Disseminated *Nocardia* infection: spontaneous resolution in response to decrease of immunosuppression

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Sir,

Here we present a patient using anti-tumour necrosis factor-α (anti-TNF-α) who developed disseminated nocardiosis, which spontaneously resolved after discontinuation of anti-TNF-α.

A 75-year-old man presented with a 4-month history of fever, night sweats and weight loss of 5 kg, accompanied by general abdominal complaints consisting of anorexia, regurgitation and nausea. For the past 6 years he had used anti-TNF-α 40 mg once every 2 weeks, methotrexate 7.5 mg once weekly and prednisone 5 mg daily for his rheumatoid arthritis. At presentation, anti-TNF-α had been discontinued for 2 months and methotrexate for 1 week. He was maintained on 5 mg prednisone daily only.

On physical examination no abnormalities were found.

His blood count was normal despite anaemia (haemoglobin was 6.6 mmol/L (7.0–9.3 mmol/L), haematocrit 0.32 L/L (0.36–0.48 L/L), leucocytes 3.6 × 10^9/L (2.5 × 10^9 to 8.2 × 10^9/L) and thrombocytes 262 × 10^9/L (150 × 10^9 to 350 × 10^9/L)). Urea was 4.8 mmol/L (3.6–4.8 mmol/L), creatinine 100 μmol/L (62–106 μmol/L), sodium 127 mmol/L (135–145 mmol/L), potassium 4.4 mmol/L (3.5–5.0 mmol/L) and C-reactive protein was 56 mg/L (<10 mg/L). Liver enzymes were slightly elevated (aspartate aminotransferase 37 U/L (<40 U/L), alanine aminotransferase 31 U/L (<45 U/L), alkaline phosphatase 131 U/L (0–120 U/L) and lactate dehydrogenase 277 U/L (<220 U/L)). An interferon-γ release assay that was performed 12 days after discontinuation of anti-TNF-α was negative.

Computed tomography (CT) scan of thorax and abdomen showed a single lesion in the upper lobe of the right lung and multiple lesions in the liver (Fig. 1a). Pathological evaluation of all biopsies from the lesions in the liver showed central necrosis without malignant cells, neutrophils or fungi. The Grocott stain for fungi was negative and bacterial culture showed no growth. The Ziehl–Neelsen stain did not show acid-fast bacteria. A positron emission tomography (PET)/CT scan 2 weeks later showed an increase of the lesion in the lung (Fig. 1b) and discrepancy in fluorodeoxyglucose uptake in the various lesions in the liver, with one active focus in the liver. At this point we considered a disseminated infection caused by *Mycobacterium tuberculosis*, *Actinomyces*, *Nocardia* or *Coxiella burnetii* as the most likely cause.

To rule out a disseminated *M. tuberculosis* infection the interferon-γ release assay was repeated 3 months after discontinuation of anti-TNF-α and remained negative. Furthermore, new biopsies of the lesion in the lung and liver were taken for histology and bacterial culture including mycobacteria. The biopsies of the lung showed granulomatous inflammation. The Ziehl–Neelsen stain did not show acid-fast bacteria. After 2 weeks a few chalky-white colonies consisting of gram-positive branching bacteria were cultured. 16S rRNA sequencing combined with biochemical tests identified the isolate as *Nocardia nova*. The patient was advised to start intravenous antibiotic treatment for disseminated *Nocardia* infection; however, he refused. Immunosuppressive therapy had been decreased recently and the patient continued to use 5 mg prednisone daily.

On follow up 1 month after the initial PET/CT scan, a chest X-ray showed a remarkable decrease of the lesion in the lung. The clinical condition of the patient had also improved. All symptoms had subsided and he had gained 1 kg. A PET/CT scan performed 2 weeks later showed a significant decrease of the lesions in the lung and a significant decrease of the size and amount of lesions in the liver (Fig. 1c).

As the patient was expected to need immunosuppressive therapy in the future and because some small lesions in the liver and the lungs had remained, although they were reduced, we again advised the patient to receive treatment. This time the patient agreed and treatment with imipenem and amikacin was started. Six weeks later the patient showed further clinical and radiological improvement and could be switched to an oral regimen of trimethoprim-sulfamethoxazole. Due to complaints about his joints, the prednisone dose was increased to 10 mg daily. As trimethoprim-sulfamethoxazole interacts with methotrexate and the rheumatoid arthritis remained in remission

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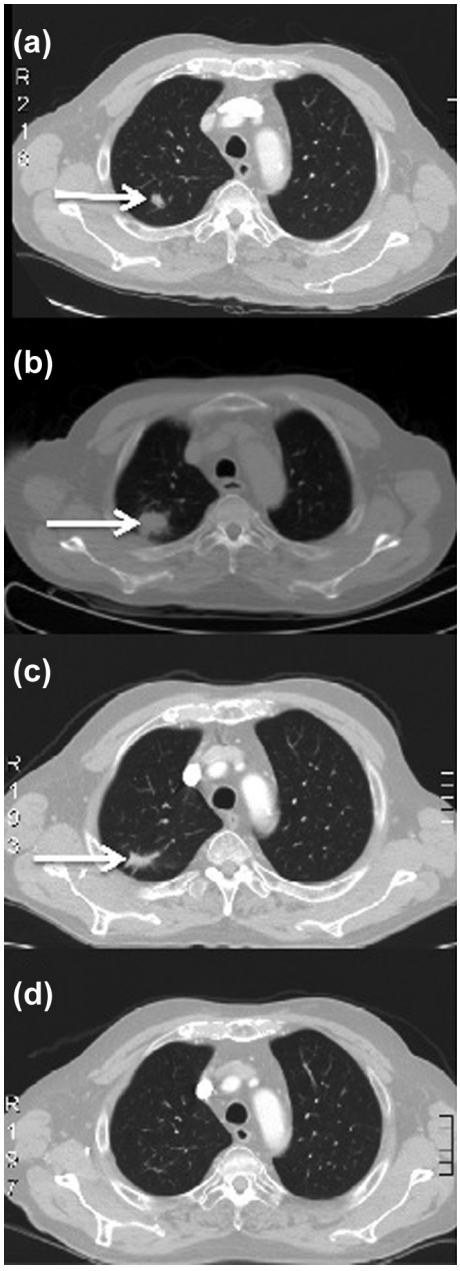

FIG. 1. (a) Computed tomography (CT) scan of the thorax at presentation showing a cavitating lesion in the right upper lobe of the lung measuring 15 × 9 mm. (b) positron emission tomography (PET)/CT scan showing progression after 2 weeks to 20 × 26 mm. (c) PET/CT scan showing regression of lesion to 14 × 18 mm. (d) CT scan showing near complete resolution after 7 months of follow up.

with this prednisone dose, methotrexate was not restarted. Seven months after presentation, the CT scan showed minimal lesions in the lung (Fig. 1d).

To our knowledge, this is the first report in the literature describing a disseminated nocardiosis in an immunocompromised patient, with spontaneous resolution of the lesions after discontinuation of anti-TNF-α and methotrexate treatment. Since 2004, nine cases have been reported of infections with *Nocardia* in patients using anti-TNF-α [1,2]. In none of these cases was spontaneous remission observed. Tumour necrosis factor-α plays an important role in host defence and contributes to the function of macrophages, granulocytes and cytotoxic effector cells in the recognition and destruction of virus-infected cells and bacteria [3]. In mice infected with *Nocardia brasiliensis* and treated with anti-TNF-α, the activity of peritoneal cells against *Nocardia* was significantly reduced compared with both cells of infected mice treated with normal rabbit serum and cells of uninfected mice [4]. It is conceivable that immune restoration after discontinuation of anti-TNF-α leads to a more effective immune response to *Nocardia*. Spontaneous resolution of *Nocardia* lung abscesses has been reported in a patient with an advanced HIV infection in response to highly active antiretroviral therapy [5]. In this case, recovery of the immune system may explain the resolution of abscesses due to *Nocardia*.

For disseminated nocardiosis, imipenem in combination with amikacin is advised with surgical treatment of deep abscesses. After initial intravenous treatment and clinical improvement, the regimen can be switched to an oral alternative, usually trimethoprim-sulfamethoxazole. In patients using methotrexate, minocycline, fluoroquinolones or linezolid can be advised as oral alternatives because of the risk of drug interaction between methotrexate and trimethoprim-sulfamethoxazole.

In conclusion, in patients on immunosuppressive therapy for chronic inflammatory diseases who develop disseminated *Nocardia* infection, decreasing the immunosuppressive therapy may contribute to recovery. Adequate antibiotic treatment should still be considered for patients in whom resumption of immunosuppressive therapy is expected in the future.

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