CASE REPORT

Disseminated *Mycobacterium haemophilum* infection in a renal transplant recipient

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SUMMARY

Opportunistic infections are a major concern in renal and transplant medicine. We present the case of a renal transplant recipient with a generalised *Mycobacterium haemophilum* infection after an increase in immunosuppressive therapy and treatment with a tumour necrosis factor- α (TNF- α) inhibitor. Infection involved skin and soft tissue, joints and bones, as well as the renal transplant with an interstitial nephritis. Rapid diagnosis using PCR and DNA sequencing allowed early appropriate treatment. Triple antibiotic therapy and reduction in immunosuppression resulted in a slow but sustained recovery. Immunosuppression causes severe opportunistic infections. TNF- α inhibitors are very effective and well tolerated but have an increased susceptibility to infections with mycobacteria. Mycobacterial infections represent a significant clinical risk to transplant recipients because of their aggressive clinical course and the need for complex toxic antibiotic treatments. In these patients, *M. haemophilum* is a cause of skin infections.

BACKGROUND

Various opportunistic infections are one of the major complications of immunocompromised patients. Managing renal transplant recipients, the goal is to avoid rejections as well as overimmunosuppression and opportunistic infections.

CASE PRESENTATION

A 27-year-old patient with renal transplant was admitted to our unit with fever, oedema, arthralgia and subcutaneous tumours along his limbs.

The patient had developed an antineutrophil cytoplasmic antibody (ANCA)-associated necrotising glomerulonephritis that led to end-stage kidney disease at the age of 16. He had then received a pre-emptive renal transplant from his father. During the following years, his immunosuppression had been changed twice. First, his calcineurin inhibitor (CNI) was switched due to drug-associated adverse events from cyclosporine A to tacrolimus 4 months post-transplantation. Then to avoid nephrotoxicity, tacrolimus was tapered and stopped 2 years ago. His remaining immunosuppression was mycophenolate mofetil (MMF) and prednisolone 5 mg/day. Since the age of 6, he had also to bear discoid psoriasis.

Four months ago, the patient was referred to a rheumatology unit with a painful swollen left knee. Joint fluid analysis was unremarkable and it was thought to be a psoriatic arthritis. A trial of steroids was unsuccessful. After a negative QuantiFERON-TB Gold test (T-cell interferon- γ release assay, TIGRA, to

detect tuberculosis) the tumour necrosis factor (TNF)- α inhibitor adalimumab was initiated 3 months ago. The patient's left knee remained painful, and his left lower leg as well as his hands started to swell. The therapy was discontinued after four courses. A month ago, the patient developed fever and little palpable lesions occurred on his left thumb. Repeated joint fluid aspirate visualised a few urate crystals. With the differential diagnosis of acute gouty arthritis, he received high doses of steroids. The oedematous swelling of his limbs progressed, especially in his left hand, and subcutaneous tumours appeared on his upper and lower limbs. Steroids were reduced gradually to 20 mg/day and a superficial biopsy of a skin lesion showed panniculitis. Bacterial and fungal cultures were negative. With the impression of a generalised relapse of his ANCA vasculitis, his immunosuppression of prednisolone and MMF was increased again a week ago, and he was referred to us for a second opinion. On admission, his daily immunosuppression was 3 g MMF and 80 mg prednisolone.

On physical examination, he was febrile, tachycardic and in slight discomfort due to his painful swollen fingers. Multiple subcutaneous tumours, indurated and tender to touch were found on his arms and legs. His limbs were swollen, his left hand being the most substantially affected with erythema, oedema and induration (figure 1A). On his fingertips and over his interphalangeal joints were small shimmering lesions, which were tender and partly suppurative.

INVESTIGATIONS

Laboratory results are summarised in table 1. Baseline serum creatinine was 2.2 mg/dL. Blood cultures remained sterile. QuantiFERON-TB Gold tests were invalid due to the lymphopaenia. A tuberculosis skin test was not performed, as skin lesions were too severe and extensive to evaluate a possible skin response. A deep biopsy of a skin lesion showed an advanced chronic active, focal necrotising panniculitis without granulomas. Direct microscopy revealed rod-like bacilli and Fite and Ziehl Neelsen staining detected acid-fast bacilli (AFB; figure 1B). Molecular detection of mycobacterial DNA by PCR for *Mycobacterium tuberculosis* complex (GenoQuick MTB) was negative. PCR and DNA sequencing using the genes *hsp65*, *rpoBC* and *dnaK* rapidly identified *M. haemophilum*.

TREATMENT AND PROGRESS OF DISEASE

Treatment with rifabutin and clarithromycin was started, while the steroids were weaned and MMF was reduced. In the first few days, the patients'

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Figure 1 (A) Patient's swollen left hand with its broadened fingers. (B) Direct microscopy of the skin biopsy with acid-fast bacilli (x1000).

Table 1 Laboratory results

Hb (13.8–17.2 g/dL)	10.2 g/dL
WCC (4.5–11.0×10 ⁹ /L)	17.0×10 ⁹ /L
Neutrophils (40–80%)	98.6%
Lymphocytes (20–40%)	0.9%
Creatinine (0.7–1.2 mg/dL)	2.8 mg/dL
Urea nitrogen (7–22 mg/dL)	39 mg/dL
C reactive protein (<5 mg/L)	131 mg/L
Antiproteinase 3 (<2.5 U/mL)	3 U/mL

Hb, haemoglobin; WCC, white cell count.

condition exacerbated. Then most of the patients' symptoms slowly started to improve. However, weight bearing on his right ankle became painful and his renal function deteriorated further (serum creatinine 3.6 mg/dL). A renal transplant biopsy identified an epithelioid granulomatous interstitial nephritis (figure 2A). No AFB were seen. An MRI of the right foot demonstrated lesions at the medial malleolus and the calcaneus suspicious of osteomyelitis (figure 2B). A bone biopsy revealed intracellular AFB in florid histiocytic infiltrates (figure 2C). DNA sequencing confirmed *M. haemophilum*.

The diagnosis was revised to a generalised atypical mycobacteriosis with arthritis, osteomyelitis and interstitial nephritis. The antituberculous therapy was extended and ciprofloxacin was added. Despite his poor renal function, the immunosuppression was readjusted from the antiproliferative agent to a CNI in order to improve the immune system.

OUTCOME AND FOLLOW-UP

During the following weeks, a very slow process of recovery could be observed and cultures of the spongiosa calcanei on chocolate agar, incubated at 28°C, yielded the strain identified as *M. haemophilum*. Over the next year, the panniculi and shimmering lesions disappeared, and renal function initially improved and stabilised. Antitubercular treatment was stopped after a total of 15 months of therapy. After 5 years of follow-up, no recurrent mycobacterial disease has been noted but the patient has reached dialysis dependence again. He received a second transplant this time from his mother in March 2016. At present, transplant function is good and immunosuppressive therapy contains tacrolimus, everolimus and prednisolone.

DISCUSSION

Opportunistic infections such as the infection with cytomegalovirus or *Pneumocystis jirovecii* in the first 6 months after renal transplantation are well known and prevented by prophylactic treatment. After the first vulnerable months, common bacteria of urinary tract infections outrank opportunistic organisms.

Figure 2 (A) Renal biopsy with an epithelioid granulomatous interstitial nephritis (PAS, x400). (B) MRI of the right foot with a cloudy dense lesion of the calcaneus suggestive of an osteomyelitis (sagittal T2). (C) Biopsy of the lesion of the calcaneus with a histiocytic infiltration with acid-fast bacilli (Fite, x400). PAS, periodic-acid Schiff stain.

Infections with non-tuberculous mycobacteria (NTM) are less common but are associated with relevant morbidity and mortality.¹ Among renal transplant recipients, the incidence is thought to be between 0.16% and 0.38%.² Over 20 different mycobacterial species have been identified causing disease in solid organ transplant recipients. *M. haemophilum* has rarely been reported to affect these patients.^{3–9} As a pathogen, it was first discovered in a subcutaneous lesion of a woman with Hodgkin's disease in 1978.¹⁰

Pathophysiology: Most NTM are ubiquitous free-living saprophytic organisms. Infections develop following exposure in the environment, although nosocomial infections via contaminated water have been reported. The slow growing *M. haemophilum* causes disease in immunocompetent and immunocompromised patients.¹¹ Its restricted temperature requirements (it grows at 30–32°C) might explain the frequency of lesions on the superficial areas of the body.¹² From patients with HIV/AIDS it is known that infections can affect bones and joints. They usually occur in the distal joints of the arms and legs and may relapse after initial response.^{13 14}

Clinical manifestations: In immunocompromised humans, *M. haemophilum* is responsible for a wide range of diseases, including skin and soft tissue infections, bone and joint infections, pulmonary and disseminated infections.^{13–16} In immunocompetent children, it is reported to cause cervicofacial lymphadenitis.¹⁵

Here, we describe for the first time a disseminated infection affecting among other organs the renal transplant. The renal biopsy did not show any AFB, but the histological pattern was highly suggestive. Tissue stains are not always positive for these bacilli and can show a low organism burden. Mycobacterial infections are typically accompanied by necrotising granulomatous inflammation.¹² As immunocompromised patients have impaired inflammatory responses, necrotising granulomas might be absent.

Diagnosis: Mycobacteria are slow growing. The turnaround time for identification is long when conventional biochemical tests are used. Additionally, growth of *M. haemophilum* depends on the presence of iron or haemin. Today, rapid species identification by DNA sequencing enables early diagnosis and appropriate antibiotic treatment.^{17 18} TIGRA assists in the diagnosis of tuberculosis; but a negative QuantiFERON-TB Gold test does not exclude an NTM infection. It also cannot be interpreted in patients with lymphopaenia. As a fastidious organism with unique growth requirements, its prevalence is probably underestimated.

Risk factors: Our patient was on long-term immunosuppressants for his renal transplant. He had been treated with high doses of steroids, his antiproliferative agent had been increased

and he had received adalimumab. The use of TNF- α inhibitors is associated with an increased risk of mycobacterial infections and has been reported as a potential trigger to cause a *M. haemophilum* infection.^{19–21} In this complex case, it is difficult to decide if the patient developed the mycobacterial infection while being treated with MMF and steroids or if adalimumab was needed as the trigger. The aggravation of the disease under TNF- α blockage is undisputable. Above all, immunosuppression causes severe opportunistic infections such as mycobacterial infections and restoring immune function seems to facilitate successful treatment.²² The reduction in immunosuppression for effective clearance of mycobacterial disease, however, needs to be balanced against the risk of graft rejection. Owing to the growing number of immunocompromised patients and the varied use of immunosuppressive and immunomodulatory drugs, *M. haemophilum* is a differential diagnosis of skin and bone infections.

Dealing with solid organ recipients, foremost it is important to minimise immunosuppression where possible. Second, mycobacterial infection should be considered in those presenting with subacute or chronic symptoms especially when skin and bones are involved.²³

Learning points

- Immunosuppression causes severe opportunistic infections. Tumour necrosis factor- α inhibitors may further increase susceptibility to mycobacterial infection.
- *Mycobacterium haemophilum* is a rare cause of skin infection in immunosuppressed patients.
- Diagnostic testing based on T-cell interferon- γ release assays is not reliable in immunocompromised patients due to their anergy. PCR and DNA sequencing enables rapid diagnosis and appropriate treatment.

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Contributors SRB was the attending physician and wrote the article. All co-authors substantially contributed to the acquisition and interpretation of data concerning this case. CI-K and UW also contributed to the drafting of this article. All co-authors critically revised and approved the final version of the report.

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