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BRIEF REPORT

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Successful medical treatment of multiple brain abscesses due to *Nocardia farcinica* in a paediatric renal transplant recipient

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Abstract Brain abscesses caused by *Nocardia* are rare, but it is very important to detect and treat them early because the associated mortality is 3 times higher than that associated with other bacterial brain abscesses. This infection is prevalent among adults on long-term immunosuppressive therapy; we report the case of a male kidney transplant recipient aged 12.7 years who developed early multiple *Nocardia*-induced brain abscesses that were successfully treated with linezolid, a novel antibiotic therapy.

Keywords *Nocardia* · Paediatric kidney transplantation · Brain abscesses · Linezolid · Antibiotic therapy

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Introduction

Nocardia organisms are ubiquitous, soil-borne aerobic actinomycetes that usually infect humans as a result of the inhalation of airborne bacilli or traumatic inoculation. Of all infections due to *Nocardia* in the USA, 22% occur in transplant recipients [1]. Nocardiosis is rare in Italy, and the majority of cases (92.3%) have involved patients in poor clinical condition, such as those affected by pulmonary diseases, haematological malignancies, AIDS, alcoholism or traumas, and kidney transplantation recipients (11.5%) [2].

The typical clinical presentation of nocardiosis includes chest symptoms, and approximately one-third of the patients have disseminated infection at the time of presentation. The central nervous system (CNS) is one of the most frequent sites of dissemination, and its involvement may be lethal, particularly in patients with multiple brain abscesses [3]. We report a case of nocardiosis with diffuse cerebral localisations occurring during the early post-transplant period in a paediatric kidney recipient.

Case report

An Italian child with chronic renal failure due to posterior urethral valves, who had been on peritoneal dialysis from the age of 5 years, received a second kidney transplant from a cadaver donor at the age of 12.7 years, when his weight was 32 kg and his height 146 cm. He had received a kidney from a living donor 7 years before, which was removed soon after transplantation because of primary non-function.

The immunosuppressive therapy was basiliximab (20 mg on postoperative days 0–4), cyclosporine A microemulsion (CyA-ME) 500 mg/m^2 per day (adjusted to reach a C2 level of 1400 ng/ml±20% during postoperative months 0–2 and 1200 ng/ml±20% during postoperative months 3–6), mycophenolate mofetil (600–800 mg/m^2 per day to reach trough levels of 1.5–3 μg/ml) and tapering doses of prednisone starting from 1 mg/kg on postoperative day 4. Prophylactic trimethoprim-sulfamethoxazole treatment against *Pneumocystis carinii* was begun soon after the transplantation. The post-transplant period was uneventful, and the patient was discharged on postoperative day 12.

He was re-hospitalised 26 days later due to mild fever and a slight increase in serum creatinine levels (from 97.24 mmol/l to 115.8 mmol/l). Laboratory tests showed a leukocyte count of 11.100/mm^3 and a C-reactive protein (CRP) level of 31 mg/l. The immunosuppressive therapy was on target (trough MMF 1.5 μg/ml and C2 CyA 960 ng/ml). A chest X-ray revealed a nodular infiltrate in the mid-field of the right lung. Serological tests for Epstein–Barr virus, cytomegalovirus and *Mycoplasma* were all negative. Bronchopneumonia was diagnosed, and, when the patient was discharged after a 7-day course of clarithromycin, he was afebrile, and his kidney function was normal.

He complained of chest pain and fever 2 weeks later, and his serum creatinine levels had increased to 119.34 mmol/l. The results of a new chest X-ray were comparable with those of the first, and the results of extensive microbiological screening (*Coxackievirus, Echovirus, Adenovirus*, *Parainfluenzaevirus*, *Parvovirus*, *Toxoplasma* and *Aspergillus*) were negative. The patient was initially treated with ceftriaxone i.v., which improved the symptoms, and was then switched to oral amoxicillin/clavulanate prophylaxis.

Despite a slight radiological improvement, a new episode of spiking fever occurred 2 weeks later. The patient was readmitted with a CRP level of 30 mg/l and a leukocyte count of 7600/mm^3. A chest contrast tomography (CT) scan revealed a fibrotic pleuroparenchymal mass in the right mid-lung. Blood cultures were negative, but a broncho-alveolar lavage culture was positive for *S. aureus* and *P. aeruginosa*. Mycophenolate mofetil was discontinued, and combined antibiotic therapy (teicoplanin and ceftriaxone) was started without any significant improvement. The patient's general condition deteriorated further, with fever (39°C), worsening kidney function (serum creatinine 143.2 mmol/l) and increasing CRP levels (70 mg/l) despite a normal leukocyte count (7600/mm^3). As a second CT scan showed that the mass had grown, a lung biopsy and scintigraphy with marked leukocytes were performed: the former contained a *Nocardia* species physiologically identified as *Nocardia farcinica*; the latter showed significant uptake in the right lung with small spots in the brain suggesting multiple cerebral abscesses, which were subsequently confirmed by an enhanced brain CT scan (Fig. 1a, b).

A bacterium sensitivity test showed an intermediate response to trimethropim-sulfamethoxazole, but the strain was very sensitive to linezolid, which was, therefore, given at a starting dose of 600 mg bid. The fever disappeared a few days later, and the patient's general condition improved. Complete resolution of the lung infiltrate and regression of the cerebral oedema were obtained 2 months later. Linezolid was discontinued because of severe anaemia (Hb 7.6 mmol/l), and antibiotic therapy was switched to i.v. meropenem for 20 days followed by full-dose oral amoxicillin/clavulanate, which was gradually reduced to a prophylactic regimen 1 year after transplantation.

The results of a contrast-enhanced CT scan 1 year later were normal (Fig. 1c, d), and the child is now doing well: his serum creatinine level is 124 mmol/l, and his immunosuppressive therapy is CyA-ME 150 mg bid and prednisone 5 mg/day.

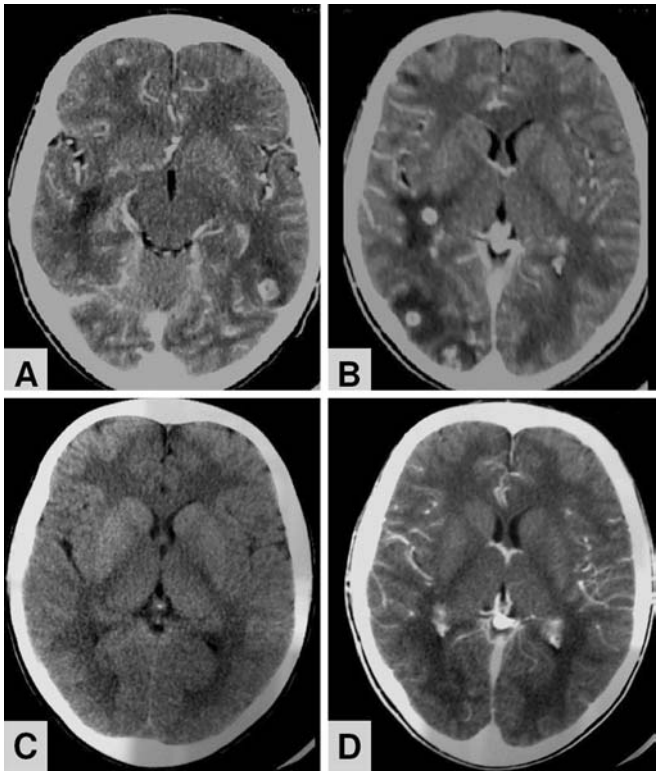

Fig. 1 Two axial sections from the first computed tomography (CT) examination showing multiple contrast-enhanced nodules surrounded by oedema, some of which have a hypodense central core (**a**, **b**). Non-contrast-enhanced (**c**) and contrast-enhanced axial sections (**d**) from the last CT examination showing the normal appearance of the brain

Discussion

Nocardia is an aerobic, variably acid-fast, branching filamentous gram-positive bacterium found in soil and decaying vegetables. Most human cases of nocardiosis are caused by *N. asteroides* or *N. brasiliensis*: there have been very reports involving *N. otitidiscaviarum* (formerly *N. caviae*), *N. nova*, *N. transvalensis* and *N. pseudobrasiliensis*, and very little is known about *N. farcinica*.

Nocardia spp. have a high propensity to invade lungs subacutely. Pulmonary nocardiosis may spread directly from the lungs to adjacent tissues or metastasise haematogeneously to the skin and CNS. Clinical and autopsy studies have shown that 15–44% of the patients with systemic nocardiosis have multiloculated cerebral abscesses, and multiple abscesses are reported in 38% of cases [4].

Every year, 150–250 cases of nocardiosis are reported in France and 500–1000 in the USA [3]. A 5-year survey in Italy revealed 26 cases, 5 caused by *N. farcinica* [2].

Among renal transplant recipients, nocardiosis is a rare but severe opportunistic infection with a broad and variable geographical distribution; its incidence varies from 1% to 20% [3, 5]. Most *Nocardia* infections are acquired by outpatients and are typically observed a few years after renal transplantation [6]. Clinically, symptom remissions and exacerbations are frequent over a period of several weeks, but the symptoms and signs of CNS involvement are less evident than those due to other bacteria [7]. Mortality in transplanted patients is usually high (10–50%), especially in the presence of CNS involvement [4], and the mortality due to *Nocardia*-induced brain abscesses is three times higher than that due to other bacterial abscesses [8].

In our young recipient, the *N. farcinica* infection developed soon after a kidney transplantation whose postoperative course was unremarkable. As the concentrations of the immunosuppressive drugs were monitored from the beginning and remained within what we consider to be

our optimal target range, we can postulate that the underlying cause was underestimated over-immunosuppression. This is also suggested by the fact that his leukocyte counts remained steadily within the normal range despite the disseminated infection.

In early series, the considerable impairment of cell-mediated immunity due to first-generation anti-metabolites such as azathioprine accounted for the relatively high incidence of *Nocardia* infections, which greatly decreased after the introduction of CyA. However, very little is known about the effects on the performance of macrophages, polymorphonuclear leukocytes and B and T cells when combined anti-CD45 and micophenolic acid is used to induce immunosuppression. Further risk factors in transplanted patients also include prolonged immunosuppression, the number of rejection episodes, the use of high-dose prednisone, cadaver kidney transplantation, granulocytopenia and uraemia [5, 6].

In our case, CNS involvement was confirmed by contrast-enhanced CT scans, the gold standard for a radiological diagnosis [8], and, to the best of our knowledge, this is the first description of the presence of multiple disseminated micro-abscesses in a renal transplant recipient.

Although *N. farcinica* is naturally resistant to most antimicrobial agents, many antibiotic treatments are effective in treating *Nocardia spp* infections [2, 7]. In our case, these were not indicated because of their inability to cross the blood–brain barrier. The multiple dissemination of the brain abscesses did not allow surgical drainage, and, in any case, the high risk of mortality associated with this procedure in immunocompromised patients was also taken into account [8].

We preferred a conservative approach using linezolid, a synthetic antibiotic of the novel oxazolidinone class, which has a broad spectrum of in vitro and in vivo activity against a wide range of gram-positive bacteria [9] and can be administered intravenously or orally. Furthermore, recent reports indicate that various strains of *Nocardia* are susceptible to linezolid [10] and that its diffusion in the central nervous system is excellent.

To the best of our knowledge, the exclusively medical treatment of CNS abscesses due to *N. farcinica* has been attempted in only two cases [11, 12], because surgery is usually the preferred choice [4, 8].

The management of immunosuppressive therapy in the presence of nocardiosis is still controversial, and it has been suggested that it should be discontinued [5, 6]. In our case, we decided merely to reduce the immunosuppression because of the patient's initially good response to linezolid and the fact that we believed an attempt to save his second transplanted kidney was justified.

In conclusion, newer immunosuppressive protocols may be responsible for the opportunistic infections appearing in transplanted patients at unconventional times. *Nocardia* infection should be suspected in kidney transplant patients even during the early post-transplantation follow-up. Linezolid is a very effective antibiotic therapy that should be considered in the case of disseminated nocardiosis.

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