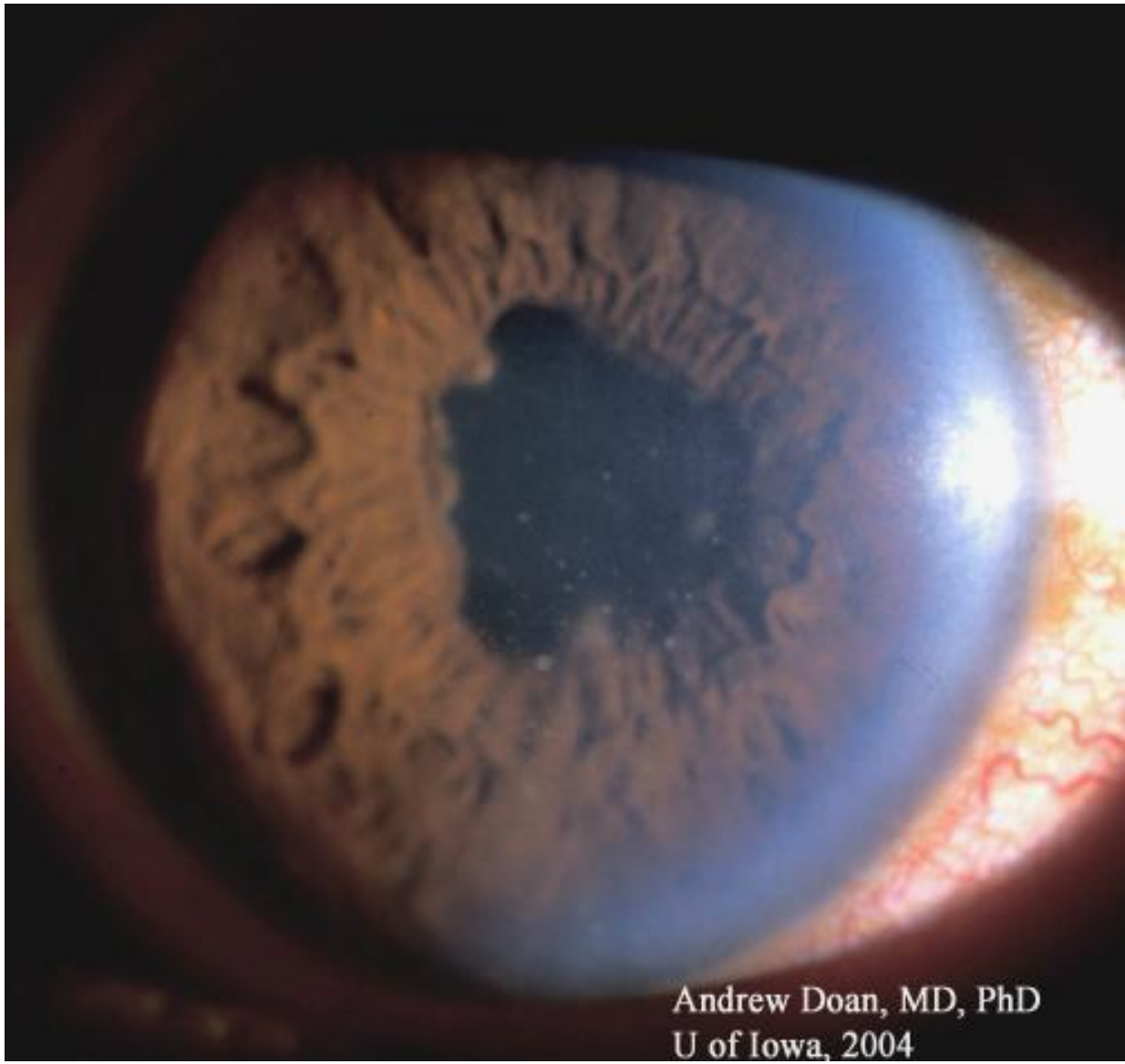
Ocular tuberculosis (Presumptive ocular tuberculosis)



- Overview of Tuberculosis
- Ocular tuberculosis
- Risk factors for developing ocular TB
- Diagnostic criteria for ocular TB
- Treatment
- Case senario

Overview of Tuberculosis

- **Primary TB:**
- involves infection and formation of a granuloma (Ghon complex) within the middle and lower lobes of the lung. However, symptoms are often non-specific and therefore primary infection goes undiagnosed in most cases.
- **Reactivation:** typically secondary to an immunosuppressive event, fever, night sweats, weight loss, and a persistent cough can develop.
- Approximately 15% of TB is characterized as **extra-pulmonary,** with common locations involving the lymph nodes, pleura, and central nervous system (CNS). Another such specific location is the **eyes**.

- **Latent TB infection is defined as TB infection without evidence of active TB disease clinical manifestations.**
- **Detection of latent infection is achieved by indirect testing of an individual's immune response to MTB antigen using a tuberculin skin test (TST) or an interferon-gamma release assay (IGRA).**
- **Active TB is defined by the British Thoracic Society (BTS) as the range of clinical manifestations that occur in symptomatic individuals infected with MTB.**

- **Latent TB** may have a positive TB skin test or a positive Interferon-Gamma Release Assay (IGRA) but the chest x-ray is negative for active TB (no hilar lymphadenopathy or cavitary lung lesions).
- **Active TB**, on the other hand, shows active lesions on chest x-ray and a sputum sample stained for acid-fast bacteria may be diagnostic.

Ocular tuberculosis

- **Most of ocular TB usually accompany latent TB infection,**
- In **extraocular** disease, the eye is the entry point of the mycobacterium and often has a predilection for the eyelids, conjunctiva, cornea, and sclera.
- The **intraocular** disease results from the hematogenous spread of infection and preferentially targets the uvea, retina, and optic nerve.

• Extraocular TB

- • **Orbit**: With orbital TB involvement, proptosis, chemosis, headache, and decreased vision can result.

- • **Eyelids/Lacrimal Glands**: TB with a predilection for the eyelids can present as “apple-jelly” nodules (lupus vulgaris). chronic blepharitis, Lid abscesses and atypical chalazions. Lacrimal glands, can also harbor TB and present as chronic dacryoadenitis.

- • **Conjunctiva/Cornea**: Phlyctenular keratoconjunctivitis, which presents as an inflammatory nodule located at the limbus, causes redness, tearing, photophobia, and epithelial erosions. Specifically for the cornea, TB can present with interstitial keratitis with associated stromal infiltrates.

- • **Sclera**: Isolated TB scleritis may result from either direct inoculation by the bacterium or through an immune-mediated inflammatory reaction, usually chronic and difficult to diagnose.

Intraocular TB

- Granulomatous anterior uveitis
- **Posterior Uveitis**: The most common presentation of ocular TB is posterior uveitis. Choroidal tubercles can be seen, Posterior uveitis due to TB classically produces a serpiginous-like lesion
- **Endophthalmitis**: Any active TB lesion within the eye can seed the vitreous fluid and lead to TB endophthalmitis.
- **Retina**: Retinal involvement in TB is typically secondary to choroidal infection with the bacterium. As with uveitis, tubercles may be present. TB vasculitis of the retina can lead to neovascularization
- **Cranial Nerves**: TB optic neuropathy may present with optic nerve edema, disc granuloma, or may be retrobulbar. Other cranial nerve involvement, particularly the abducens nerve, is common and found in over one-third of patients with TB meningitis. TB can also involve the brain parenchyma, the brainstem, cerebellum, or cavernous sinus. TB has also been reported to cause third, fourth cranial nerve palsy.

Risk factors for developing ocular TB

- **In recent years, those at the most significant risk of developing ocular TB are immunocompromised individuals.**
- **Extrapulmonary involvement is seen in more than 50% of patients who have acquired immunodeficiency syndrome and TB. Others at risk include individuals taking immunosuppressive therapy, healthcare workers, homeless and prisoner populations, immigrants from endemic countries, and patients with comorbid alcohol use disorder, chronic liver disease, chronic hemodialysis, diabetes, malignancy, or silicosis.**

Diagnostic criteria for TB uveitis (The Collaborative Ocular Tuberculosis Study) (COTS)

- 1.Clinical signs suggestive of OCULAR TB(mainly uveitis)
- 2.Exclusion of other uveitic entities, where relevant, based on clinical manifestations of disease and regional epidemiologic findings.
- 3.Investigations that document the mycobacteria or its genome: direct smear , PCR.
- 4.Investigations: TST, IGRA.

Patients having to satisfy both criteria 1 and 2 and at least one of criteria 3 and 4

- **1. Clinical signs suggestive of TB uveitis, including the following:**

a. Anterior uveitis (granulomatous or non-granulomatous), iris nodules, and ciliary body granuloma.

b. Intermediate uveitis (granulomatous or non-granulomatous with exudates in the pars plana, with or without snowballs).

c. Posterior and panuveitis, choroidal tubercle, choroidal granuloma, subretinal abscess, and serpiginous-like choroiditis.

d. Retinitis, retinal vasculitis (RV), neuroretinitis, optic neuritis, endogenous endophthalmitis, panophthalmitis, and scleritis.

- **2. Exclusion of other uveitic entities, where relevant, based on clinical manifestations of disease and regional epidemiologic findings.**

- **3. Investigations that document the mycobacteria or its genome:**

a. Demonstration of Acid-fast bacilli (AFB) on direct smear or culture of MTB from ocular samples

Pros: gold standard, definitive

Cons: low sensitivity, delayed diagnosis due to slow-growing nature of bacteria

b. Positive polymerase chain reaction from ocular fluid for IS 6110 or other conserved sequences in mycobacterial genome.

c. Evidence of confirmed active extrapulmonary TB (by microscopic examination or culture of a tissue sample from the affected tissue or sputum).

- **PCR**
- Anterior chamber fluid or vitreous humor sample can be used in molecular diagnostic testing via polymerase chain reaction (PCR). The most common target for PCR to diagnose tuberculosis is IS6110. Other targets include MPB64 or MPT64 and protein B.
- PCR is becoming the testing method of choice because of
- better accuracy
- faster test results than culture
- minimal risk of cross-contamination
- can also be helpful in identifying drug-resistant strains of Mycobacterium
- but the results of PCR have to be correlated with clinical features, specifically in endemic countries.
- Negative PCR result may help avoiding ATT in complex cases.

- **4. Investigations:**

a. Positive Mantoux test result (must be accompanied by information regarding antigen and amount of tuberculin injected ,(TST) Used to assess immunological evidence of MTB infection, latent or active

Pros: low cost and easy availability

Cons: two-step process, subjective, low sensitivity and specificity, potential false- positive in prior Bacilli Calmette-Guerin (BCG) vaccinated patients, false-negatives in immunocompromised

b. Interferon γ release assay, such as QuantiFERON TB , single-visit blood test that quantifies IFN-gamma response of T cells after in vitro stimulation of patient lymphocytes by MTB antigen

Pros: more specific, not affected by prior BCG vaccination and atypical mycobacteria

Cons: not superior to TST in sensitivity, high cost, technical difficulty; does not distinguish between latent and active disease

c. Evidence of healed or active TB on chest radiography

- The **true prevalence** of ocular TB is hard to determine, and has been reported as being between **0.2% and 10.5%** among all uveitis cases in referral ,TB-related uveitis might account for up to **48%** of uveitis cases if interferon-gamma release assay (IGRA)-positive patients are accounted for.
- The diagnosis of ocular TB is difficult. **Specimen biopsy and direct examination** to find Mycobacterium tuberculosis (MTb) under a microscope are **impractical** in proving ocular infection in many cases because the ocular manifestation may represent a **delayed hypersensitivity reaction rather than a direct infection**. Moreover, ocular TB patients can have **no clinical signs or symptoms associated with pulmonary or other systemic TB**. Mostly, the diagnosis of ocular TB is **presumptive**
- The presence of Mtb from ocular samples is mandatory for the diagnosis of **confirmed TB** .

When promising diagnostic technologies like IGRAs, as well as advancement of PCR techniques is scarce

- **Especially in resource-limited countries where ocular TB is most prominent ,many clinicians are forced to presume a diagnosis of ocular TB when other systemic signs of TB are present in conjunction with expected TST and chest x-ray findings as described above.**
- **Additionally, clinical ophthalmic improvement with anti-TB medications has often been used as a retro-diagnostic tool for ocular TB.**

Treatment of TB uveitis:

- **a. Anti-TB Drugs: -**

Standard anti-tuberculous therapy (ATT) consists of a combination of four drugs namely isoniazid, rifampin, ethambutol, and pyrazinamide, although ethambutol is avoided by some authors because of potential ocular toxicity ,The duration of therapy is as TB meningitis 9-12 months.

four drugs given for two months followed by two-drug therapy (rifampin and isoniazid)

- **b. Supplementary : -**

Various series have reported the use of oral corticosteroids along with ATT as a combination (oral prednisolone 1 mg/kg/ day) with favorable control of inflammation.

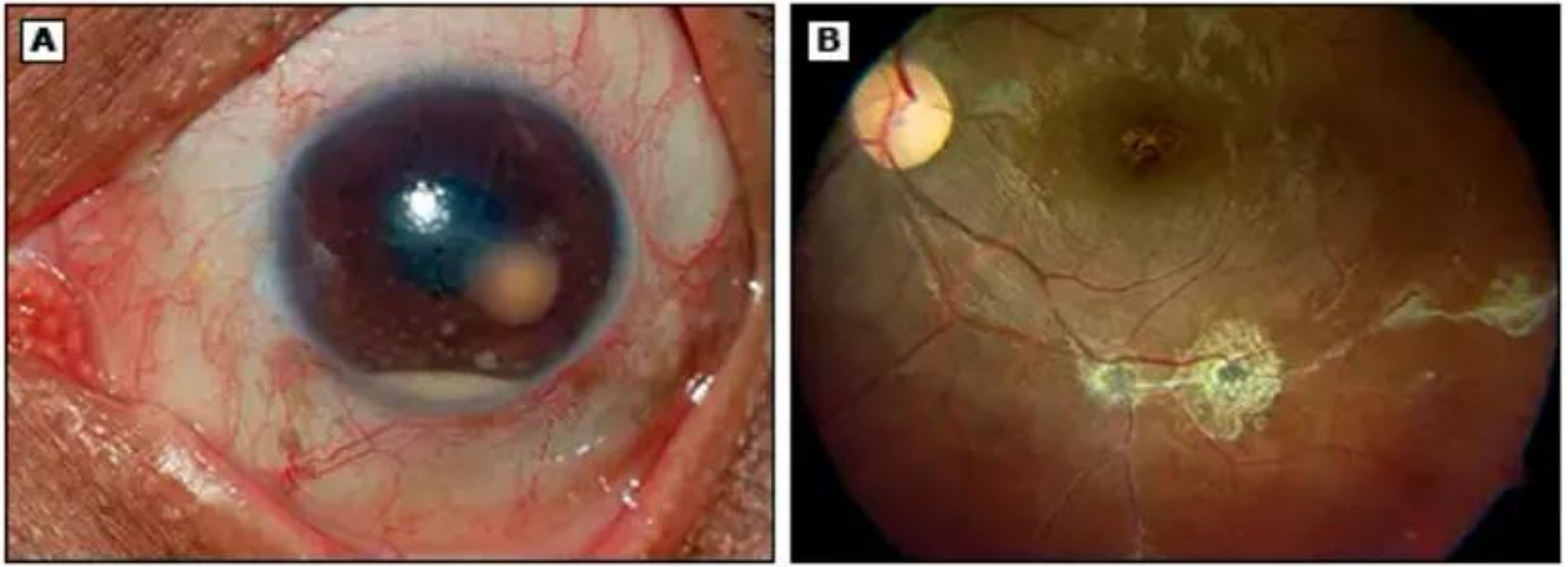
Corticosteroids can be tapered over the next 6–12 weeks depending upon the severity of inflammation and occurrence of paradoxical worsening of the disease.

Certain authors favor the use of corticosteroids only when the lesions are sight-threatening involving the macula in order to decrease macular scarring.

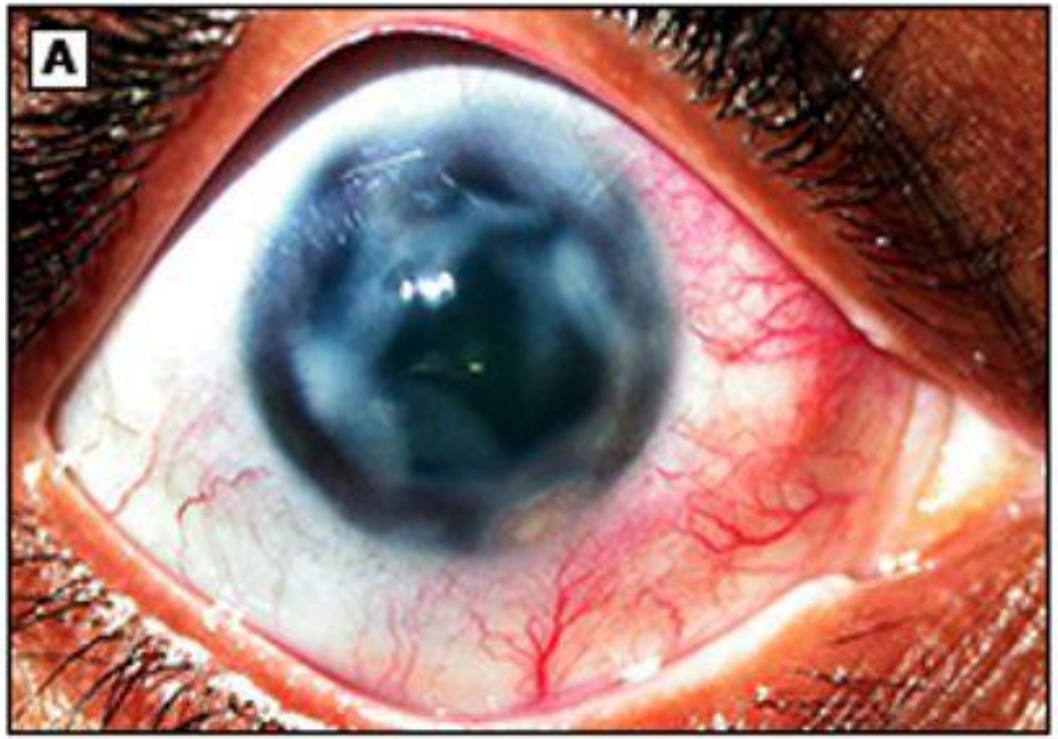
- Patients may have worsening of inflammation after starting ATT due to a Jarisch-Herxheimer reaction related to release of Mycobacterium antigens upon initiation of antimicrobial therapy.
- This reaction can be controlled with systemic steroid therapy.

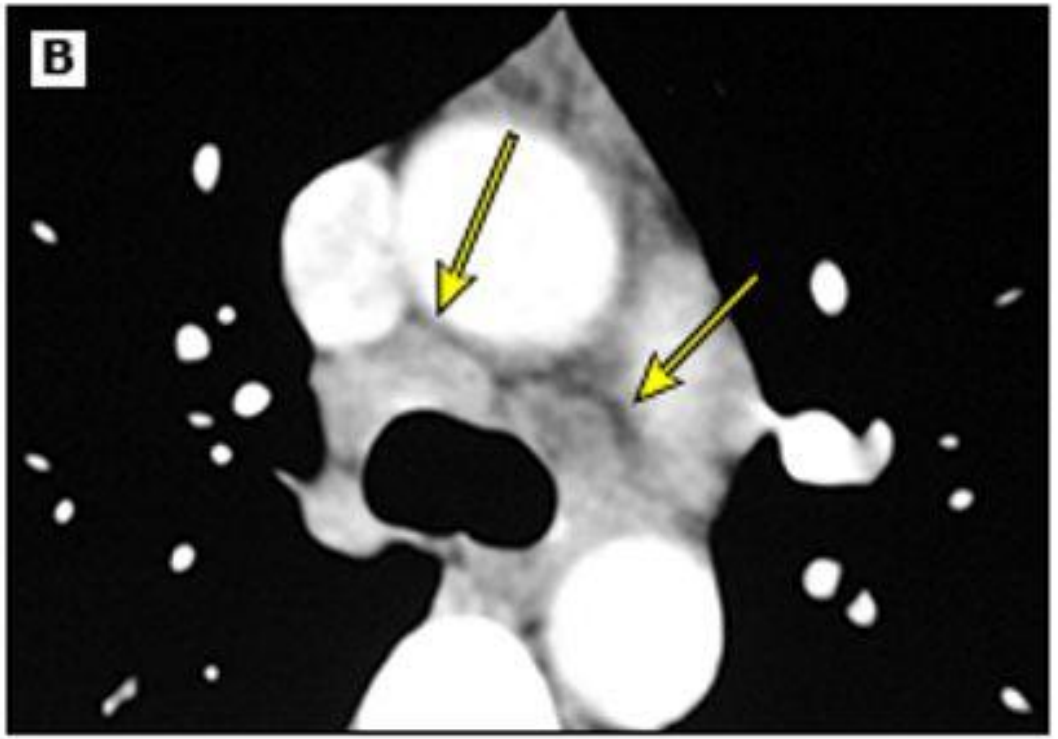
- A meta-analysis showed that multi-drug anti-TB therapy resulted in 92% improvement in ocular inflammation with 69% improved visual acuity, and 84% without recurrence of their TB after treatment.

(Panel A)anterior chamber granuloma with granulomatous keratic precipitates and hypopyon. Aspiration of the granuloma demonstrated acid fast bacilli in Ziehl-Neelsen stain. (Panel B) Following antituberculous treatment, the posterior segment demonstrates healed pigmented scars along the vasculature.

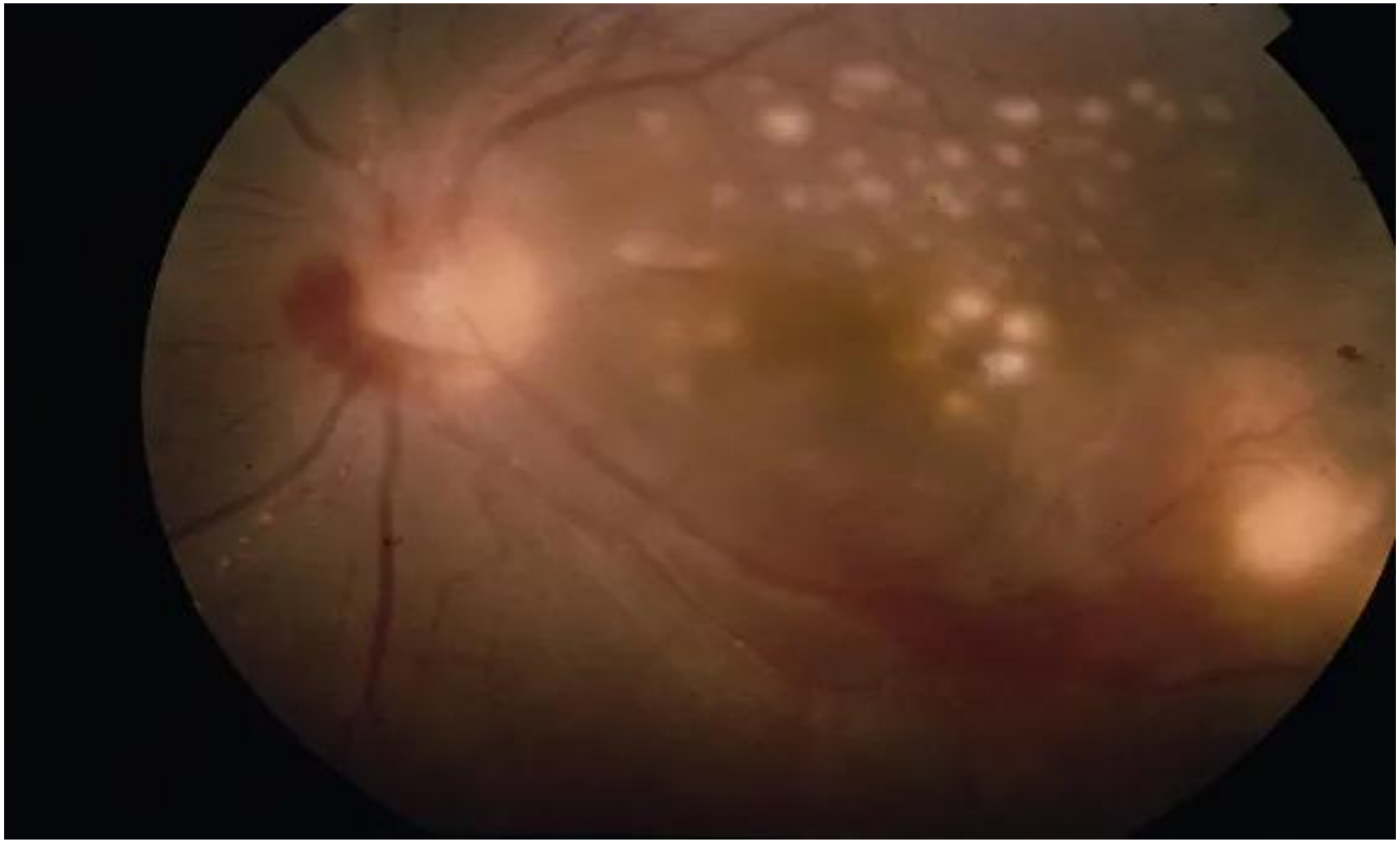


Sclerokeratitis due to ocular TB. (A) Recurrent sclerokeratitis resulting in corneal thinning and melt with adjacent active scleritis. (B) Chest computed tomography (CT) revealed enlarged lymph nodes with necrosis involving pretracheal, paratracheal, and subcarinal groups, with the largest lymph node measuring 1.89 x 1.35 cm

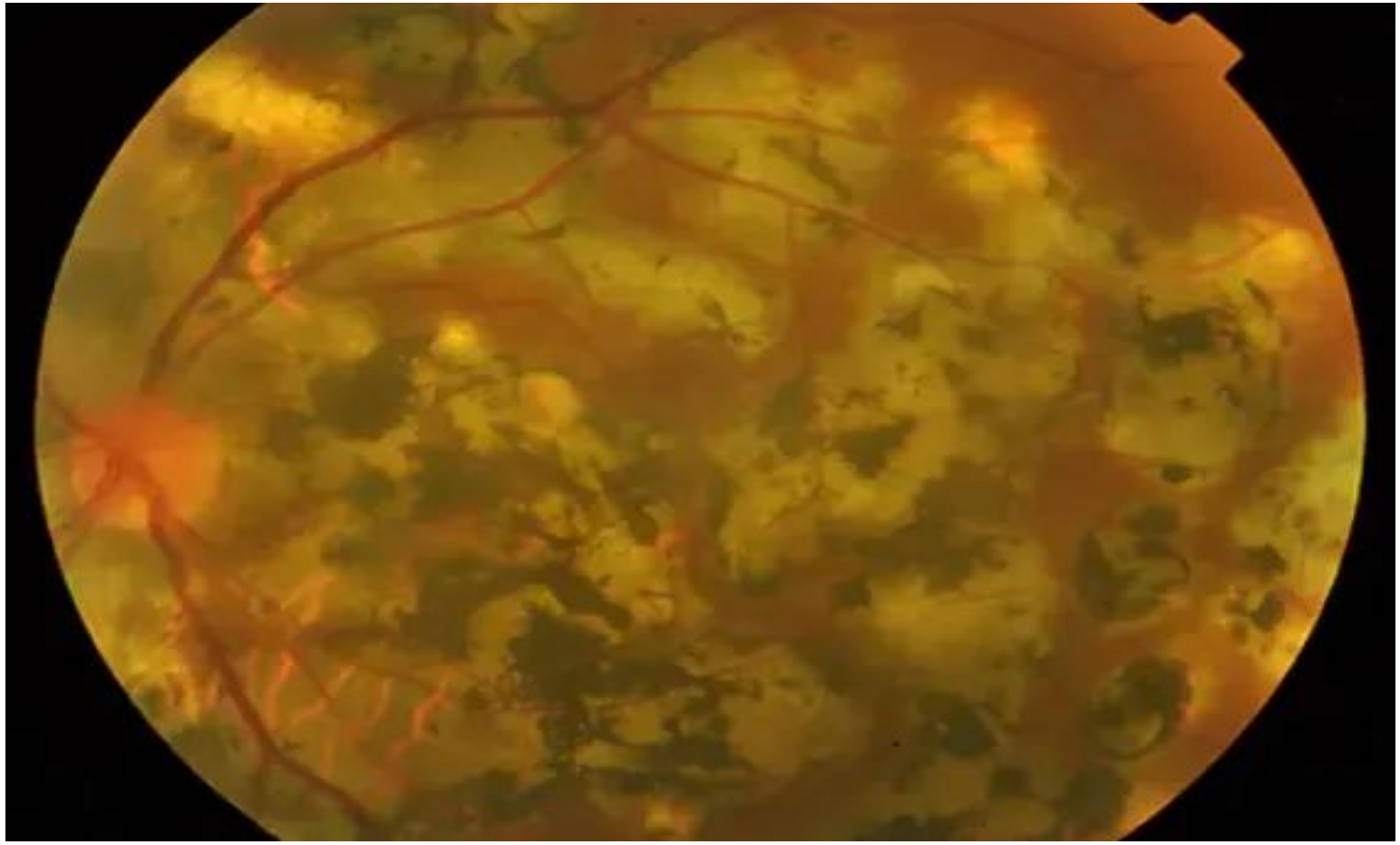




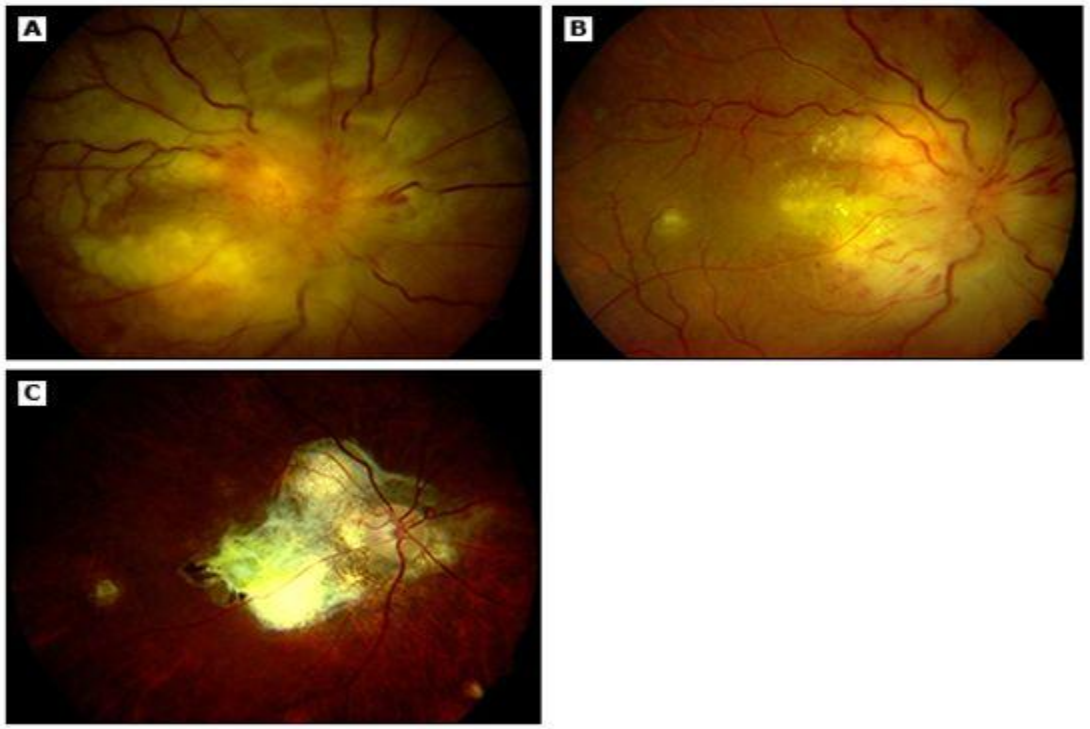
Choroidal tubercles



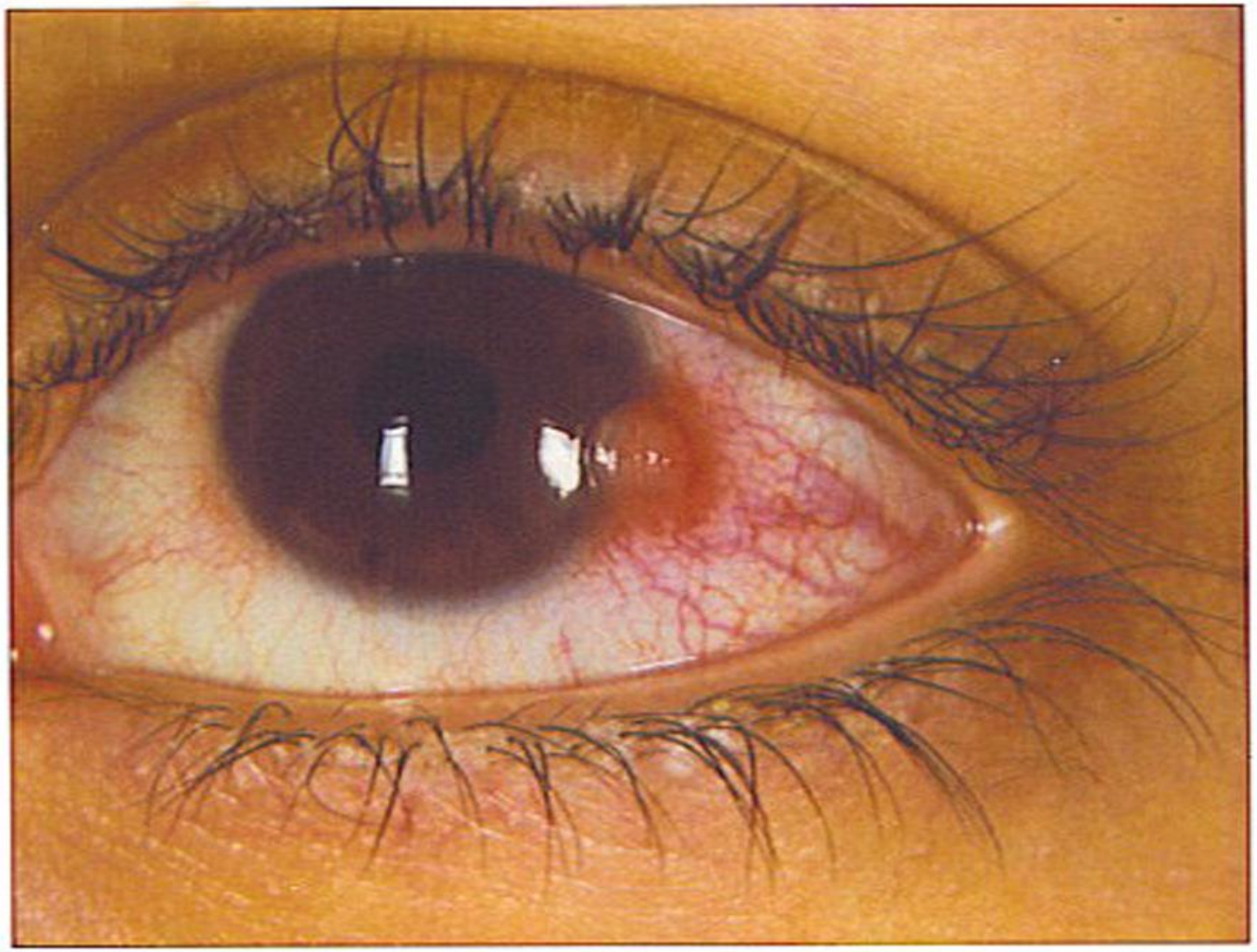
Serpiginous-like choroiditis due to ocular TB



Posterior uveitis due to ocular TB. (A) A 35-year-old woman presented with massive subretinal abscess and optic nerve granuloma with neovascularisation in her left eye. Her mantoux test was positive and necrotic, and ultrasonography demonstrated thickened choroid. (B) Interval improvement was observed after one month of antituberculous therapy (ATT). (C) Resolution of funduscopic findings and choroidal thickening was observed after three months of antituberculous therapy



phlyctenular keratoconjunctivitis



DIFFERENTIAL DIAGNOSIS

- Sarcoidosis
- Syphilis
- Herpes simplex
- Varicella zoster
- Leprosy
- Vogt-Koyanagi-Harada disease
- Sympathetic ophthalmia
- Fungal infection
- Cryptococcus meningitis
- Serpiginous choroiditis
- Toxoplasmosis

Thank you