Nontubercular Mycobacterial Infection in a Renal Allograft Recipient

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Abstract

A 71-year-old male, a renal allograft recipient, presented to us with a history of fever and right palm swelling. He had a history of fever 7 years back when he was treated with antitubercular treatment (ATT). Three years back, he was diagnosed to have gout and he was started on allopurinol. He developed severe bone marrow toxicity and allopurinol was changed to febuxostat. On admission, routine investigations did not reveal any focus of infection. The fluid aspirate from the palm revealed acid-fast bacilli (AFB). He was started on ATT; however, he did not show significant improvement. Two months later, he developed multiple subcutaneous lesions, and the pus again came positive for AFB. Due to lack of improvement, the aspirate was sent for molecular diagnostic identification. The mycobacteria was identified as *Mycobacterium haemophilum*. His treatment was changed to rifampicin, clarithromycin, and ciprofloxacin. As he showed slow improvement, his immunosuppression was tapered slowly. At 7 months of therapy, he is clinically better and his lesions are healing. His renal functions stayed stable despite tapering of cyclosporine in a patient who is on rifampicin. This case, the first report of *M. haemophilum* infection in a kidney transplant recipient in India, illustrates the difficulty in diagnosing nontubercular mycobacterial infection in transplant recipients. It also emphasizes the dilemma in tapering immunosuppressive drugs in disseminated nontubercular mycobacterial infections where there are considerable interactions between ATT and immunosuppressives.

Keywords: *Gout, nontuberculous mycobacterial infection, renal transplant*

Introduction

Mycobacterial tuberculosis is common in renal allograft recipients. The treatment with antitubercular treatment (ATT) is often started based on clinical suspicion and laboratory demonstration of acid fast bacilli in pathological specimens. However, recently non tubercular mycobacterial infections are becoming common. Hence precise identification of the mycobacterial species is often required before treatment is instituted in these patients.

Case Report

A 71-year-old renal allograft recipient presented to us with a history of high-grade fever with chills, pain and swelling of the right palm of 2-week duration. The patient underwent a kidney transplant in 2001 from an unrelated donor. Pretransplant, he had long-standing hypertension. He had no history of diabetes mellitus. He was offered triple immunosuppression (cyclosporine, azathioprine, and steroids), and his renal functions have been stable over the past 15 years.

He had a similar history of fever 7 years back when the cause of fever could not be ascertained and he was treated with antituberculous therapy (isoniazid, ethambutol, pyrazinamide, and ofloxacin) for 6 months. Ethambutol and pyrazinamide were discontinued after 2 months.

He was clinically well for the next 4 years when he was diagnosed to have gouty arthritis. He was subsequently started on allopurinol. Over the past 2 years, he started to develop weakness and weight loss, and his investigations showed progressive anemia. Extensive evaluation of anemia did not reveal any blood loss or hemolysis. A bone marrow aspiration showed hypoplasia, which was attributed to azathioprine toxicity. The dose of azathioprine was reduced to 50 mg/day. Later, allopurinol was substituted with febuxostat (40 mg/day).

He was doing well when he started to have fever and right palm swelling [Figure 1]. His initial evaluation did not reveal any focus of infection, and an aspirate of the swelling in the palm was advised. The aspirate showed the presence of acid-fast bacilli (AFB).

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An infectious disease consultation was taken and the patient was started on ATT (isoniazid, ethambutol, pyrazinamide, and ofloxacin). The fever subsided and the patient started to do well. However, the swelling in the palm continued.

After 6 weeks of ATT, the patient developed multiple erythematous subcutaneous nodules over his right arm, shin with bilateral pedal edema, and erythema over ankles [Figure 2]. There was spontaneous discharge of pus from the palm and the erythematous nodules. The pus revealed the presence of AFB. The pus was sent for mycobacterial culture and for identification of the mycobacterial species by multiplex polymerase chain reaction with DNA hybridization. The mycobacterial strain identified was *Mycobacterium haemophilum*.

The culture was tested positive for *Mycobacterium* after 12 weeks, and the identification of the bacteria confirmed the species to be *M. haemophilum*.

Magnetic resonance imaging of the right hand showed osteomyelitis of the fourth metacarpal with surrounding edema and fluid collection in the metacarpal spaces [Figure 3].

A whole body positron emission tomography-computed tomography showed increased uptake in the right hand with osteomyelitis and cortical erosions of the metacarpals. There was an increased uptake in multiple subcutaneous nodules over the right arm, both ankles and left foot. A repeat infectious disease consultant was taken. It was decided to treat his nontuberculous mycobacterial (NTM) infection with rifampicin, ciprofloxacin, and clarithromycin.

As the lesions were slow to heal [Figure 4], it was decided to taper cyclosporine slowly. At the time of reducing the dose of cyclosporine, the trough cyclosporine level was 75 ng/ml. As the patient was on rifampicin already, which is known to have an adverse effect on the therapeutic cyclosporine levels, the risk of allograft rejection on reducing cyclosporine dose was explained to the patient. On discussion with his relatives, the patient and his family felt that reduction of his immunosuppression will help improve his clinical condition. The initial cyclosporine dose was 125 mg/day, which was slowly reduced to 50 mg/day. At this dose, the trough level was around 40 ng/ml.

The lesions started to heal over the next few months. At 7 months after starting specific therapy for *M. haemophilum*, the patient was feeling better with majority of the subcutaneous lesions showing improvement [Figure 5].

His renal function remained stable throughout the past 9 months.

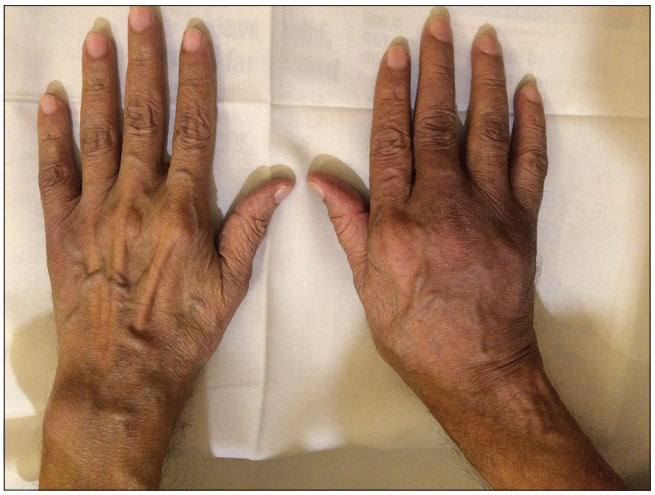

Figure 1: Right palm swelling

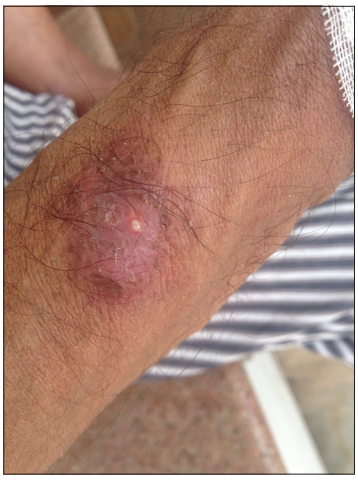

Figure 2: Skin lesions at the elbow

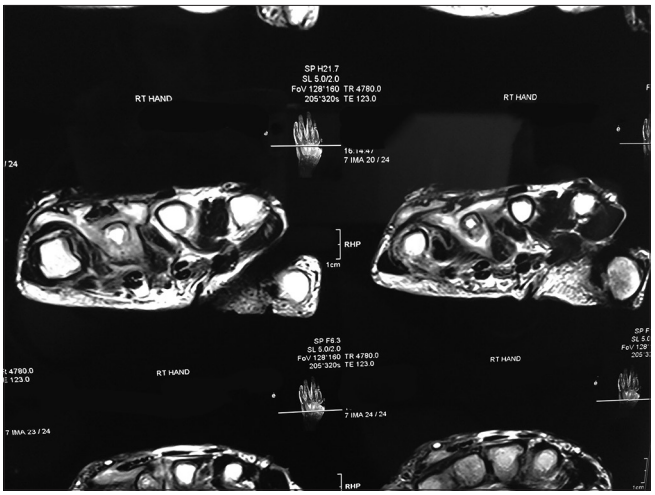

Figure 3: Magnetic resonance imaging of the right hand showing destruction of the four metacarpal bones with surrounding edema

Discussion

Mycobacterial tuberculosis is a common infection in renal allograft recipients, especially in India. The prevalence of mycobacterial tuberculosis infection in renal transplant recipient varies from 3.5% to 13.3%.[1,2] In a study in posttransplant infections in South India, the prevalence was

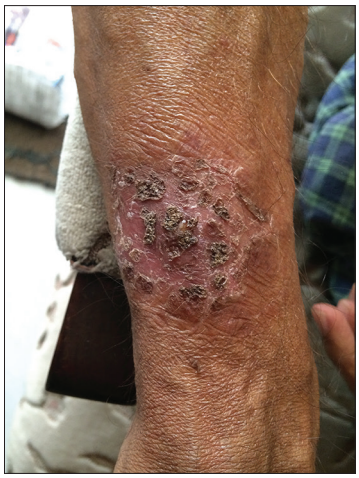

Figure 4: Persistent lesions after 1 month of therapy

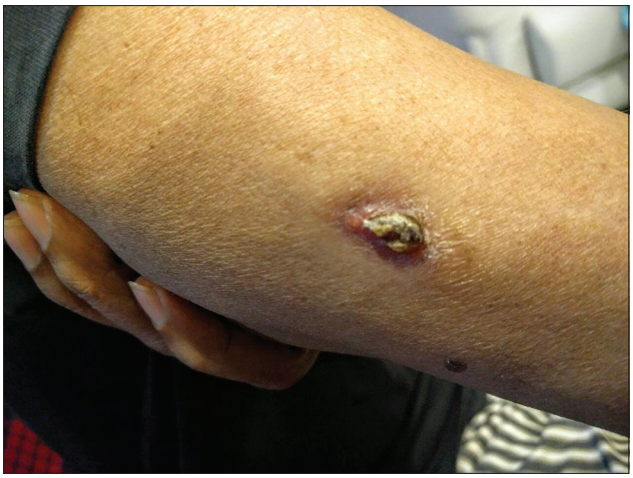

Figure 5: Healing lesions after 7 months of treatment

10.6%.[3] Two out of 169 transplant recipients who were studied presented with atypical mycobacterial infection in this study. Similarly, in a large study from Spain, 7 out of 27 patients diagnosed to have mycobacterial infection had atypical mycobacterial infection.[4] It appears atypical mycobacterial infections in renal transplant patients are not as rare as they are thought to be. It is widely believed that, in countries where mycobacterial tuberculosis is endemic, NTM infections posttransplants are rare.[5] With increasing number of transplants, newer immunosuppressive therapies, and newer diagnostic tools, NTM infections are being reported worldwide. Our patient had an NTM infection after 15 years and we believe that it was due to the profound immunosuppressive effect of the allopurinol/azathioprine interaction. The common NTM species isolated in organ transplant recipients are the fast growers such as *Mycobacterium fortuitum*, *Mycobacterium abscessus*, and *Mycobacterium chelonae*.[6] They are more often associated with hematopoietic stem cell transplantation. Slow-growing NTM species such as Mycobacterium avium complex (*Mycobacterium avium*, *Mycobacterium intracellulare*, *Mycobacterium silvaticum*, *Mycobacterium hominissuis*, and *M. paratuberculosis*), *Mycobacterium kansasii*, *Mycobacterium marinum*, *Mycobacterium ulcerans,* and *M. haemophilum* are usually associated with solid organ transplants.[7,8] The most common NTM bacteria isolated in kidney transplant recipients are *M. fortuitum*, *M. kansasii,* and *M. haemophilum*.[9]

These slow growers are often difficult to culture, and identification of the species requires additional testing. The diagnosis in our patient was delayed as he had *M. haemophilum* infection and the organism took 12 weeks to grow. It was only after molecular identification that the diagnosis was established. In renal transplant recipients, cutaneous presentation is the most common presentation as seen in our case.

M. haemophilum infection is reported in solid organ transplantation, especially in association with renal and cardiac allografts. It often presents with cutaneous manifestations and is difficult to treat.[10] Pyomyositis and osteomyelitis are also reported with this *Mycobacterium* in kidney transplant recipients.[11] Due to its stringent and laborious culture requirements (lower culture temperature and requirement for heme), this *Mycobacterium* is often difficult to culture. Hence, various molecular genetic methodologies are used for the rapid identification of this NTM as was done in our case.[12] Various line probe assays are developed for rapid diagnosis of clinically relevant mycobacterial species.[13]

Treatment is often with rifamycins (rifampicin), macrolides (clarithromycin and azithromycin), and fluoroquinolones (ofloxacin and ciprofloxacin). The treatment needs to be prolonged for at least a year.[14] It is important to be aware of the drug interactions between cyclosporine, rifampicin, and clarithromycin. Our patient is on therapy for the past 8 months with slowly healing ulcers. His cyclosporine levels are closely monitored during his therapy.

Literature search shows multiple reports regarding mycobacterial tuberculosis infection in Indian renal allograft recipients. There exists very scant information from India about NTM infections in renal transplant recipients. A case series of four proven cases of NTM infection in renal transplant recipients mention that these infections are infrequent but cause serious morbidity.[15] Another report mentions a psoas abscess caused by *M. fortuitum* infection.[16] This patient also had serious comorbidity requiring surgical drainage. Our case is the first report of a slowly growing fastidious *M. haemophilum* infection in a renal allograft recipient from India. This case illustrates the difficulty in establishing specific diagnosis in some of the NTM infections and the challenges faced in reducing immunosuppression in such cases.

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Conflicts of interest

There are no conflicts of interest.

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