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RESEARCH ARTICLE

Clinical and Radiographic Characteristics of *Nocardia* vs Non-*Nocardia* Brain Abscesses

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Abstract

Background and Objectives
Diagnosis and treatment of CNS nocardiosis is challenging and often delayed, which increases morbidity and mortality. The primary objective was to compare the clinical and radiographic characteristics of patients with CNS nocardiosis with non-*Nocardia* bacterial brain abscesses.

Methods
We performed a case-control study of patients with brain abscesses diagnosed between 1998 and 2018 at a tertiary academic center. We identified 56 patients with brain MRI demonstrating brain abscess from the institutional imaging database: 14 with culture-confirmed nocardiosis and 42 randomly selected prevalent controls with culture-confirmed non-*Nocardia* bacterial infection. The primary outcomes were the diagnosis of concomitant lung infection and history of immunosuppression. Secondary outcomes included abscess radiographic characteristics: multifocality, occipital lobe and/or infratentorial location, and bilobed morphology.

Results
Compared with patients with non-*Nocardia* brain abscesses, patients with CNS nocardiosis were older (median 61 years [IQR 59–69] vs 48 years [IQR 34–61]; $p = 0.03$), more likely to be immunosuppressed [71% (10) vs 19% (8); $p < 0.001$), have diabetes (36% (5) vs 10% [4]; $p = 0.03$), or a concomitant lung infection (86% [12] vs 2% [1]; $p < 0.001$). Radiographically, more cases of CNS nocardiosis exhibited multifocal abscesses (29% [4] vs 2% [1]; $p = 0.01$), which were located in the infratentorial (43% [6] vs 10% (4); $p = 0.01$) or occipital (36% [5] vs 5% [2]; $p = 0.008$) regions and had a bilobed (as opposed to unilobed) morphology (79% [11] vs 19% [8]; $p < 0.001$). Blood and CSF cultures were negative in most of the cases and controls, whereas neurosurgical specimen culture yielded a diagnosis in 100% of specimens.

Discussion
Patients with CNS nocardiosis were more likely to be older, have a history of diabetes or immunosuppression, or have a concomitant lung infection compared with those with non-*Nocardia* brain abscesses. Abscesses because of CNS nocardiosis were more likely to be multifocal, affect the infratentorial region or occipital lobe, or have a bilobed appearance. Neurosurgical specimen culture was most likely to yield a diagnosis for both *Nocardia* and non-*Nocardia* abscesses. The combination of clinical and imaging findings may suggest CNS nocardiosis and inform early initiation of targeted empiric treatment.

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CNS nocardiosis is an uncommon cause of brain abscess that is associated with significant morbidity and mortality for both immunocompromised and immunocompetent individuals.[1-3] *Nocardia* is a genus of gram-positive, weakly acid fast, aerobic bacteria found in soils worldwide, and the incidence of nocardiosis is increasing, presumably because of the growing number of immunosuppressed patients.[4,5] Delayed diagnosis of CNS nocardiosis is common, often because of challenges with organism isolation from clinical biospecimens, or initial misdiagnosis of brain abscesses because of an alternative bacterial organism, stroke, or tumor.[1,3,6-10] Although CNS nocardiosis may present as multiple brain lesions, additional imaging characteristics to inform clinical suspicion of this infection are lacking.[11,12] Empiric antibiotics for bacterial brain abscesses often do not cover *Nocardia* species, and clinicians instead rely on specific microbial specimen data before initiating appropriate treatment, which may delay treatment and increase morbidity.[13,14] Currently, there are no guidelines for when to suspect CNS nocardiosis to begin empiric treatment while microbial results are pending.

We compare clinical and radiographic characteristics of patients with confirmed CNS nocardiosis with those with non-*Nocardia* bacterial brain abscesses. The primary objective of this study was to identify key features that raise suspicion for CNS nocardiosis to provide guidance for when to consider empiric treatment in patients at risk for this deadly infection.

Methods

Study Design

This was a case-control study of patients with bacterial brain abscesses identified using a University of California, San Francisco (UCSF), radiologic database from 1998 to 2018 (M.M., Y.L., and S.C.). CNS nocardiosis cases were patients with MRI evidence of CNS abscess and microbiologic confirmation of nocardiosis from any site (e.g., CNS lesion, CSF, blood, or other site). Controls were patients with MRI evidence of CNS abscess and microbiologic confirmation of culture-confirmed non-*Nocardia* bacterial infection from any site (e.g., CNS lesion, CSF, blood, or other site) identified using prevalent control sampling with 3 controls for every 1 case. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[15]

Standard Protocol Approvals, Registrations, and Patient Consents

UCSF Institutional Review Board approved this study (14-13223), and informed consent was waived.

Participants and Eligibility Criteria

Inclusion criteria were (1) brain abscess diagnosis made within 1998–2018 using the UCSF radiologic database searching for "nocardia" or "nocardiosis" (cases) or "abscess" (controls), (2) confirmed bacterial infection with either *Nocardia* (cases) or a non-*Nocardia* bacteria (controls) based on microbiological testing available in the electronic medical record, and (3) MRI of the brain with at least 1 lesion consistent with brain abscess. A random number generator was used to select control patients who met these criteria. Any patient who did not meet the inclusion criteria was excluded and the next randomly selected eligible patient was included until accruing 3 times as many controls as cases.

Patient Characteristics and Clinical Data

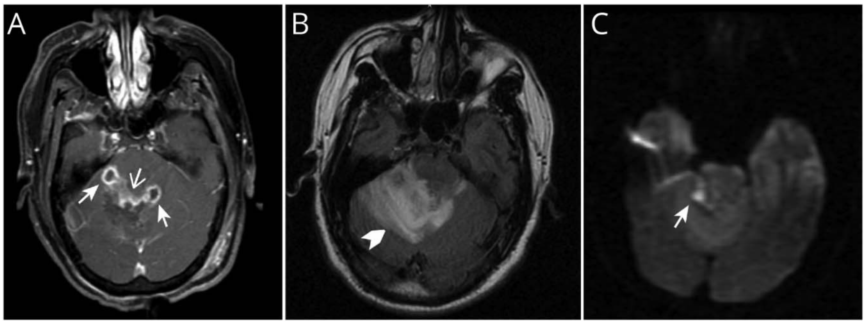
Patient demographics and known risk factors for brain abscesses were derived from the electronic health record (S.C.L.; Table).[1] Immunosuppression was defined as a history of human immunodeficiency virus, organ or hematopoietic stem cell transplantation, hematologic malignancy, and/or chronic use of an immunosuppressive medication.

Table Participant Demographics and Clinical Characteristics

Demographics and clinical characteristics	Patients with non-*Nocardia* brain abscess (n = 42)	Patients with *Nocardia* brain abscess (n = 14)	*p* Value
Median age in years (IQR)	48 (34–61)	61 (59–69)	0.03
Female sex, no (%)	20 (48)	5 (36)	0.5
Race, no (%)			
White	31 (74)	7 (50)	0.1
Black	1 (2)	0 (0)	1
Asian	1 (2)	1 (7)	0.4
Other	9 (21)	6 (43)	0.2
Hispanic or latino ethnicity, no. (%)	4 (10)	4 (29)	0.1
Medical history, no (%)			
Alcohol use disorder	5 (12)	1 (7)	1
Diabetes	4 (10)	5 (36)	0.03
Immunosuppressed[a]	8 (19)	10 (71)	<0.001
Intravenous drug use	0 (0)	1 (7)	1
Sinus disease	5 (12)	1 (7)	1
Previous neurosurgery	9 (21)	1 (7)	0.4
Neurosurgical procedure	9 (21)	1 (7)	0.4
Coexisting hospital diagnoses, no (%)			
Ear or sinus infection	16 (38)	0 (0)	0.005
Lung infection on chest imaging	1 (2)	12 (86)	<0.0001

Abbreviation: IQR: interquartile range.
[a] Immunosuppressed: the presence of human immunodeficiency virus, organ or hematopoietic stem cell transplantation, hematologic malignancy, and/or chronic use of an immunosuppressive medication.

Figure 1 Imaging Characteristics of *Nocardia* Brain Abscess



MRI brain of *Nocardia* brain abscess (A–C). Axial T1 post-contrast (A), fluid-attenuated inversion recovery (B), and diffusion-weighted (C) images demonstrating the prototypical features of conventional *Nocardia* intracranial abscesses. (A) Multilocular rim-enhancing lesion (solid arrow) with irregular borders and an adjoining tract (open arrow) situated in the posterior fossa. Similar to the non-*Nocardia* abscess, there is marked surrounding vasogenic edema (B, chevron) and internally reduced diffusion (C, arrow).

Other diagnoses made concurrent with abscess diagnosis included ear or sinus infection and imaging evidence of a lung infection on chest radiograph, or more commonly, CT; further details of lung infection were made by expert radiologist SC. Radiographic characteristics of brain abscess location (supratentorial vs infratentorial) and morphology (unilobed vs bilobed) were independently assessed (M.M and Y.L.) and adjudicated (S.C.) by expert radiologists.

Statistical Analysis

Clinical and radiographic data were analyzed using the Wilcoxon rank-sum test for continuous variables and Fisher exact test for categorical variables. All analyses were performed using Stata 16.1 (StataCorp LLC, College Station, TX).

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

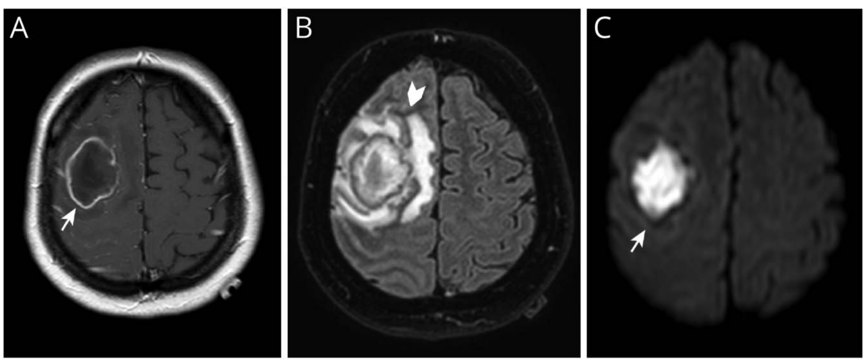
Patient Clinical Characteristics

We identified 71 patients with "*Nocardia*" listed in radiologic reports with brain abscesses: 15 with culture-confirmed nocardiosis, with 1 excluded for lacking MRI (Table). We identified 1,569 patients with brain abscesses and associated brain imaging, but with infection due to a non-*Nocardia* bacterium, which were then randomly sorted. The first 42 eligible patients were selected for 1:3 case-to-control ratio (Table). Compared with patients with non-*Nocardia* brain abscesses, patients with CNS nocardiosis were older (median 61 years [IQR 59–69] vs 48 years [IQR 34–61]; $p = 0.03$) and more likely to be immunosuppressed (71% [10] vs 19% [8]; $p < 0.001$), or have diabetes (36% [5] vs 10% [4]; $p = 0.03$). Compared with the patients with non-*Nocardia* brain abscesses, more patients with CNS nocardiosis had evidence of a concomitant lung infection identified on chest imaging (86% [12] vs 2% [1]; $p < 0.001$). More patients with non-*Nocardia* brain abscesses were found to have ear or sinus infections (38% [16] vs 0%; $p = 0.005$).

Imaging Characteristics of CNS Nocardiosis

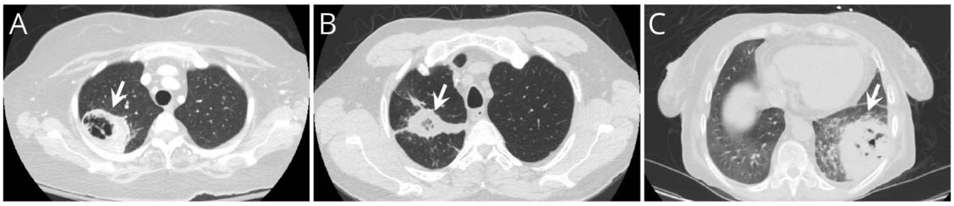
There were several differences in the location and morphology of CNS nocardiosis abscesses (Figure 1) compared with controls (Figure 2). Compared with non-*Nocardia* brain abscesses, more abscesses due to CNS nocardiosis were multifocal (29% [4/14] vs 2% [1/42]; $p = 0.01$), located in the infratentorial region (43% [6/14] vs 10% [4/42]; $p = 0.01$), located in the occipital lobe (36% [5/14] vs 5% [2/42]; $p = 0.008$), or had a bilobed morphology, as opposed to unilobed morphology (79% [11/14] vs 19% [8/42]; $p <$

Figure 2 Imaging Characteristics of Non-*Nocardia* Bacterial Brain Abscess



MR imaging of non-*Nocardia* bacterial brain abscess (A–C). Axial T1 postcontrast (A), fluid-attenuated inversion recovery (B), and diffusion-weighted (C) images demonstrating the prototypical features of conventional non-*Nocardia* intracranial abscesses. (A) Non-*Nocardia* abscess with smoothly marginated, unilocular rim-enhancing (closed arrow) lesion situated in the frontal lobe. There is marked surrounding vasogenic edema (B, chevron) and internally reduced diffusion (C, arrow).

Figure 3 Imaging Characteristics of Pulmonary Nocardiosis



CT chest of pulmonary nocardiosis (A–C). *Nocardia* lung abscess with cavitation (arrows).

0.001). All *Nocardia* abscesses had reduced diffusion similar to non-*Nocardia* bacterial abscesses.

Lung infection in patients with CNS nocardiosis on CT chest predominantly comprised of multifocal lung consolidation with foci of decreased attenuation and rim enhancement, likely reflecting abscess formation (Figure 3). Cavitation with endobronchial spread of infection was seen in approximately one-third of patients with CNS nocardiosis.

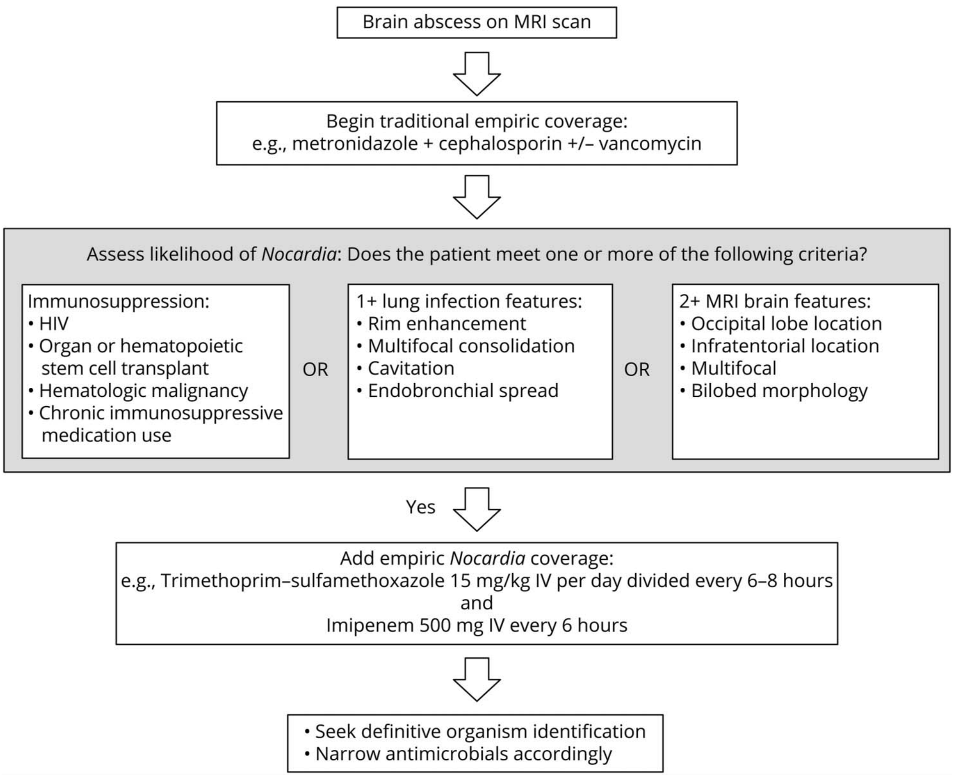
Diagnostics

Of the blood cultures that were obtained, they were negative in 93% (13/14) of cases and 87% (33/38) of controls. Of the CSF samples obtained, they were negative in 50% (3/6) of cases and 79% (11/14) of controls. Bacterial culture performed on specimens collected through neurosurgical biopsy or aspiration of the abscess yielded a diagnosis in 100% (10/10), and 100% (41/41) of the control samples collected. Three cases were diagnosed by CSF culture (one by both CSF and abscess culture), one by blood culture, and one by drainage of a concomitant retroperitoneal abscess; 1 control was diagnosed by CSF culture. Diagnosis was made by bacterial culture except in 2 cases using Universal PCR, with 1 replicated using metagenomics next-generation sequencing (mNGS).

Discussion

We found that patients with CNS nocardiosis, as opposed to brain abscesses because of other bacteria, were more likely to be older, immunosuppressed, diabetic, or have a concomitant lung

Figure 4 Suggested Empiric CNS Nocardiosis Antimicrobial Management Algorithm



Assess need for empiric CNS nocardiosis coverage using clinical and/or radiographic criteria while work-up for likely CNS infection is underway.

infection. Furthermore, when compared with non-*Nocardia* brain abscesses, brain abscesses because of *Nocardia* were more often multifocal, located in the occipital lobe or infratentorial region, or have a bilobed morphology. Diagnosis was more likely to be made using neurosurgical specimen culture compared with blood or CSF culture.

To our knowledge, this case-control study directly compares clinical and radiographic characteristics of CNS nocardiosis vs other non-*Nocardia* bacterial species. Here, we demonstrate that CNS nocardiosis is associated with the presence of lung infection and/or immunosuppression. Previous case series have suggested that *Nocardia* brain abscesses are more likely multifocal, but this has never demonstrated in comparison to a set of controls with non-*Nocardia* bacterial brain abscess.[1,11] A possible explanation for the multifocal predilection for brain abscesses because of *Nocardia* is that these result from hematogenous spread from the concomitant lung infection, as opposed to local invasion from a sinus infection that is more likely to affect the frontal lobes. Other infections that affect the posterior fossa are *Listeria monocytogenes*,[16] which can result in a rhombencephalitis and discrete abscesses, as well as *Mycoplasma pneumoniae* and *Tropheryma whippelii*.[17]

Our data suggest that there are unique clinical features of *Nocardia* brain abscesses that can be used to inform which patients may benefit from earlier empiric therapy for *Nocardia* and raise the possibility of creating a clinical algorithm (Figure 4) based upon distinguishing characteristics of CNS nocardiosis. These data have significant clinical implications because there are no current guidelines for when to suspect or begin empiric treatment for CNS nocardiosis. Establishing an evidence-based algorithm for starting empiric antimicrobial coverage for CNS nocardiosis in high-risk individuals is of critical importance given well-documented challenges with diagnosing CNS nocardiosis and the risk of poor clinical outcomes with delayed treatment.

These data augment additional clinical clues for *Nocardia* that may be present. Although CNS nocardiosis can be considered "primary" without involvement of other organ systems, *Nocardia* is known to result in pulmonary involvement because of inhalation, cutaneous infection through direct inoculation of the skin, eye infection at sites of trauma, and other organs including the thyroid and kidney.[18,19] The diverse clinical presentation of nocardiosis, and the challenges that come with recovering *Nocardia* in the laboratory, can result in significant delays in diagnosis. An invasive procedure may be required to obtain sufficient specimen as samples obtained by noninvasive means are often inadequate, as illustrated with these data. Although *Nocardia* can be visualized on gram stain, aerobic cultures may require 3 weeks for *Nocardia* growth and hence requires explicit laboratory instructions to not be discarded.[20] PCR testing using 16S ribosomal RNA PCR can be both more accurate and quicker to result than conventional culture, but this requires nocardiosis to be on the differential for targeted testing.[21] Advances in culture-independent, unbiased mNGS address both the time and differential limitations of these previous methods and is a promising alternative because this technology becomes more available.[22-24]

Several limitations are noted. This cohort is small despite leveraging a 20-year institutional radiographic database, and patients were cared for at a specialized tertiary care center which may affect the result generalizability. The potential for a brain infection to be CNS nocardiosis often comes to the attention of neurologists (e.g., S.C.L., E.L.G., M.B.R.) after identification of brain abscess on MRI. It is possible that institutional CNS nocardiosis cases were missed despite using this comprehensive radiologic database. There may be residual confounding by historical clinical factors not assessed that are different between groups, but because of the small number of patients, we elected to limit this study to the primary factors present in the literature. We included a clinical algorithm (Figure 4) based on the data described here. Owing to our limited sample size, we did not include a composite score to better predict the risk of CNS nocardiosis when a brain abscess is diagnosed radiographically. Rather, we provided this figure as a management guide. In future, amassing a larger cohort of patients with CNS nocardiosis would enable creation of an evidence-based composite score with known sensitivity and specificity, but a lack of this presently does not negate the importance of early suspicion and treatment of CNS nocardiosis.

Patients with CNS nocardiosis were more likely to be older, have a history of immunosuppression or diabetes, or have a concomitant lung infection compared with those with non-*Nocardia* brain abscesses. Abscesses because of CNS nocardiosis were more likely to be multifocal, affect the infratentorial region or occipital lobe, or have a bilobed appearance on MRI brain. Neurosurgical specimen culture was most likely to yield a diagnosis for both types of abscesses, as opposed to blood or CSF cultures. There should be a high index of suspicion for CNS nocardiosis in individuals with these high-risk characteristics, which may guide management and inform timing of empiric CNS nocardiosis treatment.

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Elan L. Guterman, MD, MAS	Department of Neurology, School of Medicine, Weill Institute for Neurosciences, Department of Neurology, University of California, San Francisco, CA	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data
Mathew Mikhail, MD	Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Yi Li, MD	Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Soonmee Cha, MD	Department of Radiology and Biomedical Imaging, University of California, San Francisco, CA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Megan B. Richie, MD	Department of Neurology, School of Medicine, Weill Institute for Neurosciences, Department of Neurology, University of California, San Francisco, CA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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