# The Risk Factors in the Development of Glaucoma Secondary to Sarcoid-Related Uveitis in Taiwan

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**Abstract: Purpose**: To characterize the clinical features and analyze the risk factor in the development of glaucoma secondary to sarcoid-related uveitis. **Method**: A retrospective study of patients with sarcoidosis were performed in three medical center and one regional hospital in South Taiwan from 2008 to 2012. We recorded the course of this disease and the methods to evaluate and treat the sarcoid-related uveitis. The information were collected including the clinical features and its complications such as uveitis and glaucoma. In these patients, we analyzed the risk factors of secondary glaucoma and the associated mechanisms. **Results**: A total of 41 patients were enrolled in this study, and 66 eyes of 39 patients (26 women and 14 men) were diagnosed as the sarcoid-related uveitis. The secondary glaucoma was found in 23 eyes (34.8%). Open-angle glaucoma occurred in 10 of 23 eyes (43.4%) and angle-closure glaucoma developed in 13 of 23 eyes (56.6%). The glaucoma mostly resulted from the coular uveitis in the group of older age (≧39 years old)(odd ratio：3.40). Moreover, the uveitis happened before the systemic sarcoidosis have higher tendency to give rise to secondary glaucoma than the ocular uveitis found after systemic sarcoidosis (odd ratio：3.58). **Conclusions**: The onset of sarcoid-related uveitis in older patients and the ocular uveitis occurred before systemic sarcoidosis seem to be the major high risk factors in the development of secondary glaucoma. Thus, we may pay attention to closely follow and control the intraocular inflammation in the two types of patients to prevent from sarcoid-related glaucoma.
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## 1. Introduction

Sarcoidosis is a multisystem immune disease of unknown etiology involving many human organs such as the eye, lung, heart, lymph node, liver, spleen, skin, muscle, and even central nervous system. This disease is initiated by one or more unknown antigens in predisposed hosts, and causes noncaseating granulomatous inflammation. Ocular involvement are found in 20 – 50% of patients with sarcoidosis（3,4）. Sarcoid-related uveitis are even more often seen over 70% of patients with ocular involvement（4,5）. The progression of sarcoid-related uveitis is subtle, however, some cases may have the potential to cause the more trouble and vision-threatening complication such as glaucoma, cataract, cystoid macular edema and macular scar（6,9,32,33）. Thus, the diagnosis is very important; any suspicious uveitis should be investigated by relevant hematologic, radiologic, and invasive tests.

Glaucoma may become visually disabled in the patients with sarcoid-related uveitis（2,3）. According to the previous reports by Jabs and Kuchtey et al., approximately 20 - 40% of sarcoid-related uveitis may develop secondary glaucoma（1,2）. The higher intraocular pressure (IOP) could arise from uveitis by various mechanisms. For example, the intraocular inflammation may result in the posterior synechiae (PS) or peripheral anterior synechiae (PAS) which may furthermore lead to the blockage of outflow of aqueous humor and the next formation of angle-closure glaucoma. Besides, trabecular meshwork also may be obstructed by the inflammatory cells and debris which may cause the open-angle glaucoma（1,7,8）. All the ophthalmologists may be surprised by the characteristics of the course of sarcoid-related uveitis which is insidious and relapsing. Even though sarcoidosis is relatively rare found in Taiwan. We still attempt to understand and analyze the clinical features and the risk factors of sarcoid-related glaucoma in this study.

## 2. Material and Methods

### Material

Patients with the diagnosis of sarcoidosis who had attended at the uveitis service of three medical

center and one regional teaching hospital in Southern Taiwan from 2008 to 2012. All patients were required to follow in outpatient service for at least 6 months and received series of evaluation in the department of medicine and ophthalmology (At least one time outpatient visit per month). The charts of these patients with sarcoid-related uveitis were retrospectively reviewed. The patients with incomplete follow up, and past history of uveitis or any type of glaucoma were excluded from this study. The diagnosis of sarcoidosis was according to the ever published articles（10,11, 12, 13）. The criteria included positive biopsy results combined with chest radiographic abnormalities, elevated serum lysozyme, higher angiotensin-converting enzyme level, and positive gallium scan. The glaucoma of patients were defined as the intraocular pressure higher than 21 mm Hg at two consecutive visits or those who needs the lowering IOP drugs to control the IOP and prevent from the irreversible pathologic change of optic nerve（14）. All the IOPs were measured by Goldmann applanation tonometer. The angle of the anterior chamber was considered as closure if the pigmented trabecular meshwork was not visible in more than 180° of the angle by the gonioscopy（15）. The posterior synechiae or peripheral anterior synechiae were observed under slit-lamp examination. All the patients were treated basically according to previously published for uveitis and glaucoma（1, 5）. A high proportion of patients with sarcoidosis required the systemic corticosteroid or immunosuppressive treatment for uveitis. Briefly, patients received topical steroids and cycplegics initially, with the addition of the oral nonsteroidal anti-inflammatory drug (NSAID) while the attempting topical steroid withdrawal. In the presence of intractable anterior uveitis ,or intermediate or posterior uveitis, the posterior sub-tenon injection of triamcinolone acetonide (40 mg) were given. In severe cases, the systemic prednisone and/or immunomodulatory treatment (IMT) were added. In addition, the uveitis-related glaucoma were treated with topical lowering IOP medications in general. However, the insufficient medical control of glaucoma should need another or combined anti-glaucoma drugs, even the surgery.

**Statistical analysis**

All values are shown with a mean ± standard deviation (SD). The risk factors in the development of glaucoma were compared using estimates of risk ratios and their 95% confidence limits, together with Fisher's exact tests. We also compared the synechiae formation before or after systemic sarcoidosis involved by t-test. A $p$ value of less than 0.05 was considered significantly. To adjust for the possible confounding effects of other prognostic factors, the multiple logistic regression was used. The factors including the age, sex, location of uveitis (including single eye or two eyes), and the order of organs involvement were considered（6, 31, 33）.

**3. Results and discussion**

Total 41 patients were included in this study and 66 eyes of 39 patients (26 women and 13 men) were diagnosed as sarcoid-related uveitis. We could find out the persistence of uveitis in both eye in 27 of 39 (69.2%) patients and single eye in 12 of 39 (30.8%) patients. Glaucoma secondary to sarcoid-related uveitis were found in 23 of 66 eyes (34.8%). The mean age of onset of uveitis was 36.6 ±1.5 (range: 14-72 Y/O; median: 34.5 Y/O). The mean follow-up period was 2.3 ± 0.6 years (range: 6 months – 4 years). The total incidence of glaucoma in sarcoidosis was 37.5% (25/66 eyes) and the result was nearly equal to the report by Korean researchers (30%)（34）. In our study, glaucoma occurred in 17 of 44 (38.6%) female and 6 of 22 (27.3%) male patients with uveitic eyes, respectively. The ocular uveitis developed glaucoma in 17 of 30 (56.6%) eyes of older patients ( > 39 Y/O), and 6 of 36 (16.6%) eyes in younger patients (< 39Y/O). Secondary glaucoma were noted in 8 of 22 (36.3%) eyes with anterior uveitis, 6 of 16 (37.5%) eyes with intermediate uveitis, 4 of 10 (40.0%) eyes with panuveitis with retinal vasculitis, and 5 of 18 (27% )eyes with panuveitis combined with choroiditis. Besides, the incidence of uveitis-related glaucoma occurred before systemic sarcoidosis was 70.0% (14 of 20 eyes), and after systemic sarcoidosis was 19.5% ( 9 of 46 eyes) (Table 1 and Table 4).

We compared the onset of synchiae formation. The occurrence of peripheral anterior synchiae and posterior synchiae before uveitis happened before systemic sarcoidosis were found were more often seen. In the same situation, the inflammatory cells were prone to the secondary glaucoma (Table 2). We also investigated the associated risk factors in the development of glaucoma by the multiple logistic regression analysis. The difference of incidence of glaucoma between male and female was not apparent. Nevertheless, sarcoid-related glaucoma significantly developed in the older patients (≧39 years old) (odds ratio 3.4; 95% confidential interval 1.190 to 9.711). Moreover, the ocular uveitis appeared before systemic sarcoidosis greatly resulted in secondary glaucoma than those after systemic involvement (odds ratio 3.578; 95% confidential interval 1.331 to 9.615) (Table 3). In our survey, secondary glaucoma was found in 23 of 66 (34.8%) patients with sarcoid-related uveitis. Under the gonioscopy, we could

further find out that the open-angle glaucoma occurred in 10 of 23 (43.4%) eyes. On the contrary, secondary angle-closure glaucoma may develop in 13 of 23 eyes (56.6%) (Table 4).

In general, the higher level of IOP in sarcoid-related glaucoma was controlled by medication at first in clinic. Three classes of the anti-glaucoma agents such as β-blockers (timotol ®), α-agonists(alphagan ®) and carbonicanhydrase inhibitors(CAI)(Azopt ®) were alone or combined used which depended on the degree of the reduction of IOPs. However, the prostaglandin analogue (Travatan®) should be used with caution in patients with acute intraocular inflammation (eg. uveitis)〔35〕. In our study, we detected that 9/23(39.1%) of the sarcoid glaucoma failed to control the IOP (The "success" of controlling IOP was defined as the IOP was under 18 mmHg after 3 month treatment or the percentage of lowering IOP over 30% lowering after 3 month treatment compared with the baseline IOP) (Table 5). To our surprise, the rate of failure was relatively high. The benefits of various laser treatment including Argon Laser Trabeculoplasty (ALT) and YAG Laser peripheral iridectomy were controversial because of the possibility of IOP elevation and mild iritis〔36,37〕. Therefore, some ophthalmologists would suggest the use of filtration surgery (eg. trabeculectomy) in controlling the IOP in sarcoid-related glaucoma〔16,27,28,29〕. However, the poor outcome of surgery was noted in our study and the reason of failure may be due to the induction of inflammation.

**Table 1**. The characteristic of the patients with Sarcoid-related uveitis and secondary glaucoma

| characteristic | **Sarcoid-related uveitis ( N=66 eyes)** | **Sarcoid-related glaucoma ( N=25 eyes)** |
|---|---|---|
| **Sex** | | |
| **Female** | 44 | 17(38.6%) |
| **Male** | 22 | 6(27.3%) |
| **Onset age** | | |
| **>39 Y/O** | 30 | 17(56.6%) |
| **<39Y/O** | 36 | 6(16.6%) |
| **Location** | | |
| **anterior uveitis** | 22 | 8(36.3%) |
| **intermediate uveitis** | 16 | 6(37.5%) |
| **posterior uveitis** | 10 | 4(40.0%) |
| **Panuveitis** | 18 | 5(27.7%) |
| **The time of uveitis occurred** | | |
| **before systemic sarcoidosis** | 20 | 14(70.0%) |
| **after systemic sarcoidosis** | 46 | 9(19.5%) |

**Table 2**. The time of occurrence of synechiae in the uveitic eyes before or after systemic sarcoidosis

| | **Uveitis before systemic sarcoidosis (N=20 eyes)** | **Uveitis after systemic sarcoidosis (N=46 eyes)** |
|---|---|---|
| **PAS** | 12* | 6 |
| **PS** | 15* | 7 |
| **Glaucoma** | 14* | 9 |

*** *P* < 0.05**

**Table 3.** The risk factors in the development of arcoid-related glaucoma

| | **Odds ratio ( 95%CI)** | **Fisher's extract P** |
|---|---|---|
| **Sex** | | |
| **Female** | 1.417 (0.4896 to 4.099) | 0.6084 |
| **Male** | | |
| **Onset age** | | |
| **>39 Y/O** | 3.400(1.190 to 9.711) | 0.0281* |
| **<39 Y/O** | | |
| **The time of uveitis-related glaucoma** | | |
| **Uveitis before systemic sacoidosis** | 3.578(1.331 to 9.615) | 0.0129* |
| **Uveitis after systemic sarcoidosis** | | |

*** *P* < 0.05**

**Table 4.** Clinic Findings in Sarcoid-related glaucoma

| | Open angle Glaucoma | Angle closure Glaucoma | Total (N=23) |
|---|---|---|---|
| **Location** | | | |
| **Isolated anterior iridocyclitis** | 3 | 5 | 8 |
| **intermediate uveitis** | 2 | 4 | 6 |
| **Panuveitis with choroiditis** | 2 | 2 | 4 |
| **Panuveitis with retinal vasculitis** | 2 | 3 | 5 |
| **Peripheral anterior synechiae** | 6 | 7 | 13(56.5%) |
| **PAS>180-degree** | 0 | 3 | 3 |
| **PAS<180-degree** | 6 | 4 | 10 |
| **Posterior synechiae** | 13 | 7 | 20(86.9%) |
| **PS>180-degree** | 5 | 4 | 9 |
| **PS<180-degree** | 8 | 3 | 11 |

**Table 5.** Treatment of sarcoid-related glaucoma

| | Open angle Glaucoma | Angle closure Glaucoma | Total glaucoma ( N=23 eyes) |
|---|---|---|---|
| **Medical treatment** | 10 | 13 | 23 |
| **poor control after medication** | 4 | 5 | 9(39.1%) |
| **Surgical treatment** | 5 | 6 | 9 |
| **poor control after surgery** | 2 | 1 | 3(13.0%) |

**4.Discussion**

The ocular involvement of sarcoidosis is frequent, and it is often the initial clinical manifestation of this disease. The most common ocular lesions include granulomatous uveitis associated with iris and trabecular nodules, string of pearl-type vitreous opacities, retinal paerivasculitis mainly affecting veins, and patchy retino-choroidal exudates. A half of the patients with typical ocular lesions suggestive of sarcoidosis did not show the systemic evidence, and they remained as sarcoidosis suspects. The risks of visual deterioration are secondary glaucoma, vitreous opacities, cystoid macular edema, and retinal neovascularization. 34% of the patients were treated with systemic corticosteroids, and some patients required other treatment such as methotraxate. However, 21 % of the patients with sarcoidosis also may result in the poor visual acuity of less than 10/20（30）.14%-37% of the patients with sarcoid-related uveitis may develop glaucoma because the nature of inflammation. It is potential to disrupt the mechanisms in place for IOP homeostasis. Two different types of glaucoma including the open-angle glaucoma and angle-closure glaucoma may be found in the sarcoid-related uveitis（16, 17）. Takahashi et al. reported that the angle of glaucoma secondary to sarcoid-related uveitis could be open（14）. Aires et al. also showed the formation of angle-closure glaucoma could be induced by inflammation in sarcoidosis（6）. In this study, we had observed that 13 of 23 (56.6%) patients with sarcoid-related glaucoma belonged to angle-closure glaucoma. Several mechanisms may involve in the occurrence of angle-closure glaucoma. For examples, angle-closure may be caused by pupillary block when inflammation causes the posterior synechiae or complete inflammatory pupillary membrane. Sarcoid-related uveitis may also produce appositional irido-corneal contact by synechiae formation. If this appositional closure is not resolved promptly, chronic intermittent appositional closure will eventually cause synechial angle- closure glaucoma（5,9）. However, our study also showed that 10 of 23 eyes (43.4%) were diagnosed with open-angle glaucoma. Interestingly, we also found three of these eyes that uveitis is active when IOP elevation developed. This result suggests that the pathogenesis in open-angle glaucoma in sarcoid-related uveitis may be due to the impairment of trabeculum outflow function. Normally, aqueous production and aqueous outflow facility is a dynamic balance in the eye. In uveitic patients, the aqueous is usually underproductive by the inflamed ciliary body. Only if the impaired perfusion rate of the trabeculum were greater than under-productive rate of aqueous humor by the inflamed ciliary body, the IOP elevation would be found. Previous studies also showed that the open-angle glaucoma in sarcoid-related uveitis may be caused by the obstruction of trabeculum. Hamanaka et al. had examined 5 eyes with sarcoid-related glaucoma with open angle by using electronic microscope. The occlusion of the Schlemm canal by

granulomata or replaced by fibrotic tissue were found in these eyes〔16〕.

In this study, we found that sarcoid-related glaucoma is relatively common in patients with older age. The rate of occurrence of patients greater than 39 Y/O with sarcoid-related glaucoma was nearly three times (odds ratio 3.44) than younger patients (age less than 39 Y/O). Past studies also revealed that eyes with older age were more likely to have worse visual acuity because of the chronic course and resultant worse prognosis〔32〕. In our study, we also perceived that the rate of occurrence of uveitis developed before systemic sarcoidosis was nearly four times (odds ratio 3.58) to develop glaucoma than uveitis happened after systemic sarcoidosis. Among these eyes, we observed that the higher percentage of synchiae formation such as posterior synechiae or peripheral anterior synechiae was noted. Systemic sarcoidosis is the immune disease with multiple organs involvement. The patients should be followed closely in ocular uveitis diagnosed after systemic sarcoidosis〔1,17〕. However, the isolated anterior uveitis often manifests as the initial presentation of sarcoidosis〔6,20〕. Underestimation is often seen because no other systemic findings suggest this uveitis resulted from sarcoidosis. Unfortunately, underestimation may lead to under-treatment and affect the medical decision of many doctors. We knew that the course of sarcoid-related uveitis is insidious, relapsing and usually presented the lower active inflammation which may be not apparent. Thus, under-treatment for sarcoid-related uveitis will result in the lasting intraocular inflammation which had become the major risk for development of secondary glaucoma〔1,19〕. How to control intraocular inflammation combined with lowering IOP aggressively and completely is the best treatment for sarcoid-related glaucoma.

Sarcoidosis may involve many organs including eyes. Even though the clinical features are well-established, the exact diagnosis also requires histological confirmation which remains difficult in patients with uveitis. Thus, the frequency of ocular sarcoidosis is overestimated. A set of criteria has been recently established in order to improve the diagnostic procedure. New imaging tools will enable the ophthalmologists to evaluate the level of ocular inflammation and to monitor its resolution after treatment. For example, the use of indocyanine green angiography (ICG) and optical coherence tomography(OCT) have dramatically improved our understanding of choroidal granulomas, choroidal neovascularization, and cystoid macular edema. This advanced instruments may help us to adopt the prompt and aggressive management in time.

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