CASE REPORT

A mimic's imitator: a cavitary pneumonia in a myasthenic patient with history of tuberculosis

Raquel Ramos Garcia, Nitin Bhanot, Zaw Min

Division of Infectious Diseases,
Allegheny General Hospital,
Allegheny Health Network,
Pittsburgh, Pennsylvania, USA

Correspondence to

Dr Zaw Min,
zmin@wpahs.org

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SUMMARY

A 77-year-old man with myasthenia gravis receiving prednisone and plasmapheresis was found to have right upper lobe cavitary pneumonia on radiological imaging studies after thymectomy. He had a remote history of treated pulmonary tuberculosis (TB) at the age of 19. On the basis of history of TB and current prednisone therapy, reactivation of pulmonary TB was highly suspected. Branching Gram-positive bacilli were identified on bronchoalveolar lavage (BAL). BAL Ziehl-Neelsen Acid-fast bacilli stain was negative, but a modified Kinyoun stain revealed branching, beaded, filamentous bacilli, suggestive of *Nocardia* spp. *Nocardia cyriacigeorgica* grew from the BAL culture. Cerebral MRI demonstrated a right frontal lobe lesion, clinically correlated to be nocardial brain abscess. The patient was treated with three-drug antimicrobial therapy (trimethoprim-sulfamethoxazole, meropenem, linezolid) for 2 months, followed by an additional 10 months of trimethoprim-sulfamethoxazole. Amikacin would have been included in the initial three-drug regimen, but its use was contraindicated in our myasthenic patient because aminoglycoside would trigger fatal myasthenic crisis by neuromuscular blockage. Follow-up imaging studies revealed resolution of the lung and brain lesions.

BACKGROUND

Reactivation of pulmonary tuberculosis (TB) is highly suspected in patients with a prior history of this disease, particularly when immunity wanes in instances such as use of immunosuppressive medications. In our patient, who had a history of treated pulmonary TB and presented with cavitary pneumonia after being on long-term steroids, the clinical suspicion of TB was very high. Although the clinical manifestations and microbiological characteristics resembled those of TB, additional tests helped us to make a definitive diagnosis of nocardiosis. Confirmation of the diagnosis was important to manage nocardial infection, which is treated differently than TB.

Mycobacteria appear as Gram-positive bacilli on Gram stain. There are other medically significant Gram-positive bacilli that would present as pulmonary cavitary lesions in immunocompromised hosts.¹ Among them, *Nocardia* spp is one of the important pathogens. TB is regarded as a well-known mimic of medicine because of protean clinical manifestations.² We describe a patient with disseminated nocardiosis that imitated reactivation of TB, the great mimicker of medicine. The important differential characteristics of other Gram-positive bacilli are elaborated to assist in diagnosis. We discuss the

different treatment options of nocardiosis depending on the clinical presentations and host immune status. Certain medications could exacerbate neuromuscular blockade, so they should be used with great caution in patients with myasthenia gravis. Aminoglycosides, which play a major role in the treatment of disseminated nocardiosis, are included in the list of drugs that are contraindicated in myasthenic patients.

CASE PRESENTATION

A 77-year-old man with a history of myasthenia gravis was admitted for thymectomy. His medical history was significant for pulmonary TB at the age of 19, and he had been treated with antituberculous therapy. The patient had been receiving weekly plasmapheresis and daily prednisone 30 mg for the treatment of myasthenia gravis for 4 months. He reported night sweats and intermittent productive cough with yellowish brown sputum for 4 weeks prior to thymectomy, but denied other symptoms. The surgical procedure was complicated by pneumomediastinum and extensive subcutaneous emphysema. A chest X-ray showed a right upper lobe cavitary lesion (figure 1), which was not seen 2 months ago. The patient was immediately placed on the airborne isolation due to the concern of pulmonary TB reactivation. Consultations with a pulmonologist and infectious diseases doctor were obtained.

On examination, the patient was afebrile, blood pressure was 125/85 mm Hg, pulse rate 110 bpm, respiratory rate 19 breaths/min and oxygen saturation was 95% on 2 L nasal supplemental oxygen. He appeared to be in mild respiratory distress. There were crepitations over the neck, anterior

Figure 1 Chest X-ray showing a solitary right upper lobe cavity without air-fluid level.

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Figure 2 A coronal view of the chest CT scan showing a markedly thick-walled right upper lobe cavitary pneumonia and extensive subcutaneous emphysema and pneumomediastinum.

chest and bilateral upper extremities on palpation, consistent with subcutaneous emphysema. The remaining physical examination was unremarkable.

INVESTIGATIONS

Basic laboratory results such as complete blood count and metabolic panel were within acceptable range. Chest CT scan demonstrated a solitary thick-walled right upper lobe cavity (3 cm×2.8 cm) with no interior content (figure 2). Evidence of pneumomediastinum and extensive subcutaneous emphysema was also noted on the imaging. There was no mediastinal or hilar lymphadenopathy.

Bronchoscopy with bronchoalveolar lavage (BAL) was performed and it revealed purulent secretions in the right main bronchial stem with no endobronchial mass. The Gram stain of multiple BAL specimens showed Gram-positive bacilli with a short-branching appearance (figure 3), but the Ziehl-Neelsen acid-fast bacilli (AFB) stain was negative. Modified Kinyoun stain was requested, and it illustrated an abundant amount of red coloured, beaded, long filamentous branching rods

Figure 3 Gram stain of bronchoalveolar lavage depicted Gram-positive bacilli with short-branching features.

Figure 4 Modified Kinyoun stain applied to bronchoalveolar lavage (BAL) specimen illustrated clusters of pathognomonic thin, filamentous, long branching, beaded bacilli, highly suggestive of *Nocardia* spp.

(figure 4). A clinical diagnosis of nocardiosis was pursued. The patient underwent MRI of the brain, which showed a small rim-enhancing right frontal lobe lesion (figure 5), suggestive of nocardial brain abscess. No malignant cells were identified in the bronchial washings. Combination therapy with oral trimethoprim-sulfamethoxazole (TMP-SMX), intravenous meropenem and oral linezolid was empirically initiated, awaiting the final culture and susceptibility data. A week later, the culture grew characteristic chalky white colonies on the blood agar medium (figure 6), and the pathogen was eventually identified as *Nocardia cyriacigeorgica* by DNA sequencing method performed at a reference laboratory. Cultures for *Actinomyces*, mycobacteria and fungi on multiple BAL specimens remained negative following 6 weeks of incubation.

Figure 5 A minute right frontal lobe brain lesion was noted on the T1-weighted axial view of cerebral MRI study with intravenous gadolinium.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses of cavitary pneumonia in immunosuppressed hosts include bacterial lung abscess, mycobacterial infections (TB, or non-tuberculous infections), actinomycosis, invasive fungal infection, and malignancy. Hence, it is imperative that microbiological and histopathological diagnosis be pursued in such immunocompromised patients.

Mycobacteria notably appear as Gram-positive bacilli on Gram stain. *Nocardia* organisms on the direct smears of tissue samples are classically seen as Gram-positive, finely beaded, branching, long filamentous bacilli. *Nocardia* organisms possess a unique property of resisting decolourisation by an acid alcohol solution due to the presence of long-chain mycolic acid in their cell walls. The decolouriser hydrochloric acid (4%) used in the Ziehl-Neelsen stain is too strong and harsh for *Nocardia* spp to retain Carbol-fuchsin stain. A special modified Kinyoun stain contains a milder decolouriser and 1% sulfuric acid, and *Nocardia* spp are able to keep the primary Carbol-fuchsin stain and appear red stained against the blue background (figure 4). Another differentiating feature against mycobacteria is the 'beaded' Acid-fast appearance on microscopy. *Nocardia* appears very similar to *Actinomyces* on Gram stain, but *Actinomyces* spp do not routinely show 'acid-fast' property, and they grow under anaerobic conditions. *Rhodococcus equi* and *Tsukamurella* spp were also considered in the differential diagnoses in our case because they are two important opportunistic Gram-positive bacilli causing cavitary pneumonia. However, the morphological appearance of *Rhodococcus* and *Tsukamurella* spp has a distinct pattern—weakly positive Ziehl-Neelsen AFB stain, no apparent branching and smooth colonies with no aerial hyphae—helping to differentiate them from *Nocardia* pathogens, which appear as characteristically dry chalky-white powdery colonies with irregularly wrinkled surfaces from aerial hyphae (figure 6).

TREATMENT

Given the disseminated nocardiosis with cerebral involvement, our patient was empirically treated with a three-drug combined therapy that included oral TMP-SMX (160–800 mg 2 tablets every 8 h), oral linezolid (600 mg every 12 h) and intravenous meropenem (500 mg every 6 h), while awaiting identification and susceptibility of the *Nocardia* isolate. We avoided using amikacin because aminoglycosides could trigger life-threatening myasthenic crisis by blockade of neuromuscular transmission.

Figure 6 Typical chalky-white, powdery, velvety and wrinkled colonies suggestive of the growth of *Nocardia* spp were observed on a blood agar plate.

Figure 7 A 2-month follow-up chest CT scan (coronal view) showing partial resolution of right upper lobe cavity with a significant decrease in wall thickness. Complete resolution of subcutaneous emphysema and pneumomediastinum was noted.

OUTCOME AND FOLLOW-UP

The patient reported significant improvement in productive cough and night sweats a week after initiation of empiric combined antimicrobial therapy. The pathogen was identified as *N. cyriacigeorgica*. The susceptibility testing of *Nocardia* isolate was reported sensitive to TMP-SMX, imipenem, meropenem, linezolid and amikacin. The patient was later transferred to the rehabilitation centre. After 2 months of the triple antimicrobial therapy, a repeat chest CT scan showed a decrease in thickness of right upper lobe cavity without new lesions (figure 7). A follow-up brain MRI revealed a complete resolution of the right frontal lobe lesion. Meropenem and linezolid were discontinued, and monotherapy with oral TMP-SMX (160–800 mg 2 tablets every 8 h) was continued for an additional 10 months. The patient was not able to follow-up with our Infectious diseases outpatient clinic owing to transportation issues. Thanks to the advancement of the electronic medical record, we were able to review his laboratory results periodically in order to assure there were no adverse reactions from a prolonged course of high-dose TMP-SMX therapy. After 1 year of antimicrobial therapy, CT of the chest was performed at the local hospital and a hard copy was sent to our institution for review. It showed a residual right upper lobe thin-walled cavity, which represented a healed pulmonary scar (figure 8). The patient reported no respiratory symptoms, fever or night sweats. Thus, TMP-SMX was transitioned to prophylaxis dosing (160–800 mg 1 tablet every 24 h) since the patient continued to require prednisone and plasmapheresis therapy for myasthenia gravis. No clinical signs of relapse were observed at the 4-month telemedicine follow-up after transition to the TMP-SMX prophylaxis regimen.

DISCUSSION

Nocardiosis is a bacterial infection caused by *Nocardia* spp, which are aerobic Gram-positive actinomycetes and found ubiquitously in soil, decomposing vegetation and in water.³ Inhalation is the most common portal of entry for infection, but oral ingestion and direct skin inoculation may also occur.^{3 4}

Figure 8 A 12-month follow-up chest CT scan (coronal view) revealed a healed right upper lobe thin-walled cavity.

With the advances in molecular sequencing for identification of *Nocardia* spp, there are now more than 92 species identified, at least one-third of which have been reported to cause disease in humans.³

Nocardia spp are considered opportunistic pathogens in patients with defects in cell-mediated immunity. Risk factors include prolonged glucocorticoid therapy, underlying haematological malignancies and solid tumours, haematological stem cell transplant, solid organ transplant, tumour necrosis factor- α inhibitor treatment, alcoholism, diabetes mellitus, AIDS, chronic granulomatous disease, chronic obstructive pulmonary disease and pulmonary alveolar proteinosis.^{2 3 5}

Clinical manifestations of nocardiosis may be localised or systemic, with the lung reported as the most common primary site of infection.³ *N. cyriacigeorgica*, *N. nova* and *N. farcinia* are reported to be the most common *Nocardia* spp involved in pulmonary nocardiosis.³ Clinical presentations of nocardial lung infections are non-specific, and they include fever, chills, night sweats, weight loss, cough, haemoptysis and dyspnoea. Typical radiographic features of pulmonary nocardiosis include reticulo-nodular infiltrates, cavitory lesions, pleural effusion or, less commonly, a 'halo sign'.^{3 4 6} *Nocardia* spp appear as Gram-positive bacilli on routine Gram stain. Other medically important Gram-positive bacilli that also cause cavitory pneumonia include mycobacteria, *Actinomyces*, *R. equi* and *Tsukamurella* spp. Salient microbiological features of these pathogens are elaborated in table 1.^{1 3}

The brain is the most common site of extrapulmonary nocardiosis secondary to high neural tropism exhibited by this bacterium and, therefore, cerebral imaging study is recommended in all patients with pulmonary nocardiosis.^{2 3} Diagnostic brain biopsy is usually not required in patients with proven pulmonary nocardiosis.³

Speciation and susceptibility testing of all *Nocardia* isolates is routinely recommended secondary to a heterogeneous pattern of antimicrobial drug susceptibilities within *Nocardia* spp.^{3 7} Optimal therapy of nocardiosis has not been firmly established because of the lack of prospective controlled clinical studies. Recommended empiric treatment of nocardiosis depends on the host immune status and sites of the infection. In most nocardial infections, TMP-SMX has long been considered the therapeutic agent of choice of any initial therapeutic regimen.³ Empiric monotherapy with TMP-SMX is recommended for localised nocardial skin disease. A dual drug combination therapy (eg, TMP-SMX plus amikacin, or TMP-SMX plus imipenem/meropenem) is recommended for immunocompromised patients with disseminated nocardiosis without brain involvement, or in patients with isolated central nervous system (CNS) nocardiosis. In patients with disseminated nocardiosis with cerebral infection, an empiric three-drug regimen (usually TMP-SMX, amikacin, plus imipenem/meropenem) is a preferred therapeutic choice until susceptibility results are available since *Nocardia* isolates have variable antimicrobial sensitivities.^{3 7 8}

Our patient's clinical presentation warranted a three-drug combination of TMP-SMX, a carbapenem agent and amikacin. Meropenem is the preferred agent in patients with cerebral nocardiosis because of comparable efficacy to imipenem and excellent CNS penetration, and it is less likely to lower seizure threshold.^{3 9 10} In our case, the patient's underlying condition (myasthenia gravis) had to be taken into consideration when choosing empiric but effective antibiotics therapy. The use of amikacin was absolutely contraindicated in our patient since aminoglycosides induce neuromuscular blockade and exacerbate myasthenia gravis.^{11 12} Thus, linezolid becomes an attractive empiric alternative in cases of myasthenia gravis because it has activity against virtually all clinically important *Nocardia* isolates and has good CNS penetration, without exacerbating underlying disease.⁷ Other antimicrobial agents have unpredictable activity against *Nocardia* spp, and they are usually not considered as first-line agents in empiric treatment of severe disseminated nocardial infection.³

In disseminated nocardiosis, an induction phase with combined parenteral and oral antibiotics is favoured for at least 4–8 weeks until clinical improvement occurs, and identification and antimicrobial susceptibility of *Nocardia* spp are known.³ It is then transitioned to single-drug oral therapy for 6–12 months, depending on the site and severity of the disease as well as the immune status of the host.^{3 8} Of note, in those

Table 1 Distinguishing differential microbiological characteristics of clinically significant Gram-positive bacilli causing cavitory pneumonia are listed^{1 3}

Gram-positive bacilli	Ziehl-Neelsen stain	Modified Kinyoun stain	Microscopic features
<i>Nocardia</i> spp	Negative	Positive	Finely 'beaded', thin, long-branching filamentous bacilli
<i>Mycobacterium</i> spp	Strongly positive	Positive	Straight or slightly curved bacilli; absence of apparent branching and 'beaded' appearance
<i>Actinomyces</i> spp	Negative	Negative	Thin, filamentous, branching bacilli; no 'beaded' pattern; grow under anaerobic condition
<i>Rhodococcus equi</i>	Weakly positive	Positive	Can appear as cocci or bacilli; absence of filamentous, apparent branching and 'beaded' patterns
<i>Tsukamurella</i> spp	Weakly positive	Positive	Straight or slightly curved long bacilli; absence of apparent branching and 'beaded' appearance

patients who require continuation of steroids or other immunosuppressants, it is reasonable to sustain daily low-dose maintenance suppressive therapy with oral TMP-SMX.^{3 13} The clinical outcome is determined by the extent of disease and host factors. Mortality is the highest (20–50%) in patients with nocardial brain abscess and in immunocompromised patients.^{8 14} A high index of clinical suspicion is required for diagnosis of nocardial infection. Nocardiosis has long been regarded as the ‘great imitator’; in this case, it mimicked the all-time ‘great mimicker’ of medicine, TB. Early recognition of the disease, performing appropriate microbiological studies, multi-disciplinary collaboration, and initiation of appropriate therapy usually lead to optimal outcomes.

Learning points

- ▶ It is important to be aware of the Gram stain property of mycobacteria microorganisms—Gram-positive bacilli.
- ▶ Recognition of the typical microbiological appearance of *Nocardia* spp—long branching, beaded, filamentous Gram-positive bacilli on modified Kinyoun stain, is mandatory.
- ▶ Recognition of other Gram-positive bacilli that are considered medically important pathogens, and appreciation of their distinct differentiating microbiological features can be useful.
- ▶ Avoidance of aminoglycoside use in the treatment of nocardiosis in patients with myasthenia gravis to prevent fatal myasthenic crisis is imperative.

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