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Title: Orbital Tuberculosis: Perspectives from Victoria, Australia

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ABSTRACT

Purpose: Orbital tuberculosis (TB) is a rare extra-pulmonary manifestation of tuberculosis and its clinical diagnosis poses unique challenges, with potential for destructive complications as well as social and public health implications. The aim of this study is to report our experience of patients presenting with orbital TB, and to identify common aspects.

Methods: A systematic search for mandatory notifications of orbital tuberculosis between 01/01/1994 and 31/12/2016 was undertaken in the Victorian Tuberculosis Database. In addition, members of the Australian and New Zealand Society of Ophthalmic Plastic Surgeons (ANZSOPS) were surveyed to identify cases of orbital tuberculosis diagnosed on biopsy in the past 20 years. Medical case notes of identified cases were reviewed retrospectively.

Results: Three cases were identified as having occurred in Victoria, aged 44-59 years old. All cases had emigrated from endemic countries with higher tuberculosis burden. Diagnosis of tuberculosis was often difficult due to few or none-viable acid fast bacilli, and low yield of positive culture in pauci-cellular orbital specimens.

Conclusions: Orbital TB is rare but remains an important differential diagnosis of orbital mass lesions. The diagnosis of orbital TB requires a high index of clinical suspicion and targeted investigations in patients originating from endemic areas. Diagnosis and treatment relies on effective collaboration between ophthalmologists, infectious disease physicians and pathologists.

Keywords: orbit, orbital masses, infection, mycobacterium tuberculosis

INTRODUCTION

Orbital tuberculosis (TB) is a rare extra-pulmonary manifestation of tuberculosis and its clinical implications pose unique challenges to ophthalmologists. Although rare in Victoria, orbital tuberculosis can be a challenging diagnosis with a diverse range of clinical presentations and is an important differential diagnosis of orbital mass lesions. Its management calls for a cohesive multidisciplinary approach between ophthalmologists, pathologists and infectious disease physicians.

A "great mimicker", the disease can affect all sites of the orbit and external eye and may lead to destructive complications to the bone and soft tissue and visual loss. Classically, descriptions of orbital TB characterise the disease process as primarily a manifestation of either periostitis or tuberculoma; in practice, however, both pathologies can be present, making it difficult to ascertain the incipient event [1,2]. Within the orbit, periostitis can lead to ulceration or the formation of a discharging sinus typically involving the outer margin of the orbit. Tuberculoma may manifest as an orbital mass, with extension into an externally palpable lesion, or may exert a mass effect in the orbit leading to proptosis, diplopia and pain [3]. Lacrimal gland involvement by TB presents as enlargement of the lacrimal gland or chronic dacryoadenitis, that can clinically resemble bacterial dacryoadenitis that fails to respond to anti-microbial treatment [3], or non-infectious causes of chronic dacryoadenitis. An orbital apex syndrome can occur with impingement on cranial nerves and loss of vision [4].

The aim of this study is to report our experience of patients presenting with orbital TB in Victoria, Australia over 20 years, and to identify the common aspects of orbital tuberculosis.

METHODS

A retrospective review of medical records of all patients identified with a diagnosis of orbital TB from 1994 to 2016 was performed. The study was approved by the Royal Victorian Eye and Ear Hospital Human Research and Ethics Committee.

A systematic search of the Victorian Tuberculosis database was performed. In Victoria, notification of TB is mandatory for both laboratories and clinicians, and includes clinically diagnosed cases whether laboratory-confirmed or not. This database includes cases managed in both public and private sectors [5]. As orbital tuberculosis is an unusual condition, case record notes were searched for the terms "eye", "orbit", "ocular" or "lacrimal", and records were reviewed by an experienced infectious diseases

physician for concordance with a diagnosis of orbital TB. To qualify, the inclusion criteria for orbital TB were: histopathology consistent with necrotizing granuloma with giant cells, and either a positive culture, presence of acid fast bacilli on microscopy, positive polymerase chain reaction (PCR) for TB antigen, or definite clinical response to anti-TB therapy.

In order to consider the possibility of non-notified cases of orbital TB, members of the Australian and New Zealand Society of Ophthalmic Plastic Surgeons (ANZSOPS) were also surveyed to identify potential cases of orbital TB. Possible additional cases identified in this manner were reviewed through evaluation of contemporaneous medical records for concordance with case definition.

RESULTS

Four potential cases from Victoria were identified from the systematic search and survey, and the clinical details were obtained from archived medical records. Of these, three cases identified from the systematic search were considered definite cases and were included in the case series. A fourth additional case, as identified on survey, was excluded due to diagnostic uncertainty.

CASE 1

A 44-year-old woman who emigrated from Iran at age 34, presented with a tender left upper lid swelling increasing over several weeks, which was first noted after accidentally striking her eye on the corner of a cupboard. Examination revealed an oedematous left upper lid with moderate erythema associated with a firm, tender mass. She did not have an existing medical or past ocular history.

Computerized tomography (CT) scan demonstrated diffuse swelling of the left lacrimal gland and lid tissues consistent with sub-acute dacryoadenitis (Figure 1), and she was subsequently commenced on a course of oral cephalexin and prednisolone starting at 50mg with slow wean. Over the subsequent weeks, lid oedema had improved, but the lacrimal gland remained swollen and tender.

Histology of the lacrimal gland biopsy revealed granulomatous inflammation with minimal central necrosis in a few granulomas, raising the possibility of sarcoidosis or tuberculosis. Initial stains for acid fast bacilli were negative, but culture revealed *Mycobacterium tuberculosis*, initially with DNA probe and confirmed with culture growth sensitive to all anti-tuberculosis antibiotics at 8 weeks. Investigation for pulmonary disease with chest X-ray followed by CT showed extensive hilar and mediastinal

lymphadenopathy, and mediastinal biopsy also demonstrated granulomas. Other than a mild dry cough, she had no systemic symptoms of tuberculosis. She was commenced on a 9-month regimen of rifampicin and isoniazid, and there was gradual resolution of lacrimal gland swelling and mediastinal lymphadenopathy.

CASE 2

A 49-year-old Indian man with frequent return travel, and a history of congenital right exotropia, presented with two weeks of a red right eye associated with tender swelling of the right lower lid. In addition, he reported 15kg of weight loss over 12 months, associated with night sweats and shivering. Examination noted a firm tender mass within the right lower lid, with surrounding oedema and mild erythema, as well as a congested right lower conjunctival fornix with follicular changes. Visual acuity was normal and there was no diplopia or restriction of eye movements.

CT imaging revealed a homogenous mass infiltrating the pre-septal tissue of the right lower lid and the inferior orbit and associated with superior globe displacement. The inferior orbit and lid mass were biopsied which showed necrotising granulomatous inflammation, with no identifiable acid fast bacilli on special stains. There was insufficient material for culture hence a repeated biopsy was performed for culture, sensitivity and PCR, which returned as negative. Chest X-ray was normal and there was no evidence of tuberculosis infection elsewhere. Orbital tuberculosis was considered to be the most likely diagnosis and the patient was advised to commence anti-tuberculosis treatment. The patient sought a second opinion in India. Based on the clinical and histological findings, he was commenced on a 9-month regimen of rifampicin, isoniazid and ethambutol. The orbital and pre-septal mass gradually resolved over a period of several months.

CASE 3

A 59-year-old man who emigrated from Sri Lanka at the age of 37, with frequent return travel, had a past history of an asymptomatic lung lesion reportedly investigated for pulmonary TB over 20 years ago with negative findings. His past medical history also included type 2 diabetes mellitus, hypertension and gout, and he had no relevant ocular history. He presented with 3 weeks of progressive right upper eyelid swelling, not responding to multiple courses of antibiotic treatment for presumed pre-septal cellulitis.

Examination demonstrated right proptosis and inferior globe displacement, with diplopia and restriction of eye movement in upgaze. A right upper lid mass was palpable centrally and there was bilateral cervical lymphadenopathy. Pupil response to light and optic nerve function were normal, and visual acuity was unaffected.

CT imaging revealed an infiltrative soft tissue mass in the right orbit surrounding the superior rectus muscle and tendon, lacrimal gland and lateral rectus tendon, which was biopsied via anterior orbitotomy. Histology revealed an inflammatory infiltrate with necrotising granulomas (Figure 2a, Figure 2b), with few organisms on microscopy that were Gram positive, most likely surface contaminants. There was insufficient specimen for microbiology studies, therefore a second biopsy was performed and returned as necrotising granulomas with positive acid fast bacilli on Ziehl-Neelson stain on histopathology. Cultures were negative and chest X-ray was clear. He was initially commenced on isoniazid, rifampicin, pyrazinamide and ethambutol for two months, before continuing on isoniazid, rifampicin and ethambutol for the remainder of the treatment course. Treatment is ongoing at this time, with clinical improvement and decrease in size of eyelid mass.

DISCUSSION

Orbital TB is a rare extra-pulmonary manifestation of TB. In Victoria, Australia, the reported cases were all immuno-competent individuals, and overseas-born. All cases responded well to combination anti-TB therapy (Table 1). The countries of origin of our cases differed in TB incidence: Iran has a TB incidence of 15 per 100,000, Sri Lanka has an incidence of 65 per 100,000, and India has one of the highest incidences of TB at 217 per 100,000 [6]. Conversely, the incidence of TB in Australia is 6 per 100,000 population with the incidence of TB in the Australian-born non-Indigenous population remaining very low at 0.7 per 100,000 [7]. Therefore, the burden of TB by the country of origin remains the single most important risk factor for the occurrence of orbital TB.

Our case series shared the demographic features of another retrospective case series of periorbital TB from the United Kingdom (UK), where all the affected patients originated from countries with higher rates of TB [8], except for a wider age range at presentation for the UK series. However, not all reported cases have been overseas-born, as evidenced by a case report from France with orbital tuberculoma leading to cirrhotic orbital changes and visual loss [9]. There is a low but comparable incidence of TB for

Australia and France (France: 8.2 per 100,000; Australia: 6 per 100,000) [6]. The age range of our cases (44-59 years old) was older compared to the international mean age of 19 [1], and is closer to the UK experience where a mean age of 56 was found [8]. The cases that have completed treatment to date responded to standard rifampicin-based anti-tuberculosis treatment regimens. No cases of drug resistant orbital tuberculosis have yet been published.

Conversely, orbital TB appears to present in a younger age group in India, ranging from 4 to 45 years in one series, 6 to 14 years in another series, and 1 to 48 years in an earlier series in the 1970s [10-12]. The clinical presentations were also significantly different, where periostitis involving the outer orbital margin complicated by chronic discharging sinuses were frequently observed in children, in addition to orbital tuberculoma [10,11]. Orbital margin bony involvement included frontal, maxillary and also zygomatic bones, and non-healing sinus resulted in cicatricial contraction and ectropion [12]. Trauma has been reportedly associated with onset of TB osteomyelitis [12]. It is interesting to observe the onset of dacryoadenitis in our first case was also preceded by trauma. It is still uncertain how trauma is associated with reactivation of TB or whether this could be a coincidental observation. All the case series have shown that orbital TB occurred either by haematogenous seeding with secondary reactivation as orbital tuberculoma, dacryoadenitis, periostitis, or contiguous spread from the paranasal sinus into the orbit [1,2,10-12]. Vision threatening orbital TB invariably is caused by reactivation of TB at the orbital apex, or involving the greater sphenoidal wing leading to optic nerve compression, and rarely due to cicatricial ectropion complicated by uncontrolled exposure keratitis [4,8,12,13].

The clinical presentation from our cohort varied and consisted of lid swelling, periocular discomfort, proptosis and globe displacement, which were non-specific to orbital TB and commonly shared by other orbital diseases. One patient had cervical lymphadenopathy and another had constitutional symptoms. Generally, the Victorian cases presented with chronic dacryoadenitis and orbital soft tissue tuberculoma. The diagnosis of orbital TB was established based on clinical and pathological correlation, demonstration of acid fast bacilli or positive culture for TB. The characteristic histopathological features of tuberculosis are granulomas with multinucleated giant cells and caseous necrosis [1,14], although in some instances it may be difficult to differentiate from other causes of granulomatous inflammation [8].

Culture of *Mycobacterium tuberculosis* is the gold standard for diagnosing TB and has important treatment implications regarding drug susceptibility testing. However, as in other sites of extra-pulmonary

TB, the orbital biopsy specimens are pauci-bacillary, the sensitivity of culture is low for orbital TB and a high index of clinical suspicion is paramount in the appropriate instance [8]. A review of 79 published cases of orbital TB found positive cultures in only 19 cases (24%), including 5 cases where the positive culture was obtained elsewhere in the body. In 59 orbital TB cases with microscopy data, acid fast bacilli were detected in 18 cases (30%) [1].

Further testing with polymerase chain reaction amplification of mycobacterial DNA, although unable to exclude TB with negative tests as in Case 2 [2], can improve the diagnostic yield and has rapid turnaround times. The newer nucleic acid amplification test assay Xpert MTB/RIF [15], is additionally helpful as a test for rifampicin resistant mutation [10], and has a reported sensitivity of 69% in tissue specimens [11]. In the absence of definitive microbiology, some authors have argued that response to treatment could be considered retrospective confirmation of diagnosis [9].

Positive ancillary tests such as tuberculin skin tests (e.g. Mantoux test) and interferon gamma releasing assay (e.g. Quantiferon TB-Gold test) are supportive evidence but are not a diagnostic tool of active TB, being unable to differentiate between latent and active disease. The Mantoux test can result in false positive results in patients who were previously immunized with Bacillus Calmette-Guerin (BCG) vaccination or have been exposed to different species of mycobacteria or multiple tuberculin skin tests. False negative Mantoux tests are also seen in immunocompromised patients [1,3,14]. Quantiferon Gold is specific to *M. tuberculosis*, but the high rate of false positives makes this test fit for TB screening only [3,14]. Interferon gamma release test and tuberculin skin test has also been reported negative in patients with extra-pulmonary tuberculosis [14]; this was demonstrated in our cases as well.

Orbital TB, owing to its pauci-bacillary nature, is not thought to be an infectious risk in and of itself [1]. However, evaluation for concomitant pulmonary TB is an important aspect to the management of all cases of suspected extra-pulmonary TB [9]. Up to 53% of cases of orbital TB may also have radiographic evidence of pulmonary involvement on chest X-ray [1].

Treatment of orbital TB is individualised, primarily consisting of multiple anti-tuberculosis drug therapies in conjunction with surgery for diagnosis and surgical rehabilitation in appropriate cases. Standard regimens usually include two months of rifampicin, isoniazid, pyrazinamide and ethambutol, followed by four months of rifampicin and isoniazid [1]. Moxifloxacin may be used as a substitute for ethambutol in cases where there is concern regarding optic neuropathy. The prognosis for recovery with adequate

treatment is generally favourable, although complications from the disease can include visual loss, bony destruction or intracranial extension [1,8,13].

Tuberculosis is a notifiable disease in Victoria within 5 days of presumptive or confirmed diagnosis [16]. A strength of the present study is its systematic search of the Victorian Tuberculosis Database, which records data regarding all notifications from positive culture, molecular or clinical diagnosis of *Mycobacterium tuberculosis*. As such, the case series should comprehensively reflect the diagnosis and management of orbital tuberculosis in Victoria in the past 20 years, across multiple centres. All of our cases had microscopy and cultures sent for TB, but only one underwent PCR assay for TB. As the test sensitivities of all microbiological testings are limited, future cases should also include PCR TB assay. The present study demonstrated the importance of considering orbital tuberculosis in the differential diagnosis for orbital mass lesions, particularly in the setting of emigration from a country with higher TB burden. Orbital tuberculosis can be difficult to diagnose. The diagnosis of orbital TB is often made based on a high index of clinical suspicion, with direct tissue biopsy coupled with targeted microbiological investigations and PCR to ultimately prove the disease process. Orbital TB has both social and public health implications, therefore screening for pulmonary TB upon diagnosis, followed by adherence to a complete course of anti-tuberculosis treatment, is paramount.

FIGURE CAPTIONS

Figure 1: CT scan in Case 1 demonstrated diffuse swelling of the left lacrimal gland and lid tissues consistent with sub-acute dacryoadenitis.

Figure 2a: Figure 2a: Low power field demonstrating granuloma in Case 3.

Figure 2b: Figure 2b: High power field with multinucleate giant cell in Case 3.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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Conflict of Interest: All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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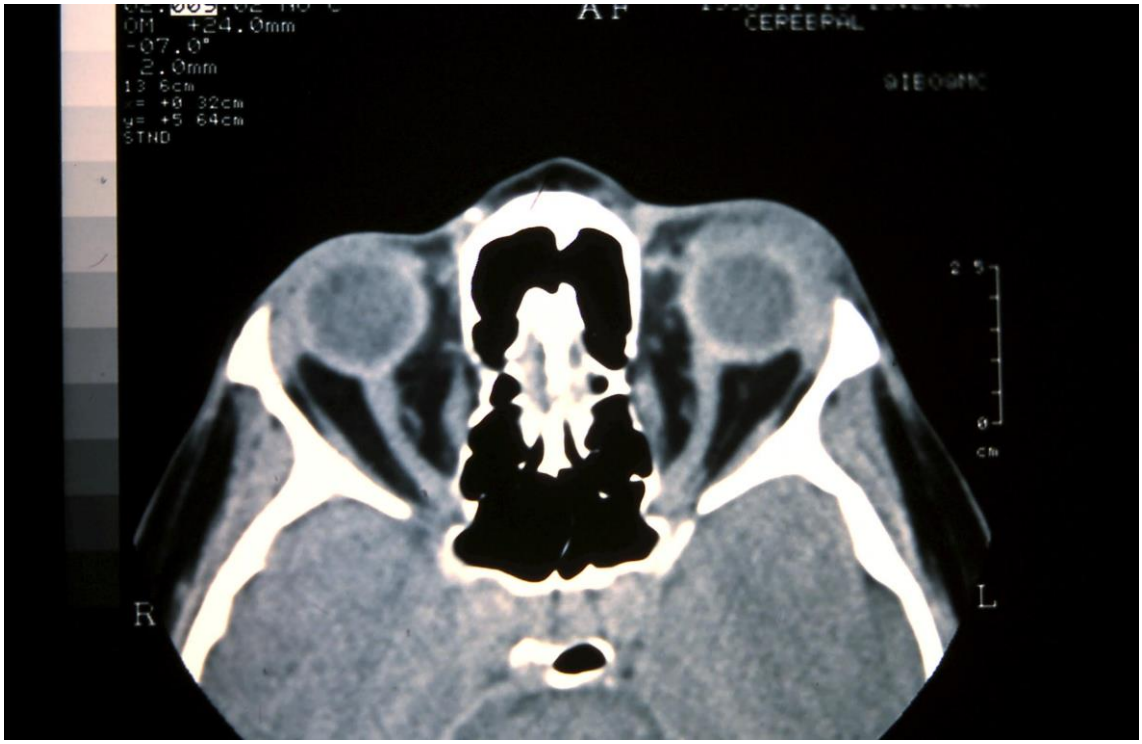
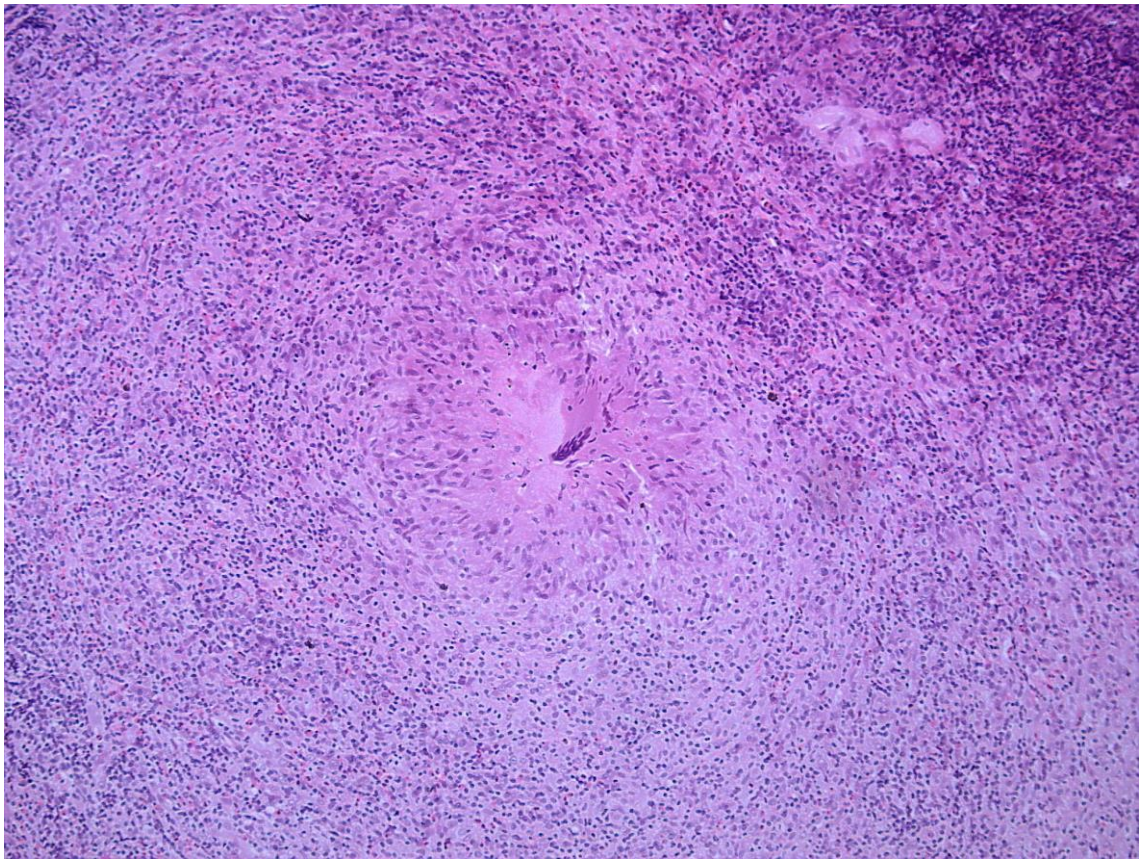
17. 

18. 

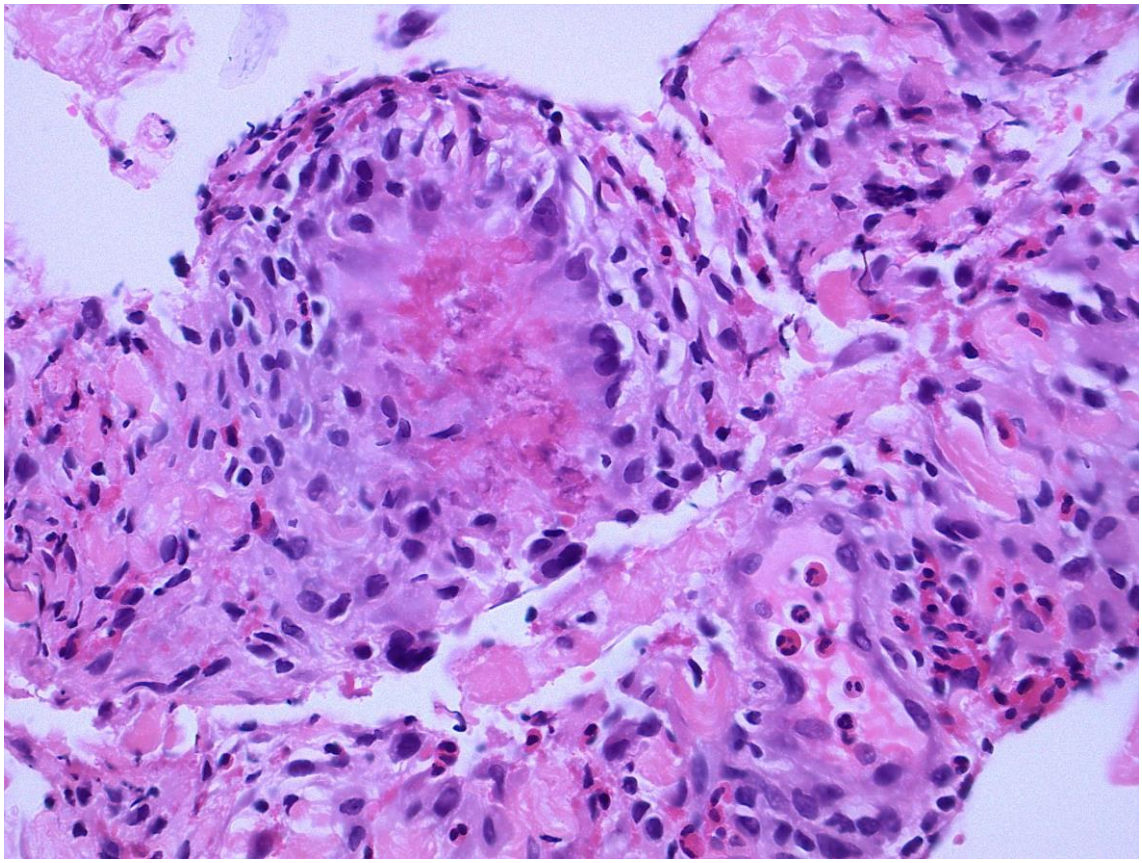
19. 

Table 1: Clinical characteristics and management of the orbital tuberculosis cases from Victoria, Australia

Case	Age	Country of Origin	Presentation	Diagnosis	Treatment
1	44	Iran	Dacryoadenitis, tender lacrimal gland swelling with surrounding oedema and erythema; bulky hilar and mediastinal lymphadenopathy	Positive *M. tuberculosis* culture	Rifampicin and isoniazid (9 months)
2	49	India	Follicular conjunctivitis, tender lower lid mass with surrounding oedema and erythema, night sweats, loss of weight	Necrotising granulomatous inflammation on histopathology and clinical correlation	Rifampicin and isoniazid (9 months)
3	59	Sri Lanka	Upper lid mass with proptosis and inferior globe displacement, diplopia and restriction of eye movement, bilateral cervical lymphadenopathy	Necrotising granulomatous inflammation on histopathology with positive acid fast bacilli	Rifampacin, isoniazid, pyrazinamide and ethambutol (2 months) followed by rifampicin, isoniazid and ethambutol (7 months)

20.