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A patient with central nervous system tuberculomas and a history of disseminated multi-drug-resistant tuberculosis

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ABSTRACT

Tuberculosis (TB) is one of the leading causes of death worldwide, particularly in low- and middle-income countries. The global rates and numbers of drug resistant TB are rising. With increasing globalization, the spread of drug-resistant strains of TB has become a mounting global public health concern. We present a case of a young man previously treated for multi-drug resistant (MDR) TB in India who presented with neurological symptoms and central nervous system TB in the United States. His case highlights unique diagnostic and treatment challenges that are likely to become more commonplace with the increase of patients infected with drug-resistant TB and complicated extrapulmonary disease.

1. Introduction

Tuberculosis (TB) remains one of the top ten causes of death worldwide. In 2015, an estimated 10.4 million people worldwide developed TB and 1.8 million died; over 95% of these deaths occurred in low- and middle-income countries [1]. Resistance to standard anti-TB regimens is becoming widespread in the form of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis. MDR-TB is defined as resistance to isoniazid and rifampin, two of the most potent first-line TB drugs; XDR-TB is resistance to isoniazid, rifampin, the fluoroquinolones, as well as any of the second line injectable agents [1]. Globally, MDR-TB and XDR–TB notifications are both increasing. There were an estimated 480,000 people globally who developed MDR-TB in 2015; the largest numbers of these cases were reported in India, China, and Russia, and 9.5% of MDR cases met the definition of XDR-TB [1]. While TB most commonly infects the lungs, TB can occur in any organ in the body, including the central nervous system (CNS). CNS TB occurs in approximately 1% of patients with TB disease and is associated with major morbidity and mortality.

We present a complicated case of CNS TB in a young man with a history of previously treated MDR-TB. The diagnosis and treatment of this patient presented unique challenges to the treatment team. While MDR and XDR-TB are presently uncommon in patients treated in the United States, rising numbers of cases of drug resistant TB globally and increasing globalization and international travel raise concerns that such cases could be encountered more frequently both in the US and worldwide.

2. Case history and presentation

The patient's TB history is illustrated in Fig. 1 and Table 1 and is summarized here. The patient is a 28-year-old man from India who moved to the United States to attend university in 2004. In 2009, he developed night sweats, fever, weight loss, and cough. He returned to India shortly afterwards, where he was diagnosed with pulmonary and extrapulmonary TB with cervical lymphadenitis. Initial drug susceptibility testing from a lymph node aspirate revealed resistance to pyrazinamide. He was initially treated with a reportedly standard regimen (records not available) but his symptoms did not improve. Two months after start of treatment, he was diagnosed with disseminated TB involving the lungs, spine, and lymph nodes, and required surgery for stabilization of the spine. He was presumed to have MDR-TB, and was

Age 23: Developed TB sx, dx disseminated TB via cervical LN bx. Started RIPE.

Surgery for Pott's disease

4 months after TB dx: dx MDR TB via culture/DST. Started MDR regimen x 18 mos

Age 25: Completed first MDR TB tx course

4 months later: MDR TB relapse with pulmonary sx. Repeat MDR tx (empirical) for 24 months

Age 27: Completed second MDR TB tx course

Presents with seizure; MRI indicates 2 CNS lesions

Surgical removal of frontal lobe tuberculoma; admission for further workup

Age 28: Started presumed XDR CNS TB treatment

Age 30: Completed XDR treatment

Timeline

2009   2011   2013   2014   2016

bx: biopsy; CNS: central nervous system; DST: drug susceptibility testing; dx: diagnosed; LN: lymph node; MDR: multi-drug resistant; mos: months; MRI: magnetic resonance imaging; RIPE: rifampin / isoniazid / pyrazinamide / ethambutol; sx: symptoms; TB: tuberculosis; XDR: extensively drug-resistant

Fig. 1. Case narrative timeline.

Table 1

Categories of antituberculous drugs and patient's TB treatment and drug susceptibility testing history, adapted from the 2016 WHO TB Treatment Guidelines [2].

WHO classification	Drug	Presumptive MDR regimen, 2009 (4 months, pre-DST)	MDR regimen (2 courses)[a]	Total # of months from previous regimens	Resistant on previous DST?	# Of months in "XDR" regimen[b]
First-line agents (drug-sensitive TB)	Isoniazid	x	x	46	x	
	Rifampin	x		4	x	
	Ethambutol	x	x	46		
	Pyrazinamide	x		4	x	
Group A: fluoroquinolones	Levofloxacin			0		
	Moxifloxacin	x		1		24
	Gatifloxacin			0		
	(Ofloxacin)			0	x	
Group B: Second-line injectable agents	Amikacin			0		
	Capreomycin			0		24
	Kanamycin	x	x	8		
	(Streptomycin)			0	x	
Group C: Other core second-line agents	Ethionamide/ Protionamide	x	x	43		
	Cycloserine/Terizidone	X	x	43		
	Linezolid			0		24
	Clofazimine		x	42		
Group D: Add-on agents D1	Pyrazinamide	x		4	x	15[c]
	Ethambutol	x	x	46		
	High-dose isoniazid	x	x	46	x	15[c]
D2	Bedaquiline			0		18
	Delamanid			0		
D3	p-aminosalicylic acid		x	42		
	Imipenem-cilastatin			0		
	Meropenem			0		24
	Amoxicillin-clavulanate			0		24
	(Thioacetazone)			0		

DST: drug susceptibility testing; MDR: multi-drug resistant; TB: tuberculosis; WHO: World Health Organization; XDR: extensively-drug resistant.

[a] Prescribed in 2009 and 2011, before some of the agents in this table were available.

[b] Prescribed in 2014, before some of the agents in this table were available.

[c] Added seven months into treatment course for increased CNS penetration.

started on an empiric eight-drug regimen; bronchoscopy mycobacterial culture was also taken as this time (Table 1). The patient admitted to missing doses of the TB medications during the first two weeks of treatment due to medication-induced nausea and vomiting, but tolerated the regimen thereafter. Four months after his initial presentation, the diagnosis of MDR-TB was microbiologically confirmed; TB drug susceptibility testing (DST) from the initial bronchoscopy revealed resistance to isoniazid, rifampicin, pyrazinamide, ofloxacin, and streptomycin (Table 1). Based on these results, he was changed to a seven-drug regimen, omitting pyrazinamide, rifampin, and moxifloxacin, and adding clofazimine and p-aminosalicylic acid (Table 1, Fig. 1), which he completed after 18 months; directly observed therapy (DOT) was not provided. In 2011, four months after completion of TB therapy with this regimen, while still in India, symptoms including fever, night sweats, weight loss, and fatigue recurred. Bronchoscopy was repeated but cultures were negative for *M. tuberculosis.* He was empirically treated with his previous seven-drug regimen for an additional 24 months (Table 1, Fig. 1). The patient reported adherence to the treatment, supported by later direct confirmation in conversation with his treating physician in India; however, DOT was again not provided. By September 2013, he had successfully completed his second course of treatment for MDR-TB, for a total of 46 months of therapy, and returned to the United States.

The patient was well until February 2014, when he collapsed at work with a seizure. A brain magnetic resonance imaging (MRI) scan revealed two enhancing lesions, one in the superior left frontal lobe measuring $9 \times 7 \times 7$ mm and one in the medulla oblongata measuring $5 \times 5 \times 6$ mm; each demonstrated mild to moderate ring enhancement and edema. A lumbar puncture was negative for *M. tuberculosis* using polymerase chain reaction (PCR) testing. Mycobacterial culture was not performed. Serologies for HIV, syphilis, toxoplasmosis, brucella, echinococcus, cysticercosis, and *B. burgdorferi* were negative. Excision of the frontal lobe lesion for pathological and microbiological diagnosis was recommended.

A repeat MRI in June 2014 showed an interval increase in vasogenic edema around the lesion in the medulla oblongata when compared with imaging from three months prior (Fig. 2A–C). He underwent left craniotomy with removal of a yellowish granular firm mass lesion from his frontal lobe. Pathology of the brain lesion revealed tuberculous abscess with multiple granulomas at varying stages including several caseating granulomas, surrounded by numerous lymphocytic and macrophage inflammatory cells as indicated on stains for T cell, B cell, and macrophage markers (CD3, CD20, and CD68) (Fig. 3). The specimen stained positive for acid-fast bacilli (AFB). Nucleic acid amplification testing (GeneXpert®) was positive for *M. tuberculosis* and rifampin resistance. Mycobacterial and fungal cultures were negative after eight weeks of incubation.

The patient was admitted in July 2014 for further workup and treatment. On admission, he denied fever, chills, weight loss, cough, hemoptysis, chest pain, urinary symptoms, nausea, vomiting, diarrhea, or constipation. His surgical scar was well healed. His mental status was normal, neurologic examination was non-focal, and the remainder of the physical examination was unremarkable. Complete blood count (CBC) was normal except for a mild leukocytosis (14,300), likely due to the patient being on steroids prescribed after his neurosurgery. Other routine blood tests (complete metabolic panel including liver function tests, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), thyroid stimulating hormone (TSH)) were within normal limits.

3. Further imaging and microbiologic studies

The patient underwent a chest computerized tomography (CT) scan that revealed calcified lung nodules consistent with prior granulomatous disease. An abdominal/pelvis CT demonstrated scattered calcified granulomas and non-enlarged calcified peritoneal lymph nodes also suggestive of prior granulomatous disease. Post-operative changes were seen at the site of his previous spinal surgery (T8-T12).

Six induced sputum specimens were negative for AFB and culture for *M. tuberculosis* was negative after eight weeks of incubation. GeneXpert® was negative on three specimens. Urine and blood mycobacterial cultures were also negative. Bronchoscopy with bronchoalveolar lavage (BAL) and biopsy of a heavily calcified granuloma in the left upper lobe (LUL) were performed, which showed mild chronic inflammation and no granulomas. AFB stains of both specimens were negative and cultures of both samples were reported as no growth. A repeat brain MRI post-surgery indicated the medulla lesion similar in appearance to the previous scan, with no interval change in edema.

Formalin fixed paraffin embedded brain tissue was sent to the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia to amplify any *M. tuberculosis* genetic material (DNA) present and test for common resistance mutations to TB medications; however, the sample was small and did not contain a sufficient amount of genetic material for amplification.

4. Treatment course and follow-up

Given the radiological and pathological interpretations, the patient was diagnosed with probable active CNS TB disease with tuberculoma formation. In light of his documented history of prolonged treatment for extrapulmonary MDR-TB, lack of current positive cultures, and inability to obtain current TB drug susceptibilities, combined with the precarious location of the lesion in his brainstem, he was started on an empiric TB drug regimen. The regimen was chosen after review of medical records obtained from India and extensive discussions with local clinicians, the Connecticut Department of Public Health, and national TB experts (Table 1). This regimen consisted of moxifloxacin 400 mg orally daily, capreomycin 1000 mg intravenous (IV) daily, linezolid 600 mg orally daily, bedaquiline (provided through the Connecticut Department of Public Health) loading dose 400 mg orally daily × 14 days, then 200 mg orally three times per week, meropenem 2 g IV every eight hours, and amoxicillin-clavulanate 500 mg/125 mg orally every eight hours. A dexamethasone taper (starting at 2 mg orally every six hours) was also initiated due to concerns for worsening edema surrounding the medulla lesion.

The patient remained hospitalized for four weeks to ensure medication adherence and tolerance and to arrange support services including a visiting nurse for intravenous therapy monitoring and case management including DOT by the local health department. He lived with a very supportive family, who provided strong social support and were educated about and involved in his care and medication adherence. Drug safety monitoring was employed, given the wide array of possible adverse effects with this regimen. Daily electrocardiograms were performed to monitor QTc prolongation for bedaquiline and moxifloxacin use while in hospital and weekly to monthly thereafter. Renal function, electrolytes, and baseline and follow-up audiology exams were performed to monitor for capreomycin toxicity. Weekly CBC was performed while on linezolid. Liver function tests were also monitored for hepatotoxicity.

The patient was followed in the Infectious Disease outpatient clinic every six to eight weeks for the 24-month duration of his treatment. The local health department also saw him 3–5 times per week at home for DOT and medication monitoring, including toxicity assessment. Meropenem administration was carefully monitored and the patient learned to self-administer it every eight hours via a CADD® pump, carried in a backpack for continuous infusion. His CNS lesion was monitored by serial MRI examinations every two to three months, with assessment of the size of the medulla lesion and surrounding edema. He completed his first course of bedaquiline and other drugs after six months of treatment without incident. Dexamethasone dose was gradually tapered from 2 mg daily to 1 mg every other day. At seven months into treatment, MRI results indicated re-demonstration of a ring-enhancing lesion of the dorsal medulla, which was slightly larger in size measuring 7×6 mm compared to pre-treatment lesion of
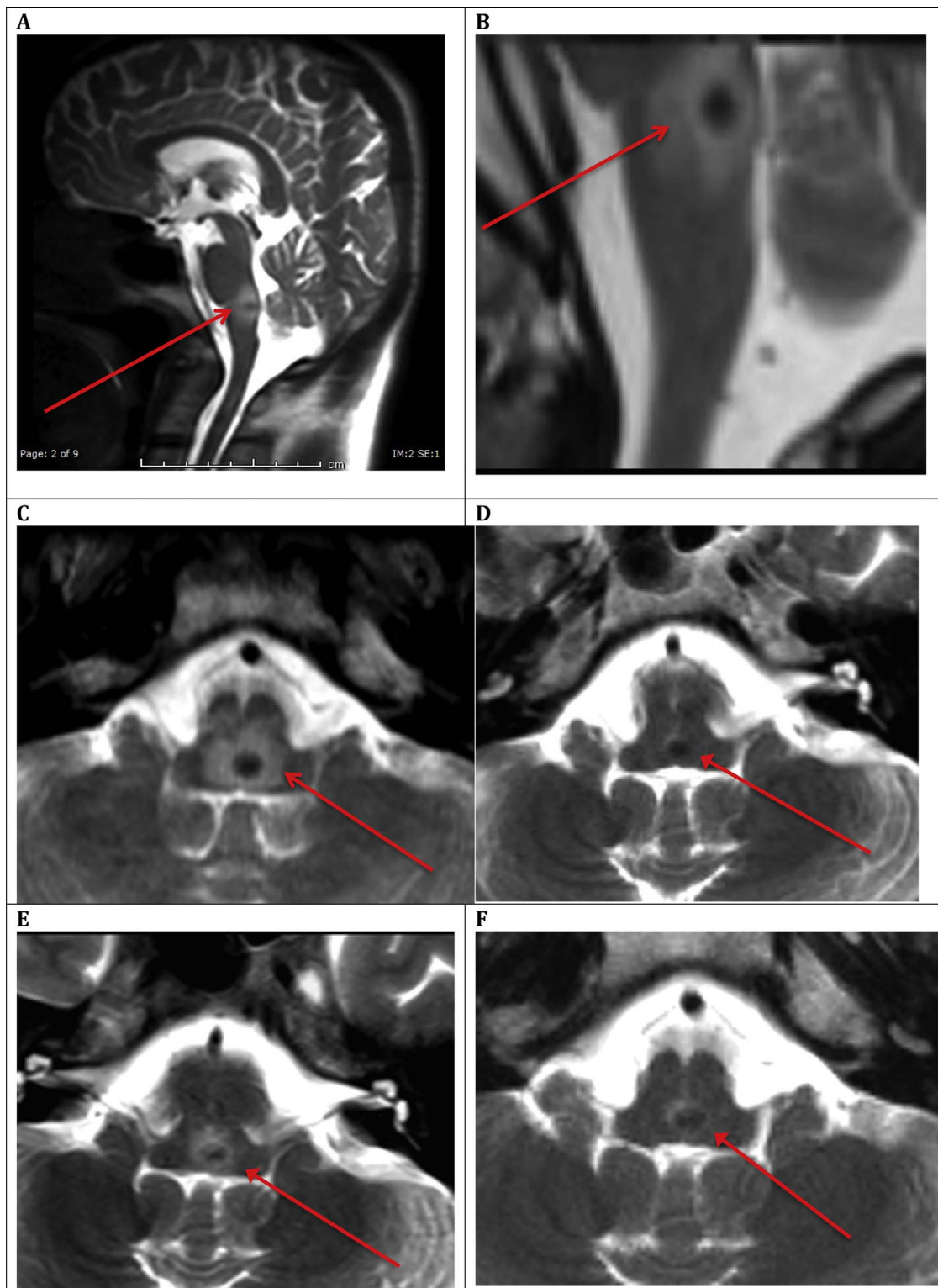
Fig. 2. Serial MRIs of medulla lesion. (A) June 2014: pre-treatment. T2 sagittal. Arrow points to location of lesion in the medulla (B) June 2014: pre-treatment. T2 sagittal, enlarged (C) June 2014: pre-treatment, T2 axial (D) October 2014: two months into treatment, T2 axial (E) March 2015: seven months into treatment, T2 axial (F) July 2016: at completion of treatment course, T2 axial. This image shows similar size lesion compared with pre-treatment, but marked diminution of edema around lesion. (All images are Spin Echo T2 WI without contrast).

5 × 4 mm. The peripheral rim enhancement was also thicker than on the prior exam. In addition, there was interval increase in peri-lesional edema (Fig. 2E). His regimen was re-evaluated with input from local and national TB experts. Drug resistance or lack of sufficient drug potency within the central nervous system was a concern, but it was concluded that the most likely explanation for the increase in edema was a tapering of the dexamethasone dose from daily to every other day dosing with possible paradoxical reaction (immune reconstitution) after several months of therapy. As a result, the dexamethasone dose was increased again to daily dosing (1 mg), and the anti-TB drug regimen
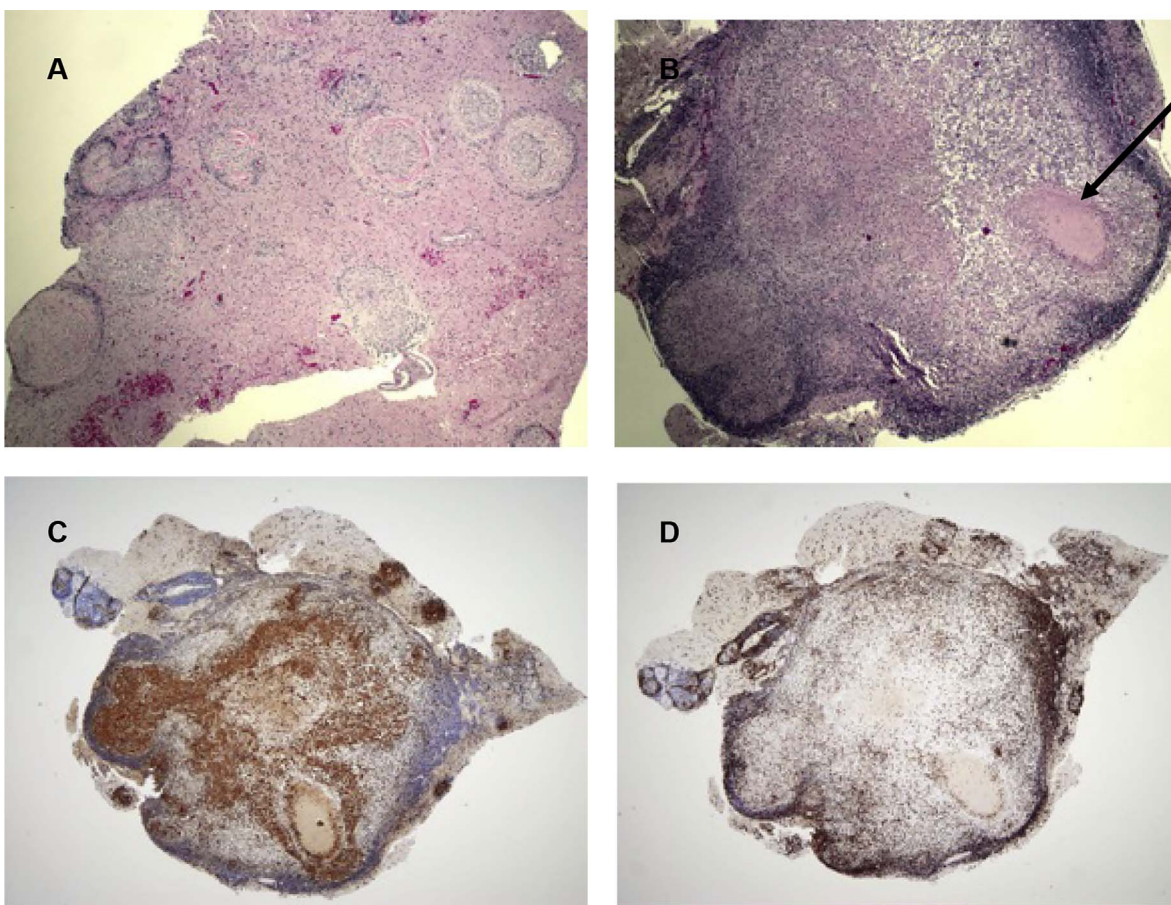
Fig. 3. Pathology from frontal lobe lesion (A and B). The hematoxylin & eosin stained biopsy samples show several granulomas, including one granuloma with necrotic center ('caseating necrosis', arrow in B). Numerous inflammatory cells are present throughout the biopsy, (C) demonstrates CD68 positive macrophages and (D) shows CD3 positive T-lymphocytes.

was also revised: bedaquiline was restarted, with loading dose 400 mg orally daily × 14 days, then 200 mg three times per week. Isoniazid 600 mg orally daily (with vitamin B6 100 mg) and pyrazinamide 2000 mg orally daily were also added because of their favorable CSF penetrative properties. Meropenem 2 g IV every eight hours, amoxicillin-clavulanate 500 mg/125 mg orally every eight hours, linezolid 600 mg orally daily, and moxifloxacin 400 mg orally daily were maintained. DOT was also increased at this time to once per day, including weekends, either in person or by internet-based video (FaceTime®) methods.

He continued the regimen for a total of 24 months and completed treatment on August 20, 2016. He has remained clinically stable for nine months after treatment completion, without return of seizures or neurologic sequelae. MRI at time of treatment completion showed the stable 7 mm peripherally enhancing lesion at the ponto-medullary junction, unchanged in size, with no new lesions identified. There was minimal edema, markedly decreased back to the level of the prior scans (Fig. 2F). He tolerated his complicated treatment course well, experiencing surprisingly minimal toxicity from this regimen, apart from moderate bilateral peripheral neuropathy in his feet felt to be due to linezolid, which responded to gabapentin. Through the course of the treatment, he remained optimistic, and he and his family were fully engaged in decision-making and the arduous treatment course. He was also able to work as a math tutor and accountant during the latter half of his treatment. His treatment course was complicated, however, by weight gain, general deconditioning, fatigue, and avascular necrosis of the left hip (which has since required a total hip replacement), all likely attributable to long-term steroid use. He will continue to follow up at the infectious disease outpatient clinic for an additional two years after

his treatment completion date.

5. Discussion

This case of a young man with a history of multidrug-resistant TB who presented with a seizure and CNS lesions posed an array of complex diagnostic and therapeutic challenges. The first challenge in caring for this patient was to determine whether he had an active tuberculoma or CNS brain abscess. His previously complicated history of confirmed extrapulmonary MDR-TB in India, with prolonged MDR-TB therapy, did not include CNS disease. His clinical presentation was with a seizure, without other more usual systemic signs or symptoms of active TB disease. Under our care, two lesions were seen on MRI with surrounding edema, and tissue obtained at brain biopsy was AFB positive and positive on nucleic acid amplification testing (GeneXpert®) for *M. tuberculosis* and rifampin resistance. However, TB culture was negative. The reason for this discrepancy between the positive AFB stain and GeneXpert® results and the negative culture is not clear. One possibility is that the organisms seen on stain and detected on PCR were actually dead as both Xpert and AFB stain will pick up dead as well as live organisms. Alternatively, there may have been a falsely negative culture result for technical reasons.

Further, multiple pulmonary specimens were also culture negative for TB. The location of the patient's lesion in the medulla oblongata within the brainstem was further challenging diagnostically, as confirmation via biopsy of the lesion itself was contraindicated because of its anatomic location. We therefore had to rely on the use of radiologic imaging and interpretation of the pathology of tissue obtained from a coexisting frontal lobe lesion to make the diagnosis of active CNS TB

disease. Other reported studies have used radiological diagnosis using MRI and CT for tuberculomas and to assess their activity; notably, lesions are frequently surrounded by a halo of contiguous vasogenic white matter edema, the amount of which is thought to be inversely proportional to the maturity and activity of the lesion [3,4]. In this case, the edema surrounding the patient's medulla lesion on MRI led neuroradiologists to conclude that the lesion was most likely active, particularly given the interval increase in edema when compared with the MRI from three months prior (Fig. 2A–C).

Histopathological findings of caseating granulomas and multinucleated giant cells and inflammatory cells as indicated on stains for T cell, B cell, and macrophage markers (CD3, CD20, CD68,) in the patient's frontal lobe brain specimen also strongly supported the diagnosis of active disease (Fig. 3). A retrospective study of 23 patients with CNS tuberculomas found caseating granulomas and epithelioid histiocytes on pathology but AFBs were not usually seen [5]. In another study of 17 cases of intramedullary tuberculomas of the spinal cord, similar pathological findings of well circumscribed masses with caseating granulomas were present, but AFB were seen in less than half the cases, with only one culture-positive specimen [6]. A case study of a patient with a tuberculoma in the medulla oblongata, similar to this patient, showed a granulomatous lesion containing multinucleated giant cells and inflammatory cells with caseous necrosis [7]. In the present case, we were able to employ the GeneXpert® test on the frontal lobe specimen, which was positive for both *M. tuberculosis* and rifampin resistance. The World Health Organization has summarized information on the use of GeneXpert® for extrapulmonary TB tissue specimens and affirms its utility in individual cases, but does not make a general recommendation for this use as data is limited. However, available limited data suggests that the use of GeneXpert® on tissue samples has high sensitivity and specificity in detecting *M. tuberculosis* organisms, including in brain tissue [8–10]. This was helpful in confirming the diagnosis but not whether the lesion was active or not. Although these findings were from the frontal lobe and not the medulla lesion, we assumed that the patient had active TB disease within the medulla based on these characteristic pathologic and radiologic findings, despite the negative culture. Given the mortality of CNS tuberculoma without treatment is estimated between 35–85%, and the precarious location of the lesion in question and its likely activity, we concluded that there was sufficient urgency to treat this patient empirically and aggressively [7,11].

A second challenge in the management of this patient, given his previous extensive and prolonged treatment for MDR-TB, was constructing an effective treatment regimen. We were fortunate to be in contact with his treating physician in India and have access to his previous files, including his available drug resistance reports and type and duration of treatment regimens. Although guidelines exist for MDR and XDR-TB treatment, treatment is often based on expert opinion and tailored to individual patients, particularly for extrapulmonary disease, as was the case for this patient [12]. The drugs for which resistance was known and those used extensively before treatment relapse left an extremely limited array of drugs from which to choose (Table 1). These recommendations generally apply to both pulmonary and extra-pulmonary MDR/XDR-TB, but recommendations for treatment of CNS MDR or XDR-TB are further problematic because of limited data on CNS penetration and a lack of evidence of clinical success for many of the recommended medications. Among first-line agents, classic CNS-penetrating drugs used successfully in other tuberculoma cases include isoniazid, rifampin, ethambutol, and pyrazinamide [5,6,13], but available previous resistance data and previous treatment history for this patient indicated likely resistance to these agents. Second-line TB drugs with good CNS penetration include ethionamide, cycloserine, later generation fluoroquinolones (e.g. moxifloxacin), and linezolid [11,14–16]. Newly developed and available bedaquiline was an obvious choice; however, there were no data on the CNS penetration of bedaquiline. While drug susceptibility tests could not be obtained presently, previous resistance information was available for some of the

drugs, and it was assumed that the patient was probably resistant to the medications that he received during his previous treatment courses (Table 1).

At the time of the decision to initiate treatment in this patient, we recognized that there were only three truly new agents available for him: bedaquiline, linezolid, and meropenem/amoxicillin-clavulanate (solely for clavulanate, which is not available as a single agent in the United States). In addition, moxifloxacin was prescribed despite his brief treatment history with this drug, given its favorable CNS penetration and that it has shown to be a predictor of successful outcomes in XDR-TB [17], including in a prospective study of heavily pre-treated patients with MDR-TB in the private sector in Mumbai, India, where the patient likely acquired his initial infection [18]. Furthermore, although there was reported resistance to streptomycin and ofloxacin, and previous use of kanamycin, we chose to administer capreomycin in addition to moxifloxacin, recognizing that class cross-resistance was possible.

Bedaquiline was, at the time, the newest TB medication and the first new anti-TB drug in 40 years. Bedaquiline inhibits mycobacterial ATP synthase and has been approved by the United States Food and Drug Administration (FDA) and the World Health Organization for use in drug-resistant TB [2,19]. Bedaquiline has been shown to effect more rapid sputum culture conversion in both MDR and XDR-TB patients [20–24], and there are ongoing studies indicating its effectiveness in treating pulmonary XDR-TB in combination with other new drugs [25]. There is very limited information and a lack of formal research regarding bedaquiline CNS penetration and pharmacokinetics. We located a single case report in which multiple CSF measurements of bedaquiline were completed in a patient being treated for TB meningitis. In this case study, bedaquiline was not detected in the CSF [26]. Information on how this may relate to the penetration of the drug into a brain abscess is similarly limited. In this case, with such limited therapeutic options and available information and an extremely dangerous clinical scenario, we felt justified to aggressively treat with bedaquiline. We recognize a critical need to develop more information on the CNS penetration of most of the older TB drugs and bedaquiline and other newer drugs in the future. While bedaquiline is normally prescribed for 24 weeks, our patient underwent an 18-month regimen without adverse effects. To our knowledge, this is one of the longest administered bedaquiline regimens in the United States.

Meropenem combined with clavulanate has been shown to be effective against XDR and MDR strains in vitro, demonstrating that the specific beta-lactamase of *M. tuberculosis* can be overcome with an effective beta lactamase inhibitor such as clavulanate [27–32]. From limited experience, effectiveness of this regimen in combination with linezolid has also been shown in patients with MDR and XDR [29,33,34], adding to the evidence for linezolid's effectiveness in achieving culture conversion in XDR patients [35]. As meropenem is only available in an intravenous formulation, administration of this drug required the use of a CADD® pump and the patient's ability to perform home IV therapy. We recognize that this may not be a feasible solution for every patient. Of note, although he tolerated his anti-tuberculosis medications well and without major toxicities, the patient had mild residual neuropathy at the time of completion of treatment, attributable to linezolid.

Monitoring the response to TB treatment requires documentation of negative smear and culture. Current international guidelines recommend continuing therapy for a minimum of 24 months after culture conversion for XDR-TB [36]. In some circumstances, particularly if resistance patterns are known, more prolonged therapy may be beneficial [37,38]. Because our patient did not have a positive culture and his lesion was inaccessible to sample, it was not possible to use microbiological criteria to determine exactly when to end treatment. We elected to treat for 24 months, with careful radiologic and clinical monitoring and continued follow-up after treatment completion.

An additional challenge was the use of steroids to treat this patient.

Although still controversial, reviews suggest that steroids are effective in reducing mortality for all forms of TB [39]. There is more general agreement that steroids are of benefit in reducing mortality and focal neurological deficits in patients with tuberculous meningitis [40,41]. There has also been some evidence suggesting that corticosteroids are effective in managing cerebral edema and symptoms related to tuberculomas, but data are limited and based solely on anecdotes and case reports [11,42]. However, because of the persistent and recurring edema noted on the patient's MRI scans and the location of the lesion in a high-risk area of his brainstem, we felt obliged to add dexamethasone, with very gradual taper, to his regimen. As noted, this unfortunately resulted in his only serious medication toxicity, aseptic necrosis of the left hip.

Close collaboration between clinical medicine and public health colleagues was vital to the successful treatment of this patient. The state public health department facilitated discussion of this patient on a national conference call between clinical and public health TB experts to come to a consensus on the best treatment regimen for the patient and then again when the patient's brain lesions appeared worse on imaging. This resulted in a change in the regimen that the patient ultimately completed. The state public health department procured bedaquiline and received permission for its continued use beyond the recommended 24-week course, and facilitated local health department DOT and monitoring of the patient's medication supply and symptoms. The use of live internet-based video DOT (via HIPAA compliant FaceTime® on the patient's iPhone®) facilitated interaction with the patient on a daily basis (including weekends), even if the patient travelled or a public health staff member was away. Such methodology has been used effectively and efficiently in other settings [43–45]. In addition to the medical care received, critical to the therapeutic success were the patient's supportive home setting and his own stamina and resilience.

6. Conclusions

In summary, this case outlines the difficult diagnostic and therapeutic challenges and decisions made in a non-immunocompromised young man from India with previous extensive treatment for MDR-TB and presumed CNS XDR-TB. While the case represents a rare TB presentation, the issues discussed in diagnosing and treating this patient have broader relevance. There is mounting evidence of growing numbers of drug-resistant TB cases globally, and transmitted primary drug-resistant TB is increasingly more common than resistance due to inadequate or unsuccessful TB treatment [12,46–50]. As drug-resistant TB strains spread throughout populous countries such as India and China, as well as countries of the former Soviet Union and sub-Saharan Africa, and extend to lower prevalence areas such as the United States, using second and third-line regimens in combination with newer drugs will become increasingly commonplace. This case illustrates not only complexities of diagnosis and treatment, but also the continuing need for an array of new effective TB agents and rigorous documentation of their effectiveness in the clinical setting. In addition, further experience is needed in their use in managing not only pulmonary but also extrapulmonary drug-susceptible and drug-resistant TB. Finally, we note that this case illustrates the greater issue of increasing TB and drug resistant TB as a global public health emergency at a time when, paradoxically, cases are declining in the United States. In an era of globalization and continuing disparities of health and resources that underlie the spread of TB, we acknowledge the need to support global TB efforts to prevent the spread of drug-resistant TB, and to maintain TB expertise and patient supportive services in the United States.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

References

[1] World Health Organization. Tuberculosis fact sheet 2016 19 October Available from: http://www.who.int/mediacentre/factsheets/fs104/en/; 2016.

[2] World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis: 2016 update. World Health Organization; 2016.

[3] Bernaerts A, Vanhoenacker FM, Parizel PM, Van Goethem JW, Van Altena R, Laridon A, et al. Tuberculosis of the central nervous system: overview of neuroradiological findings. Eur Radiol 2003;13(8):1876–90.

[4] Donmez FY, Coskun M, Guven G. Medulla oblongata tuberculoma mimicking metastasis presenting with stroke-like symptoms. Neurol Sci. 2009;30:349–52.

[5] Bayindir C, Mete O, Bilgic B. Retrospective study of 23 pathologically proven cases of central nervous system tuberculomas. Clin Neurol Neurosurg 2006;108(4):353–7.

[6] MacDonell AH, Baird RW, Bronze MS. Intramedullary tuberculomas of the spinal cord: case report and review. Rev Infectious Dis 1990;12(3):432–9.

[7] Gulsen S, Caner H. Tuberculoma in the medulla oblongata and medulla spinalis: two case reports. Balkan Med J 2013;30(4):442–5.

[8] Miller MB, Popowitch EB, Backlund MG, Ager EP. Performance of Xpert MTB/RIF RUO assay and IS6110 real-time PCR for Mycobacterium tuberculosis detection in clinical samples. J Clin Microbiol 2011;49(10):3458–62.

[9] Scott LE, Beylis N, Nicol M, Nkuna G, Molapo S, Berrie L, et al. Diagnostic accuracy of Xpert MTB/RIF for extrapulmonary tuberculosis specimens: establishing a laboratory testing algorithm for South Africa. J Clin Microbiol 2014;52(6):1818–23.

[10] World Health Organization. Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children: policy update. 2013.

[11] Thwaites G, FIsher M, Hemingway C, Scott G, Solomon T, Innes J. British infection society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. J Infect 2009;59:167–87.

[12] Dheda K, Gumbo T, Maartens G, Dooley KE, McNerney R, Murray M, et al. The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. Lancet Respir Med 2017;5(4):291–360.

[13] Gropper MR, Schulder M, Sharan AD, Cho ES. Central nervous system tuberculosis: medical management and surgical indications. Surg Neurol 1995;44(4):378–84. Discussion 84-5.

[14] Daley CL, Caminero JA. Management of multidrug resistant tuberculosis. Semin Respir Crit Care Med 2013;34:44–59.

[15] Sun F, Ruan Q, Wang J, Chen S, Jin J, Shao L, et al. Linezolid manifests a rapid and dramatic therapeutic effect for patients with life-threatening tuberculous meningitis. Antimicrob Agents Chemother 2014;58(10):6297–301.

[16] Nau R, Sörgel F, Eiffert H. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clin Microbiol Rev 2010;23(4):858–83.

[17] Jacobson KR, Tierney DB, Jeon CY, Mitnick CD, Murray MB. Treatment outcomes among patients with extensively drug-resistant tuberculosis: systematic review and meta-analysis. Clin Infect Dis 2010;51(1):6–14.

[18] Udwadia Z, Moharil G. Multidrug-resistant-tuberculosis treatment in the Indian private sector: results from a tertiary referral private hospital in Mumbai. Lung India.

[19] Bedaquiline: drug information [Internet]. 2017 [cited 4 April 2017].

[20] Diacon AH, Donald PR, Pym A, Grobusch M, Patientia RF, Mahanyele R, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. Antimicrob Agents Chemother 2012;56(6):3271–6.

[21] Pym AS, Diacon AH, Tang SJ, Conradie F, Danilovits M, Chuchottaworn C, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. Eur Respir J 2016;47(2):564–74.

[22] Ndjeka N, Conradie F, Schnippel K, Hughes J, Bantubani N, Ferreira H, et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. Int J Tuberculosis Lung Dis 2015;19(8):979–85.

[23] Guglielmetti L, Le Du D, Jachym M, Henry B, Martin D, Caumes E, et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. Clin Infect

Dis 2015;60(2):188–94.

[24] Diacon AH, Pym A, Grobusch M, Patientia R, Rustomjee R, Page-Shipp L, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med 2009;360(23):2397–405.

[25] Conradie F, Diacon AH, Everitt D, Mendel C, van Niekerk C, Howell P, et al. The NIX-TB trial of pretomanid, bedaquiline, and linezolid to treat XDR-TB. Conference on retroviruses and opportunistic infections (CROI); Seattle, WA. 2017.

[26] Akkerman OW, Odish OF, Bolhuis MS, de Lange WC, Kremer HP, Luijckx GJ, et al. Pharmacokinetics of Bedaquiline in cerebrospinal fluid and serum in multidrug-resistant tuberculous meningitis. Clin Infect Dis 2016;62(4):523–4.

[27] Kurz SG, Bonomo RA. Reappraising the use of beta-lactams to treat tuberculosis. Expert Rev Anti Infect Ther 2012;10(9):999–1006.

[28] Hugonnet JE, Tremblay LW, Boshoff HI, Barry 3rd CE, Blanchard JS. Meropenem-clavulanate is effective against extensively drug-resistant Mycobacterium tuberculosis. Science 2009;323(5918):1215–8. (New York, NY).

[29] Dauby N, Muylle I, Mouchet F, Sergysels R, Payen MC. Meropenem/clavulanate and linezolid treatment for extensively drug-resistant tuberculosis. Pediatr Infect Dis J 2011;30(9):812–3.

[30] Davies Forsman L, Giske CG, Bruchfeld J, Schon T, Jureen P, Angeby K. Meropenem-clavulanic acid has high in vitro activity against multidrug-resistant mycobacterium tuberculosis. Antimicrob Agents Chemother 2015;59(6):3630–2.

[31] England K, Boshoff HIM, Arora K, Weiner D, Dayao E, Schimel D, et al. Meropenem-clavulanic acid shows activity against mycobacterium tuberculosis in vivo. Antimicrob Agents Chemother 2012;56(6):3384–7.

[32] Diacon AH, van der Merwe L, Barnard M, von Groote-Bidlingmaier F, Lange C, Garcia-Basteiro AL, et al. B-lactams against tuberculosis – new trick for an old dog? N Engl J Med 2016.

[33] De Lorenzo S, Alffenaar JW, Sotgiu G, Centis R, D'Ambrosio L, Tiberi S, et al. Efficacy and safety of meropenem-clavulanate added to linezolid-containing regimens in the treatment of MDR-/XDR-TB. Eur Respir J 2013;41(6):1386–92.

[34] Tiberi S, Payen MC, Sotgiu G, D'Ambrosio L, Alarcon Guizado V, Alffenaar JW, et al. Effectiveness and safety of meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. Eur Respir J 2016;47(4):1235–43.

[35] Lee M, Lee J, Carroll MW, Choi H, Min S, Song T, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. N Engl J Med 2012;367(16):1508–18.

[36] Curry International Tuberculosis Center and California Department of Public Health. Drug-resistant tuberculosis: a survival guide for clinicians. 3rd ed. 2016.

[37] Ahmad Khan F, Gelmanova IY, Franke MF, Atwood S, Zemlyanaya NA, Unakova IA, et al. Aggressive regimens reduce risk of recurrence after successful treatment of MDR-TB. Clin Infect Dis 2016;63(2):214–20.

[38] Yuen CM, Kurbatova EV, Tupasi T, Caoili JC, Van Der Walt M, Kvasnovsky C, et al. Association between regimen composition and treatment response in patients with multidrug-resistant tuberculosis: a prospective cohort study. PLoS Med 2015;12(12):e1001932.

[39] Critchley JA, Young F, Orton L, Garner P. Corticosteroids for prevention of mortality in people with tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis 2013;13(3):223–37.

[40] Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev 2008(1). Cd002244.

[41] Kadhiravan T, Deepanjali S. Role of corticosteroids in the treatment of tuberculosis: an evidence-based update. Indian J Chest Dis Allied Sci 2010;52:153–8.

[42] Afghani B, Lieberman JM. Paradoxical enlargement or development of intracranial tuberculomas during therapy: case report and review. Clin Infect Dis 1994;19(6):1092–9.

[43] Chuck C, Robinson E, Macaraig M, Alexander M, Burzynski J. Enhancing management of tuberculosis treatment with video directly observed therapy in New York city. Int J Tuberculosis Lung Dis 2016;20(5):588–93.

[44] Story A, Garfein RS, Hayward A, Rusovich V, Dadu A, Soltan V, et al. Monitoring therapy compliance of tuberculosis patients by using video-enabled electronic devices. Emerg Infect Dis 2016;22(3):538–40.

[45] Garfein RS, Collins K, Munoz F, Moser K, Cerecer-Callu P, Raab F, et al. Feasibility of tuberculosis treatment monitoring by video directly observed therapy: a binational pilot study. Int J Tuberculosis Lung Dis 2015;19(9):1057–64.

[46] Shah NS, Auld SC, Brust JC, Mathema B, Ismail N, Moodley P, et al. Transmission of extensively drug-resistant tuberculosis in South Africa. N Engl J Med 2017;376(3):243–53.

[47] Moro ML, Gori A, Errante I, Infuso A, Franzetti F, Sodano L, et al. An outbreak of multidrug-resistant tuberculosis involving HIV-infected patients of two hospitals in Milan, Italy. Italian multidrug-resistant tuberculosis outbreak study group. Aids. 1998;12(9):1095–102.

[48] Ritacco V, Di Lonardo M, Reniero A, Ambroggi M, Barrera L, Dambrosi A, et al. Nosocomial spread of human immunodeficiency virus-related multidrug-resistant tuberculosis in Buenos Aires. J Infect Dis 1997;176(3):637–42.

[49] Pearson ML, Jereb JA, Frieden TR, Crawford JT, Davis BJ, Dooley SW, et al. Nosocomial transmission of multidrug-resistant mycobacterium tuberculosis. A risk to patients and health care workers. Ann Internal Med 1992;117(3):191–6.

[50] O'Donnell MR, Jarand J, Loveday M, et al. HIgh incidence of hospital admissions with multidrug-resistant and extensively drug-resistant tuberculosis among South African health care workers. Ann Intern Med 2010;153(8):516–22.