Epidemiology, clinicopathology, and diagnosis of cutaneous nocardiosis: A case series and population-level analysis

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INTRODUCTION

Cutaneous nocardiosis is a rare, opportunistic infection that occurs secondary to systemic disseminated infection or as a primary infection following direct penetration of the skin by *Nocardia*, often from contaminated soil.[1] Distinct clinical presentations of cutaneous nocardiosis include superficial skin infection, lymphocutaneous infection, and actinomycetoma. Cutaneous nocardiosis presents variably and mimics other cutaneous infections including sporotrichosis, tuberculosis, atypical mycobacteria, leishmaniasis, and syphilis.[2] Variability in clinical presentation poses challenges in diagnosis, leading to delayed diagnosis and treatment.

Nocardia appear as filamentous bacteria with hyphae-like branching and varying acid-fastness, highlighted using Grocott methenamine silver and Ziehl-Neelsen stains. Collection of neutrophils (abscesses) and granules (grains) may be seen. Culture confirms the diagnosis of nocardiosis. Treatment of choice is trimethoprim-sulfamethoxazole, although a variety of alternatives exist.[3] Prompt treatment is recommended due to potential for significant morbidity and mortality, especially in cases of disseminated nocardiosis with cutaneous involvement.[4-6]

Known risk factors for cutaneous nocardiosis include immunosuppression and local trauma related to plants and soil.[4] Previous research characterizing cutaneous nocardiosis is limited to case reports and 1 case series. To date, there is a research gap in systematic, population-scale analyses examining cutaneous nocardiosis. The current study investigated the demographic and clinicopathologic characteristics of cutaneous nocardiosis by performing a retrospective review of the cases from a tertiary hospital and by analyzing data associated with cutaneous nocardiosis from the Cerner Health Facts database, a multisite electronic health record database that stores de-identified data from over 65,000,000 patients, 1.3 billion laboratory results, and detailed demographic, billing, and hospital admission data.[7]

Abbreviations used:

CNS: central nervous system
CT: computed tomography
ICD: International Classification of Diseases

CASE SERIES

The current study was approved under exemption category by the Institutional Review Board for Protection of Human Subjects in Research at the University of Kansas Medical Center. The pathology database at a tertiary hospital in Kansas was queried, and all biopsy-positive cases of cutaneous nocardiosis were identified. All identified biopsy-positive cases with positive *Nocardia* culture were included. Clinical data, including data on age, sex, anatomic site, clinical presentation, comorbidities, occupation, urban/rural status, histopathologic features, immunohistochemistry, culture results, treatment, and outcome were recorded. The United States Office of Management and Budget criteria were used for rural and urban classification.[8]

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The Cerner Health Facts database was queried using International Classification of Diseases (ICD)-10 code A43.1 and ICD-9 code 039.0 for cutaneous nocardiosis between 01/2000 and 02/2020. Demographic and clinical data collected included data on age, sex, race/ethnicity, census region, urban/rural status. All descriptive analyses were conducted using SAS software.

A total of 6 in-house cutaneous nocardiosis cases were identified (Table I). All (6/6) of the patients were males (age range, 37-72 years), and 83.3% (5/6) were identified as non-Hispanic White, with 16.7% (1/6) being identified as non-Hispanic Black. All patients were immunosuppressed: 5/6 received chronic prednisone, 1/6 received chemotherapy, and 2/6 received tumor necrosis factor inhibitors. Comorbidities included renal transplant (1/6), graft-versus-host disease (2/6), sarcoidosis (1/6), Crohn disease (1/6), and leukemic malignancy (3/6). A total of 83.3% (5/6) resided in urban (versus rural) areas, and 33.3% (2/6) of the patients worked in manual labor at the time of diagnosis.

The most common clinical presentation that prompted dermatologic evaluation was a painful, unresolving rash, wound, or lesion (Fig 1). Two patients had a known injury prior to the development of skin manifestations, including a fall with abrasion and pole injury. Skin examination findings included papules, plaques, nodules, erosions, and vesicular lesions involving the extremities, forehead, and abdomen. A total of 33.3% (2/6) were cases of limited cutaneous nocardiosis, whereas 66.7% (4/6) also had systemic infection, defined as involvement of any extracutaneous site, most commonly brain and lung. Chest radiography, chest computed tomography (CT), sputum culture, pleural fluid culture, bronchoalveolar culture, head CT, brain abscess culture, and abdominal CT aided diagnosis in cases, where systemic involvement was suspected. In the systemic cases, it was unknown whether the skin infection predated systemic involvement or *vice versa*. Extracutaneous involvement was observed most commonly in the lungs (66.7%, 4/6), but other sites included the jaw, abdominal wall muscles, and central nervous system (CNS).

Histopathology of each case revealed filamentous bacteria, highlighted by Grocott methenamine silver stain. Histologic findings included pseudoepitheliomatous hyperplasia, neutrophilic infiltrate, necrotizing granulomas, sinus formation, and neutrophilic panniculitis (Fig 2). Culture results were diagnostic in all cases: 3/6 were confirmed with superficial swab, and 3/6 with tissue culture.

All patients were treated with trimethoprim/sulfamethoxazole, though only 1 had resolution of skin lesions with trimethoprim/sulfamethoxazole alone. Other treatments utilized included a combination of linezolid, cefepime, ceftriaxone, doxycycline, meropenem, imipenem/cilastatin, and moxifloxacin (Table I). In one case, therapeutic excision was performed for a nonresolving lesion. With chronic therapy, 4 patients experienced improvement; 1 did not have clearly documented resolution, and 1 died from systemic disease complications.

Within the Cerner Health Facts system, a total of 699 cutaneous nocardiosis cases were identified from 2000 to 2020. The median age of affected patients was 53 years (range, 15-90 years). Cutaneous nocardiosis was more common in men (53.4%, 373/698) and occurred more frequently in non-Hispanic Whites (69.5%, 486/699) than in other race/ethnicity groups. The Midwest (31.1%, 218/697) and South census regions (28.1%, 196/697) were more heavily impacted than the Northeast (20.9%, 146/697) and West (19.7%, 137/697). A majority of cases occurred in urban areas (84.2%, 587/697) versus rural areas (15.8%, 110/697).

DISCUSSION

Chronic immunosuppression is an important risk factor for *Nocardia* infection, and in immunosuppressed populations, there is greater potential for dissemination to the CNS.[4] Consistent with this, all of our in-house patients were immunocompromised or immunosuppressed, and there was 1 case of CNS involvement.

Multiple reports in the literature have noted the onset of primary cutaneous nocardiosis associated with direct soil inoculation in rural environments by way of hazards, including splinter injury, wasp sting, and other methods of skin trauma.[9-15] However, the majority of in-house and Health Facts database cases (84.2%, 587/697) occurred in urban (as opposed to rural) settings. Our findings suggest that certain urban exposures may be risk factors for primary cutaneous nocardiosis. Such exposures could include occupational settings, suggested by our finding that several of the in-house patients worked in urban manual labor at the time of diagnosis. Limited research exists regarding the risk of cutaneous nocardiosis in urban settings, and to date, this is the largest study to report a higher occurrence of nocardiosis in urban versus rural locations.

The nonspecific clinical presentation of cutaneous nocardiosis poses a diagnostic challenge; our study identified a spectrum ranging from a single crusted papule to multiple spreading violaceous erosions and nodules with serous drainage. Other

Table I. Summary of demographic, clinical presentation, histologic, and diagnostic culture examination of cutaneous Nocardia cases

No.	Age/Sex	Race	Occupation	Urban/ Rural	Location of skin affected	Clinical presentation	Clinical examination	Extracutaneous	Comorbidities	Treatment	Resolution	Histologic findings	GMS	Gram stain	Fite acid-fast stain	Giemsa stain	Method of diagnosis	Species
1	72/Man	White	Retired	Urban	Left forearm	Small, enlarging wound	Crusted pink plaque	No	AML status postbone marrow transplant and chronic prednisone	Trimethoprim-sulfamethoxazole	Yes	PEH with collections of neutrophils with structures suggestive of filamentous bacteria	Filamentous bacteria	Gram-positive	NA	NA	Swab culture	*Nocardia abscessus*
2	60/Man	White	Delivery service	Rural	Left calf	Painful, red "bug-bites"	Violaceous punched-out erosions with serous drainage	No	Sarcoidosis on mycophenolate mofetil and infliximab	Trimethoprim-sulfamethoxazole and linezolid in combination followed by 4-month course of trimethoprim-sulfamethoxazole	Yes	Abscess	Filamentous bacteria	Indeterminate staining	(-)*	NA	Tissue culture	*Nocardia brasiliensis*
3	69/Man	White	Construction work	Urban	Forehead	Rash following abrasion	Erythematous, excoriated, and crusted papules, nodules, and plaques	Lung	AML on azacitidine	Cefepime and doxycycline, then trimethoprim-sulfamethoxazole alone for 6-month course	Yes	"Consistent with *Nocardia*"	Filamentous bacteria	NA	(-)*	(-)*	Swab culture	*N. brasiliensis*
4	37/Man	White	Information technology	Urban	Forehead	Nonhealing wound after pole injury	Crusted papule within linear scar, erythematous, and edematous plaque with studded vesicles	Lung	Crohn disease and receiving adalimumab. Also received short prednisone course, dapsone, and topical clobetasol prior to diagnosis	Trimethoprim-sulfamethoxazole, meropenem, ceftriaxone, and eventual excision	Yes	Biopsy 1: PEH with foreign-body granuloma and trace birefringent material Biopsy 2: atypical squamous proliferation containing pustules and possible sinus tracts Biopsy 3: necrotizing granulomas	Filamentous bacteria only on biopsy #3	Gram-positive	(-)*	(-)*	Swab culture	*Nocardia arthritidis*
5	53/Man	White	Unknown	Urban	Abdomen	Lethargy, difficulty ambulating, and skin nodule on abdomen	Erythematous nodule	Lung, abdominal wall	CML status postbone marrow transplant with chronic GVHD managed with high-dose steroids and mycophenolate mofetil	Unknown	NA	Suppurative panniculitis with rare filamentous bacteria	Filamentous bacteria	NA	NA	NA	Tissue culture	*Nocardia asteroides*
6	69/Man	Black	Retired	Urban	Bilateral upper and lower extremities	Painful nodules that spread from lower to upper extremities	Multiple indurated, erythematous nodules with purulence	Lung, CNS	ESRD status postkidney transplant on chronic immunosuppression	Ciprofloxacin, linezolid, imipenem, moxifloxacin, trimethoprim-sulfamethoxazole	No (death due to complications of infection)	Left thigh: neutrophil-rich, lobular panniculitis Chest wall: abscess with filamentous bacteria	Filamentous bacteria	Gram-positive	(-)*	Filamentous bacteria	Tissue culture	*Nocardia pseudo-brasiliensis*

AML, Acute myeloid leukemia; *CML,* chronic myeloid leukemia; *CNS,* central nervous system; *ESRD,* end-stage renal disease; *GMS,* Grocott methenamine silver stain; *GVHD,* graft-versus-host disease; *NA,* not available/applicable; *PEH,* pseudoepitheliomatous hyperplasia.
*Negative (-).

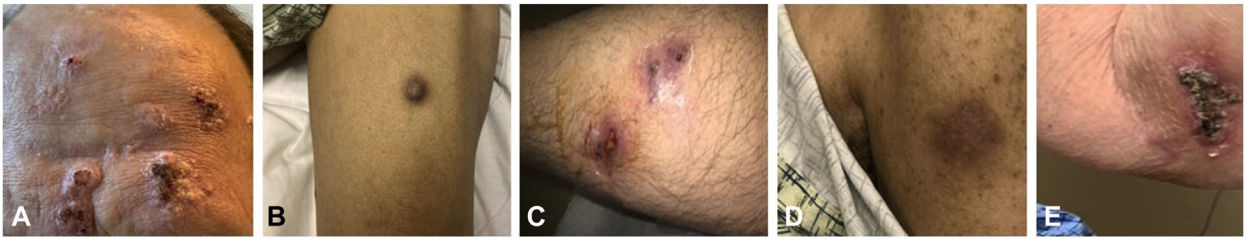

Fig 1. Spectrum of clinical presentation of cutaneous nocardiosis. **A,** Crusted papules, plaques, and nodules on the forehead. **B,** Hyperpigmented nodule on the lower extremity. **C,** Violaceus crusted plaques with purulent and hemorrhagic drainage located on lower extremity. **D,** Hyperpigmented plaque on the upper extremity. **E,** Crusted plaque with surrounding erythema on the upper extremity.

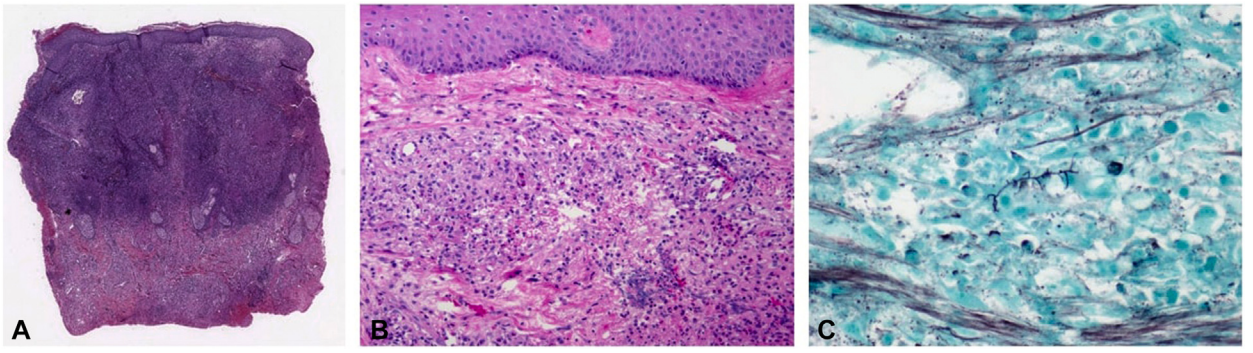

Fig 2. Histopathologic findings. **A,** Diffuse granulomatous dermatitis (hematoxylin-eosin staining, original magnification ×3). **B,** Ill-defined suppurative granuloma (hematoxylin-eosin staining, original magnification ×200). **C,** Branching filamentous organism (Grocott methenamine silver, original magnification ×400).

symptoms included lethargy, difficulty ambulating, and pain. Grocott methenamine silver was a useful tool in all in-house patients to identify filamentous bacteria and thus encourage confirmatory culture. Prompt treatment is necessary, as the mortality rate has been reported from 7% to 64% for nocardiosis overall.[4-6] The mortality rate of nocardiosis in immunosuppressed patients is higher and is further compounded in cases of dissemination with CNS involvement. Despite long-term antimicrobial therapy, immunocompromised patients are susceptible to relapses and multiple episodes of nocardiosis,[6] highlighting the importance of early clinical detection.

The current study was limited by the small number of in-house cases. Only cases of biopsy-consistent cutaneous nocardiosis with confirmatory culture were included. Cases of cutaneous nocardiosis diagnosed via culture (without biopsy) may have been missed. Another limitation was the possibility for misclassification of cutaneous nocardiosis using ICD9/ICD10 codes within the Cerner Health Facts database. Despite these limitations, our study found a common trend in immunosuppression associated with cutaneous nocardiosis and identified geographic disparities related to cutaneous nocardiosis incidence.

Conclusions

This systematic population-level study reports a greater incidence of cutaneous nocardiosis in urban compared to rural U.S. areas and in the Midwest and South regions. Given the nonspecific clinical presentation of cutaneous nocardiosis, our findings highlight the need for biopsy and microbial evaluation of persistent, treatment-refractory cutaneous lesions, especially when infection is suspected. The data herein also supports the systemic workup via relevant imaging (chest radiograph, CT, head CT) and culture studies in patients with cutaneous nocardiosis suspected of systemic involvement, particularly in the setting of chronic immunosuppression. The clinical and histologic findings as well as the risk factors identified in the in-house patients serve to characterize an infectious disease not commonly encountered. Further large-scale studies are needed to continue to elucidate these findings.

Conflicts of interest

None disclosed.

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