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Review

Sarcoidosis and uveitis

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ABSTRACT

Uveitis is a frequent (20–50%) and early feature of sarcoidosis. Typical sarcoid uveitis presents with mutton-fat keratic precipitates, iris nodules, and anterior and posterior synechiae. Posterior involvement includes vitreitis, vasculitis, and choroidal lesions. Cystoid macular edema is the most important and sight-threatening consequence. Histologic proof from a biopsy is the gold standard for the diagnosis of ocular sarcoidosis. An international workshop has recently established diagnostic criteria for sarcoidosis uveitis when biopsy is unavailable or negative: these are based on a combination of ophthalmological findings and laboratory tests. The value of recent techniques, such as PET-scan and endoscopic ultrasound-guided, fine-needle aspiration of intrathoracic nodes needs to be assessed in future studies. Corticosteroids are the mainstay treatment for sarcoidosis. Systemic corticosteroids are indicated when uveitis does not respond to topical corticosteroids or when there is bilateral posterior involvement, especially macular edema and occlusive vasculitis. In up to 15% of cases, additional immunosuppression is used, including methotrexate, azathioprine, and mycophenolate mofetil. Infliximab and adalimumab have been recently proposed for the treatment of refractory or sight-threatening systemic sarcoidosis.

Contents

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1. Introduction

Sarcoidosis is a systemic inflammatory disorder of unknown etiology that is characterized, pathologically, by non-caseating epithelioid-cell granulomas that primarily affect the lungs and lymphatics, and, clinically, by its variable manifestations and disease course [1].

Its incidence is estimated at between 15.3 and 21.7/100,000 according to gender and which series [2,3]. The estimated prevalence varies from 1 to 40 cases per 100,000 individuals, with a particular proclivity for adults aged <40 years. The lifetime incidence is higher in women (1.3%) than in men (1%), and higher in Blacks (2.4%) than in Caucasians (0.8%). The female/male ratio is between 1.2 and 1.5/1 [2,4–6]. About 70% of cases occur in those aged 25–40 years at presentation [2,5,7] whereas 30% are aged >50 years [4,8]. The clinical presentation of sarcoidosis depends on epidemiological factors such as age, gender and race, the duration of the disease, and the anatomical sites involved [1,4,9,10]. Asymptomatic presentations, erythema nodosum, and hypercalcemia are more frequent in Europeans, while symptomatic and multivisceral manifestations are more frequent in African-Americans. Overall, sarcoidosis is mostly revealed by the following symptoms: (i) respiratory, a persistent dry cough in ~30% of cases, (ii) extrathoracic localizations, mainly peripheral lymph nodes, eyes, or skin, (iii) constitutional symptoms, such as fatigue (27%), weight loss (28%), fever (10–17%) or night sweats, and (iv) erythema nodosum (3–44%). The incidental discovery of sarcoidosis on a chest X-ray in asymptomatic patients is common (8–60%).

About 30–60% of patients with sarcoidosis develop ophthalmic changes. Ocular sarcoidosis may develop in the absence of any apparent systemic involvement or may be the main site of the disease without significant clinical disease elsewhere. All ocular structures may be involved (Table 1), but uveitis is the most frequent form of ocular manifestation and may affect up to 20–30% of sarcoidosis patients [11].

The diagnostic criteria for sarcoidosis-related uveitis have been better defined recently and the therapeutic strategies have benefited from large cohorts on ocular sarcoidosis and several studies using biological agents. This review on uveitis and sarcoidosis will mainly focus on these two topics.

2. Epidemiology

2.1. Ocular sarcoidosis

The frequency of ocular involvement varies between reports. American and European studies report eye disease in 10–50% of sarcoidosis patients, including extraocular disorders, such as lacrimal-gland enlargement or sicca syndrome [12]. Japanese studies on sarcoidosis, mostly reported by ophthalmologists, only mention eye involvement and found ocular disease in 64–89% of patients. The low rate reported in other series may be due to the lack of thoroughness in looking for ocular disease. In America, ocular sarcoidosis is more prevalent in Blacks than in Caucasians. Relative to Caucasians, African-American patients with sarcoidosis tend to be younger when they first present to the ophthalmologist and have more frequent uveitis and/or adnexal granulomas [13,14]. On the other hand, chronic uveitis more commonly affects Caucasian female patients with late-onset disease. In our experience, sarcoidosis is the leading cause of uveitis in the elderly [15].

2.2. Uveitis

The reported proportion of sarcoidosis in a population with uveitis depends on the patients' characteristics (age, gender, geographic location and ethnic origin), the definition of sarcoidosis, and on the recruitment method (tertiary center or not, uveitis inaugural or not) (Table 2) [16]. Uveitis attributed to sarcoidosis is most common in Japan, where sarcoidosis accounts for ~15% of cases of uveitis [17]. In patients referred to a hospital for the etiologic diagnosis of uveitis, the rate of uveitis due to sarcoidosis ranges from 2 to 14.9% [17–22]. In a French retrospective study, sarcoidosis accounted for 7% of 524 cases of posterior uveitis or panuveitis, seen at a center that specialized in severe uveitis [19]. The recently observed increased rate of uveitis attributed to sarcoidosis may be explained by more sensitive paraclinical investigations, such as chest computed tomography (CT) and/or nuclear imaging [15,23,24].

In retrospective series of (histologically) proven sarcoidosis, symptomatic uveitis affects 20–50% of patients [25–27], with 80% of cases being diagnosed within the first year, and of which 30% have uveitis as a presenting complaint. No specific extraocular manifestation of sarcoidosis has been associated with the development of ocular involvement or uveitis. Two peaks of incidence are reported: the first in those aged 20–30 years, and the second in those aged 50–60 years [12,27]. There is a female predominance with a gender ratio ranging from 1 to 6.5:1 [24–28]. In the ACCESS study (A Case Control Etiologic Study of Sarcoidosis), a prospective study that included 727 patients with (histologically) proven sarcoidosis, 11.8% of patients had ocular manifestations as presenting symptoms [4].

3. Genetics

The availability of high-throughput genotyping and large collaborative clinical networks has facilitated genome-wide scans and candidate-gene studies to identify susceptibility alleles for sarcoidosis [29,30].

Table 1
Involvement of ocular and adnexa in sarcoidosis (except uveitis) [12,107–109].

Location	Description
Lacrimal glands	Kerato-conjunctivitis sicca (15–31%). Enlargement of the glands is less frequent; the diagnosis can be made by biopsy of the lacrimal gland
Orbit	Women aged >50 years. Diffuse orbital inflammation, usually unilateral, can result in ptosis, limitations in movement and diplopia. Ocular nerve palsy can occur from sarcoid involvement of the 3rd, 4th, and 6th cranial nerves
Lid	Granuloma
Conjunctiva	Granuloma, conjunctivitis (6–40%)
Sclera	Scleritis, episcleritis: rare (<3%); diffuse inflammation, plaque or nodule; the diagnosis may be made by biopsy of a scleral nodule
Cornea	Interstitial keratitis (extremely rare)
Optic nerve	1–5% optic neuropathy (++), granuloma, retrobulbar optic neuropathy Predominantly Caucasian females. Frequently accompanied by uveitis and other findings of neuro-sarcoidosis. Patients often have chronic disease and require steroid-sparing alternatives.
Other	Rare: Horner syndrome, tonic pupil and optic-tract involvement