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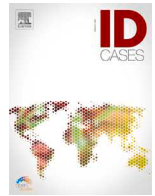
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Case report

Chronic relapsing neutrophilic meningitis as the sole manifestation of nocardiosis in a patient with mixed connective tissue disease



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ABSTRACT

We describe a rare case of a patient with mixed connective tissue disease maintained on chronic oral corticosteroids, who was hospitalized on five occasions over five consecutive months due to persistent relapsing neutrophilic meningitis caused by *Nocardia asteroides*. Immunosuppression due to the chronic use of corticosteroids was identified as the underlying mechanism of susceptibility. Our report highlights the challenges associated with systemic Nocardiosis, particularly in the immunocompromised host.

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Introduction

Persistent neutrophilic meningitis (PNM), characterized by cerebrospinal fluid (CSF) neutrophilia, hypoglycorrhachia and meningismus lasting more than seven days despite antibiotic therapy, is an infrequent variant of chronic meningitis caused by heterogeneous infectious and non-infectious etiologies [1]. Due to the highly variable clinical manifestations associated with Nocardial infections, diagnostic and therapeutic challenges are commonly encountered that, if not recognized and addressed early and appropriately, may result in high levels of morbidity and mortality [2,3]. *Nocardia* meningitis in the absence of a cerebral abscess, trauma or extracranial foci is extremely rare with only seven well-documented cases reported in the English literature [4–7]. We describe a patient with polymyositis-predominant mixed connective tissue disease (MCTD), well-controlled on hydroxychloroquine and chronic glucocorticoid therapy, who was hospitalized on five occasions over five consecutive months due to relapsing neutrophilic meningitis. A prompt, albeit transitory, salutary response to poly-antimicrobial regimens occurred during each admission, eventually followed by the identification of *Nocardia asteroides*. To our knowledge, this is the first

reported case of primary relapsing neutrophilic *Nocardia* meningitis in the absence of a cerebral abscess in a patient with a connective tissue disease.

Case report

The patient is a 48-year-old African-American female diagnosed on May 7th with MCTD featuring biopsy-proven polymyositis with a peak CK of 5400 in the company of very low-grade limited cutaneous scleroderma, mild symmetrical polyarthralgias and a high-titer RNP antibody. Prednisone 30 mg bid and hydroxychloroquine 200 mg bid were started concurrently with the diagnosis. Seven weeks after tapering prednisone to 12.5 mg daily, and the continued use of hydroxychloroquine, clinical and laboratory myopathic abnormalities normalized. On August 2, she developed the abrupt onset of a 101.2 degree fever with chills, prominent fatigue and profound anorexia. Over the ensuing 48 h, fevers climbed to 103 degrees which led to hospitalization on August 8th. On admission, vitals were BP 130/70, temperature of 103.1, respirations 14 and heart rate 108. She appeared non-toxic with a normal mental status and in good humor. Other than mild cutaneous tumefaction involving the dorsal aspect of both hands, the remainder of the examination was normal. A lumbar puncture revealed meningitis that improved with antimicrobial therapy. Headaches and fevers preceded all subsequent hospitalizations, yet the patient's physical examinations never revealed meningeal signs or the presence of focal neurological, myopathic or new extra-neural abnormalities. During each hospital stay,

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Table 1

Laboratory, imaging, and therapeutic data from 5 hospital admissions over a consecutive 5-month period.

HOSPITAL ADMISSIONS	FIRST 8/5-8/20	SECOND 8/28-9/20	THIRD 9/27-10/14	FOURTH 11/10-11/21	FIFTH 11/29-12/20
CSF FLUID ANALYSIS	<div>8/5</div> <div>WBC: 2599 Neu: 2339 Eos: 0 Lymph: 164</div> <div>Protein: 54 CSF GS: Neg CSF Cx: NG</div> <div>8/10</div> <div>WBC: 7 Neu: 0 Lymph: 1</div> <div>Protein: 15 Glucose: 119</div>	<div>8/28</div> <div>WBC: 1170 Neu: 1053 Protein: 66</div> <div>Glucose: 40 CSF GS: Neg CSF Cx: NG</div> <div>9/13</div> <div>WBC: 50 Neu: 45 Lymph: 5</div> <div>Glucose: 70 Protein: 40</div>	<div>9/27</div> <div>WBC: 875 Neu: 788 Lymph: 438 Protein: 60</div> <div>Glucose: 37 CSF GS: Neg CSF Cx: NG</div>	<div>11/10</div> <div>WBC: 1420 Neu: 1278 Lymph: 128 Protein: 94</div> <div>Glucose: 14 CSF GS: Neg CSF Cx: NG</div>	<div>11/29</div> <div>WBC: 2300 Neu: 2254 Lymph: 46 Protein: 107</div> <div>Glucose: 25 CSF GS: Neg</div> <div>12/19</div> <div>WBC: 80 Neu: 72 Lymph: 30</div> <div>Protein: 72 Glucose: 32</div>
ANTIBIOTICS	Ceftazidime & Ampicillin	Vancomycin, Gentamycin Ceftriaxone & Ampicillin	Ceftriaxone & Ampicillin	TMP-SMX, Ceftazidime, Vancomycin & Penicillin	a-TMP-SMX, Ampicillin, Imipenem, Ceftriaxone b-TMP-SMX & Imipenem
ANTIBIOTIC DURATION	8/5-8/20	8/28-9/20	9/27-10/28	11/10-11/21	a-11/29-12/19 b-12/23-4/20
IMAGING	CT Brain, CXR, MRI of Brain, C,T & LS Spine, X-rays Sinuses & Dental (All WNL)	MRI of Brain*, Tagged WBC scan, Total Body Bone Scan (All WNL)	MRI of Brain* (WNL)	CT of Brain* (WNL)	MRI of Brain* (WNL)
SEROLOGIES, CULTURES, BIOPSIES	HIV, RPR, PPD: Neg Blood-NG CSF: Bacterial, Fungal, AFB Cx & Serologies- NG/Neg	CSF & Blood: NG, Brucella, HSV, Mycoplasma, Candida, Lyme Cx & Serologies: NG/Neg	Histoplasma, Coccidioides, Blastomyces, Aspergillus: Cx & Serologies: Neg/NG	Brucella, Candida, AFB/TB: Cx & Serologies: NG/Neg	<ul style="list-style-type: none"> • Meninges Biopsy (12/3): -Cx: NG -No vasculitis -No neoplasia • CSF culture: Nocardia Asteroides (12/21)**

Neu: Neutrophils; Eos: Eosinophils; GS: Gram stain; Cx: Cultures; WNL: Within normal limits; NG: No growth; C: Cervical Spine; T: Thoracic Spine; LS: Lumbar Spine

TMP-SMX: Trimethoprim-Sulfamethoxazole; (*) Contrast Enhanced; (**) Sensitive to TMP-SMX and Imipenem

mild anemia, leukocytosis and elevation of ESR were consistently present without notable biochemical abnormalities. Immunodeficiency studies and a leptomenigeal biopsy were unremarkable. A summary of pertinent clinical and laboratory data during the five hospitalizations is presented in Table 1. After long-term susceptibility-based antimicrobial therapy was completed, the patient returned to her healthy premorbid state and remained disease-free for 6 years at which point she moved out of state and was lost to follow-up.

Discussion

Nocardiae are ubiquitous, saprophytic, weakly gram-positive bacilli characterized by their ability to cause disseminated disease involving any organ and to worsen or relapse even in the presence of appropriate bactericidal therapy [2,3]. In immunocompromised patients with persistent infectious neutrophilic meningitis, *Nocardia*, *Aspergillus*, *Mycobacteria* and a number of fungal species represent the most commonly encountered organisms [2]. Due to advancements over the past three decades in molecular genetics and the detection of species-specific susceptibilities to antibiotic therapy, the taxonomy of *Nocardia* has been greatly refined, with the identification of greater than 50 species that are disease-inducing in humans [8]. The frequency of species varies depending on geographic location with *Nocardia nova* most commonly isolated in the U.S. (28%), followed in frequency by *N. brasiliensis* (14%), *N. farcinica* (14%), *N. cyriacigeorgica* (13%), *N. brevicatena* (7%), and *N. abscessus* (6%) [9]. *Nocardia* exhibits a heightened proclivity to invade neural tissues, particularly in the setting of disseminated disease, and does so most commonly in the form of an intracerebral abscess [10–12]. However, immunocompetent and immunosuppressed patients may exhibit little to no symptoms or signs suggestive of central nervous system

(CNS) infection. In a noteworthy report of 28 patients with *Nocardia* meningitis, over 30% did not exhibit fever, headaches or meningismus, despite the presence of isolated or multiple cerebral abscesses in 43% of patients [3]. The clinical and CSF features of *Nocardia* meningitis lack any distinctive features that would permit differentiation from other causes of bacterial meningitis [3]. Moreover, there are no historical, physical examination, laboratory or imaging findings pathognomonic of Nocardiosis. Dissemination of infection is typically via the hematogenous route, whereas presenting manifestations are most commonly in the form of pulmonary findings, followed by CNS and cutaneous features [8]. A mode of acquisition was not established in our patient. Approximately two-thirds of patients suffering from *Nocardia* infections are immunosuppressed, most commonly by virtue of cell-mediated dysregulation in the context of chronic corticosteroid usage [8,10]. Solid organ and bone marrow transplantation, non-corticosteroid immunosuppressive pharmacotherapies, malignancies, and an array of chronic debilitating illnesses represent the remainder of major predisposing factors [8]. The clinical manifestations of MCTD in our patient were overrepresented by polymyositis mediated activity, with low-grade acral cutaneous scleroderma and polyarthralgias. In the absence of corticosteroid or other immunosuppressive therapies, patients with polymyositis and scleroderma are not considered to have an inherently higher risk of developing an opportunistic infection.

Delays in the diagnosis of Nocardiosis are well recognized and most commonly due to a potentially wide spectrum of clinical manifestations, a reduced index of suspicion, inadequate or inappropriate laboratory methodologies, the fastidious, slow-growing nature of the organism, and the abbreviated duration and/or bacteriostatic effects of empiric antibiotic therapy [11]. It has been reported that the time required to establish a diagnosis ranges from 6

weeks to 12 months [8,13]. The gold standard for confirming Nocardial infection is culture-proven identification of the pathogen from an afflicted site, which, in most cases of *Nocardia* infection, requires an invasive procedure to retrieve the compromised tissue [2,3,11]. The armamentarium of available microbiologic diagnostic methodologies include dual gram and modified acid-fast staining, culture of affected tissues, histopathological analysis and molecular biologic techniques [3]. From an imaging perspective, with the possible exception of cutaneous infection occurring in an immunologically intact host, it is recommended that all patients with Nocardiosis, particularly those infected with *N. asteroides*, with or without neurological abnormalities, obtain an MRI or less preferably a CT of the brain [14].

In patients with PNM, bacterial infection is the most commonly identified etiology, with rheumatologic, neoplastic and drug-induced conditions less frequently represented [2]. In most cases, relapsing infectious meningitis is due to improperly selected antimicrobials, host immune deficiencies, and pathogen-related barriers, be they drug resistance or mechanical impairment to drug penetration as occurs with an abscess or anatomic anomalies [10,12]. In the diagnosis and management of chronic meningitis, great emphasis should be placed on conducting a meticulous analysis of epidemiological and clinical findings as early pathogen identification, particularly in the context of opportunistic organisms, frequently results in favorable outcomes [10,13]. In a review of the connective tissue disease population, primary non-relapsing *Nocardia* meningitis is limited to two patients with systemic lupus erythematosus, one with chronic meningitis not responsive to antibiotics in which the diagnosis was made post-mortem and the other associated with the use of belimumab and mycophenolate [6,7].

Nocardia species determination, clinical presentation, and antibiotic susceptibility profiles are major factors that determine the selection of appropriate antibiotic regimens [10,11]. Low *Nocardia* resistance rates of 2% to trimethoprim-sulfamethoxazole (TMP-SMX) or sulfamethoxazole alone, coupled with the ability of TMP-SMX to penetrate most body tissues and achieve high CNS concentrations, explains why this agent is considered the cornerstone of induction and maintenance therapy [12,13]. In view of the inherent relapse potential seen in Nocardiosis, in-depth patient education, drug toxicity assessment and close clinical monitoring are strongly recommended [3,12,13]. A defined sequence of MRI scanning of the brain both during and after completion of therapy in patients with CNS disease has been formulated [15].

In this report, our patient, who was maintained on chronic corticosteroid therapy, demonstrated no clinical, laboratory or imaging findings suggesting a primary focus of Nocardial infection, nor evidence of any anatomic defect that could facilitate contiguous spread to the brain. Moreover, a leptomeningeal biopsy was performed with the dual aim of facilitating pathogen identification and excluding neoplastic, vasculitic or other inflammatory diseases. Initial and subsequent presentations were typical of bacterial meningitis, and on each occasion, cultures failed to grow any organism, potentially due to transient sterilization and difficulty cultivating the organism from the CSF. Meningitis recurred when empiric antimicrobial therapy was discontinued and, on one occasion, while on ineffective antibiotics. Once a diagnosis was established and drug sensitivities were available, the introduction of an appropriate antibiotic regimen resulted in a complete, multi-year resolution of clinical and CSF abnormalities.

As our case reveals, Nocardiosis, although an infrequent cause of meningitis, should be considered in the differential diagnosis of PNM, particularly in an immunocompromised host exposed to long-

term corticosteroid therapy. Multiple clinical and laboratory obstacles contribute to the delay of appropriate therapy in this subset of patients thereby greatly heightening the risk of life-threatening outcomes.

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Ethical approval

Yes.

CRediT authorship contribution statement

Marco Anthony Alborno: Principal writing, study design, Data collection and analysis. **Lawrence Livornece:** Writing and editing. **Michael Baldassari:** Data gathering; Table design; Literature review. **Erin Threlfall:** Data gathering, Literature review, Table design.

Declaration of Competing Interest

No conflicts of interested are present

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