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BRIEF REPORT

Role of Therapeutic Drug Monitoring in the Treatment of Persistent *Mycobacterium abscessus* Central Nervous System Infection: A Case Report and Review of the Literature

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A patient presenting with recurrent ventriculoperitoneal shunt infection was found to have *Mycobacterium abscessus* growing from cerebrospinal fluid (CSF), which remained persistently positive. Therapeutic monitoring of clarithromycin, imipenem, and linezolid in CSF and plasma revealed lower than expected concentrations, prompting alternative therapy and culture clearance on hospital day 42.

Keywords. mycobacterial infections; NTM; pharmacokinetics; therapeutic drug monitoring; ventriculitis; ventriculoperitoneal shunt.

Mycobacterium abscessus complex (*M abscessus*) is a group of rapidly growing nontuberculous mycobacteria (NTM) typically associated with skin and soft tissue or pulmonary infections [1]. Central nervous system (CNS) infections caused by *M abscessus* are relatively rare; to our knowledge there have been 21 prior cases of *M abscessus* CNS infections, of which 6 were subspecies *massiliense*. Among those 21 cases, 13 patients had a history of neurosurgery (11 with ventriculoperitoneal or lumboperitoneal shunts), 3 suffered penetrating injury to the head or neck (1 had an ocular prosthesis), 3 had chronic otitis media or otomastoiditis, and 2 had disseminated disease. Ultimately, 12 of 21 patients survived their infections (additional details and references are available in the Supplementary Materials).

Mycobacterium abscessus is notoriously difficult to treat owing to mutational and inducible antibiotic resistance mechanisms [2]. Given the high rates of antibiotic resistance, toxic nature of agents used in treatment, and difficulty achieving full eradication, *M abscessus* infections are often considered a "nightmare" to effectively manage [2]. Generally, treatment of CNS infections has followed the Infectious Diseases Society of America's recommendations for treatment of *M abscessus* pulmonary disease, with antibiotic regimens of at least 3–4 active drugs plus a macrolide (primarily for immunomodulation) as induction therapy followed by maintenance therapy with at least 2–3 active drugs for a prolonged course [3]. Herein, we report a case of persistent ventriculitis caused by *M abscessus* subspecies *abscessus* and highlight the unique challenges of treating CNS infections caused by this pathogen. We employed therapeutic drug monitoring (TDM) to help inform medical decision making that led to changes in empiric therapy which, combined with shunt revision, resulted in pathogen clearance.

METHODS

Patient Characteristics and Clinical Course

A 40-year-old man who had suffered a gunshot wound to the head with penetrating brain injury complicated by cerebrospinal fluid (CSF) leak and retained bullet fragments, and recent *Candida albicans* ventriculoperitoneal shunt infection treated with shunt revision and antifungal therapy, presented with fevers, headaches, and agitation. Brain computed tomography demonstrated a new subgaleal collection around the shunt reservoir. CSF sampling on hospital day 1 revealed white blood cell count 129 cells/μL (54% neutrophils), red blood cell count 7 cells/μL, glucose 67 mg/dL, and protein 55 mg/dL. While initial aerobic bacterial cultures were negative, repeat aerobic culture sent on hospital day 10 grew *M abscessus* at 4 days, and the patient was started on empiric 4-drug therapy (Figure 1).

Microbiology and Susceptibility Testing

Mycobacterium abscessus was initially identified by the Northwestern Memorial Hospital Clinical Microbiology Laboratory in aerobic and mycobacterial cultures from CSF. Antibiotic susceptibility by broth microdilution method and resistance-gene testing were performed by National Jewish Health (Denver, Colorado).

Plasma and CSF Concentrations

Plasma and CSF samples were analyzed by the Infectious Diseases Pharmacokinetics Laboratory (IDPL) at the

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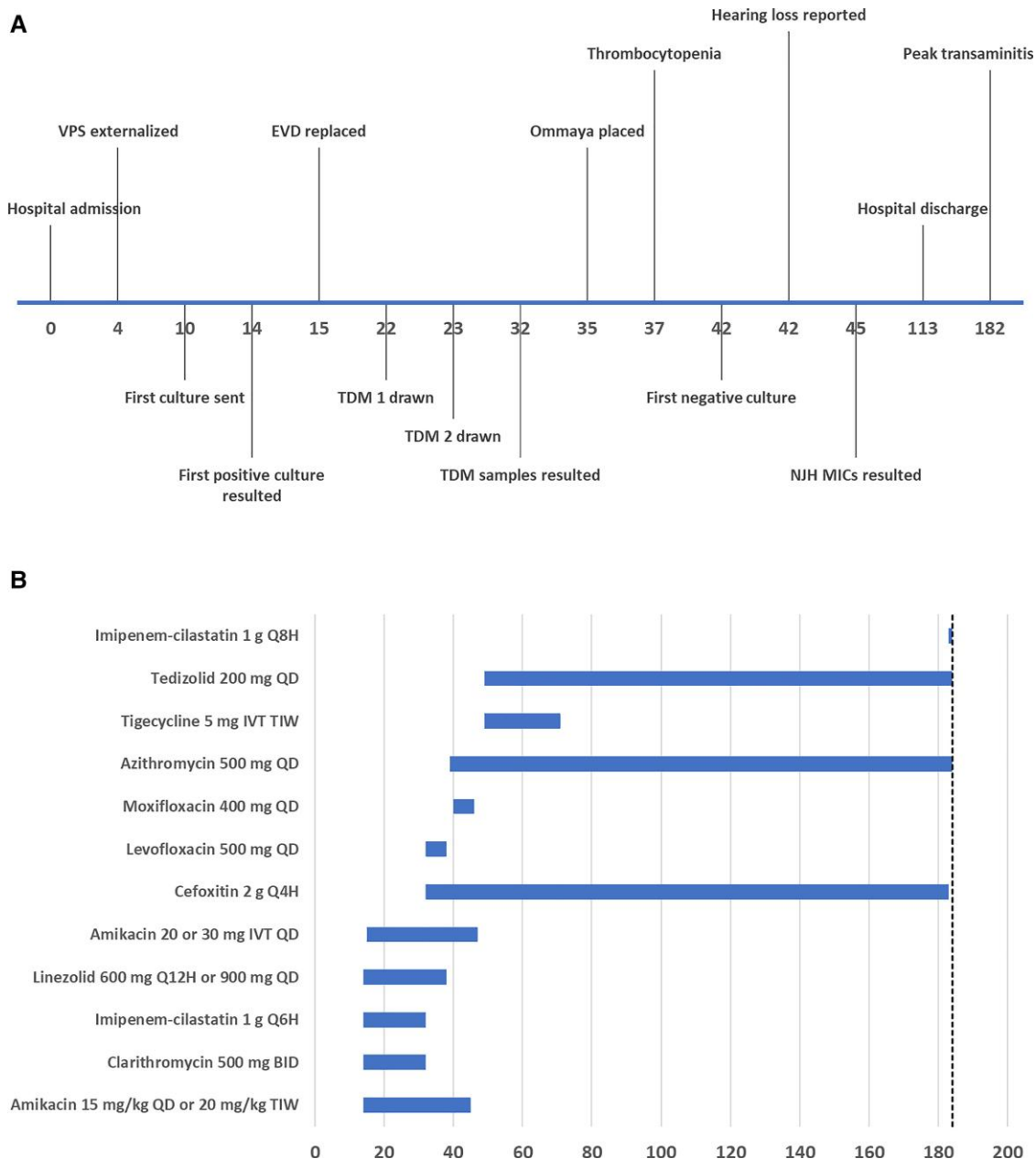

Figure 1. Timeline of events (*A*) and antibiotics (*B*) from admission until patient transferred to another center. The x-axes show days from hospitalization. Dashed line indicates end of patient follow-up prior to transfer. Abbreviations: BID, twice a day; EVD, external ventricular drain; IVT, intraventricular; MIC, minimum inhibitory concentration; NJH, National Jewish Health; Q4H, every 4 hours; Q6H, every 6 hours; Q8H, every 8 hours; QD, daily; TDM, therapeutic drug monitoring; TIW, 3 times a week; VPS, ventriculoperitoneal shunt.

University of Florida in Gainesville, where assays for clarithromycin, imipenem, and linezolid were performed. Samples were collected as random observations relative to the dose times for each drug with postdose sample times listed in Table 1. Two random plasma samples (1 initial and 1 confirmatory on subsequent day) and a single CSF sample were collected and directly transported to the referred testing laboratory where samples were maintained at −80 °C prior to shipment to IDPL on dry ice. Mean plasma concentration and CSF-to-plasma ratio were calculated.

RESULTS

Microbiology and Susceptibility Testing

Sequencing performed at National Jewish Health was notable for an *erm*(41) T28C loss of function mutation and no

mutations at *rrl* (suggesting susceptibility to macrolides), and no mutations at *rrs* (suggesting susceptibility to aminoglycosides). The isolate was confirmed as *M abscessus* subspecies *abscessus* with the following antibiotic susceptiblity pattern (minimum inhibitory concentrations [MICs], in mg/L): Susceptible to amikacin (16) and clarithromycin (≤0.25); intermediate to cefoxitin (32) and imipenem (8); and resistant to ciprofloxacin (>8), doxycycline (>16), linezolid (>16), and moxifloxacin (>4). Azithromycin (≤16), clofazimine (≤0.5), minocycline (>8), and tigecycline (2) had no Clinical and Laboratory Standards Institute interpretative guidelines for the antibiotic/organism combination.

TDM and Clinical Course

Prior to results of antibiotic susceptibility testing, TDM was performed to aid in the understanding of pharmacokinetics within the CSF of the 3 systemically administered antibiotics. Absolute values and estimates of CSF to plasma ratio are shown in Table 1 for each drug. Both clarithromycin and imipenem absolute CSF and plasma values and ratios fell below expected levels based on breakpoint MICs. Clarithromycin CSF concentration at 4.9 hours postdose was undetectable. Imipenem CSF concentration at 4.1 hours postdose was 0.28 mg/L, well below the MIC breakpoint of 8 mg/L. Linezolid CSF concentration at 8.5 hours postdose was 4.9 mg/L, compared to MIC breakpoint of 8 mg/L. These findings prompted changes in the empiric treatment regimen from clarithromycin and imipenem to levofloxacin (later azithromycin) and high-dose cefoxitin, respectively. Further complicating treatment, the patient developed thrombocytopenia after 29 days of linezolid therapy and ototoxicity while on intravenous plus intraventricular amikacin; these antibiotics were changed to tedizolid and intraventricular tigecycline, respectively. To optimize tigecycline exposure in the CSF, we created a novel hospital-specific protocol for the intraventricular or intrathecal administration of tigecycline as a 5 mg in 5 mL normal saline solution (available at: asp.nm.org); this was dosed 3 times weekly from hospital day 39 to hospital day 71, when it was stopped to facilitate discharge.

An Ommaya reservoir was placed for long-term intraventricular antibiotics. The first negative CSF mycobacterial culture occurred on hospital day 42 (32 days after initial positive culture). The patient was discharged on azithromycin, cefoxitin, and tedizolid with a plan to continue 3-drug therapy 12 months from the first negative CSF culture. After 5 months of cefoxitin, the patient developed possible drug-induced liver injury (aspartate aminotransferase 292 U/L and alanine aminotransferase 441 U/L), which improved after changing cefoxitin to imipenem. At 6-month follow-up he was clinically stable and appeared to be tolerating azithromycin, imipenem, and tedizolid.

DISCUSSION

Our case highlights the unique challenges faced when selecting an optimal medical treatment regimen for CNS infections caused by *M abcessus* specifically and NTM in general. Site of infection is a major factor in effectively managing infections; CSF represents a sequestered site where many antibiotics achieve very limited penetration across the blood-brain barrier [4]. Whereas linezolid CSF penetration has been shown to be relatively high, a review of the literature suggests that systemic bedaquiline, tedizolid, and tigecycline appear to have limited CSF penetration, leading to insufficient concentrations at the site of infection [5–7]. Clofazimine is undetectable in cadaveric brain tissue [8], but the CSF penetration ratio of clofazimine is unknown. Because limited CSF penetration data were available to guide initial antibiotic selection and dosing, TDM was performed for the 3 systemically administered antibiotics. The results of TDM led to alterations in our therapeutic approach. In contrast to the adequate CSF clarithromycin concentrations demonstrated previously [9], we found clarithromycin to be undetectable in CSF in our patient. Differences in meningeal inflammation, underlying patient disease, and comedications (eg, steroids) may play a role in the ability of antibiotics to reach adequate CSF levels. While a combination of shunt revision and intravenous and intraventricular antibiotics ultimately resulted in pathogen clearance and clinical resolution of the

Table 1. Results of Antibiotic Therapeutic Drug Monitoring

		Plasma and CSF Drug Concentrations (Hours Postdose)		
Measurement	Unit	Clarithromycin 500 mg Twice Daily	Imipenem-Cilastatin 1 g Every 6 h	Linezolid 600 mg Every 12 h
First plasma (day 1)	mg/L	1 (4.7 h)	10 (3.8 h)	5.6 (8.25 h)
Second plasma (day 2)	mg/L	0.29 (5.5 h)	4.6 (5 h)	3.85 (8.7 h)
CSF	mg/L	<0.1 (4.9 h)[a]	0.28 (4.1 h)	4.9 (8.5 h)
MIC	mg/L	≤0.25	8	>16
CSF/first plasma ratio	…	<0.1	0.028	0.875
CSF/MIC ratio	…	<0.32	0.035	<0.3

Abbreviations: CSF, cerebrospinal fluid; MIC, minimum inhibitory concentration.

[a]Clarithromycin in CSF was below the limit of assay quantification.

infection, we caution that correlation between use of TDM and this positive outcome does not imply causation. We were unable to repeat TDM following changes in therapy from clarithromycin to levofloxacin (and later azithromycin) and imipenem to cefoxitin pending the formal addition of IDPL as a hospital-specific referred testing laboratory, by which time the patient had been discharged.

Our patient's course also highlights the severe morbidity of drug treatment for deep-seated NTM infections. Aminoglycosides are associated with high rates of ototoxicity [10]; macrolide therapy can also predispose to hearing loss [11]. Cephalopsorins are generally well tolerated but can produce transient elevations in aminotransferases. Linezolid is well known to cause exposure-dependent thrombocytopenia [12]. All of these complications were observed in our patient's course and prompted changes to his treatment regimen. Close monitoring is required to rapidly identify the emergence of drug toxicities, which can have lifelong consequences.

The results of TDM in our case demonstrate the unique value that access to CSF and plasma drug monitoring can provide in difficult-to-treat infections. Taken together, the results raised concern that our patient had been receiving only 1 active agent (amikacin) with adequate site of infection pharmacokinetics for 2 weeks prior to TDM. Early TDM in patients such as ours may promote a faster time to pathogen clearance and permit earlier selection of more active therapy while awaiting final susceptibility results.

Deep-seated infections including CNS infections caused by *M abscessus* are complex and difficult to effectively manage. We engaged a multidisciplinary team of infectious diseases specialists, neurosurgeons, and pharmacometrics to create a treatment plan that resulted in pathogen eradication. We leveraged knowledge of antibiotic pharmacokinetics at the site of infection to select alternative therapies sooner than would be possible when awaiting standard culture and susceptibility data. Patients receiving antibiotics targeting *M abscessus* are at high risk for toxicities and require close monitoring to prevent serious adverse events that can result in long-term sequelae.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Patient consent statement. The patient's legally authorized representative provided written consent. The design of the work as a case report conforms to standards currently applied by the Northwestern University Institutional Review Board.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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