Failure of Treatment for Chronic Mycobacterium abscessus Meningitis Despite Adequate Clarithromycin Levels in Cerebrospinal Fluid

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We report a case of posttraumatic meningitis due to Mycobacterium abscessus, treated initially with oral clarithromycin and intravenous amikacin plus intrathecal amikacin. Despite cerebrospinal fluid (CSF) levels of clarithromycin and amikacin in excess of their in vitro minimum inhibitory concentrations for the organism, the CSF cultures remained continuously positive for M. abscessus. To our knowledge, this is the first documented case of M. abscessus meningitis and the first report of measured CSF levels of clarithromycin in a patient with meningitis, showing that even therapeutic CSF levels of clarithromycin and amikacin might not be successful in eradicating M. abscessus meningitis.

Mycobacterium abscessus is one of the 8 taxonomic groups of rapidly growing mycobacteria [1]. Clinical disease due to M. abscessus most often consists of skin or soft-tissue infection following trauma [2–4]. Iatrogenic infections have been documented involving soft-tissue abscesses secondary to injections with contaminated needles [5–7]. Nosocomial disease has included surgical wound infections, catheter-related infections, and pseudoepidemics of contaminated bronchoscopic washings, as well as peritonitis and disseminated disease in patients undergoing dialysis [8–10]. Disseminated cutaneous disease, usually in immunocompromised hosts, due to hematologic malignancies or chronic immunosuppressive therapy also has been documented [11]. To our knowledge, the case we report herein is the first of meningitis due to M. abscessus.

Case report. A 59-year-old woman without a significant medical history sustained a stab wound from a knife to the neck 6 months prior to admission to our institution. The injury resulted in quadriplegia and left facial droop. Her neurological symptoms gradually abated over the ensuing 2 months. At that point, the patient developed urinary retention, confusion, and worsening muscular weakness. An MRI of the brain revealed abnormal meningeal enhancement, particularly in the basilar cisterns, as well as an intrinsic spinal cord anomaly at the C4 level. MRI of the spine showed abnormal enhancement of the cervical and thoracic spine.

A lumbar puncture was performed, and examination of the CSF specimen revealed pleocytosis with lymphocyte predominance, elevated protein concentration, and decreased glucose concentration. Cytology, stains, and cultures were negative. A meningeal biopsy revealed focally caseating granulomatous inflammation, but staining for acid-fast bacilli (AFB) was negative. A second lumbar puncture yielded an AFB-positive specimen, and empirical therapy for tuberculosis with isoniazid, rifampin, ethambutol, and pyrazinamide was initiated. The antituberculous therapy was stopped after the patient developed hepatotoxicity. The AFB later were identified as M. abscessus, and therapy with iv amikacin and oral clarithromycin was started. The patient was transferred to our facility after an Ommaya reservoir was implanted. Following a determination of in vitro susceptibility, intrathecal amikacin was added to the treatment regimen.

On day 24 of clarithromycin therapy, at a dosage of 1000 mg twice daily, samples of serum and CSF were simultaneously obtained. Levels were determined for clarithromycin and its 14-(R)-hydroxymetabolite. The analysis was conducted at the Drug Analysis Department of Abbott Laboratories (Abbott Park, IL) with use of a high-performance liquid chromatography procedure with electrochemical detection. Chromatography was conducted with a reverse-phase C-8 column (5 μm, 4.6 mm inner diameter × 25 cm; Spherisorb, Phenomenex) with a mobile phase consisting of acetonitrile (48% vol/vol), methanol (10%), 0.05 mol/L acetic acid, and NaOH, to produce a pH of 7.5. The effluent was monitored by electrochemical detection (model 5100A; Environmental Sciences Associated), with electrical potentials of the first and second electrodes set at +0.5 V and 0.78 ± 0.04 V, respectively. The lower limits of detection for both components were 0.04 mg/L in plasma and 0.08 mg/L in CSF [12]. The zero-hour sample was obtained prior to the dosing, followed by sampling at 4 and 9 h. The CSF samples were obtained from the Ommaya reservoir. A CSF
Table 1. Concentrations of clarithromycin and its 14(R)-OH metabolite in serum and CSF.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Time, h</th>
<th>Clarithromycin, µg/mL</th>
<th>Metabolite, µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum</td>
<td>CSF</td>
<td>Ratio, c/s</td>
</tr>
<tr>
<td>Patient 0</td>
<td>11.196</td>
<td>2.037</td>
<td>0.182</td>
</tr>
<tr>
<td>Patient 4</td>
<td>12.769</td>
<td>1.966</td>
<td>0.154</td>
</tr>
<tr>
<td>Patient 9</td>
<td>11.869</td>
<td>2.136</td>
<td>0.180</td>
</tr>
<tr>
<td>Control</td>
<td>--</td>
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<td>0b</td>
</tr>
</tbody>
</table>

* Indicates concentration rates in CSF/serum.

b Concentrations below the lower quantitation limit of the assay, 0.04 µg/mL for the parent drug and 0.08 µg/mL for the metabolite.

control specimen from another patient was run simultaneously. The results are shown in table 1.

Initial M. abscessus susceptibility testing revealed the following MICs (µg/mL): 0.125 for clarithromycin, 16 for amikacin, and 8 for imipenem plus cilastatin. The strain was resistant to all other antibiotics tested. On multiple repeated testing, the peak and trough CSF levels of amikacin were 43.8 µg/mL to 129 µg/mL, and 5.9 µg/mL to 18 µg/mL, respectively. Despite therapeutic levels of antibiotics and signs of clinical improvement, especially after corticosteroids were added to the regimen, repeated cultures of CSF obtained from the Ommaya reservoir and by lumbar puncture yielded persistent growth of M. abscessus. The susceptibility pattern of the strain remained the same, with MICs still within 1 dilution of those for the first isolate. Imipenem plus cilastatin was added to the antibiotic regimen, but the CSF cultures remained positive.

Because of the concern of possible M. abscessus colonization of the Ommaya reservoir, we recommended that it be removed and that a second reservoir be implanted several days later. The patient refused and also decided to discontinue the iv and intrathecal therapy after >2 months of hospitalization. A psychiatric evaluation concluded that she was competent to make the decision. She was discharged to a nursing home, at which point she was receiving oral clarithromycin (1500 mg orally b.i.d.). She died 1 month later with overwhelming meningitis. A summary of the clinical course, CSF cultures, and antibiotic levels is shown in figure 1.

Discussion. M. abscessus, formerly known as M. chelonae
subspecies *M. abscessus*, is an environmental rapidly growing mycobacterium that has been recognized as an etiologic agent of human infections. The first documented case of *M. abscessus* infection was reported in 1953, when the organism was cultured from synovial fluid and a gluteal abscess in the same patient [13]. Since then it has been described as the cause of various infections, but to our knowledge, not as the etiologic agent of human meningitis. In the case we present here, repeated growth of *M. abscessus* from ventricular and lumbar spinal fluid, without radiological evidence of abscess formation, confirmed the diagnosis of meningitis. Multiple negative blood cultures demonstrated no evidence of disseminated disease.

The best therapy for infections due to *M. abscessus* is a controversial topic. On the basis of in vitro susceptibility studies, the preferred parenteral antibiotics have been amikacin and cefoxitin, whereas the oral drug of choice has been clarithromycin since its release. Additional potentially useful agents are imipenem and clofazimine [2]. Clarithromycin is the most active macrolide against rapidly growing mycobacteria, but the MICs frequently increase with incubation with isolates of *M. abscessus* [14]. Monotherapy with clarithromycin has been successfully used, although resistance to clarithromycin among isolates of *M. abscessus* from patients with disseminated disease or chronic lung disease has been observed. These resistant strains were recovered after clarithromycin monotherapy.

It has been shown that resistance relates to a point mutation in the gene coding for 23S rRNA and occurs in limited clinical situations [15]. Therefore, it is usually recommended that combinations of ≥2 drugs should be used, especially for disseminated disease [16]. In one study, the clarithromycin-amikacin combination demonstrated the most important additive effect, and the combination of clarithromycin-amikacin-ethambutol resulted more frequently in synergistic effects than the combination of clarithromycin-rifabutin-ethambutol [17]. Usually, a long course of antibiotic therapy is advocated. Surgical debridement (if possible) has been advocated, especially for localized skin infections.

Very little information is available on the penetration of clarithromycin into CSF in humans. One study reported the penetration of clarithromycin into the CSF of 4 healthy volunteers after 1 or 2 oral doses (500 mg; [18]). CSF levels of clarithromycin were 2.3% of simultaneous plasma levels after one dosing. With multiple dosings, steady-state therapeutic concentrations of clarithromycin and its metabolite are achieved, as in our patient [19]. CSF levels of clarithromycin and its metabolite in the presence of meningeal inflammation were 15%–18% of simultaneous serum levels of clarithromycin and 25%–27% of its metabolite. The levels were 15–17-fold higher than the MIC for clarithromycin. Despite therapeutic CSF levels of the drugs and the continued susceptibility of the organism, therapy failed to eradicate the *M. abscessus* in our patient.

It has been reported that clarithromycin lacks bactericidal activity in CSF in experimental pneumococcal meningitis in rabbits, despite clarithromycin CSF levels that exceeded the MBC of the test strain and a bactericidal in vitro effect in time-kill studies [20]. A possible explanation, at least in part, would be the fact that the MBC of clarithromycin is substantially increased when the pH of the medium is acidified [21], and it has been shown that in cases of meningitis, the CSF becomes acidic [22]. We suspect that the presence of the Ommaya reservoir contributed to the failure to sterilize the CSF.

References

17. Gevaudan MJ, Bollet C, de Micco P. Evaluation of the extra- and


