TUBERCULOSIS MENINGITIS PRESENTING AS REFRACTORY UNILATERAL PANUVEITIS:CASE REPORT IN JORDAN

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ABSTRACT

Tuberculous (TB) meningitis and endophthalmitis are extrapulmonary TB manifestations and are rare TB manifestations in Jordan. We are describing a case involving a 30-year-old male patient. He is HIV-negative and has no known chronic medical conditions. The patient came to our clinic with refractory panuveitis in one eye. Upon observing the disease course and the response to different medications, along with a battery of investigations, a suspicion of endogenous TB endophthalmitis arose. The Magnetic Resonance Imaging (MRI) also showed features consistent with TB meningitis. Interestingly, there was a great decrease of inflammation once the steroids and other medications were stopped. Following this, the patient was initiated on anti-TB medications. After three weeks, the steroids were reintroduced. The response to this treatment approach was promising. The abrupt positive reaction upon stopping initial medications and beginning anti-TB treatment, followed by the cautious reintroduction of steroids, highlighted the complexity of the case. In this case, we also emphasize the importance of evaluating the disease response to treatment as a pillar in prioritizing and validating the list of differential diagnoses in any presenting case. This case also highlights the significance of having an ongoing working differential for each presenting case that includes even the conditions that might be considered rare. Remember that “it is not rare if it is in your chair.”

Keywords: Tuberculosis, Meningitis, Uveitis, Case Report

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INTRODUCTION

Tuberculosis (TB), a contagious disease caused by Mycobacterium tuberculosis, is a significant cause of ill health and one of the leading causes of death. Prior to the coronavirus (COVID-19) pandemic, TB was the leading cause of death from a single infectious agent, ranking above human immunodeficiency virus (HIV). (1) The disease typically affects the lungs (pulmonary TB). However, in less than a quarter of the cases, it resides outside the lungs; this manifestation, known as extrapulmonary TB, can occur in virtually any body system. In this manuscript, we present the case of a 30-year-old HIV-negative male with challenging unilateral panuveitis that was clinically presumed to be TB-endophthalmitis, based on the disease course and response to treatment, as well as MRI features of TB meningitis that responded well to anti-TB medications.

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CASE PRESENTATION

A 30-year-old male, not known to have any chronic illnesses, with no history of traveling outside Jordan, presented in early February 2022 with floaters in the left eye. When examined, his left eye showed numerous cells in the anterior chamber (+4) with mild corneal edema and fine keratic precipitates (KPs), as well as elevated intraocular pressure (IOP) of 30 mmHg. No findings were observed in the fundus. The right eye was not involved in the process. His vision was 0.6 in both eyes with glasses. Topical steroids and an antiglaucoma medication (Timolol) were prescribed for the next two weeks. Only the IOP was controlled to under 15 mmHg, with no change in the anterior segment reaction of +4 cells. When the patient was seen almost two weeks later, Koeppe's nodules were visible on the pupillary margins as well as posterior synechiae. His vision had deteriorated to counting fingers at one meter (CF1m). Fundus examination showed some haziness (+1), with no apparent involvement of the optic disc, macula, retinal periphery, retinal vessels, or choroid. Herpetic keratouveitis was suspected, due to corneal stromal edema and elevated IOP in the uveitic eye. An oral antiviral agent (acyclovir 800 mg five times daily) was prescribed, followed by 40 mg of oral prednisolone two days later. One week later (in late February 2022), the patient's vision fell to CF close with an increased vitreous haze (VH) of +4, and once the attending senior ophthalmologists found a continually challenging case, they referred the patient to the medical retina and uveitis team in King Hussein Medical City.

Once the patient seen in the medical retina clinic, he had been on relatively high dosages of oral steroids, oral antivirals, topical steroids, and antiglaucoma medication for more than one week, with no significant change in the anterior segment cellular reaction. The most striking features upon examination were dispersed mutton-fat KPs all over the corneal endothelium, more prominent on the periphery and relatively decreased in size toward the center (Images 1A and 1B), and Busacca and Koeppe's Nodules on the iris. As there was no improvement in the patient's condition, we suspected infectious rather than viral causes to be the culprit behind this "refractory" uveitis. The plan was to stop all medications and observe the disease course, while ordering the following battery of investigations and imaging for a unilateral granulomatous panuveitis that is most likely infectious: complete blood count (CBC), kidney function test (KFT), liver function test (LFT), QuantiFERON-TB Gold (QFT), anti-toxoplasmosis IgG and IgM, Treponema pallidum hemagglutination (TPHA), HIV profile, purified protein derivative (PPD) skin test, angiotensin-converting enzyme (ACE), and chest computed tomography (CT) scan.

In addition, for further evaluation and to assess possible future treatment plans, we ordered human leukocyte antigen (HLA) B-51, antinuclear antibody (ANA), perinuclear and cytoplasmic anti-neutrophil cytoplasmic antibody (p-ANCA and c-ANCA respectively), and rheumatoid factor (RF) tests. The patient was followed closely after stopping the medications, and the anterior uveitis started to improve after three days. PPD at the three-day follow-up visit was less than 5 mm, with mild erythema and no induration. The panuveitis was resolved in two weeks with no KPs (Images 2A and 2B), iris nodules, or cellular reaction in the anterior segment. With the exception of a few pigmentary anterior vitreous cells, the vitreous was almost transparent (VH + 0.5), and the retina showed no retinal or choroidal lesions.

The patient's vision improved to 0.4 from CF close upon presentation.

Most systematic investigations came back negative, while others were still pending (Table 1). The dramatic improvement the uveitis showed in response to steroid cessation made infectious causes seem most likely. With the almost complete resolution of inflammation without medication and no retinitis, choroiditis, or vasculitis, we began to consider tuberculosis as the probable cause of the infection, with toxoplasmosis as a less likely alternative and herpes simplex excluded due to complete absence of response to full-dosage of systemic Acyclovir. With a normal high-resolution chest CT scan and a PPD of less than 5 mm in a low-risk patient, along with an inability to perform Q-Gold testing at that moment due to technical issues (Q-Gold was negative a couple of weeks later), we started to hunt for other extrapulmonary involvement, ordering magnetic resonance imaging (MRI) of the brain along with CT scans of the abdomen and pelvis, all with contrast.

The abdominal and pelvic CT scans were clear of significant pathology, except for two small lesions in the liver that mandated a follow-up abdominal ultrasonic examination, which ascertained that they were merely small haemangiomas to be followed up on in six months.

The brain MRI showed diffuse pachymeningeal enhancement over both frontal lobes and the basal cisterns and around the cavernous sinus, with a hyperintense signal on the FLAIR images over the left cerebellar vermis folia, with no shift in the midline structures and a normal ventricular system. These features were suggestive of TB meningitis. A suspicious filling defect involving the superior sagittal sinus necessitated magnetic resonance venography (MRV), which ruled out sinus thrombosis.

The patient was sent to be assessed by an internist. He denied recent weight loss, appetite loss, night sweats, fever, and fatigue, and he did not report any bouts of coughing, hemoptysis, or chest pain. There were no localizing neurological signs or symptoms, except for an occasional left-sided headache. The internist decided that the patient should be seen by a specialized TB team in the Ministry of Health (MOH), who agreed on the probable diagnosis of suspect TB meningitis and presumptive endogenous endophthalmitis in light of the absence of other pertinent investigations. The plan was to do a lumbar puncture for cerebrospinal fluid analysis and culture, admit the patient for observation, and start him on anti-tuberculosis medication: pyrazinamide (500 mg), isoniazid (75 mg), rifampicin (150 mg), and ethambutol (400 mg).

The patient was admitted to the MOH TB hospital in Al-Mafraq, Jordan. Our clinic's weekly follow-up showed that the patient was improving, with no recurrence of inflammation. A follow-up brain MRI was performed one month later. The previously observed pachymeningeal enhancement was still present but indistinct, and the hyperintense signal on the FLAIR image over the left cerebellar vermis folia was not seen, with an impression of disease regression.

The hospital discharged the patient on anti-TB treatment. The patient experienced a slight worsening of his vision and increased vitreal haze but no active vitreous; the vitreous had regressed and was controlled well with oral prednisolone dosed at 0.5 mg/kg weight (a total of 30 mg).

As of this report in September 2022, the patient is stable, with no signs of ocular inflammation relaps
e. His recent MRI scan
was free of pathology, and he is still on anti-TB medications.

DISCUSSION

About a quarter of the world's population, or up to two billion people, have contracted Mycobacterium tuberculosis; however, only a tiny percentage of these cases will progress and become active tuberculosis. The likelihood of this is much higher among HIV-positive individuals and those with risk factors like malnutrition, diabetes, active smoking, and alcohol consumption (> 40 g/day) (1, 2). Around 90% of people affected are adults with males being afflicted by TB more frequently than females (1), and the disease usually affects the lungs (pulmonary TB). However, the probability that it will impact other body sites varies depending on the area of the world in which the patient lives, ranging from 8% probability in the Western Pacific Region to 24% in the Eastern Mediterranean Region, according to the World Health Organization (3).

The WHO estimates the TB burden in Jordan at an incidence of 4.7 (3.6-6 uncertainty interval) per 100,000 population, with 480 (370-610 uncertainty interval) cases reported in 2020 (4). Our patient was HIV-negative, a non-smoker, and a non-alcohol drinker; he was not known to have any chronic illnesses and had a body mass index of 20.1

Clinical Central Nervous System (CNS) TB accounts for roughly 8% of all extra-pulmonary cases. It affects 1-2% of all patients with active TB. It is acknowledged as the least expected but most devastating form of human mycobacterial infection known to affect immunocompetent people. CNS TB can be categorized as subacute or chronic meningitis, intracranial tuberculoma, or spinal tuberculous arachnoiditis (5). Maintaining a high level of suspicion is necessary to avoid missing or postponing the diagnosis of TB meningitis (TBM). Subacute lymphocytic meningitis and a low glucose level in the CSF are common TBM presentations. However, fewer than 20% of patients presented with these two conditions at the time of their diagnosis (6). Therefore, once TBM is considered in a patient with compatible and suggestive clinical findings and suspicious laboratory abnormalities, a rapid but thorough assessment for supporting evidence should be conducted, and the attending clinician should then decide whether to start empirical treatment (5).

Dural masses and pachymeningeal enhancement, which often impact the basilar meninges rather than the convexities of the cerebral hemispheres, can be seen as neuroimaging characteristics of TBM on MRI with contrast (7). Our patient had diffuse pachymeningeal enhancement over both frontal lobes (Image 3A), the basal cisterns (Images 3B and 3C) and around the cavernous sinus, with a hyperintense signal on the FLAIR images over the left cerebellar vermis folia (Image 3D), with no shift in the midline structure and a normal ventricular system. These MRI features, along with the fact that these changes completely disappeared after switching to only anti-TB medications, made the probability of TB higher (Image 4 as an example showing complete resolution of the pachymeningeal enhancement over both frontal lobes).

Regarding the supporting clinical or laboratory tests, our patient had negative Mantoux tuberculin skin testing (TST) and QuantiFERON-TB (QF and T) tests. The TST only assesses the level of

Table 1: Blood Investigations

Test	*Result*	*Comment*
Toxoplasma Gondi	149.8 U/mL	positive if > 34U/mL
Toxoplasma Gondi	negative	
TPHA	non-reactive	
ACE	47 U/L	normal < 65 U/L
HLA-B51, B52, and	negative	
HIV-1	negative	
ANA	negative	
p-ANCA and c-ANCA	negative	
RF	negative	
CRP	negative	
ESR	20 mm/hr.	borderlines normal
Q-Gold	Negative	
HLA-B51	Negative	
HLA-B27	Negative	

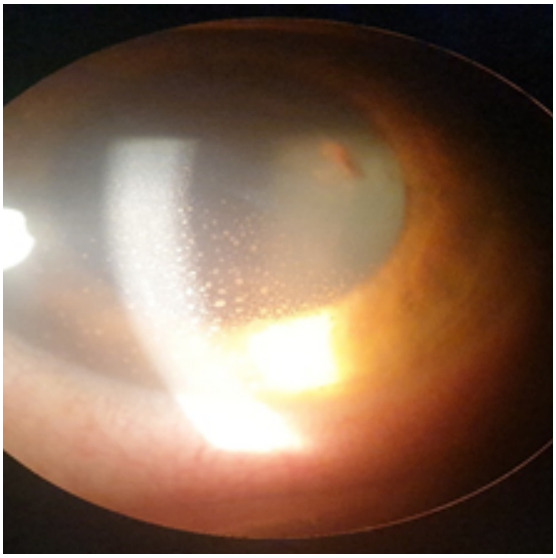


Image 1 A

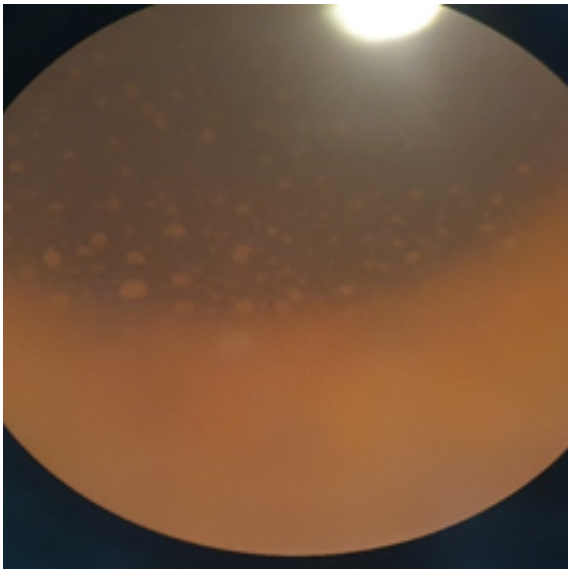


Image 1 B

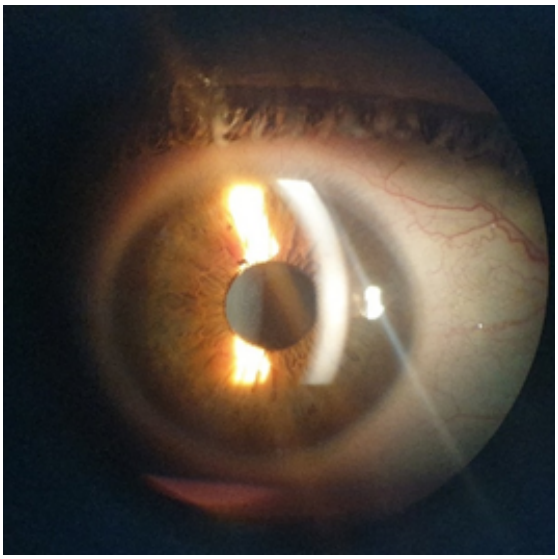
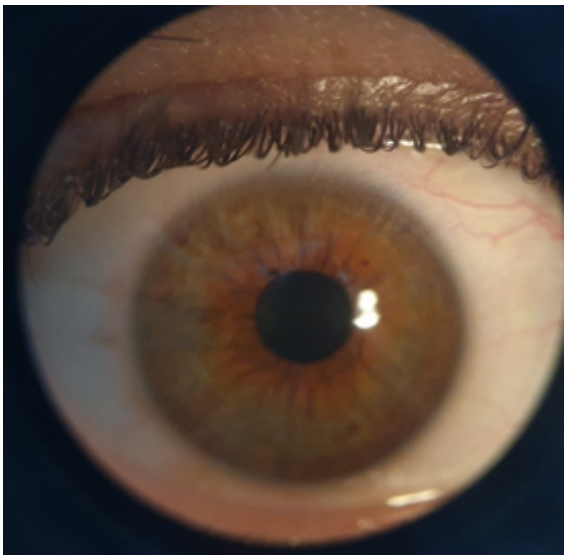


Image 2 A



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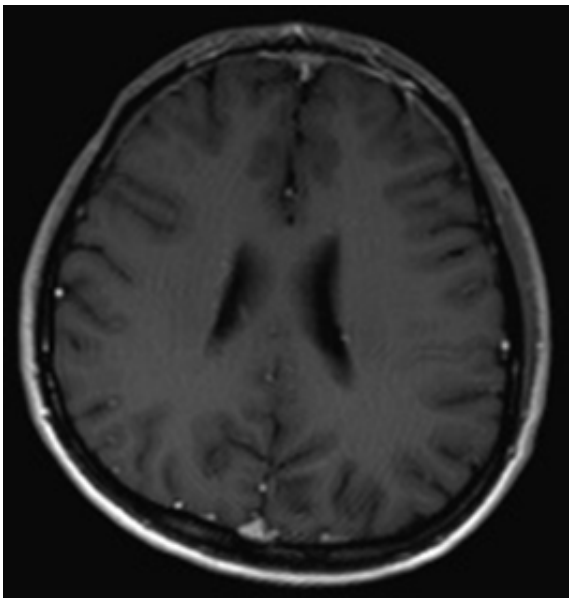

Image 3 A

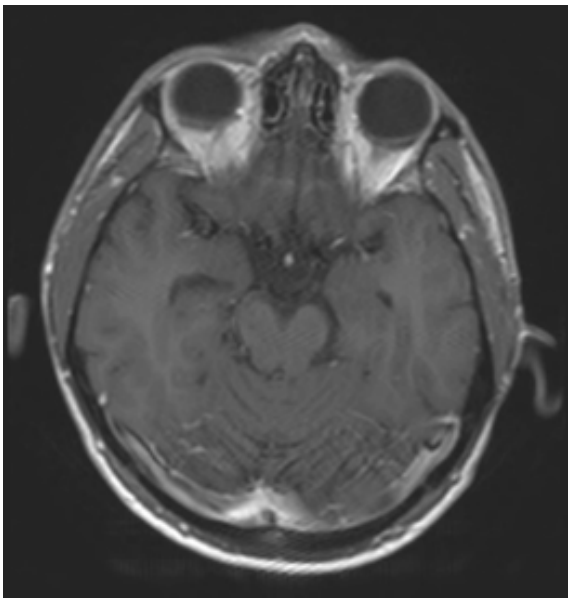

Image 3 B

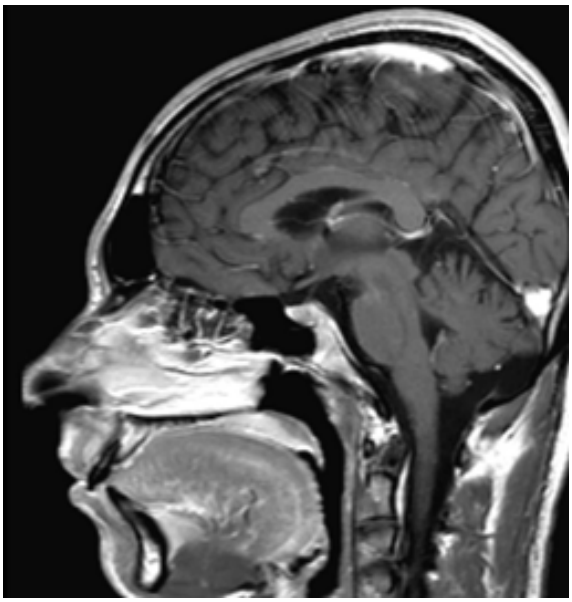

Image 3 C

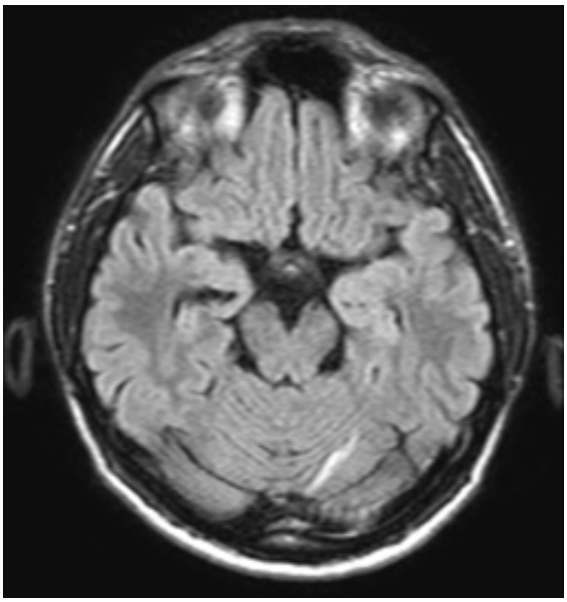

Image 3 D

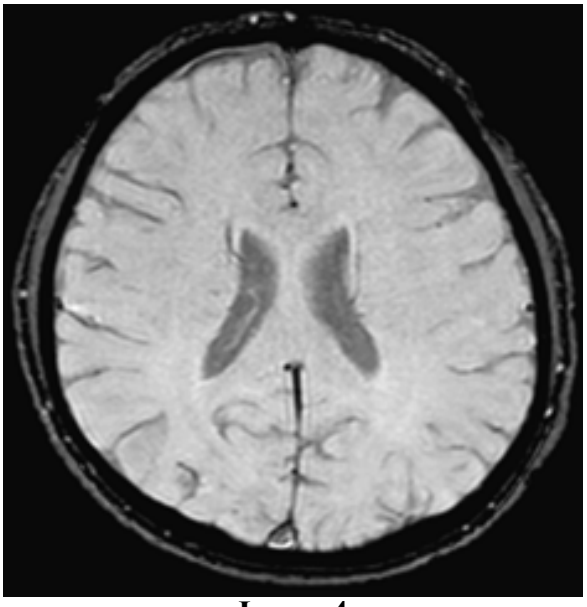

Image 4

tuberculin hypersensitivity; it does not measure TB immunity, and it has a poor positive predictive value for currently active TB. The probability of currently active TB illness does not correlate with the amount of the induration. However, the reaction size is associated with the likelihood of contracting TB in the future (8, 9). The quantitative response of interferon-gamma assays (IGRA), including the QFT test, has been demonstrated in studies to be greater in active TB than in latent TB and to generally decrease after anti-TB therapy (10). It is not yet known if an enhanced IGRA response is related to severe disease or if it may be used to identify active TB. Additionally, it has been observed that extrapulmonary TB has a more significant rate of negative QFT values than pulmonary TB among patients with proved and suspected TB. It is unclear if IGRA aids in the diagnosis of EPTB (11, 12).

Intraocular inflammation can be classified as granulomatous or non-granulomatous uveitis. The former is characterized by large, greasy-appearing, yellowish-white mutton fat keratic precipitates (KPs) on the corneal endothelium and Busacca and Koeppe nodules on the iris. The differential diagnosis of granulomatous uveitis per se includes sarcoidosis, sympathetic ophthalmia, uveitis associated with multiple sclerosis, lens-induced uveitis, intraocular foreign body, Vogt-Koyanagi-Harada syndrome, syphilis, tuberculosis, and other infectious agents (13). Systemic steroids altered our patient's presentation, which can be summarized as granulomatous uveitis with elevated intraocular pressure (IOP). The patient's history, examination, lab tests, and --most importantly-- the disease response to treatment have decreased the likelihood of most of these differentials in favor of tuberculosis.

Ocular involvement occurs in about 1-2% of TB patients (14), with a wide variety of presentations, from non-granulomatous anterior uveitis to occlusive retinal vasculitis. There are no specific uveitis characteristics typical to TB uveitis (15). If Mycobacterium tuberculosis is demonstrated in an ocular fluid or tissue sample by a microbiologic or histopathologic study, the condition is diagnosed as ocular tuberculosis; otherwise, it is assumed ocular TB with or without confirmed active systemic illnesses (16). Due to small sample volumes and low bacterial loads in intraocular samples, it is difficult to definitively diagnose TB uveitis. In these situations, the diagnosis is thus presumptive.

The dilemma of making a preferential differential diagnosis short by labeling our patient's condition as presumed tuberculosis meningitis and uveitis. Given reasonable suspicion of TBM, empirical therapy should be started as soon as feasible to lower morbidity and mortality, because currently available anti-tuberculosis medications are not especially harmful in the short term (6). There is evidence that TBM patients treated with steroids in addition to anti-TB treatment had lower death rates, severe disability rates, and disease recurrence rates. This beneficial impact is amplified by increasing the severity of TB meningitis in terms of lowering mortality (17). Our patient did not have significant meningitis-related symptoms or signs, except for an occasional headache and his neuroimaging findings. Hence, the TB specialist started him on anti-TB medication alone, without accompanying steroids. Nevertheless, in the following weeks, steroids were added to his treatment regime to treat his worsening vitritis, which responded fully. Follow-up MRI and eye examinations showed full resolution of the presenting pathology in both sites.

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