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Nocardiosis in Heart Transplant Recipients

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ABSTRACT

Nocardia has emerged as an important opportunistic pathogen, especially in organ transplant recipients. Heart transplant (HT) recipients initially had an especially high rate of Nocardia infection, but this could be reduced by the routine use of cyclosporine. Our objective was to clarify the prevalence and presentation of Nocardiosis in HT recipients in a retrospective cross-sectional analysis.

INTRODUCTION

We are reporting on our patients who were diagnosed with Nocardiosis after heart transplantation. Their ages at heart transplant (HT) were 59-25 years. The onset of Nocardiosis took place between 1-4 months after transplantation respectively. The sites of illness were pleura, skin, and lung. In 2 patients, Nocardia disseminated to the brain 2-3 months after the onset of Nocardia. In all of the patients, antibiotic therapy with imipenem/cilastatin was effective. However, in 2 of the 3 patients, Nocardiosis recurred in the brain after the stop of antibiotic therapy. Two patients expired in the late follow-up. The prevalence of Nocardiosis was low (0.4%), but the prognosis was poor (mortality 67%). Prolonged therapy with imipenem/cilastatin was recommended.

Nocardia has emerged as an important opportunistic pathogen, especially in organ transplant recipients, although it was previously a rare infection with a high mortality. Prevalence of Nocardiosis in renal transplant patients cited in the literature varies from 0% to 20% [Chapman 1990; Peleg 2007]. Before the routine use of cyclosporine, HT recipients had an especially high rate of Nocardia infection, varying from 3.1% to 37.5%, mean 13.4%. However, the routine use of cyclosporine could reduce the incidence of Nocardiosis to between 0% and 6.3%, mean 4.5% [Chapman 1990; Hofflin 1987; Kirklin 1988; Dresdale 1985]. We reviewed the records of patients with HT and proven Nocardiosis in their follow-up periods, in order to determine the prevalence and presentation of Nocardiosis at our center.

The records of 716 patients who underwent orthotopic HTs during a 7.0-year period at the Heart Center North Rhine-Westphalia, Germany were reviewed and analyzed. During this period, 727 orthotopic HTs were performed. The duration of follow-up ranged from 1 month to 7.0 years. Nocardiosis developed in 3 patients (0.4%).

The basic immunosuppressive therapy was based on double-drug therapy (cyclosporine + azathioprine, without the use of monoclonal or polyclonal antibodies for the induction of immunosuppressive therapy). In early postoperative terms, 4 × 250 mg methylprednisolone were given over 3 days. Immunosuppressive therapy was intensified by pulsed steroids with 4 × 250 mg methylprednisolone/24 hours over 3 days. If there were more than 3 episodes of ongoing rejection, prednisone (1 mg/kg/day) was given orally, and then tapered slowly to at least 0.05 mg/kg/day.

PATIENT I

A 59-year-old man underwent an orthotopic HT due to end-stage ischemic cardiomyopathy. His clinical course with immunosuppressive therapy was induced with cyclosporine and azathioprine alone, without steroids or antibody therapy. The postoperative course was complicated three times by rejection episodes requiring methylprednisolone for up to one month. Prednisone was also applied. Direct microscopic examination of pleural effusion suggested Nocardia. Positive cultures on Nocardia farcinica were available on postoperative day (POD) 163. The initial antibiotic therapy was initiated with clavulanic acid/amoxicillin (750 mg/day) and ofloxacin (200 mg/day). The pleural effusion was reduced. Brain CT and MRI revealed multiple brain abscesses. Further antibiotic therapy with amikacin (500 mg × 3/day) and imipenem/cilastatin (2 g × 3/day) was started and continued for 6 weeks. The condition was satisfactory with neither complication nor recurrence during the next three years.

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PATIENT 2

A 62-year old man underwent an orthotopic HT due to end-stage ischemic cardiomyopathy with revascularization of the left anterior descending coronary artery and internal thoracic artery. Immunosuppressive therapy was induced with cyclosporine and azathioprine alone, without steroids or antibody therapy. The postoperative course was complicated more than 10 times by rejection episodes requiring methylprednisolone. Prednisone was required orally from POD 84. The patient developed fever, with a multiple skin abscess in his chest wall. Chest radiography revealed alveolar infiltrate in the right middle and lower lung field, which occurred due to Streptococcus salivarius. Antibiotic therapy with ofloxacin (200 mg/day) and thereafter mezlocillin (2 g × 3/day) was performed. On the other hand, a culture of purulent material in the skin abscess developed Nocardia farcinica on POD 164. The initial antibiotic therapy was started with amikacin (500 mg × 2/day) and imipenem/cilastatin (2 g × 3/day) and was continued for two weeks. However, he was admitted again with high fever and a neurological disorder. Brain CT scan revealed a brain abscess near the third ventricle. The antibiotic therapy with amikacin and imipenem/cilastatin was started again for 2 weeks. He died on sepsis on POD 259. On autopsy, Nocardia infection was confirmed in the skin and brain.

PATIENT 3

A 2-year-old man underwent an orthotopic HT for a primitive dilated cardiomyopathy on June 7th, 1994. His clinical course is shown. Immunosuppressive therapy was induced with cyclosporine and azathioprine alone, without steroids or antibody therapy. The early postoperative course (1 month) was complicated 4 times by rejection episodes requiring methylprednisolone, and prednisone was required orally from POD 6. Furthermore, renal dysfunction required hemofiltration, prolonged until 2 months after HT. On POD 36, he developed a progressive nodular non-cavitary infiltrate in the left middle lung field on chest X-ray. Antimycotic drugs (liposomal amphotericin B (250 mg × 1/day), flucytocin (250 mg × 2/day), and itraconazol (100 mg/day) were given due to suspected Aspergilloma. However, on POD 93, cultures of sputum and gastric juice revealed Nocardia; later Nocardia asteroids developed. He was treated with imipenem/cilastatin (1 g × 2/day) for 2 weeks. On the other hand, subacute rejection, requiring not only methylprednisolone (twice) but also rescue therapy with monoclonal antibodies (OKT3), appeared. He developed progressive liver and renal failure and thrombocytopenia. On POD 86, a rethoracotomy was performed due to hematoma. He died of multiple organ failure due to ongoing rejection on POD 118. On autopsy, lung abscess due to Nocardia disseminated to the right side.

DISCUSSION

Nocardiosis is a well-recognized complication from the immunosuppression required for transplantation. Cellular immune function is the major defense against infection, leaving transplant patients at high risk. The incidence of Nocardiosis in our HT recipients was only 0.4%. We have routinely used cyclosporine and azathioprine for immunosuppression, without steroids or antibody therapy. It is interesting to note that the frequency of Nocardia infection dropped threefold after cyclosporine was used routinely for immunosuppression at other centers [Hofflin 1987]. Furthermore, we do not use monoclonal or polyclonal antibodies for the induction of immunosuppressive therapy, nor do we use steroids from the start of immunosuppressive therapy. The steroids within immunosuppressive drugs are particularly known to predispose to infections with Nocardia [Makay 1994]. We think that the protocol described above explains the low incidence of Nocardiosis in our HT recipients. The highest incidence of Nocardia infection is in the first year after transplantation, and is often temporally related to intensive immunosuppressive therapy for rejection. The postoperative courses of our three patients with Nocardiosis were complicated by frequent rejection episodes and the need for oral steroids.

We no longer perform prophylactic therapy against Nocardia infection. However, we do believe that prophylactic therapy is necessary in patients whose clinical courses are complicated by frequent rejection episodes, as the rate of Nocardia infections has fallen in renal transplant centers using prophylactic therapy with sulfa regimens [Peterson 1982]. In 2 patients, we experienced brain abscesses 3 months after the initial appearance of Nocardia infection. We used clavulanic acid/amoxicillin as the initial antibiotic therapy for Patient 1 for 3 weeks and amikacin and imipenem/cilastatin for Patient 2 for 2 weeks.

The central nervous system is the most frequent site of secondary involvement in disseminated infection, usually in the form of a brain abscess, which may be single or multiple. Although the efficacy of prolonged therapy has not been well documented, our results do recommend it. In immune-competent hosts with minor infections, therapy is usually given for 2 or 3 months, or at least for 6 weeks after resolution of the disease. For major infection in immunosuppressed patients, therapy should be continued for up to one year [Chapman 1990; Peleg 2007; Palmer 1974]. The development of sulfonamides provided a successful treatment for Nocardia, and they remain the mainstay of therapy. However, the concurrent administration of cyclosporine and trimethoprim/sulfamethoxazole has been associated with reversible nephrotoxicity [Sands 1989]. Recently, imipenem/cilastatin seems to be a good option, without evident side effects such as interference with the cyclosporine [Simmons 1992; Thaler 1992]. Reduced concentration of cyclosporine and a protective effect against cyclosporine nephrotoxicity by imipenem/cilastatin have been reported in rats [Sido 1987]. In our HT recipients, results of disk diffusion susceptibility testing suggested that imipenem/cilastatin had a sufficiently high level of activity.

We experienced 3 HT recipients with Nocardiosis. The prevalence of Nocardiosis in the HT recipients was low (0.4%), but the prognosis was poor. Prolonged therapy with imipenem/cilastatin was recommended.

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