Advances in Ophthalmology Practice and Research 2 (2022) 100047

Contents lists available at ScienceDirect

Advances in Ophthalmology Practice and Research

journal homepage: www.journals.elsevier.com/advances-in-ophthalmology-practice-and-research

Case Report

Sarcoid uveitis: A case report and systematic review of literature

Junhui Shen [a,b], Zhitao Su [a,b], Lei Feng [a,b,*]

[a] Eye Center, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, China
[b] Key Laboratory of Ophthalmology of Zhejiang Province, Hangzhou, China

1. Introduction

Sarcoidosis is a disease that involves multiple systems and organs and is characterized by non-caseous necrotizing granulomas whose etiology is not fully understood.[1] About 25%–80% of patients have eye and adnexal involvement.[2] Uveitis, secondary glaucoma, cataracts, and macular edema are the most common complications of ocular sarcoidosis.[3] Sarcoid uveitis refers to uveitis that occurs in patients with sarcoidosis and typically manifests as granulomatous anterior uveitis, posterior uveitis, or panuveitis. Symptoms of sarcoid uveitis include blurred vision, eye pain, photophobia, and tearing. In the anterior segment, iris nodules or mutton-fat keratic precipitates (KPs) are generally the most common clinical signs. In the vitreous cavity, the typical appearance is a snowball-like vitreous opacity. The fundus typically manifests as peripheral chorioretinal granulomas and peripheral phlebitis. Herein, we present a case of sarcoid uveitis with fungal endophthalmitis-like vitreitis.

2. Case presentation

A 54-year-old woman was referred by the ophthalmologist in June 2021, because of a dark shadow floating in front of the left eye. The best-corrected visual acuity (BCVA) was 20/20 in the right eye (OD) and 20/40 in the left eye (OS). KPs were not visualized in either eye. Ultrawide-field fundus photography revealed a punctate white lesion in front of the retina of the right eye (Fig. 1A1), and obvious vitritis appeared as a string of pearls (Fig. 1A2). Fundus fluorescein angiography (FFA) revealed multiple round and relatively brighter fluorescences at the peripheral retina in the right eye (Fig. 1B1 and 1B2), and retinal vascular wall and optic disk dyeing with fluorescein in the late phase of the left eye (Fig. 1B3 and 1B4). Swept-source optical coherence tomography (OCT) revealed no obvious abnormality in the right eye (Fig. 1C1); clumps of lesions on the retinal nerve fiber layer and macular edema in the left eye (Fig. 1C2). She had a five-year history of diabetes. She had no history of joint pain, tinnitus, oral ulcers, skin rash, dyspnea, or chest pain. She had no relevant family history. Blood tests showed that fasting blood glucose was 7.44 mmol/L and postprandial 2-h blood glucose was 14.10 mmol/L. The level of serum angiotensin-converting enzyme (ACE) was 15 U/L (normal: 16–72 U/L). She tested negative for hepatitis B virus, mycobacterium tuberculosis, human immunodeficiency virus (HIV), and syphilis. She was diagnosed with bilateral uveitis and was suspected of having fungal endophthalmitis in her left eye.

Her left eye was immediately given pars plana vitrectomy (PPV) surgery. During the operation, string of pearl-type vitreous opacities were seen in the vitreous cavity near the temporal, supratemporal, and infratemporal retinas (Fig. 2A and B). A white sheath could be seen in the infratemporal and supratemporal vessels (Fig. 2C). A round grayish-yellow lesion could be seen in the middle circumference of the infratemporal region (Fig. 2D). The vitreous fluid was then acquired, and the pathogens were measured by PCR analysis. Surprisingly, no pathogens were found in either the peripheral blood or intraocular fluid.

A differential diagnosis must be considered. A CT scan chest (Fig. 3A and B) revealed multiple enlarged lymph nodes in the mediastinum and two hilar lungs, and the main lesions were distributed under the pleura in the lower lobes of both lungs. Although ACE was normal, the possibility of sarcoidosis remained. To rule this out, the patient was sent to the respiratory department. Pulmonary function examination revealed that pulmonary ventilation function and pulmonary diffusion function were within normal ranges. No bacteria, fungi, mycobacterium tuberculosis, or rifampicin-resistant genes were detected in the alveolar lavage fluid. B-ultrasound examination showed that the left supraclavicular lymph node was enlarged; no obvious enlarged lymph nodes were found on the right clavicle, bilateral axilla, neck, or groin. After an endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) biopsy of enlarged hilar intrathoracic lymph nodes, the specimen showed the presence of nonnecrotizing granulomas, including a small number of bronchial mucosal cells and inflammatory cells (Fig. 3C). Her histological diagnosis was sarcoidosis. She was given methylprednisolone 24 mg qd orally, supplemented with vitamin D, calcium, potassium, and stomach protection drugs. Follow-up was conducted over three months.

* Corresponding author. Eye Center, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang 310009, China.
E-mail address: leifeng@zju.edu.cn (L. Feng).

https://doi.org/10.1016/j.aopr.2022.100047
Received 26 January 2022; Received in revised form 20 March 2022; Accepted 28 March 2022
Available online 18 April 2022

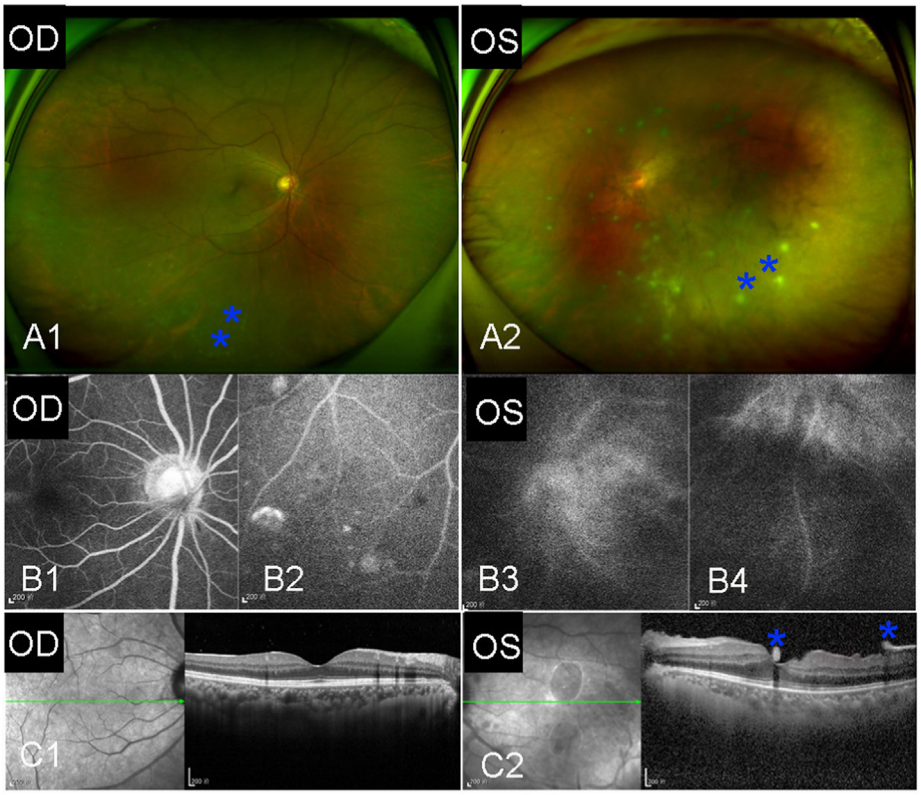

Fig. 1. The findings of fundus photography, fundus fluorescein angiography (FFA), and swept-source optical coherence tomography (OCT). Fundus photography showed punctate white lesion (blue asterisk) in front of the retina of the right eye (A1), and string of pearl-type vitreous opacities (blue asterisk) of the left eye (A2). FFA revealed multiple round relatively higher fluorescence at the peripheral retina in the right eye (B1-B2); retinal vascular wall and optic disc dyeing with fluorescein in the late phase of left eye (B3-B4). OCT revealed no obvious abnormality in the right eye (C1); clumps lesions (blue asterisk) on the retinal nerve fiber layer, and macular edema in the left eye (C2).

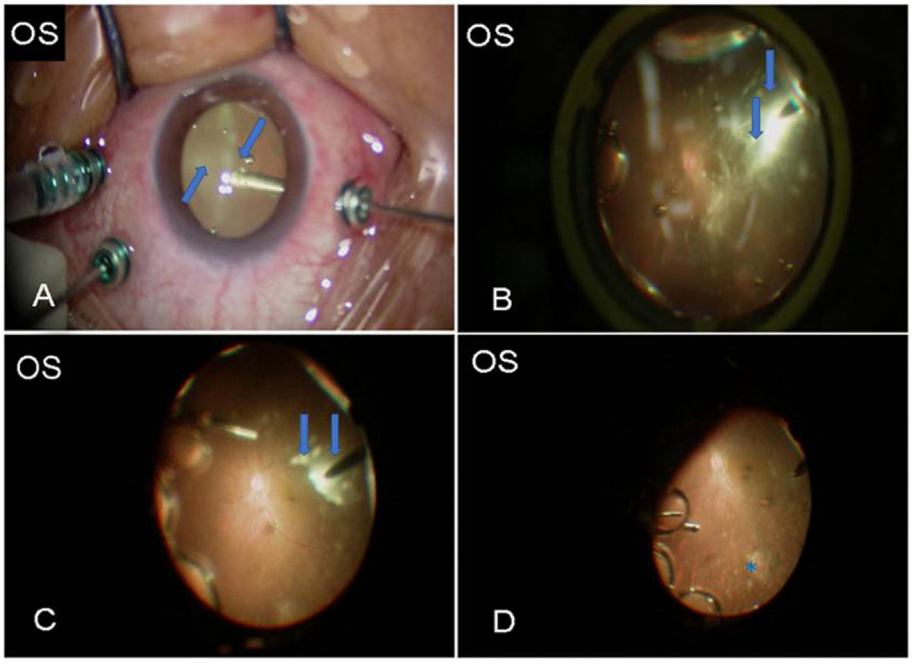

Fig. 2. Images obtained during the vitrectomy surgery. Snowball opacity (blue arrow) (A-C) and a chorioretinal lesion (blue asterisk) (D) were found.

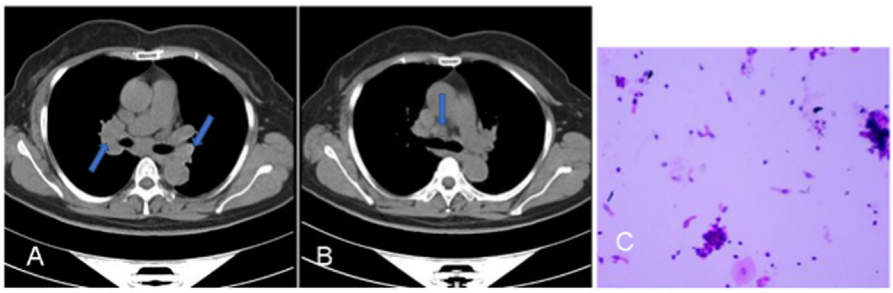

Fig. 3. Systemic findings of the patient. A. CT chest (hilar). B. CT-chest (mediastinum) demonstrated multiple enlarged lymph nodes in mediastinum and two hilar lungs, and the main lesions are distributed under pleura in the lower lobes of both lungs. C. Histopathological examination from bronchoscopic biopsy showed the presence of non-necrotizing granulomas, including a small number of bronchial mucosal cells and inflammatory cells.

3. Discussion and literature review

3.1. Sarcoidosis and uveitis

Sarcoidosis is a disease that occurs when groups of cells in the immune system form lumps (called granulomas) in various organs of the body. The characteristic morphological features of sarcoidosis are non-caseous epithelioid cell granuloma.[4] The inflammation that causes these granulomas to form can be triggered by an infection or something in the environment. Sarcoidosis can affect any organ. Most commonly, it affects the lungs and lymph nodes in the chest. Patients present with ocular symptoms first in only 2%–3% of cases.

Clinical manifestations may vary by race, age, and other general conditions. African Americans are more prone to eye complications. It has been reported that 12%–23% of sarcoidosis cases in the United States have eye involvement, and uveitis is the most common manifestation.[5] Between 30% and 70% of patients with systemic sarcoidosis worldwide may be affected by uveitis. In the Asia-Pacific region, sarcoidosis accounts for 1.5%–14.9% of all uveitis.[6] Studies have reported that eye involvement may be the first manifestation of sarcoidosis. In our case, the patients did not present with other systemic manifestations, such as pulmonary, cardiac, or neurologic involvement. Both men and women are affected, and the proportion of women is higher.[7] Nagata et al. conducted a study to determine if age- and gender-related differences are correlated with the clinical aspects of posterior ocular lesions in sarcoidosis patients, and they found that lesions were located around the peripheral area at the posterior segment in older patients.[8]

3.2. Symptoms and signs

Sarcoidosis has a variety of clinical manifestations. Lofgren syndrome is a group of typical symptoms and signs of sarcoidosis. Symptoms include swollen lymph nodes in the chest, neck, jaw, armpit, or groin; erythema nodosum; skin changes; blurred vision; joint pain; and fever. Pulmonary sarcoidosis can cause cough, wheezing, or chest pain. It can sometimes cause neurological problems such as headaches. Sarcoidosis may not have these symptoms, depending on the organ involved. Cardiac sarcoidosis patients can have heart complications, and digestive-system sarcoidosis patients may have spleen or liver enlargement. In our case, the patient presented with only a dark shadow floating in front of the left eye. She did not have any general symptoms.

3.3. Diagnosis

Sarcoidosis is diagnosed based on symptoms, physical examination, imaging examination, and biopsy. Before diagnosing ocular sarcoidosis, infectious and other noninfectious uveitis should be ruled out. The diagnosis of ocular sarcoidosis needs to be made through characteristic biopsy results and exclusion of other diseases, especially syphilis and pulmonary tuberculosis. The International Workshop on Ocular Sarcoidosis (IWOS) identified the diagnosis of intraocular sarcoidosis in 2009.[9] The criteria were revised in 2019 (see Table 1).[10] Patients with a biopsy showing compatible uveitis can be diagnosed as definite ocular sarcoidosis; those with compatible uveitis and bilateral hilar adenopathy, but no biopsy, can be considered presumed ocular sarcoidosis. Those with neither a biopsy nor hilar adenopathy, but at least three suggestive intraocular signs and two supportive investigational tests, can be considered probable ocular sarcoidosis; those with a negative biopsy, but at least four suggestive intraocular signs and two supportive studies can be classified as possible ocular sarcoidosis.[10]

Table 1
Revised IWOS criteria for the diagnosis of ocular sarcoidosis.

Seven intraocular clinical signs suggestive of ocular sarcoidosis:
(1) mutton-fat keratic precipitates (KPs)/small granulomatous KPs and/or iris nodules (Koeppe/Busacca)
(2) trabecular meshwork (TM) nodules and/or tent-shaped peripheral anterior synechiae (PAS)
(3) vitreous opacities displaying snowballs/strings of pearls
(4) multiple chorioretinal peripheral lesions (active and/or atrophic)
(5) nodular and/or segmental peri-phlebitis (± candlewax drippings) and/or retinal macroaneurism in an inflamed eye
(6) optic disc nodule(s)/granuloma(s) and/or solitary choroidal nodule
(7) bilaterality
Eight systemic investigation results in suspected ocular sarcoidosis:
(1) bilateral hilar lymphadenopathy by chest X-ray and/or chest computed CT scan
(2) Negative tuberculin test or interferon gamma releasing assay
(3) Elevated serum angiotensin converting enzyme
(4) Elevated serum lysozyme
(5) Elevated CD4/CD8 ratio (>3.5) in bronchoalveolar lavage fluid
(6) Abnormal accumulation of Gallium-67 scintigraphy or 18F- fluorodeoxyglucose PET imaging
(7) Lymphopenia
(8) Parenchymal lung changes consistent with sarcoidosis, as determined by pulmonologists or radiologists

Sarcoid uveitis may present with granular KP or no obvious KP.[11] In our case, we did not observe any obvious KP. Serum angiotensin-converting enzyme (ACE) and lysozyme are markers of granulomatous inflammation and may be elevated in patients with sarcoidosis.[12] However, ACE levels lack sensitivity and specificity.[13] It is reported that the sensitivity of ACE detection is 58–84% and the specificity is 83–95%. The sensitivity of lysozyme was 60–78%, and the specificity was 76–95%.[14,15] Serum ACE levels seem to be associated with the process of active disease because they decrease with treatment.[16] ACE levels were not high in our case.

3.4. Differential diagnosis

Ocular sarcoidosis is usually bilateral. Tubulointerstitial nephritis-uveitis syndrome and other infectious diseases, such as toxoplasmosis, viral retinitis, syphilis, HIV, and tuberculosis, need to be excluded. In children, ocular sarcoidosis may be similar to juvenile idiopathic arthritis-associated uveitis. In adults, intermediate uveitis can cause ocular

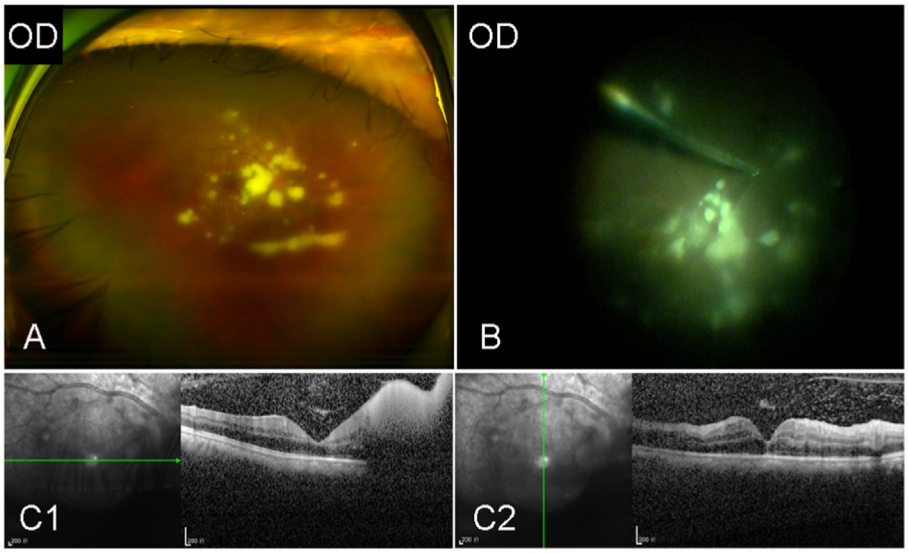

Fig. 4. A 43-year-old female patient with endogenous fungal endophthalmitis confirmed by intraocular fluid examination. Fundus photography A. and images obtained during the vitrectomy surgery B. showed string of pearl like vitreous opacity in the right eye. C1-2. OCT examination revealed lesions located in the retina of the right eye.

sarcoidosis, and multiple sclerosis must be excluded; in older adults, intraocular lymphoma must be excluded. There are many differential diagnoses for posterior uveitis, and posterior uveitis that does not cause vitreitis should be excluded. Ocular sarcoidosis is characterized by vitreous snowball opacity, peripheral chorioretinal granuloma, and peripheral phlebitis, which are rarely seen in patients with other types of uveitis.

Vitreous opacity is a common feature of intermediate uveitis, posterior uveitis, and panuveitis. Vitreous opacity, which makes the fundus difficult to see, can occur in both infectious and noninfectious uveitis.[17] The former includes infections caused by bacteria, fungi, spirochetes, viruses, parasites, etc.; the latter includes idiopathic, autoimmune, rheumatic diseases, traumatic, masquerade syndrome, etc.[18] Endophthalmitis is a medical emergency in ophthalmology, and timely diagnosis and treatment are essential to save vision. Endogenous endophthalmitis is caused by fungal *Candida* species. An eye examination usually reveals fluffy white chorioretinopathy, possibly covering the vitreous or extending to the vitreous. The vitreous "puffballs" may appear as "a string of pearls." Diagnosis is made by blood or intraocular fluid culture.[19] However, granulomatous intermediate uveitis can also be characterized as "snowball vitreous opacities" or "strings of pearls".[18]

Sometimes, it is difficult to identify the cause of vitreous opacity. OCT can detect the location of a lesion. Some differences between endophthalmitis and sarcoid uveitis can be found in OCT. A recent study analyzed the OCT features of endogenous endophthalmitis in 16 patients from China and described four OCT patterns of retinal endogenous endophthalmitis lesions: type 1 (subretinal macular lesions), type 2 (lesions are located in the inner retinal layer), type 3 (lesions involve the full-thickness retina and accompanied with macular edema), and type 4 (sub-inner limiting membrane lesions).[20] Another patient with endogenous fungal endophthalmitis was confirmed by intraocular fluid examination; the vitreous opacity and the OCT examination are shown in Fig. 4. Fundus photography (Fig. 4A) and images obtained during the vitrectomy surgery (Fig. 4B) showed string of pearl like vitreous opacity in the right eye. OCT examination revealed lesions located in the retina of the right eye (Fig. 4C1-2). Furthermore, a previous study found that patients with ocular sarcoidosis had thinner choroids in the quiescent phases when compared to normal subjects.[21]

Diabetes is one of the major risk factors for fungal endophthalmitis.[22] In our case, the patient's vitreous opacity looks like "a string of pearls," and with a history of diabetes, we first suspect fungal endophthalmitis. Vitrectomy is necessary for infectious uveitis and severe vitreous inflammation. Vitrectomy allows for detailed fundus observation and analysis of vitreous samples.[23] Testing for CD4/CD8 T-lymphocyte ratio and bacterial or fungal features in bronchoalveolar lavage fluid can help distinguish malignancy and infections. Biopsies of enlarged intrathoracic lymph nodes or lung parenchyma are essential in the diagnosis of sarcoidosis.

3.5. Therapy

A previous study reported that anterior segment inflammation is the most common site of ocular sarcoidosis.[3] However, more studies reported that panuveitis was the most common localization of sarcoidosis uveitis.[8,24] For patients with mild anterior uveitis are treated with topical steroids. For posterior uveitis, the first-line treatment recommended is to use systemic corticosteroids. According to the International Workshop on Ocular Sarcoidosis (IWOS),[25] the initial dose of systemic prednisolone is 0.5–1.0 mg/kg/day, up to 80 mg/day. The mean duration of the initial dose of systemic prednisone/prednisolone is 2–4 weeks, and it is tapered gradually for a total of 12 months, while evaluating the response to treatment every 1–3 months. Treatment typically also adds vitamin D, calcium, potassium, and stomach protection drugs (H2 blockers or proton pump inhibitors). Non-responders or those with inflammation recurrence need to use immunosuppressive agents (hydroxychloroquine, methotrexate, chlorambucil, and azathioprine) in combination.[26] Periocular or intravitreal injections of triamcinolone injections or steroid implants are recommended when macular edema is severe. Anti-VEGF agents can also be tried. Topical steroids are reserved only for active anterior segment inflammation. If such therapies are insufficient, biological drugs are considered. Adalimumab, a tumor necrosis factor (TNF) inhibitor, was approved for refractory noninfectious uveitis. It has shown encouraging results in refractory sarcoidosis.[27]

4. Conclusions

The clinical manifestations of sarcoidosis vary, and uveitis may be the main complaint. Vitreous opacity is a common feature of uveitis, and it is important to understand the characteristic intraocular signs and look for them through comprehensive ocular examinations. Diagnosis is based on compatible clinical manifestations, multimodal imaging findings, laboratory examinations, and noncaseating granulomas confirmed by biopsy. Oral glucocorticoids are typically the first line of sarcoid uveitis when systemic treatment is required.

Study Approval

The authors confirm that any aspect of the work covered in this manuscript that involved human patients or animals was conducted with the ethical approval of all relevant bodies and the study was performed in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Second Affiliated Hospital, School of Medicine, Zhejiang University (approval number: 2020-878).

Author Contributions

The authors confirm contribution to the paper as follows: LF, JS: conceived the manuscript, performed analysis and interpretation of clinical data. ZS: patient treatment. LF, JS: Funding acquisition. JS: Writing—original draft. LF: Writing—review & editing. All authors contributed to the article and approved the submitted version. All authors reviewed the results and approved the final version of the manuscript.

Acknowledgments

Thanks to all the peer reviewers and editors for their opinions and suggestions.

Funding

This work was supported by the National Natural Science Foundation of China (81870648, 82070949, 82000886), and Natural Science Foundation of Zhejiang Province (No.LQ20H120011).

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Ungprasert P, Tooley A, Crowson C, et al. Clinical characteristics of ocular sarcoidosis: a population-based study 1976-2013. *Ocul Immunol Inflamm*. 2019;27(3):389–395. https://doi.org/10.1080/09273948.2017.1386791.
2. Obenauf C, Shaw H, Sydnor C, et al. Sarcoidosis and its ophthalmic manifestations. *Am J Ophthalmol*. 1978;86(5):648–655. https://doi.org/10.1016/0002-9394(78)90184-8.
3. Dana M, Merayo-Lloves J, Schaumberg D, et al. Prognosticators for visual outcome in sarcoid uveitis. *Ophthalmology*. 1996;103(11):1846–1853. https://doi.org/10.1016/s0161-6420(96)30417-x.
4. Iannuzzi M, Rybicki B, Teirstein A, et al. Sarcoidosis. *N Engl J Med*. 2007;357(21):2153–2165. https://doi.org/10.1056/NEJMra071714.
5. Baughman R, Teirstein A, Judson M, et al. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med*. 2001;164(10 Pt 1):1885–1889. https://doi.org/10.1164/ajrccm.164.10.2104046.
6. Hsu Y, Huang J, Tao Y, et al. Noninfectious uveitis in the Asia-Pacific region. *Eye*. 2019;33(1):66–77. https://doi.org/10.1038/s41433-018-0223-z.
7. Siltzbach L, James D, Neville E, et al. Course and prognosis of sarcoidosis around the world. *Am J Med*. 1974;57(6):847–852. https://doi.org/10.1016/0002-9343(74)90160-0.
8. Nagata K, Maruyama K, Sugita S, et al. Age differences in sarcoidosis patients with posterior ocular lesions. *Ocul Immunol Inflamm*. 2014;22(4):257–262. https://doi.org/10.3109/09273948.2013.855796.
9. Herbort C, Rao NMochizuki M. International criteria for the diagnosis of ocular sarcoidosis: results of the first International Workshop on Ocular Sarcoidosis (IWOS). *Ocul Immunol Inflamm*. 2009;17(3):160–169. https://doi.org/10.1080/09273940902818861.
10. Mochizuki M, Smith J, Takase H, et al. Revised criteria of international Workshop on ocular sarcoidosis (IWOS) for the diagnosis of ocular sarcoidosis. *Br J Ophthalmol*. 2019;103(10):1418–1422. https://doi.org/10.1136/bjophthalmol-2018-313356.
11. Cao X, Wang HPeng X. [Clinical characteristics of patients with biopsy-proven sarcoid uveitis]. *Zhonghua Yixue Zazhi*. 2020;100(32):2498–2502. https://doi.org/10.3760/cma.j.cn112137-20200426-01323.
12. Iannuzzi M, Rybicki BTeirstein A. Sarcoidosis. *N Engl J Med*. 2007;357(21):2153–2165. https://doi.org/10.1056/NEJMra071714.
13. Ungprasert P, Carmona E, Crowson C, et al. Diagnostic utility of angiotensin-converting enzyme in sarcoidosis: a population-based study. *Lung*. 2016;194(1):91–95. https://doi.org/10.1007/s00408-015-9826-3.
14. Hwang DSheu S. An update on the diagnosis and management of ocular sarcoidosis. *Curr Opin Ophthalmol*. 2020;31(6):521–531. https://doi.org/10.1097/icu.0000000000000704.
15. Liu DBirnbaum A. Update on sarcoidosis. *Curr Opin Ophthalmol*. 2015;26(6):512–516. https://doi.org/10.1097/icu.0000000000000207.
16. Dhont S, Leys M, De Sutter E, et al. Uveitis as a window to diagnosis of sarcoidosis - case report and review of the literature. *Acta Clin Belg*. 2020;75(4):245–249. https://doi.org/10.1080/17843286.2019.1613309.
17. Jabs D, Nussenblatt RRosenbaum J. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol*. 2005;140(3):509–516. https://doi.org/10.1016/j.ajo.2005.03.057.
18. Takase H. Characteristics and management of ocular sarcoidosis. *Immunol Med*. 2021:1–10. https://doi.org/10.1080/25785826.2021.1940740.
19. Durand M. Bacterial and fungal endophthalmitis. *Clin Microbiol Rev*. 2017;30(3):597–613. https://doi.org/10.1128/cmr.00113-16.
20. Zhuang H, Ding X, Gao F, et al. Optical coherence tomography features of retinal lesions in Chinese patients with endogenous Candida endophthalmitis. *BMC Ophthalmol*. 2020;20(1):52. https://doi.org/10.1186/s12886-020-01337-9.
21. Güngör S, Akkoyun I, Reyhan N, et al. Choroidal thickness in ocular sarcoidosis during quiescent phase using enhanced depth imaging optical coherence tomography. *Ocul Immunol Inflamm*. 2014;22(4):287–293. https://doi.org/10.3109/09273948.2014.920034.
22. Sadiq M, Hassan M, Agarwal A, et al. Endogenous endophthalmitis: diagnosis, management, and prognosis. *J Ophthal Inflam Infect*. 2015;5(1):32. https://doi.org/10.1186/s12348-015-0063-y.
23. Sato T, Kinoshita R, Taguchi M, et al. Assessment of diagnostic and therapeutic vitrectomy for vitreous opacity associated with uveitis with various etiologies. *Medicine*. 2018;97(2), e9491. https://doi.org/10.1097/md.0000000000009491.
24. Rothova A. Ocular involvement in sarcoidosis. *Br J Ophthalmol*. 2020;84(1):110–116. https://doi.org/10.1136/bjo.84.1.110.
25. Takase H, Acharya N, Babu K, et al. Recommendations for the management of ocular sarcoidosis from the international Workshop on ocular sarcoidosis. *Br J Ophthalmol*. 2021;105(11):1515–1519. https://doi.org/10.1136/bjophthalmol-2020-317354.
26. Reich J. Corticosteroid therapy and relapse in sarcoidosis. *Chest*. 1998;113(2):559–561. https://doi.org/10.1378/chest.113.2.559-b.
27. Baughman RLower E. Treatment of sarcoidosis. *Clin Rev Allergy Immunol*. 2015;49(1):79–92. https://doi.org/10.1007/s12016-015-8492-9.