El desafío de la Enfermedad Granulomatosa Ocular

Ocular Granulomatous Disease's Challenge

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ABSTRACT

Sarcoidosis and tuberculosis are granulomatous systemic diseases, with many clinical features in common, namely their ocular involvement.

We describe a case of a 50-year-old woman that presented with bilateral parotiditis, sudden painless vision loss, weight loss and anorexia for 2 months, with history of contact with tuberculosis within the past 3 years.
Ophthalmological evaluation revealed bilateral iridocyclitis with granulomatous precipitates, retinal vasculitis and optic disc edema. Angiotensin-converting enzyme (ACE) and lysozyme levels were increased, antinuclear antibodies (ANA) and interferon gamma release assay (IGRA) were positive. Chest computerized tomography (CT) revealed bilateral hilar lymphadenopathy and the bronchoalveolar lavage (BAL) presented lymphocytosis (65%), ratio CD4/CD8 3,14 and was negative for *Mycobacterium tuberculosis*.

Treatment with corticosteroids and antituberculous drugs was initiated, with clinical improvement. The possibility of ocular sarcoidosis, the consequent need to implement imunossupressors, and the incapacity of excluding tuberculosis, leads to treatment with antituberculous drugs. Relying on diagnostic and treatment challenges, is crucial that these patients have a multidisciplinary management.

Keyword: Ocular sarcoidosis, ocular tuberculosis, ocular inflammation, granulomatous disease.

RESUMEN

Sarcoidosis y Tuberculosis son enfermedades sistémicas granulomatosas con muchas características clínicas en común, particularmente la afectación ocular.

Describimos el caso de una mujer de 50 años que presenta parotiditis bilateral, pérdida de campo visual lateral con ausencia de dolor, pérdida de peso y anorexia durante 2 meses y antecedentes de contacto con tuberculosis durante los últimos 3 años.

Evaluaciones oftalmológicas revelaron iridociclitis bilateral con precipitados granulomatosos, vasculitis retiniana y edema del disco óptico. Enzima de conversión de la angiotensina (ECA) y los niveles de lisozima aumentaron, anticuerpos antinucleares (AAN) y ensayo de liberación de interferón gamma (ELIG) fueron positivos. Tomografía computarizada de tórax (TC) reveló adenopatías hiliares bilaterales y el lavado bronco alveolar (LBA) presentó linfocitosis (65%), la relación CD4/CD8 3,14 y fue negativa para Tuberculosis micobacteriana.

Se inició tratamiento con corticoides y antituberculosos con mejoría clínica. La posibilidad de sarcoidosis ocular, la consiguiente necesidad de implantar inmunosupresores y la imposibilidad de excluir la tuberculosis, lleva a tratamiento con medicamentos antituberculosos. Confiar en los desafíos de diagnóstico y tratamiento es crucial para que estos pacientes tengan un manejo multidisciplinario.

Palabras clave: Sarcoidosis ocular, tuberculosis ocular, inflamación ocular, enfermedad granulomatosa.

INTRODUCTION

Sarcoidosis is a systemic inflammatory multiorganic disease characterized by the presence of non-caseating granulomas[1–3]. Although the physiopatological mechanism is still unknown, it appears to result from a complex immunological process mediated by Th1 and Th17 cellular response[2,4]. It can affect people of any age, gender or ethnic group, however it is more common in young women, between 20-40's and in afro-americans[2,3]. Although lung involvement is the most common presentation (up to 90% of the cases), it can affect any organ or system, with eye involvement being reported in about 60% of patients[2,4]. Parotid involvement can occur in 5–10% of patients, and when is present, it is important to exclude Heerfordt-Waldestrom syndrome, an acute form of sarcoidosis in which enlargement of the parotid or salivary glands, facial nerve paralysis and anterior uveitis are present[4]. Ocular Sarcoidosis (OS) can be the first, and even the only, manifestation of the disease and it can affect any part of the ocular structure, being the granulomatous anterior uveitis the most frequent presentation[2]. It may be acute, often presenting with ocular pain, photophobia and hyperaemia, or chronic with progressive visual loss[4]. Typically, the diagnosis of sarcoidosis involves the identification of non-caseating granulomas in biopsied tissue, however, the biopsy of intraocular tissue carries great risks so, the International Workshop on Ocular Sarcoidosis (IWOS) proposed international criteria for the diagnosis of OS. The criteria combine intraocular clinical signs and systemic non-invasing investigation results classifying the diagnosis of OS in definite, presumed or probable[1] (Box 1). Other causes of granulomatous uveitis must be excluded. The treatment of OS aims to control the inflammatory activity and includes systemic immunosuppressive drugs, like corticosteroids, azathioprine, methotrexate or cyclosporine, and topical agents.[2]

Tuberculosis (TB) is a systemic chronic infection caused by *Mycobacterium tuberculosis*, characterized by the formation of granulomas[5,6]. The World's Health Organization estimates that about a quarter of the world's population is infected with *M. tuberculosis*, being the leading cause of death from a single infection agent worldwide[7]. It affects mainly adults (90%) and there are more cases among men than women. In the majority of cases, the primary infection is in the lungs, but it may spread to distant sites, mainly via lymphatic or haematogenous

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Cómo citar este artículo: Abreu C, Ferreira M, Marques J, Reis A, Pina S, Martos F. Ocular Granulomatous Disease's Challenge. Galicia Clin 2024; 85-1: 28-31.
Recibido: 10/01/2023 ; Aceptado: 30/01/2023 // https://doi.org/10.22546/72/4055

Box 1. Revised International Workshop on Ocular Sarcoidosis (IWOS) criteria for the diagnosis of ocular sarcoidosis (OS) (2017)

I. Other causes of granulomatous uveitis must be ruled out.
II. Intraocular clinical signs suggestive of OS.
1. Mutton-fat keratic precipitates (large and small) and/or iris nodules at pupillary margin (Koeppe) or in stroma (Busacca).
2. Trabecular meshwork nodules and/or tent-shaped peripheral anterior synechia.
3. Snowballs/string of pearls vitreous opacities.
4. Multiple chorioretinal peripheral lesions (active and atrophic).
5. Nodular and/or segmental periphlebitis (±candle wax drippings) and/or macroaneurysm in an inflamed eye.
6. Optic disc nodule(s)/granuloma(s) and/or solitary choroidal nodule.
7. Bilaterality (assessed by ophthalmological examination including ocular imaging showing subclinical inflammation).

III. Systemic investigation results in suspected OS.
1. Bilateral hilar lymphadenopathy (BHL) by chest X-ray and/or chest computed CT scan.
2. Negative tuberculin test or interferon-gamma releasing assays.
3. Elevated serum ACE.
4. Elevated serum lysozyme.
5. Elevated CD4/CD8 ratio (>3.5) in bronchoalveolar lavage fluid.
6. Abnormal accumulation of gallium-67 scintigraphy or 18F-fluorodeoxyglucose positron emission tomography imaging.
7. Lymphopenia.
8. Parenchymal lung changes consistent with sarcoidosis, as determinied by pulmonologists or radiologists.

IV. Diagnostic criteria.
- Definite OS: diagnosis supported by biopsy with compatible uveitis.
- Presumed OS: diagnosis not supported by biopsy, but BHL present with two intraocular signs.
- Probable OS: diagnosis not supported by biopsy and BHL absent, but three intraocular signs and two systemic investigations selected from two to eight are present.

Box 2. IOTB diagnosis proposed classification

Confirmed IOTB (both 1 and 2)
1. At least one clinical sign suggestive of IOTB;
2. Microbiological confirmation of *Mycobacterium tuberculosis* (MTB) from ocular fluids/tissues.

Probable IOTB (1, 2, and 3 together)
1. At least one clinical sign suggestive of IOTB (and other etiologies excluded)
2. Evidence of chest X-ray consistent with TB infection or clinical evidence of extraocular TB or microbiological confirmation from sputum or extraocular sites
3. At least one of the following:
   a. Documented exposure to TB
   b. Immunological evidence of TB infection

Possible IOTB (1, 2, and 3 together) (or 1 and 4)
1. At least one clinical sign suggestive of IOTB (and other etiologies excluded)
2. Chest X-ray not consistent with TB Infection and no clinical evidence of extraocular TB
3. At least one of the following:
   a. Documented exposure to TB
   b. Immunological evidence of TB infection
4. Evidence of chest X-ray consistent with TBection or clinical evidence of extraocular TB but none of the characteristics given in 3

rout[5,6]. The extrapulmonary manifestations occur in about 16 to 27% and are more common in patients over 40 years old, women and HIV co-infection[6]. Ocular involvement is common and it seems to be more important in endemic areas, reaching up to 10% in these places[8]. Parotid involvement is extremely rare, even in countries in which tuberculosis is endemic. Intraocular tuberculosis (IOTB) can occur as a primary infection (when the eye is the primmary entry site), secondary to an haematogenous spread or as a hypersensitivity reaction to *M. tuberculosis* antigens from a distant site of infection, in this case, causing inflammation of the eye despite the absence of the bacteria *in locus*[5,6,8]. The most common ocular manifestation of TB is the uveitis, typically granulomatous, and more commonly posterior (in 35-42% of the cases), but it also can appear as anterior (12-36%) or panuveitis (11-20%).[6,8]

Like sarcoidosis, the diagnosis of IOTB is challenging, as the gold standard is the demonstration of *M. tuberculosis* in the ocular tissue, which is extremely rare, and it is not present in the hypersensitivity reaction to *M. tuberculosis* antigens from a distant infection[5,8,9]. Gupta *et al.* suggested a IOTB diagnosis criteria that classifies the disease in confirmed, probable or possible IOTB[5] (Box 2). The treatment of ocular tuberculosis uses the same quadruple-drug regimen used in the pulmonary TB (isoniazid, rifampin, pyrazinamide and ethambutol) for 2 months, followed by dual therapy (isoniazid and rifampin) for 4 to 10 months.[8,9]

Being both systemic granulomatous diseases, affecting the eye with similar manifestations, and having major difficulties in the diagnosis and management of these patients, we present a case in which both diseases were part of the differential diagnosis.

CASE REPORT

A 50-year-old woman, born in Angola and living in Portugal for 30 years, presented in the emergency department referring a fifteen-day history of pain and swelling in the parotid zone, bilaterally and painless, and blurred vision in the days before the admission. She also stated weight loss of approximately 10 kilograms and anorexia for about 2 months, with no other symptoms. Her past medical history was significant for arterial hypertension, and exposure to pulmonary tuberculosis 3 years before.

Physical examination at presentation showed bilateral parotid edema with palpable painful, stiff and adherent nodules. The parotid ultrasound was compatible with bilateral parotitis. In the ophthalmological exam, her best corrected visual acuity was 10/10, and presented bilateral anterior uveitis with granulomatous precipitates and tortuosity of retinal vessels. Fluorescein angiography (FA) revealed retinal segmental venous vasculitis and optic disc edema, which was compatible with papilitis, and the indocyanine green angiography showed stromal choroiditis, later confirmed by the optical coherence tomography (OCT) (Figure 1). Initial basic work-up with complete blood-count (CBC), C-reactive protein, erythrocyte sedimentation rate (ESR) and urinalysis were within normal limits. The patient was treated with topical tropicamide 10mg/mL, bromofenac 0,5mg/mL and dexamethasone 1mg/mL and referred to the Ocular Inflammation clinic (with the internist and ophtalmologist).

Figure 1

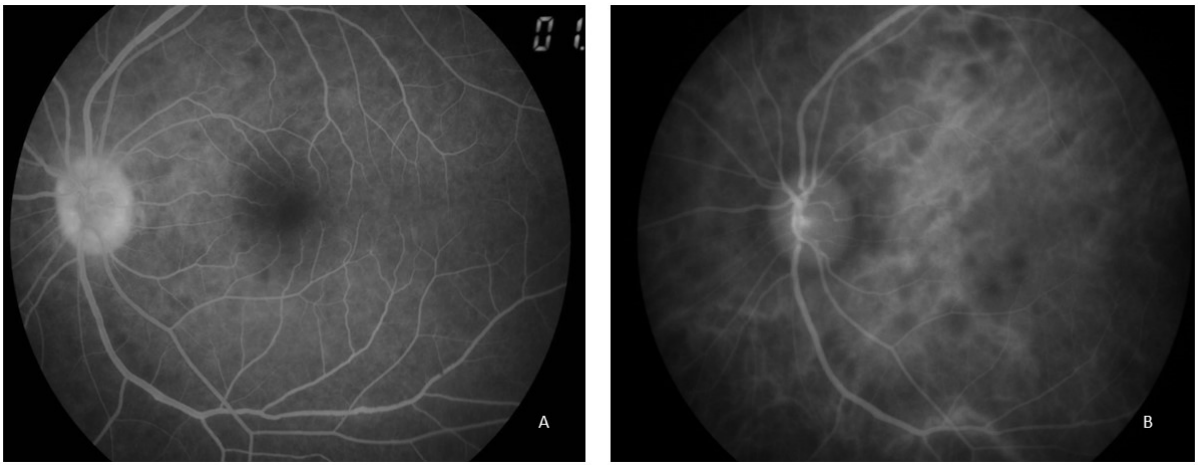


Figure 2

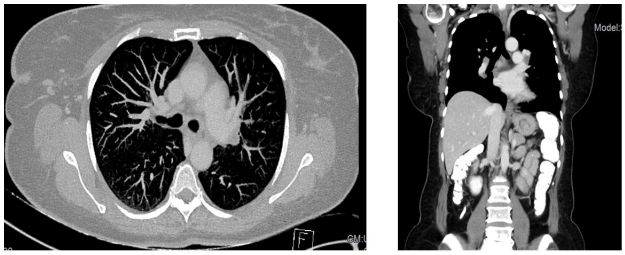
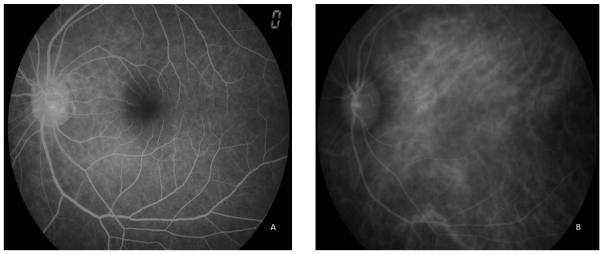


Figure 3



After three weeks, the patient presented an improvement of the opthalmological manifestations , no longer presenting parotid swelling, however maintaining the granulomatous precipitates and the retinal vasculitis. The laboratory examination showed increased angiotensin-converting enzyme (ACE) levels (98,6 UI/L, reference range 23-57 UI/L) and lysozyme levels (21,5 mg/L, reference range 9.6-17.1 mg/L), as well as positive antinuclear antibodies (ANA) (with a titer>1280) and positive interferon gamma release assay (IGRA). The remaining study was unremarkable, including negative infectious serologies, anti-SSA and SSB antibodies, rheumatoid factor as well as the rest of the autoimmunity tested. Due to the constitutional symptoms, a chest, abdominal and pelvic computerized tomography (CT) was performed, revealing bilateral hilar lymphadenopathy without pulmonary parenchymal abnormalities or any other findings (Figure 2).

Admitting the possible diagnosis of ocular sarcoidosis, treatment with prednisone was initiated and, not being able to exclude an active tuberculosis infection, based on the exposure and presentation, we started antituberculous treatment.

The patient was submitted to a bronchofibroscopy, without any macroscopic abnormalities and a biopsy of an infracarinal node was perfomed, without granulomas or malignant cells. The bronchoalveolar lavage (BAL) revealed lymphocytosis (65%) with a ratio CD4/CD8 of 3,14. The polymerase chain reaction (PCR) detection for *Mycobacterium tuberculosis* was negative, as well as the cultures on samples from BAL, blood and bronchial aspirate.

The patient was asymptomatic after 9 months of antituberculous drugs and with immunomodulatory treatment with prednisolone and methotrexate as a steroid-sparing treatment with weight gain and with no parotid alterations. The ophthalmological observation showed an improvement of the retinal vasculitis as well as of the optic disc edema (Figure 3).

DISCUSSION AND CONCLUSION

We have presented a case of a 50-year-old women with bilateral parotiditis, constitutional symptoms and granulomatous panuveitis with retinal venous vasculitis and. The differential diagnosis is broad, however, according to the presented case, we can consider two main causes of granulomatous uveitis: sarcoidosis or tuberculosis.

In this case, the presence of bilateral hilar lymphadenopathy in the chest CT, the high levels of ACE and lysozyme, as well as the lymphocytosis in the BAL with a ratio CD4/CD8 of 3,14 (<4), point to a sarcoidosis diagnosis. According to the IWOS, the presence of bilateral hilar lymphadenopathy and 2 or more intraocular clinical signs (considering segmental periphlebitis, optic disc granulomas and bilaterality), we can assume a presumed ocular sarcoidosis.

However, the history of exposure to TB in the past, as well as the positive IGRA cannot exclude a tuberculosis infection, and, if we apply the IOTB classification proposed by Gupta *et al.*, we can still consider a possible IOTB, since the patient presents one clinical sign suggestive of IOTB (the granulomas), with an x-ray not consistent with TB, but having a documented exposure to TB.

Although the most probable diagnosis is an ocular sarcoidosis, the exposure to TB, the positive IGRA and the constitutional symptoms

could not rule out the presence of tuberculosis, so the patient started antituberculous drugs.

The difficulties underlying the diagnosis of both diseases, relying on different proposed criteria, and the need to define the most probable one, turns the management of these patients a major challenge. The Ocular Inflammation Clinic, shared between Ophthalmology and Internal Medicine, allows not only a multidisciplinary evaluation and management of the disease, but also of the therapy and its complications, which carries great advantages to these patients.

CONFLICT OF INTEREST
The authors declare that they have no conflict of interests.

SOURCE OF FUNDING
This research had no funding sources.

ETHICAL ASPECTS
All participants submitted a consent form to be included in this study.

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