Ocular Tuberculosis

by C. Michael Samson, M.D.

Definition

The term "ocular tuberculosis" encompasses any infection by *Mycobacterium tuberculosis*, or one of three related mycobacteria species (sp. *bovis, africanum, and microti*), in, on, or around the eye. Historically, authors have used the terms "primary" and "secondary" ocular tuberculosis. The definition of primary ocular tuberculosis (TB) has varied: some authors have used it to describe ocular disease in the absence of systemic involvement, while others take it to describe disease in which the eye is the initial port of entry of the mycobacterium into the body. Secondary ocular tuberculosis is defined as ocular involvement as a result of seeding by hematogenous spread from a distant site, or direct invasion from adjacent areas, like the sinus or cranial cavity.

There are known cases of ocular involvement with other species of mycobacteria. Though many share similar clinical presentations as TB, they are considered distinct separate pathologic entities.

History

TB has existed since ancient times. Fragments of spinal columns from Egyptian mummies show evidence of tuberculous pathology. In ancient Greece, the disease was known as consumption, and was uniformly fatal. Hippocrates even cautioned his colleagues, warning them not to visit patients with consumption, because the inevitable death of the patient might damage their reputations.

In the mid 19th century, sanatoriums were created; these sites, in conjunction with improved social and sanitary conditions, helped control TB's prevalence. In 1882, Robert Koch discovered a staining technique to demonstrate *M. tuberculosis*. In 1895, X-rays were discovered, giving physicians a new tool with which to follow the disease. In 1943, Streptomycin was proved to be safe in humans, and the following year, was administered for the first time to a patient critically ill with TB, and with amazing results as this terminally sick patient recovered in the following months.

Maitre-Jan is credited with the earliest written description of ocular tuberculosis in 1711, when he described a case of an iris lesion, which eventually caused perforation. In 1830, Guenea de Mussy was the first to recognize choroidal tubercles. The year after acid-fast stain was discovered, mycobacteria organisms were found in ocular tissue in a case of panophthalmitis.

Epidemiology

The number of TB cases worldwide corresponds with economic conditions: the highest incidences are seen in the countries of Africa, Asia, and Latin America that have the lowest GNP. The WHO estimates that 8 million people get TB every year, 95% in developing countries. Nearly 3 million people die from TB each year.

From 1953 through 1984, the number of TB cases fell, mostly in industrialized countries: the rate in the US dropped approximately 6% per year during this period. However, around 1985, there was an increase in number of new cases; new cases in the US rose from 22,201 in 1985 to 25,313 in 1993. Several factors have been sited to explain why this occurred:

1. HIV
2. High rate of immigration from countries with a high incidence of TB
3. Inadequate funding for TB control and other health efforts
4. Emergence of multi-drug resistance of TB

However, since 1993, the number of new cases has begun to drop again, both worldwide and in the US; new cases of TB in the US had dropped to 21,337 in 1996. Factors that have contributed to this decrease include new and better treatments for HIV, increased physician awareness and better institution of Direct Observed Therapy (DOT), and the use of multi-drug therapy. The main lesson is that TB is still present, and may continue to be a significant pathogen going into the new millenium: physicians must always keep it in mind in the relevant clinical settings.

There has been a dramatic change in the epidemiology of ocular tuberculosis since the 19thcentury. During that time, TB was considered a common cause of uveitis. It was considered so common, that prominent ophthalmologists of the time were able to classify TB uveitis into different types. Some investigators of the time found TB to account for up to 10% of all uveitis

cases. In the 1940s, Guyton and Woods placed TB as the cause of 80% of all granulomatous uveitis. Over the subsequent decades, the number of uveitis cases attributed to *M. tuberculosis* declined. There are many reasons for this, most citing the fact that other previously unknown etiologies, like sarcoid, toxoplasmosis, and Histoplasmosis, were now recognized. Also, with new diagnostic tests, diagnostic criteria for ocular tuberculosis have become more strict. Today, ocular tuberculosis is extremely rare. For example, there was a recent publication of an epidemiological review of the cases of uveitis seen over a 2 year period at a uveitis referral clinic in India, a country in which TB is endemic. Of a total of 1273 cases, they only found 5 cases of ocular TB, despite fairly broad diagnostic criteria. It should be noted that in all 5 cases, the diagnosis was definitive, in that they were able to demonstrate acid-fast bacilli in either ocular fluid or in tissue specimen. Since the 1980's, reports in the literature cite TB as an etiology of uveitis from 0 – 4%.

Clinical Presentation

The most common manifestation of ocular involvement is uveitis, usually presenting as a chronic anterior uveitis, panuveitis or as a choroiditis. Holland and Helm, at the Jules Eye Institute, wrote a review published in Survey of Ophthalmology in 1993, and found a total of 40 cases of histologically confirmed intraocular TB in the literature, dating back to 1869. There were several conclusions one could draw from the data. First, the age ranged from 1 yr to 75, showing that any age can be affected. There was no gender predilection. The majority of cases were chronic. The papers indicated that most presentations were granulomatous, which is in concordance with current thinking, but many reports did not specify the type of inflammation. However, there are histologically-confirmed cases of intraocular TB that present as non-granulomatous uveitis, so non-granulomatous uveitis does not exclude TB. Iris nodules were rare. The majority of cases were unilateral, and both anterior and posterior segments were involved.

One other important note from the older literature was that when tuberculosis was more prevalent, and TB was still considered one of the important causes of uveitis, it was rarely seen in patients with active pulmonary tuberculosis. One study reported only 3 cases of iritis among 1073 cases of pts with systemic TB. Another series reported no cases of iritis in a series of 1000 pts with pulmonary TB. Donahue, in the 1960's, did a review of 10,535 patients being treated at TB sanatoriums, and only found 28 cases of iritis.

On the other hand, the presence of choroidal lesions, with or without inflammation, is strongly correlated with systemic disease, and is an indicator of hematogenous spread of mycobacteria. A review in 1948 showed choroidal tubercles were present in 28% of cases of miliary TB. In 1964, another study looked at cases of pulmonary TB without evidence of miliary TB, and showed a similar prevalence of choroidal tubercles.

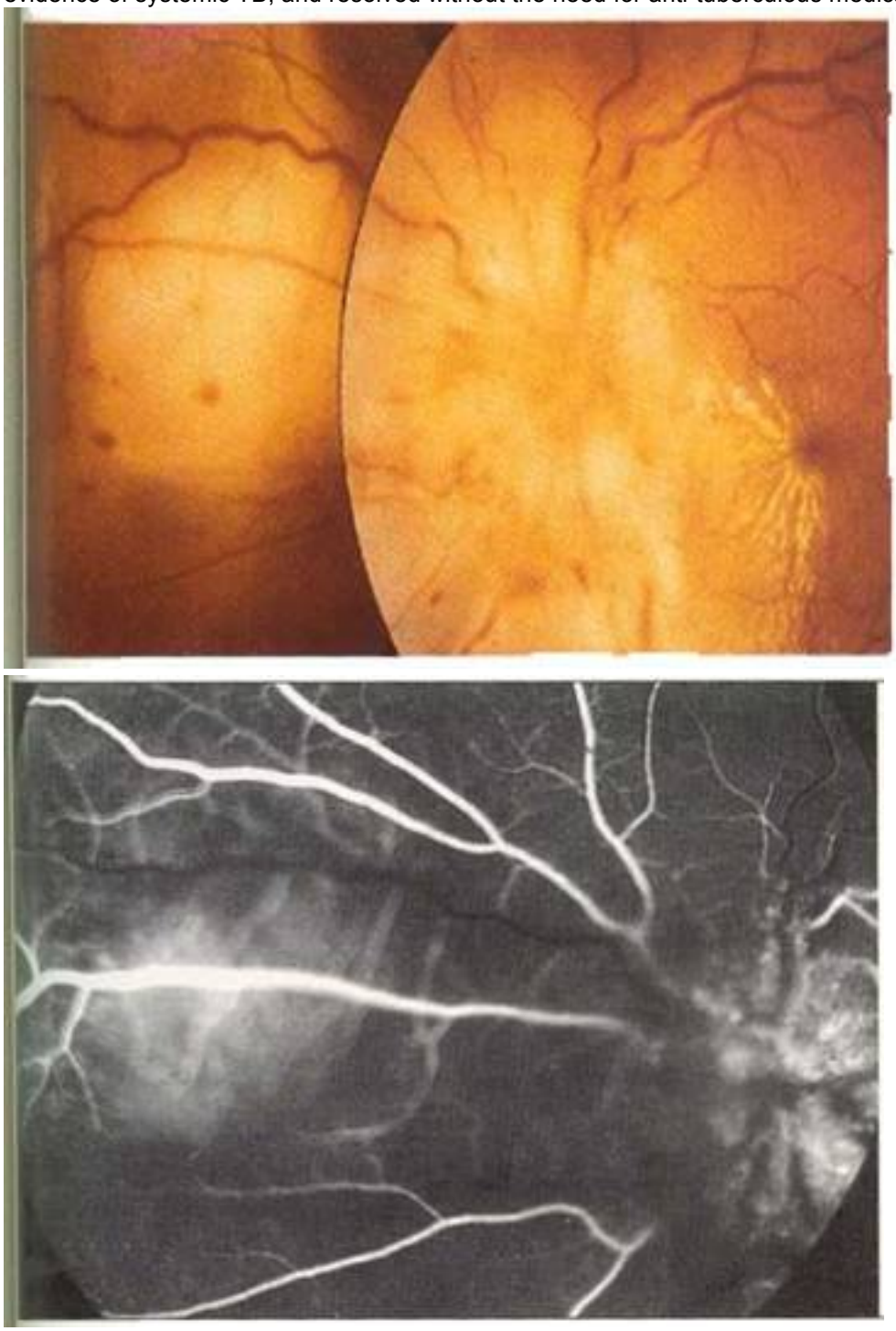
Upon examination of the literature, several characteristics of the choroidal tubercles become evident. The majority are unilateral, and can range in size from 1-4 to several disk sizes in diameter. Most of the lesions are found around the posterior pole, and although there are cases of 50-60+ lesions, there are usually less than 5. The lesions appear yellow early on, and become more pigmented as time passes. Occasionally, they can be associated with an overlying serous RD.

There are other ocular manifestations of TB. The retina is rarely involved primarily, but there are case reports of retinal vasculitis or vascular occlusions with associated periphlebitis. Tuberculous conjunctivitis has been reported several times in the literature; usually unilateral, chronic conjunctivitis, occasionally associated with conjunctival mass or ulceration. Most do not have systemic manifestations of TB, and may represent primary ocular tuberculosis.

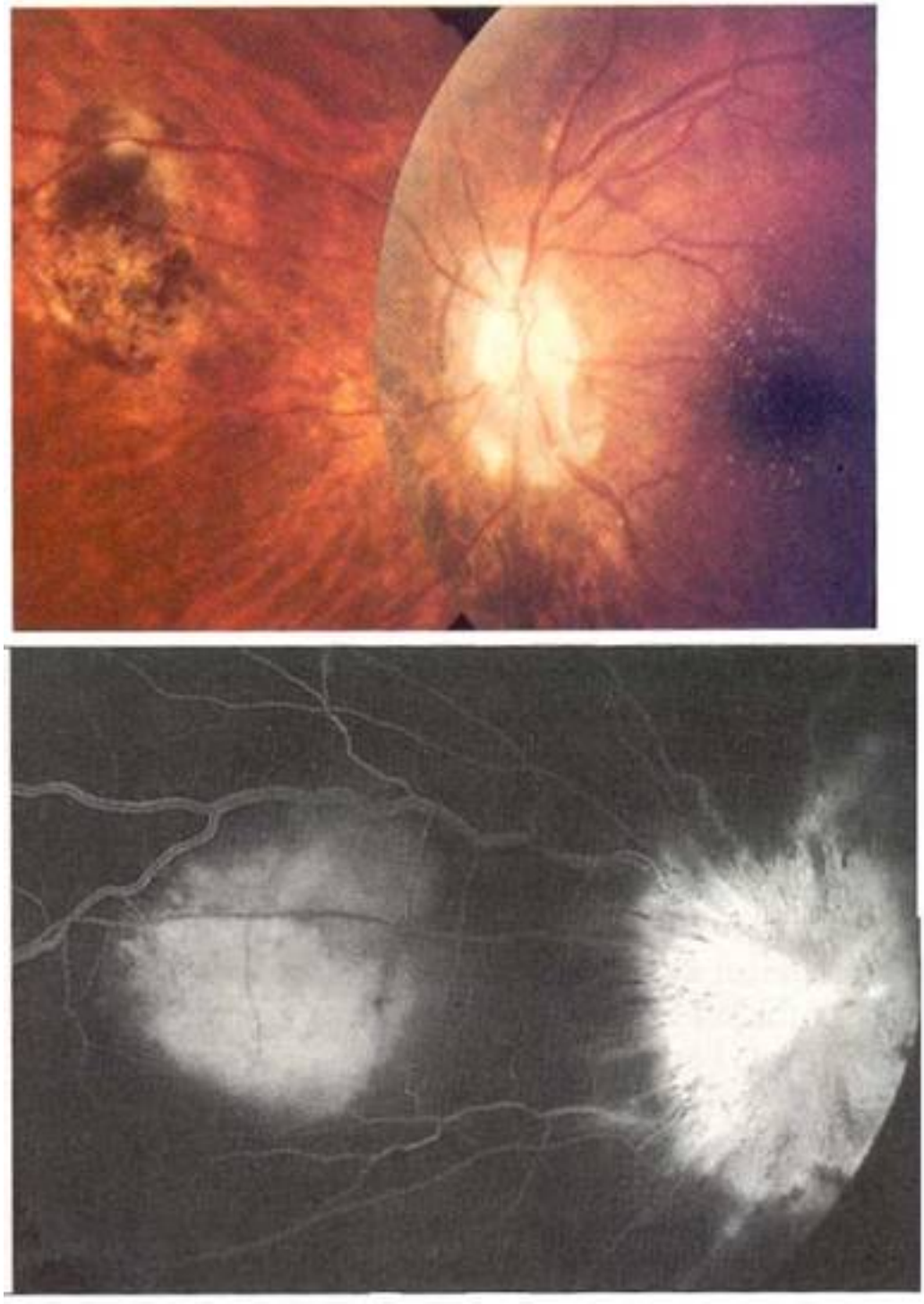
Tuberculosis can also present as orbital mass, or as a eyelid abscesses. There are biopsy-proven cases of TB scleritis. Phylectenulosis is a Type IV Hypersensitivity reaction that presents as an inflammatory mass on the cornea, and can be associated with*Staphylococcus aureus*, as well as tuberculosis.

There are two other ocular entities that are related to TB. The first is Eales' disease. This is a rare disorder that is not associated with *M. tuberculosis* specifically, but with a positive tuberculin skin test. It is characterized by recurrent vitreous hemorrhages in young men. Retinal periphlebitis is the prominent finding, along with peripheral capillary nonperfusion. In the few cases where pathology was examined, there was no evidence of mycobacterium infection.

The other entity is uveitis associated with tuberculin skin testing. This is a bilateral granulomatous anterior uveitis that responds to topical and oral steroids. The few reported cases did not find evidence of systemic TB, and resolved without the need for anti-tuberculous medications.



Figures 1&2. Fundus photographs and corresponding fluorescein angiogram of presumed choroidal tubercle, nasal to the disk. The patient was strongly PPD reactive, and was treated with anti-tuberculous medications. Photos courtesy of Joseph Walsh, M.D., Chairman of Ophthalmology at the New York Eye & Ear Infimary.



Figures 3&4. Fundus photo and corresponding fluorescein angiogram of same patient, after 6 months of treatment with anti-tuberculous medications. Courtesy of Joseph Walsh, M.D., Chairman of Ophthalmology at the New York Eye & Ear Infirmary.

Pathology

Our knowledge of the pathology of ocular tuberculosis is limited, not only because of the rarity of cases, but also because rarely does one have the need or opportunity to remove a piece of the eye, let alone the entire eyeball. However, such instances do occur, and they occur in one of four circumstances: after an eye becomes phthisical from chronic, drawn out inflammatory episodes;

from an acute tuberculous panophthalmitis; enucleation when a tumor is suspected (like retinoblastoma or a ciliary body tumor); and lastly, if the patient dies of systemic tuberculosis. Histologic exam usually shows granulomatous inflammation of the choroid, characterized by lymphocytes, epithelioid cells, and giant cells, in the presence of caseating necrosis. Overlying retina can be involved. Granulomatous inflammation can extend into the iris and ciliary body, but frank granulomas in these areas are not common. The sclera involvement can range from mild to frank perforation.

Diagnosis

Definitive diagnosis is achieved by identifying the *M. tuberculosis* in ocular tissue or fluid. Historically, this proved difficult and confirmation usually only followed enucleation of the eye. However, in modern days, there are several tools that have madeit possible to obtain a definitive diagnosis while keeping the eye intact.

Pars plana vitrectomy allows removal of intraocular specimens. Acid-fast stains may identify mycobacteria immediately, and cultures can be used to identify antibiotic sensitivities and resistance. A team of retinal specialists at the University of Wisconsin published a report of diagnosing TB choroiditis by chorioretinal endobiopsy, using standard three-port pars plana vitrectomy technique. Post-operatively, the patient did well, vision improved from CF to 20/70, with an epiretinal membrane as the only post-operative consequence.

More recently, PCR has been used to diagnosis ocular TB. Case reports show that both aqueous and vitreous specimen may be used to make the diagnosis. However, false-positives are an expected difficulty when using a test that is extremely sensitive.

However, there are many times when a uveitic patient is not a surgical candidate, or one is not able to demonstrate *M. tuberculosis* from an ocular specimen. In these circumstances, it is important to try find systemic evidence of TB. Chest X-ray findings shows infiltration, sometimes with evidence of cavitation or pleural effusion. Acid-fast stains and cultures can be done from urine, spinal fluid, or sputum.

A common dilemma is the patient who presents with uveitis and demonstrates a positive tuberculin skin test. Since the treatment of proven active TB infection is different from prophylaxis in PPD+ patients without evidence of active TB, the decision falls on the ophthalmologist to decide if the uveitis is indeed a sign of active TB infection. It is probably not indicated to treat every uveitis patient with a positive PPD with long-term anti-tuberculous medication in the absence of other evidence of tuberculosis, but each case should be treated individually, looking at the risks and benefits of treating or not treating with TB medications.

Treatment

When TB is confirmed, treatment is begun immediately, since treatment will last at least 6 months, and will sometimes require treatment up to 2 years. Treatment for ocular tuberculosis is the same as for pulmonary tuberculosis. Because of the prevalence of resistant TB, especially to isoniazid (INH) and rifampin, multi-drug therapy is now used routinely. If primary isoniazid resistance exceeds 4% in the region, it is recommended to use 4 drug therapy. Unfortunately, there are only a few states where resistance is less than 4%: these include Arkansas, Arizona, Nevada, Minnesota, Maine, North & South Dakota, and Wyoming. INH, rifampin, and pyrazinamide (PZA) are used for the first 2 months; a fourth drug, streptomycin or ethambutol, is also used until susceptibilities are available. For the second part of treatment, INH and rifampin are used for 4 months, for a total of 6 months therapy. The FDA has licensed fixed-dose combination drugs of this regimen: Rifater (isoniazid/rifampin/pyrazinamide) and Rifamate (isoniazid/rifampin). There is an alternative 9 month regimen for people that cannot tolerate PZA: INH/Rif is used, with ethambutol or streptomycin until susceptibilities are confirmed.

TB & HIV

There are some points to keep in mind when considering Tuberculosis in the HIV infected patient. First, there are multiple case reports of HIV patients with biopsy or culture proven systemic TB who do not respond to tuberculin skin testing: tuberculin skin testing is not reliable in this group. Ocular tuberculosis manifestations are the same as in immunocompetent patients, and disseminated choroiditis is the most commonly cited manifestation. Not only does their immunocompromised status retard recovery, but drug malabsorption is additionally a common problem in HIV infected individuals, mandating longer therapy.

Complications

Patients should be followed for side effects of medication. Isoniazid, rifampin, and pyrazinamide have each been associated with drug-induced hepatitis; liver enzymes should be followed, as well as warning the patients of symptoms of hepatitoxicity. Rifampin is associated with thrombocytopenia: complete blood counts should be followed as well. Pyrazinamide is associated with hyperuricemia, but acute gout is not common, and asymptomatic hyperuricemia is not an indication to stop the medication. Isoniazid is associated with peripheral neuropathy: patients with conditions associated with neuropathy should also take pyridoxine, which has been shown to prevent isoniazid-associated neuropathy.
Streptomycin has been associated with hearing loss. Experts recommend a baseline audiometry before beginning therapy.
Ethambutol is associated with optic neuritis/ optic neuropathy; the development of signs or symptoms of this complication may warrant discontinuation of the drug.
Intraocular tuberculosis can cause complications seen in other types of uveitis: cataracts, glaucoma, and in posterior disease, retinal detachment. Subretinal neovascularization has also been reported, and responded to retinal photocoagulation in at least two reports.

Prognosis

The most common reason sited for treatment failure in pulmonary tuberculosis is nonadherance to the therapeutic regimen. In New York City in 1991, a study showed 89% of 189 patients failed to complete therapy. 80% of those brought back failed therapy a second time. Isoniazid resistance in New York City in 1991 was 23%. Then, Direct-Observed-Therapy (DOT) became a routine part of treatment. DOT involves the direct monitoring of the patient taking the pills by a health care worker. Current recommendations are that all patients should be treated under DOT because there is no way to predict which patients will not comply with the required six to nine month therapy. Recently, Iioniazid resistance in New York City is down to around 5%.
There is little data on prognosis of ocular TB, again because of rarity of cases. However, it is reasonable to assume that TB in the eye requires prolonged treatment to eradicate the organism, just as it does in other organs.

Ocular Tuberculosis

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True or False

1. The most common ocular manifestation of tuberculosis is uveitis. TRUE. It usually presents as a chronic anterior uveitis, panuveitis, or as a choroiditis.

2. Unlike systemic pathology, ocular histological examination of tuberculous lesions are usually non-granulomatous. FALSE. Histologic examination shows granulomatous inflammation of the choroids, characterized by lymphocytes, epitheliod cells, and giant cells, in the presence of caseating necrosis. The overlying retina can be involved. Granulomatous inflammation can extend into the iris and ciliary body, however, frank granulomas in these areas are rare. Scleral involvement can range from mild to frank perforation.

3. Definitive diagnosis of ocular tuberculosis is made by the demonstration of iris nodules. FALSE. Definitive diagnosis is achieved by identifying the organism *Mycobacterium tuberculosis* in ocular tissue or fluid. Acid-fast stains, cultures, and PCR analysis have been used to identify *M tuberculosis*.

4. Ethambutol is contraindicated in the treatment of ocular tuberculosis because of its association with optic neuropathy. FALSE. Monitoring for the development of signs or symptoms relating to the use of ethambutol is advised. The presence of signs or symptoms of optic neuropathy may require discontinuation of the use of ethambutol.

5. Intraocular administration of anti-tuberculous drugs is the route of choice for treatment of intraocular tuberculosis. FALSE. The treatment of intraocular tuberculosis is the same as that given for pulmonary tuberculosis. Multidrug therapy (isoniazid, rifampicin, pyrazinamide, streptomycin or ethambutol), is given.

PEARL QUESTIONS

1. What is the etiologic agent for ocular tuberculosis? Answer: *Mycobacterium tuberculosis*. It is an acid-fast bacilli.

2. What is the most sensitive diagnostic procedure for isolating *Mycobacterium tuberculosis*? Answer: PCR analysis.

3. Describe the clinical findings of a choroidal tubercle. Answer: Majority are unilateral and range in size from 1Š4 to several disc sizes in diameter. They are mostly localized in the posterior pole. These lesions may number from less than 5 to more than 60 lesions. The appearance is yellow early on, and pigmentation occurs in time. Occasionally, choroidal tubercles are associated with serous retinal detachments.

4. What are the drugs of choice (DOC) for ocular tuberculosis? Answer: Isonizid, rifampicin, pyrazinamide, streptomycin or ethambutol.

5. What is the most common complication of anti-tuberculosis drug use? Answer: Drug-related hepatotoxicity. The patient should be advised of symptoms of hepatotoxicity and liver enzymes should be monitored.