American Journal of Medical Case Reports, 2016, Vol. 4, No. 7, 251-254
Available online at http://pubs.sciepub.com/ajmcr/4/7/10

DOI:10.12691/ajmcr-4-7-10

Nocardia arthritidis Infection in an Immunocompetent Human in the United States

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Abstract Patients with T-cell defects are at the highest risk for nocardiosis, a potentially life-threatening infection caused by several species of the genus, *Nocardia*. We report a case of disseminated *Nocardia arthritidis* in a patient who had no recognizable risk factors for immunodeficiency. A 43-year-old woman was noted to have a left upper lobe cavitary lesion on an outpatient computerized tomography (CT) scan that was performed for evaluation of pelvic congestion syndrome. She subsequently had an image-guided biopsy of the lesion, but the results were still pending when she presented at the emergency department with a transient episode of aphasia. A CT scan of the patient's head revealed hypodensities in the right frontoparietal and left frontal lobes. A modified acid-fast stain on the lung biopsy specimen demonstrated variable, branching, filamentous bacteria with morphology consistent with *Nocardia* species. Matrix-Assisted Laser Desorption / Ionization – Time-of-Flight (MALDI-TOF) Mass Spectrometry at a reference laboratory later identified the bacteria as *Nocardia arthritidis.* This case highlights that disseminated nocardiosis can occur in an apparently healthy population. A more detailed immunologic evaluation that include screening for chronic granulomatous disease, anticytokine autoantibody deficiency and interleukin-12-gamma interferon pathway deficiency may further assist in the diagnosis of patients' underlying diseases.

Keywords: *Norcadiosis, Norcadia arthritidis Immunocompromised*

Cite This Article: Osamuyimen Igbinosa, Owen Igbinosa, Krishna Dass, and Glenn Wortmann, "*Nocardia arthritidis* Infection in an Immunocompetent Human in the United States." *American Journal of Medical Case Reports*, vol. 4, no. 7 (2016): 251-254. doi: 10.12691/ajmcr-4-7-10.

1. Introduction

Nocardiosis is a potentially serious / life-threatening infection caused by several species of the genus Nocardia. *Nocardia* species are ubiquitous, filamentous, Gram-positive, aerobic actinomycetes. *Nocardia* is considered an opportunistic pathogen, but it can be isolated in about 15% of otherwise immune-competent patients without a definable predisposing condition [1]. Patients at the highest risk of infection are those with a history of hematopoietic stem cell transplantation, solid organ transplantation, chronic glucocorticoid therapy, malignancy, human immunodeficiency virus (HIV), or infection [2].

The *Nocardia* genus includes a variety of species that are important human pathogens. Systemic disease is mostly due to the Nocardia asteroides group, which includes N. asteroides sensu stricto, N. farcinica, N. nova, *and* N. transvalensis complex [2]. Nocardia species were originally classified by their biochemical properties, but an improved classification system based on a polyphasic approach (e.g. antibiotic susceptibility profiles, analysis of the 16S ribosomal RNA [rRNA] gene, restriction fragment length polymorphisms [RFLP], and Matrix-Assisted Laser Desorption / Ionization – Time-of-Flight [MALDI-TOF] Mass Spectrometry) has revealed marked heterogeneity in *Nocardia* genera [3]. For instance, molecular studies have shown that N. brasiliensis, N. otitidiscaviarum, and N. transvalensis, once thought to be homogeneous genera, also exhibit diverse characteristics [4]. This improved classification scheme has also provided an invaluable framework for the recognition of additional species with varied characteristics.

N. arthritidis was first described after the organism was isolated from a sputum sample of a Japanese man with rheumatoid arthritis who was on chronic corticosteroids [5]. A case of an immunocompromised Caucasian female from the United States who was co-infected with *N. beijingensis* and *N. arthritidis* pulmonary nocardiosis was reported in the year 2014 [6]. To the best of our knowledge, our patient is the first case of disseminated *N. arthritidis* reported in a human with no known risk factors for an impaired immune function.

2. Case Report

A 43-year-old woman presented to the emergency department of an outside hospital with sudden onset aphasia (difficulty expressing her words), but her speech returned to normal within 10 to 20 minutes. A computerized tomography (CT) scan of her head demonstrated hypodensities in the right frontoparietal and

left frontal lobes. The patient was subsequently transferred to our hospital for further management.

She was in an excellent state of health until a recent CT scan of her chest (to evaluate pelvic congestion syndrome) revealed a left upper lobe cavitary lesion. She underwent an image-guided biopsy of this lesion, but at the time of this presentation, results of the lung biopsy were unavailable. Her significant past medical history included varicose veins (treated by vein stripping), and this prompted an evaluation for pelvic congestion syndrome. She was not taking any medications. As part of her social history, she raced horses competitively, had two dogs and one cat (all healthy), did not smoke tobacco or use other illicit drugs, and had not traveled outside the United States within the last two years.

On physical examination, she appeared well and her face was symmetric. Vital signs included a temperature of 36.9^{o}C, blood pressure of 100 / 55 mmHg, heart rate of 56 beats/minute, and oxygen saturation of 100% on room air. Her extra-ocular movements were intact and speech was back to normal. There were no oral or skin lesions, cervical / axillary / inguinal lymphadenopathy, nor focal motor or sensory deficits. The rest of the patient's physical exam was normal.

3. Investigations

Laboratory evaluation revealed hemoglobin of 13.4 g/dL, hematocrit of 41%, and white blood cell (WBC) count of 7 × 10^3/mm^3 (bands 4%, monocytes 64%, eosinophils 1%, lymphocytes 10%). The patient had serum creatinine of 0.7 mg/dL, blood urea nitrogen (BUN) of 15 mg/dL, aspartate transaminase (AST) of 21, alanine transaminase (ALT) 22, alkaline phosphatase (ALP) of 68, total bilirubin of 0.5 mg/dL, hemoglobin A1c of 5.4%, and was negative for HIV.

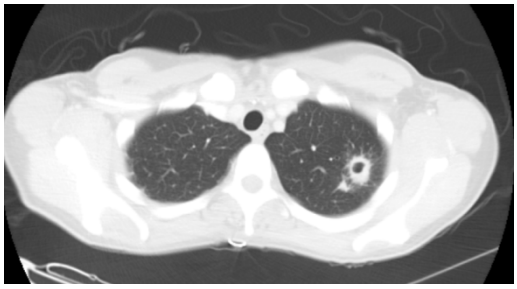

Figure 1. Chest CT scan without contrast showing left upper lobe cavitary lesion

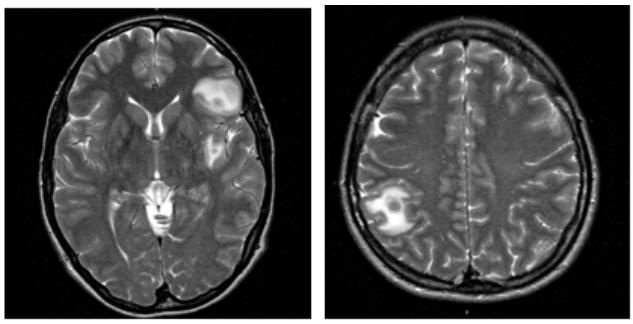

Figure 2. MRI brain (Flair) Showing multiple supratentorial ring enhancing lesions with surrounding vasogenic edema

A non-contrast CT scan of the chest revealed a cavitary left upper lobe lesion (Figure 1). Magnetic resonance imaging (MRI) of the brain with gadolinium demonstrated multiple supratentorial ring enhancing lesions with surrounding vasogenic edema (Figure 2).

There was no growth on three sets of blood cultures. A modified acid-fast stain on lung biopsy specimen displayed variable, branching, filamentous bacteria with morphology consistent with *Nocardia* species (Figure 3). The organism was later identified as *Nocardia arthritidis* by MALDI-TOF at a reference laboratory. Table 1 contains the antibiotic susceptibility profile of *N. arthritidis* isolated from our patient.

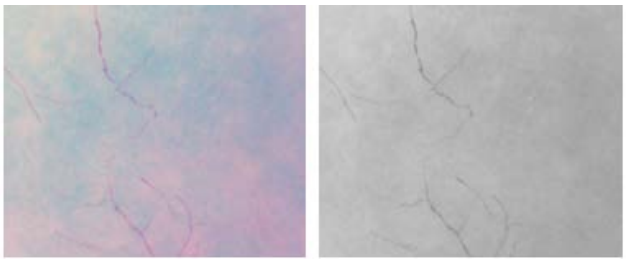

Figure 3. Modified acid Fast stain of lung aspirate showing beaded and branching positive rods.

4. Treatment

Based on antibiotic susceptibility results (Table 1), patient received six weeks of ceftriaxone 2g intravenously twice daily and trimethoprim-sulfamethoxazole 15mg/kg/day orally for a total of 6 months.

Table 1. *Nocardia arthritidis* isolate antimicrobial susceptibility results

Antibiotics	MIC (mcg/ml)	Interpretation
Amoxicillin/clavulanate	<=2/1*	S
Cefepime	16	I
Ceftraxone	<=4	S
Imipenem	8	S
Ciprofloxacin	>4	R
Moxifloxacin	4	R
Clarithromycin	4	I
Amikacin	<=1	S
Tobramycin	<=1	S
Doxycycline	0.25	S
Minocycline	<=1	S
Trimethoprim-sulfamethoxazole	<0.25/4.75*	S

Key: S= Susceptible; I= Intermediate; R=Resistant
*The second value is for clavulanate and sulfamethoxazole

4.1 Outcome and follow up

Repeat chest and brain imaging showed decrease in lesion sized after 8 weeks of treatment. The patient continues to do well.

5. Discussion

Nocardia are ubiquitous, saprophytic, Gram-positive bacteria in the aerobic actinomycetes group. From 1995 to

2004, the most common *Nocardia* species of 765 isolates in the United States were *N. nova* (28%), *N. brasiliensis* (14%), *N. farcinica* (14%), and *N. cyriacigeorgica* (13%) [8]. The majority of patients with nocardiosis were immunocompromised, most often with cell-mediated abnormalities [9]. Since the protective immune response against *Nocardia* is T-cell mediated, *Nocardia* infection is most commonly seen in solid organ transplant recipients, persons with HIV infection (especially with CD4 counts less than 100cells/mm3), lymphoreticular malignancy, and individuals on chronic corticosteroid therapy [10]. Rituximab, an anti-CD20 monoclonal antibody, is also a potential risk factor for developing cerebral nocardiosis [11]. Patients with pulmonary alveolar proteinosis are at an increased risk of nocardiosis, as well [12].

The differential diagnoses in our case included infective endocarditis with septic emboli to lung and brain (bacterial growth on blood cultures would have been expected) and disseminated tuberculosis (TB) because of an upper lobe lung lesion (however, the patient had no risk factors or symptoms of active TB). We also considered invasive fungal infection, such as aspergillosis, cryptococcosis, and histoplasmosis (but these were systematically excluded) and *Rhodococcus equi* infection, due to the patient's exposure to horses (however, this was very low on the list of possible differential diagnoses as the patient was not immunocompromised).

Patients can acquire a *Nocardia* infection through an airborne route from soil inhabited by latent forms. Bacteria colonize the respiratory tract and activate T lymphocyte mediated cellular immunity after phagocytosis of the organism ([13,14]). Depending on the host and strain, *Nocardia* infection may remain localized or disseminate promptly. Although *N. farcinica* has been linked to the majority of clinically aggressive infections (particularly in immunocompromised patients), a retrospective analysis of *N. farcinica* sepsis in 53 patients found eight cases (15%) where no predisposing factors for infection were identified [15]. Similarly, in a review of 67 published case reports on *N. farcinica* infection between 2000 and 2012, there were 59 patients (88%) with risk factors associated with diminished immunocompetence. Although the mechanisms for explaining the susceptibility of *Nocardia* infection in immunocompetent host remains elusive, the role of anticytokine autoantibodies is an emerging cause of pathogen-specific susceptibility in previously healthy patients [16].

The clinical presentation of nocardiosis varies, as it appears in three major patterns: pulmonary, primary cutaneous, and disseminated disease. The lungs are the most common / primary site of infection [17]. The most common symptoms include fever, productive cough, dyspnea, chest pain, and constitutional symptoms. These nonspecific symptoms make diagnosis difficult, with studies showing that the time from development of symptoms to diagnosis can range from 42 days to 12 months [18]. It was surprising in our case that despite the cavitary lesion on the chest CT scan, our patient never reported pulmonary symptoms. Radiographic data is variable, as chest radiographs can display focal or multifocal disease with nodular and/or consolidation infiltrates, as well as cavitary lesions [18]. *Nocardia* can disseminate to virtually any organ, but since the central nervous system (CNS) is also a likely site, brain imaging should be considered for any patient with pulmonary nocardiosis regardless of CNS symptoms.

The diagnosis of *Nocardia* infection requires the isolation and identification of organisms from a clinical specimen. *Nocardia* is slow growing bacteria and may take between 48 hours to three weeks to appear on most nonselective media [7]. Molecular techniques and MALDI-TOF have revolutionized the identification of specific *Nocardia* species. Of course, species identification is important as each bacterium has a different antibiotic resistance profile.

N. arthritidis was first isolated in 2004 from a Japanese patient with rheumatoid arthritis [5]. Chemotaxonomic and morphological characteristics of *N. arthritidis* were consistent with its assignment to the genus *Nocardia*, since the bacteria contained galactose and arabinose as its characteristic whole-cell sugars. In addition, analyses of its fatty acids by gas-liquid chromatography revealed the expected pattern diagnostic for *Nocardia*, which includes straight-chain saturated and unsaturated fatty acids with a diagnostic amount of tuberculostearic acid (10-methyl branched octadecanoic acid). *N. arthritidis* was separated from closely related species (*N. farcinica* and *N. beijingensis*) and from *N. nova* and *N. asteroides* via a combination of qualitative and quantitative differences in fatty acid patterns [19]. Phenotypically, *N. arthritidis* was distinguished from other well-described *Nocardia* species by the bacteria's ability to decompose xanthine, utilize carbohydrates, and grow at specific maximum temperatures [5].

The second human case of *N. arthritidis* lung infection was reported in 2014 in an immunocompromised patient who was co-infected by *N. beijingensis* [6]. In this case, *N. arthritidis* was diagnosed by 16S rRNA gene-targeted polymerase chain reaction (PCR) sequencing. Most commercial laboratories in the United States now utilize MALDI-TOF Mass Spectrometry for identifying *Nocardia* species. N. beijingensis was categorized only as an opportunistic infection [20] until Crozier *et al*. reported the first case of N. beijingensis *pulmonary infection in an immunocompetent patient* [21].

To the best of our knowledge, our patient is the first case of disseminated *N. arthritidis* infection in an immunocompetent host. Thus, disseminated nocardiosis can occur in an apparently healthy population, but a detailed immunologic evaluation (considering the interleukin-12-gamma interferon pathway and anticytokine autoantibody deficiencies) may further assist with diagnosing patients' underlying conditions in the future.

Acknowledgement

Special thanks to Dr. Ligia Pic-Aluas for contributing this case

Funding

None.

Competing Interests

None.

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