Review Article

Progress in the diagnosis of ocular sarcoidosis

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Sarcoidosis is a multisystem granulomatous inflammation that affects multiple organ systems. The spectrum of extraocular and ocular involvement is wide and may precede systemic involvement. The diagnosis of ocular sarcoidosis relies on a combination of clinical findings, laboratory investigations, and radiographic findings. These include but are not limited to serum angiotensin-converting enzyme (ACE), lysozyme, plain-film radiographs of the chest, computed tomography (CT) scans of the chest, pulmonary function testing, bronchoalveolar lavage, and retinal imaging among others. In this review, we highlight current and evolving systemic investigations and approaches to ophthalmic imaging when considering the diagnosis of ocular sarcoidosis.

Key words: Ocular inflammation, ocular sarcoidosis, posterior uveitis, retinal imaging

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Sarcoidosis is a multisystem granulomatous disease that frequently affects the lungs, skin, eyes, and lymph nodes. The severity of involvement and expression of disease in different organ systems varies on an individual and population level. The spectrum of ocular involvement is similarly wide, with some individuals having aggressive ocular involvement with minimal to no identifiable systemic involvement, while others have ocular involvement in addition to diffuse systemic disease. Ocular disease may also precede systemic involvement by years. In situations where no tissue is available for biopsy, the diagnosis relies on a combination of clinical examination findings (in the eye) and systemic laboratory and radiographic findings, including but not limited to serum angiotensin-converting enzyme (ACE), lysozyme, plain film radiographs of the chest, computed tomography (CT) scans of the chest, pulmonary function testing, and bronchoalveolar lavage. Aside from a histological diagnosis, no other test is perfect in its ability to either diagnose or rule out sarcoidosis due to the varying sensitivities of the testing and the overlap with other conditions such as tuberculosis or chronic pulmonary diseases that make the test results unequivocal.

The prevalence of ocular involvement in sarcoidosis varies from 7% to 60%.[1–4] CNS involvement may be more common when there is posterior involvement of the eye. General rates of CNS involvement in sarcoidosis are 2%, but among those with posterior uveitis, CNS involvement may be seen in 20%–35% of patients.[5–7]

The gold standard in supporting the diagnosis of sarcoidosis is non-necrotizing granulomas on histology with negative staining for infectious organisms and foreign material. No other test can correctly identify the disorder and rule out conditions that mimic the clinical findings. The inconsistency of clinical manifestations also makes diagnosing the condition difficult. As mimicking conditions can span from infectious etiologies to infiltrative processes, a correct diagnosis is important for the appropriate management of the patient. Sarcoidosis is frequently treated with corticosteroids as first-line therapy, which would be contraindicated in infectious processes, and long-term treatment often involves steroid-sparing immunomodulators, which would be contraindicated in infectious, infiltrative, or malignant conditions. To obtain a tissue diagnosis, a biopsy is required but not always possible, especially for ocular sarcoidosis. While biopsies are possible of extraocular tissues, such as the conjunctiva and lacrimal gland, intraocular biopsies carry a high risk of complications.

With the aim of arriving at a diagnosis of ocular sarcoidosis in the absence of supporting histopathology, in 2009, the International Workshop on Sarcoidosis (IWOS) held in Tokyo, Japan voted on recommendations to create four categories of diagnosis of ocular sarcoidosis: definite, presumed, probable, and possible.[8] When these criteria were applied to an international cohort of patients with uveitis, including sarcoidosis, the criteria demonstrated low sensitivities for tests in the diagnosis of ocular sarcoidosis, except for the clinical findings of bilateral hilarity lymphadenopathy (BHL). Many patients suspected of having sarcoidosis did not meet the criteria laid out.[9] In response to the difficulty in applying

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the above criteria, the IWOS revised guidelines based on a consensus discussion and voting. The revised IWOS criteria were published in 2019. Specifically, the laboratory guideline of abnormal liver function testing was removed, elevated CD4/CD8 ratio of >3.5 in bronchoalveolar lavage fluid was added, abnormal positron emission tomography (PET) imaging, lab findings of lymphopenia, and the demonstration of parenchymal changes consistent with sarcoidosis as determined by a pulmonologist or radiologist were added.[10] The latter criteria from 2019 demonstrated an improvement in sensitivities in two reports but have yet to be studied in a diverse international population.[11,12]

The reliance on clinical and laboratory abnormalities outside of the eye in patients who present without significant extraocular manifestations limits the utility of advanced imaging techniques. In patients who present without significant pulmonary complaints or a lack of lymph node involvement, high-resolution contrast-enhanced CT (HRCT) scanning and transbronchial lung biopsy may be neither appropriate nor available.[9] Another issue arising with the diagnosis is that the clinical disease can present differently in different races, in different parts of the world, and in different age groups. The differential diagnosis of sarcoidosis also varies depending on the geographic location and age group affected. For example, distinguishing between ocular sarcoidosis and ocular tuberculosis is more important in South Asia than in certain other regions of the world where the prevalence of tuberculosis is lower. Both conditions can have similar systemic manifestations, can appear similar on chest X-ray scans, and can have similar forms of uveitis. However, distinguishing between the two is important due to the diverging treatment paradigms of the two conditions. In this review, we have attempted to highlight current and evolving systemic investigations and approaches to ophthalmic imaging when considering the diagnosis of ocular sarcoidosis.

Prevalence of Sarcoidosis

There are two peaks of incidence for sarcoidosis: 20–30-years old and 50–60-years old.[13] Females are more likely to develop ocular involvement compared with males.[14] Sarcoidosis can also uncommonly affect pediatric patients.[15,16]

In the United States, Black patients with sarcoidosis are afflicted earlier (mean age: 44 years) than White patients (mean age: 52 years) and have higher mean angiotensin-converting enzyme (ACE) levels.[17,18] Non-White patients in Europe also have a lower age of onset compared to their White counterparts.Click here to enter text.[19] Black male patients more commonly presented with uveitis, and Black female patients presented more frequently with adnexal granulomas.[17]

Serum ACE levels can be affected by polymorphisms that cause insertion or deletion changes in the ACE gene. In a case-control study between Black and White patients in 1998, no polymorphisms were noted in the White patients with sarcoidosis compared to healthy controls; however, there were marked genetic differences between 183 Black patients with sarcoidosis compared to 111 healthy controls. In Black patients, the risk for sarcoidosis was 1.30 for heterozygotes, and 3.17 (95% CI: 5 1.50–6.71) for homozygotes; this latter risk was higher in those with a positive family history (odds ratio: 54.83). The genotype was not found to be associated with disease severity, extrathoracic involvement, or short-term progression of disease (within 4 years of diagnosis).[20]

In a review of patients from Japan, those who were older were more likely to present with fewer detectable ocular signs and laboratory results consistent with sarcoidosis than younger patients. The diagnosis of probable or possible ocular sarcoidosis was more likely than definite or presumed ocular sarcoidosis. This complicates the ability to make a definitive diagnosis and reinforces the importance of having good criteria in place that will apply to a broad range of patients with their varying presentations.[21]

Clinical Findings in Ocular Sarcoidosis

Ocular involvement occurs in a large majority of patients with sarcoidosis (up to 60%) and ocular findings can precede non-ocular signs of sarcoidosis in almost a third of patients.[4]

Clinically, keratoconjuncitivitis sicca or dry eye disease is the most common manifestation of sarcoidosis but does not usually cause permanent vision loss.[17,22] [Table 1] Anterior uveitis is the most common form of uveitis, Click here to enter text.[17,23] though posterior or panuveitis is more common in certain populations and regions of the world.[18,19,24] The main cause of visual loss is attributed to cystoid macular edema.[4] A poor visual prognosis has been associated with older age of onset, Black race, female sex, chronic systemic disease, posterior segment involvement, peripheral punched out chorioretinal lesions, and the presence of cystoid macular edema and glaucoma.[25]

Anterior uveitis may either present as acute iridocyclitis or as chronic granulomatous uveitis with keratic precipitates, which may vary from small and fine to large "mutton fat" keratic precipitates. In chronic uveitis, nodules may be seen on the iris and in the angle on the trabecular meshwork. These can be small but can also enlarge significantly, taking on a vascularized appearance. Tent-shaped peripheral anterior synechiae may also be present. Chronic anterior uveitis may lead to additional

Table 1: Clinical and imaging findings in ocular sarcoidosis

Extraocular findings	Anterior segment	Posterior segment
Conjunctival granulomas	Angle nodules	Choroidal granulomas
Lacrimal gland enlargement	Iris and angle granulomas	Snowballs and snowbanking
	Broad-based PAS	String of pearl opacities
	Tent shaped PAS	Periphlebitis or Candlewax phlebitis
	Posterior synechiae	Cystoid macular edema
	Mutton fat keratic precipitates	Hypopigmented chorioretinal scars
	Cataract	Choroidal thickening

complications causing vision loss such as cataract, glaucoma, cystoid macular edema, and band keratopathy.[4,25,26]

Posterior involvement may include vitritis, intermediate uveitis, panuveitis, posterior uveitis, retinal vasculitis, and optic nerve involvement. Retinal vasculitis presents as a peri-phlebitis and may exhibit a candlewax dripping appearance. Cystoid macular edema occurs in posterior uveitis or intermediate uveitis and has been correlated with the activity of disease and delay in treatment.[25]

Imaging and Laboratory Investigations in the Diagnosis of Ocular Sarcoidosis

Ocular sarcoidosis does not have a consistent presentation. Because a biopsy of intraocular tissue is frequently not feasible to fulfill the criteria of a gold standard, multiple tools are utilized to aid in the diagnosis of this disease. These tools include ophthalmic imaging such as enhanced depth imaging optical coherence tomography (EDI-OCT), fundus photography, and various dye-based images such as fluorescein and indocyanine green in conjunction with angiography. Secondarily, systemic imaging (such as chest radiographs and computed tomography (CT) scans), pulmonary function testing (PFT), and bronchoalveolar lavage (BAL) are utilized to identify the presence of concurrent systemic disease. Finally, laboratory testing, such as serum calcium, ACE, and lysozyme, is utilized to differentiate ocular sarcoidosis from mimickers of the disease.

Ophthalmic imaging

EDI OCT for the evaluation of granulomas

Enhanced depth imaging (EDI) is an advancement of spectral-domain OCT that allows detailed visualization of deeper structures in the eye, including the choroid and inner sclera. Reports have been published on utilizing EDI-OCT to visualize choroidal granulomas and changes in thickness in Haller's and Sattler's layers to better identify the underlying conditions.

Invernizzi *et al*.[27] reviewed 44 choroidal granulomas (from sarcoidosis, tuberculosis, and Vogt Koyanagi Harada disease) and compared the findings to those seen on indocyanine green angiography (ICG). EDI-OCT was able to visualize all lesions seen on ICG within the location constraints. Lesions were more commonly hyporeflective but could also be isoreflective. The internal reflectivity of the lesions was more homogenous than the surrounding tissue of the choroid. Compared with small lesions, large granulomas were more likely to be full thickness, round, with defined margins, hyporeflective, and have high internal homogeneity. TB-related granulomas were more likely to be lobulated in shape and were less homogenous internally.

In a comparison of patients with sarcoid and tubercular-related granulomas, Mehta *et al*.[28] evaluated the difference in thickness between Haller's and Sattler's layers on EDI-OCT. They noted that Sattler's layer was thicker in patients diagnosed with ocular sarcoidosis (128.69 microns) than in those with ocular tuberculosis (95.72 microns). Thus, the ratio of Haller's to Sattler's layers was significantly different in those with TB (1.47) compared to those with sarcoidosis (1.07).

In another study evaluating the difference in granulomas between patients with tuberculosis and sarcoidosis, granulomas secondary to tuberculosis were more frequently solitary, intense yellow, lobulated, full-thickness, in the perivascular region, larger, and more likely to be vascularized. The vascularization of tuberculomas is likely the reason why they were also more likely to be associated with vascular anomalies such as overlying pre-retinal hemorrhages or retinal angiomatous proliferation (RAP) lesions. Granulomas larger than 6.45 mm^2 had the highest area under the receiver operating curves (0.94) for differentiating tuberculomas from sarcoid granulomas. Sarcoid-related granulomas were more likely to be small, multiple, oval-shaped, distributed diffusely in the retina, and with a dull yellow color, making them more difficult to distinguish on the clinical exam from the normal retina. Granulomas secondary to sarcoidosis were also more likely to be associated with retinal vasculitis, and disc hyperfluorescence was present in every fluorescein angiogram.[29] Fig. 1 demonstrates an example of a choroidal granuloma and subretinal fluid in a patient with sarcoidosis.

The studies discussed above are useful in their ability to discern between different conditions by utilizing specific findings on imaging technologies. While these articles are helpful in making a clinical determination between specific entities, one should keep in mind that the studies are reinforcing findings associated with a diagnosis that has already been made by the clinicians and can reinforce circular logic. In addition, it is important to note that as most of these studies are coming from regions with high rates of both sarcoidosis and tuberculosis, the focus on a majority of these papers is the ability to distinguish between these two specific conditions.

OCT angiography

OCT Angiography (OCTA) technology utilizes the movement of erythrocytes in blood vessels as captured over time by using sequential B-scans in the same area. Signals are captured from movement, and a lack of a signal is viewed as a flow void. Choroidal granulomas can be viewed on OCTA as the granuloma is a space-encompassing lesion that will displace normal choroidal tissue and thus alter the appearance of the vasculature in the choroid. It can be utilized to follow the size of granulomas over time to assess improvement on treatment.[30] However, due to current limitations of a small field of view, inability to show vascular leakage, and high rates of artifact secondary to patient movement that needs to be addressed before the image is analyzed, the clinical utility of this technology remains limited though it has significant potential as a non-invasive modality.

Fluorescein angiography and indocyanine green angiography

Fluorescein angiography (FA) utilizes an intravenous dye to evaluate retinal pathology. It has been demonstrated to be useful in evaluating subclinical sarcoidosis and peripheral disease that may be subclinical, especially when utilizing ultra-widefield angiography.[4,22]

Classic findings on fluorescein angiography that are consistent with a diagnosis of ocular sarcoidosis include periphlebitis, which can be quite extensive, segmental cuffing, or sheathing with perivenous exudates termed "candle wax drippings." Disc leakage may be apparent on examination and related to the uveitis but may also correlate with optic nerve involvement. Cystoid macular edema can also be identified on fluorescein angiography.[4] Fig. 2 demonstrates a patient with phlebitis and disc hyperfluorescence on FA.

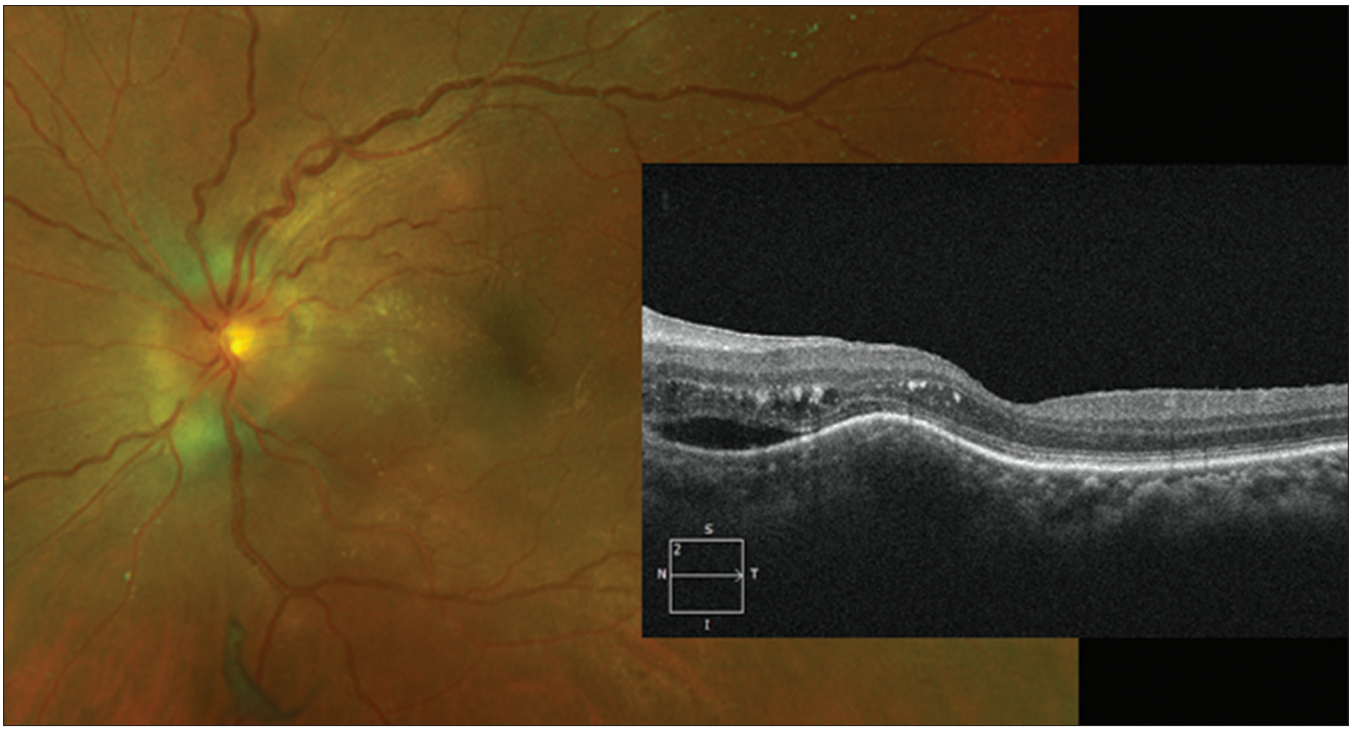

Figure 1: Optos ultra-widefield image of the left eye demonstrating a choroidal granuloma and subretinal fluid. Inset: OCT image of the left eye demonstrating a choroidal granuloma with adjacent subretinal fluid

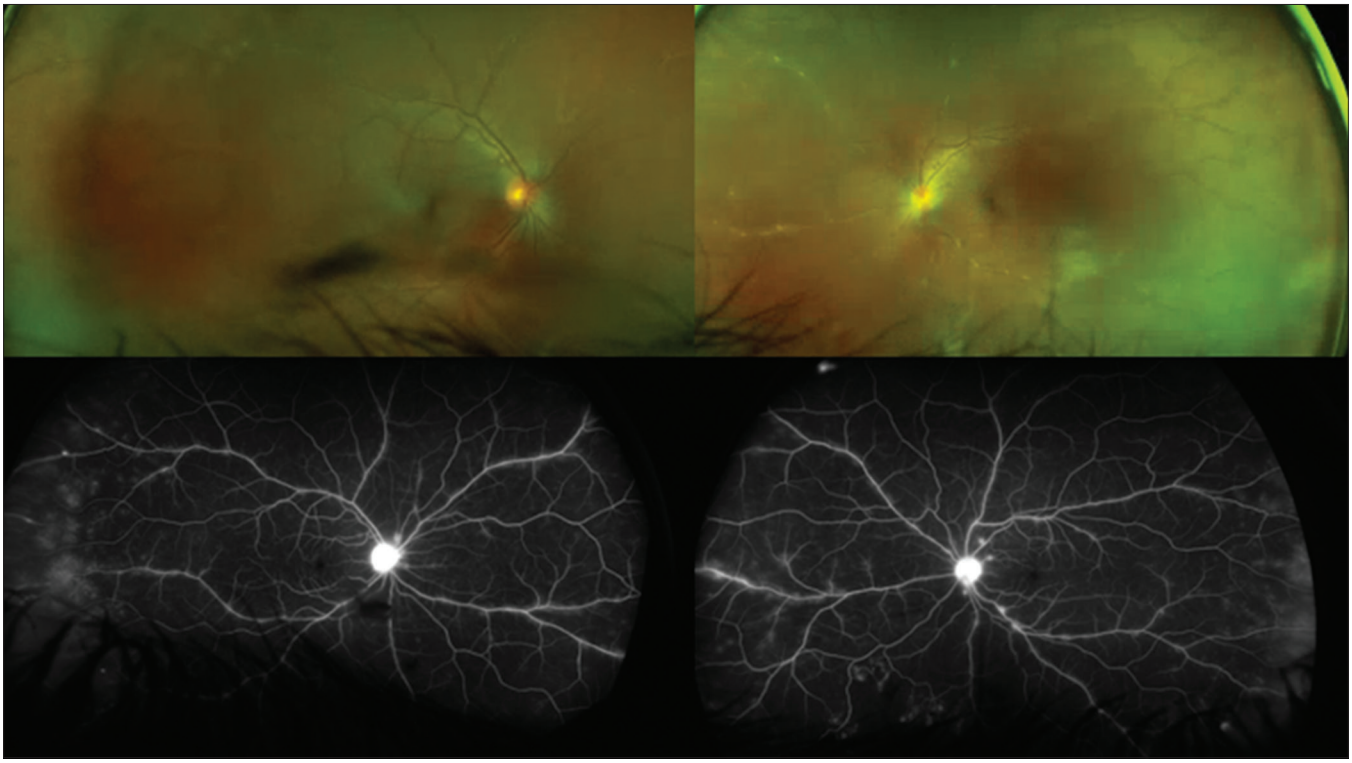

Figure 2: Ultra-widefield (UWF) fluorescein angiography (FA) demonstrating disc hyperfluorescence and phlebitis in a patient with sarcoid uveitis

When differentiating between sarcoidosis and tuberculosis, fluorescein angiography can be helpful. Agarwal *et al*.[29] described the increased likelihood of sarcoidosis having concurrent retinal vascular changes on fluorescein angiography as well as disc leakage. Retinal vasculitis secondary to tuberculosis was more likely to be occlusive and associated with pinpoint retinal pigment epithelium (RPE) leaks surrounding the main choroidal granuloma. Eyes with tuberculosis were also noted to have increased vascularity, exudation, and hemorrhage, and can develop RAP lesions.

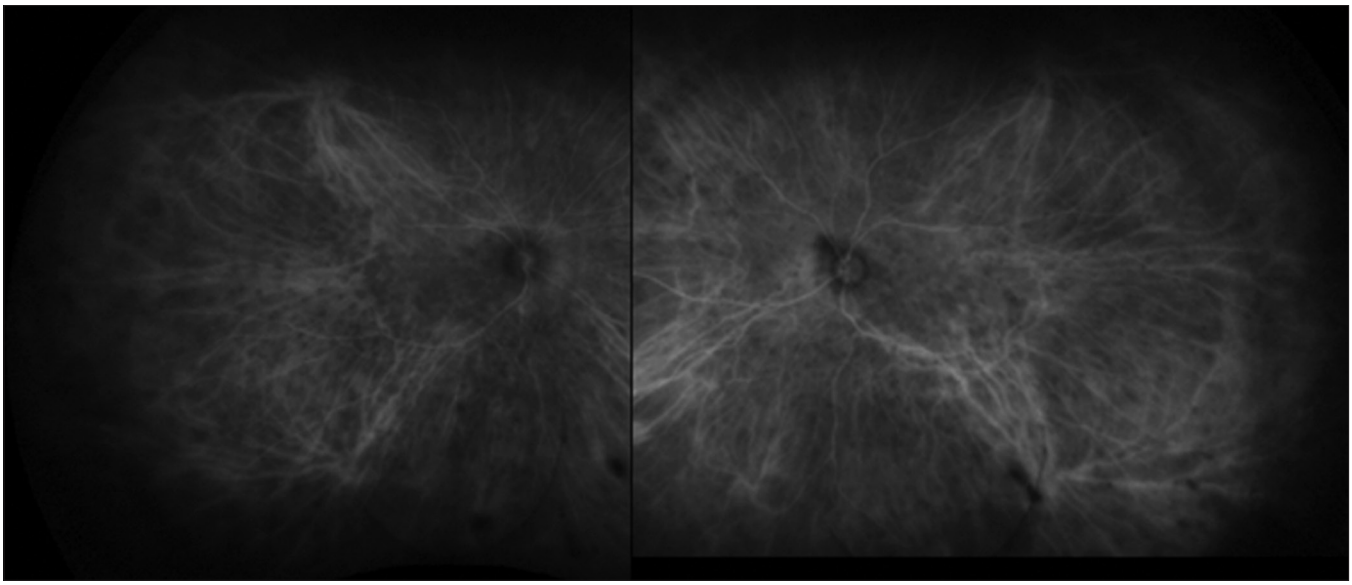

Figure 3: Ultra-widefield (UWF) Indocyanine green angiography (ICG) demonstrating scattered hypocyanescent dots of varying shapes and sizes in a patient with sarcoid uveitis

Indocyanine green angiography (ICG) has been shown to be helpful in supporting the diagnosis of ocular sarcoidosis due to its ability to evaluate the choroidal vasculature. Wolfensberger and Herbert described four key features of ICG angiography noted in ocular sarcoidosis: hypocyanescent dark spots, fuzzy choroidal vasculature, late diffuse hypercyanescence, and focal pinpoint hypercyanescent spots. They noted that the first three findings were non-specific and seen in other uveitides that involved the choroid such as birdshot chorioretinopathy, Vogt–Koyanagi–Harada syndrome, and multiple evanescent white dot syndrome (MEWDS). However, the uneven zonal distribution of lesions and the occurrence of late focal pinpoint hypercyanescent dots were considered by the authors as specific for sarcoidosis.[31] Further studies are required to determine the importance of late focal pinpoint hypercyanescent dots in distinguishing ocular sarcoidosis from other choroidal granulomatous uveitides. Fig. 3 demonstrates ICG findings in a patient with sarcoid uveitis. Note the hypocyanescent dots of varying size and distribution in both eyes.

Fundus autofluorescence

Fundus autofluorescence (FAF) is a non-invasive diagnostic tool that provides information about RPE changes and displays retinal or chorioretinal abnormalities more clearly than color fundus photography or ophthalmic examination alone. FAF may reveal subclinical uveitis in an eye and its strength is its non-invasive functionality. Increased autofluorescence usually signals increased inflammation, and with successful treatment, the hyperautofluorescent signal usually resolves. Sometimes, a hypoautofluorescent signal remains if damage has occurred to the RPE. This tool can be used to follow the response to treatment over time.[32] In sarcoidosis, hyperautofluroescence can be seen in areas of active disease, but more frequently, multiple small hypoautofluorescent dots are seen, which also correspond to findings on ICG angiography.[33]

Systemic imaging

Chest radiographs (CXR) have been utilized for the diagnosis of sarcoidosis since the 1960s when it was determined that involvement of the lungs on CXR could be diagnostic for sarcoidosis. Four stages of changes are noted on CXR in sarcoidosis: stage I, bilateral adenopathy alone; stage II, hilar lymphadenopathy with pulmonary infiltrates; stage III, pulmonary infiltrates alone; and stage IV, pulmonary fibrosis. Stage I has been deemed to be sufficiently characteristic to be considered diagnostic in an asymptomatic patient.[34,35] Chest X-ray has a 100% specificity for the diagnosis of sarcoidosis but a sensitivity of 50%.[21] A gallium scan can also be used to detect inflammation with uptake in the hilar chest (lambda sign) and uptake in the lacrimal glands (panda sign), but in patients already on systemic corticosteroids, a false-negative scan is possible.[36]

18F-fluorodeoxyglucose (FDG)–positron emission tomography (PET) can be utilized for evaluating systemic inflammatory activity and is more sensitive than gallium scanning but may also be positive in patients with other granulomatous diseases, infections, or neoplasms. L-[3-18F]-a-methyltyrosine (18F-FMT), an amino acid analog, has a higher specificity for tumor cells, and can be utilized in combination with FDG-PET to differentiate between sarcoidosis lesions and malignancies.[34]

Contrast-enhanced computed tomography scans of the chest demonstrate improved detection of BHL (82.7%) than CXR (29.5%). Chest CT may also distinguish lung involvement from sarcoidosis from lymph node enlargement secondary to tuberculosis. Tuberculosis-related lymph node enlargement will show a central hypodensity corresponding to the area of necrosis and peripheral contrast enhancement.[24] In a study evaluating the utility of high-resolution chest CT (HRCT) in the diagnosis of ocular sarcoidosis or ocular tuberculosis, HRCT demonstrated hilar lymphadenopathy and fissural nodules more frequently in sarcoidosis. Symmetrical enlargement of hilar lymph nodes was also more common in sarcoidosis, whereas apical fibrosis was more common in tuberculosis. However, in nearly half of the 140 cases in this study, the diagnosis of tuberculosis versus sarcoidosis could not be made on HRCT alone. A combination

of clinical, radiologic, and laboratory testing was necessary to arrive at the correct diagnosis.[37]

Laboratory investigations

For many years, the diagnosis of sarcoidosis has been reliant on systemic laboratory investigations such as ACE, lysozyme, and serum and urinary calcium. Limitations to these tests include their low sensitivity, low levels if the burden of disease is low in the individual, and effects of medications that may alter the results. Advances have been made to utilize changes of the immune system that are specific to sarcoidosis and harness their potential in making the diagnosis. These tests are not without their flaws, but within a larger arsenal of investigations, these can aid in making the correct diagnosis.

Lymphopenia

Lymphopenia is considered a feature of sarcoidosis. Severe lymphopenia is described as a level lower than 0.5×10^9/L. In contrast, significant lymphopenia was described by Jones *et al*.[38] as 1.0×10^9/L in supporting the diagnosis of sarcoidosis. When comparing 112 patients with sarcoid-associated uveitis and 398 controls with other forms of uveitis, Jones *et al*.[38] noted that of those with sarcoid-associated uveitis, 26.8% had significant lymphopenia compared with 6.0% of the control group. The mean lymphocyte county was 1.43×10^9/L in sarcoid patients compared with 2.04×10^9/L for other forms of uveitis. They noted a 31.6% risk of ocular sarcoidosis in a patient with significant lymphopenia.

Lower white blood cell counts exist in healthy Black adults, though the subset of lymphocytes tends to be higher. Further studies need to be performed evaluating the utility of lymphopenia as a supporting diagnostic tool for ocular sarcoidosis in different populations.

KL-6 mucin

Krebs von den Lungen-6 (KL-6) protein is a lung epithelium-specific protein found to be increased in the serum of patients with sarcoidosis. It was noted to have a high sensitivity for the diagnosis of sarcoidosis and correlated well with the clinical course.[39,40] In the diagnosis of ocular sarcoidosis, KL-6 has a lower sensitivity than soluble interleukin 2 receptor (sIL2R) in one study, but has high specificity.[12] Due to its function as a lung protein, it is elevated non-specifically in settings of interstitial pneumonia and pulmonary fibrosis; thus, it is also elevated in pulmonary tuberculosis and thus likely has limited utility in distinguishing between sarcoidosis and tuberculosis.[41]

Serum soluble IL-2 receptor

Elevated levels of serum sIL-2R levels are known to correlate with T-cell mediated disease. Sarcoidosis is characterized by T-cell activation. These T-cells express IL-2 receptors on their surface and release a soluble form of IL-2 receptors. This marker has been found to be more sensitive than ACE in pulmonary sarcoidosis.[42] In a study comparing sIL-2R with ACE in uveitis patients with sarcoidosis, sIL2R specificity was 94% with a sensitivity of 98% whereas ACE had a specificity of 99.5% and a sensitivity of 22%.[42]

Serum sIL-2 receptor levels and ACE and lysozyme levels were compared in a population of patients with dermatologic manifestations of sarcoidosis. sIL-2R levels were noted to be more sensitive (52.8%) than ACE (29%) or lysozyme (26.4%) in this population. Levels were also noted to be significantly higher in patients with multiple areas of skin involvement, pulmonary involvement, higher levels of C-reactive protein (CRP), ACE, and lysozyme. Changes in sIL-2R in 90% of the patients in the study over time correlated with clinical involvement.[43]

In a study of ocular sarcoidosis in Japan, sIL-2R was noted to be more sensitive than serum ACE, KL-6, or calcium levels but had equivalent specificity. They calculated the Youden Index, an integration of both sensitivity and specificity, and noted a better Youden index for sIL2R (0.70) than for ACE (0.35), KL-6 (0.26), and Ca (0.07).[12]

Sarcoidosis in TB-Endemic Regions

Previous reports demonstrated low rates of sarcoidosis in regions with endemic tuberculosis.[44] However, in recent decades, the rates of sarcoidosis have been increasing. The reasons hypothesized are a greater awareness of sarcoidosis as a disease and improved rates of identification of this condition.[24,45,46] In a report from 1976, disease identification was made by reviewing chest radiograph (CXR) films over the prior decades;[44] however, CXR is not as sensitive as identifying lymphadenopathy or pulmonary nodules consistent with sarcoidosis compared with HR-CT. Advances have been made in distinguishing between sarcoidosis and tuberculosis and improved laboratory and imaging techniques; for example, HR-CT scans have likely assisted in the identification of sarcoidosis in these populations. In addition, the availability of fiberoptic bronchoscopy to obtain trans-bronchial lung biopsy tissue has also helped in the diagnosis of sarcoidosis.[37,44,46] However, challenges remain in distinguishing between the two conditions. Both tuberculosis and sarcoidosis present similarly in patients, including the miliary pattern classically associated with tuberculosis. Furthermore, there are reports of mycobacterial nucleic acid material in up to half of biopsy tissues, consistent with a diagnosis of sarcoidosis. Furthermore, immune responses to mycobacterial proteins have been identified in blood and bronchoalveolar lavage specimens of patients with diagnosed sarcoidosis.[24,46–48]

In a study performed on the utility of HR-CT scans in a population in India with endemic tuberculosis, mediastinal lymphadenopathy was noted in both patients with ocular sarcoidosis and with tuberculosis. HRCT findings were more commonly abnormal in those with sarcoidosis (96.3%) as compared with tuberculosis (64.7%). Hilar lymphadenopathy and fissures nodules were more common in ocular sarcoidosis ($P = 0.001$). However, necrosis, which is usually associated with tuberculosis and identified as a central hypodensity in the lymph node with peripheral contrast enhancement,[24] was also noted in 3 out of 86 patients with ocular sarcoidosis. This study suggests that imaging alone cannot differentiate between these two conditions. However, when combining imaging findings with other clinical signs and laboratory markers, the ability to distinguish between these conditions is improved.[37]

In a review of patients with biopsy-proven granulomatous uveitis as either ocular sarcoidosis or tuberculosis (with a response to anti-tubercular therapy), a low score on a Schirmers test, the presence of bilateral disease, depigmented chorioretinal scars, candle wax retinal vasculitis, a negative QuantiFERON Gold or Mantoux test, the presence of bilateral hilar lymphadenopathy or

fissural nodules were all more consistent with a diagnosis of ocular sarcoidosis than of tuberculosis.[49] In a similar study from the same group, in patients with biopsy-proven granulomatous uveitis and a Schirmer test ≥10 mm, a positive Mantoux test, and pigmented multifocal choroiditis along retinal blood vessels, the likelihood ratio of uveitis being secondary to tuberculosis was reported to be approximately 77%.[50]

Evaluation of choroidal granulomas, as mentioned above, can also help distinguish between sarcoidosis and tuberculosis. Tubercular granulomas tend to be large, solitary, lobular, have low internal homogeneity, are vascularized, and are located in perivascular areas of the retina. Sarcoid granulomas are small, multiple, oval-shaped, distributed diffusely, dull yellow, and associated with vasculitis and disc hyperfluorescence on fluorescein angiography.[27,29]

The aforementioned findings point to a stronger role of clinical evaluation and radiographic imaging than relying on laboratory results such as an angiotensin-converting enzyme (ACE) to distinguish between these conditions, especially because ACE can be elevated in both diseases. As it is produced by epithelioid cells derived from macrophages in granulomas, it is thought to signify the burden of granulomas in the body.[12,24,51,52]

Similarly, while KL-6 and serum IL2 receptors have been shown to be elevated in patients with sarcoidosis, they have also been reported as elevated in patients with tubercular lung disease, limiting their utility in differentiating ocular sarcoidosis from tuberculosis. However, in studies following the prognosis of patients with tuberculosis, sIL2R levels were noted to decline after successful therapy with anti-tubercular treatment. Thus, following sIL2R levels over a period of anti-tubercular treatment may serve a role in the small population of patients in whom the distinction between tuberculosis and ocular sarcoidosis cannot be made definitively.[41,52–54]

PCR testing can be utilized to distinguish between the two conditions, reducing the need to identify acid-fast bacilli in biopsy tissues. Specific genes that can be detected are *IS6110*, *MPB64*, and *protein b*. As the reported diagnostic sensitivity of a single target has been low (<40% for IS6110 and 66.6% for MPB64),[55] an approach utilizing simultaneous amplification of multiple genes has been utilized, increasing the sensitivity of PCR to 77.7%.[56] Limitations of this methodology include a lack of widespread utilization of testing, lack of standardization of protocols, and low sensitivity, which is demonstrated in cases where patients have widespread systemic tuberculosis but have negative PCR test results.[57]

Current Recommended Approaches to the Diagnosis of Ocular Sarcoidosis

Sarcoidosis should be considered in patients who have uveitis, anterior or otherwise, alongside dry eye disease as evidenced by decreased Schirmers testing.[49] It should be considered in patients who have bilateral intermediate or posterior uveitis with candlewax phlebitis, the presence of snowballs, or a string of pearls appearance of vitreous condensation.[9,10,49] In those with anterior uveitis, bilateral disease, the presence of mutton fat keratic precipitates, iris nodules, or broad-based peripheral anterior synechiae should be considered suspicious for sarcoidosis.[9,10] Posterior findings such as bilateral peripheral hypopigmented chorioretinal lesions, granulomas, or scattered hypocyanescent lesions on indocyanine green angiography (ICG) are also consistent with sarcoidosis.[9,10] In those patients in whom sarcoidosis is suspected, an interferon-gamma release assay and rapid plasma reagin test should be performed, not only to rule out alternate infections but in case high-dose corticosteroids are needed to control the ocular inflammation. ACE and lysozyme levels continue to be useful, but serum soluble IL2 receptor levels may be more useful, especially prior to ordering radiographic studies.[12] If sIL2R levels are elevated, a high-resolution chest CT scan may be warranted to get an adequate level of detail to evaluate for parenchymal disease, lymphadenopathy, or fissural nodules consistent with sarcoidosis, along with a complete blood count to identify lymphopenia to assist in differentiation sarcoidosis from other diseases involving the lungs.[37]

Future Directions

As inflammation in sarcoidosis is thought to be due to continued stimulation of T helper lymphocytes,[58] much attention has been devoted to the determination of CD4+/CD8+ ratios in the aqueous and vitreous humors of the eye, especially as compared with serum levels. This arises from the realization that serum laboratory investigations remain an imperfect method of diagnosing ocular sarcoidosis. Testing aqueous and vitreous humor is an exciting possibility as we already frequently utilize it for infectious testing (polymerase chain reaction) and for vitreoretinal lymphoma, but also because it would allow for a diagnostic test to be performed on the involved organ (the eye). Another possible direction involves gene expression profiling, which is based on the fact that sarcoidosis as a disease affects multiple organ systems but causes the same fundamental changes to these tissues, thus leaving behind a "fingerprint." This form of approaching a diagnosis is useful because it looks for unifying changes despite variations in organ involvement, though its major limitation is still the need for a tissue biopsy.

The ratio of CD4+/CD8 + in the vitreous and aqueous humor

Levels of CD4+/CD8+ ratios in the vitreous and aqueous humors have been evaluated based on their utility in pulmonary sarcoidosis. Bronchoalveolar lavage (BAL) indicates a CD4+/CD8+ ratio of >3.5, demonstrating a 94%–96% specificity for sarcoidosis, though the sensitivity is 52%–59%.[34] A relative BAL/peripheral blood CD4+/CD8 + ratio of >2 may help discriminate sarcoidosis from other interstitial lung conditions.[59] Two studies published recently, one with 22 eyes of 22 patients with ocular sarcoidosis and another with 51 eyes of 38 patients with ocular sarcoidosis who underwent pars plana vitrectomy, evaluated the utility of CD4+/CD8+ levels in the vitreous fluid compared with either peripheral blood or bronchoalveolar lavage. All patients had high levels of CD4+/CD8+ ratios in the vitreous fluid, and the vitreous fluid ratios were considered to be of equivalent diagnostic value to bronchoalveolar lavage for the diagnosis of ocular sarcoidosis.[60,61]

However, a complete pars plana vitrectomy is an invasive procedure that, in the absence of a compelling reason, may not be reasonable to undertake in patients for diagnostic purposes. Dave *et al*.[62] published a case-control study of 61 patients with

uveitis, 21 of whom were identified as having ocular sarcoidosis as per the 2009 criteria of the International Workshop on Ocular Sarcoidosis (IWOS), and evaluated the aqueous humor using flow cytometry. The total volume used for flow cytometry for 0.05 cc. The CD4+/CD8+ ratio of those with sarcoid uveitis was significantly higher (median: 4.7, mean: 6.3 ± 1.4) than in those patients without sarcoid uveitis (median: 1.6, mean: 1.6 ± 0.1). However, in this study, there was no statistically significant difference between CD4+/CD8 + ratios in those with and without sarcoid uveitis in peripheral blood. The ratio between aqueous humor and peripheral blood was higher (median: 4.0, mean: 4.6 ± 0.9) in those with sarcoid uveitis but not in those with other types of uveitis. The sensitivity and specificity of aqueous humor ratios were 65.7% and 95%, respectively.[62] As the study was based on the original 2009 IWOS criteria for ocular sarcoidosis, it likely categorized some patients as non-sarcoid uveitis that may have had ocular sarcoidosis due to their more stringent diagnostic recommendations. This may have affected the results of this and any study that relied on the 2009 criteria to make a diagnosis of ocular sarcoidosis. That being said, it remains to be seen whether there are appreciable CD4+/CD8+ ratio differences in patients of varying ages or during the course of the disease that could affect the clinical utility of this specific marker.

Gene expression profiling of tissues in patients with sarcoidosis

Rosenbaum *et al*.[63] evaluated gene expression profiles in 12 patients with orbital sarcoidosis and 6 patients who were either healthy controls, had thyroid eye disease, nonspecific orbital inflammation, or granulomatosis with polyangiitis. They determined that similar genes were upregulated regardless of the site of inflammation in sarcoidosis; for example, the intracellular signaling molecule STAT 1 was determined to be elevated in both the peripheral blood, orbital tissue, and in the lacrimal gland. This is supported by findings that implicate other signaling proteins including interferons, GBP-5, AIM-2, and SLAMF8 in the development of sarcoidosis, all of which belong in the same pathway.[64–66] Finding similar gene expressions in tissues affected by sarcoidosis can help identify the diagnosis for patients, and the diagnosis can be made with a peripheral blood draw, preventing invasive and expensive testing, regardless of where their sarcoidosis manifests, the reasons for which are still a mystery.

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Conflicts of interest

There are no conflicts of interest.

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