First report of a brain abscess caused by *Nocardia veterana*

Running title: brain abscess by *Nocardia veterana*

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Abstract:

Among Nocardia infections, *Nocardia veterana* is rarely isolated and mostly described in pulmonary infections. This is the first presentation of a brain abscess attributable to a *Nocardia veterana* infection in a patient with type 2 diabetes. Prolonged antibiotic therapy with trimethoprim/sulfamethoxazole led to successful clinical recovery.
Case report

A 73-year old man was admitted to a regional hospital with complaints of stomach ache and weight loss since a few days. His past medical history revealed type 2 diabetes mellitus (DM2) without secondary complications, hypertension, an appendectomy and a transient ischemic attack. The clinical suspicion of an intestinal obstruction led to a laparotomy revealing no abnormalities. Post-operatively, behavioral changes occurred with passive behavior, slow speech and an abnormal head positioning to the right side. No vomiting was observed. A CT-scan of the brain showed a large abscess in the left cerebral hemisphere with surrounding edema (figure 1). Further radiological examination with CT-scan of the thorax and abdomen did not show any other abscesses. Immediately, dexamethasone was started resulting in neurological improvement. The patient was transferred to our academic center where at presentation his physical examination was unremarkable while neurological examination revealed no abnormalities except for disorientation in place and time. Furthermore, brainstem reflexes and lower and upper extremity reflexes were normal. Laboratory analysis at admission showed the following: AF 202 U/L, y-GT 277 U/L, ASAT 46 U/L, ALAT 108 U/L, LDH 225 U/L, CRP <2 mg/L, Hb 7.4 mmol/L, leucocytes 20x10E9/L, neutrophils 18,1x10E9/L, thrombocytes 383x10E9/L, ESR 9 mm in first hour, creatinin 83 µmol/L, glucose 11.8 mmol/L.

After trepanation and drainage of the abscess, a Gram-stain revealed branching, beady-staining, gram-positive rods, acid fast in a modified Ziehl-Neelsen staining. Cultures on blood agar plates produced pure growth of Nocardia sp. after two days. Using phenotypic tests, the national reference laboratory (LIS-RIVM) identified the isolate as Nocardia veterana (aerobic growth at 37°C and 45°C, D-glucose negative, catalase positive, negative for production of nitrate reductase and...
positive for urease, negative for utilization of Simmons citrate as a sole source of carbon, positive for hydrolysis of esculin, but negative for tyrosine and xanthine).

Using 16S rDNA gene sequence analysis of 500 bp (ABI MicroSeq500 16S rDNA Bacterial Identification Kit) and GenBank and the Ribosomal Database for data analysis, *N. veterana* was identified with 100% similarity to the reference strain (similarity with *N. nova* 98.76%, *N. otitidiscaviarum* 98.54%, *N. transvalensis* 98.22%, *N. brevicatena* 97.47%). Matrix Assisted Laser Desorption Ionization Time of Flight (MALDI-TOF) mass spectrometry (Bruker Daltonics, Bremen, Germany) also revealed *N. veterana* with an identification score of 2.078.

Using this method, a score of >= 2 has been validated for species identification and the Bruker database contains 36 Nocardia species including *N. africana, N. elegans, N. nova* and *N. kruczakiae*. Therefore, three different methods identified the isolate as *N. veterana*. Since immediate microscopy after drainage led to a high suspicion of a nocardia infection, high dose meropenem intravenous (i.v.) was started, which was changed to trimethoprim-sulfamethoxazole (TMP-SMX) 3 dd 1920 mg when the results of the antimicrobial susceptibility testing were available (initially i.v. for 6 weeks and orally for another 10 months). Using broth microdilution according to CLSI methods and breakpoints (M24-A2 Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes), the minimal inhibitory concentration of TMP-SMX was 0.063/1.2 \( \mu \text{g/ml} \), amoxicillin 2 \( \mu \text{g/ml} \), clarithromycin \( \leq 0.125 \mu \text{g/ml} \), imipenem 0.5 \( \mu \text{g/ml} \), ceftriaxone 16 \( \mu \text{g/ml} \), ciprofloxacin 16 \( \mu \text{g/ml} \) and amikacin \( \leq 0.5 \mu \text{g/ml} \).

A thorough analysis for a possible immunodeficiency showed no abnormalities besides his known DM2, his older age and a low CD4 cell count of 85/mm3 with a negative HIV serology. Furthermore, dental, ear, nose, and cardiac evaluation revealed no other abscesses serving as possible focus for the brain abscess. Blood
cultures were negative. The patient clinically improved and was discharged to the regional hospital for further recovery which was uneventful. Routine laboratory evaluation 3 months later at the out-patients clinic showed a CD4 count of 619/mm$^3$. A CT-scan of the brain, made 3 months after discontinuation of antibiotic treatment, showed no recurrence of abscess.

Together with our patient, only 13 patients with a *Nocardia veterana* infection have been reported so far (1-3,6-9,11,13,14). In most of these patients a pulmonary infection was diagnosed while 2 patients had an abdominal localization (6,14) and another patient had a mycetoma (8). Here, we report the first description of a brain abscess caused by *Nocardia veterana*. In 9 of 13 patients a clear underlying immunocompromised condition could be diagnosed such as the use of immunosuppressive drugs (3,13), human immunodeficiency virus (HIV) infection (6,11) or an autoimmune disorder like Systemic Lupus Erythematosus (SLE) (8,9,13). Four patients had no apparent cause of immunodeficiency (7,13,14). However, it has been suggested that both DM2 and older age do contribute to some degree of impaired immunity (4,12) leading to a higher susceptibility for opportunistic infections. The median age in the immunocompromised patients was lower compared to the other patients (73 and 44 years respectively; p=0.004 (Mann-Whitney test)). The initial low CD4 cell count in our patient is most likely explained by previous dexamethasone use and the ongoing infection, since his CD4 cell count returned to normal several months after treatment and cessation of the dexamethasone. However, since no earlier CD4 cell count was available we cannot exclude that a lymphocytopenia facilitated the development of the Nocardiosis.
The initial hospital presentation of acute abdominal pain, deviant liver ultrasound and elevated liver enzymes might suggest an abdominal origin of the *N. veterana* infection. However, neither the abdominal CT-scan nor the operating surgeon noted abnormalities of the liver. Moreover, the elevated liver enzymes could also be explained by the anticoagulant therapy (enoxaparin) the patient received in hospital.

In the previous described cases the duration of treatment varied from a few weeks to years. In our patient, we opted for a duration of 1 year based on expert opinion on the treatment of other *Nocardia sp.* infections (5,10). To date, more than 6 months after cessation of antibiotic therapy, the patient is doing well without any signs of recurrence.

**Conclusion**

This is the first report of an elderly patient with a brain abscess caused by *Nocardia veterana* who responded very well to long term antibiotic therapy and recovered without any signs of recurrence.


1 **Figure 1:**
2 A CT-scan of the abscess in the left hemisphere of the cerebellum caused by
3 *Nocardia veterana* (see arrow).