Diagnosis of Ocular Sarcoidosis

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I. Background

Sarcoidosis is a chronic inflammatory disorder with an unknown etiology characterized by non-caseating granulomas. [1-3] The disorder is a multisystem and affects many organs, including the lung, lymph nodes, skin, heart, liver, muscles, and the eye. A very high proportion (30-60%) of patients with sarcoidosis develop ocular changes, and bilateral granulomatous uveitis is the most common presentation. [4-13] The characteristic ocular lesions may occur without apparent systemic involvement.

It is universally accepted that the gold standard for the diagnosis of sarcoidosis is histopathological proof on biopsy tissue showing non-caseating granulomas, and exclusion of other diseases which produce granulomatous lesions, such as tuberculosis. [14] Skin, peripheral lymph nodes, and lung are the common biopsy sites for sarcoidosis. However, biopsy of intraocular tissues is not performed due to its high risk for vision and is hardly accepted by uveitis patients. Therefore, many attempts have been made to establish diagnostic criteria for sarcoidosis with and without biopsy. One example of the diagnostic criteria for systemic and ocular sarcoidosis are those established by the Japanese Society of Sarcoidosis and Other Granulomatous Disorders in 1991, and recently revised by the same group. [15,16] Another example for international diagnostic criteria for ocular sarcoidosis are the proceedings of the 1st International Workshop on Ocular Sarcoidosis (IWOS) which was held in 2006 in Tokyo, Japan. [17] The diagnostic criteria focused on the diagnosis of ocular sarcoidosis when ocular changes are present with or without apparent clinical signs of systemic sarcoidosis.

II. Basic concepts of international criteria for the diagnosis of ocular sarcoidosis put forward at IWOS.

The IWOS diagnostic criteria are proposed to ophthalmologists to enable them to make the diagnosis of ocular sarcoidosis without invasive investigations. The criteria consist of seven clinical ocular signs (Table 1) and five laboratory tests/investigations (Table 2). Based on these ocular signs and laboratory tests, four categories of certainty of sarcoidosis were established relying on the combination of ocular signs and positive results of laboratory tests, resulting in four levels of diagnostic certainty, namely (1) definite, (2) presumed, (3) probable, and (4) possible ocular sarcoidosis (Table 3).

III. Ocular clinical signs suggestive of ocular sarcoidosis

Many reports in the literature described granulomatous uveitis as the hallmark of sarcoidosis. It was the task of IWOS, consisting of a panel of international uveitis specialists and pulmonologists, to define, based on their clinical experience, what clinical signs were most suggestive for ocular sarcoidosis. Seven clinical signs or group of signs were identified.
1. Mutton-fat/granulomatous keratic precipitates (KPs) and/or iris nodules (Koeppe/ Busacca).
   ([figure 1])
   These two sings are the expression of granulomatous changes in the anterior segment of the eye. KPs can be large (mutton-fat KPs) or can take the form of smaller granulomatous KPs. The nodules at the pupillary margin (Koeppe nodules) and those in the iris stroma (Busacca nodules) are classic manifestations of chronic anterior granulomatous uveitis.

   **Figure 1. Granulomatous KPs and iris nodules.** Several examples of granulomatous KPs from large mutton-fat KPs (A) to medium-sized granulomatous KPs (B) and to smaller granulomatous KPs (C). On the right (D) 2 Koeppe nodules at the pupillary margin.

2. Trabecular meshwork (TM) nodules and/or tent-shaped peripheral anterior synechiae (PAS).
   Small nodules are commonly seen on the surface of the TM. The small size of the nodules and their color (white or whitish grey) on TM (white) make it difficult to find. Careful gonioscopic examination with high magnification may help to detect the TM nodules. Tent-shaped PAS is much easier to find by a gonioscopy. This tent-shaped PAS is considered to be the consequence of the resolution and scarring of TM nodules representing the same pathology at a different stage of inflammation. TM nodules can disappear soon after the treatment with topical or systemic corticosteroids, while tent-shaped PAS stay there and can be found at any time once they occurred.

   These types of vitreous opacities represent granulomatous changes in the vitreous. These vitreous opacities are usually located at the inferior segment of ocular fundus, and can be single or multiple and forming a shape of "string of pearls". They are commonly seen in sarcoidosis,
but also can be seen in pars planitis and intermediate uveitis associated with multiple sclerosis.

4. Multiple chorioretinal peripheral lesions (active and/or atrophic). (Figure 2)

Multiple chorioretinal lesions in sarcoidosis are round in shape, small in size, white or whitish-yelllow in color and present in clusters, located at random in the periphery up to 360 angle degrees. The lesions are more whitish when active and become more yellowish-greyish with more sharp margins when cicatricial.

Figure 2. Peripheral chorioretinal granulomas.

5. Nodular and/or segmental periphlebitis (± candlewax drippings) (Figure 3)

Nodular or segmental sheathing of retinal veins is a typical manifestation of retinal vasculitis in sarcoidosis. They can cause obstruction of the retinal veins, resulting in areas of non-perfusion causing retinal neovascularization. In addition to these signs of periphlebitis, the presence of macroaneurisms in an inflamed eye is considered to be a significant although rare ocular sign of sarcoidosis. (Figure 4)

Figure 3. Segmental sheathing of retinal veins, shown on fundus photography (top, black arrows) and fluorescein angiography (bottom)
Figure 4. Retinal macroaneurism in a case of sarcoidosis. Macroaneurism (yellow arrows) shown on fundus picture (top right), on FA intermediate angiographic phase (top left), in late FA phase (bottom left), on ICGA intermediate phase (center picture) and ICGA late phase (right middle picture). Note also on ICGA frames numerous hypofluorescent dark areas (black arrows) indicating occult granulomas not seen on fundus picture and FA.

6. Optic disc nodules/ granulomas (Figure 5) and/or solitary choroidal nodule.

Although these two signs are rare, they are very typical signs of granulomatous uveitis such as sarcoidosis and tuberculosis. Optic disc nodules can be large or small in size. The solitary choroidal nodule is usually round shaped and the color is whitish grey.

Figure 5. Optic disc nodule in a patient with sarcoidosis. Swollen disc (left) due to optic disk granuloma shown on MRI of orbit (right, black arrow)


More than 80% of patients with ocular sarcoidosis have bilateral uveitis. [18] Bilaterality can be established either by clinical examination or by adjuvant methods capable of showing subclinical disease, such as laser flare photometry showing abnormal flare or indocyanine green angiography which demonstrates the presence of choroidal vasculitis and/or hypofluorescent dots representing choroidal inflammatory involvement. (Figure 6) Bilaterality can also be documented when, in addition to activity in one eye, there are sequels of previous inflammation in the other eye, such as PAS found on gonioscopic examination.
Figure 6. Bilaterality of lesions detected by ICGA. Patient with granulomatous right anterior uveitis (not shown) with normal fundus (left picture) and normal FA frames of left eye (top trio of figures on the right). Only ICGA (bottom trio of pictures on the right) positively identifies granulomas in the choroid indicating bilateral involvement.

IV. Investigations/laboratory tests supportive for the diagnosis of ocular sarcoidosis.

1. Chest x-ray showing bilateral hilar lymphadenopathy (BHL)

BHL is the most frequent radiological finding in systemic sarcoidosis. It is present in 50-89% of systemic sarcoidosis. [19,20] Other disorders presenting BHL include lymphoma, but it is usually accompanied by systemic lymph node involvement.

2. Negative tuberculin test in a BCG-vaccinated patient or in a patient with a previously positive tuberculin skin test.

This test is useful in communities where BCG vaccination is routinely performed in all individuals and the majority of people in the community are positive to tuberculin test, such as Japan. On the other hand, the usefulness of this test might be less in countries where BCG vaccination is not performed on a large scale.

3. Elevated serum angiotensin converting enzyme (ACE) and/or elevated serum lysozyme

ACE was elevated in 60% of 125 sarcoidosis patients[21] and in 58% of biopsy-proven sarcoidosis patients in another study against only 5% of the control patients[18]. Therefore, serum ACE is a valuable parameter to suggest the presence of sarcoidosis. Serum ACE is known to be higher in children. Serum ACE in patients taking ACE inhibitors is known to be undetectable. Therefore, serum ACE is less useful in children and is useless in patients on ACE inhibitors. In such situations serum lysozyme is a valuable adjunct as it also measures the presence of granulomas. In any case, if available performing both tests is recommended.

4. Abnormal liver enzyme tests

It is well known that hepatic involvement in sarcoidosis is one of the sites where undetected granulomas can form. Although little is known about the importance of liver enzymes in ocular sarcoidosis, the international criteria for the diagnosis of ocular sarcoidosis included abnormal liver enzymes: three times the upper limit of normal values for alkaline phosphatase or elevation twice over the upper limit of two of the following liver enzyme - aspartate aminotransferase
(ASAT), alanine aminotransferase (ALAT) or alkaline phosphatase.

5. Chest CT scan in patients with a negative chest x-ray

This test is not a first-line test, but used for patients where sarcoidosis is strongly suspected but where the chest radiography is negative for BHL.

V. Interventional diagnostic tests

1. Broncho-alveolar lavage fluids (BALF)

Examination of BALF includes cytology and subset of lymphocytes in the fluids. Lymphocytosis and an increase of CD4/CD8 ratio in non-smoking individuals are considered to be characteristic in sarcoidosis. In fact, this is included in the diagnostic criteria for sarcoidosis by the Japanese Society of Sarcoidosis and Other Granulomatous Disorders (16). BALF samples can be used for various tests (smears, cultures) for mycobacterium in case of need to differentiate from tuberculosis.

2. Transbronchial lung biopsy (TBLB)

TBLB is the most commonly performed biopsy in sarcoidosis. Non-caseating granulomas with Langhans type epithelioid cells are present in sarcoidosis. However, unlike biopsies of the skin or lymph nodes, it is not a lesion-guided biopsy. It can be false negative when the biopsy site is not appropriate.

VI. Other investigational tests.

The IWOS criteria allow to reach a certain level of diagnostic certainty in a large proportion of cases and have the merit to standardize diagnostic parameters in sarcoidosis apparently limited to the eye. Nevertheless most of the laboratory tests/investigations used by IWOS criteria to make the diagnosis of ocular sarcoidosis rely on the fact that there is systemic occult involvement because purely ocular sarcoidosis cannot account for the fact for instance that elevation of lysozyme and/or ACE in serum are caused by granulomas merely limited to the eye. Additionally, by definition, if hilar adenopathy, one of the IWOS investigational tests, is found, this automatically implies systemic (pulmonary) involvement. Moreover the low grade of specificity and sensitivity of most of the investigational/laboratory tests at our disposal justifies to resort to other tests at hand to increase the level of diagnostic certainty, even though the latter are also of low sensitivity and specificity.

1. Gallium scan [22]

\(^{67}\)Gallium is a radioactive isotope with a half-life of 78 hours that is taken up by activated macrophages so marking areas where epithelioid cell granulomas are formed. During its decay gamma photons are emitted and captured by a gamma camera from the sites of uptake. After intravenous injection of \(^{67}\)Gallium citrate, the radioisotope has a half-life in the blood pool of 12
hours. Gallium uptake is assessed and graded in the lacrimal gland, salivary glands, thorax, spleen, liver and the eyes 48 hours after injection. In a retrospective study of 18 patients diagnosed as ocular sarcoidosis a high sensitivity for Gallium scan was found. [23] In the context of a disease lacking sensitive and specific tests, Gallium scan is an additional tool in cases where diagnosis is hard to ascertain.

2. Polyclonal immunoglobulin activation

Sarcoidosis is at the origin of immunologic changes modifying the balance between the cellular and humoral immunity that can serve as a diagnostic test. [24] CD4 lymphocytes are attracted to the foci of inflammation in tissues with a decrease of efficiency of cellular immunity and a polyclonal increase of antibodies due to a take over of humoral immunity [25, 26] which explains the anergy found in sarcoidosis. [27] This immune dysfunction is well known by internists and has been reported for patients with systemic sarcoidosis. [28-30] A clinical study used the fact that a very high percentage of the adult population has been exposed to most herpes viruses to search for increased titers to herpes viruses in sarcoidosis suspect patients. [31] This study showed that a polyclonal activation score was significantly more elevated in a group with proven sarcoidosis when compared to control groups of HLA-B27 uveitis, pars planitis uveitis and healthy controls.

3. Indocyanine green angiography (ICGA)

ICGA allows not only to detect bilaterality of disease as mentioned hereabove but allows also to detect occult choroidal lesions when nothing lets suspect fundus or posterior segment involvement. [31] In patients with scarce ocular signs and no apparent fundus lesions, ICGA can be useful to reinforce the suspicion of sarcoidosis. It was shown that in a collective of 19 sarcoidosis patients all patients had choroidal involvement some of which were not suspected by fundus examination or fluorescein angiography. [12] ICGA signs consisted of hypofluorescent dark dots, fuzziness of large choroidal vessels and late diffuse choroidal hyperfluorescence. An additional sign was hyperfluorescent pinpoints present in 89% of patients. These signs are not specific for sarcoidosis but can be present in other granulomatous diseases of the choroid. Several reports document the fact that ICGA allows to detect occult choroidal lesions in sarcoidosis. [12,31,32] Therefore in patients with uveitis suspected to be due to sarcoidosis, especially in those cases presenting with limited signs for granulomatous uveitis, ICGA represents an additional help to establish the clinical picture and diagnosis of ocular sarcoidosis and should be part of the recommended work-up. (Figures 6 & 7)

Although all these diagnostic modalities are of limited specificity and sensitivity they should be considered in the armamentarium to diagnose ocular sarcoidosis.
Figure 7. Occult choroidal granulomas seen only on ICGA. 23-year-old patient presenting with right irido-corneal synechiae (not shown) and several granulomatous KPs OD (not shown) and an increased flare by laser flare photometry OU (32.4 ph/ms OD versus 17.9 ph/ms OS) with elevated serum ACE and lysozyme. The top two duets of pictures are FA frames of both eyes which are practically normal except for slight disc hyperfluorescence OD, whereas ICGA frames show extensive choroidal involvement in form of numerous hypofluorescent dark dots (HDDs) (squares,circles and arrows) and fuzzy indistinct choroidal vessels. ICGA was the only way to determine bilateral posterior inflammatory involvement.

VII. Exclusion of other entities

In addition to the clinical signs and laboratory tests indicative of sarcoidosis, exclusion of other entities that can be mistaken for sarcoidosis is equally important for the diagnosis of sarcoidosis. Some uveitis entities, particularly entities with granulomatous uveitis must be excluded. Hereunder the principal entities to be excluded are listed and the specific clinical signs to be looked for as well as the laboratory tests and investigations to be performed are exposed..

(1) Exclusion of ocular tuberculosis

Tuberculosis is the first and most important entity to be excluded. It classically presents as a granulomatous uveitis undistinguishable from sarcoid uveitis. Exclusion of Tuberculosis has become more easy since the availability of gamma-interferon release assays (IGRA, Quantiferon®-gold or TB Elispot® test) as false-negatives are very rare. Classical bacterial tests for Mycobacterium tuberculosis should be performed in case of need.

(2) Exclusion of Vogt-Koyanagi-Harada disease

In certain areas and populations including the Asian continent, Hispanic populations and Amerindians, Vogt-Koyanagi-Hadara (VKH) disease should be excluded. If acute VKH can be differentiated easily from sarcoidosis, chronic VKH presents granulomatous anterior uveitis with iris nodules, nodules at the trabecular meshwork and tent-shaped PAS resembling ocular sarcoidosis. However, chronic VKH also presents typical depigmentation of the fundus which can be seen in sarcoidosis when it is patchy as well as sunset-glow fundus, which is not seen in
sarcoidosis.

(3) Exclusion of HTLV-1 uveitis

In the southern shores of Japan and in the Caraibbes, human T-cell leukemia virus type 1 (HTLV-1) is an entity to be excluded. HTLV-1 uveitis is characterized by vitreous opacities (intermediate uveitis) and mild retinal vasculitis. In some patients with HTLV-1 uveitis can present iris nodules as well as nodules at trabecular meshwork. Therefore, serological test to search for anti-HTLV-1 antibodies is important in countries where HTLV-1 is endemic.

(4) Exclusion of herpetic anterior uveitis.

Anterior uveitis caused by human herpes viruses, such as herpes simplex (HSV), vallecella zoster virus (VZV), and cytomegalovirus (CMV), are ubiquitous and present as a granulomatous uveitis characterized by mutton-fat KPs, ocular hypertension and iris atrophy especially in case HSV and VZV uveitis. These clinical signs are similar to those of ocular sarcoidosis. However, the clinical manifestations of these two diseases are sufficiently distinctive to allow to exclude herpetic conditions. Herpetic anterior uveitis is nearly always a unilateral condition whereas ocular sarcoidosis is bilateral in approximately 80% of cases. [18] In addition, fine changes on the iris surface in the acute stage followed by iris atrophy (diffuse or segmental) a few months later are present in anterior uveitis caused by VZV or HSV.

(5) Exclusion of bilateral Fuchs’ uveitis (FU) (Figure 8)

When Fuchs’ uveitis (FU) is unilateral the diagnosis is easy. However when it presents as a bilateral uveitis, which is the case in up to 8% of Fuchs’ cases [33], it can be mistaken for ocular sarcoidosis especially when the microgranulomatous stellate Fuchs’ KPs are slightly larger than usual. Fuch’s uveitis is also ubiquitous and should be one of the conditions to be excluded. Characteristic FU signs should be identified to exclude this condition. They include spread of KPs above the midline and allover the endothelium, iris structural changes, abnormal vessels in the iridocorneal angle and absence of synechiae.

Figure 8. Fuchs’ uveitis signs to be excluded in the diagnosis of ocular sarcoidosis. Small granulomatous KPs distributed all over the cornea, a disposition typical of Fuchs’ uveitis. On the left picture iris structural changes are identified (black arrows).
(6) Exclusion of intermediate uveitis, especially of the pars planitis type.

Sarcoidosis can present as an intermediate uveitis. Therefore any type of intermediate uveitis, particularly pars planitis, should be excluded. Pars planitis is a bilateral condition presenting with snowballs and snowbanking, scarce anterior segment inflammation, absence of synechiae and negativity of laboratory tests. Sarcoidosis can present with snowballs and snowbanking in a similar fashion to pars planitis and the presence of granulomatous KPs (not seen in pars planitis) and irido-crystalline synechiae allow to exclude pars planitis and strongly speak for sarcoidosis or another granulomatous disease.

(7) Exclusion of multiple sclerosis

As indicated hereabove sarcoidosis can present as intermediate uveitis and peripheral vasculitis. When it presents in this form, one disease that should be excluded is multiple sclerosis, one of the systemic associations with intermediate uveitis. In countries where multiple sclerosis is a common clinical uveitis entity, oriented history taking and MRI are therefore recommended to exclude or confirm multiple sclerosis.

(8) Exclusion of masquerade syndromes

Conditions masquerading for uveitis such as intraocular lymphoma and amyloidosis, present vitreous opacities similar to those in ocular sarcoidosis. There are two types of clinical presentations in primary intraocular lymphoma: one with multiple retinal/sub-retinal lesions and the other with vitreous opacities with/without retinal lesions. There are some differences in the clinical pictures of vitreous opacities between intraocular lymphoma and sarcoidosis. The vitreous opacities in intraocular lymphoma are diffuse with large cells in the vitreous. The characteristic features of vitreous opacities in ocular sarcoidosis are granulomatous opacities, such as snow ball opacities or string of pearls opacities, together with diffuse vitreous opacities. Vitreous opacities in lymphoma have poor response to corticosteroid therapy whereas those in sarcoidosis respond well to corticosteroids. If intraocular lymphoma is suspected, cytological examination of the vitreous cells, cytokine assay in the aqueous humor (interleukin-10) or detection of rearrangement of immunoglobulin genes by polymerase chain reaction are necessary.

VIII. Practical processes of diagnosis

In a considerable proportion of cases it is the ophthalmologist who first sees patients presenting with the ocular expression of sarcoidosis. When any of the ocular signs in Table 1 are present on ocular examination, we should suspect ocular sarcoidosis together with all clinical entities to be excluded. In countries where sarcoidosis is very common and the leading
cause of uveitis, such as in Japan, all laboratory tests listed in Table 2 should be performed and the patient is then sent for internal medecine work-up, often performed by the pulmonologist. The pulmonologists perform all necessary systemic examination for systemic sarcoidosis which include chest CT scan, gallium scintigraphy, bronchoalveolar fluid lavage, and lung biopsy. However, when the clinician wants to by-pass such an invasive approach or in countries where sarcoidosis is less common a non-invasive approach may be warranted at first.

Figure 9 illustrates the practical approach on how diagnosis of ocular sarcoidosis can be done when the primary invasive approach is avoided.

The first line of systemic examinations in such conditions is a standard chest x-ray, tuberculin skin test, serum ACE (and/or serum lysozyme), and liver enzymes. After all other diseases are ruled out, BHL is present on standard chest x-ray then the patients can be diagnosed as “presumed ocular sarcoidosis”. However, if BHL is not detected by standard chest x-ray, then further laboratory/investigational tests should be performed including CT scan Gallium scan or search for polyclonal activation. If the results of the further laboratory/investigational tests are positive (two positive tests in Table 2 and three of the ocular signs in Table 1), the patients will be diagnosed as “probable ocular sarcoidosis”. However, if the patients do not meet these criteria, it is recommended to send the patients to the pulmonologists for further systemic examinations including biopsy (lung biopsy), or the dermatologists for skin biopsy if skin lesions are present. If histopathological examination on the biopsy tissues is positive, the patients are diagnosed as “definite ocular sarcoidosis” (biopsy-proven sarcoidosis). However, if biopsy is negative, the patients are not diagnosed as ocular sarcoidosis, and other causes of uveitis should be ruled out in those cases. Because lung biopsy is a blind biopsy and can generate false negatives if the biopsy site is not appropriate, in patients with a negative lung biopsy the disease can still be due to sarcoidosis. Following the IWOS criteria, in these rare cases, when four of the suggestive ocular signs and two of the supportive laboratory/investigational tests are positive, these patients will still be diagnosed as “possible” ocular sarcoidosis.

Figure 9. Approach for the diagnosis of ocular sarcoidosis (OS) Dot line indicates a diagnostic approach in countries where OS is very common, whereas solid line illustrates a practical approach on how diagnosis of OS can be done when the primary invasive is avoided. TBLB: transbrochial lung biopsy.
References


Bouchenaki N, Herbort CP. Fuchs’ uveitis: failure to associate vitritis and disc hyperfluorescence with the disease is the major factor for misdiagnosis and diagnostic delay. MEAJO 2009; 16:239-44.
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<td>7</td>
<td>Bilaterality (assessed by clinical examination or investigational tests showing subclinical inflammation).</td>
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Table 2. Laboratory investigations in suspected ocular sarcoidosis

1. Negative tuberculin test in a BCG vaccinated patient or having had a positive PPD (or Mantoux) skin test previously
2. Elevated serum angiotensin converting enzyme (ACE) and/or elevated serum lysozyme
3. Chest x-ray: look for bilateral hilar lymphadenopathy (BHL)
4. Abnormal liver enzyme tests (any two of alkaline phosphatase, ASAT, ALAT, LDH or γ-GT)
5. Chest CT scan in patients with negative chest x-ray

* Test required in patients treated with ACE inhibitors.
All other possible causes of uveitis, in particular tuberculous uveitis, have to be ruled out. Biopsy supported diagnosis with a compatible uveitis.

1. Biopsy not done; presence of bilateral hilar lymphadenopathy (BHL) with a compatible uveitis.
2. Biopsy not done and BHL negative; presence of three of the suggestive intraocular signs and two positive investigational tests.
3. Biopsy negative, four of the suggestive intraocular signs and two of the investigations are positive.

*Used in the sense of intraocular inflammatory lesions both in patients with systemic disease seemingly limited to the eye without any clinically detectable involvement.*

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