Ocular sarcoidosis

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Available online: 15 May 2012

Summary

Sarcoidosis, a chronic multisystem disease, is a common cause of ocular inflammation. Even though clinical features are well-established, diagnosis 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 ophthalmologist to evaluate the level of ocular inflammation and to monitor its resolution after treatment initiation. Indocyanine green angiography and optical coherence tomography have dramatically improved our understanding of choroidal granulomas and macular edema. Treatment is based on topical and systemic corticosteroids in most of the cases, but immuno-suppressive agents may be necessary. The visual outcome remains favorable but severe complications, including glaucoma, cystoid macular edema and choroidal neovascularization, may need a prompt and aggressive management.

E ven though sarcoidosis was initially described as early as 1877, it remains a diagnostic and therapeutic challenge. Ocular sarcoidosis may develop in the absence of any apparent systemic involvement or may be the main site of disease without significant clinical disease elsewhere [1]. All ocular structures may be involved. Uveitis is the most frequent form of ocular manifestation and may affect up to 20 to 30% of patients with sarcoidosis during the course of the disease. On the other hand, sarcoidosis accounts for 3 to 7% of all uveitis cases [2–5]. In 2006, the first International workshop on ocular sarcoidosis has proposed a set of criteria based on characteristic ocular features and different investigational tests supportive for the diagnosis of uveitis [6]. Unfortunately, analysis of ocular fluids is insufficient for an accurate diagnosis of the disease and tissue biopsy remains difficult to perform for pathological studies. In 2010, ocular sarcoidosis was presented as the disease of the year by Ocular Immunology and Inflammation, one of the journals
dedicated to the field of ocular inflammation [7,8]. Imaging techniques such as indocyanine green angiography and optical coherence tomography are valuable tools for the evaluation of the posterior segment involvement. Severe and sight-threatening complications are rare but may occur in up to 25% of cases.

**Epidemiology**

The prevalence in the Western world is approximately 20 per 100,000 (although in some countries it is higher), and 25–50% of patients may have ocular involvement at some time during the course of the disease. This large range may be due to the fact that a proportion of these cases are not biopsy-proven [9–11]. In a study published in 2007, the clinical features of 81 consecutive patients with biopsy-proven sarcoidosis, referred to a tertiary eye care center over a 16-year period, were retrospectively reported. Most of the patients (43.2%) were Caucasian. Ocular sarcoidosis was identified in 80% of all cases. Interestingly, uveitis, adnexal granulomas and keratoconjunctivitis sicca were noted in 40.7%, 14.8% and 30.8%, respectively. Uveitis is more frequent and severe in African American patients compared with Caucasian [12]. Recent data show that sarcoid uveitis occurs in African American patients who are younger than 50 years compared with Caucasian patients [13]. Recent evidence from Japan shows that sarcoidosis is currently the most prevalent etiology of uveitis replacing Behçet's disease [14]. In Europe, sarcoidosis is a major etiology of uveitis, whereas in the Middle-East, tuberculosis is more frequently observed.

**Diagnostic features**

Histopathologic proof remains the gold standard for the diagnosis of sarcoidosis. However, biopsy of ocular tissue is not easily available, especially in patients presenting with isolated ocular involvement. Moreover, despite promising data that were recently published, ocular fluids do not help in establishing the final diagnosis or even in providing a possible orientation [15]. Lacrimal gland infiltration has been noted in 30% of cases. It is often bilateral and may be associated with parotid swelling and dacryoadenitis (Heerfordt syndrome). Miyara et al. reported that CD4 + CD25(bright)FoxP3+ cells accumulate at the periphery of sarcoid granulomas, in bronchoalveolar lavage fluid, and in peripheral blood of patients with active disease [16]. Preliminary results show that the level of regulatory T-cells may be altered in patients with ocular sarcoidosis.

Anterior uveitis is the most common anatomical form of intraocular inflammation, followed by posterior uveitis, intermediate uveitis, and panuveitis. Frequently, anterior uveitis is the sole ocular finding and may occur in up to 85% of patients with ocular sarcoidosis. It is usually chronic, bilateral and granulomatous with mutton-fat keratic precipitates, iris nodules and posterior synechiae. Tent-shaped peripheral anterior synechiae have also been described. Acute anterior uveitis with ciliary injection is much less prevalent.

Posterior segment involvement is seen in 25% of cases with ocular sarcoidosis, presenting in up to one third of patients as an intermediate uveitis including vitritis, œufs de fourmis, snowballs and snowbank. Posterior uveitis is observed in 12% of cases. Retinal periphlebitis and choriorretinitis are important findings at the posterior segment. Lesions are typically multifocal and located predominantly in the inferior fundus. The “candle-wax” aspect of periphlebitis is a hallmark of the disease. Cystoid macular edema is observed in 19 to 72% of posterior uveitis. It is important to remember that sarcoidosis involving the posterior segment may be accompanied by disease of the central nervous system in 25 to 30% of patients. Minor salivary gland biopsy is most useful for assessing the diagnosis of sarcoid uveitis in a second-line investigation for patients with granulomatous uveitis and a radiologic pattern compatible with sarcoidosis [17]. Rahmi et al. have reported that increasing age at onset of uveitis, posterior synechiae and alterations of high-resolution chest CT are associated with (18)F-FDG PET scan abnormalities consistent with sarcoidosis [18].

**New diagnostic criteria for ocular sarcoidosis**

The first international workshop on ocular sarcoidosis (IWOS) to attempt to establish international diagnostic criteria for ocular sarcoidosis was held on October 28–29, 2006, in Tokyo, Japan by members of an international study group consisting of uveitis specialists and pulmonologists from Asia, Africa, Europe, and America. The goal of this set of criteria is to enable the ophthalmologist to suspect the diagnosis without further invasive investigations. The criteria consist of seven clinical ocular signs and five laboratory tests.

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**Glossary**

- **BHL** bilateral hilar lymphadenopathy
- **IWOS** international workshop on ocular sarcoidosis
- **KPs** Keratic precipitates
- **NPV** negative predictive value
- **OCT** optical coherence tomography
- **OS** ocular sarcoidosis
- **PAS** peripheral anterior synechiae
- **PPV** positive predictive value
- **TM** Trabecular meshwork
Intraocular signs suggestive for the diagnosis of ocular sarcoidosis

Intracocular signs are as follows:
- Mutton-fat Keratic precipitates (KPs) (large or small) and/or iris nodules (Koeppe/Bussacca);
- Trabecular meshwork (TM) nodules and/or tent-shaped peripheral anterior synchiae (PAS);
- Snowballs/strings of pearls vitreous opacities;
- Multiple chorioretinal peripheral lesions (active and/or atrophic);
- Nodular and/or segmental peripheritis (± candle-wax drippings) and/or retinal macroaneurysm in an inflamed eye;
- Optic disc nodule(s)/granuloma(s) and/or solitary choroidal nodule;
- Bilaterality.

Investigational tests supportive for ocular sarcoidosis

Investigational tests are as follows:
- Negative tuberculin test in a BCG vaccinated patient or in a patient who had a positive tuberculin skin test previously;
- Elevated serum angiotensin converting enzyme (ACE) levels and/or elevated serum lysozyme;
- Positive chest X-ray (BHL);
- Abnormal liver enzyme tests
- Abnormal chest CT scan in patients with a negative chest X-ray.

Diagnostic criteria of ocular sarcoidosis were worked out in four levels of certainty

Diagnostic criteria of ocular sarcoidosis were worked out in four levels of certainty as below, i.e.:
- Definite ocular sarcoidosis (OS);
- Presumed OS;
- Probable OS, and;
- Possible OS, based on 7 suggestive ocular signs (see above), 5 supporting investigational tests (see above) and histopathological examination results.
- Definite ocular sarcoidosis: biopsy supported diagnosis with a compatible uveitis;
- Presumed ocular sarcoidosis: presence of bilateral hilar lymphadenopathy (BHL) with a compatible uveitis, if biopsy is not done;
- Probable ocular sarcoidosis: presence of three findings of suggestive intraocular signs and two positive results of supportive investigational tests, if biopsy is not done and the chest X-ray does not show BHL;
- Possible ocular sarcoidosis: presence of at least four suggestive intraocular signs with at least two positive investigational tests, if lung biopsy was done and negative. The IWOS criteria have been retrospectively validated in Japan [19] The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the IWOS criteria, which were based on the combined results of the clinical signs and laboratory tests, were 1.000, 0.956, 0.781, and 1.000, respectively. More recently, the criteria have been undergoing an international, multicenter validation process, which may show higher predictive values for diagnosing ocular sarcoidosis.

Differential diagnosis

In the absence of strong evidence for ocular sarcoidosis, differential diagnosis must be considered and some important entities should be excluded, depending on the anatomic site of inflammation. The first major step is to consider an infectious condition. In the face of a bilateral ocular inflammation with granulomatous features, ocular tuberculosis is the main etiology to rule out. Past medical history, tuberculin skin test, chest X-ray and, more recently, the IGRA tests will be performed in priority. A study in South India found useful the combination of Schirmer test > 10 mm, retinal vasculitis with areas of multiple, pigmented chorioretinal atrophy along blood vessels, and PPD skin test to differentiate tubercular from sarcoid uveitis [20]. Other infections such as syphilis, Lyme disease, leptospirosis and rickettiosis may mimic the clinical features of sarcoidosis. Serology will help to confirm the diagnosis. In cases with intermediate uveitis, multiple sclerosis and HTLV-1 infection should be considered. Autoimmune conditions such as Vogt-Koyanagi-Harada disease, sympathetic ophthalmia and birdshot chorioretinopathy may present with clinical features such as papillitis, retinal vasculitis and choroidal granulomas suggestive of sarcoidosis. Moreover, in patients with dense vitritis, retinal pigment epithelium alterations and retinal vasculitis, primary intraocular lymphoma may mimic ocular sarcoidosis. Dosage of IL-10 levels in the aqueous humor and contributive cytopathological analysis of the vitreous will confirm the diagnosis of malignancy.

Complications

Anterior uveitis is usually chronic and may be diagnosed late in the course of the disease. The rate of complications depends on the diagnostic delay. Band keratopathy is a corneal opacity, which occurs in 5 to 10% of cases. Posterior synechiae may induce scleouir iris bombé, pupillary block and a rapid increase of intraocular pressure requiring a surgical iridectomy. Secondary glaucoma is observed in up to one third of the patients. Cataract may happen with the same frequency. Degree and chronicity of inflammation, together with the
long-term use of corticosteroids, explain the frequency of these 2 complications [9,21,22]. Surgery may be required in both cases with a variable outcome, depending on anatomical lesions but also on the control of intraocular inflammation. Macular edema is the most common complication of ocular sarcoidosis (20–70% of cases). New noninvasive imaging tools such as optical coherence tomography (OCT) are widely used for the diagnosis, quantification and follow-up of macular edema before and during therapy. Other retinal complications such as epiretinal membrane, serous retinal detachment and macular hole are also easily diagnosed with OCT imaging. Fluorescein and ICG angiography are mandatory in patients with retinal

**Figure 1**

A. Slit-lamp biomicroscopy showing mutton-fat keratic precipitates and granulomas in the inferior part of the anterior chamber. 
B. Koepppe nodules in a patient with granulomatous uveitis. 
C. Fundus photography showing choroidal granulomas in a patient with sarcoidosis. 
D. Fundus photography disclosing papillitis in a case of neurosarcoidosis. 
E. Sight-threatening choroidal neovascularization complicating ocular sarcoidosis. 
F. Indocyanine green angiography disclosing multiple choroidal granulomas in a case of systemic sarcoidosis.
vein occlusion and choroidal neovascularization. Vitreous hemorrhage is a rare event but may explain an acute visual loss. Finally, optic disc alterations such as optic disc swelling may occur in patients with posterior or panuveitis and in patients with a neurosarcoidosis.

**Therapeutic strategy**

The conventional therapy of extra- and intraocular sarcoidosis is based on topical and/or systemic corticosteroids. The literature on the medical treatment of intraocular inflammation (uveitis) is littered with case reports, uncontrolled studies, and small case series [23]. Topical steroids are only helpful in mild presentations of anterior uveitis. Mydriatic agents are useful to prevent synechiae formation. In most of the cases, ocular involvement remains isolated and systemic therapy becomes necessary in severe forms of the disease, and especially in cases presenting with posterior uveitis, panuveitis or neurosarcoidosis. Immuno-modulatory agents may be recommended. Azathioprine, methotrexate, tacrolimus and mycophenolate mofetil are used but based mostly on experience rather than on evidence. Caution must be observed with biological agents, such as anti-TNF agents and interferon-alpha, as sarcoidosis has been reported to develop during treatment with these agents or rheumatic disease [24,25]. Etanercept may induce sarcoid intermediate uveitis [26]. Choroidal neovascularization is a sight-threatening lesion requiring the control of ocular inflammation on one hand, and intravitreal administration of anti-VEGF agents on the other hand [27]. A variety of ocular complications such as cataract, glaucoma, vitreous hemorrhage and epiretinal membrane may require a surgical management. Argon laser photoagulation is mandatory in patients with retinal ischemia, especially after inflammatory retinal vein occlusion and vasculitis.

**Ocular prognosis**

Sarcoid uveitis has usually a favorable outcome if detected early and treated adequately. Anterior cases are responding well to topical agents but may need long-term therapy. Posterior uveitis may be more difficult to control and induce sight-threatening complications such as degenerative macular edema and choroidal neovascularization. Severe visual loss may occur in up to 24% of cases with permanent blindness or visual handicap in 10% of cases. Illustrations are available in (figures 1 and 2). The optic neuritis is treated in the article on Neurosarcoidosis [28].

**Disclosure of interest:** the authors declare that they have no conflicts of interest concerning this article.

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