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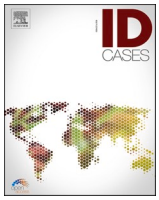

Case report

Septic arthritis by *Nocardia farcinica*: Case report and literature review

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ABSTRACT

Nocardiosis is a bacterial infection caused by organisms of the *Nocardia* genus. The disease typically involves the skin, central nervous system or pulmonary system. Very rarely nocardiosis can cause disease of other organs including bone and joints. Nocardiosis is typically a chronic, somewhat indolent infection, occurring in patients with defective cell mediated immunity. We describe a 78-year-old female with right shoulder septic arthritis resulting from *Nocardia farcinica* with associated involvement of her skin and lungs as well. She was treated with surgical debridement and combination antibiotic therapy. We also share a literature review of bone and joint infection caused by the *N. farcinica* species, highlighting its rarity. Understanding uncommon manifestations of nocardiosis allows for early recognition and treatment of the condition and optimal patient care.

Case presentation

A 78-year-old female with a history including myasthenia gravis (MG) presented to our hospital with worsening right shoulder pain. She reported that the pain had been intermittent for the past three months but in the last week it had been persistent and worsening in severity. Her medical history also included hypertension, chronic kidney disease, and obesity. Her surgical history was significant for proctosigmoidectomy for rectal cancer in 2020 and L3-L4 laminectomy and foraminotomy for spinal stenosis in 2019 which was followed by implantation of a percutaneous spinal cord stimulator in 2020.

Five months prior to this presentation the patient was admitted to the intensive care unit for a myasthenic crisis after she presented with dysphagia, ptosis and dysarthria. At the time she was intubated for airway protection and was treated with plasma exchange, prednisone and reinitiation of her pyridostigmine. She was discharged home on pyridostigmine and prednisone 60 mg daily. At her neurology follow up appointment one month later she was started on mycophenolate and her prednisone dosage was decreased to 40 mg daily which she's continued since.

One month prior to this presentation the patient was admitted to our hospital for left hand and wrist purulent cellulitis. At the time a contrasted computerized tomography (CT) of her left upper extremity revealed soft tissue ulceration with cellulitis extending into an ill-defined intramuscular abscess (Fig. 1). She was evaluated by the hand surgery team who had recommended no surgical intervention. The patient was treated with ceftaroline for three days while inpatient and was discharged home on a one-week course of doxycycline for the cellulitis as well as new initiation of trimethoprim-sulfamethoxazole (TMP-SMX) for *Pneumocystis jirovecii* prophylaxis given chronic steroid use of at least three months. A culture of her purulence acquired on admission grew several colonies of *Nocardia farcinica* after she was discharged.

During this presentation (day 1) the patient's only concern had been intermittent right shoulder pain for the past three months, now much more painful and persistent in the past week. She denied any recent trauma or any other symptoms including fevers, chills, and sweats. She also reported that her left-hand cellulitis had resolved at this time. Her vitals on presentation were as follows: temperature of 35.8 °C, heart rate of 88 beats per minute, respiratory rate of 18 breaths per minute, blood pressure of 135/85 mmHg, oxygen saturation of 97 % on room air. The examination of her right shoulder was notable for pain with passive range of motion, significantly limited active range of motion due to discomfort, but no overlying erythema, warmth or swelling. Her initial blood work revealed a white blood cell count of 14,300/μL, absolute neutrophil count of 11,930/μL, c-reactive protein (CRP) of 7.63 mg/dL, erythrocyte sedimentation rate (ESR) of 45 mm/h. Comprehensive metabolic panel was largely unremarkable. Imaging on arrival included a contrasted CT of her right shoulder revealing multi loculated collections throughout the shoulder concerning for abscesses, moderate fluid within subacromial bursa concerning for bursitis, as well as moderate glenohumeral joint effusion concerning for septic arthritis (Fig. 2). On

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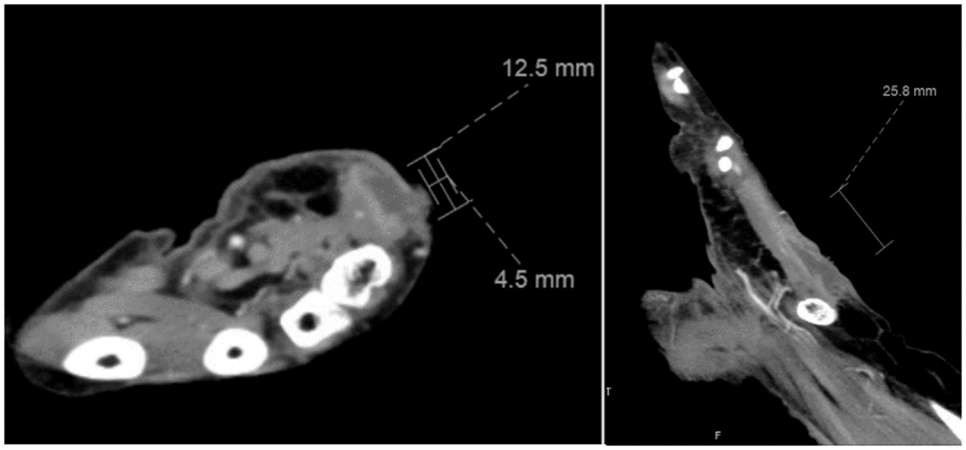

Fig. 1. Axial (left) and coronal (right) views of contrasted computerized tomography of left hand revealing soft tissue ulceration along the ulnar aspect of wrist/proximal hand with subjacent cellulitis and an ill-defined intramuscular abscess extending from the ulceration into the hypothenar musculature.

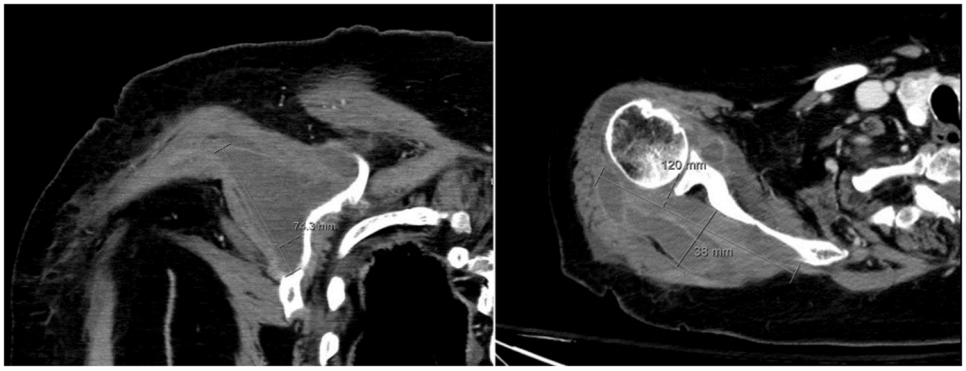

Fig. 2. Coronal (left) and axial (right) views of contrasted computerized tomography of right shoulder revealing large lobular, multi loculated collections throughout the shoulder involving the rotator cuff musculature both anterior and posterior to the scapula. Moderate amount of fluid within the subacromial bursa and associated punctate densities concerning for subacromial bursitis as well as moderate glenohumeral joint effusion concerning for septic arthritis are also seen.

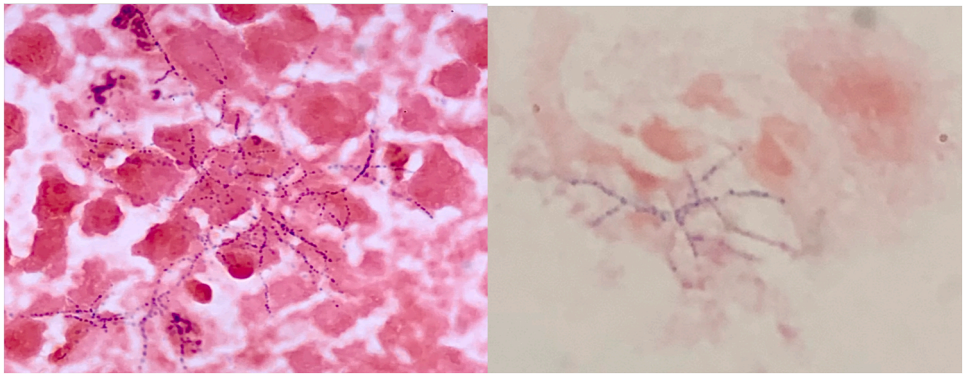

Fig. 3. Thin beaded branching Gram positive bacilli seen on Gram stain of right shoulder synovial fluid (left) and periscapular abscess (right).

day 2 she underwent bedside arthrocentesis of the right shoulder synovium with fluid analysis revealing a white blood cell count of 107,865/μL, 95 % neutrophilic, 1 % lymphocytic and 5 % monocytic. No crystals were seen in fluid. Gram stain of the fluid revealed gram positive beaded bacilli and culture grew *N. farcinica* (Fig. 3). Antibiotic susceptibility had finalized long after her discharge and is presented in Table 1. CRP and ESR post-arthrocentesis were 26.32 mg/dL and 71 mm/hr, respectively. On day 3 the patient underwent operative debridement of the right shoulder. Intra-operatively, there was gross, foul smelling purulent material in the glenohumeral joint as well as extra-articularly along the posterior aspect of the scapula. The abscesses were well organized loculations that were difficult to break up in order to evacuate, consistent with a more chronic infection. Approximately 15 cc and 40 cc of purulent material was evacuated from the intra and extra articular spaces, respectively. The culture of the periscapular fluid removed during this procedure grew *N. farcinica* as well.

The patient had been treated with meropenem 2 g twice daily and TMP-SMX 320–1600 mg three times daily with improvement of leukocytosis (8400/μL) and CRP (0.5 mg/dL), ESR (23 mm/h) by day 10. Repeat contrasted CT of her right shoulder revealed markedly decreased

Table 1
Susceptibility data for the *Nocardia farcinica* isolated from our patient. MIC = minimal inhibitory concentration.

Antibiotic	MIC	Interpretation
Amikacin	≤ 0.5	Sensitive
Amoxicillin/Clavulanate	8/4	Sensitive
Ceftriaxone	> 64	Resistant
Ciprofloxacin	0.5	Sensitive
Clarithromycin	> 16	Resistant
Imipenem	16	Resistant
Minocycline	2	Intermediate
Tobramycin	8	Intermediate
Linezolid	1	Sensitive
Trimethoprim/Sulfamethoxazole	0.25/4.7	Sensitive
Doxycycline	4	Intermediate
Moxifloxacin	0.12	Sensitive

fluid collections. Given nocardial infection at multiple sites the decision was made to evaluate for pulmonary and intracranial disease. Non-contrasted CT of her chest showed small bibasilar effusions and bibasilar infiltrates as well as small scattered nodularity with no abscesses (Fig. 4). The patient was unable to undergo magnetic resonance imaging (MRI) of her brain as her spinal cord stimulator was not MRI compatible. However, a noncontrasted CT of her head did not show evidence of intracranial abscesses. Given evidence of disseminated disease but limitations in ruling out CNS infection, the infectious disease team opted to treat with dual antimicrobial therapy with intravenous meropenem and oral high dose TMP-SMX until follow up. After she was released from the hospital the culture susceptibility testing had resulted and revealed resistance to carbapenems. She was continued on only TMP-SMX for two months at which point she was seen in infectious disease clinic and was found to have severe thrombocytopenia thought to be due to the antibiotic. She was then transitioned to amoxicillin-clavulanate for chronic suppression. Shortly after the patient was admitted for altered mentation and failure to thrive. Her family had opted to focus on her comfort and she was transitioned to hospice care before she was thoroughly evaluated.

Discussion

Nocardia is the genus of aerobic, filamentous, weakly acid fast, gram-positive bacillus first described by French microbiologist and veterinarian Edmond Nocard in 1888 [1,2]. Edmond initially made this discovery when studying bovine farcy disease involving granulomas and abscesses. Further classification of *Nocardia* was made in the following years, specifically *Nocardia farcinica* characterized in 1889, as well as *Nocardia abscessus*, *Nocardia brasiliensis*, *Nocardia nova*, and *Nocardia* asteroides, among many others [3,4]. *Nocardia* is ubiquitously found in soil and decaying vegetation and infections can be transmitted by inhalation, ingestion or direct innoculation [2].

Pulmonary nocardiosis is the most common clinical manifestation and can include development of multifocal pneumonia with nodularities, pleural effusions and cavitary lesions. Extrapulmonary manifestations commonly include cerebral nocardiosis (brain abscesses and meningitis) as well as cutaneous nocardiosis (cellulitis, skin abscesses, lymphocutaneous disease). Bloodstream infections and diseases of solid organs including eyes (keratitis, endophthalmitis), liver, spleen, and glands are quite rare but have been reported [3,5]. Immunocompromised individuals including solid organ and stem cell transplant, those living with HIV, and those on chronic corticosteroids are the most affected. Males are at a higher risk of infection than females with a 3:1 incidence [6].

Diagnosis of nocardiosis involves gram staining, culture, polymerase chain reaction testing, or histopathology of tissue or fluid in question and can include blood, sputum sample, bronchioalveolar lavage fluid, abscesses, or cerebrospinal fluid [2]. It is important to consider that the organism is slow growing and can require a prolonged incubation period

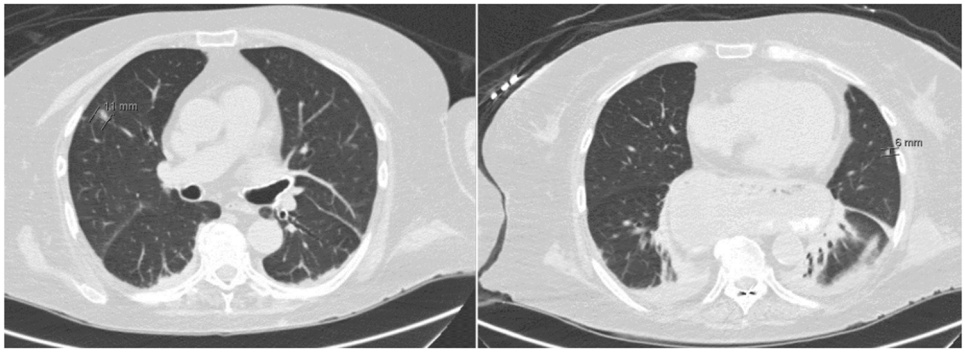

Fig. 4. Two axial views of computerized tomography of chest revealing scattered areas of tiny nodules (left and right), bibasilar effusions (right) and bibasilar posterior infiltrates (right).

Table 2
Review of literature from 2002 to 2022 using PubMed for cases of bone/joint infection specifically caused by *Nocardia farcinica* species. M = male, F = female, COPD = chronic obstructive pulmonary disease.

Author	Study year	Age/ Sex	Nocardia Dissemination	Immunocompromising conditions	Other
Audenaert, Emmanuel et al.	2004	68M	Knee	Yes, chronic steroids	COPD
Babilas, P et al.	2007	61F	Talocalcaneal joint, brain, liver	Yes diabetes	None
Budzik, Jonathan M et al.	2012	78M	Lung, knee	None	Steroid injection to same knee 1 week ago
Graat, Harm C A et al.	2002	54M	Osteomyelitis (spine), epidural abscess, discitis, brain, psoas	Yes, chronic liver disease	None
Ishiguro, Takashi et al.	2017	82M	Lung, knee	Yes, diabetes, pneumoconiosis	None
Ma, Fei et al.	2018	50M	Epidural and paravertebral abscesses	Yes, diabetes	None
Ozan, Firat et al.	2013	78M	Knee	None	Recent total knee arthroplasty
Tripathi, Swapnil et al.	2021	81M	Osteomyelitis (rib), lung	None	None

of up to three weeks, though most isolates grow within 3–5 days. Imaging to assess organ involvement, especially of the chest and brain, should be considered especially if patients are immunocompromised or if disseminated disease is of concern. While treatment is largely medical and involves antimicrobial therapy, surgical procedures such as incision and drainage or debridement should be considered to acquire source control. Antibiotic selection can be quite challenging as susceptibility varies significantly by species, geography and individual isolates. Commonly used antibiotics include trimethoprim-sulfamethoxazole (TMP-SMX), amikacin, imipenem, and linezolid. Optimal duration of therapy is unclear, however immunocompetent patients without central nervous system manifestation are generally treated for 6–12 months, while those who are immunocompromised or with CNS disease are treated for at least 12 months and may need maintenance therapy thereafter [3].

We present this case to share a rare manifestation of nocardial disease- septic arthritis. Our patient presented with a recent history of purulent cellulitis due to *N. farcinica* and was found to have septic arthritis of the glenohumeral joint with associated subacromial bursitis and adjacent abscesses. Septic joint infection due to *Nocardia spp* is very rare but has been previously reported. A literature review from 2022 identified only 37 cases of nocardial septic arthritis- 32 of them involving native joints [7]. Sixty percent had infection due to hematologic dissemination, and of these 82 % were immunocompromised. Eighty percent of those with native joint infections had knee involvement. Of those five patients with prosthetic joint infection, three had knee involvement while two had disease of the hip.

We performed literature review using PubMed to search for cases of bone and joint infection specifically due to *N. farcinica spp* from 2002 to 2022 (Table 2). Eight patients were identified, three of which were of osteomyelitis or spinal cord disease. Five patients had joint disease, most commonly of the knee. Five patients had immunocompromising conditions including diabetes mellitus, chronic steroid use, chronic liver disease and underlying pneumoconiosis.

Both of these literature reviews highlight the rarity of septic arthritis due to the *Nocardia* genus and especially of the *N. farcinica* species. Our patient presented with infection of the shoulder which seems to be scarce in the literature and likely under reported. She has no history of prosthesis of the joint or trauma suggestive of direct inoculation. While initial mode of transmission is unclear in this case, skin translocation and inhalation are both likely given cellulitis and chest CT findings suggestive of pulmonary nocardiosis. Regardless of origin, her use of immunosuppressants placed her at a high risk for disseminated disease. Our patient was managed well with antibiotics and surgical debridement for source control with improvement of inflammatory markers and leukocytosis.

Two major challenges arose in the management of this patient. First, given her immunocompromised state and disseminated disease, MRI of the brain was warranted to evaluate for cerebral nocardiosis. Unfortunately, the patient was not able to have this done due to her MRI-incompatible spinal cord stimulator. Her CT of the head did not show evidence of cerebral disease; however, this is much less sensitive than MRI. Given that the patient didn't have CNS symptoms suggestive of cerebral disease and her need for long term antibiotic regardless, brain imaging likely would not change her management unless she has clinical change.

The second challenge was in antibiotic selection. Due to her underlying myasthenia gravis and recent severe crisis, antibiotics selection was limited. Antibiotic classes that most notably unmask or lead to exacerbations of myasthenia gravis include macrolides, fluoroquinolones, and aminoglycosides [8]. Penicillins have rarely been reported as causes of exacerbations and other classes including cephalosporins, TMP-SMX and clindamycin are generally considered safe. Our patient's culture data was initially reported as *Nocardia* genus without the species identified. At this point the decision was made to treat her with TMP-SMX and meropenem (the carbapenem available at our hospital) as combination therapy is frequently used in those with severe disseminated disease. Eventually the organism was determined to be *N. farcinica* for which therapy options based on susceptibility include amikacin, ciprofloxacin, imipenem and linezolid [9]. With that said, some studies have shown this species to have imipenem resistance ranging from 47 % to 86.8 % [10,11]. The species is frequently cephalosporin resistant and has mixed susceptibilities to TMP-SMX. Given her intolerance to aminoglycosides and fluoroquinolones and concerns for linezolid's side effect profile (cytopenia with long term use) her regimen was kept as TMP-SMX and meropenem at time of discharge.

Unfortunately, after she was released from the hospital, susceptibility testing had finalized and revealed carbapenem resistance. This was further complicated by thrombocytopenia thought to be an adverse reaction to TMP-SMX. This removed linezolid as an option of therapy given the risk of worsening thrombocytopenia. Amoxicillin-clavulanate was deemed the next best option for our patient and she was placed on this therapy for chronic suppression. Treatment of this patient's *N. farcinica* infection was largely limited by her neuromuscular disease and adverse reactions to antibiotics. Ideal options to treat this species would include combinations of amikacin with either a fluoroquinolone, TMP-SMX or linezolid.

Due to varied antibiotic susceptibility and diversity in disease presentation the management of nocardiosis can be quite complex. Given the low prevalence of the disease and the rarity of involvement seen in organs other than skin, lungs and brain, conditions such as septic arthritis or osteomyelitis from *Nocardia* is underrecognized. Here we present this case to add to the current literature on septic arthritis due to *Nocardia farcinica* and to increase awareness among practitioners so they may consider this diagnosis when clinically appropriate as early detection and therapy can improve long term patient outcome.

Conclusion

Nocardia farcinica is a gram positive, aerobic, filamentous bacterium that can cause disease especially in immunocompromised hosts. Clinical manifestations are diverse and diseases specifically of bone and joint are rare. Here we describe a case of a female with septic arthritis due to *Nocardia farcinica*- an extremely rare presentation that is underrecognized in the scientific community. Better understanding of the degree of involvement resulting from this pathogen allows for prompt diagnosis, early treatment and better outcomes.

CRediT authorship contribution statement

Abhishek Thakur: Data collection, data analysis, Writing – original draft, Writing – review & editing, final review. **Eapen:** Writing – original draft, Writing – review & editing, data analysis, final review. **Cherian:** Writing – original draft, Writing – review & editing, data analysis.

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Ethical approval

N/A.

Consent

Informed consent obtained from patient.

Declaration of interest

None.

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Informed consent

Informed consent was obtained from the individual participant included in the study.

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