Nocardia nova as the causative agent in spondylodiscitis and psoas abscess

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Abstract

We describe the first case of *Nocardia nova* spondylodiscitis accompanied by a psoas abscess due to spread from pulmonary nocardiosis. *Nocardia* was cultured from all affected sites.

After one-year of an appropriate antimicrobial therapy and a surgical drainage of the abscess which was required, the patient’s clinical condition had improved.
Case report

In 2001, a 27-year-old female was admitted to The Department of Nephrology-Transplantation Section because of abdominal and back pain accompanied by a high-grade fever. In 1991, she was diagnosed with end-stage renal disease due to focal segmental glomerular sclerosis. She was treated for one year using haemodialysis, and in 1992, she received her first renal cadaveric transplant, but it was rejected one year later.

In March 2000, she received a second renal transplant. Because of several episodes of acute rejection despite treatment with prednisone, cyclosporine and mycophenolate mofetil, the haemodialysis was restarted six months later and the graft was removed.

Following this surgery, she developed Staphylococcus epidermidis septicemia and an Aspergillus fumigatus pulmonary infection. Immunosuppressive therapy was discontinued and, despite antimicrobial therapy directed against these two infections, one month later (October 2000) she developed a second pulmonary infection with high fever, non-productive cough, and dyspnea. A chest X-ray and computed tomography (CT) showed multiple nodules without cavitations.

Bronchial aspirate, bronchoalveolar lavage fluid, and a lung biopsy were performed. Direct Gram-stained smear of all specimens showed branched gram-positive rods, and a modified acid-fast stain was positive. Cultures of all specimens grew a Nocardia species. Growth on blood agar and chocolate plates occurred within 3 days of inoculation and showed white opaque and dry colonies, which became chalky and orange with prolonged incubation. The presumptive diagnosis as N. nova complex was obtained from a combination of growth characteristics, aerial hypha production, lysozyme resistance, and drug susceptibility test which was performed by disk diffusion method (5, 20).
The patient became afebrile seven days after the start of a six-week treatment with intravenous antibiotics including amikacin (500 mg once daily), imipenem (500 mg three times daily) and trimethoprim-sulfamethoxazole (TMP-SMZ; 80 mg TMP/400 mg SMZ; two vials of 5 mL twice daily), followed by two months with the latter two antibiotics alone. Her clinical condition improved rapidly. She was discharged from the hospital and was treated by haemodialysis three times a week.

In August 2001, she complained of abdominal and back pain and progressive fever. Her temperature was above 39°C with a normal physical examination except that her back was painful, with the pain exacerbated when she moved. The spine was tender to palpation at the level of L4-L5 without neurological signs.

Laboratory evaluation showed an elevated C-reactive protein (CRP) level of 115 mg/L, leukocytes 12000 /mm³. All blood cultures were negative for bacterial growth. Abdominal ultrasound found a non-complicated left ovarian cyst, and 99mTc scintigraphy of the skeleton indicated an increased signal at L4-L5. Subsequently, a magnetic resonance imaging (MRI) scan of the lumbar spine confirmed increased signal intensity in the same location compatible with the diagnosis of spondylodiscitis at L4-L5 [Figures 1+2, 3], and revealed a psoas abscess.

A CT-guided needle aspiration of the affected vertebra was performed. No organisms were seen on a Gram-stained smear of the specimen. The aspirate of the affected vertebra was inoculated onto blood agar and chocolate plates that were incubated in a CO₂-enriched atmosphere at 37°C for 10 days and was reported as negative. The specimen was also processed through BacT/Alert broth medium (bioMérieux, Marcy l’Etoile, France) which was incubated for 4 weeks in aerobic condition because the previously pulmonary
Nocardia species. The recovery of the organism from the BacT/Alert broth confirmed the presence of nocardiae at this site.

Antimicrobial treatment with amikacin, imipenem and cotrimoxazole was restarted. No other localization of the disease was found at this time.

One month later, amikacin was stopped despite a temperature above 39°C and an increased CRP above 200 mg/L following each haemodialysis session. Amoxicillin (2 g three times daily by the oral route) was started.

In October 2001, a new CT scan revealed a voluminous psoas abscess [Figure 3]. It was drained surgically under tomographic guidance.

A Gram stain of the evacuated pus showed a branched-positive rod, and a modified acid-fast stain was positive for organisms morphologically consistent with Nocardia species. Bacteriologic culture grew a Nocardia species.

The lumbar pain improved, the patient became afebrile and the CRP decreased to 30 mg/L two weeks after drainage. Imipenem was switched to erythromycin (1 g three times daily by the oral route) because of adverse side effects (a seizure). Again, the CRP began to increase, and another CT scan was performed. The abscess had increased in size, so open surgery was performed to drain the psoas abscess. After the surgical procedure and a one-year treatment with oral erythromycin and amoxicillin, the patient’s clinical condition had improved.

The Nocardia isolates were referred to the “Nocardiosis French Observatory” where they were subsequently identified as N. nova by biochemical testing including the positive 2-week arylsulfatase assay, the negative decomposition of casein, xanthine, tyrosine, and hypoxanthine. Accurate species identification was determined by sequencing of the 5’end
606-base-pair fragment of the 16S rRNA gene and concluded to *N. nova* sensu stricto.

The gene was amplified as previously described (15) with primers Noc1 (5′-GCTTAACACATGCAAGTCG-3′) (position 46 to 64, *Escherichia coli* numbering system) and Noc2 (5′-GAATTCCAGTCTCCCCCTG-3′) (position 663 to 680, *E. coli* numbering system) and the sequencing gene was based on the search of the phylogenically closest known species inferred from database of “Nocardiosis French Observatory”. This database included 16S rRNA sequences from reference strains of all validated nocardial species. The database comparison, using Bibi software (7), generated a list of the closest matches with pairwise distance scores indicating the percentage difference between the unknown sequence and the database sequences. The three strains which were recovered from our patient were formed a phylogenetical individualized cluster with *N. nova* ATCC 33726T (data not shown) and showed 100 % similarity to the type strain.

Comparison of the relapse isolates with the agent from the primary pulmonary infection was performed by random amplified polymorphic DNA (RAPD), using DKU49 (5′-CCGCCGACC GGAG-3′) primer as previously described (13). This procedure established that isolates from the second and the third samples were of the same genotype as the first isolate.

At this time, there has been no recurrence of the infection even though the patient remained on haemodialysis. Clinical follow-up evaluation has continued regularly.

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The nocardiae are infrequently recognized to cause clinical disease in normal patients, but they are more frequently diagnosed causing disease in immunocompromised patients. The predisposing factors are long term corticosteroid therapy, chronic lung disease, hematologic and other malignancies, and organ transplantation. Renal transplant recipients are a sub-group of immunocompromised patients for whom \textit{Nocardia} is an important cause of morbidity and mortality and the prevalence of nocardiosis has been reported to be as high as 5\% (9, 22). Risk factors for nocardiosis in renal transplant recipients include multiple early rejection, intensive immunosuppressive therapy, and granulocytopenia (1). Recently, mycophenolate compounds, which block the proliferation of T and B cells, inhibit antibody formation and prevent the generation of cytotoxic T cells, have been implicated as predisposing factors for nocardial infection (11, 14). Our patient had all of these predisposing factors.

Pulmonary nocardiosis is the primary clinical finding which may be either self-limited or subclinical. It may progress to an acute, subacute, or chronic process mimicking tuberculous, mycotic infections or a neoplasm (10). Once blood-borne, the organisms can invade other anatomic locations, with the frequency of disseminated disease ranging between 28\% and 56\% (17, 19). The most common sites for dissemination are the central nervous system, skin and subcutaneous tissues, eyes (especially the retina), kidneys, joints and the heart (12). Osteomyelitis due to nocardiae is uncommon. Only 12 cases of \textit{Nocardia} osteomyelitis of the spine have been published over the past 40 years and four of them were lumbar sites (8).

The clinical diagnosis of nocardiosis is difficult. Signs, symptoms, and radiology are not pathognomonic. However due to the nature and gravity of nocardiosis, rapid and precise
identification of these agents are important. In routine clinical laboratory, the evaluation of appropriate specimens by smear and culture remains the principal method of diagnosis. Phenotypic characteristics are often used in conjunction with antimicrobial susceptibility patterns to help identification some nocardial isolates (4, 5, 6, 18, 21). *N. nova* complex has a distinct antimicrobial susceptibility pattern; they are susceptible or moderately susceptible to both amoxicillin and erythromycin and resistant to both amoxicillin-clavulanic-acid and tobramycin (5, 6, 18, 20). Although, phenotypic methods and susceptibility patterns are used for identification, but they are not reliable as definitive identification methods. Gene sequencing provides a more reliable identification and, the 16S rRNA gene sequence has become the new gold standard (3). Accurate strain identification is essential for defining the spectrum of disease caused by each species, predicting antimicrobial susceptibility, and for general comparisons of clinical isolates for epidemiological reasons.

Nocardiosis is also often difficult to treat and can be guided by susceptibility testing. Early and prolonged treatment with a combination of antibiotics is necessary in order to avoid either recurrence of infection, or metastatic spread, or drug resistance. Even though cotrimoxazole remains the drug of choice for the treatment of nocardiosis, combinations with imipenem and amikacin have been utilized successfully (10, 16). *N. nova* is characterized by susceptibility to amoxicillin and erythromycin and combination of these drugs offers a potential oral therapy for patients with nocardial infection (10).

The duration of therapy for nocardiosis is uncertain, but it should be protracted because of the high incidence of relapse following shorter courses of therapy (2).
The spondylodiscitis and psoas abscess reported above followed dissemination from the lung, which was the primary site of nocardial infection. *Staphylococcus aureus* remains the etiologic agent most commonly identified in patients with spondylodiscitis and psoas abscess. Nevertheless, a wide variety of other etiologic agents have been identified such as *E. coli* and *Proteus mirabilis*. Nocardiae as the causative agent of spondylodiscitis and psoas abscess is uncommon finding. No case of disseminated *N. nova* osteomyelitis has been reported in the English literature even though dissemination is especially prevalent with *N. farcinica* (16).

The bacteriologic etiology of this spondylodiscitis was not obtained by direct culture of the aspirate of the affected vertebra onto blood agar and chocolate plates may be due to the very low level of bacteria at this site. *Nocardia* species was detected at this site by using the BacT/Alert system and when the sample was subcultured late (after 4 weeks incubation) onto blood agar medium. So, we recommend the processing of the such sample through the Bact/Alert system or similar system for increase the growth sensitivity of nocardiae.

Once the diagnosis of pulmonary nocardiosis was made, the patient described above had received three months of antimicrobial therapy included imipenem, amikacin and cotrimoxazole for pulmonary nocardiosis. Obviously this duration was insufficient, explaining the spread of the disease eight months after the discontinuation of the therapy. Treatment of the spondylodiscitis and the psoas abscess with cotrimoxazole, imipenem and amikacin, did not result in clinical improvement probably because the antibiotics could not adequately reach the *Nocardia* through the thick layer of pus present in the psoas abscess. For this reason, surgical drainage was necessary.
In conclusion, the microbiological diagnosis is not difficult if clinician and clinical microbiologist are aware of the possibility of nocardiosis.

Long-term antibiotic therapy for six months to a year or longer (8, 12) is needed to treat *Nocardia* due to both the slow replication rate of the organisms and their ability to become intracellular pathogens which can persist as cryptic forms in the host. In addition, in patients with abscesses, surgical drainage may be required in order to ensure adequate penetration of antibiotics and clearance of the bacteria.

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References


**Figures 1+2:** Magnetic resonance imaging scan of the lumbar spine revealed an increased signal of L4-L5
Figure 3: Computed tomography scan of the chest showing voluminous psoas abscess
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Nocardia nova as the Causative Agent in Spondylodiscitis and Psoas Abscess

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