Published in final edited form as:

Infect Dis Clin Pract (Baltim Md). 2016 May ; 24(3): 180–182. doi:10.1097/IPC.0000000000000333.

Diagnosis of Concurrent Pulmonary Tuberculosis and Tuberculous Otitis Media Confirmed by Xpert MTB/RIF in the United States

Kathleen M. Tompkins, MD¹, Melissa A. Reimers, MD², Becky L. White, MD, MPH³, and Michael E. Herce, MD, MPH, MSc^{3,4}

¹ The University of North Carolina at Chapel Hill School of Medicine

² University of North Carolina at Chapel Hill, Department of Internal Medicine

³ University of North Carolina at Chapel Hill School of Medicine, Department of Medicine, Division of infectious diseases

⁴ Centre for Infectious Disease Research in Zambia (CIDRZ)

Abstract

Tuberculosis (TB) remains an important cause of infectious morbidity in the United States (US), necessitating timely and accurate diagnosis. We report a case of concurrent pulmonary and extrapulmonary TB presenting as tuberculous otitis media in a hospitalized US patient admitted with cough, night sweats, and unilateral purulent otorrhea. Diagnosis was made by smear microscopy and rapidly confirmed by Xpert MTB/RIF—a novel, automated nucleic acid amplification test for the rapid detection of drug-susceptible and drug-resistant TB. This case adds to the growing body of evidence validating Xpert MTB/RIF as an effective tool for the rapid diagnosis of extrapulmonary TB, even in low TB-prevalence settings such as the US, when testing is performed on non-respiratory specimens.

Keywords

Xpert; extrapulmonary tuberculosis; chronic otitis media; nucleic acid amplification test; otorrhea

Introduction

While tuberculosis (TB) incidence in the United States (US) has decreased over the last two decades, the disease remains an important cause of infectious morbidity, with nearly 10,000 new cases diagnosed in 2012.[1] The majority of these represent pulmonary tuberculosis (PTB), with extrapulmonary tuberculosis (EPTB) comprising 20% of cases. A more

Corresponding author: Kathleen Tompkins, Address: 211 Grindall Street, Baltimore, MD 21230, Phone: 720-878-3366, Fax: 1-561-828-3366, Kathleen.Tompkins@jhmi.edu.

Address for reprints: Same as corresponding author

Conflicts of Interest: None

uncommon clinical presentation is concurrent PTB and EPTB, representing only 10% of reported US cases.[1]

Tuberculous otitis media (TOM) is a rare form of EPTB, making up just 0.06% of all chronic otitis media cases.[2] With so few cases, a high index of suspicion is required to diagnose TOM and thereby minimize the risk of its associated complications. TOM may present with or without pulmonary involvement and can lead to debilitating sequelae, including facial palsy, mastoiditis, central nervous system invasion, and permanent hearing loss.[3] These potential complications underscore the need for rapid and accurate diagnosis.

Case Report

A 43-year-old, foreign-born, Mexican-American male without significant past medical history was admitted to the inpatient infectious disease service for evaluation of suspected PTB. The patient reported 8 months of cough with subsequent worsening shortness of breath, unintentional 30 pound weight loss, recent-onset fevers, and night sweats. Four months prior to admission, an outside provider treated the patient empirically with clarithromycin for community-acquired pneumonia with transient symptomatic improvement. On review of systems, the patient reported chronic right ear drainage of approximately 6 months' duration. The drainage was painless, worse in the morning, foul-smelling, and associated with hearing loss in the affected ear. Physical exam of the right ear revealed purulent discharge in the external auditory canal with possible perforation of the tympanic membrane. The left ear appeared normal.

The patient emigrated from Mexico 5 years prior to presentation with a single return visit in the preceding 3 years. He had no known TB contacts and no prior TB history. He tested sero-negative for HIV-1/2 during his hospitalization. He was newly diagnosed with type 2 diabetes mellitus on admission, with a hemoglobin A1C of 8.4%. He had no other known TB risk factors.

A chest CT on admission demonstrated cysts and cavities associated with severe bronchiectasis in both apices with marked architectural distortion suggestive of extensive PTB. Expecterated sputum was obtained on the day of admission, and Kinyoun staining revealed 3+ acid fast bacilli (AFB). Xpert MTB/RIF (Cepheid, Inc., Sunnyvale, California, USA)[4] was performed on the remaining sample, confirming the presence of *Mycobacterium tuberculosis* (*MTb*) complex sensitive to rifampin.

The purulent otorrhea was sampled for bacterial culture, which returned positive for oxacillin-susceptible *Staphylococcus aureus* (OSSA). The extent of the patient's PTB and the prolonged duration of otorrhea, raised concern for concurrent TOM. The otolaryngology service obtained an otorrhea aspirate, and Kinyoun staining revealed 3+ AFB. Xpert MTB/RIF confirmed the presence of *MTb* complex sensitive to rifampin. Both sputum and otorrhea were submitted for mycobacterial culture in liquid media using the BACTEC™ MGIT™ 960 system (BD, Franklin Lakes, New Jersey, USA) and returned positive 24 days later for *MTb* sensitive to isoniazid, rifampin, pyrazinamide and ethambutol (HRZE). A CT of the brain without contrast was obtained to assess for *MTb* invasion of the surrounding soft

tissues and bony structures. Imaging revealed abscess formation of the right mastoid air cells extending into the right middle ear with bone dehiscence of the tegmen, horizontal semicircular canal, geniculate ganglion, and ossicles (**Figure 1**). An MRI/MRA with and without contrast revealed a rim-enhancing fluid collection of the right mastoid communicating with the external auditory canal and middle ear canal, but without intracranial extension.

Treatment was initiated the day after admission with HRZE for the patient's PTB. Following Xpert confirmation of rifampin-sensitive TOM, the patient continued medical management with daily HRZE. He had no indication for surgical intervention. He was treated with ciprofloxacin eardrops for OSSA superinfection.

The patient was discharged on hospital day 10 and received directly observed therapy and clinical follow-up from his local health department. Sputum smear conversion occurred after 5 months of HRZE. Repeat sputum cultures obtained 2 and 3 months after treatment initiation redemonstrated pan-sensitive *MTb*. Due to the prolonged time to smear conversion, the patient completed 39 weeks of therapy. Culture negativity was documented after 3 months of therapy. At the time of treatment completion, the patient's cough and night sweats had resolved, but his dyspnea continued, thought due to pulmonary scarring. Repeat chest imaging 8 months after treatment initiation revealed significant improvement in infiltrates bilaterally but extensive volume loss, bilateral upper lobe cavities and scarring, and rightward mediastinal shift. The patient experienced complete resolution of otorrhea, but had permanent perforation of the tympanic membrane. He did not return to the hospital for repeat cranial imaging.

Discussion

TOM is exceedingly rare in the US and requires a high index of suspicion for diagnosis. Even in confirmed PTB cases, such as ours, concurrent TOM is reported less than 2% of the time.[2] Inner ear TB involvement is thought to occur through hematogenous dissemination, direct extension via the Eustachian tube, or inoculation from a ruptured tympanic membrane.[5]

The presentation of TOM is highly variable, and may be characterized by non-specific signs and symptoms.[2,3,6] Our patient presented with features classic for TOM, including chronic painless otorrhea with associated conductive hearing loss. These findings have been observed in over 90% of patients with TOM in published case series.[2] Additionally, our patient had a single perforation of the tympanic membrane, but in contrast to the majority of reported cases, did not have granulation tissue apparent on otoscopy.[7]

Establishing a diagnosis of TOM can be challenging, particularly since TOM may mimic other rare causes of chronic otitis media, including nocardiosis and non-tuberculous mycobacterial infection,[8-9] and because the sensitivity of Kinyoun staining and culture performed on otorrhea or intraoperative specimens is typically low.[2,8,10]

Xpert MTB/RIF is a new TB diagnostic test with excellent sensitivity for the simultaneous detection of *MTb* complex and rifampin resistance.[4] Xpert MTB/RIF employs real-time

polymerase-chain-reaction technology to amplify the *MTb*-specific sequence of the *rpoB* gene and returns a result in about 2 hours.[4] In a recent meta-analysis involving 9,557 patients, a single Xpert MTB/RIF test used to replace smear microscopy was found to identify 89% of culture-confirmed TB cases, and detected 98% of smear-positive, culture-confirmed TB cases among patients suspected of having PTB.[11] Xpert MTB/RIF also performs well for the detection of rifampin resistance when compared to phenotypic drug-susceptibility testing, with a sensitivity and specificity of 95% and 98%, respectively.[11] Based on these and other findings, largely from studies in low- and middle-income countries, Xpert MTB/RIF is the World Health Organization-recommended initial TB diagnostic test for adults suspected of having multi-drug resistant tuberculosis or HIV-associated TB in high prevalence settings.[12] In July 2013, the Food and Drug Administration approved Xpert MTB/RIF for the diagnosis of PTB on sputum in the US. [13]

Emerging data suggest that Xpert MTB/RIF may also have utility for the diagnosis of EPTB when testing is performed on cerebrospinal fluid and non-sterile biological specimens. In these cases, Xpert MTB/RIF has moderately high sensitivity (>80%) and excellent specificity (>98%) when compared to the reference standard, mycobacterial culture.[14] As such, it is currently the preferred initial test for the diagnosis of TB meningitis in high prevalence, low-resource settings,[12] and may replace conventional diagnostic methods for testing other non-respiratory specimens, including lymph node aspirates and biopsies, gastric fluid, and samples from other tissues.[12] One important limitation of Xpert MTB/RIF is that it cannot distinguish between DNA from live or dead bacilli, and as such it is not recommended for monitoring response to treatment.[12,15,16] However, emerging selective DNA amplification techniques may enable treatment monitoring with Xpert MTB/RIF in the future.[17]

We report one of the first cases from a low TB prevalence setting of using Xpert to rapidly confirm a diagnosis of concurrent PTB and EPTB. We confirmed our EPTB diagnosis of TOM by testing an otorrhea sample with Xpert MTB/RIF. To our knowledge, this represents the first reported case of a positive Xpert result obtained from a clinical otorrhea specimen, and argues for the potential utility of this approach even in low prevalence settings, despite a recent case report from Italy suggesting the contrary.[18]

Our patient was promptly initiated on HRZE within 24 hours of presentation. HRZE forms the cornerstone of TOM treatment, with surgical intervention reserved for incision and drainage of post-auricular abscesses and removal of extensive granulation tissue.[19] As our patient had no evidence of intracranial lesions or facial palsy, he received chemotherapy alone, without surgical intervention. While awaiting DST results, we were able to rapidly ascertain that the patient did not have a rifampin-resistant *MTb* isolate, and were reassured that HRZE was the appropriate initial therapy.

In summary, a high index of suspicion is necessary to diagnosis TOM to prevent unnecessary delays in treatment and resultant complications, as occurred with our patient pre-admission. Xpert MTB/RIF may be a useful rapid diagnostic aid in cases of suspected EPTB, including TOM, even in low-prevalence settings like the US, when used on non-

sterile biological specimens, such as otorrhea. Treatment for TOM consists of standard HRZE chemotherapy for a minimum of 6 months, with surgical intervention reserved for cases of intracranial abscess extension or failure of medical management.

Acknowledgements

The authors would like to thank the patient represented in this article who provided consent for publication. The authors also wish to thank Dr. Jason Stout for providing input on the patient's post-hospital discharge course.

Sources of Support: This work was made possible, in part, by the National Institutes of Health grant 5 T32 AI007001-36.

References

1. Department of Health and Human Services (US DHHS), Centers for Disease Control and Prevention (CDC), Division of TB elimination. Online tuberculosis information system. <http://wonder.cdc.gov/tb-v2012.html> (accessed 19 June 2014)
2. Skolnik PR, Nadol JB, Baker AS. Tuberculosis of the middle ear: review of the literature with an instructive case report. *Reviews of Infect Dis.* 1986; 8:403–410.
3. Cho YS, Lee HS, Kim SW, et al. Tuberculous otitis media: a clinical and radiologic analysis of 52 patients. *Laryngoscope.* 2006; 116:921–927. [PubMed: 16735889]
4. Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med.* 2010; 363:1005–1015. [PubMed: 20825313]
5. Kirsch CM, Wehner JH, Jenson WA, Kagawa FT, Campagna AC. Tuberculous otitis media. *South Med J.* 1995; 88:363–366. [PubMed: 7886539]
6. Abes GT, Abes FL, Jamir JC. The variable clinical presentation of tuberculosis otitis media and the importance of early detection. *Otol Neurotol.* 2011; 32:539–543. [PubMed: 21532520]
7. Yaniv E. Tuberculous otitis: an underdiagnosed disease. *Am J Otolaryngol.* 1987; 8:356–360. [PubMed: 3434672]
8. Chirch LM, Ahmad K, Spinner W, Jimenez VE, Donelan SV, Smouha E. Tuberculous otitis media: report of 2 cases on Long Island, N.Y., and a review of all cases reported in the United States from 1990 through 2003. *Ear Nose Throat J.* 2005; 84:488–490. 492 passim. [PubMed: 16220854]
9. Tsai LT, Wang CY, Lin CD, et al. Nontuberculous mycobacterial otomastoiditis: A case report. *Ear Nose Throat J.* 2013; 92:31–33. [PubMed: 23354889]
10. Dale OT, Clarke AR, Drysdale AJ. Challenges encountered in the diagnosis of tuberculous otitis media: case report and literature review. *J Laryngol Otol.* 2011; 125:738–740. [PubMed: 21693076]
11. Steingart KR, Schiller I, Horne DJ, et al. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev.* 2014; 1:CD009593. DOI: 10.1002/14651858.CD009593.pub3. [PubMed: 24448973]
12. The World Health Organization. Policy update: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Jun. 2013 Available at http://apps.who.int/iris/bitstream/10665/112472/1/9789241506335_eng.pdf?ua=1. Accessed 23 July 2014
13. US Food and Drug Administration. Press release: FDA permits marketing of first U.S. test labeled for simultaneous detection of tuberculosis bacteria and resistance to the antibiotic rifampin. Jul. 2015 Available at <http://www.fda.gov/NewsEvents/Newsroom/%20PressAnnouncements/ucm362602.htm>. Accessed 14 May 2015
14. Denking CM, Schumacher SG, Boehme CC, et al. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *Eur Respir J.* 2014; 44:435–446. [PubMed: 24696113]
15. Freidrich SO, Rachow A, Saathoff E, et al. Assessment of the sensitivity and specificity of Xpert MTB/RIF assay as an early sputum biomarker of response to tuberculosis treatment. *Lancet Respir Med.* 2013; 1:462–470. [PubMed: 24429244]

16. Nicol MP. Xpert MTB/RIF: monitoring response to treatment. *Lancet Respir Med*. 2013; 1:427–428. [PubMed: 24429228]
17. Miotto P, Bigoni S, Migliori GB, et al. Early tuberculosis treatment monitoring by Xpert® MTB/RIF. *Eur Respir J*. 2012; 39:1269–1271. [PubMed: 22547737]
18. Petrucci R, Lombardi G, Corsini I, Visciotti F, Pirodda A, Cazzato S, et al. Use of transrenal DNA for the diagnosis of extrapulmonary tuberculosis in children: a case of tubercular otitis media. *Journal of clinical microbiology*. Jan; 2015 53(1):336–8. PubMed PMID: 25339389. Pubmed Central PMCID: 4290950. [PubMed: 25339389]
19. Singh B. Role of surgery in tuberculous mastoiditis. *J Laryngol Otol*. 1991; 105:907–915. [PubMed: 1761944]

Figure 1.

CT scan of right temporal bone demonstrating obliteration of right mastoid air cells with destruction of ossicles, horizontal semicircular canal, geniculate ganglion, and tegmen.