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Title: *When the tip of the iceberg is presented in the orbit.*

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CASE REPORT

A 68-year-old woman with a medical history of colon neoplasia treated with surgery and chemotherapy 4 years earlier with no evidence of disease in subsequent check-ups was attended at the emergency department of our centre due to an inflammation of the left upper eyelid of 1 month of evolution and horizontal binocular diplopia of 4-5 days of evolution. The physical examination highlighted complete ptosis of the left eye, limitation to left supra-elevation of -2 and diplopia in all positions without pain. The conjunctiva was normal coloured and the cornea was transparent. There was no evidence of changes in the eye fundus. In the entire anterior orbit, in front of the orbital rim, painful stony palpation was observed, without fornix masses.

With the diagnostic suspicion of metastasis of malignant neoplasia of the colon, a biopsy was performed. Histologically, the lesion was formed by epithelioid granulomas with a lymphocytic crown without necrosis. Histochemical techniques (PAS, Methenamine Silver, Giemsa, Gram, Warthin Starry and Zihel Neelsen) rule out the presence of fungal, microorganisms, spirochetes and acid-fast bacilli. Given the suspicion of sarcoidosis, serology was requested and the immunosuppressive treatment and the follow-up were started.

Two years later, a left supraclavicular adenopathy appeared and a Fine Needle Aspiration Cytology was performed. The diagnosis made was non-necrotizing granulomatous lymphadenitis. PET revealed orbital uptake and multiple mediastinal lymph nodes. Finally, the patient was diagnosed with sarcoidosis.

DIAGNOSIS: SARCOIDOSIS

COMMENT

It is well known that many different systemic disorders can involve the orbit or its adnexa such as inflammatory, endocrine, hematologic and hematopoietic diseases and disorders of connective tissue and joints [(1)]. In terms of granulomatous inflammatory disease, orbital lesions comprise a huge group of diseases of various etiologies: infection by several bacterial pathogens and a variety of immune-mediated diseases (Wegener's granulomatosis, sarcoidosis, Langerhan's cell histiocytosis, Sjögren's syndrome, Erdheim.Chester disease and xanthogranulomatous disease) that have a common histopathological lesion [(1)]: the granuloma.

Sarcoidosis is a systemic chronic inflammatory disorder [2,3] characterized histopathologically by non-necrotizing granulomas which are composed predominantly of epithelioid histiocytes with scattered giant cells and lymphocytes at the periphery without caseating necrosis [2].

It has a worldwide prevalence (varies from 0.04 to 64 cases per 100.000 inhabitants) with a variable incidence among different geographical regions and certain ethnic groups [3, 4, 5]. (See tables 1 and 2). The age at presentation is usually under 50 years (adults between 20-40 years) [4,6] and affects predominantly woman with a bimodal age distribution (25-29 and 65-69 years) [3].

In spite of unknown etiology, some authors believe that the immune reaction in sarcoidosis is triggered by either infectious agents or exposure to environmental substances [5]. After this exposure macrophages (antigen presenting cells) promotes T cell immune reaction (Th1 cellular immune response) and by secreting certain cytokines and chemokines, the activated macrophages and T cells form granulomas. Moreover, it seems that this immunomodulated response would depend on genetic susceptibility [4, 5]. Family clustering and differences in the incidence between ethnical groups suggest this. Besides, recent genome studies have identified susceptible genes in sarcoidosis [8, 9] (see table3).

The most common affected organs are: lungs and mediastinal lymph nodes, the eye and ocular adnexa, the peripheral lymph nodes, the skin, the central nervous system and the heart [6].

As far as ophthalmologic region is concerned, the incidence of its involvement has been reported as varying from 10% to 80% of cases, depending on the literature [2, 3, 4, 6]. The disease can involve the orbit, lacrimal gland, and the eyeball (anterior and posterior segments) [3,4] (see table 4). Of all the ocular manifestations observed in sarcoidosis the most frequent is uveitis, followed by vitreitis, fundus and choroidal lesions and orbit lesions [3, 6].

If we focus on the orbit, involvement occur in 10% of cases [6] predominantly in old women patients (mean age 55.9 years with a female/male ratio 4:3) [2]. Lacrimal gland is the most common affected orbital site followed by the remaining soft tissue and depending on the tissue injured there is a wide spectrum of clinical presentation being the orbital mass the most frequent [6,7] (see table 5).

Diagnosis of sarcoidosis is based on three major criteria: a compatible clinical laboratory and radiologic context, the finding of non-caseating epithelioid granulomas in one or more tissue samples and the exclusion of alternative causes of granulomatous disease (10). This could be challenging because half of all ocular sarcoidosis involvement occurs in patients who were not previously given the diagnosis of sarcoidosis and leads to find out the diagnosis of systemic sarcoidosis (2). On the one hand, in patients with unknown systemic sarcoidosis affection and with a clinical presentation of orbital mass a diagnostic biopsy performed from the mass is usually done and can confirm the presence of granulomas. At this point, the differential diagnosis is established with entities that present with orbital granulomatous inflammation, including: lipogranulomas, pseudotumor, Wegener granulomatosis, tuberculosis, syphilis, fungal infections, parasites, panophthalmitis and sarcoidosis (4).

To rule them out, histochemical stains can be of great help. Moreover, a systematic search for sarcoidosis affection in other sites should be carried out with the aid of ancillary tests: chest X-ray or CT scan to see lung and mediastinal involvement, elevated angiotensin converting enzyme (ACE) in serum and abnormal calcium metabolism (hypercalcemia and hypercalcalciuria). Since sarcoidosis involves the lungs in 85-95% of patients, transbronchial lung biopsy or transbronchial needle aspiration of mediastinal lymph nodes increases the diagnostic yield to nearly 20 and 90% respectively and reduces the need of mediastinoscopy for the diagnosis (5). On the other hand, in patients with a known diagnosis of systemic sarcoidosis and a palpable mass in the orbit, the use of diagnostic biopsy is recommended due to the increased risk of developing malignant tumors (6) which is important to rule out.

As far as treatment is concerned, the management of patients with orbital and adnexal sarcoidosis is made with biopsy, observation, intralesional, systemic or a combination of steroid therapy depending on the severity of the local and systemic disease. If the patient doesn't have active systemic sarcoidosis and the orbital lesion is asymptomatic, some groups perform a biopsy with debulking and then observed the patient because most of them, show regression of the disease or remind stable. If the patient has active systemic disease, the orbital lesion is symptomatic or both, the same groups recommend treatment with corticosteroids, either intralesional or systemically. Complete or partial responses are achieved in the vast majority of cases (6).

The prognosis for systemic and ocular sarcoidosis is usually good. Demirci H. reported in his series that systemic sarcoidosis developed in 8%, of patients with only orbital and adnexal sarcoidosis at presentation, in 5 years of follow up. For this reason, he recommends a long-term systemic follow-up annually by an internist or pulmonologist in those patients (6). On the contrary, regarding the prevalence of ocular involvement in systemic sarcoidosis, the American Thoracic Society in its clinical practice guideline suggest that patients with sarcoidosis who do not have ocular symptoms should undergo screening for ocular sarcoidosis by routine eye examination because most of the treated patients had improvement or stabilization of their visual acuity (10).

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ANNEXES:

Table 1: Prevalence of sarcoidosis by geographic region (3)

Region	Prevalence per 100.000 inhabitants
Finland	100
Sweden	50
Denmark	50
United States (black)	50
France	20
Latin America	10
Asia	10
Eastern Europe	10

Table 2: Prevalence of sarcoidosis among different ethnic groups (5)

Ethnic group	Prevalence per 100.000 inhabitants
African Americans	35-80
Northen Europeans	15-20
European Americans	3-10
Southern Europeans	1-5
Japanese	1-2

Table 3: Genes associated with sarcoidosis and its expression depending on ethnical groups (8, 9)

Gene name	Race
HLA-DR1	British, Dutch, japanese
CARD15 (NOD2)	White (English)
BTNL2	German, Caribean, Danish, Dutch
ANXA11	German, Czech
CCL24, STYXL1-SRRM3, C1orf141-IL23R	Japanese
C10orf67, RAB23, OS9, CCDC88B, NOTCH4, and XAF1	European descent, African-Americans
SH2B3-ATXN2, IL12B, NFKB1-MANBA, and FAM117B	European descent, not African-Americans

Table 4: Involvement of the eye and ocular adnexa in sarcoidosis (3, 4)

Region	**Structure**	**Characteristic affection**
Orbit	Orbit soft tissue	Orbital masses
	Lacrimal gland	Hypertrophy, ptosis, swelling of upper eyelid, dry eye symptoms
Adnexa	Lids	Nodular lesions, granuloma, ptosis
Eyeball	Conjunctiva	Nodules, conjunctivitis, symblepharon, cicatricial entropion, dry eye syndrome
	Sclera	Scleritis, episcleritis
	Cornea	Interstitial keratitis
	Uveal tract	Anterior, intermediate, posterior uveitis, panuveitis
	Viterous	Vitreitis
	Retina	Periphlebitis, retinitis, macular edema
Optic nerve		Papillitis, papilledema, granuloma, retrobulbar optic neuropathy

Table 5. Clinical presentation of orbital sarcoidosis involvment (7)

Symptoms and signs	**%**
Palpable mass	65
Swelling	55
Ptosis	45
Globe displacement, proptosis, redness,	25
Pain, vision loss, tearing	15
Blurring	10
Diplopia	5