, collection and assembly of data; Han Y, Li CM and Fan ZG: conception and design, data analysis and interpretation, manuscript writing.

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