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Challenges in Clinical Neuroinfectious Disease: CNS Nocardiosis

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An 18 year old man was referred to the NIH for further evaluation and treatment after being diagnosed with central nervous system Nocardiosis. Initially presenting with several weeks of worsening headache, magnetic resonance imaging (figure 1) showed a 3.9×2.7 cm solitary ring-enhancing mass in the right frontal lobe. Gram-positive filamentous branching hyphae were found when the lesion was aspirated and the culture grew *Nocardia transvalensis*.

Despite continuous antibiotics over three years, he has developed numerous cerebral and extramedullary spinal cord lesions, including the pons, cerebellum, and suprasellar region (figure 2). Persistent meningitis has given way to arachnoiditis (figure 3). Extension of the suprasellar abscess has led to pan-hypopituitarism. Debridement of a dorsal spinal cord lesion resulted in improved spinal cord compression and edema, but persistent loss of dorsal column function below the lesion, with sensory ataxia impairing his gait. High-dose steroids (as high as prednisone 60 mg daily) have been used for symptoms related to brain and spinal cord edema from the lesions, resulting in profound steroid-dependence characterized by increase in neurological symptoms with attempts to wean the steroid dose, as well as complications related to prolonged steroid use such as avascular necrosis of the femur and tibia. His current antibiotic regimen includes ceftriaxone 2 gm twice daily, ertapenem 1 gm daily, ciprofloxacin 500 mg twice daily, amikacin 1000 mg daily, linezolid 300 mg daily, and trimethoprim-sulfamethoxazole 200/1000 mg twice daily. Interferon-gamma 1B 90 mcg three times weekly and monthly IVIG 35 gm (approximately 40 mg/kg) have been added for empiric enhancement of his immune response. While he lives in an area in the Southwestern U.S. with a higher prevalence of Nocardiosis, no other risk factor has been identified despite

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The authors declare that they have no conflict of interest.

an exhaustive search of genetic immunodeficiencies including whole exome sequencing, and functional assays of immune function including lymphocyte phenotyping and flow cytometry as well as evaluation for presence of autoantibodies.

Nocardia are ubiquitous in the environment and are found throughout the world in soil or dust. Dry, warm, windy climates such as the southwestern U.S. may thus allow for *Nocardia* to be inhaled. More than 50 species have been identified by advances in molecular pathology; the *transvalensis* complex of species has been found worldwide but particularly in the southwestern U.S. and Australia.¹ Nocardiosis is a rare infection and most often occurs in those with cell mediated immunodeficiency.² Hence, patients with Nocardiosis should be evaluated for immunodeficiency such as HIV infection, occult malignancy, glucocorticoid use, or diabetes mellitus. In a review of 238 cases of CNS *Nocardia*, 100 (42%) were in patients with no known immunodeficiency,² although this data represents cases prior to 1994 and thus identification of novel immunodeficiency syndromes has increased over time. *Nocardia* often disseminates widely via hematogenous spread throughout the body. Involvement of the central nervous system is found in almost half of all disseminated cases, typically as a parenchymal abscess in any part of the brain although spinal cord abscesses and meningitis have also been described. Approximately one-third of CNS *Nocardia* cases in a large series were “primary” CNS Nocardiosis without evidence of systemic infection.² In patients presenting with only extrapulmonary disease, *Nocardia* is presumed to have spread hematogenously from an asymptomatic or healed pulmonary site.³ The unusual features of this case are the absence of any identifiable immune dysfunction and of any systemic infection with *Nocardia*. Furthermore, of the various species of *Nocardia*, *transvalensis* has only rarely been associated with brain infections.

No prospective controlled trials of therapy for *Nocardia* exist, and thus optimal treatment regimens are not known. Central nervous system disease is one of the characteristics by which Nocardiosis is considered “severe,” typically requiring a different course of treatment.⁴ One possible regimen recommended by multiple authors for patients with CNS disease is parenteral trimethoprim-sulfamethoxazole (TMP-SMX, 10–20 mg/kg/d of TMP in 3 divided doses) with imipenem 500 mg qid, plus amikacin 15 mg/kg/d if other organs are involved, for at least six weeks.^{4–6} However, *Nocardia transvalensis* in vitro is resistant to aminoglycosides including amikacin. In these patients treatment with linezolid may be effective.⁷ Because of the severe nature of our patient’s course, and the lack of susceptibility data as the organism was only able to be grown from the first culture at the outside institution, we have employed a broad treatment regimen including both amikacin and linezolid, as well as ceftriaxone and ciprofloxacin, both of which have been associated with clinical utility against *Nocardia*.^{4–6} Clinical and radiological improvement should be demonstrated prior to converting to two-drug oral therapy, which should be continued for at least one year in patients with CNS Nocardiosis.⁴

Identification of *Nocardia* in the clinical laboratory can be challenging. While *Nocardia* is classically described as gram-variable, aerobic, filamentous, branching, weakly acid-fast bacilli, in various sub-optimal growth conditions *Nocardia* may appear gram-negative and acid-fast-stain negative. While the organism may appear within 4 days, cultures may require 2–4 weeks to show growth. Faster-growing non-pathological colonizing organisms may

overgrow cultures during this time, masking the appearance of *Nocardia*.⁴ Ideally, treatment should be guided by speciation and susceptibility testing, although this is not always available and the first sample taken from a patient may be the only opportunity to grow the organism. Some authors have argued that *Nocardia trasvalensis* and other less common isolates may be underreported due to the difficulty of identifying these in certain practice areas.⁸

CNS *Nocardia* may progress or relapse despite the physician's best efforts to control the infection with antimicrobial therapy, with cure rates in brain abscesses reported at 50% and mortality as high as 55%.⁴ The clinical manifestations may be subtle, the appearance on imaging may mimic other entities such as malignancy, and the organism requires multiple days to grow in culture, thus detection and early treatment may be delayed. The transvalensis complex of *Nocardia* species is characterized by these species' high degree of antibiotic resistance, particularly to aminoglycosides.¹ Virulent *Nocardia* species both inhibit neutrophilic killing by macrophages via high levels of enzymes catalase and superoxide dismutase, and possess the ability to survive within macrophages in altered cellular forms (bacterial L-forms). As an intracellular pathogen this organism can survive within the host for life. The organism can pass through endothelial cells to invade the brain where it infects both microglia and astrocytes.² Studies have demonstrated more than adequate penetration of antimicrobials into brain abscesses but differences in outcomes based on surgical treatment, whether patients received stereotactic aspiration alone or craniotomy as well.⁹ This difference in outcomes may be related to the thick-walled, multiloculated nature of *Nocardia* brain abscesses, requiring more definitive treatment than aspiration alone. A multidisciplinary approach, utilizing speciation and sensitivity testing as well as surgical treatment when appropriate, is critical to early microbial control in CNS *Nocardia*, but further studies are needed to demonstrate the best approach to preventing relapse.

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Figure 1.

Brain MRI showing R frontal lobe abscess. From left to right, the abscess appears to be a ring enhancing lesion on the axial and coronal gadolinium-enhanced T1-weighted images, with surrounding vasogenic edema seen on the FLAIR sequence; the lesion is bright on diffusion weighted imaging and dark on the corresponding apparent diffusion coefficient map, consistent with an abscess.

Figure 2. Brain and thoracic spine MRI 3 years after initial presentation showing persistent inflammation in the pituitary and infundibulum as well as multiple dural-based lesions in the spinal cord, with significant cord compression and edema associated with the lesions at T8–T9.

Figure 3. Lumbosacral spine MRI 3 years after presentation showing multiple enhancing lesions in the cauda equina as well as bulky abnormal enhancement filling the canal from L4 into the sacrum.