Sarcoidosis is a granulomatous disease which frequently involves eyes and adnexal tissues. Its prevalence of ocular involvement is reported as about 20%, although it varies widely according to authors, from 12% to 73%. Ocular sarcoidosis is present as various forms - uveitis, conjunctival involvement, optic nerve involvement, and orbital involvement. All the forms of uveitis - anterior uveitis, intermediate uveitis, posterior uveitis and panuveitis - can be shown in sarcoidosis. Because clinical manifestation, prognosis and treatment are determined by the location of uveitis, it is important to classify uveitis. Conjunctival involvement is not a sight-threatening condition in general, its diagnostic value may be of use. Optic nerve is the most commonly involved cranial nerve, which can impair vision. Subjects with visual impairment without any evidence of uveitis, optic nerve involvement should be suspected. Orbital involvement, especially lacrimal gland involvement is common, and it may cause mass-effect. Besides systemic administration of drugs, there are several localized treatments for ocular sarcoidosis - topical eye drops, intra/peri-ocular injection of agents.

Key Words: Sarcoidosis; Uveitis; Granuloma

INTRODUCTION

Sarcoidosis is a systemic granulomatous disease, which may involve any part of the eye and its adnexal tissues. Although the first manifestation of systemic sarcoidosis is often ophthalmic involvement, non-ophthalmologists are not familiar with its ocular manifestations, especially when described in ophthalmologic terms. In this article, the author intends to describe the ocular manifestations of sarcoidosis in the terms of a non-ophthalmologist.

EPIDEMIOLOGY

The prevalence of ocular involvement of sarcoidosis ranges widely. Ocular involvement has been reported in 12-23% of biopsy-proven sarcoidosis cases in the United States [1], and was reported in 13% of cases in Turkey and 79% in Japan [2,3]. In South Korea, prevalence was reported at 21% in 2009, which was similar to that of the United States [4]. It is notable that the prevalence in South Korea was different from that in Japan. This discordance may be due to the relatively small sample size of patients in these observations. Both of the studies in South Korea and in Japan were conducted using about 100 patients, which is a large number for a single institute, but not for the result of a large study. Thus, it is somewhat challenging to determine the prevalence of ocular involvement in all patients with sarcoidosis based on the results of this single study.

However, among patients with uveitis, the prevalence of sarcoidosis as a pre-existing condition is another interesting topic for ophthalmologists. A review of 209 patient records with diagnosed uveitis in Thailand showed that 4 patients (2%) were also diagnosed with pulmonary sarcoidosis [5]. In a retrospective study performed with 3,060 patients in 41 university hospitals in Japan in 2007 [6], the root cause of uveitis was found to be sarcoidosis in 407 (13.3%) of all uveitis cases. On the other hand, in the report of a single institute in the United States in 2008, sarcoidosis was identified as a root cause in only 7% of the uveitis cases [7]. The study result from Japan may differ from the United States study because the Japa-
nese cases were analyzed in tertiary medical facilities. Korea has yet to issue a report regarding this topic. Overall, ocular involvement is found in more than 20% of all patients diagnosed with sarcoidosis, and it has been reported that sarcoidosis is the root cause in approximately 4-13% of patients with uveitis, showing a substantially high prevalence.

**CLINICAL MANIFESTATION**

Ocular sarcoidosis can be the first symptom of systemic sarcoidosis and may include the involvement of all orbital tissues such as the eyelids, conjunctiva, sclera, cornea, iris, retina, optic nerve, lacrimal gland, and extraocular muscle. The manifestations of ocular sarcoidosis may range from no symptoms to severe visual impairment. This article intends to articulate primarily about uveitis in addition to other conjunctival involvement with diagnostic value.

**UVEITIS**

Uveitis is difficult to define, but usually indicates an inflammation in the eyes. Uveitis is often considered the inflammation of tissues known as the uvea: the choroid, ciliary body, and iris. This is in fact a misnomer, because uveitis includes not only iritis (inflammation of the iris) and choroiditis (inflammation of the choroid) but also retinitis (inflammation of the retina) and vitritis (inflammation of the vitreous body). Thus, it must be understood as an inflammation of the eyes rather than merely an inflammation of the uvea.

Uveitis is divided into anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis (a combination of anterior and posterior uveitis), according to the anatomical location. This classification is location based, because the symptoms vary by location, and the treatment method is also different owing to the penetration of therapeutic agents. This article will be structured according to the above classification, as the mechanism of visual impairment varies by the location of uveitis.

**ANTERIOR UVEITIS**

Anterior uveitis is the most common form of uveitis. The anterior part of the uvea includes the iris that surrounds the pupil and the adjacent ciliary body that synthesizes aqueous humor, the fluid that fills the front of the eye. In sarcoidosis, the development of anterior uveitis is common, with about 40% of cases presenting with anterior uveitis according to a report in Korea [4].

The anterior chamber—the space including the cornea, iris, and lens—is filled with aqueous humor, and its inflammation is one of the most common findings in patients with sarcoidosis. It has been reported that about 90% of patients with sarcoidosis and ocular involvement display anterior chamber inflammation [8]. As this finding is very common, it does not have great value in diagnosing sarcoidosis. However, because it can cause co-morbidity as well as symptoms such as pain, redness, photophobia (sensitivity to light), increased ocular pressure, and posterior synechiae (iris-lens adhesion), it is necessary to identify and control this inflammation.

Granulomatous uveitis is known to occur specifically when there is ocular involvement of sarcoidosis. The term “granuloma” in “granulomatous uveitis” is different from the usage of “granuloma” describing sarcoidosis in “granulomatous inflammation.” The term “granuloma” in “granulomatous uveitis” does not indicate “granuloma” in “granulomatous inflammation.” The term “granulomatous uveitis” is applied when at least one of the following clinical signs are observed: (1) large mutton-fat keratic precipitates (an accumulation of inflammatory leukocytes that deposit on the corneal endothelium), (2) iris or trabecular meshwork nodules, or (3) choroidal granulomas [9]. In other words, even though “granulomatous uveitis” as a clinical term can be readily found in reference to sarcoidosis, it can also be found in uveitis not associated with sarcoidosis, and is seen in Vogt-Koyanagi-Harada Syndrome, multiple sclerosis, Fuchs’ heterochromic iridocyclitis, metastatic tumors, and ocular infections as a non-specific finding [10]. Nevertheless, an iris nodule is a relatively specific finding in sarcoidosis, and has clinical value as it may resolve with medical treatment.

**INTERMEDIATE UVEITIS**

Intermediate uveitis refers to inflammation localized to the vitreous and peripheral retina. Intermediate uveitis manifests with symptoms such as visual floaters and visual impairment (media opacity and cystoid macular edema). Cystoid macular edema is a cystic change in the macula, mostly affecting vision in regions of the retina, and involves blood-retinal barrier breakdown due to inflammation [11]. Intermediate uveitis is a relatively common ocular manifestation of sarcoidosis, and accounts for about 31% of all uveitis in sarcoidosis patients, according to one domestic report in Korea [4].
POSTERIOR UVEITIS

Posterior uveitis involves the retina and choroid, and manifests in sarcoidosis as retinal vasculitis with or without panuveitis, and multifocal choroiditis (punched out chorioretinal scarring) with or without evidence of posterior segment inflammation such as vitritis or cystoid macular edema [12]. Posterior uveitis has been known to occur more commonly in elderly white females, but conflicting data exists regarding prevalence among different reports [2]. In a domestic report from Korea [4], it was reported that posterior uveitis was observed in about 28% of patients with definitively diagnosed ocular sarcoidosis, and retinal perivasculitis and spotty retinochoroidal exudates were seen in 67.3% and 53.9%, respectively [3]. It is also known that generally posterior involvement occurs in both eyes, but they are not always symmetric. The manifestation of choroidal granulomas also vary, as do the patterns of manifestation— they may be uniform, or scattered granulomas of different sizes may be observed within one eye. This size variation is one reason why sarcoidosis is often mistaken for a Dalen-fuchs nodule found in Vogt-Koyanagi-Harada disease or a choroidal tumor [13,14]. If choroidal and retinal nodules develop in the peripheral retina rather than the central retina, vision is not greatly affected. However, if nodules are located in the central retina, they can cause severe visual impairment as well as choroidal neovascularization [15].

Perivascular sheathing, the infiltration of inflammatory cells around retinal vessels, and perivascular exudate are often found in ocular sarcoidosis, demonstrating the presence of vasculitis. Although vasculitis is often not very severe in sarcoidosis, caution is required in cases where severe vasculitis is observed because there are several case reports of branch retinal vein occlusion or central retinal vein occlusion [16-18].

CONJUNCTIVAL INVOLVEMENT

The conjunctiva is the tissue which lines the outer wall of the eyeballs, sclera, and the inner surface of the eyelids. Although conjunctival involvement of sarcoidosis is relatively common, it is frequently overlooked because there are often no clinical symptoms. Conjunctival involvement can occur both in the palphebral conjunctiva and the bulbar conjunctiva with symptoms of redness and irritation, or can present as cicatrical conjunctivitis. Conjunctival involvement is significant because the conjunctiva is at the most superficial part of the eyeball, and biopsy in this area is very easy. In patients with biopsy-proven sarcoidosis, conjunctival involvement was found in 55-71% of conjunctival biopsies [19,20].

OPTIC NERVE INVOLVEMENT

In addition to the facial nerve, the optic nerve is the nerve that is most commonly involved in cranial neuropathies of sarcoidosis [21]. The symptoms vary by the location of the granuloma, and visual impairment or even loss of vision may occur depending on the involvement of the optic nerve as well as the visual pathway. Papilledema may be also found depending on the increased intracranial pressure, but papillitis is sometimes found because of uveitis alone even though there is no increase in intracranial pressure. Irreversibly impaired visual acuity occurs in more than half of those with direct optic nerve involvement [22].

ORBITAL INVOLVEMENT

Sarcoidosis can have various symptoms because it can involve orbital fat, the optic nerve sheath, lacrimal gland, and extraocular muscles. Caution is required because there is a mass effect within the eyeballs, and clinical findings may be similar to thyroid orbitopathy [23].

The lacrimal gland is the organ that is most commonly affected within the orbit. The involvement of the lacrimal gland was found in 63% of patients with a definitive diagnosis of orbital sarcoidosis in one study which reviewed 30 patients in a single facility [24]. The involvement of the lacrimal gland often does not have symptoms and is not clinically significant. If the size of the sarcoid mass is large, the mass may be palpable and there may be symptoms due to the mass effect. When the extraocular muscles are involved, diplopia is occasionally presented [25].

IS OPHTHALMOLOGIC TESTING REQUIRED FOR ASYMPTOMATIC PATIENTS WITH SARCOIDOSIS?

Tent-shaped peripheral anterior synechiae (PAS) and posterior synechiae of trabecular meshwork can cause an increase in ocular pressure, and may not be apparent in the early stages. It has been reported that 8 of 22 patients (36.4%) with ocular sarcoidosis were asymptomatic [4], so ophthalmic screening may be necessary.
DOES THE PREVALENCE OF CENTRAL NERVOUS SYSTEM INVOLVEMENT INCREASE WHEN OCULAR SARCOIDOSIS IS FOUND IN OPHTHALMIC SCREENING?

The prevalence of central nervous system (CNS) involvement when ocular sarcoidosis was found in ophthalmic screening has been reported to vary between 2-37% [9]. Therefore, it is difficult to determine if ocular sarcoidosis is associated with CNS involvement.

WHAT ARE THE DIAGNOSTIC CRITERIA FOR OCULAR SARCOIDOSIS?

In 2009, the International Workshop on Ocular Sarcoidosis (IWOS) defined ocular manifestations of sarcoidosis by the following seven signs [26]:
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 synchiae (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 (with or without candlewax drippings) and/or retinal macroaneurism in an inflamed eye
6. Optic disc nodule(s), granuloma(s) and/or solitary a choroidal nodule
7. Bilaterality

The laboratory investigations or investigational procedures that were judged to provide value in the diagnosis of ocular sarcoidosis in patients having the above intraocular signs included (1) negative tuberculin skin test in a BCG-vaccinated patient or in a patient having had a positive tuberculin skin test previously, (2) elevated serum angiotensin converting enzyme (ACE) levels and/or elevated serum lysozyme, (3) thoracic radiograph revealing bilateral hilar lymphadenopathy (BHL), (4) abnormal liver enzyme tests, and (5) chest CT scan in patients with a negative thoracic radiograph result. Four levels of certainty for the diagnosis of ocular sarcoidosis (diagnostic criteria) were recommended in patients in whom other possible causes of uveitis had been excluded: (1) biopsy-supported diagnosis with a compatible uveitis was labeled as definite ocular sarcoidosis; (2) if biopsy was not done but thoracic radiograph was positive showing BHL associated with a compatible uveitis, the condition was labeled as presumed ocular sarcoidosis; (3) if biopsy was not done and the thoracic radiograph did not show BHL, but there were 3 of the above intraocular signs and 2 positive laboratory tests, the condition was labeled as probable ocular sarcoidosis; and (4) if lung biopsy was done and the result was negative, but at least 4 of the above signs and 2 positive laboratory investigations were present, the condition was labeled as possible ocular sarcoidosis [26].

OPHTHALMOLOGIC TREATMENT OF OCULAR SARCOIDOSIS

Because sarcoidosis is a disease involving the entire body, a systemic treatment needs to be considered prior to ophthalmic treatment. However, as there are ophthalmic complications and localized treatment is necessary for these, this discussion is limited to the treatment for complications of sarcoidosis in ophthalmology only.

1. Use of corticosteroid

Administration of a systemic steroid is possible, but topical administration can be also considered, as shown below, for the treatment of ophthalmic complications.

1) Topical corticosteroid

A topical corticosteroid is used to control anterior uveitis, and the systemic effects are minimal. Topical steroids administered as an eye drop do not reach the therapeutic dose as their concentration in the vitreous body is too low. Therefore, administration of a topical corticosteroid eye drop is usually used only in the treatment of anterior uveitis. Its well-known side effects include an increase of ocular pressure and cataracts.

2) Regional corticosteroid injection and implant

(1) Periocular injection

Periocular injection of a corticosteroid is possible, and the most commonly used is triamcinolone acetonide. This is placed under Tenon’s capsule following the outer layer of the eye or injected in the orbital septum, and the therapeutic effect can last 4-6 weeks. The concentration in the lateral ventricle reaches the therapeutic concentration, and lasts for about 30 days. Therefore, it can be used
in cystoid macular edema, posterior uveitis, panuveitis, and intermediate uveitis [27]. As this treatment method may increase ocular pressure, this must be monitored.

(2) Intraocular implant

Two types of slow-releasing steroid implants with similar potency [28], Ozurdex (dexamethasone) and Retisert (fluocinolone acetone) have been commercialized. They are different in that the therapeutic effect of Ozurdex lasts up to 6 months, while the effect of Retisert lasts up to 30 months. Retisert has been reported to have more side effects, requiring increased caution in its use.

2. Biologic agent

For the treatment of non-responsive uveitis, using a biologic agent such as tumor necrosis factor-α inhibitor can be considered. Etanercept (Enbrel; Pfizer Inc.; New York, NY, USA), Infliximab (Remicade; Schering-Plough, Rathdrum, Ireland), Adalimumab (Humira; AbbVie Inc., North Chicago, IL, USA), Golimumab (Simponi; Centocor, Horsham, PA, USA, and Schering-Plough, Rathdrum, Ireland), Certolizumab (Cimzia; UCB Pharma, Brussels, Belgium) have been commercialized, and among these, intravitreal injections of infliximab may benefit cases of persistent noninfectious posterior uveitis and refractory pseudophakic cystoid macular edema [29].

CONCLUSION

Because sarcoidosis is a disease involving the entire body, the eyes, orbits, and optic nerve may be all involved. The rate of ocular involvement among patients with sarcoidosis is high, and because asymptomatic ocular involvement among these is also high, ophthalmic screening is necessary. Specifically, ophthalmic screening such as conjunctival biopsy can be helpful in the definitive diagnosis of sarcoidosis, and it is essential for establishing a system of collaborative treatments. For the management of ophthalmic complications, there are not only systemic medications, but also localized treatment for use in the eyes only, and these may be used separately from the systemic medications.

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