Case Report

**IMIPENEM-RESISTANT *NOCARDIA CYRIACIGEORGICA* INFECTION IN A CHILD WITH CHRONIC GRANULOMATOUS DISEASE**

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Abstract

Nocardia spp can lead to local or disseminated infections especially in immunocompromised patients. Combination therapy of amikacin and imipenem is commonly used to treat severe nocardial infections. We describe a patient with imipenem-resistant Nocardia cyriacigeorgica, which, to our knowledge, has not been previously reported in isolates of this species.
Abbreviations:

- BAL: bronchoalveolar lavage
- CGD: chronic granulomatous disease
- CRP: C-reactive protein
- PCR: polymerase chain reaction
A 9-year-old boy with an X-linked chronic granulomatous disease (CGD) was admitted in our hospital after a 5 days history of fever >39°C, cough, rhinorrhea, vomiting and loose stools, as well as macroscopic hematuria. His primary care physician had prescribed empirically amoxicillin/clavulanate three days prior to admission after finding mildly elevated leukocytosis (17.3 G/l) and a serum C-reactive protein (CRP) of 158 mg/l. He had a negative rapid Streptococcal test of the throat, and a urinalysis showing hematuria and proteinuria. The urine culture was negative. A possible glomerulonephritis without edema or hypertension was suspected, and he was admitted.

He had received allogeneic bone marrow transplantation from his sister at the age of 1 year, with a neutrophil activity (NADPH oxidase) two years ago of 7%. Despite this, he never had a serious infection. He was prescribed routine trimethoprim-sulfamethoxazole and itraconazole prophylaxis for at least 6 months prior to this episode, but his parents admitted bad compliance.

On admission, the physical examination revealed that the child was not septic, but febrile at 38.8°C with a normal physical exam. His white blood cell count was at 12.4 G/l, with 75.5% segmented and 9% non-segmented neutrophils, hemoglobin 12.6 mg/dl, platelets 301,000/mm³, CRP 97 mg/l, procalcitonine 0.58 µg/l, and erythrocyte sedimentation rate at 103 mm/h. Proteinuria was confirmed with microscopic hematuria and normal glomerular filtration rate. An abdominal ultrasonography was compatible with acute glomerulonephritis.

The pediatric nephrologists concluded that this child had a glomerulonephritis of unknown etiology, with a subsequent spontaneous resolution of the proteinuria. Because of the persistent fever in an immunocompromised patient, a chest radiography and CT scan were requested and showed an opacity in the upper left lobe. A bronchoalveolar lavage (BAL) was performed, and, while waiting for the microbiological results, an empirical treatment with intravenous amoxicillin/clavulanate was started on hospital day 1. Because of persisting fever, intravenous antibiotics were changed on day 2 to intravenous imipenem (100 mg/kg/day and trimethoprim-sulfamethoxazole (15 mg/kg/day of trimethoprim) to cover broadly...
opportunistic microorganisms. Voriconazole was added on day 3. He rapidly improved clinically after that day. All cultures, including for fungal, viral or mycobacterial organisms, were initially negative in the BAL by routine cultures. Polymerase chain reaction (PCR) in the BAL for multiple respiratory virus (including adenovirus, enterovirus, influenza A virus, pandemic influenza A virus (H1N1/09), influenza B, metapneumovirus, parainfluenza, rhinovirus, and RSV), *Mycobacterium tuberculosis*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*, and a broad-range bacterial PCR in the blood were also negative. Tuberculin skin test, interferon-gamma release assay, antistreptolysin O titre, and mannan and galactomannan tests were also negative. Culture from the BAL from hospital day 1 grew nine days later. Small chalky white colonies were observed on blood agar plates. These colonies showed vegetative white aerial hyphae with branch points. Preliminary morphological characteristics were compatible with *Nocardia* species. No other organism grew on hospital day 1 BAL cultures. Consequently, treatment was changed on day 9 to intravenous imipenem 100 mg/kg/day and amikacin 20 mg/kg/day for a suspected disseminated nocardiosis (pulmonary, renal and intestinal) despite his good general status, and itraconazole prophylaxis was restarted. Blood cultures and urine culture for *Nocardia spp.* were negative. A PET scan showed pathologic and non-specific hypermetabolism in the upper left lobe, but also an inflammatory process in the supra-clavicular lymph node. A cerebral MRI didn’t show intracerebral lesions. Echocardiography was normal. The *Nocardia spp.* strain was partially amplified, sequenced and identified by using a 600-nt fragment of 16S rRNA gene as previously described by Rodriguez-Nava et al. (9). Susceptibility pattern was tested by using broth microdilution method following the M24A guidelines from the Clinical and Laboratory Standards Institute (CLSI). The results were recorded after 72 hours and interpreted according to the MIC breakpoints published by CLSI (8). The sequenced fragment presented 100% similarity to the *Nocardia cyriacigeorgica* type strain DSM 44484.

Antibiotics susceptibilities are shown in Table 1. Because of its resistance pattern, imipenem was then discontinued, and trimethoprim-sulfamethoxazole 20 mg/kg/day (of
trimethoprim) restarted combined with amikacin 20 mg/kg/day on day 21. Repeat chest radiograph showed significant resolution of his opacity. The patient was discharged 50 days after admission. The patient has completed 3 months of therapy with amikacin and is currently receiving trimethoprim-sulfamethoxazole for at least 12 months.

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Nocardia spp can cause severe infections in patients with CGD, usually in the lungs (4). Pulmonary nocardiosis can be either acute or chronic, or both (2). Radiographic findings include infiltrates, nodules, cavities and empyema (2, 4). However, images are nonspecific and may mimic other infections such as *Aspergillus*, *Staphylococcus spp.*, or *Mycobacterium* explaining why broad spectrum antimicrobial coverage is usually initiated, as in our patient. Extrapulmonary disease can complicate up to 50% of cases of pulmonary nocardiosis: cerebral abscess, for example, should be actively searched by MRI (2, 4). Patients receiving sulfonamide prophylaxis are less likely to have disseminated nocardiosis (4); however, some patients may have nocardiosis despite trimethoprim-sulfametoxazole prophylaxis (2, 7). Sulfonamide-based regimens generally maintain their efficacy for treatment in patients who previously received sulfonamide prophylaxis. Combination therapy with carbapenem (either imipenem, or meropenem) or a third generation cephalosporin with amikacin is recommended for severely ill patients (1). Our patient was clinically stable and the efficacy of treatment couldn’t be established by clinical response. Knowing that nocardiosis has a tendency to recur and that it has high morbidity and mortality rates in immunosuppressed patients, we treated our patient with a combination therapy. Combining imipenem and amikacin appears to be more effective than trimethoprim-sulfametoxazole alone because of a synergistic effect (1, 2). Furthermore, amikacin and imipenem have a bactericidal effect, which contrasts with the bacteriostatic effect of sulfonamides. Resistance and therapeutic failures may require using other antimicrobials, such as linezolid, tigecycline and moxifloxacin: these antimicrobials have shown promising results in adults (6).
Although identification may be “useful” to predict susceptibility patterns of the Nocardia species, this case shows that it is paramount to perform timely susceptibility testing, as identification may not always predict antimicrobial efficacy. N. cyriacigeorgica was first described by Yassin and colleagues in 2001 (10). It is a newly named but long-recognized agent of human disease and only few cases have been published using this new name (3). N. cyriacigeorgica belongs to the group of Nocardia previously classified as having type VI drug pattern (3). It appears that N. cyriacigeorgica is identical to N. asteroides drug susceptibility pattern type VI, which accounts for approximately 60% of clinical N. asteroides complex strains (5). In addition to sulfonamide susceptibility, type VI complex strains are generally susceptible to amikacin, broad-spectrum cephalosporins, imipenem and linezolid, but resistant to amoxicillin-clavulanate, ampicillin, ciprofloxacin and clarithromycin (3). Linezolid appears to be the most effective agent in vitro against Nocardia but clinical experience is limited (5). Other complexes have been described such as the highly antimicrobial-resistant N. transvalensis (type IV), or N. farcinica (type V).

While the usual combination therapy of amikacin and imipenem is commonly used to treat severe nocardial infections, this case report suggests that a three-drug regimen (trimethoprim-sulfamethoxazole, amikacin, and ceftriaxone or imipenem), as suggested by some authors (1, 2), should be started initially in patients with serious disease and/or disseminated infection until species and susceptibility patterns are available. Moreover, there are no previous published reports of imipenem resistance in N. cyriacigeorgica strains, and susceptibilities may not be routinely performed due to the assumption that all strains will be susceptible to imipenem. Thus, we recommend antimicrobial susceptibility testing for all Nocardia spp.
Table 1. Described patient’s *Nocardia cyriacigeorgica* susceptibility table

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>≤4 (S)</td>
</tr>
<tr>
<td>Trimethoprim-Sulfametoxazole</td>
<td>1/19 (S)</td>
</tr>
<tr>
<td>Linezolid</td>
<td>2 (S)</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>8 (S)</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanate</td>
<td>&gt;16 (R)</td>
</tr>
<tr>
<td>Imipenem</td>
<td>16 (R)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>16*</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>16*</td>
</tr>
<tr>
<td>Doripenem</td>
<td>32*</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≥4 (R)</td>
</tr>
<tr>
<td>Tigecyclin</td>
<td>≤1*</td>
</tr>
</tbody>
</table>

MIC: minimum inhibitory concentration; S: Susceptible; R: Resistant

* No interpretation of susceptibility available with used method
References


