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Case report

Cutaneous *Nocardia arthritidis* infection in an orthotopic liver transplant recipient

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ABSTRACT

Nocardiosis is a potentially life-threatening infection that affects both immunocompetent and immunosuppressed hosts. We discuss a case of an elderly gentleman with history of orthotopic liver transplantation who presented with cellulitis of his left forearm. When he did not respond to the typical antibiotic coverage for bacterial cellulitis, skin biopsy was performed. *N. arthritidis* was identified as the pathogen, a relatively newly identified human pathogen first described to cause human disease in 2004.

Introduction

Nocardiosis is a potentially life threatening infection that may affect both immunocompetent and immunosuppressed individuals [1]. It can cause either limited or disseminated disease with the latter occurring more commonly in immunosuppressed individuals. In immunocompromised hosts, infection typically involves multiple organ systems, mostly commonly, the skin, respiratory, and/or central nervous system [1].

Several species of *Nocardia* are known to cause infections in humans [2]. Application of newer molecular identification and classification techniques has led to an expanded spectrum of pathogenic *Nocardia* species [2]. Commonly encountered *Nocardia* species in clinical practice are *N. abscessus, N. ostitidiscaviarum, N. brasiliensis, N. cyriacigeorgica, N. pseudobrasiliensis, N. farcinica, N. wallaei, and N. nova* [1,2]. *Nocardia arthritidis* is a recently identified distinct species of *Nocardia* that has been reported to cause human disease, primarily in immunosuppressed hosts [2,3]. *N. arthritidis* was first identified in 2004 when two different *Nocardia* species were identified in sputum and inflammatory exudates collected from a patient with rheumatoid arthritis [4]. It was further classified using chemotaxonomic characterization and 16S rDNA sequencing and was found to be distinctly different than *N. farcinica,* but similar to other *N. asteroides* group species [4]. Given its identification in a patient with rheumatoid arthritis, the name *N. arthritidis* was proposed [4].

Case

An 84-year-old male presented to our hospital with complaints of painful left arm swelling associated with purulent drainage. His past medical history was significant for orthotopic liver transplant (OLT) in 2004 with preserved graft function on monotherapy with tacrolimus, and end stage renal disease requiring hemodialysis *via* an arteriovenous fistula. Approximately five weeks prior to presentation, he had sustained an abrasion to the left forearm after crashing his tractor into a river embankment. Soon after the injury, he noted swelling in the left arm and sought medical attention from his primary care physician. He was prescribed amoxicillin for skin and soft tissue infection, which was did not result in improvement. This prompted him to come to our hospital.

At presentation, there was erythema and tenderness in addition to multiple pustular lesions present on his left forearm (Fig. 1). He was treated empirically with vancomycin and cefepime for purulent cellulitis. While on empiric therapy he continued to have significant pain and limited clinical improvement. Due to lack of response and suspicion of an atypical infection in an immunocompromised host, a skin biopsy was performed. Histopathology results revealed dermal edema accompanied by both superficial and deep interstitial suppurative infiltrates. Additionally, a few tiny ovoid structures were seen on the Periodic Acid-Schiff (PAS-D) and Grocott's methenamine silver (GMS) staining. The dermatopathologist considered those to be artifacts; though possibility of cryptococcal infection was not excluded.

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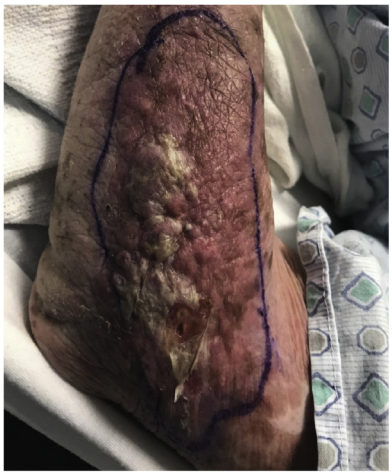

Fig. 1. Left arm erythema, adherent slough, and purulent lesions noted on presentation.

Consequently, antifungal therapy with fluconazole was added to the antimicrobial regimen for possible cutaneous cryptococcosis. However, further evaluation including serum cryptococcal antigen along with mucicarmine staining of the skin biopsy did not confirm this presumptive diagnosis. Fungal cultures were non-revealing; bacterial culture from the skin biopsy, however, revealed modified acid-fast positive, branching gram-positive rods. Based on these culture results, his antimicrobial regimen was changed to trimethoprim/sulfamethoxazole (TMP/SMX) along with meropenem due to suspicion of possible nocardiosis. The immunosuppressive medication (tacrolimus) dose was concomitantly decreased. Bacterial cultures were sent to a reference laboratory (LabCorp, Burlington, North Carolina) for further identification and susceptibility testing.

With culture data indicating a presumed *Nocardia* spp, he underwent imaging studies including CT studies of the chest and head along with MRI of the brain to evaluate for possible disseminated infection. The chest CT was notable for a nodular consolidation in the right lower lobe. The head CT did not demonstrate evidence for an acute intracranial abnormality and brain MRI was negative for any evidence of space occupying lesions. Given the nonspecific findings of the chest CT, bronchoscopy with bronchoalveolar lavage (BAL) was performed. However, BAL cultures did not confirm the presence of any identifiable pathogens.

After four days of TMP/SMX and meropenem, the patient began to have significant improvement of the local erythema and pain (Fig. 2). On discharge, TMP/SMX 320 mg/1600 mg daily (adjusted for renal failure) and linezolid 600 mg twice daily were prescribed while further identification and susceptibility data were awaited.

Confirmatory culture results revealed growth of *Nocardia arthritidis,* identified *via* matrix-assisted laser desorption/ionization (MALDI) with susceptibility data showing resistance to imipenem/cilastatin MIC = 16 mcg/mL and ciprofloxacin MIC = 4.0 mcg/mL, and susceptibility to TMP/SMX MIC = 0.25/4.8 mcg/mL, linezolid MIC $\leq$ 1.0 mcg/mL, ceftriaxone MIC $\leq$ 4.0 mcg/mL, amikacin MIC $\leq$ 1.0 mcg/mL, amoxicillin/clavulanate MIC = 2/1 mcg/mL, clarithromycin MIC = 2.0 mcg/mL, and minocycline MIC $\leq$ 1.0 mcg/mL.

When seen for follow up, the patient appeared well; pain and erythema had resolved. Only post-inflammatory hyperpigmented changes of the skin were evident (Fig. 3). The patient was instructed to discontinue linezolid and continue monotherapy with TMP/SMX as the infection appeared to be limited only to the skin. He was advised to complete a minimum of 6 months of treatment.

Discussion

Nocardia spp. has long been known to cause infection in humans [1,2]. However, historically it has primarily been associated with infections in animals, specifically in bovine species. While greater than 100 distinct species of *Nocardia* have been identified, only a minority of these species have been associated with human disease [1,2]. The predominant species that are associated with human disease include *N. abscessus, N. ostitidiscaviarum, N. brasiliensis, N. cyriacigeorgica, N. pseudobrasiliensis, N. farcinica, N. wallaei, and N. nova* [1]. Recently, improved molecular identification techniques, including 16 s rRNA sequencing, have led to better classification of *Nocardia* spp. and a wider variety of species that can cause human disease have been identified [1,2]. Specifically, *N. arthritidis* has been increasingly identified as a human pathogen, resulting in both localized and disseminated disease in immunocompromised patients.

We conducted PubMed and Google Scholar searches to identify cases of human infection due to *N. arthritidis.* Various combinations of MeSH terms including "*Nocardia arthritidis*", "infection", and "human" were utilized to retrieve the data. Five cases were identified from 2004 to date (*N. arthritidis* was first described as a valid species in 2004). Four of the five patients were immunocompromised and/or on immunosuppressive medications. One patient had no documented immunosuppressive condition; however, the patient was known to have underlying silicosis [3–7]. The demographics, comorbid conditions, medications, and site of involvement have been summarized in Table 1.

To summarize, four of the five reported cases of *N. arthritidis* infection, including the patient described above, had impairment of cellular immunity, which has been described as a key risk factor for developing nocardiosis [3–7]. Steroid use, chronic hematologic malignancy, and/or chronic iatrogenic immune suppression to prevent graft rejection in solid organ transplantation all contribute to impairment in cellular immunity and thus are known risk factors for nocardiosis [1]. The patient who did not have any reported immunodeficiency or on immunosuppressive therapy did have underlying parenchymal lung disease (silicosis), which has

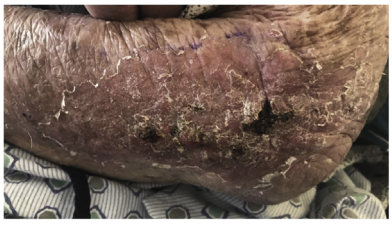

Fig. 2. Improvement in erythema and presence of scabbing after 4 days of targeted antimicrobial therapy.

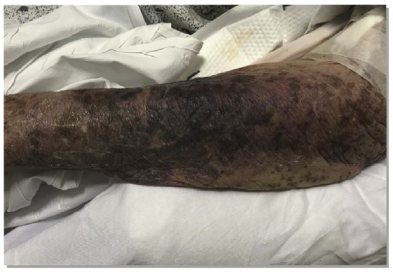

Fig. 3. Post-inflammatory hyperpigmentation noted on follow-up.

Table 1
Clinical characteristics of patients with *N. arthritidis.*

Sex	Age (years)	Co-morbid Condition	Immunosuppression	Location of infection	Treatment
Female	71	CLL, RA	Prednisone 5 mg daily, IVIG, chlorambucil	Pulmonary, CNS, cutaneous	TMP/SMX
Male	65	RA	Prednisone 8 mg daily	Cutaneous, pulmonary	TMP/SMX, imipenem + cilastatin, minocycline
Female	50	Kidney / Pancreas transplant	Tacrolimus, prednisone, mycophenolate mofetil	Pulmonary	TMP/SMX
Unknown	Unknown	SLE	Azathioprine, methylprednisolone	CNS	ceftriaxone, amikacin, TMP/SMX
Male	71	Silicosis	Unknown	CNS, pulmonary	TMP/SMX, meropenem

CLL - Chronic lymphocytic leukemia; RA - Rheumatoid arthritis; SLE - Systemic lupus erythematosus.

also been shown to be a risk factor for the development of pulmonary nocardiosis [1,7].

In addition to host risk factors such as impairment of cellular immunity, either acquired from underlying hematological abnormalities or iatrogenic from immunosuppression, patients must have environmental exposure to the pathogen [1]. *Nocardia* spp. are ubiquitous throughout the environment, mostly occurring in soil or other organic material and water [1,2]. While the cases reported previously do not discuss a clear environmental exposure history, our patient did have such an exposure, and likely sustained traumatic inoculation of his forearm when he had wrecked his tractor five weeks prior to presenting for left arm cellulitis.

Treatment of nocardiosis is largely dictated by susceptibility testing of a specific isolate which should be used to guide therapy [1,2]. There have not been optimized antimicrobial treatment guidelines established for *N. arthritidis* and thus selection of antimicrobial regimens should be predicated on the severity of disease, the location of the infection, the patient's immune status, and potential drug interactions and toxicities [1,2]. In the five cases of *N. arthritidis* reported in the literature, antimicrobial regimens varied. However, all utilized TMP/SMX as the backbone of therapy. Antimicrobial susceptibility guidelines are available for some *Nocardia* spp [1,2]. However, overall there is a paucity of data regarding these pathogens and these guidelines should be used with caution as many newly identified species, such as *N. arthritidis,* have limited clinical data to base therapeutic decisions upon. Additionally, there has been little correlation between *in vitro* susceptibility and clinical outcomes for this infection.

In summary, the diagnosis of nocardiosis may be difficult and we recommend maintaining a high level of clinical suspicion for nocardiosis in immunosuppressed patients, specifically those that may have evidence of disseminated disease, along with relevant epidemiological risk factors. Although a skin biopsy is generally not performed in most cases of skin and soft tissue infection, this is warranted for accurate diagnosis in the right clinical setting. Additionally, as microbiological techniques improve, there will likely be further identification of *Nocardia* spp. that were not previously classified or those for which limited clinical and therapeutic data exist, such as *N. arthritidis*. Ultimately, clinical data is too limited to recommend empiric or preferred antimicrobial regimens, and definitive treatment should be based on susceptibility testing for specific isolates and other pertinent host factors. Our report adds to the limited number of cases described in the literature to date for this relatively new species of *Nocardia*.

Consent

Written informed consent was obtained from the patient for publication of this case report and

accompanying images. A copy of the written consent is available for review by the Editor-in Chief of this journal on request.

CRediT author statement

All the authors – Nicholas Cheronis, Dustin Carr, and Nitin Bhanot contributed to the writing of the manuscript of the case report.

Declaration of Competing Interest

None of the authors have any potential conflict of interest to disclose.

References

[1] Sorrell Tania C, Mitchell David H, Iredell Johnathon R. Nocardia species. Mandell, Douglass and Bennett's principles and practice of infectious disease. 8th ed. Philadelphia: Elsevier; 2015. p. 2853–63.
[2] Brown-Elliott BA, Brown JM, Conville PS, Wallace RJ. Clinical and laboratory features of the *Nocardia* spp. based on current molecular taxonomy. Clin Microbiol Rev 2006;19:259–82.
[3] Roberts AL, Davidson RM, Freifeld AG, Iwen PC. *Nocardia arthritidis* as a cause of disseminated nocardiosis in a patient with chronic lymphocytic leukemia. IDCases 2016;6:68–71.
[4] Kageyama A, Torikoe K, Iwamoto M, Masuyama J-I, Shibuya Y, Okazaki H, et al. *Nocardia arthritidis* sp. nov., a new pathogen isolated from a patient with rheumatoid arthritis in Japan. J Clin Microbiol 2004;42:2366–71.
[5] Aragaki-Nakahodo A, Benzaquen S, Kirschner M. Coinfection by *Nocardia beijingensis* and *Nocardia arthritidis* in an immunocompromised patient diagnosed by endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA). Respir Med Case Rep 2014;12:22–3.
[6] Tamarit M, Poveda P, Barón M, Del Pozo JM. Four cases of nocardial brain abscess. Surg Neurol Int 2012;3:88.
[7] Yildiz O, Alp E, Tokgoz B, Tucer B, Aygen B, Sumerkan B, et al. Nocardiosis in a teaching hospital in the Central Anatolia region of Turkey: treatment and outcome. Clin Microbiol Infect 2005;11:495–9.