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International Criteria for the Diagnosis of Ocular Sarcoidosis: Results of the First International Workshop on Ocular Sarcoidosis (IWOS)

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ABSTRACT

Aim: To report criteria for the diagnosis of intraocular sarcoidosis, taking into account suggestive clinical signs and appropriate laboratory investigations and biopsy results. *Design*: Concensus workshop of an international committee on nomenclature. *Methods*: An international group of uveitis specialists from Asia, Africa, Europe, and America met in a concensus conference in Shinagawa,

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Tokyo on October 28–29, 2006. Based on questionnaires that had been sent out prior to the conference, the participants discussed potential intraocular clinical signs eligible for a diagnosis of ocular sarcoidosis. A refined definition of clinical signs, which received two-thirds majority of votes, was included in the list of signs consistent with ocular sarcoidosis. Laboratory investigations were similarly discussed and those tests reaching a two-thirds majority were retained for the diagnosis of ocular sarcoidosis. Finally diagnostic criteria were proposed based on ocular signs, laboratory investigations, and biopsy results. *Results*: The concensus conference identified seven signs in the diagnosis of intraocular 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, and (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) chest x-ray revealing bilateral hilar lymphadenopathy (BHL), (4) abnormal liver enzyme tests, and (5) chest CT scan in patients with a negative chest x-ray 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 chest x-ray 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 chest x-ray 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*. *Conclusion*: Various clinical signs, laboratory investigations, and biopsy results provided four diagnostic categories of sarcoid uveitis. The categorization allows prospective multinational clinical trials to be conducted using a standardized nomenclature, which serves as a platform for comparison of visual outcomes with various therapeutic modalities.

Sarcoidosis is a multisystem chronic inflammatory disorder of unknown etiology characterized histologically by noncaseating granulomas.[1–3] About 30–60% of patients with sarcoidosis develop ophthalmic changes and bilateral granulomatous intraocular inflammation is a frequent presentation.[4–13] This eye disease may occur in the absence of apparent systemic involvement or may be the main site of disease without significant clinical disease elsewhere, in which case it is impossible by the present definitions or criteria to be affirmative about the diagnosis.

Sarcoidosis is one of the major uveitis entities in many countries and ethnic groups. Making a diagnosis is challenging as no clinical sign or investigation is diagnostic. Even histology is not pathognomonic. Furthermore, international diagnostic criteria are still not available at present. The gold standard for the diagnosis of sarcoidosis is histopathological proof using biopsy tissue. However, biopsy of intraocular tissue is not commonly performed and is reluctantly accepted by uveitis patients unless it is taken from an easily accessible site. If transbronchial lung biopsy is not performed, a definitive diagnosis in a considerable proportion of patients with ocular sarcoidosis is not clinched (false-negatives).[14] In Japan, sarcoidosis has become the leading cause of uveitis, surpassing even Behçet uveitis. Efforts have been made in the past to achieve diagnostic criteria for ocular sarcoidosis.[15,16] In Japan, diagnostic criteria for sarcoidosis were established in 1991 by the Japanese Society of Sarcoidosis and Other Granulomatous Disorders[16] and have been recently revised by the same group.[17] However, it is not clear whether such criteria are universally applicable.

The aim of the current international workshop was to discuss whether it is possible to make the diagnosis of ocular sarcoidosis based on a combination of ophthalmic clinical signs and laboratory investigations in the absence of apparent systemic involvement, and to reach a concensus on diagnostic criteria for "intraocular sarcoidosis" (sarcoidosis uveitis) that is internationally applicable.

METHODS

An international group of uveitis specialists from Asia, Africa, Europe, and North America as well as two pulmonologists specializing in sarcoidosis met in a concensus conference hosted by the Department of Ophthalmology and Visual Science, Tokyo Medical and Dental University at the Tokyo Conference Centre in Shinagawa, Tokyo. The workshop was held on October 28–29, 2006. Delegates took up the task to define clinical intraocular signs suggestive of the diagnosis of ocular sarcoidosis and the laboratory investigations that support such a diagnosis. Questionnaires had been sent out prior to the conference to the participants in order to list intraocular signs that were deemed suggestive of the diagnosis of intraocular sarcoidosis and investigational tests that were judged supportive of the diagnosis. As a first step, following the wish of some of the participants, the goals of the conference were discussed and voted upon.

A paper comparing the clinical signs and investigations of 67 patients with biopsy proven sarcoidosis with 111 uveitis controls was initially presented to the group by the Japanese colleagues among the group.[18] Later during the conference, the important intraocular clinical signs were shown. The terminology describing each sign was discussed, refined, and agreed upon. The value of these signs in suggesting the diagnosis of ocular sarcoidosis was voted upon. If a sign reached a two-thirds majority, it was included in a list of signs suggestive of ocular sarcoidosis. Similarly investigational tests that were deemed appropriate to ascertain the diagnosis were discussed and their diagnostic (supportive) value was voted upon. Finally, diagnostic criteria were worked out based on ocular signs, investigational tests, and biopsy results reaching 4 levels of certainty of the diagnosis and were voted on.

RESULTS

Goals of Workshop and Preliminary Discussions

The goals of the workshop voted upon were (1) to establish a number of clinical signs that "make the clinician think that the intraocular inflammatory changes seen in a given patient are sufficiently suggestive of sarcoidosis" to pursue investigations in that direction; (2) to establish an appropriate list of laboratory investigations to confirm the diagnosis of ocular sarcoidosis, and (3) to establish criteria for the diagnosis of ocular sarcoidosis with increasing degrees of certainty based on a combination of clinical signs, laboratory investigations and biopsy results.

The group wishes to highlight several points discussed:

1. As sarcoidosis can have protean manifestations, presenting acutely or chronically with both granulomatous and sometimes nongranulomatous uveitis, investigations to rule out sarcoidosis should be performed in any patient presenting with uveitis.
2. Intraocular inflammation due to sarcoidosis is not a different disease from systemic sarcoidosis. Therefore, the term ocular sarcoidosis should be applied both to isolated ocular disease as well as to ocular involvement in systemic disease.
3. To diagnose sarcoidosis, other causes of uveitis, especially tuberculosis, should be excluded. As the differential diagnosis of ocular sarcoidosis varies from one part of the world to another and because of the limited time frame of the workshop, the group decided not to give specific and more precise guidelines on how best to proceed to exclude other uveitic conditions. It was felt that this question should be left open and could become part of the agenda for discussion in future IWOS workshops.

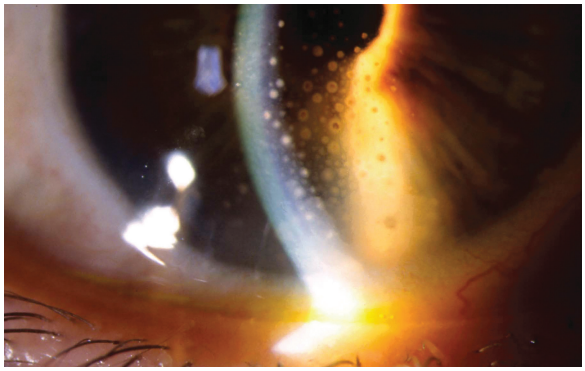
Clinical Signs Suggestive of Ocular Sarcoidosis

The group then proceeded to determine the signs that best qualify ocular sarcoidosis. The term "pathognomonic sign" was felt to be too strong by some members of the group and the chararcterisitc clinical signs were finally defined as "intraocular signs that make the clinician think of" or that are "suggestive of" ocular sarcoidosis.

The delegates were asked at the end of each discussed clinical sign or laboratory test to vote on the relevance of the item. The votes were obviously based on the clinical experience of the delegates. In addition to this they were aided by recently available and presented data on the sensitivity, the specificity, and the predictive values of five of the clinical signs and five of the investigational tests under discussion. These data were obtained from a Japanese study including 67 uveitis patients with biopsy proven sarcoidosis compared to 111 control uveitis patients.[18]

The concensus conference identified a group of seven signs of intraocular inflammation, which received a two-thirds majority, and these were labeled as signs suggestive for the diagnosis of ocular sarcoidosis:

1. *Mutton-fat/granulomatous keratic precipitates (KPs) and/or iris nodules (Koeppe/Busacca)* (Figure 1). These two signs were associated in one set of clinical signs representing granulomatous reaction of the anterior segment. The type of KPs was not limited to the



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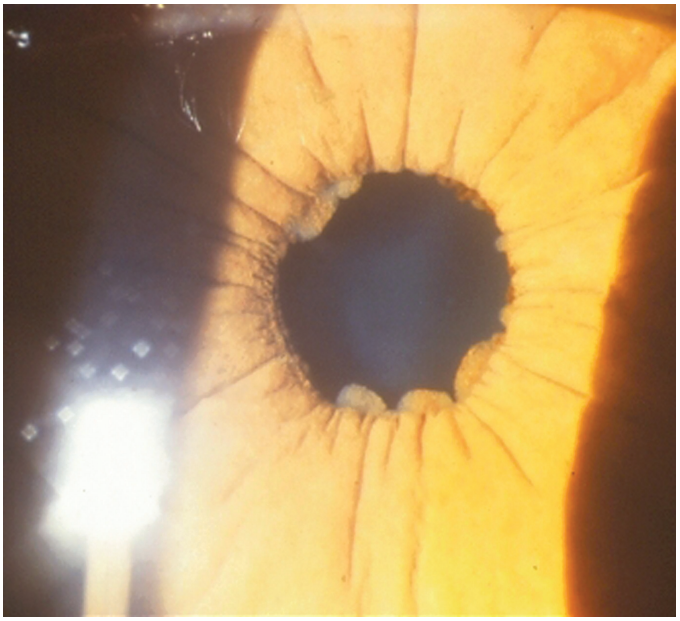

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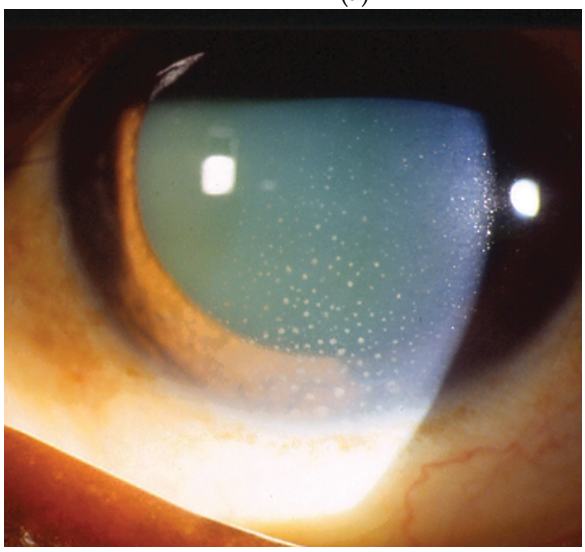

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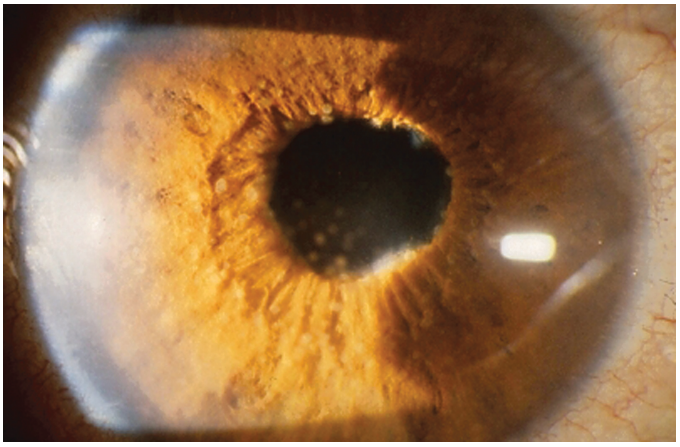

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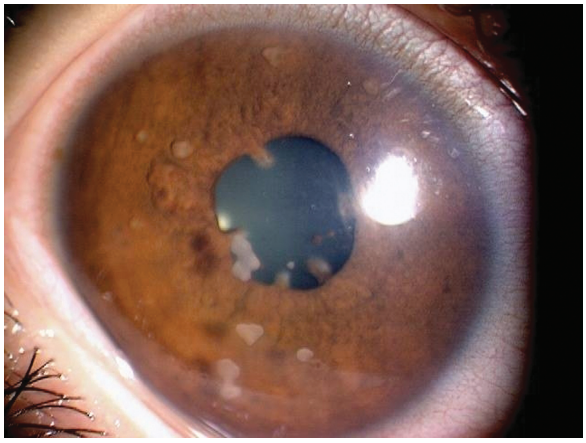
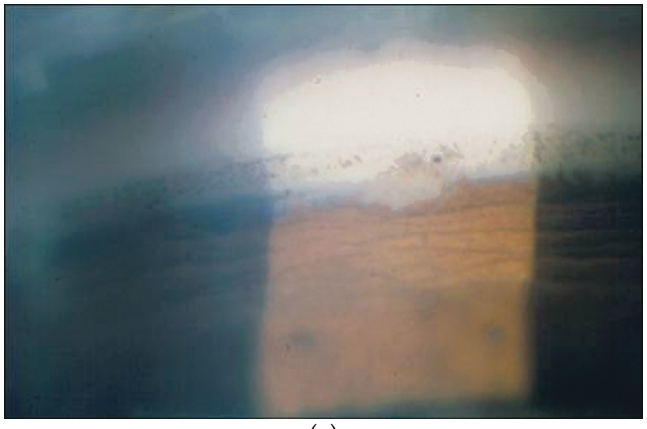


(e)

Figure 1. (a) Large granulomatous (mutton-fat) keratic precipitates (KPs). (b) Small granulomatous keratic precipitates (KPs). (c) Iris pupillary margin and/or superficial nodules (Koeppe nodules). (d) Picture showing pupillary margin and superficial fluffy iris nodules (Koeppe nodules) as well as a thickened stroma without distinct Busacca being visible, as well as posterior synechiae. (e) Iris stromal nodules (Busacca nodules). Note also large granulomatous (mutton-fat) KPs.

large mutton-fat type (Figure 1a) but also included smaller granulomatous KPs (Figure 1b). The nodules comprised pupillary margin nodules (Koeppe nodules) (Figure 1c) and fluffy nodules at the surface of the iris margin (Figure 1d) as well as iris stromal nodules (Busacca nodules) (Figure 1e).

2. *Trabecular meshwork (TM) nodules and/or tent-shaped peripheral anterior synechiae (PAS)* (Figure 2). This sign was estimated by some of the delegates to be associated with sarcoidosis uveitis in a high proportion. Additionally in the Japanese study, this factor had by far the highest values for all factors, including sensitivity, specificity, and positive and negative predictive values.[18] The two signs were combined as they are believed to be the consequence of the resolution and scarring of TM nodules representing the same process at different evolutionary stages.
3. *Snowballs/string of pearls vitreous opacities* (Figure 3). This type of vitreous involvement was estimated to be very suggestive of a granulomatous process, such as occurs in ocular sarcoidosis, especially in Japan.



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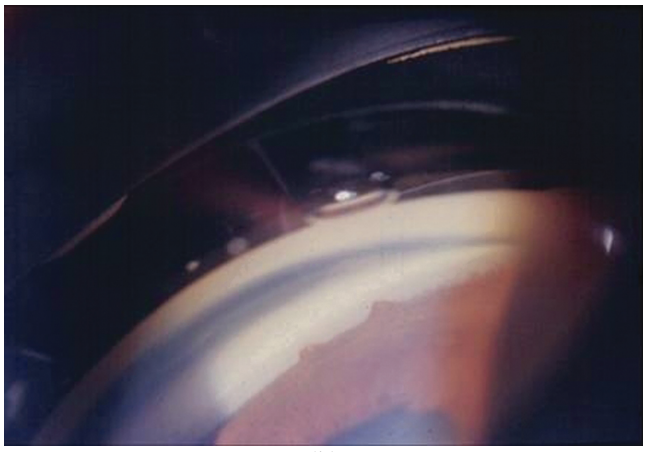

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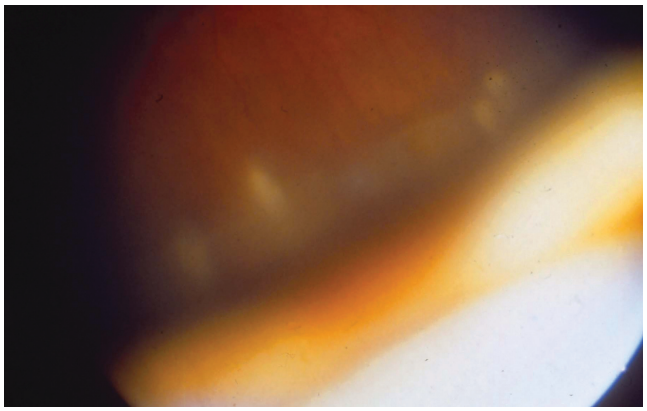
Figure 2. (a) Trabecular meshwork nodules. (b) Tent-shaped PAS.



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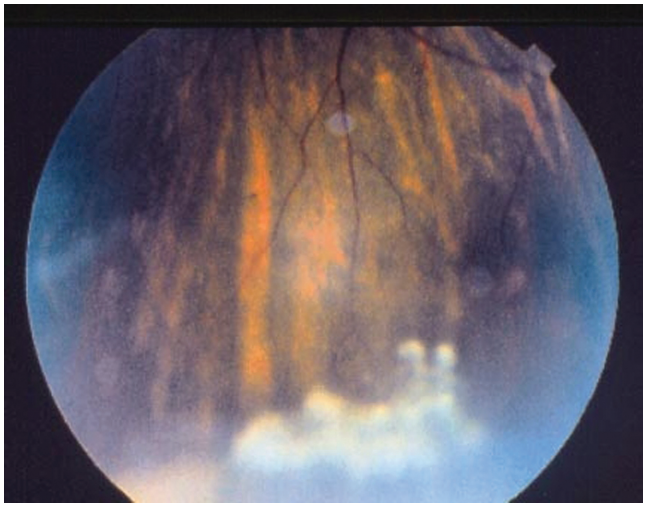
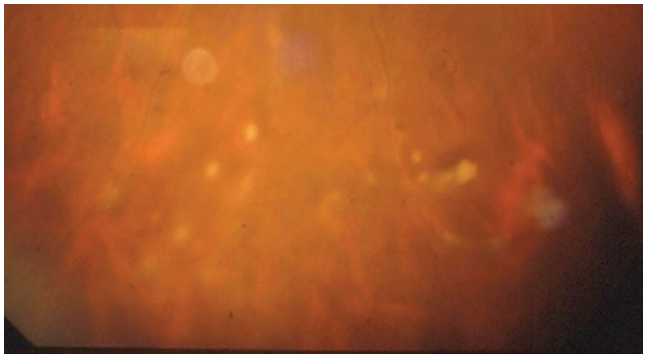


(b)

Figure 3. (a) Snowballs. (b) String of pearls vitreous opacities.

However, snowballs may also be seen in intermediate uveitis of the pars planitis type and in uveitis related to multiple sclerosis, the two diseases occurring more frequently among Caucasians. In this situation the presence of posterior irido-lenticular synechiae is another argument for ocular sarcoidosis but it was not deemed necessary to include this fact in the definition of this clinical sign.

4. *Multiple chorioretinal peripheral lesions (active and/or atrophic)* (Figure 4). This sign, preferentially seen in middle aged to elderly women, was felt to be strongly suggestive of ocular sarcoidosis.[19,20]
5. *Nodular and/or segmental periphlebitis (± candlewax drippings) and/or retinal macroaneurysm in an inflamed eye* (Figure 5). Although these signs were felt to be strongly associated with ocular sarcoidosis, this group of vascular signs stimulated extensive discussion on how to qualify the type of vascular involvement and as result several descriptive terms were



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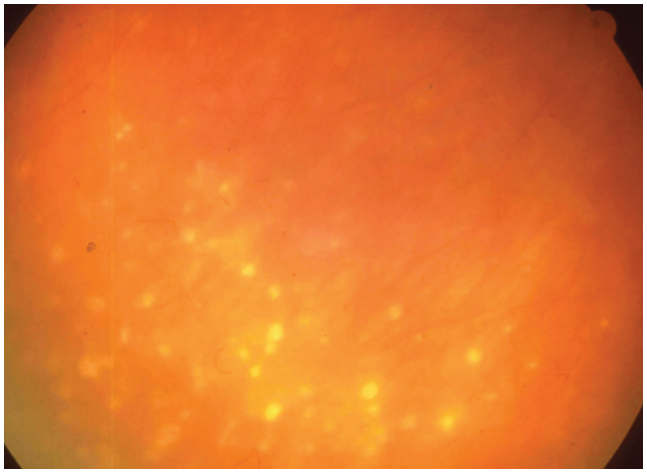


(b)

Figure 4. (a) Multiple chorioretinal peripheral lesions. (b) Peripheral lesions (retinochoroidal).

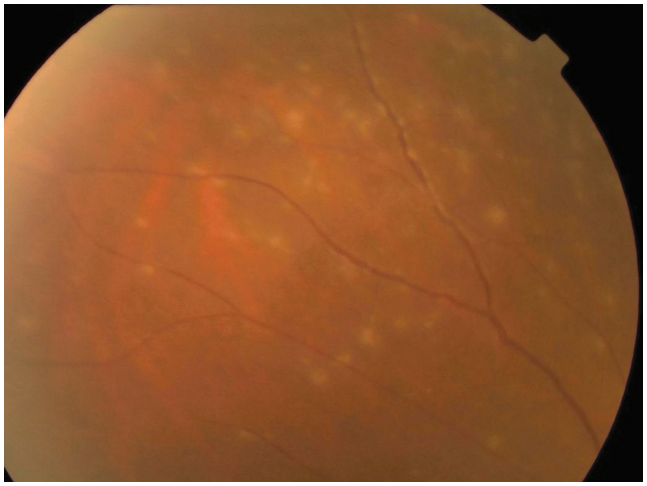
used. Furthermore, the last item of this group of signs, macroaneurism, did not initially reach a two-thirds majority, with the argument that noninflammatory vascular conditions could produce retinal macroaneurisms. As a result, the sign was defined as "retinal macroaneurysm in an inflamed eye."[21–23]

6. *Optic disc nodule(s)/granuloma(s) and/or solitary choroidal nodule* (Figure 6). This sign was readily accepted by the group, provided all steps were taken by the ophthalmologist to exclude tuberculous uveitis.
7. *Bilaterality*. It was found to be a useful criterion to define ocular sarcoidosis. Bilaterality can be established either by clinical examination or by adjuvant methods capable of showing subclinical disease, such as laser flare photometry when flare values were elevated[24] or indocyanine green angiography, which demonstrates the presence of choroidal vasculitis and/or hypofluorescent dots representing choroidal inflammatory foci.[12]

Laboratory Investigations or Investigational Procedures

There are no tests that are diagnostic for sarcoidosis. The following investigations were regarded to be of value in supporting the diagnosis of ocular sarcoidosis in patients having suggestive intraocular signs:

1. *Negative tuberculin test in a BCG-vaccinated patient or in a patient with a previously positive tuberculin skin test*. This test is especially useful in communities



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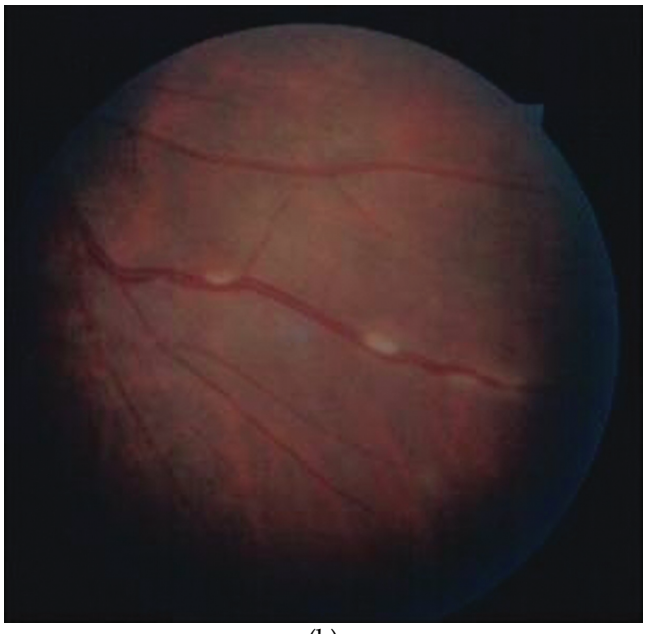

(b)

Figure 5. (a) Nodular and/or segmental peri-phlebitis. Note also scattered choroidal nodules. (Courtesy Dr. N. Ohguro, Osaka, Japan) (b) Nodular and/or segmental peri-phlebitis with candlewax drippings. (c) Macroaneurism in an inflamed eye. *(Continued)*

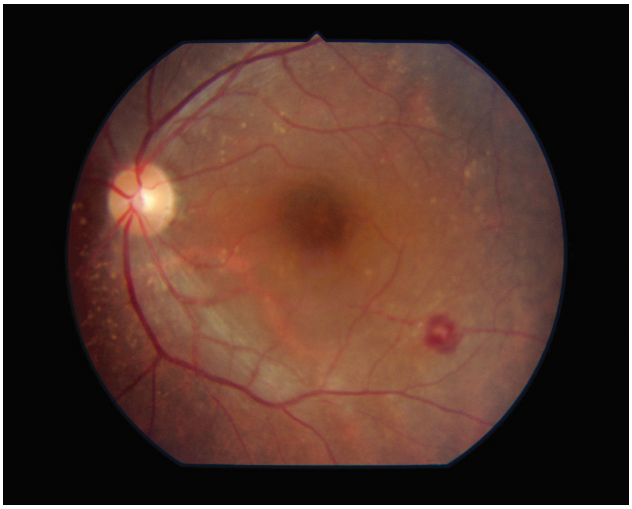

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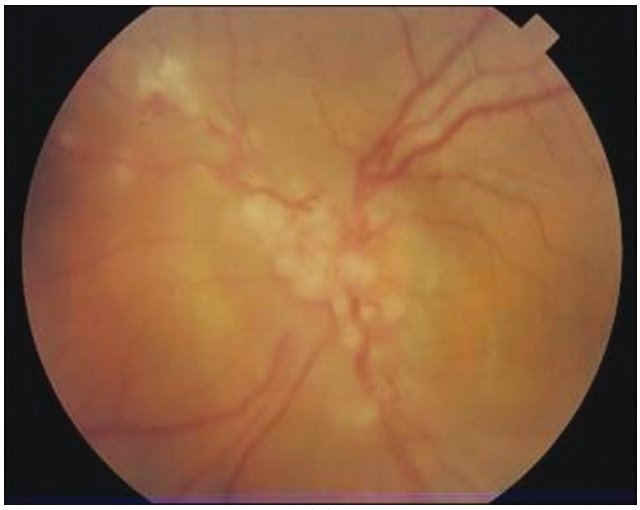
Figure 5. Continued



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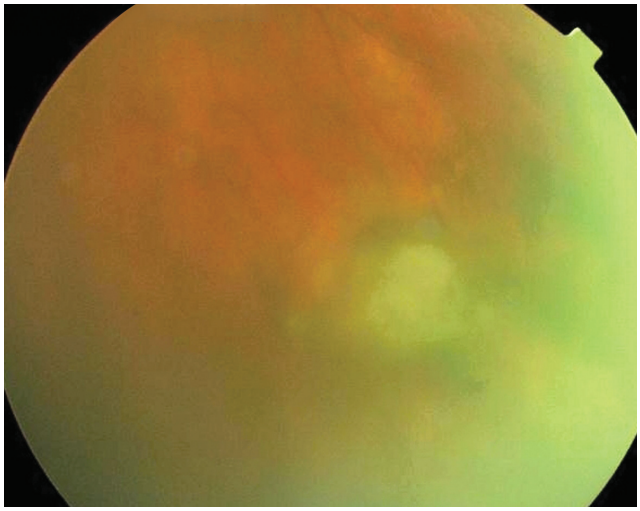

(b)

Figure 6. (a) Optic disc nodules. (b) Solitary choroidal nodule.

Table 1. Clinical signs suggestive of ocular sarcoidosis

1. Mutton-fat KPs (large and small) and/or iris nodules at pupillary margin (Koeppe) or in stroma (Bussacca)
2. Trabecular meshwork (TM) nodules and/or tent-shaped peripheral anterior synechiae (PAS)
3. Snowballs/string of pearls vitreous opacities.
4. Multiple chorioretinal peripheral lesions (active & atrophic)
5. Nodular and/or segmental peri-phlebitis (± candlewax drippings) and/or macroaneurism in an inflamed eye
6. Optic disc nodule(s)/granuloma(s) and/or solitary choroidal nodule
7. Bilaterality (assessed by clinical examination or investigational tests showing subclinical inflammation).

where BCG vaccination is routinely performed in all individuals.

2. *Elevated serum angiotensin converting enzyme (ACE) and/or elevated serum lysozyme*. As both tests measure the same parameter, macrophage products produced by granulomas, they were grouped together. The more commonly performed test is measurement of serum ACE levels. In a study on 125 sarcoidosis cases this parameter was elevated in 60% of patients.[25] ACE is significantly more elevated in children than in adults, the difference, though, never reaching levels found in pathological situations such as sarcoidosis, and the test may be therefore less useful in children despite the elevated values.[26] When talking about serum ACE levels this corresponds to serum ACE activity, as routinely used assays are, in fact, measuring ACE enzyme activity.[26] Therefore, serum ACE levels or, more exactly, serum "ACE activity" falls below detectable levels in patients tak-

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[a]
3. Chest x-ray; look for bilateral hilar lymphadenopathy (BHL)
4. Abnormal liver enzyme tests (any two of alcaline phosphatase, ASAT. ALAT, LDH or γ-GT)
5. Chest CT scan in patients with negative chest x-ray

[a] Test required in patients treated with ACE inhibitors.

Table 3. Diagnostic criteria for ocular sarcoidosis

All other possible causes of uveitis, in particular tuberculous uveitis, have to be ruled out.	
1. Biopsy supported diagnosis with a compatible uveitis	→ Definite ocular[a] sarcoidosis
2. Biopsy not done; presence of bilateral hilar lymphadenopathy (BHL) with a compatible uveitis	→ Presumed ocular[a] sarcoidosis
3. Biopsy not done and BHL negative; presence of three of the suggestive intraocular signs and two positive investigational tests	→Probable ocular[a] sarcoidosis
4. Biopsy negative, four of the suggestive intraocular signsand two of the investigations are positive	→ Possible ocular[a] sarcoidosis

[a] Used in the sense of intraocular inflammatory lesions both in patients with systemic disease and in patients with disease seemingly limited to the eye without any clinically detectable involvement of another organ.

ing ACE inhibitors.The test is therefore not useful in patients who are on ACE inhibitors. In such patients serum lysozyme is recommended. The same report that studied ACE levels in 125 sarcoidosis patients also showed that lysozyme was elevated even more frequently than ACE with 76% of patients having elevated lysozyme levels.[25] Serum lysozyme is more rarely used because many laboratories don't run this test. The Japanese study on biopsy-proven ocular sarcoidosis also showed that the combination of sensitivity, specificity, and positive and negative predictive values was better for elevated serum lysozyme than for elevated serum ACE.[18]

3. *Positive chest x-ray, showing bilateral hilar lymphadenopathy (BHL)*. Bilateral hilar lymphadenopathy (BHL) is the most frequent radiological finding in systemic sarcoidosis, being present in 50–89% of cases.[27,28] As there are rarely any other systemic conditions that cause BHL, except perhaps lymphoma, although symmetrical lymph node involvement is unusual, this is thought to be pathognomonic of sarcoidosis. In the classification of pulmonary sarcoidosis, presence of BHL determines stage 1 of the disease.[29] The group also discussed the option of considering other radiological signs to call an x-ray positive for sarcoidosis, but this was not decided, leaving this as one of the topic to be addressed in future meetings.
4. *Abnormal liver enzyme tests*. This laboratory test was included on the advice of the internist-pulmonologists. Hepatic involvement in sarcoidosis is one of the occult sites where undetected granulomas can form. Little or no literature exists on the importance of investigating liver enzyme test abnormlties in ocular sarcoidosis. The laboratory test, however, obtained a two-thirds majority and needs to be investigated in future studies that will test the present diagnostic criteria. The test is considered to be positive when serum levels of alkaline phosphatase are more than three times the upper limit of normal values or when two of the following liver enzymes—aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), and alkaline phosphatase—are more than twice the upper limit of normal values.[30]
5. *Chest CT scan in patients with a negative chest x-ray*. This investigational test was included not as a first-line test but for cases where sarcoidosis was strongly suspected but the chest radiography was negative for BHL. In most cases of sarcoidosis, CT scan has been shown to be unnecessary as a screening test but was found to be useful in providing more precise information and has been shown to be especially helpful in atypical cases and patients with normal chest x-rays.[27–29,31] This diagnostic test was thought to be especially useful for diagnostic group 3, "probable sarcoidosis," where BHL is not found on standard chest radiographies.

Diagnostic Criteria of Ocular Sarcoidosis

The concensus conference established four levels of certainty for the diagnosis of ocular sarcoidosis (diagnostic criteria). It should be emphasized that the prerequisite for considering a diagnosis of sarcoidosis is that all other possible causes of uveitis, in particular tuberculosis, had been appropriately ruled out.

1. Biopsy-supported diagnosis with a compatible uveitis was labeled as *definite ocular sarcoidosis*; Some members of the group found this definition too broad as far as the qualification of uveitis was concerned and wanted to define the uveitis more precisely. However, two-thirds of the delegates were satisfied and voted for the term "compatible uveitis," which includes both granulomatous and

nongranulomatous uveitis, rather than a more restrictive term such as "suggestive uveitis."
2. The second diagnostic category,*presumed ocular sarcoidosis*, was applied to patients with a compatible uveitis, where the chest x-ray or CT scan revealed the presence of bilateral hilar lymphadenopathy (BHL) but biopsy was not done. For this category also some of the delegates suggested that a more restrictive term to define uveitis would be more appropriate but the majority was satisfied with this wording.
3. The third category, *probable ocular sarcoidosis*, was considered for patients where biopsy was not done and in whom the chest x-ray did not show BHL but 3 suggestive intraocular signs and 2 supportive investigations were present. This category was designed for patients having a strong combination of suggestive ocular signs and investigational tests without the typical radiographic findings and in whom biopsy was not performed. It has been shown that over 60% of such patients were finally diagnosed as having sarcoidosis when biopsy was obtained subsequently.[14]
4. When lung biopsy was done but was found negative and there were at least 4 suggestive intraocular signs with at least 2 positive laboratory results this clinical condition was labeled as *possible ocular sarcoidosis*. This category was designed for the relatively infrequent but still real situation of patients with a uveitis very strongly suggestive of sarcoidosis and a presumed false negative lung biopsy. It is worth noting that lung biopsy is a blind biopsy and not a lesion-guided procedure.

The three first categories were accepted unanimously while the fourth category, which was voted upon by e-mail, was accepted by 79% of delegates.

DISCUSSION

We report here the results of the first international workshop on ocular sarcoidosis (IWOS), which was attended by international delegates made up of uveitis specialists from 4 continents as well as 2 pulmonologists. Decisions were made mainly based on the experience of the participants. They were helped by the thorough work performed on predicitve values of clinical signs and laboratory tests by a recent Japanese study [18] that confirmed past reports.[32] However it should be noted that these values can vary slightly depending on the epidemiology of uveitis in the geographical areas where they are performed. This is not the case for ACE, for which a similar predictive value was found in a European study when ACE was 2SD above normal.[33] The first three diagnostic categories, namely definite ocular sarcoidosis, presumed ocular sarcoidosis, and probable ocular sarcoidosis, were accepted unanimously and the fourth one, possible sarcoidosis, was accepted by a two-thirds majority. The latter category was controversial as some of the participants thought that 3 levels of diagnostic categories were sufficient to cover the vast majority of clinical scenarios. When looking at the ATS/ERS/WASOG criteria,[34] some of the patients in the "possible" category would be likely labeled as probable or presumed when judged by these criteria. Patients may be shifted upward in the category level as the certainty of the diagnosis increases with increasing systemic manifestations over time.

In future, conducting studies to validate these diagnostic criteria will be necessary. These definitions and diagnostic criteria are open for improvement should additional diagnostic tests become available, especially those specific for ocular involvement. Examples of such tests include bronchioalveolar lavage (BAL) looking for the CD4/CD8 ratio, Gallium scan and serum/urine calcium levels. Newer investigational techniques such as PET-scan may also be considered once sufficient data on the sensitivity, specificity, and predictive values of such a test have become available.[35]

The Tokyo IWOS criteria certainly represent an attempt at standardizing the diagnostic criteria for future multicentre studies on a disease that seems to be on the rise and that can present with selective ocular involvement. In the latter case, the existing diagnostic criteria that ask for histological proof did not allow the ophthalmologist to make the diagnosis in most cases as the invasive diagnostic investigations required are difficult to justify. On the other hand, we are aware that a large proportion of ocular sarcoidosis cases with occult systemic involvement yield histological proof when transbronchial lung biopsy is performed.[14] A system was therefore needed to enable the clinician to make the diagnosis of ocular sarcoidosis with a reasonable degree of certainty without having to resort to invasive diagnostic measures.

Guidelines on how to rule out other entities were not discussed and are open for debate at future workshops. Epidemiology of uveitis varies in different parts of the world and tests necessary to rule out other entities would vary from place to place. Regardless, the most important condition that may present in a similar manner is ocular tuberculosis. In the case of a granulomatous uveitis compatible with both sarcoidosis and tuberculosis, the IFN-gamma release assay, such as Quantiferon-gold or TB spot test, is perhaps the most useful test that allows the clinician to distinguish between the 2 entities. This test is able to exclude both latent and active tuberculosis if negative. In this test blood lymphocytes are incubated with antigens from

Mycobacterium tuberculosis (different from the antigens present in the BCG vaccine) and the production of gamma-interferon is assayed. If the level of gamma-interferon is high, then the diagnosis of latent or active tuberculosis is made.[36] This test has an extremely low rate of false-positive results (very high specificity) and tuberculosis can reasonably securely be ruled out when negative. Until such time when additional specific characteristics and investigational tests become available, allowing a more accurate appraisal of the disease, we suggest the use of these diagnostic criteria for future uveitis studies on ocular sarcoidosis. The use of the proposed four categories of sarcoid uveitis in future prospective clinical epidemiological studies and clinical trials will allow for the collation of data from which the ophthalmic community can make meaningful comparisons and draw useful conclusions based on diagnoses made on the same basis from different institutions around the world.

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