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BRIEF REPORT

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Atypical mycobacterium infection with dermatological manifestation in a renal transplant recipient

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Abstract In April 1997, a 58-year-old renal transplant recipient presented with abscess-like nodules in his left calf and on his right foot. Furuncular disease was suspected and the patient was treated with flucloxacillin. However, the lesions increased in size and became ulcerative. In the following 3 months, cultures of punctuated material, blood, and urine remained negative and gram stains did not reveal micro-organisms. In June 1997, acid-fast stains were positive. A diagnosis of a nontuberculous mycobacterium (NTM) infection was made and empirical antimycobacterial therapy was started. The combination of relatively minor symptoms with enlarged purulent lesions, causing severe morbidity, raises the possibility of NTM infection in the immunocompromised patient.

Key words Nontuberculous mycobacterium, immunosuppression, kidney transplantation · Immunosuppression, nontuberculous myobacterium, kidney transplantation · Kidney transplantation, nontuberculous myobacterium

Introduction

Infection is a major threat to immunocompromised transplant recipients [5, 6]. Opportunistic infections most frequently occur between the 2nd and 6th month post-transplantation. Beyond 6 months, infections are comparable to those seen in the general community, though they are associated with higher morbidity and mortality rates [3]. We report a case of a renal transplant recipient who developed an atypical infection in the late post-transplantation period.

Case report

A 58-year-old man was found to have renal failure in 1990 due to hypertensive nephropathy. Chronic ambulant peritoneal dialysis was initiated, followed by chronic intermittent hemodialysis. One year later, he received a living nonrelated renal transplant from his wife. Immunosuppression included prednisone and cyclosporin, the latter being replaced by azathioprine in July 1993. In December 1993, renal function rapidly deteriorated (serum creatinine 540 μmol/l, urea 40.1 mmol/l), due to atherosclerotic obstruction of the right iliac artery, proximal to the anastomosis with the renal artery of the renal transplant. Balloon angioplasty was successfully

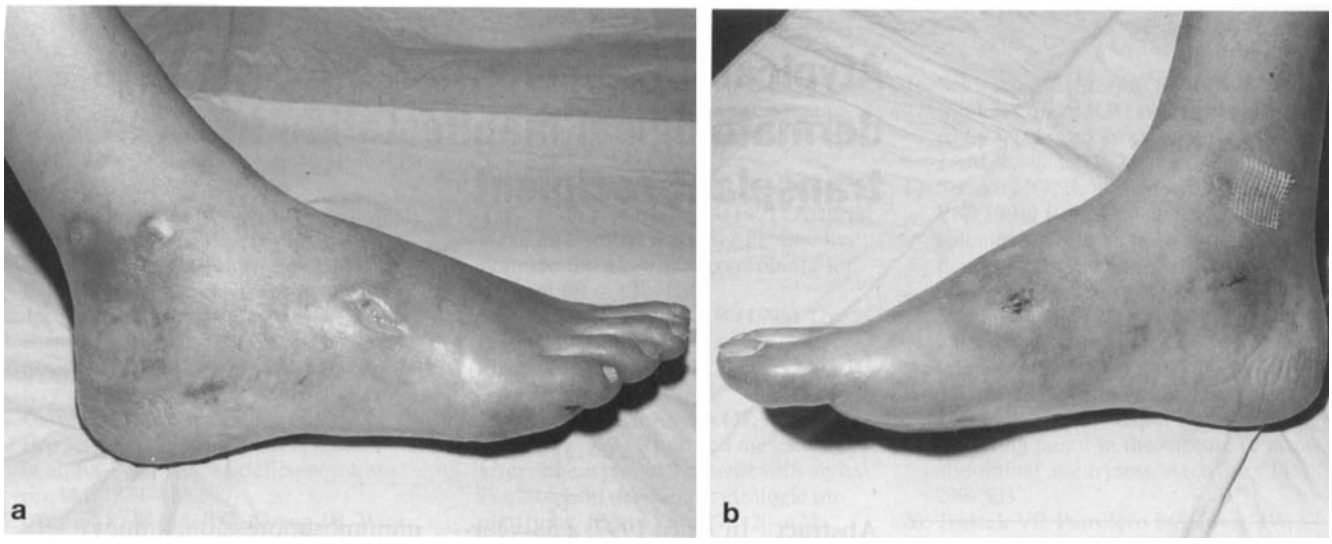

Fig. 1 a Lateral view of the right foot, showing a red, swollen ankle and a purulent lesion on the dorsum of the foot. **b** Medial view of the right foot, showing one purulent lesion on the foot and one just below the medial malleolus, which is already healing

performed, resulting in recovery of renal function to a serum creatinine of 119 μmol/l and urea of 8.6 mmol/l.

In April 1997, this patient presented with two erythematous nodules with minimal purulent excretion in his left calf. He had neither fever, night sweats, nor weight loss. White blood cell count was normal (7.2×10^6/l) and the X-thorax yielded no signs of pulmonary involvement. A clinical diagnosis of furuncular disease was made and oral treatment was started with flucloxacillin 500 mg q.i.d.. Five days later, the lesions had become larger and ulcerative with a large amount of purulent excretion. Also, abscess-like nodules were seen on the dorsum of the patient's right foot. His right ankle was red, swollen, and tender (Figs. 1 a, b).

Ultrasound-guided aspiration of the lesion in the left calf was performed. Ultrasonography of the right ankle showed no signs of arthritis. Routine cultures of punctuated material remained negative and a second aspirate was taken in May 1997. The gram stain revealed many polymorphonuclear leukocytes but no micro-organisms. Routine aerobic and anaerobic cultures were negative again. In June 1997, acid-fast stains, including auramine and Ziehl-Neelsen, were positive. The culture, however, remained negative. Mycobacterial cultures of blood specimens remained negative as well. Although infections caused by other organisms like *Nocardia* and fungi were considered, the diagnosis of a nontuberculous mycobacterium (NTM) infection was made, based on the distinct clinical symptoms and the visualization of the acid-fast bacilli.

In the meantime, C-reactive protein levels were found to be extremely elevated (116 mg/l). An MRI scan was done in June 1997 to visualize the lesions in the left calf in relation to the surrounding soft tissues since they were found to be enlarged upon physical examination. This scan revealed an abnormal fluid collection, localized dorsomedial between subcutis and gastrocneminus fascia, covering the latter almost totally in length.

Therapy was given in the form of a combination of surgical treatment and empirical antimycobacterial therapy. Surgical treatment was conservative, except for the abscesses on the right foot, which were drained. The following antimycobacterial regimen was given: rifampicin 600 mg once daily, ethambutol 800 mg once daily, clarithromycin 500 mg twice daily, and ofloxacin 400 mg once daily.

In the following 4 months, the cutaneous lesions gradually healed. The antimycobacterial regimen was continued for a period of 9 months. Three months after the oral treatment had been stopped, the patient was doing well and there were no signs of recurrence. C-reactive protein levels were down to below 1 mg/l. However, in June 1998, a recurrence was detected on the right foot. C-reactive protein was slightly elevated (11 mg/ml) and, again, acid-fast rods were found to be present. Treatment was restarted. Cultures remained negative once more.

Discussion

In the immunocompromised patient presenting with cutaneous or subcutaneous nodules, primary infection as well as systemic, metastatic infection should be considered. In the first category, organisms like NTM and *Prototheca sp.* are frequently seen. Fungi like *Candida*, *Aspergillus*, and *Rhizopus* are even more threatening because of the potential of secondary disseminated disease. *Nocardia*, *Cryptococcus neoformans*, *Candida*, and *Aspergillus* may cause (sub)cutaneous nodules as a result of disseminated disease [8]. In one study, 8 of 31 immunocompromised patients (26%) with a dermatological infection were found to suffer from systemic infection. In six of these eight patients, the cutaneous lesions were the first sign of disseminated disease. In another series, life-threatening cryptococcal meningitis was preceded by skin lesions in up to 20% [9, 10].

With immunocompromised patients suffering from skin infection, the optimal diagnostic approach is of utmost importance. Prevention of serious, local complications is likely to be the most successful when the infectious agent is identified. The same is true for prevention and treatment of disseminated infection. With cutaneous

lesions and solid, subcutaneous nodules, skin biopsy is preferred. Appropriate cultures and stains, as well as histological and immunological examination, should be performed. For abscess-like lesions, as in our patient, needle aspiration can be performed, followed by culturing and staining of punctated material. Blood cultures, detection of cryptococcal antigen in serum and in cerebrospinal fluid, and X-thorax can be of additional value [8–10].

Infections with NTM in solid organ transplant recipients are infrequent [4]. While the incidence of tuberculosis is reported to be 0.8 %–1.7 % in (renal) transplant recipients, causing potentially life-threatening disease [1, 2], NTM infections occur less frequently and, reviewing previously reported cases, a clear relationship between infection due to NTM and death is rarely observed [4]. However, in terms of morbidity, the outcome of NTM infection can be very serious.

NTM are ubiquitous organisms. In contrast to tuberculosis, person-to-person transmission of NTM is not assumed to occur. NTM infections are characteristically seen in the late post-transplantation period [3]. The most common signs are cutaneous lesions of the extremities, arthritis, and tenosynovitis. Less common are renal graft infection, colonic disease, and disseminated infection. More than one-half of the patients present with multifocal disease. Typical symptoms of tuberculosis, such as fever, night sweats, weight loss, and lymphadenopathy, are rare in NTM disease. Skin and joint infections are most frequently caused by the *M. fortuitum/ M. chelonae* complex. Other NTM include *M. kansasii, M. abscessus, M. haemophilum,* and *M. marinum.*

Diagnosis should be made on the basis of clinical presentation and laboratory tests. When a patient does not respond to a standard antimicrobial therapy, like our patient, the possibility of an atypical infection should be considered. Complications of (sub)cutaneous nodules caused by NTM include ongoing destruction of the tissues surrounding the primary lesion(s), causing bone or joint destruction, soft tissue necrosis and compartment syndrome, and disseminated infection. For this reason, and because of the remarkable tolerance that most patients have to the early symptoms of NTM disease, the physician should be alert to the possibility of NTM infection in the immunocompromised patient.

The case described is a striking example of NTM disease. There is an impressive discrepancy between the relative absence of symptoms, on the one hand, and the enlarged, multiple, purulent lesions with extremely high CRP levels on the other hand. This case indicates the need to consider and treat NTM disease in such patients. Modalities of treatment include surgery, dose reduction of immunosuppressive treatment, and the administration of antimicrobial agents. As for the latter, no uniformly accepted regimens have been defined. Susceptibility of NTM to antimicrobials varies widely, and susceptibility testing of mycobacteria is difficult and not standardized. However, rifampicin, rifabutin, isoniazid, ethambutol, and streptomycin are most commonly used in various combinations [4, 8], and clarithromycin and azithromycin have also been proven to be effective in the treatment of NTM disease [7].

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