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Case Report

Adjuvant interferon-gamma immunotherapy in a patient with progressive cerebral Nocardia abscesses

Jenneke Leentjens[a,b], Mark S. Gresnigt[a], Frank L. van de Veerdonk[a], Matthijs Kox[b], Bart Jan Kullberg[a], Peter Pickkers[b], Annemarie E. Brouwer[c], Mihai G. Netea[a,*]

[a] Department of Internal Medicine, Radboud university medical center, Radboud Institute for Molecular Life Sciences (RILMS), Nijmegen, the Netherlands
[b] Department of Intensive Care Medicine, Radboud university medical center, Radboud Institute for Molecular Life Sciences (RILMS), Nijmegen, the Netherlands
[c] Department of Internal Medicine, Elisabeth Hospital, Tilburg, the Netherlands

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SUMMARY

Despite advances in medical care, mortality due to cerebral Nocardia abscesses remains unacceptably high. The case of a typical immunocompromised patient, who deteriorated clinically despite optimal antimicrobial treatment, is reported here. Adjuvant immunotherapy with interferon-gamma resulted in partial restoration of the immune response and a corresponding clinical and radiographic recovery.

Introduction

Nocardiosis is a rare Gram-positive bacterial infection caused by aerobic actinomycetes of the genus *Nocardia*. *Nocardia* species can cause both localized and disseminated infection (Wilson, 2012). Mortality rates of up to 66% have been reported in patients with multiple lesions (Lee et al., 2002). Because nocardiosis is most commonly observed in individuals with immune defects (Wilson, 2012), adjunctive immunotherapy is a potentially attractive strategy to improve host defence and the outcome of patients with disseminated nocardiosis. Interferon-gamma (IFN-γ), a well-known immunostimulatory cytokine (Leentjens et al., 2013), has shown promising results in the adjunctive treatment of other opportunistic infections (Delsing et al., 2014). Therefore, IFN-γ represents a promising candidate to improve the outcome of invasive Nocardia infections. However, to date, no reports of adjunctive treatment with IFN-γ for patients with Nocardia infections have been reported.

Case report

A 50-year-old male patient with multiple Nocardia cerebral abscesses was referred to the university hospital because of clinical deterioration despite adequate antimicrobial treatment. The patient had been treated with high-dose corticosteroids over the past 6 months for an unidentified interstitial pneumonitis. Two months prior to admission to the university hospital, two cerebral abscesses had been found on cerebral magnetic resonance imaging (MRI). The largest lesion is depicted in Figure 1A. Stereotactic cultures revealed *Nocardia asteroides* (confirmed by 16S RNA analysis: a 100% match with *N. asteroides*). Initial treatment consisted of cefotaxime, ceftazidime, and metronidazole intravenously, which was changed to high-dose trimethoprim–sulfamethoxazole (TMP–SMX, 1920 mg three times daily, intravenously) as soon as culture results became available. Additional susceptibility testing revealed the strain to be susceptible to the prescribed antibiotics. In addition, meropenem treatment was added at day 47 of admission after urine cultures became positive for multi-resistant *Escherichia coli*. Despite this treatment, the patient's clinical condition deteriorated due to exudation of the left abscess into the left ventricle. In addition, after an initial decrease in size (Figure 1B), subsequent sequential

* Corresponding author at: Department of Internal Medicine (463), Radboud University Nijmegen Medical Center, PO Box 9101, 6500 HB Nijmegen, the Netherlands. Tel.: +31 24 3618819. Fax: +31 24 3541734.
E-mail address: mihai.netea@radboudumc.nl (M.G. Netea).

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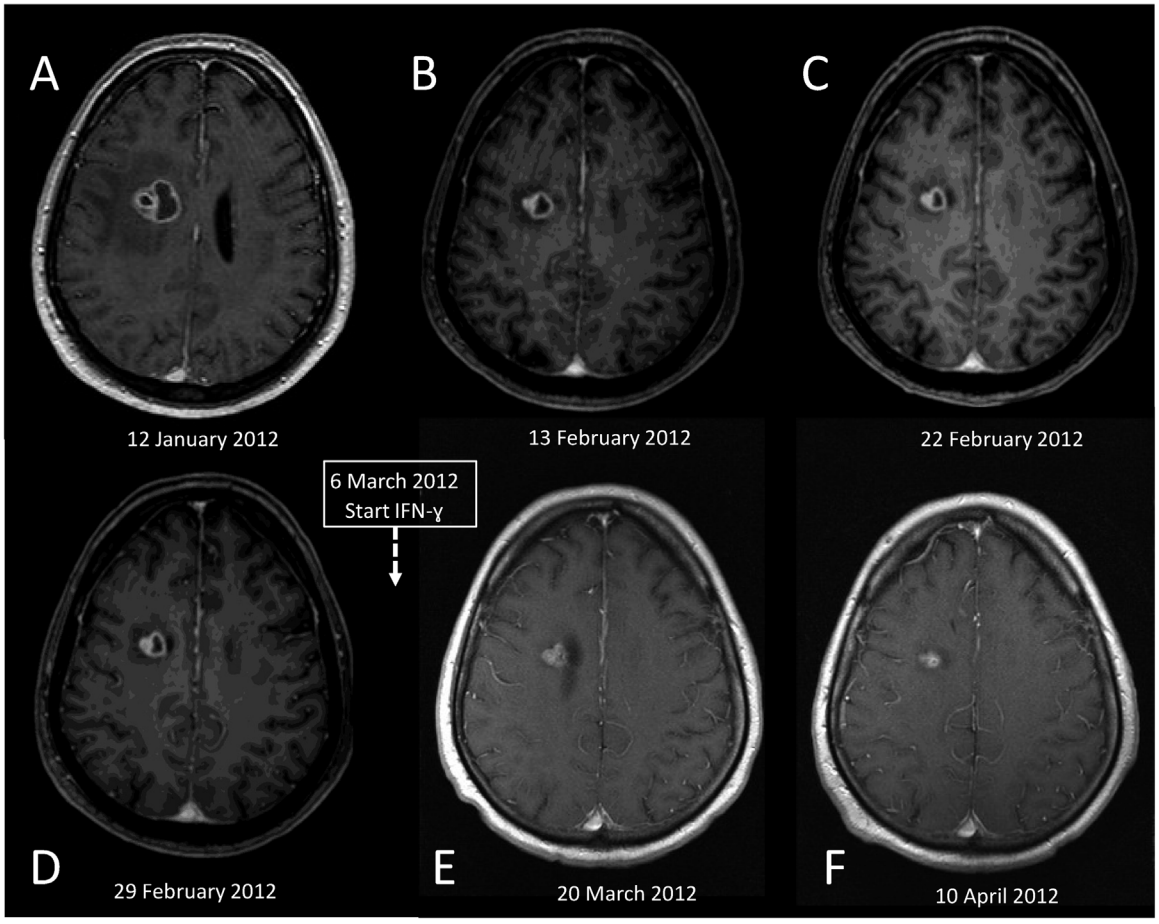

Figure 1. Studies of the largest right paraventricular brain lesion by magnetic resonance imaging (MRI). (A) T1-weighted contrast-enhanced hyperintense MRI image of the right brain lesion at admission on January 12, 2012 (size of lesion 25 × 22 × 20 mm, with extensive surrounding oedema). (B) Culture-guided initial treatment with trimethoprim–sulfamethoxazole resulted in an initial decrease in size and reduction of the oedema (size of lesion 17 × 15 × 17 mm). However, subsequent imaging showed little to no further reduction of the abscess: (C) size of lesion 15 × 13 × 19 mm, (D) size of lesion: 16 × 13 × 19 mm. Therefore, adjunctive immunotherapy with interferon-gamma treatment was initiated on March 6. (E) MRI performed 12 days later showed a decrease in the right paraventricular lesion (size of lesion 12 × 13 × 17 mm). (F) Further improvements were observed on MRI 3 weeks later (size of lesion 12 × 9 × 12 mm). All images are published with the permission of the patient's legal representative.

MRI scans showed no further reduction in size of the lesions and surrounding oedema (Figure 1C, D).

It was considered that the patient would benefit from adjunctive immunotherapy as 'therapy of last resort'. Therefore, IFN-γ (Boehringer-Ingelheim, Arnhem, the Netherlands) treatment was initiated on day 55 of admission (50 μg/m^2 subcutaneously, three times weekly). Furthermore, 2 days after the initiation of IFN-γ therapy, ceftriaxone was started alongside TMP–SMX and meropenem because of persistent fever. Four days later, meropenem was stopped, as no clear effects on the clinical course were noted despite treatment for 14 days. Compared with the MRI performed 1 week before the initiation of IFN-γ treatment, the MRI performed 14 days later showed a decrease in the right paraventricular lesion (Figure 1E). The fever disappeared 12 days after the initiation of IFN-γ treatment. However, despite combination antimicrobial therapy (TMP–SMX and ceftriaxone), resolution of the fever, and signs of improvement on radiography, the cerebrospinal fluid (CSF) remained purulent and hence intrathecal amikacin was added. Within 2 weeks, the patient's headache had subsided and the CSF became normal; amikacin could be discontinued. One week later, only trunk balance impairment and vertigo with a tendency to fall remained. The patient's condition improved further, and 3.5 months after the initiation of IFN-γ treatment he was discharged. He was able to walk at this time. MRI showed further improvement (Figure 1F). He was discharged on TMP–SMX and IFN-γ treatment, which were well tolerated.

Unfortunately, 4 days after discharge the patient was readmitted because of free subdiaphragmatic air with pneumatosis intestinalis, a rare complication of high-dose corticosteroid administration. Abdominal surgery showed no additional cause for the free air. He died 17 days later due to cardiovascular problems that were not directly related to the Nocardia infection, which was confirmed on autopsy.

Immunological analysis

Although the patient had been treated with corticosteroids, his personal and family histories were negative for immune deficiencies. Additional testing revealed a CD4 lymphopenia (140 cells/mm^3) in the absence of HIV infection. This may have been related to the steroid treatment, but a primary cause cannot be excluded. Additional blood was collected to analyze immune responses before and during IFN-γ treatment (see **Supplementary Material** online for methods of blood sampling and cytokine assays). Before IFN-γ treatment, the capacity of peripheral blood mononuclear cells (PBMCs) to produce cytokines upon ex vivo stimulation with *Candida albicans*, lipopolysaccharide (LPS), and phytohaemagglutinin (PHA) was severely blunted (Figure 2A–F). IFN-γ treatment was associated with an increased production of