Case Report

Unveiling the Complexity of Nocardia Septic Arthritis in an Immunocompromised Patient: A Case Report

Steven A Kessler, BS[1]; Meghan R Mansour, BS[1]; Ali Khreisat, MD[2]; Mamon Tahhan, MD[2]

Author affiliations are listed at the end of this article.

Correspondence to:
Steven A Kessler, BS
(stevenkessler@oakland.edu)

Abstract

Background
Nocardiosis is the systemic manifestation of *Nocardia* infection, often found in immunocompromised individuals. *Nocardia* are transmitted via inhalation or skin wounds, disseminating hematogenously to organs and rarely, joints. We present a patient with immunosuppression who developed gout of the knee with superimposed Nocardial septic arthritis and a possible subsequent systemic infection.

Case Presentation
A 74-year-old man presented with left lower extremity swelling and pain. He was taking immunosuppressive medication for antineutrophilic cytoplasmic antibody-positive vasculitis. A week prior, an arthrocentesis test was positive for gout. He received prednisone without improvement. A repeat arthrocentesis was positive for *Nocardia farcinica* septic arthritis. Chest imaging showed subpleural nodules. After failed antibiotics, a susceptibilities test yielded results that favored linezolid. The patient exhibited acute anemia from hematomas intramuscularly above the infection, which resolved with transfusions. Immunosuppression was stopped, and the patient recovered appropriately after the correct antibiotics were administered.

Conclusion
This case involves septic arthritis with possible pulmonary nodule involvement, showcasing the complexity of infections in immunocompromised individuals. Clinicians should maintain adequate suspicion for an infectious cause of arthritis in patients with immunosuppression. In our case, the hematomas are a curious finding, without known etiology. The question of when and how to reintroduce immunosuppressive agents while preventing the recurrence of nocardiosis remains a complex consideration.

Keywords
Nocardia; *Nocardia* infections; arthritis; infectious; immunosuppression therapy; gout; case reports

Introduction
Nocardiosis is the systemic manifestation of *Nocardia* infection often found in immunocompromised individuals. These gram-positive, filamentous, aerobic organisms are commonly found in soil and organic matter, and their potential to become pathogens in susceptible hosts is well-recognized. The incidence of infections in the United States is 500 to 1000 cases per year.[1] Those taking immunosuppressive medications have almost a 5-fold increased risk of infection.[2] Nocardial infections vary from localized cutaneous to invasive disease. *Nocardia* are transmitted via inhalation or through direct inoculation via trauma or wound in the skin, disseminating hematogenously to organs and, rarely, joints. Septic arthritis is a very rare presentation of Nocardiosis, with a limited number of documented cases in the literature.[3] The insidious onset of symptoms can compli-

cate early diagnosis, and clinical presentation may mimic other arthritic conditions, leading to delays in appropriate management. Managing immunocompromised nocardiosis requires a nuanced approach, balancing immune control and pathogen defense. Our case highlights a 74-year-old man with antineutrophilic cytoplasmic antibody (ANCA)-positive vasculitis with subsequent immunosuppression who developed gout of the knee with superimposed nocardial septic arthritis and subsequent systemic infection. The interplay between his underlying conditions, immunosuppressive regimen, and the challenges of his septic arthritis management are illustrated.

Case Description

A 74-year-old man presented with a 2-week history of left lower extremity swelling and pain, initially centered at the left knee and progressively extending to the lower leg and foot. This presentation was accompanied by nausea, vomiting, weakness, and difficulty in walking over the week prior to admission. He did not exhibit any other systemic symptoms, such as fever, chills, weight loss, night sweats, or rigors. His medical history included chronic kidney disease with associated anemia and ANCA-positive vasculitis, managed with mycophenolate mofetil 500 mg twice a day and prednisone 10 mg once a day, as well as intermittent rituximab infusions. He was also intermittently taking prophylactic trimethoprim-sulfamethoxazole due to immunosuppression. A week prior to presentation, he underwent a left knee arthrocentesis and tested positive for gout, for which he received an increased prednisone dosage of 20 mg twice a day for 5 days with no relief. Fluid from the arthrocentesis was not sent out for microbiology studies at that time.

Physical examination revealed a warm, swollen, and erythematous left knee. Laboratory results indicated leukocytosis with elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. **Table 1** shows the values of the complete blood count, metabolic panel, ESR, and CRP on admission. An x-ray showed a significant knee joint effusion with an air bubble, while venous Doppler ultrasound ruled out deep venous thrombosis (DVT). Subsequent arthrocentesis, incision and drainage revealed purulent fluid containing monosodium urate and calcium pyrophosphate crystals, suggestive of gout and pseudogout with superimposed septic arthritis. The cell count in the collected fluid consisted of 90 220 total nucleated cells and 20 000 red blood cells. The fluid was also sent for culture. Infectious disease was consulted, and the patient was initiated on vancomycin and cefepime. Also, rheumatology was consulted, mycophenolate mofetil was paused, and prednisone continued due to the ongoing infection. One day later, the cultures from the joint fluid resulted positive for *Nocar-*

Table 1. Values of the Complete Blood Count, Metabolic Panel, ESR, and CRP on Admission

Component	Result	Reference range	Units
WBC	29.3	3.5-10.1	bil/L
RBC	2.69	4.31-5.48	tril/L
Hemoglobin	9.4	13.5-17.0	g/dL
Platelet	539	150-400	bil/L
Na	137	135-145	mmol/L
K	3.8	3.5-5.2	mmol/L
Cl	99	98-111	mmol/L
Bicarbonate	22	20-29	mmol/L
BUN	36	7-25	mg/dL
Creatinine	2.03	0.60-1.30	mg/dL
CRP	380.6	<8.0	mg/L
ESR	71	0-15	mm/hr

Abbreviations: WBC = white blood cell; RBC = red blood cell; Na = calcium; K = potassium; Cl = chlorine; BUN = blood urea nitrogen; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate

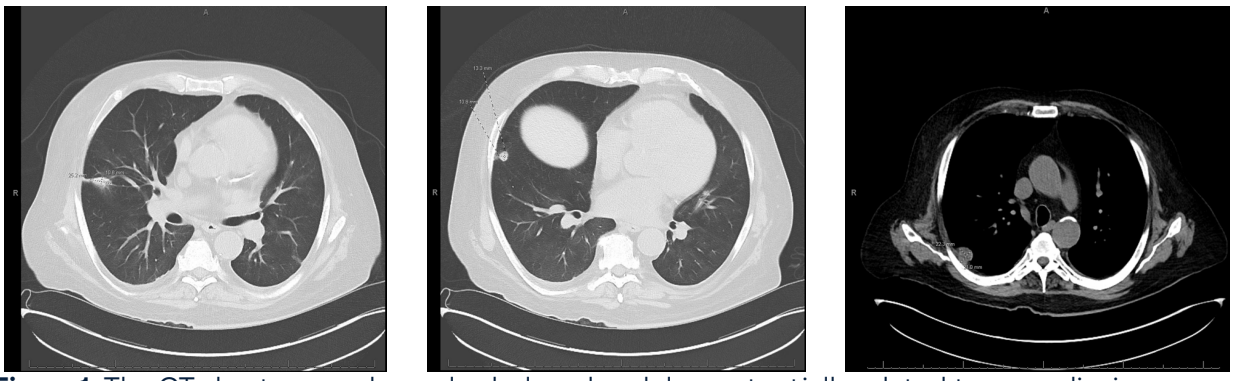

Figure 1. The CT chest scans showed subpleural nodules, potentially related to nocardiosis.

dia farcinica. This led to a computed tomography (CT) chest scan to investigate pulmonary involvement, given the suspicion for systemic nocardiosis. Blood cultures were negative. The patient was switched to intravenous (IV) trimethoprim-sulfamethoxazole and cefepime pending susceptibility results. The CT chest scan showed subpleural nodules, potentially related to nocardiosis (**Figure 1**). Brain magnetic resonance imaging was conducted to rule out central nervous system involvement, which was negative for any intracranial processes. Daptomycin and meropenem were added to the already prescribed trimethoprim-sulfamethoxazole and cefepime as susceptibilities were still pending and the patient did not improve with the initial antibiotic regimen.

Subsequent procedures and assessments revealed acute DVT, managed with heparin. The patient also exhibited acute anemia from muscle hematomas in the quadriceps above the infected knee, evident on a CT scan of the extremity, which resolved with 3 units of blood. The patient had acute pain in the knee, and a week after admission, a repeat incision and drainage of the knee was completed, which was largely bloody fluid. Growth of the fluid was again positive for the *Nocardia* species. After this incision and drainage, the pain resolved and the patient did not require any other transfusions for anemia. Susceptibility testing yielded results that favored linezolid as the optimal choice for the antibiotic regimen, and he was started on 600 mg twice a day. Throughout his hospital course, he had 4 more needle aspirations of the joint due to swelling and pain. All of the aspirations grew *Nocardia*, but they decreased in number after linezolid was started, the last of which showed no growth. The patient's knee pain and ambulation improved over time, and he was discharged after a 22-day hospital stay in a stable condition to a subacute rehab facility, on a well-defined antibiotic regimen of 3 additional weeks of linezolid with transition to trimethoprim-sulfamethoxazole after completion, along with a follow-up with the infectious disease department. The subpleural nodules were not reevaluated due to a lack of systemic symptoms and an adequate antibiotic regimen. The patient was advised to discontinue mycophenolate mofetil to prevent increased immunosuppression until a follow-up with his rheumatologist. Overall, he responded positively to treatment, demonstrating progressive improvement throughout his hospitalization.

Discussion

This case is an intriguing example of *Nocardia farcinica* septic arthritis, showcasing the complexity of infections in immunocompromised individuals. The possibility for pulmonary involvement also shows the complexity of these infections. This case also represents the overlap in symptoms that patients may exhibit with acute gout and pseudogout flares and septic arthritis. Clinicians should maintain adequate suspicion for an infectious cause in patients with any kind of immunosuppression, given our patient received inadequate treatment with steroids, which could have worsened his infection. Although the steroids may have improved the symptoms of knee pain related to his gout or pseudogout, an approach with a different medication may have been warranted to avoid more immunosuppression. In hindsight, the correct treatment was ultimately linezolid, given his symptoms were likely from his superimposed septic arthritis.

A case report and review of the literature completed from 2002 to 2022 showed 9 total cases of bone or joint infection caused by *Nocardia farcinica*.[3] The majority of these patients also had immunocompromising conditions. When appropriate antibiotics were started in previous cases of septic arthritis, a majority resulted in favorable outcomes with over 80% survival.[4] Ensuring appropriate antibiotics are started early and for an adequate duration for the manifestation is key in improving outcomes, a challenge noted in our case. Antibiotic susceptibilities for the *Nocardia* species in our patient had to be sent out to an outside facility, and repeat cultures were needed. The wait for results delayed clinical improvement and required many changes and additions of antibiotics to ensure coverage. The consequences of this delay included worsening of the infection and possible increased antibiotic resistance. Trimethoprim-sulfamethoxazole is a first-line defense for the infection, with recommendations to add 1 or 2 more agents due to the variable resistance of the organism.[5,6] The majority of the subspecies of *Nocardia* are susceptible to linezolid, the antibiotic deemed necessary in our case. This drug is not usually started immediately due to myelosuppression and neurotoxicity.[6] Ensuring an early and adequate culture and a multidisciplinary approach, with infectious disease and microbiologists, can aid in the correct antibiotic regimen.

The patient's CT chest scan revealed subpleural nodules, prompting consideration of pulmonary involvement in nocardiosis. *Nocardia* pulmonary infections can manifest as nodules, infiltrates, or abscesses, often resembling other infectious or neoplastic processes.[7] MRI is considered a necessity in systemic cases to rule out intracranial involvement, another common manifestation of nocardiosis. It has been shown that over half of the cases with pulmonary involvement disseminate hematogenously, most commonly to the brain.[8] This case underscores the diagnostic challenge of differentiating nocardial infections from other conditions, especially in immunocompromised individuals without pulmonary symptoms.

Our patient’s complication of acute anemia with several hematomas of his upper leg above the infected knee is a curious finding. This is not a known association of septic arthritis but could be secondary to the infection in our case. Another possibility for the hematomas is the repeated drainage and procedures on the limb during hospitalization. The patient did not have a history of hematomas or bleeding, and the etiology of this finding is ultimately unknown.

The patient's immunosuppression, a cornerstone of his vasculitis management, posed a unique challenge in balancing infection control and immunosuppressive therapy. Pausing mycophenolate mofetil while continuing prednisone for his vasculitis aimed to mitigate further immunosuppression. Some cases of *Nocardia* infection and immunosuppression have yielded favorable results after a decrease in immunosuppression, but others have exhibited recurrence.[9,10] The question of when and how to reintroduce immunosuppressive agents while preventing the recurrence of nocardiosis remains a complex consideration.

Conclusion

This case illustrates the intricate interplay between immunosuppression, nocardiosis, and a rare presentation of septic arthritis, emphasizing the importance of early recognition, tailored antibiotic therapy, and collaborative interdisciplinary management. The rarity of nocardial septic arthritis and its potential coexistence with pulmonary nodules highlight the diagnostic and therapeutic challenges in such cases. Further research is warranted to better define optimal strategies for managing nocardial infections in the context of immunosuppression and to explore the potential long-term implications of such infections on immunosuppressive therapy.

Conflicts of Interest

The authors declare they have no conflicts of interest.

Author Affiliations

1. Oakland University William Beaumont School of Medicine, Rochester Hills, MI
2. Corewell Health William Beaumont University Hospital, Royal Oak, MI

References

1. Beaman BL, Burnside J, Edwards B, Causey W. Nocardial infections in the United States, 1972-1974. *J Infect Dis*. 1976;134(3):286-289. doi:10.1093/infdis/134.3.286

2. Margalit I, Goldberg E, Ben Ari Y, et al. Clinical correlates of nocardiosis. *Sci Rep*. 2020;10(1):14272. Published 2020 Aug 31. doi:10.1038/s41598-020-71214-4
3. Thakur A, Eapen J, Cherian SS. Septic arthritis by *Nocardia farcinica*: case report and literature review. *IDCases*. 2022;31:e01668. Published 2022 Dec 23. doi:10.1016/j.idcr.2022.e01668
4. Fazili T, Bansal E, Garner D, Bajwa V, Vasudeva S. Septic arthritis due to Nocardia: case report and literature review. *Am J Med Sci*. 2022;364(1):88-91. doi:10.1016/j.amjms.2022.01.012
5. Wilson JP, Turner HR, Kirchner KA, Chapman SW. Nocardial infections in renal transplant recipients. *Medicine (Baltimore)*. 1989;68(1):38-57. doi:10.1097/00005792-198901000-00003
6. Restrepo A, Clark NM; Infectious Diseases Community of Practice of the American Society of Transplantation. Nocardia infections in solid organ transplantation: guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation. *Clin Transplant*. 2019;33(9):e13509. doi:10.1111/ctr.13509
7. Martínez R, Reyes S, Menéndez R. Pulmonary nocardiosis: risk factors, clinical features, diagnosis and prognosis. *Curr Opin Pulm Med*. 2008;14(3):219-227. doi:10.1097/MCP.0b013e3282f85dd3
8. Coussement J, Lebeaux D, van Delden C, et al. Nocardia Infection in Solid Organ Transplant Recipients: A Multicenter European Case-control Study. *Clin Infect Dis*. 2016;63(3):338-345. doi:10.1093/cid/ciw241
9. van Dijk K, van Kessel DA, Schijffelen MJ, Staartjes WR, Tersmette M. Disseminated Nocardia infection: spontaneous resolution in response to decrease of immunosuppression. *New Microbes New Infect*. 2014;3:10-11.Published 2014 Oct 14. doi:10.1016/j.nmni.2014.10.001
10. Yetmar ZA, Wilson JW, Beam E. Recurrent nocardiosis in solid organ transplant recipients: An evaluation of secondary prophylaxis. *Transpl Infect Dis*. 2021;23(6):e13753. doi:10.1111/tid.13753