Clinical aspects of ocular sarcoidosis

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Sarcoidosis can involve any part of the eye and may be the major manifestation of the disease, even leading to severe impairment. It can occur early or late in the disease course, and may even "pre-date" the disease, since some patients initially diagnosed with idiopathic uveitis will eventually develop systemic signs of sarcoidosis [1]. Therefore, it is important that all sarcoidosis patients are evaluated for eye disease and that sarcoidosis should be considered as the cause of abnormal eye findings.

Epidemiology, risk factors and genetics

The frequency of ocular involvement differs between various reports (table 1) [2–18]. American and European studies report eye disease in 10–50% of sarcoidosis patients and

Table 1. – Ocular involvement in sarcoidosis

First Author [ref.]	Year	Ethnicity of majority of patients	Ocular involvement/ total cases studied n	Percentage	Comments
CRICK [4]	1961	English	93/185	50	
JAMES [9]	1964	English	123/442	28	
SILTZBACH [17]	1974	Worldwide	354/1609	22	Survey of centres around world
JAMES [8]	1976	Worldwide	539/3676	15	Survey of centres around world
OBENAUF [14]	1978	USA	202/532	38	
JABS [7]	1986	USA	47/183	26	
JAMES [10]	1986	Worldwide	572/5742	10	Survey of centres around world
JAMES [10]	1986	English	224/818	27	
KARMA [11]	1988	Finland	79/281	28	
ANGI [2]	1991	Italian	69/645	10	
FITE [5]	1996	Catalonian	35/245	14	
BAUGHMAN [3]	2001	USA, Caucasians	30/393	8	At initial presentation, part of a larger study
BAUGHMAN [3]	2001	USA, African Americans	55/325	18	At initial presentation, part of a larger study
PIETINALHO [16]	1996	Finnish	39/571	8	Part of two centre study
PIETINALHO [16]	1996	Japanese	344/686	50	Part of two centre study
IWATA [6]	1976	Japanese	55/70	78	
UYAMA [18]	1976	Japanese	87/136	64	
NAKAGAWA [13]	1978	Japanese	65/73	89	
MIZUNO [12]	1986	Japanese	82/102	80	
OHARA [15]	1992	Japanese	126/159	79	

include extraocular disorders, such as lacrimal gland enlargement or sicca syndrome. Reports of Japanese sarcoidosis patients, that mention only eye involvement, found ocular disease in 64–89%. These studies were mostly reported by ophthalmologists. In a study using standard criteria for diagnosis, ocular disease was ten times more frequent in Japanese patients *versus* Finnish patients [16].

The low rate reported in some series may be due to the lack of thoroughness in examining for ocular disease. Mass screening for sarcoidosis by physicians may result in a low percentage of ocular involvement if an ophthalmological examination is not routinely performed. However, there are probably true differences in the prevalence of eye disease in different populations. To support this contention, ANGI *et al.* [2] used a diagnostic contact lens and performed a thorough eye examination and still found a low prevalence of ocular sarcoidosis in an Italian population.

In America, ocular sarcoidosis is more prevalent in Blacks than Whites [3, 19]. In one study, where a more detailed analysis of specific types of eye disease was performed, additional racial disparities were identified; anterior uveitis was more common in Black sarcoidosis patients, whereas posterior uveitis was more common in Whites. In addition, chronic uveitis was more common in Whites, and was most commonly seen in White female patients with late onset of systemic disease [19]. In another study examining the phenotypic features of sarcoidosis at presentation in the USA, ocular disease was more common in Blacks compared with Whites. It was more common in Black females when the patient was diagnosed at an age <40 yrs, but more common in Black males if the patient was aged >40 yrs at presentation [3]. Sarcoidosis eye disease is more common in patients with the human leukocyte antigen polymorphism DRB1*0401 than in age-, race- and sex-matched controls, which suggests that there is a genetic basis for this disease phenotype [20].

Intraocular manifestations of ocular sarcoidosis

General comments

Primary and secondary intraocular manifestations are illustrated in figure 1 and 2. Among various intraocular lesions, some lesions are selected as primary and significant
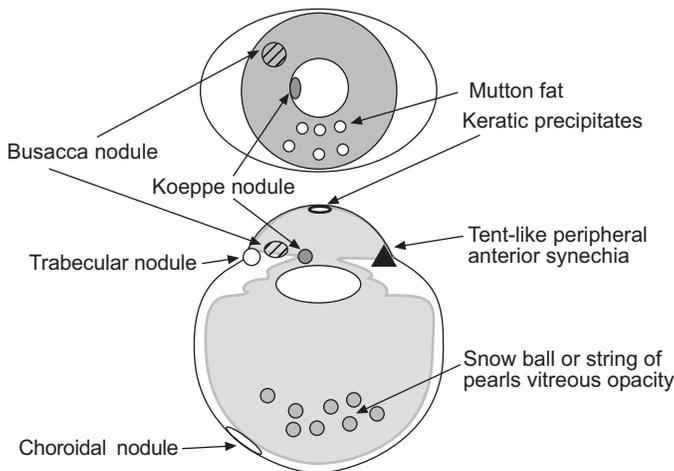

Fig. 1. – Schema of intraocular manifestation of sarcoidosis. Frontal and sagittal sections are illustrated.
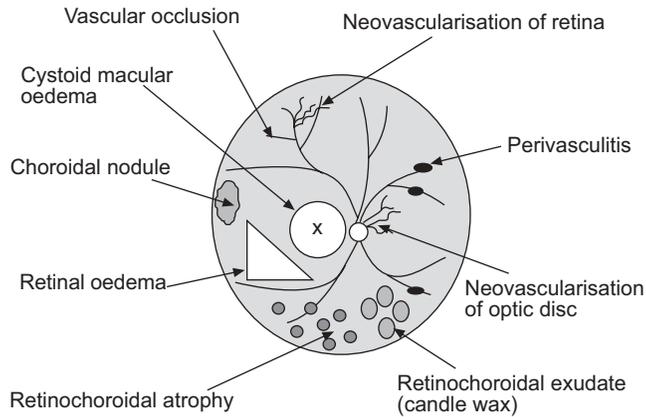
Fig. 2. – Schema of intraocular manifestation of sarcoidosis. Fundus view is illustrated.

and are suggestive of sarcoidosis; their frequency in one series is shown in table 2 [15]. Lesions that are not solely seen in sarcoidosis, but are suggestive of sarcoidosis, include granulomatous iritis or iridocyclitis, associated with "mutton-fat" keratic precipitates at the posterior corneal surface (fig. 3), iris nodules at the pupillary margin (Koeppe's nodule; fig. 4) or iris surface (Busacca nodules). Trabecular nodules are also highly suggestive of sarcoidosis (fig. 5) [6, 12]. Gray nodules are seen at the anterior chamber angle. Nodules are situated on the trabecular meshwork, which serves as an outlet of the aqueous humour to regulate intraocular pressure. Frequently, the nodules protrude to the surface of the ciliary body or iris root. Tent-like peripheral anterior synechia (PAS) has a conical shape and its conical top adheres to the trabecular meshwork (fig. 6). The present authors assume that tent-like PAS is a scar and is formed when protruding trabecular nodules retract the iris upward to the trabeculum. It is also probable that the nodules in the iris root or ciliary body pull the iris toward the trabeculum [21].

"Snowball" or "string of pearls" type vitreous opacities are known as a sign of sarcoidosis (fig. 7). The opacities are mostly situated in the inferior vitreous. Some ophthalmologist feel snowballs form as an intermediate uveitis, a specific condition called pars planitis [22]. Retinal perivasculitis is frequently found in sarcoidosis. In many cases, perivasculitis is seen as segmental periphlebitis (fig. 8), and the vascular changes often are located at the equatorial or peripheral retina (fig. 9). Normally, periphlebitis at the central retina does not induce retinal exudation. When periphlebitis occludes the venous circulation, the retinal haemorrhage appears, mimicking branch retinal vein occlusion [23]. If the occlusion is extensive, neovascularisation, vitreous haemorrhage and

Table 2. – Intraocular lesions found in ocular sarcoidosis

Lesions	Percentage
Iritis	74
Mutton-fat precipitates[#]	51
Iris nodules[#]	30
Trabecular nodules	61
Tent-like peripheral anterior synechia	54
Snowball or string of pearls vitreous opacity	45
Retinal perivasculitis	67
Retinochoroidal patchy exudates	53

[#]: Forms of iritis. Adapted from OHARA et al. [15].

Fig. 3. – Slitlamp photograph showing mutton-fat keratic precipitates in granulomatous iritis.

Fig. 4. – Slitlamp photograph showing Koeppe's nodule in granulomatous iritis.

proliferative vitreoretinopathy follow. Relatively well-defined, discrete chorioretinal exudates, seen as patchy exudates, are another sign suggestive of sarcoidosis. When patchy exudates appear along the vein, and if periphlebitis is extensive, their appearance resembles dripped candle wax (fig. 8). Histopathological studies disclosed intraocular lesions which consisted of epithelioid cell granulomas [24, 25].

Ocular examination

The ocular examination should include intraocular pressure measurement, the use of a slitlamp, gonioscopy (using a diagnostic contact lens to see the anterior chamber angle, peripheral vitreous and retina; fig. 10), and indirect ophthalmoscopy. The slitlamp allows the anterior inflammation to be seen. It provides binocular vision to perform gonioscopy so that the anterior chamber angle may be viewed where the characteristic lesions, such as trabecular nodules and tent-like PAS, are observed. The diagnostic contact lens, under
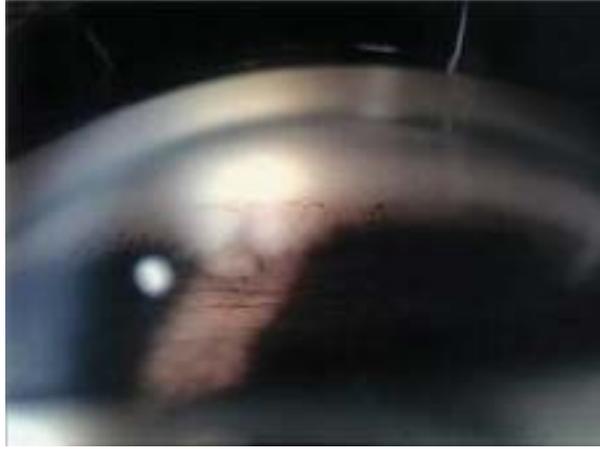
Fig. 5. – Gonioscopic photograph of anterior chamber angle showing trabecular nodules.
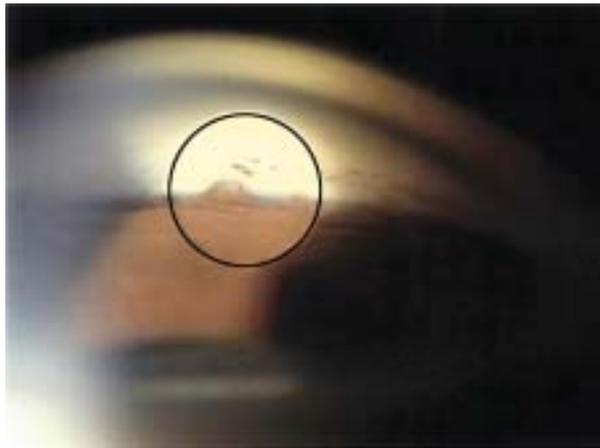

Fig. 6. – Gonioscopic photograph of anterior chamber angle showing tent-like peripheral anterior synechia (circled).

higher magnification, also allows the ocular fundus periphery to be examined where retinal vascular and retinochoroidal exudation frequently occur, suggesting sarcoidosis. Indirect ophthalmoscopy discloses the central and peripheral retina. Fluorescein fundus angiography helps to detect subtle vascular leakage, and to see the presence of cystoid macular oedema, which is a risk factor leading to decreased central vision (fig. 11).

Specific eye findings

Conjunctiva

Sarcoidosis involves the conjunctiva in 6–40% of cases [7, 14, 26–29]. Three-quarters of cases of conjunctival involvement are present at diagnosis [7]. Conjunctival involvement is less commonly seen with chronic sarcoidosis [7]. Macroscopic lesions may appear as
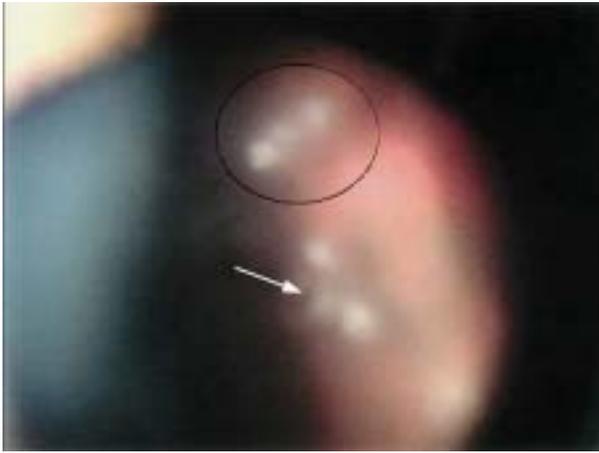
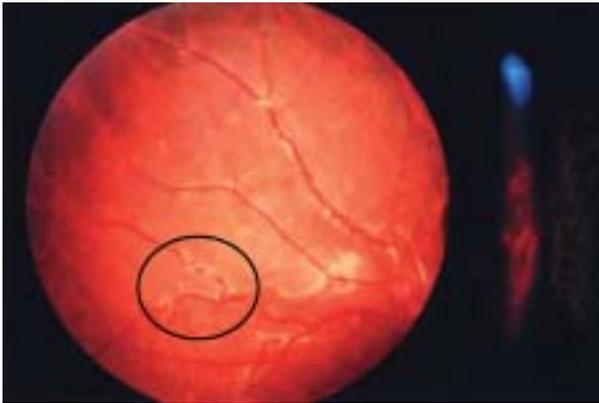Fig. 7. – Snowball (arrow) and a string of pearls-like vitreous opacities (circled).

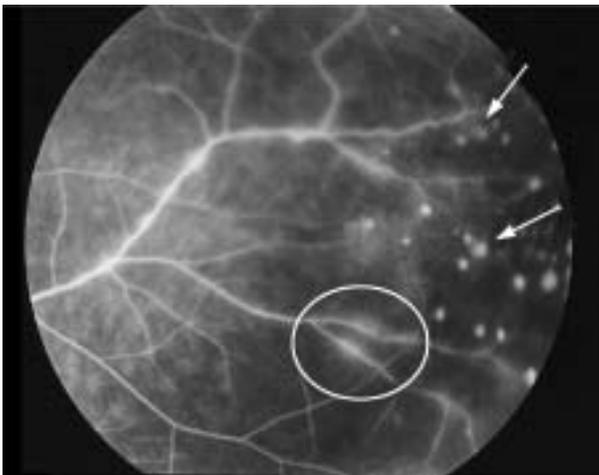Fig. 8. – Retinal periphlebitis with candle wax drippings (circled).

Fig. 9. – Fluorescein angiography showing vascular leakage (circled) and patchy exudation (arrows).

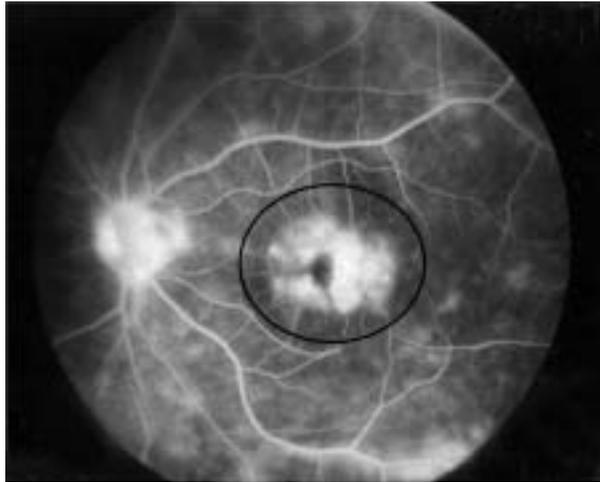Fig. 10. – Gonioscopy using a diagnostic contact lens and slitlamp.

Fig. 11. – Typical cystoid macular oedema (circled) shown by fluorescein fundus angiography.

golden fleshy nodules located on the upper as well as lower and forniceal conjunctivae [30]. These lesions may also be microscopic without evidence of visible lesions. The yield of conjunctival biopsy (fig. 12) for the diagnosis of sarcoidosis is ∼33% in unselected sarcoidosis patients [27, 29] and is unaffected by the presence or absence of uveitis [27]. The diagnostic yield of biopsy may be as high as 67% if conjunctival nodules are present [29]. It is controversial whether or not blind biopsy of normal-appearing conjunctival tissue is of value, with one study reporting a yield of 30% [29], while others have found such biopsies to be fruitless [31, 32]. Recently, it has been suggested that *in vivo* confocal microscopy may be useful in the diagnosis of conjunctival sarcoidosis based on a typical appearance [33]. This technique may also be useful to determine when a conjunctival biopsy will confirm the diagnosis of sarcoidosis [33].

Anterior uveitis

Anterior uveitis occurs in 22–70% of patients [1, 7, 14, 28] and typically presents as an iritis or iridocyclitis [34]. Symptoms include red eyes, pain, photophobia and blurred

Fig. 12. – Nondirectional biopsy of the conjunctiva at lower conjunctival fornix.

vision. However, in up to 34% of cases, a patient may present without ocular symptoms (a "quiet eye") [19]. It is for this reason that all patients with sarcoidosis, regardless of the presence of ocular symptoms, undergo an eye evaluation that includes a slit lamp examination. Large mutton-fat keratic precipitates, which are small aggregates of inflammatory cells, are often seen with a gravitational distribution along the middle and inferior region of the corneal endothelium (fig. 3) [34].

A distinction is usually made between acute and chronic anterior sarcoid uveitis. Some series find acute anterior sarcoid uveitis more common [7], whereas others find the opposite [14]. In general, patients with acute anterior sarcoid uveitis tend to be younger, usually aged 20–35 yrs, while those with chronic anterior sarcoid uveitis tend to be aged 35–50 yrs [30]. Those with chronic disease tend to have milder eye symptoms. Anterior chamber cell and flare and anterior vitreous cells can be seen in both acute and chronic anterior sarcoid uveitis. Busacca nodules, almost exclusively seen with chronic anterior sarcoid uveitis, are true granulomatous lesions found on the iris and are much less common than keratic precipitates [30]. Another lesion of chronic anterior sarcoid uveitis is the Koeppe nodule (fig. 4), which is a granulomatous lesion found only on the papillary margin, and may become the nidus for the development of posterior synechiae [30]. Occasionally, patients with chronic anterior sarcoid uveitis will demonstrate lesions that are pathognomonic of granulomatous uveitis: pink, vascular and opaque iris granulomas that are larger and much less common than either Busacca or Koeppe nodules [30]. Chronic anterior sarcoid uveitis can lead to band keratopathy, glaucoma, and cataract formation. Since corticosteroids (CS) may cause glaucoma and cataracts, it is sometimes problematic to determine if these sequellae are from the disease or its treatment.

Intermediate uveitis

Intermediate uveitis, a common manifestation of eye sarcoidosis, is defined as inflammation of the vitreous, pars plana, and peripheral retina [1, 35]. The pars plana is a narrow section of the ciliary body. Pars planitis, a subset of intermediate uveitis, results in cellular accumulations in the vitreous known as "snowballs" (fig. 7). Some cases demonstrate a unique opacified ridge in the peripheral retina along the pars plana, especially inferiorly, known as a snowbank [1, 19, 35]. Patients with intermediate uveitis

may be asymptomatic, or may have symptoms of floaters and blurred vision [1, 35]. Intermediate uveitis is not specific for sarcoidosis. It is most commonly idiopathic [19] but may also be associated with multiple sclerosis and other inflammatory diseases [1, 35].

Posterior uveitis

Up to 28% of patients with eye sarcoidosis have posterior uveitis [14, 34]. Characteristic findings of posterior segment involvement include periphlebitis associated with segmental cuffing, extensive sheathing and perivenous infiltrates referred to as "candle wax drippings" or "taches de bouge" (fig. 8) [36]. These lesions may be subclinical and only visible on fluorescein angiography (fig. 9) [36]. Candle wax drippings are seen on funduscopic examination in up to 70% of patients with posterior sarcoid uveitis [37], but they are not pathognomonic [30]. Capillary closure and ischaemia can result in neovascularisation and vitreous haemorrhage [37–40]. Choroidal granulomas are observed in some cases as cream-colored lesions that may measure more than one disc diameter [30, 34]. On resolution of the granuloma, an area of pigment epithelial atrophy or scar may occur [30]. Cystoid macular oedema can result from chronic inflammation associated with anterior, intermediate, or posterior uveitis [36, 41]. Rare complications of posterior sarcoid uveitis include retinal detachment, optociliary shunts, where dilated collateral veins on the optic head connect the central retinal vein to the choroidal venous plexus, and arterial marcoaneurysms [36].

A major concern is that posterior sarcoid uveitis is associated with neurological involvement in up to 27% of cases [36]. It is, therefore, imperative that a careful funduscopic examination should be done on all patients with suspected posterior sarcoid uveitis to differentiate it from optic nerve disease because of the therapeutic consequences. In addition, the presence of uveitis and optic neuritis can be seen with multiple sclerosis.

The differential diagnosis of uveitis

There are many infectious and noninfectious causes of uveitis (table 3). Sarcoidosis is not a common cause of uveitis in unselected patients. In two separate series, sarcoidosis was the cause of uveitis in only 2.5 and 12% of cases, respectively [42, 43]. In a third study, where subjects all lived in south-eastern USA, the frequency of sarcoidosis as the cause of uveitis was 11% [44]. Even when the Black subgroup in this study was examined, sarcoidosis was the cause of uveitis in only 25% [44]. Therefore, uveitis of unknown cause should not be assumed to be from sarcoidosis and appropriate diagnostic steps should be undertaken to determine the cause.

Table 3. – Differential diagnosis of uveitis

Noninfectious causes	Infectious
Sarcoidosis	Toxoplasmosis
Idiopathic panuveitis	HIV/CMV
Spondyloarthropathy	Lyme disease
Systemic lupus erythematosis	Tuberculosis
Bechet's disease	Fungi
Wegener's granulomatosis	Syphilis
Relapsing polychondritis	Herpes simplex virus

CMV: cytomegalovirus.

Optic neuropathy

Although optic neuropathy from sarcoidosis is rare, it is a feared complication in that in can rapidly cause permanent vision loss [1, 30]. Patients typically present with a rapid decrease in vision in one eye [33]. Disturbances in colour perception and contrast sensitivity may be detected [1]. Optic nerve involvement may be associated with papillitis, papilloedema secondary to increased intracranial pressure, neovascularisation, and granulomas of the optic head [30]. Optic atrophy may be the ultimate result of optic nerve involvement [30]. Optic neuropathy requires systemic therapy. Patients often have chronic disease and steroid sparing alternatives are commonly used for this condition.

Lacrimal gland

Sarcoidosis involvement of the lacrimal gland occurs in 15–28% of patients with sarcoid eye disease [7, 14]. The rates of asymptomatic lacrimal gland involvement with sarcoidosis may be much higher, as one retrospective study found that 88% (101/114) of sarcoidosis patients demonstrated gallium-67 (^{67}Ga) uptake in the lacrimal glands [45]. Although lacrimal gland involvement usually causes no symptoms, some patients develop keraotconjunctivitis sicca [46]. Enlargement of the lacrimal glands may be palpable on physical examination and rarely enlargement is so massive that it may cause proptosis [47]. The diagnosis of sarcoidosis can be made by biopsy of the lacrimal gland. Biopsy is often considered when the gland is palpable or there is uptake of ^{67}Ga scanning.

Extraocular muscles

Oculomotor nerve palsy can occur from sarcoid involvement of the 3rd, 4th, and 6th cranial nerves. Although the facial nerve is the most common cranial nerve affected by sarcoidosis, the 6th cranial nerve is the second most common cranial nerve affected [48–51]. Unilateral involvement is more common, but bilateral involvement can be seen [1]. Rarely, the extraocular muscles may be infiltrated with sarocid granulomas [1, 52]. These patients usually present with diplopia and associated pain [52]. Magnetic resonance imaging of the orbits is useful in the evaluation of sarcoidosis-associated ocular motility abnormalities to distinguish extraocular muscle from cranial nerve involvement [1].

Miscellaneous eye conditions

Scleritis. Scleral involvement is rare in sarcoidosis. In two series of patients with sarcoidosis eye disease, <3% had scleral involvement [7, 53]. Sarcoidosis scleral involvement may manifest as diffuse inflammation, a plaque, or nodule (fig. 13) [54]. The diagnosis may be made by biopsy of a scleral nodule [1].

Orbits. Diffuse orbital inflammation occasionally occurs in sarcoidosis [1]. Orbital connective tissue involvement is usually unilateral and can result in ptosis, limitations in extraocular muscle movement, and diplopia [1, 34].

Dacrocystitis. Dacrocystitis (inflammation of the tear duct system) can also occur in sarcoidosis [1]. Granulomatous inflammation of the tear ducts may impair drainage and cause painful swelling [1].

Cornea. Four patterns of corneal involvement with sarcoidosis have been noted: 1) inferior corneal thickening; 2) calcific band keratopathy; 3) stromal thinning; and 4)
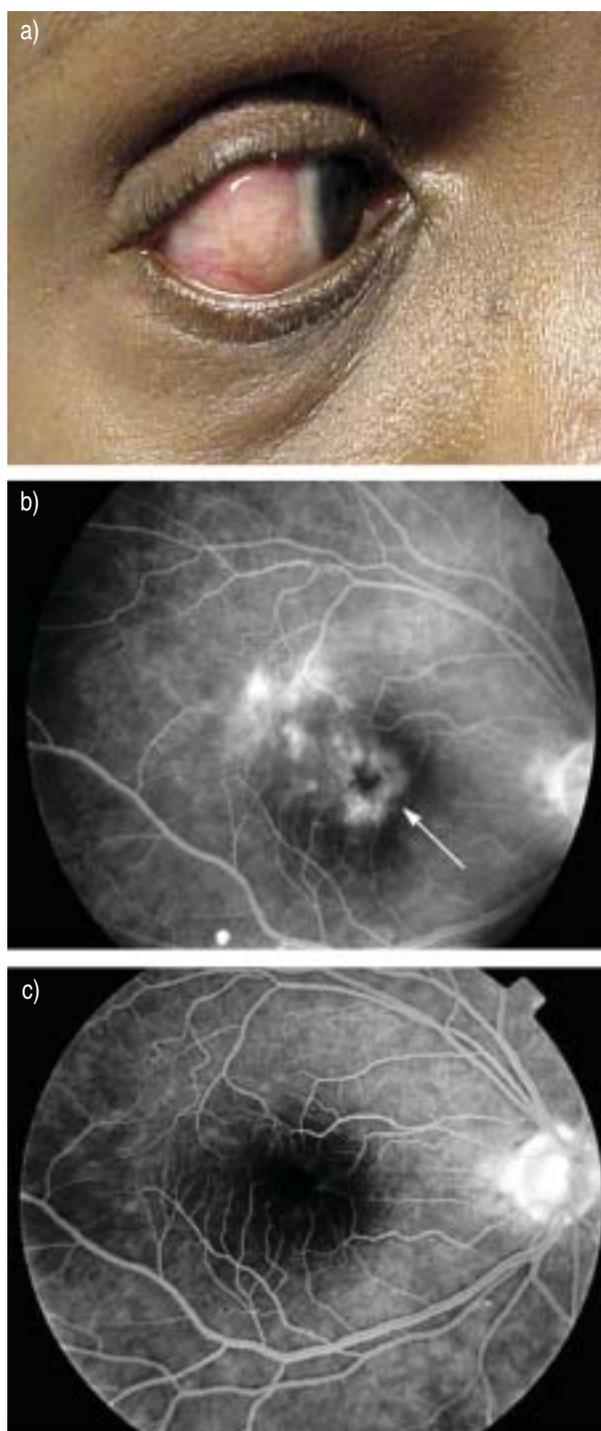
Fig. 13. – a) Scleral lesion due to sarcoidosis. Right eye of a sarcoidosis patient with macular oedema (arrow); b) before treatment; and c) a year after treatment with infliximab (figs b and c courtesy of M. Drent).

interstitial keratitis [30]. Inferior corneal thickening is the most common of these presentations [30]. Corneal band keratopathy, a white band on the cornea, usually causes no symptoms. It is found in patients with chronic uveitis and is often associated with hypercalcaemia [1].

Glaucoma. Open angle glaucoma may develop from sarcoidosis when granulomatous inflammation forms in the trabecular area causing obstruction of the Schlemm canal [21, 43]. To complicate matters, glaucoma may also occur as a result of treatment of sarcoidosis with CS.

Cataract. Cataracts have been reported in 8–17% of patients with ocular sarcoidosis [7, 14] and may be attributable to chronic granulomatous inflammation or from corticosteroid treatment [14].

Common syndromes

Two classic presentations of sarcoidosis are associated with ocular involvement. Löfgren's syndrome is the association of erythema nodosum and bilateral hilar lymph adenopathy (BHL) due to sarcoidosis. Arthritis and iritis may be present in Löfgren's syndrome [55]. Heerfordt's syndrome may occur characterised by kerotconjunctivitis sicca, parotid dysfunction with swelling, facial nerve paralysis and lacrimal gland dysfunction [30, 56, 57].

Blau's syndrome

Blau's syndrome is an autosomal dominant condition with variable penetration that consists of granulomatous arthritis, iritis and skin rash [58, 59]. The age of onset is usually prior to 12 yrs of age [4, 58]. It is considered a separate entity from childhood sarcoidosis on the basis of lack of visceral (including pulmonary) involvement, absence of fever or vasculitis, and the mode of inheritance [58]. There appears to be a gene-environmental interaction that results in the development of the syndrome [60]. The genetic markers associated with Blau's syndrome were not found in sarcoidosis patients [61].

The diagnosis of ocular sarcoidosis: general considerations

Sarcoidosis is a systemic granulomatous disease of unknown cause. The diagnosis of sarcoidosis requires a compatible clinical picture, histological demonstration of noncaseating granulomas, and exclusion of other diseases capable of producing a similar histological or clinical picture [62]. Mycobacterial and fungal diseases must always be considered as alternative diagnoses, regardless of the organ biopsied. Therefore, stains and cultures for mycobacteria and fungi should be routinely performed when sarcoidosis is a consideration. Since sarcoidosis is a diagnosis of exclusion, the diagnosis can never be confirmed with 100% certainty.

The presence of noncaseating granulomas in a single organ does not establish the diagnosis of sarcoidosis because, by definition, sarcoidosis is a systemic disease that should involve multiple organs. There are idiopathic granulomatous diseases of individual organs that are distinguished from sarcoidosis. For example, in the case of eye disease, idiopathic panuveitis is defined as a granulomatous uveitis confined to the

eye. It may be reclassified as a case of sarcoidosis if clinical features of extraocular disease consistent with sarcoidosis develop [63].

The present authors define the intraocular lesions listed in table 2, though not pathognomonic, as highly specific signs of sarcoidosis. Any two of these lesions make the authors suspect sarcoidosis. Trabecular nodules, tent-like PAS or retinal perivasculitis are assumed as highly characteristic, and the presence of any of these three makes the current authors suspect sarcoidosis. The differential diagnosis of these lesions includes other granulomatous and nongranulomatous diseases, and they must be excluded from consideration before the diagnosis of sarcoidosis is secure. Behcet's disease, although not granulomatous, sometimes produces intraocular lesions mimicking perivasculitis and snowball vitreous opacities of sarcoidosis. The recurring Vogt-Koyanagi-Harada syndrome may show the granulomatous iridocyclitis.

The clinician may be faced with one of three diagnostic challenges concerning confirming the diagnosis of ocular sarcoidosis: 1) diagnosis by ocular biopsy; 2) diagnosis when the diagnosis of sarcoidosis has previously been confirmed in an extraocular organ; and 3) diagnosis by an extraocular biopsy when sarcoidosis has not yet been diagnosed. These situations will be discussed separately.

Making the diagnosis of ocular sarcoidosis by ocular biopsy

Biopsy of the eye is an invasive procedure. Therefore, it is rarely performed to make a diagnosis of sarcoidosis. As previously discussed, conjunctival biopsy (fig. 12) has a reasonable yield for the diagnosis of sarcoidosis if conjuctival nodules are observed [29]. Data is conflicting concerning the utility of a blind conjunctival biopsy for the diagnosis of sarcoidosis when no macroscopic conjunctival lesion is seen [29, 31, 32]. Lacrimal gland biopsies have a high yield when the lacrimal gland is palpable or there is uptake of ^{67}Ga on nuclear scanning. As lacrimal gland uptake on ^{67}Ga scanning may occur in up to 88% of sarcoidosis patients [45], it is reasonable to perform this test when faced with a patient who would otherwise require a more invasive biopsy for diagnosis.

Making the diagnosis of ocular sarcoidosis in an established sarcoidosis patient

If the diagnosis of sarcoidosis has been established in an extraocular organ, the diagnosis of ocular sarcoidosis may be made clinically without performing a biopsy. Table 4 shows the relationship between finding ocular lesions in patients who present with either eye or chest manifestations in a Japanese population [15]. Clinical criteria have been established as part of the A Case Control Etiologic Study of Sarcoidosis (ACCESS) [64]. Ocular findings consistent with sarcoidosis are listed in table 2. The frequency of various ocular findings in sarcoidosis in one series is presented in table 2

Table 4. – Initial clinical manifestations and intraocular lesions in sarcoidosis

Initial clinical manifestation	Intraocular lesion present	Intraocular lesion absent	Total
Ocular	87	0	87
Chest#	39	33	72
Total	126 (79.2)	33 (20.8)	159 (100)

Data are presented as n or n (%). #: Chest manifestations include bilateral hilar adenopathy or respiratory symptoms. Adapted from OHARA et al. [15].

[15]. It is essential to exclude alternative causes for the eye abnormalities before accepting sarcoidosis as the cause.

The incidence of intraocular involvements was studied in 159 Japanese patients with systemic sarcoidosis [15]. All patients were Japanese. BHL was found in 153 patients, and histological diagnosis was made in 148 out of 159 patients (table 4). A total of 87 patients (54.7%) who presented ocular lesions suggestive of sarcoidosis as an initial manifestation were diagnosed after a systemic survey. Moreover, 72 patients (45.3%) had chest signs or symptoms as initial manifestations and were referred to ophthalmic examination during a diagnostic survey. Of 159 patients, 126 (79.2%) showed intraocular involvements at diagnosis.

In patients with intraocular involvement, iritis including nongranulomatous iritis was the most frequent lesion, being seen in 74.7% (table 2). Gonioscopic examinations using a diagnostic contact lens revealed trabecular nodules and tent-like peripheral anterior synechia in 61.2% and 54.5% of the patients, respectively. Snowball or string of pearls vitreous opacities were seen in 45.5%. Retinal perivasculitis and spotty retinochoroidal exudates were seen in 67.3% and 53.9% of the patients, respectively. High incidence of anterior uveitis seen as iritis or trabecular lesions was compatible with the incidence reported in previous studies [6, 12]. Posterior uveitis shown by vitreous opacities, perivasculitis or retinochoroidal exudates were also frequent in the study.

Age distribution of the patients at diagnosis is shown in figure 14. This figure was obtained from 169 diagnosed Japanese patients who showed intraocular involvement [65]. The male/female ratio was 1/1.8. There was one peak at the third decade in male patients, but there were two peaks in female patients at the third and sixth decades. The second peak at sixth decade indicates a large number of female ophthalmic patients showing uveitis as an initial manifestation of sarcoidosis. In a study in America, the second peak of female patients was also noted. However, the American study demonstrated a rise in the number of cases in males who were diagnosed with sarcoidosis after the age of 40 yrs [3].

The data shown in table 2 indicates the presence of intraocular lesions in a significant number of patients with sarcoidosis. Slight or mild iritis does not necessarily show symptoms. Without slitlamp examination, iritis may be underdiagnosed. Trabecular nodules and tent-like PAS cannot be detected without a slitlamp and diagnostic contact
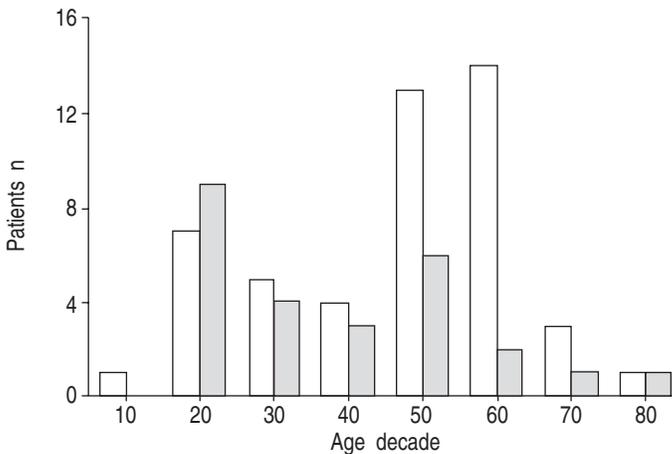

Fig. 14. – Age and sex distribution of Japanese patients with ocular sarcoidosis at the first visit. □: males; ■: females. Adapted from OHARA *et al.* [15].

lens. Trabecular nodules are frequently seen in sarcoidosis but they are rarely found in other uveitis. Trabecular nodules are often associated with a transient intraocular pressure rise or glaucoma. It was postulated that trabecular nodules, called trabecular sarcoidosis, and inflammatory lesions in the trabecular meshwork and Schlemm's canal block the aqueous outflow and increase the intraocular pressure [6, 21].

Making the diagnosis of ocular sarcoidosis in an extraocular organ when the diagnosis of sarcoidosis is not established

Since ocular biopsy is an invasive procedure, it is usually preferable to make the diagnosis of sarcoidosis in an extraocular organ. In addition, it may be important to determine if extraocular disease is present, such as to separate idiopathic panuveitis from sarcoid uveitis. Sarcoidosis should be considered as a potential diagnosis in all patients with unexplained uveitis or another eye disease that may be a manifestation of sarcoidosis. Such patents should undergo screening tests for sarcoidosis that should include a chest radiograph. A complete medical history and physical examination should be performed, and a further diagnostic work-up should be directed towards any abnormalities that are detected. For example, if a skin lesion is found on physical examination, it should be biopsied. Additional diagnostic tests to consider include serum liver function tests and calcium. Positive results on these tests should prompt a further diagnostic work-up. A serum angiotensin converting enzyme (ACE) may be obtained; however, it is neither highly sensitive nor specific for the disease [44, 45]. However, an elevated serum ACE should prompt a further work-up.

The evaluation is also affected by the underlying frequency of ocular sarcoidosis. For example, ocular involvement is very common in Japanese sarcoidosis patients (table 1), therefore, patients with unexplained uveitis are routinely evaluated for sarcoidosis. In Japan, the diagnosis of ocular sarcoidosis is divided into histological and clinical. The diagnostic criteria were established by the Research Committee for Diffuse Lung Diseases (Ministry of Health, Labour and Welfare) in 1989 and were modified in 1997. Briefly, histological diagnosis is made when clinical findings and/or diagnostic test data suggestive of sarcoidosis are supported by histological specimen. Clinical diagnosis is made if clinical findings are supported by the diagnostic test data. The diagnostic test data require six examinations, including: 1) negative tuberculin skin test; 2) increased serum γ-globulin; 3) increased serum ACE; 4) increased serum lysozyme; 5) positive ^{67}Ga scan; and 6) positive bronchoalveolar lavage fluid (BAL). Clinical diagnosis is made only if more than three of these six diagnostic test data are positive including either 1) or 3).

The most common scenario is that sarcoidosis eye disease will present in association with an abnormal chest radiograph, as was reported in >92% (187/202) of ocular sarcoidosis patients in one series [14]. The yield of bronchoscopy for the diagnosis of sarcoidosis in patients with suspected eye involvement has been reported in several series.

OHARA et al. [65] has performed prospectively transbronchial lung biopsy (TBLB) in 60 patients of ocular sarcoidosis suspects who showed no BHL and sparse contributory data. The patients had a combination of the six intraocular lesions shown in table 2. The TBLB specimen showed noncaseating epithelioid granuloma in 37 patients (61.7%), and the patients were diagnosed as having systemic sarcoidosis. There was no difference in ocular manifestations between TBLB positive and negative patients. BAL data indicate there were a significant number of patients with an increased percentage of lymphocytes in TBLB-positive patients, but no difference was observed regarding the patients with an increased ratio of CD4+/CD8+ between TBLB-positive and negative patients. The data support the present authors' assumption that the six intraocular manifestations described

are highly characteristic to sarcoidosis. Increase in the percentage of lymphocytes and CD4+/CD8+ ratio in patients with negative TBLB indicates a subclinical alveolitis and suggests these patients might have sarcoidosis at the cellular level, not forming granuloma yet. Others have found BAL fluid lymphocytosis useful in supporting the diagnosis [66]. However, an increase in BAL fluid lymphocytes and increased CD4+/CD8+ ratio has been found in idiopathic uveitis [67] with no cases demonstrating systemic sarcoidosis during a prolonged follow-up period. However, these patients may still have sarcoidosis.

In a separate group of 39 ophthalmic Japanese patients suggesting ocular sarcoidosis, TAKAHASHI et al. [68] performed high-resolution computed tomography (HRCT) of the chest, BAL and TBLB to study the clinical relevance of lymphocytosis in BAL fluid for the diagnosis of ocular sarcoidosis (table 5). HRCT was used to assess lung involvement, and to compare the validity of lymphocytosis in BAL fluid and HRCT. There were 12 male and 27 female patients, and 21 of them were aged >40 yrs. All patients underwent examination of serum ACE and serum lysozyme level, tuberculin skin test, chest radiograph and ^{67}Ga scintigram. The patients were divided into groups according to HRCT findings: no involvement (HRCT-0; n=13), BHL without lung involvement (HRCT-I; n=6), BHL and lung involvement (HRCT-II; n=20), and no BHL but lung involvement (HRCT-III; n=0).

A total of 20 patients were histologically diagnosed as having sarcoidosis by TBLB, and 19 patients remained undiagnosed. TBLB was positive in 19 out of 20 patients in the HRCT-II group, but in one out of 19 patients in the HRCT-0 and HRCT-I group (table 5; p<0.0001). Lymphocytosis (>15%) in BAL was identified in 16 out of 19 patients in the HRCT-0 and HRCT-I group and in all patients in the HRCT-II group. Percentages of patients having increased CD4+/CD8+ ratios (>3.5) was not significantly different among groups of HRCT-0, HRCT-I, and HRCT-II. TAKAHASHI et al. [68] concluded that HRCT yield was similar to TBLB regarding the degree of diagnostic accuracy. BAL revealed significant lymphocytosis in patients with negative pulmonary involvement in HRCT. TBLB-negative patients with an increased lymphocytosis might suggest the presence of patients with sarcoidosis who manifest the disease clinically by ocular involvements and subclinically by lymphocytosis of the lung. It may be possible that the patients with negative TBLB and positive lymphocytosis in BAL are at the pre-granulomatous stage, and they may disclose intrathoracic or other manifestations after many years following the initial investigational study [63]. However, the lymphocytosis may not be associated with sarcoidosis [67].

Analysis of the T-lymphocyte CD4+/CD8+ ratio in cells recovered from induced sputum has been examined in 17 patients with uveitis, 10 patients with sarcoidosis but without uveitis, and five normal controls [69]. All subjects with a CD4+/CD8+ ratio of >2.5 and undiagnosed uveitis had sarcoidosis. The concentration of ACE in tears has been found to be elevated in sarcoidosis patients [70]. However, the utility of this test for the diagnosis of sarcoidosis is unknown.

Table 5. – High-resolution computer tomography (HRCT) classification of the chest and results of transbronchial Lung Biopsy (TBLB) and bronchoalveolar lavage (BAL) in ocular sarcoidosis patients

HRCT classification[#]	Patients n	TBLB positive for granulomas	BAL fluid lymphocytes >15%	BAL fluid lymphocyte CD4+/CD8+ ratio >3.5
0, I	19	1	16/19	11/16
II	20	19[¶]	20/20	16/20

[#]: HRCT classification: 0=no involvement, I=bilateral hilar adenopathy without lung involvement, II=bilateral hilar involvement and lung involvement; [¶]: differs significantly from classification 0, I (p<0.0001). Adapted from TAKAHASHI et al. [68].

Treatment

The primary lesions in table 2, if they are slight or mild, do not necessarily cause deterioration of vision. Most visual deterioration is caused by secondary changes to primary lesions, or when the inflammation is severe and extensive.

CS are the mainstay treatment of ocular sarcoidosis. Anterior uveitis (iritis) is treated with eye drops. When iritis is severe and does not respond to eye drops, subconjunctival injection of CS may suppress the inflammation. Mydriatics are always instilled to suppress the inflammation and to avoid posterior synechia (adhesion of the iris to the lens). Intraocular pressure should be monitored during the course of the disease, because CS can induce intraocular pressure rise. Trabecular nodules, frequently seen without signs of anterior segment inflammation, also induce pressure rise and glaucoma.

Systemic CS (prednisolone or prednisone at 40 mg·day^{-1} and tapered over 6–12 months) are indicated if anterior uveitis is severe and it does not respond to local CS. Systemic CS are also given to simultaneous inflammation of anterior and posterior segments of the eye (panuveitis), mild-to-severe vitreous opacity, extensive retinal oedema, extensive perivasculitis with or without vascular occlusion, optic disc changes, and cystoid macular oedema. Cystoid macular oedema (fig. 11) appears secondary to intraocular inflammation, and is a principal cause of visual deterioration. Side-effects of systemic CS are always monitored. Table 6 summarises the various areas of involvement of 18 patients with chronic ocular sarcoidosis [41], demonstrating that chronic patients often have multiple eye lesions.

Due to the toxicity of systemic CS, CS-sparing alternatives have been used in sarcoidosis. Methotraxate is a steroid-sparing agent used for many chronic inflammatory eye conditions. It has been reported as useful in chronic uveitis. In a series of 160 patients with chronic uveitis due to various conditions, methotrexate was effective in 76% of the cases [71]. In a study of 11 patients with sarcoidosis associated uveitis, DEV et al. [72] found that the drug worked in 10 cases. In a retrospective analysis of 56 sarcoidosis patients treated at one instituiton, two-thirds of the patients responded after ≥6 months of methotrexate therapy (fig. 15). Of the 21 patients who did not respond to methotrexate, only six responded to azathioprine as a single agent [73].

Leflunomide is a another cytotoxic agent which has a similar effect as methotrexate. It has been reported that it was useful in treating 23 out of 28 (82%) chronic sarcoidosis-associated eye conditions [74]. In rheumatoid arthritis, methotrexate plus leflunomide has been shown to be superior to methotrexate alone [75]. In sarcoidosis-associated eye diseases, 12 out of 15 cases responded to the combination therapy [74].

The new anti-tumour necrosis factor (TNF) agents have been studied in sarcoidosis. Etanercept, a TNF receptor antagonist, was studied in a randomised, double-blind trial of chronic ocular sarcoidosis. All patients had been treated with ≥6 months of methtotrexate

Table 6. – Areas of eye involvement in patients with chronic ocular sarcoidosis

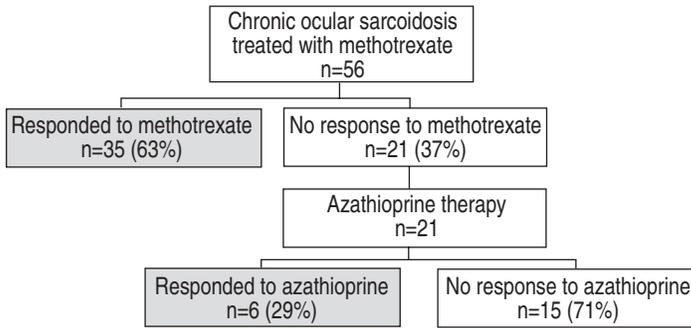| Manifestation	Number
Total patients	18
Anterior uveitis	16
Posterior uveitis	5
Pars planitis	7
Vitreous	7
Retinal vasculitis	3
Cystoid macular oedema	2
Optic neuritis	2

Adapted from BAUGHMAN et al. [41].

Fig. 15. – Clinical outcome of 56 patients with chronic ocular sarcoidosis treated with methotrexate. Of the original group, 63% responded to methotrexate alone. All patients who did not respond to methotrexate were then treated for ≥6 months with azathioprine. Only six out of the 21 patients responded to azathioprine as a single agent [73].

but still had active disease. There was no difference in the response rate between the etanercept and placebo groups [41]. In a study of chronic uveitis of all causes, FOSTER *et al.* [76] placed patients on either etanercept or placebo and then withdrew the methotrexate. The rate of relapse was the same in the etanercept and placebo group. Others have noted that uveitis can occur while patients are receiving etanercept [77].

Infliximab is a monoclonal antibody directed against TNF. It has been reported as useful in treating chronic uveitis in patients with Crohn's disease, rheumatoid arthritis, Behcet's disease and idiopathic uveitis [77–80]. In a study of seven cases of chronic ocular sarcoidosis, all responded to infliximab [80]. This latter study included three patients who had not responded to etanercept. Figure 13b and c are photographs from another patient who received infliximab.

Figure 16 shows the visual outcome of 129 patients with intraocular involvements. The outcome was generally favourable, but 7.3% of eyes resulted in visual deterioration with visual acuity of <0.1 after 5 yrs [15]. In another study, 17 out of 106 eyes (16%) had a visual acuity of <0.1 [81]. The major causes of visual deterioration were a history of
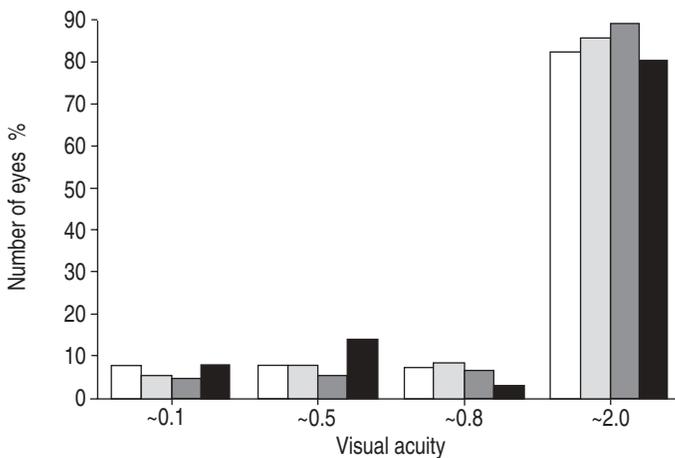

Fig. 16. – Visual outcome of 129 sarcoidosis patients with intraocular involvements at various intervals. The outcome was generally favourable but 7.3% of eyes resulted in visual acuity of <0.1 after 5 yrs. □: initial; ▨: 1 yr; ▦: <5 yrs; ■: >5 yrs. Adapted from OHARA *et al.* [15].

glaucoma, uncontrollable glaucoma during the course and treatment, cataract, vitreous opacities, and macular degeneration due to cystoid macular oedema. Surgical treatment can prevent blindness due to cataract. A preliminary report demonstrated that the vitreous opacities and cystoid macular oedema were surgically treated successfully by vitrectomy [82]. Vitrectomy is also used for proliferative vitreoretinopathy, and the mechanisms and effectiveness of this surgical approach in long-lasting sarcoidosis may be further elucidated.

Conclusion

Ocular disease is an important manifestation of sarcoidosis. While the incidence varies among different sarcoidosis groups, all patients should have a specific ocular examination [62]. Untreated ocular sarcoidosis can lead to cataracts, glaucoma, and even blindness. Therapy is usually successful. The use of the cytotoxic and anti-cytokine therapies is still under investigation. However, they hold great promise in reducing the amount of CS used for chronic ocular sarcoidosis.

Summary

Ocular involvement is seen in a significant number of patients with sarcoidosis. Involvement is more common in Japanese patients, where over half the sarcoidosis patients have ocular disease. In Europe, up to one-third of patients may be affected. Since eye disease may be silent, a detailed examination of the eye is strongly recommended on all sarcoidosis patients. The most common ocular manifestation is uveitis, but any portion of the eye may be affected.

In some cases, inflammation can be controlled by local therapy usually topical steroids. When systemic therapy is needed, corticosteroids are usually effective. However, the ocular toxicity of corticosteroids includes glaucoma and cataract formation. For chronic ocular disease, there has been interest in use of methotrexate and other cytotoxic agents.

Keywords: Corticosteroids, diagnosis, eye, lacrimal gland, ocular, sarcoidosis, treatment, uveitis.

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