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Multifocal Choroiditis of Presumed Tuberculous Origin: Report of a Case

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Abstract **Case Report**

Multifocal choroiditis is a rare affection of unknown etiology, and tuberculosis is one of its numerous causes. Our study highlights the need to look for tuberculosis in case of multifocal choroiditis, even without clinical history or signs suggestive of pulmonary tuberculosis. We present the case of an immunocompetent patient with isolated multifocal choroiditis, which strongly suggests tuberculosis. The positive diagnosis was made based on the positivity of the QuantiFERON-TB® Gold immunoassay, given the low sensitivity and specificity of conventional diagnostic methods. Further tests revealed a positive tuberculin skin test in this patient. The plasma interferon assay represents a valuable new tool in diagnosing primary ocular tuberculosis. Although the disease is presumed to be autoimmune, our patient responded well to a carefully managed nine-month course of anti-tuberculosis and anti-inflammatory treatment.

Keywords: Choroiditis; ocular tuberculosis; quantiferon; multifocal.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis (MT) [1]. It has become a major public health issue over the past fifteen years. While ocular TB is rare, it can impact any part of the eye, although choroidal involvement is uncommon [2-4]. Diagnosing isolated ocular tuberculosis can be challenging due to the difficulty of accessing sample sites. A definite diagnosis typically requires the observation or culture of the tubercle bacillus from the affected tissue or the amplification of its DNA from the tissue. In this case, we present a patient who was immunocompetent and showed signs of choroiditis strongly suggestive of isolated tuberculosis without systemic involvement. The diagnosis was made using an immunological diagnostic method: the QuantiFERON-TB® Gold test, which measures interferon levels in plasma.

CASE REPORT

This was a 57-year-old male patient, BCG+ vaccinated, chronic smoker, with a history of a father previously treated for pulmonary tuberculosis. For the past four years, our patient has presented with episodes of redness, ocular pain, and gradual visual loss in both eyes. Corrected visual acuity was 3/10 P4 in the right eye (OR) and 2/10 P5 in the left eye (OS), and eye pressure was 14 mmHg in both eyes. Biomicroscopic examination revealed a calm anterior segment on both sides. Fundus examination revealed bilateral vitritis in both eyes, as well as deep, creamy-white chorioretinal foci with blurred contours in the posterior pole of different ages, active on the right rather than scarred on the left (Fig 1). Fluorescein angiography confirmed the multifocal choroidal lesions seen on the fundus, with macular damage in the left eye, raising suspicion of a choroidal neovessel (Figs 2 and 3).

Optical coherence tomography revealed hyper-reflective sub-retinal material associated with exudation related to sub-retinal neovascularization (Fig 4). Viral serologies and syphilis tests were negative.

The tuberculin skin test (TST) was strongly positive at a phlyctenular level of 15 mm, but the search for tuberculosis infection in the lungs (using a chest CT scan and repeated gastric tubes) or urine (by cytobacteriological examination of the urine) was negative. The QuantiFERON-TB® Gold immunoassay, performed before the TST, was positive (negative control: 0.05 IU/ml, antigen: 6.59 IU/ml, mitogen: 5 IU/ml; threshold value for positivity >0.35 IU/ml). The patient was diagnosed with primary ocular tuberculosis, and after consulting the internists, anti-tuberculosis treatment was started (rifampicin, isoniazid, ethambutol,

pyrazinamide). After four months of treatment, we switched to dual therapy with oral corticosteroids for two months. The patient also received three intravitreal anti-VEGF injections one month apart in the left eye.

The evolution was marked by a progressive reduction in vitritis with slow healing of the foci and neovessel. Final visual acuity was 6/10 P2 on the right and 3/10 on the left.

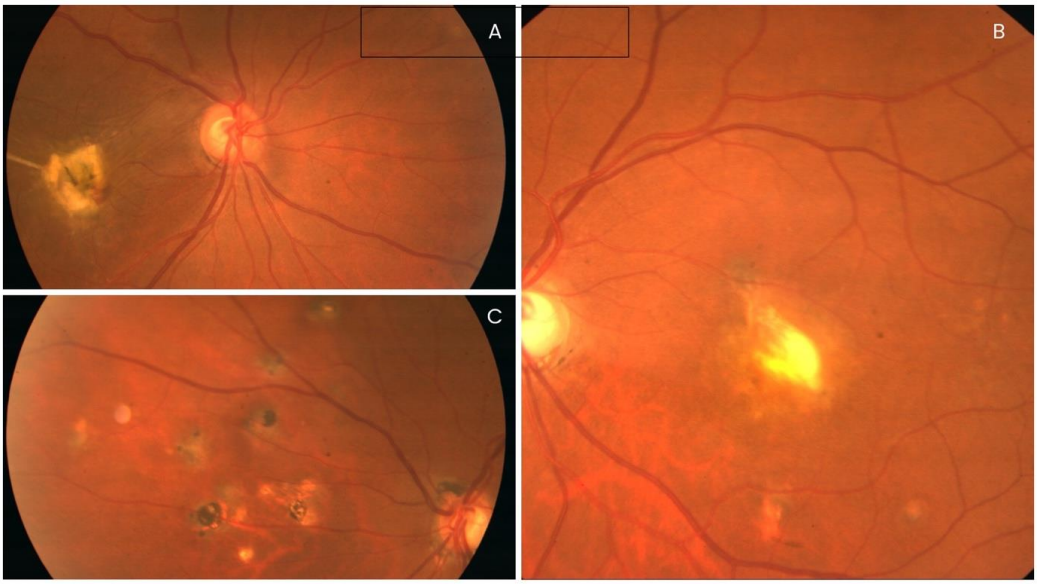

Figure 1: Fundus A: macula of the right eye; B: macula of the left eye; C: periphery of the left eye: deep creamy white chorioretinal foci with blurred contours at the posterior pole of different ages, active on the right rather cicatricial on the left; bilateral macular cicatricial lesions

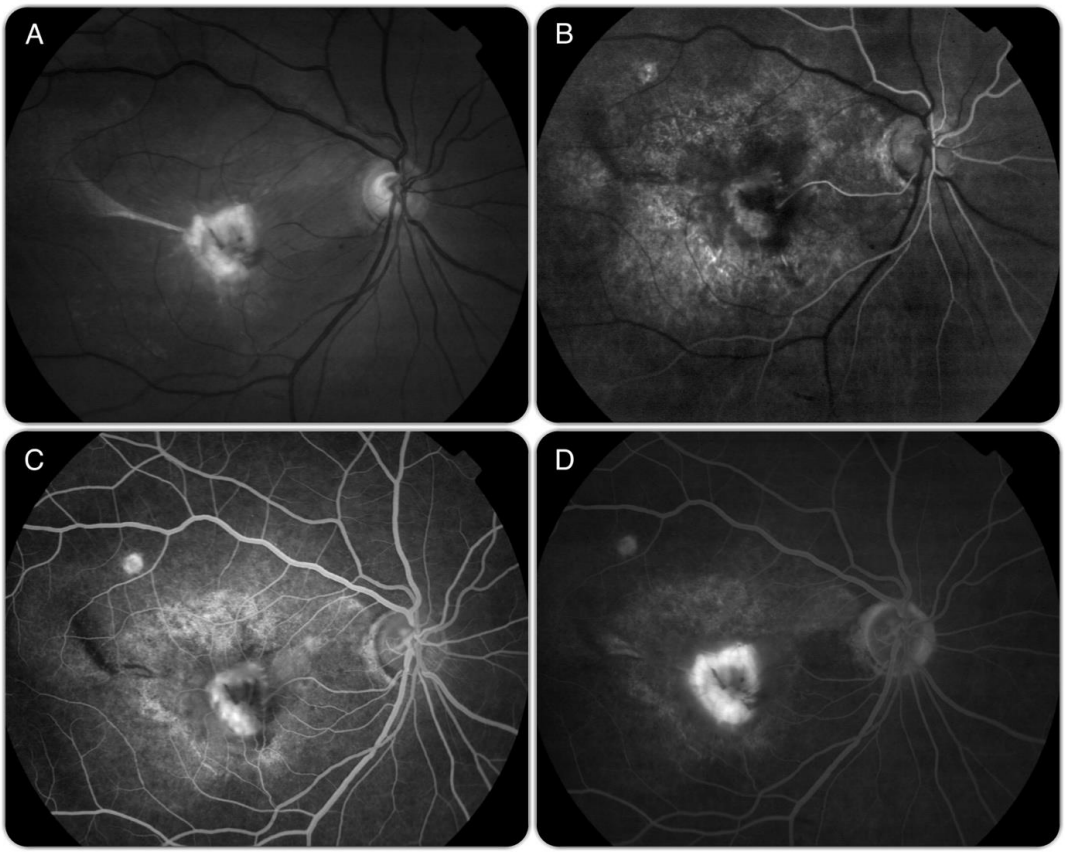

Figure 2: Fluorescein angiography of the right eye: early macular choroidal hyperfluorescence with diffusion and late retention. A: Anerythetic image; B: early time; C: Intermediate time; D: Late time

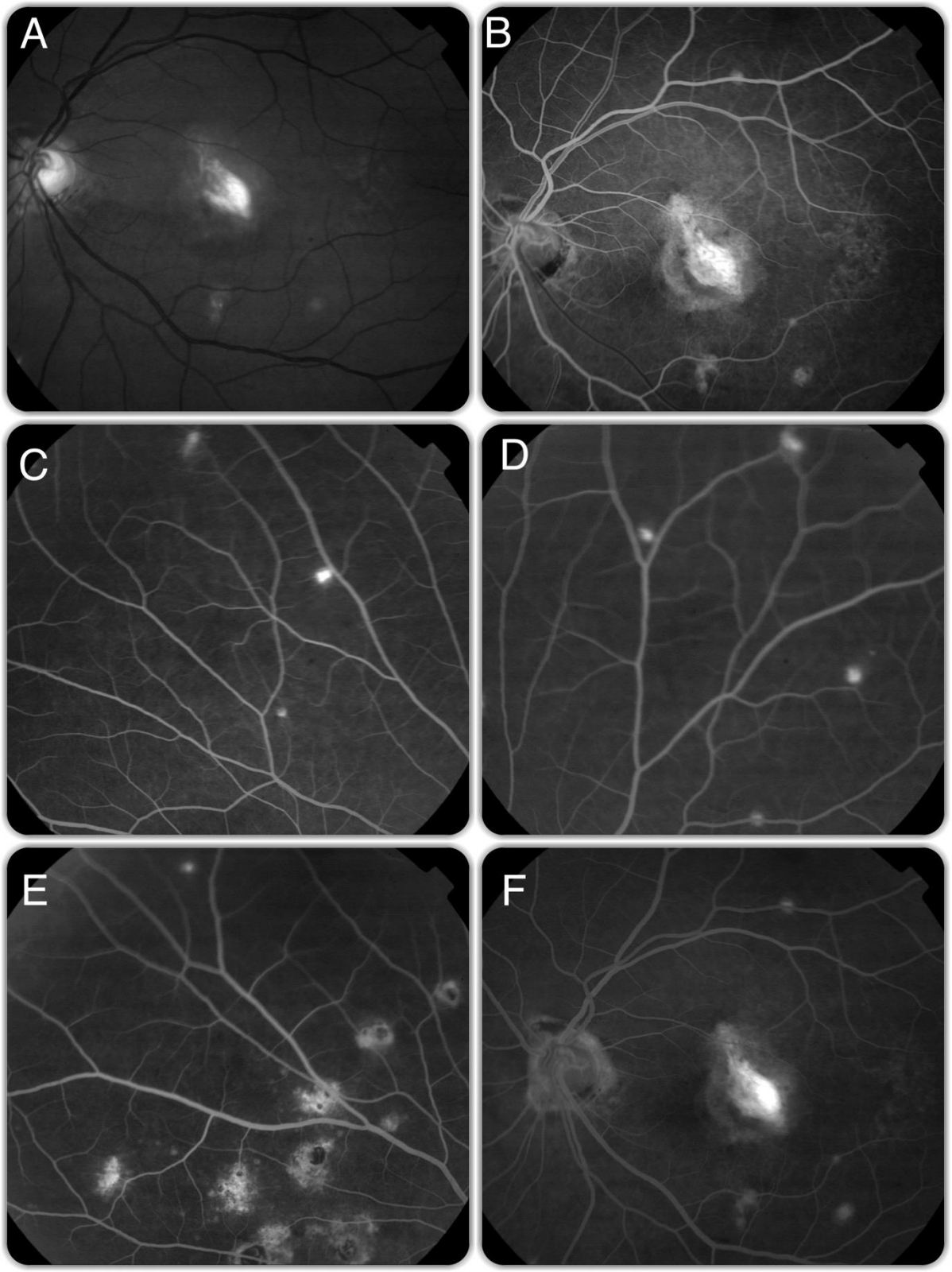

Figure 3: Fluorescein angiography of the left eye: peripheral and macular hyperfluorescence with diffusion and late retention associated with cicatricial lesions. A: anerythetic image; B: early time; C, D, E: Peripheral punctate hyperfluorescence; D: Late time

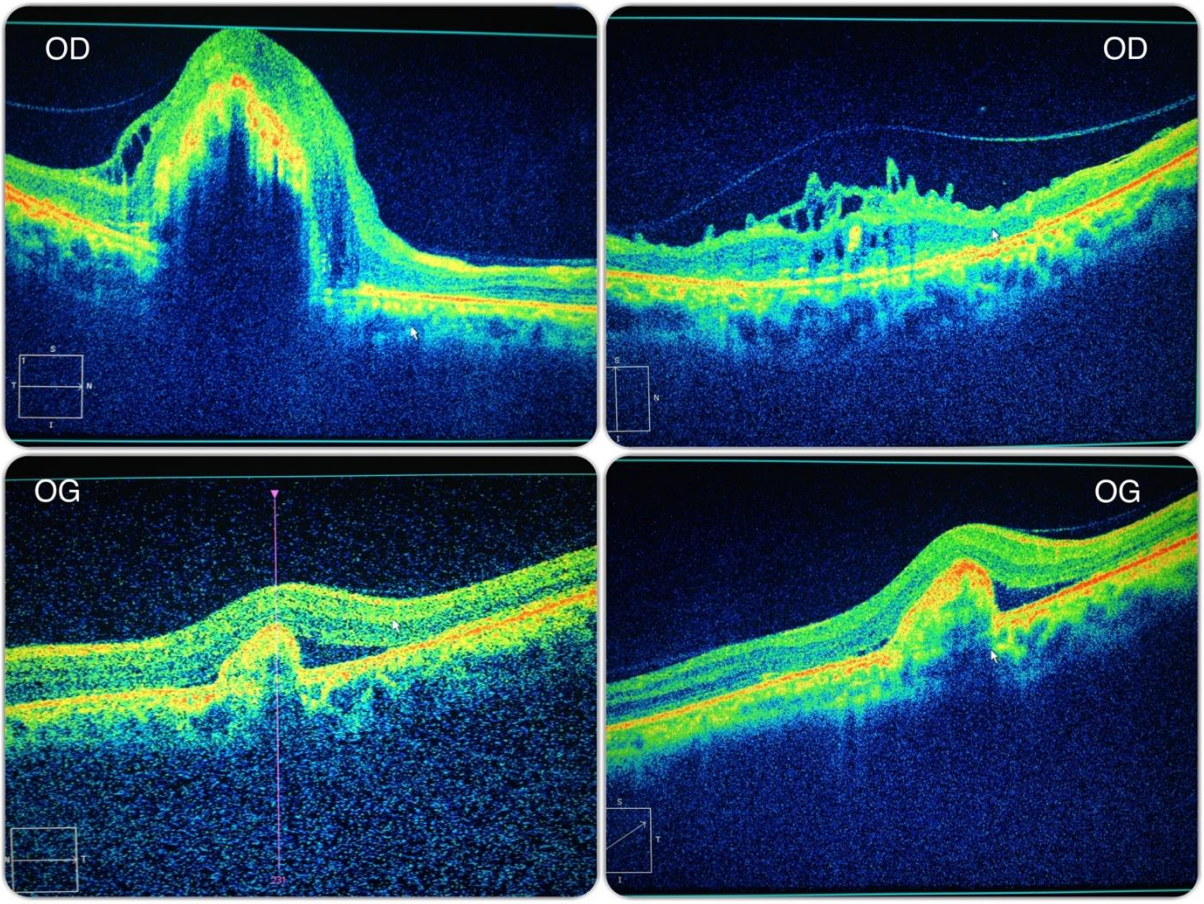

Figure 4: OCT: hyper-reflective subretinal material associated with exudation related to subretinal neovascularization

DISCUSSION

Tuberculosis, an infectious disease with a historical presence, is attributed to TB and stands as a prominent cause of global illness and mortality [5]. Data from the World Health Organization (WHO) reveals that over two billion individuals, approximately one-third of the world's population, are impacted by this condition. Recent findings suggest that 10% of those afflicted exhibit symptomatic manifestations, while 90% harbor latent tuberculosis [6-8].

Tuberculosis mainly affects the lungs, but can also affect other organs, such as the eye. The extrapulmonary localization of tuberculosis reaches 20%, and ocular tuberculosis (OT) ranges from 3.5 to 5.1% [9, 11]. The incidence of OT is increasing in parallel with the rise in new tuberculosis cases each year [12].

Anterior uveitis accounts for 30-50% of presumed ocular tuberculosis, while other types of involvement are choroidal (multifocal choroiditis, choroidal tuberculoma, or pseudo serpiginous choroiditis) or retinal (peri phlebitis) [13, 14]. Patients with tuberculosis presumed choroiditis are mainly from countries where tuberculosis is endemic and who have emigrated from these countries to nonendemic regions or who have a history of contact with active pulmonary tuberculosis. Male preponderance has also been more frequently reported [15].

The described disorders have a definitive histological impact on the pigment epithelium and the choriocapillaris, manifesting as multifocal and recurrent, and the pathophysiological hypothesis of ischemia of the choriocapillaris as the initial damage is discussed by many teams. However, the etiology of this occlusive vasculitis remains unknown [16].

Tubercular choroiditis is distinctly characterized by multifocal choroidal lesions of varying size and shape, which may appear solitary or multiple and are typically unilateral. A large tuberculoma can be found anywhere in the choroid, including the macula, the posterior pole, the equator, or in a juxtapapillary location. These lesions are visualized using fundus autofluorescence. Thus, a considerable inflammatory cellular reaction in the vitreous body or anterior chamber may be present.

Tuberculous multifocal choroiditis is a chronic, progressive inflammatory disease whose complications are often structural involving the posterior pole. When the foveolar and parafoveolar areas are directly affected

by the lesions or when the lesions are complicated by extrafoveal choroidal neovascularization (CNV), which develops in up to 35% of eyes, central visual loss can occur. This neovascularization may lead to retinal and vitreous hemorrhage. Retinal vasculitis or ischemia due to vascular occlusions has also been reported [17].

The clinical presentation has a wide range of possible presentations; chronic posterior uveitis is the most widely recognized sign of intraocular tuberculosis, partially responsive to corticosteroid therapy, and marked by frequent relapses. It is impractical to perform a uveal biopsy for culture and direct histopathological examination to provide definitive proof of ocular infection [18].

The detection of Mycobacterium tuberculosis (MT) in endocular swabs to make a definitive diagnosis of TO is exceptional. It may be done either by direct examination with Ziehl-Neelsen staining or by culture in Löwenstein-Jensen and Middlebrook media to identify the pathogenic strain of MT and produce an antibiogram or by amplification of mycobacterial deoxyribonucleic acid (DNA) by Polymerase Chain Reaction (PCR) [19].

When the infectious site is not easily accessible for sampling, as is the case with isolated ocular tuberculosis, diagnosis is made using the tuberculin TST, which is of poor help in countries with wide vaccination coverage, such as Morocco [20]. This makes the etiological diagnosis often presumptive, and countries with low endemicity are more frequently limited to a positive QuantiFERON® test (QFT) [21, 22]. Moreover, the response to the test anti-tuberculosis treatment (TAT) allows a posteriori to make the diagnosis of presumed tuberculous uveitis. The QuantiFERON®-TB Gold Plus test currently in use is based on antigenic stimulation of CD8+ lymphocytes in addition to CD4+ and enables detection of in vitro production of interferon-gamma (IFN) - the central element in the cell-mediated immune response - by the patient's T lymphocytes (CD4 and CD8) in a blood sample in the presence of two MT-specific antigens.

The threshold value for positivity is 0.35 IU/ml. It is compared with in vitro IFN production in response to a negative control and a positive or mitogenic control. Unlike the TST, the QFT test has the advantage of an objective reading, with a rapid result (obtained in 24 hours) and no need for a second consultation at 72 hours [24].

It does not cause any subsequent anamnestic reaction but may be influenced by previous TSTs. The limitations of this test are the need to process the blood sample within 12 hours of collection, and the impossibility of establishing a differential diagnosis between active and latent tuberculosis infection [25].

The QuantiFERON-TB®-Gold test demonstrates a sensitivity ranging from 70 to 89%, as reported in various studies [26, 27], which is similar to that of the TST, particularly in cases of active tuberculosis. Its specificity, reported to be 96-98% [24, 28], notably surpasses the specificity of the TST. The enhanced specificity of the QuantiFERON-TB®-Gold test, in conjunction with its objectivity and promptness in delivering results, positions it as a compelling diagnostic approach for suspected ocular tuberculosis cases [29], particularly in isolated instances. In our scenario, this test proved instrumental in diagnosing ocular tuberculosis, where the TST yielded inconclusive results.

In total, it is the combination of a cluster of arguments: history of tuberculosis, clinical findings, and paraclinical explorations such as chest radiography, TST positivity, and PCR that allows the diagnosis of TO. A new classification of TO was proposed by Gupta *et al*., in 2015, not including the criterion of good response to TAT, to define patient status at the time of OI management into three categories: confirmed TO, probable TO, and possible TO [30].

Tuberculosis-related multifocal choroiditis is not usually accompanied by signs of active or healed pulmonary tuberculosis on chest X-ray, nor by a history of extrapulmonary tuberculosis [31].

OCT reveals alteration of the outer retina and increased reflectivity of the outer retina and choroid in the areas involved.

The progressive evolution of choroiditis and the apparition of new lesions generally appear slowed by anti-tuberculosis treatment.

Today, the treatment of TO still faces many challenges, as there is no standard treatment regimen or duration of treatment. According to the recommendations of the American Thoracic Society, it should combine Rifampicin, Isoniazid, Ethambutol or Streptomycin, and Pyrazinamid for two months, then dual therapy (Isoniazid-Rifampicin) for four months. In the event of contraindication to Pyrazinamide or resistance to one of the antibiotics, it is replaced by Ethambutol for nine months [32]. The disease is considered immunogenic and responds to corticosteroids (local or systemic) and systemic immunosuppressants, which may be combined depending on the degree of associated inflammation. Corticosteroid therapy must be combined with antibacillary agents.

Naturally, possible resistance and side effects, especially ocular, must be considered during monitoring [33]. This rapid anti-inflammatory treatment may reduce the incidence of CVN. In the meantime, all patients should be made aware of the clinical signs of metamorphopsia, so that they can carry out daily self-

monitoring with Amsler grids for early detection of CVN lesions.

The treatment of tuberculosis remains primarily preventive, through improved living conditions, treatment of patients carrying Koch's bacillus to reduce transmission, and vaccination.

In conclusion, TO has a highly variable presentation and can involve any eye structure, producing a variety of clinical manifestations. Its diagnosis is often difficult, and clinical features must be interpreted judiciously and in collaboration with other subspecialties. Appropriate TAT is essential and can lead to favorable results.

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