Pleural Infection Caused by Nocardia farcinica: Two Cases and Review of the Literature

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Abstract

Nocardia farcinica is a rare Nocardia species causing localized (lung, brain, skin) and disseminated infections. Predisposing factors include the chronic use of corticosteroids, organ transplantation and other immunocompromise conditions. Pleural empyema caused by this microorganism has scantily been reported. We describe two cases of pleural infection by N. farcinica that occurred in patients with a kidney transplant and cirrhosis, respectively. The first patient died soon after hospitalization, while the second survived nocardiosis (despite having significant adverse events to antibiotics) but eventually succumbed to other infectious complications. In this infectious disease, in which the duration of therapy is typically long and pleural space drainage is frequently required, bacterial susceptibility to antimicrobial agents should be tested.

Categories: Pulmonology
Keywords: nocardia farcinica, empyema, pleural effusion, antibiotics

Introduction

Nocardia farcinica is a particularly virulent Nocardia species that causes both localized and disseminated infections, mostly in the setting of immunocompromised conditions (e.g., glucocorticoids, calcineurin inhibitors and other immunosuppressive medications, hematologic and solid-organ transplant recipients, malignancy, HIV disease, diabetes). The infection is mainly acquired by inhalation, less commonly by direct inoculation through the skin, and frequently results in disseminated disease. In a Spanish series of 1,119 strains of the Nocardia genus, N. farcinica represented 11.4% of the isolates [1]. About 60% of N. farcinica strains were isolated from bronchial secretions, but only 4% from lung/pleural fluid samples [1].

Even though pneumonia is the most common manifestation of N. farcinica, pleural involvement is infrequent, with only a few cases being reported [2-14]. This article describes two additional patients with pleural empyema by this gram-positive aerobic actinomycetes and succinctly reviews the literature on the subject.

Case Presentation

Case 1

A 73-year-old man was hospitalized for a two-week history of dyspnea. He had undergone a kidney transplant two years earlier and was taking prednisone (5 mg/d), tacrolimus (2.5 mg/d) and mycophenolate mofetil (1 g/d). A chest X-ray and CT showed multiple pulmonary nodules, some of which were cavitated, along with consolidations and a left free-flowing pleural effusion occupying about 25% of the hemithorax (Figure 1). A diagnostic thoracentesis displayed a non-purulent exudate with the following characteristics: erythrocyte count 38,500 cells/µL, leukocytes 987 cells/µL (80% neutrophils), lactate dehydrogenase 737 U/L, glucose 95.5 mg/dL, adenosine deaminase 14.4 U/L, pH 7.30 and C-reactive protein 133 mg/L. Empiric antibiotic therapy with ceftriaxone and trimethoprim-sulfamethoxazole (TMP-SMX) was initiated. Subsequently, ceftriaxone was replaced by piperacillin-tazobactam. N. farcinica was isolated from the pleural fluid and blood cultures after eight days of incubation. The antibiogram showed that it was susceptible to TMP-SMX, linezolid, amikacin, imipenem and amoxicillin-clavulanate. Also, an active cytomegalovirus (CMV) infection was diagnosed based on the presence of CMV replication in the blood (240,000 copies/mL). Tacrolimus was discontinued because of its high blood levels (13.35 ng/mL). The patient died six days after hospital admission before any of the previous microbiological results became available. The autopsy confirmed the presence of bilateral pulmonary and pleural nocardiosis, as well as CMV pneumonitis; both entities probably contributing to death.
Case 2

A 49-year-old woman with a history of alcoholic liver cirrhosis (Child Pugh C and MELD score 19) was admitted to the hospital because of fever, dyspnea and right pleuritic chest pain of one-week duration. In some areas of ground-glass opacification, a large loculated right-sided pleural effusion and ascites were seen on the chest CT. A diagnostic pleural tap showed a non-purulent exudate with the following characteristics: erythrocyte count 34,900 cells/µL, leukocytes 2,411 cells/µL (58% neutrophils), lactate dehydrogenase 595 U/L, glucose 63.1 mg/dL, adenosine deaminase 17.6 U/L, pH 7.43 and C-reactive protein 52 mg/L. The analysis of peritoneal fluid was consistent with portal hypertension (serum-ascites albumin gradient >1.1 g/dL). Empirical antibiotic therapy with cefotaxime was started along with two serial therapeutic thoracenteses of 600 mL each. *N. farcinica* grew on pleural fluid cultures after 6 days of incubation, but an antibiogram was not done. Blood cultures were negative. Cefotaxime was replaced by linezolid 600 mg po q12h. One month later, the patient developed myelosuppression secondary to linezolid, which had to be withdrawn. At that time, there remained a small pleural effusion. The patient needed colony-stimulating factors (filgrastim), platelet and red cell transfusion. Ciprofloxacin (500 mg po q12h) was initiated. After three months with the new antibiotic regimen, the patient suffered a cardiorespiratory arrest due to an acquired long QT syndrome that was attributed to fluoroquinolones. A long ICU stay (two months) was needed during which meropenem, vancomycin and fluconazole were administered for a number of infectious complications and cirrhosis decompensation. At hospital discharge, no further antibiotics were prescribed. One year later, the patient required a total right hip arthroplasty and died of septic shock secondary to an early-onset prosthetic hip infection.

Discussion

Pleural infection by *N. farcinica* is rare, with about 16 cases previously reported in the literature (Table 1), according to a PubMed search (keywords: [pleural or empyema or pleuritis] and Nocardia farcinica; time period from inception to March 2021) [2-14]. The general series of nocardiosis briefly mention a few additional cases of pleural involvement by *N. farcinica*, but with information so incomplete that they cannot be incorporated into this review.

| Reference        | Age | Sex | Predisposing factors                           | Site of Infection | Diagnostic samples | Therapy                                  | Death due to nocardiosis |
|------------------|-----|-----|-----------------------------------------------|-------------------|---------------------|------------------------------------------|--------------------------|
| Nakajima et al. 1999 [2] | 21  | F   | Systemic lupus erythematosus; corticosteroids | Pleura            | Pleural fluid       | Pleural drainage + intrapleural IMP + Mino + TMP-SMX | No                       |
### TABLE 1: Previous cases of pleural empyema by *N. farcinica* reported in the literature

| Reference | Age | Gender | Comorbidities | Sites | Fluids | Treatments | Outcome |
|-----------|-----|--------|---------------|-------|-------|------------|---------|
| Torres et al. 2000 [3] | NA | NA | CLL | Lung, pleura | Pleural fluid | NA | NA |
| Torres et al. 2000 [3] | 70 M | None | Lung, pleura | Pleural fluid, sputum | SMX | No |
| Torres et al. 2000 [3] | 44 M | None | Lung, pleura, brain | Pleural fluid | Pleural drainage + IMP + CIP + AG | Yes |
| Ando et al. 2001 [4] | 69 F | ITP; corticosteroids | Pleura | Pleural fluid | Therapeutic thoracentesis + IMP + TMP-SMX + Mino | No |
| Arunthathi et al. [5] | NA M | Corticosteroids, thalidomide | Pleura | Pleural fluid | AMK + Mino | NA |
| Severo et al. 2005 [6] | 75 M | Corticosteroids | Lung, pleura, thyroid, heart, kidneys, brain, bone, lumbosacral soft tissue | Blood, thyroid, sputum | TMP-SMX | Yes |
| Rivero et al. 2008 [7] | 42 M | Heart transplantation; corticosteroids, cyclosporine, and mycophenolate mofetil | Pleura, pericardium, brain | Pleural fluid, pericardial fluid | Pleural and pericardial drainages + TMP-SMX + IMP + AMK + linezolid | No |
| Parande et al. 2010 [8] | 27 M | HIV | Lung, pleura | Pleural fluid, sputum | Pleural drainage + TMP-SMX + AMK | Yes |
| Budzik et al. 2012 [9] | 78 M | Intraarticular corticosteroids | Knee joint, lung, pleura | Synovial fluid, blood, lung | TMP-SMX | Yes |
| Ishiguro et al. 2017 [10] | 82 M | Diabetes mellitus | Pleura, lung, knee | Pleural fluid, blood, synovial fluid | Pleural and joint drainages + Amp-sulb + Mino + IMP + Levo | No |
| Canouï et al. 2017 [11] | 30 M | Hematopoietic stem cell transplantation; corticosteroids, chemotherapy, rituximab | Pleura, lung | Pleural fluid, pleural biopsy, BAL | Pleural drainage + MER + AMK + doxycycline | No |
| Huang et al. 2019 [12] | 56 M | NA | Pleura, lung | Pleural fluid | NA | NA |
| Huang et al. 2019 [12] | 76 M | NA | Pleura, lung | Pleural fluid | NA | NA |
| Nasri et al. 2019 [13] | 91 M | Astrocytoma | Meninges, lung, pleura | Cerebrospinal fluid | TMP-SMX + IMP | Yes |
| Zayet et al. 2020 [14] | 68 M | Corticosteroids | Pleura, lung, brain | Pleural fluid, BAL | Pleural drainage + Amox-clav + IMP + TMP-SMX | No |

**Legend:**
- AG: aminoglycoside
- AMK: amikacin
- Amox-clav: amoxicillin-clavulanate
- Amp-sulb: ampicillin-sulbactam
- BAL: bronchoalveolar lavage
- CIP: ciprofloxacin
- CLL: chronic lymphocytic leukemia
- CIP: ciprofloxacin
- F: female
- HIV: human immunodeficiency virus
- IMP: imipenem-cilastatin
- ITP: immune thrombocytopenic purpura
- Levo: levofloxacin
- M: male
- MER: meropenem
- Mino: minocycline
- NA: not available
- SMX: sulfamethoxazole
- TMP-SMX: trimethoprim/sulfamethoxazole

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Nocardiosis mostly affects patients with impaired cell-mediated immunity, as exemplified by these two new observations where the infection developed in the context of a renal transplant recipient under immunosuppressive therapy and advanced cirrhosis, respectively. In a retrospective compilation of 53 patients with *N. farcinica* infections up to the year 1999, 85% had predisposing factors, among which the most frequent was the chronic use of corticosteroids [3]. In fact, at least half of the patients with a nocardial pleural infection listed in Table 1 had a history of corticosteroid treatment.

Pneumonia, brain abscesses and skin infections are the major clinical presentations of *N. farcinica* infection, though in nearly one-third of the cases the disease disseminates, particularly to the central nervous system [3]. Other infections, such as aspergillosis, CMV disease (Case 1) and gram-negative bacteria, may occur concomitantly to nocardiosis [15]. In pulmonary nocardiosis, findings on chest imaging may be variable and include solitary or multiple nodules (Case 1), as well as multifocal consolidations or ground-glass opacities (Cases 1 and 2). Cavitation is usually restricted to immunocompromised patients [15]. Sometimes, the disease may initially resemble tuberculosis, particularly if upper lung lobes are involved and weakly acid-fast filaments are seen on respiratory samples. Nocardia filaments may or may not be acid-fast. Although Nocardi a may grow in most routine bacterial, fungal and mycobacterial media, the laboratory should be notified of this possibility in order to use selective media (e.g., modified Thayer-Martin, Columbia blood agar). In one review series, the median time required for the isolation of *N. farcinica* in various samples was four days, but growth may take several weeks [3]. If available, molecular diagnostics (e.g., 16S RNA gene sequencing) may allow the identification and speciation of Nocardia isolates.

Two-thirds of pleural infections by *N. farcinica* reported in the literature were managed with tube thoracostomy or therapeutic thoracentesis, in addition to antibiotics (Table 1), as is generally indicated in patients with positive pleural fluid cultures [16]. Antibiotic susceptibility testing is mandatory because treatment should be based on it. According to large series, *N. farcinica* is uniformly susceptible to linezolid and amikacin, commonly susceptible to imipenem and amoxicillin-clavulanate, variably susceptible to TMP-SMX, usually resistant to ciprofloxacin, and typically resistant to third-generation cephalosporins, minocycline and aminoglycosides other than amikacin (Table 2) [1,17-19].

| Country [ref.] | No. of isolates | TMP-SMX | IMP | AMK | Linezolid | Mino | Amox-clav | Cefotaxime | Ceftriaxone | CIP |
|----------------|----------------|---------|-----|-----|-----------|------|-----------|-------------|-------------|-----|
| Spain [1]      | 128            | 45.3%   | 3.9%| 1.6%| 3.1%      | 89.1%| 18%       | 54.7%       | -           | 48.4% |
| France [17]    | 149            | 4%      | 23% | 1.4%| 0%        | 12.8%| 20.1%     | 79.7%       | 80.5%       | 41.9% |
| USA [18]       | 105            | 80%     | 25% | 0%  | 0%        | 79%  | 10%       | 93%         | 72%         |
| USA [19]       | 319            | 1%      | 17% | 0%  | 0%        | 93%  | 4%        | -           | 97%         | 51%  |

**TABLE 2: Antimicrobial resistance (non-susceptible isolates) of Nocardia farcinica according to different series (n>100)**

Amox-clav, amoxicillin-clavulanate; AMK, amikacin; CIP, ciprofloxacin; IMP, imipenem-cilastatin; Mino, minocycline; USA, United States of America; TMP-SMX, trimethoprim/sulfamethoxazole

Suggested initial regimens for pleuropulmonary nocardiosis usually include the combination of TMP-SMX (15 mg/kg/day of the TMP component IV/po divided in 2-4 doses) plus imipenem (500 mg IV q8h), with the option to add amikacin (7.5 mg/kg IV q12 h) in severe infections [20]. After 5-4 weeks of intravenous therapy and documented clinical improvement, patients may be switched to oral monotherapy. Duration of antibiotic treatment is generally long (6-12 months). Although these guidelines apply to nocardiosis in general, once the Nocardia species is identified and susceptibility testing results are available, the antibiotic regimen must be adapted. We suggest the combination of imipenem and amikacin for the induction therapy of *N. farcinica* infections. Although linezolid seems an attractive option, its use for more than a few weeks is normally precluded by the risk of hematologic toxicity (Case 2) and neurotoxicity. The mortality of *N. farcinica* pleural infections is not negligible, with more than one-third of fatalities occurring among the reviewed patients (Table 1). To reduce mortality, an early diagnosis and prompt initiation of adequate antibiotic treatment are imperative.

**Conclusions**

Pleural infection by *N. farcinica* is rare, with only 16 previously reported cases prior to the new ones exposed herein. This condition should be suspected in immunocompromised subjects with pleural effusions and pulmonary nodules/consolidations. Pleural fluid is an optimal specimen for the isolation of the microorganism. In patients with severe disease or immunocompromise, combination empirical therapy (≥2 drugs) is initially warranted. In particular, consideration should be given to the use of amikacin, imipenem and linezolid.
Additional Information

Disclosures

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