Brain abscess associated with multidrug-resistant *Capnocytophaga ochracea* infection


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Running title: Brain abscess and *Capnocytophaga ochracea* infection

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Abstract

Brain abscesses are occasionally associated with a dental source of infection. An unusual case of frontal lobe abscess in a nonimmunocompromised child infected with multidrug resistant Capnocytophaga ochracea is described and confirms the pathogenic potential of this organism to cause human disease in the central nervous system.

Key words: Multidrug resistant, Capnocytophaga ochracea, brain abscess, nonimmunocompromised
Case report

A 7-year 11-month-old boy was admitted on December 12, 2005 with a six–month history of intermittent fever, headache, and vomiting. The only significant medical history was extraction of several teeth between age three and seven years, the most recent extraction having been in May, 2005. He had no pets and was a well-developed child.

Upon admission he appeared severely ill, with a temperature of 38.0°C. The left mandibular cheek was erythematous and swollen. He complained of toothache in his left mandibular jaw. His examination was not significant for meningismus and was without positive Brudzinski and Kernig signs. The initial laboratory findings included a C-reactive protein of 2.11, a WBC count of 9,800/mm$^3$ (with 70.6% neutrophils and 21.2% lymphocytes), and a platelet count of 613,000/mm$^3$. Lumbar puncture revealed a CSF with WBC (12/mm$^3$; 100% lymphocytes), glucose 65 mg/dl, and protein 67.1 mg/dl. CSF Gram stain revealed no bacteria. Analysis of an MRI on the date of admission showed a large, regular, thin-walled ring-enhanced lesion (about 5.6 cm × 4.7 cm × 3.8 cm) with severe perifocal edema in left deep frontal lobe (Figure 1), severe intracranial pressure, and slight anterior midline shift to the right. Craniotomy was performed on the second day and more than 50 ml of purulent pus was aspirated from the left frontal lobe. Gram negative bacilli were isolated from aerobic and anaerobic cultures of the pus after 3 days of incubation. After subculture on blood agar plates incubated in a CO$_2$ atmosphere, the bacteria were motile by gliding and grew into yellowish orange colonies. The organisms were identified as *Capnocytophaga* species with a similarity of 99% by bioMerieux Vitek anaerobe identification. Empirical antimicrobial therapy (ceftriaxone [CRO; 1 g every 12 h], penicillin G [PEN G; 1.5 million units every 4 h], and metronidazole [250 mg every 8
was initiated, but on day 6 after surgery he developed fever and generalized
seizure. The antimicrobial susceptibility test showed resistance to PEN, CRO,
vancomycin (VAN), gentamicin (GEN), and cefpirome and susceptibility to imipenem
(IMP)/cilastin, ciprofloxacin (CIP), and clindamycin (CLI) (Table 1). Treatment was
shifted to intravenous IMP/cilastin (250 mg every 6 h for 4 weeks), CIP (200 mg
every 12 h for 2 weeks), and metronidazole (250 mg every 8 h for 4 weeks). To detect
possible local disease, abdominal examination, cardiac echogram, and
otorhinolaryngologic examination were performed, all of which yielded normal
results. However, a dental examination revealed caries in the left second primary
molar, which may have been the focus of infection. The isolate was subsequently
identified by 16S rRNA gene amplification and sequencing. The PCR was performed
with the bacteria-specific primers 8FPL (5′-AGAGTTTGATCCTGGCTCAG -3′) and
1492 (5′-GGTTACCTTGTTACGACTT-3′) to amplify 16S rRNA gene of the bacteria.
The amplification reaction mixtures contained 50 µl of 10 mM Tris-HCl (pH 8.3), 50
mM KCl, 1.5 mM MgCl2, 0.001% gelatin, 1 U of Taq polymerase (Perkin-Elmer;
Norwalk, Conn.), 200 µM each of deoxynucleotide triphosphates (dATP, dCTP, dGTP,
and dTTP; Perkin-Elmer), 50 pmol each of the primers, and 2 µl of the DNA sample.
The PCR (30 cycles of denaturation [94°C, 1 min], annealing [55°C, 1 min], and
extension [72°C, 1 min] followed by a single final extension step [72°C, 7 min]) was
carried out in a DNA thermal cycler (MJ Research Inc.; Watertown, MA, USA). The
partial sequence (640 nucleotides) was compared to published sequences in the
GenBank database of National Center for Biotechnology Information using the Blast
N algorithm. The closest match was obtained with *Capnocytophaga ochracea*
(GenBank accession number U41354, 98% identity). The results of biochemical
testing (acid production from galactose and raffinose; no starch hydrolysis; and no
oxidase/catalase activity) were consistent with species identification of the isolate as *Capnocytophaga ochracea*.

The patient’s clinical condition improved and brain MRI on January 12, 2006 revealed left frontal abscess shrinkage to 2.3 cm. He was discharged in good condition on January 26, 2006. At his most recent follow-up (three months), the brain MRI revealed the left frontal abscess shrinkage to less than 1.0 cm and encephalomalacia was noted with no neurological sequellae.

*Capnocytophaga* species are Gram-negative gliding bacteria that require CO₂ for both micro-aerobic and anaerobic growth and produce yellow colonies on solid media (7). Using DNA hybridization and 16S rRNA gene sequencing, five species with clinical significance in humans have been identified: *C. ochracea*, *C. sputigena*, *C. gingivalis*, *C. haemolytica*, and *C. granulosa*(4). They may play a role in the pathogenesis of juvenile periodontitis (6, 10) and cause disease (e.g., empyema, lung abscess, conjunctivitis, etc.) in both immunocompromised and nonimmunocompromised hosts (14). *C. canimorsus* (an oral commensal of dogs and cats) can also be a pathogen in humans. *Capnocytophaga* species have been isolated from patients with endocarditis, meningitis, endophthalmitis, and septicemia in immunocompromised hosts (3, 7, 8, 11, 12, 13, 15, 17). A Medline search of the literature found only four cases of *Capnocytophaga* spp. brain abscess (5, 16, 18). The association of frontal brain abscess with upper teeth infections may be due to the connection of the apical venous drainage with the cavernous sinus, which could allow a septic embolus to enter *via* reverse flow during yawning and mastication (9).

Most capnocytophaga strains are susceptible to PEN, ampicillin (AMP), CLI,
chloramphenicol, tetracycline (TET), metronidazole, and erythromycin (ERY). In recent years, PEN- and amoxicillin (AMOX)-resistant strains have been isolated that produce β-lactamase. Our strain was found to be highly resistant to cephalosporins including cefuroxime, ceftazidime, CRO, cefepime, and cefixime (MIC >256 µg/ml). Susceptibility to AMP, ticarcillin, or piperacillin (PIP) was not tested. If capnocytophaga species are resistant to AMP or PIP but sensitive to AMP/sulbactam, AMOX/clavulanic acid, or PIP/tazobactam, they may be β-lactamase producers (1, 7). Our isolate was very susceptible to CLI and ofloxacin and moderately susceptible to TET and azithromycin, and to a lesser degree, to quinupristin/dalfopristin, VAN, teicoplanin, and GEN. The child had intermittent fever with toothache for 6 months and his treatment with oral antibiotics may have caused the emergence of multidrug resistant bacteria. First-generation cephalosporins are the most commonly used antimicrobials in local clinics in Taiwan. Our strain was found to be highly resistant to cephalosporins. IMP/cilastin, CIP, and metronidazole treatment was selected because 1) Capnocytophaga ochracea had good susceptibility to CIP, 2) the poor oral condition of the patient was due to anaerobes, 3) IMP/cilastin is a very effective way to treat brain abscess, either alone or combination with neurosurgical drainage of pus (2), and 4) IMP penetrates well the blood/CSF barrier.

In conclusion, a previously unreported antibiotic regimen can be used to successfully treat brain abscess due to multidrug-resistant Capnocytophaga and gene sequencing can be used for rapid identification of the species of Capnocytophaga, which is especially important when treating central nervous system infection. The evidence suggests that dental caries are the focus of infection.
References


Table 1. E-test results for a multidrug-resistant strain of *C. ochracea*.

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC (µg/ml)</th>
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<tbody>
<tr>
<td>Clindamycin</td>
<td>0.016</td>
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<tr>
<td>Ofloxacin</td>
<td>0.047</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>0.08</td>
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<tr>
<td>Piperacillin/tazobactam</td>
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<tr>
<td>Tetracycline</td>
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<tr>
<td>Azithromycin</td>
<td>2</td>
</tr>
<tr>
<td>Ampicillin/sulbactam</td>
<td>2</td>
</tr>
<tr>
<td>Amoxicillin/clavulanic acid</td>
<td>8</td>
</tr>
<tr>
<td>Quinupristin/dalfopristin</td>
<td>32</td>
</tr>
<tr>
<td>Vancomycin</td>
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</tr>
<tr>
<td>Teicoplanin</td>
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</tr>
<tr>
<td>Gentamicin</td>
<td>&gt;256</td>
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<tr>
<td>Cefepime</td>
<td>&gt;256</td>
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<tr>
<td>Cefixime</td>
<td>&gt;256</td>
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<tr>
<td>Cefuroxime</td>
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<td>Ceftazidime</td>
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<tr>
<td>Oxicillin</td>
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<tr>
<td>Ceftriaxone</td>
<td>&gt;256</td>
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Figure legends

Figure 1. Gadolinium–enhanced T1-weighted MR image obtained before aspiration, revealing a ring-enhancing lesion with significant perilesional edema in the left frontal lobe region.