Soft-tissue abscess as the initial manifestation of miliary tuberculosis in a renal transplant recipient with prolonged fever

Robin G. Parry, E. Geoffrey Playford, David F. M. Looke and Michael Falk

Renal Unit and Department of Infectious Diseases, Princess Alexandra Hospital, Brisbane, Queensland, Australia

Introduction

*Mycobacterium tuberculosis* infection is a rare complication of renal transplantation. Reports of its prevalence varying between 0.4–1.7% in Western nations [1,2] and 3.5–10.5% in nations with higher rates of endemic tuberculosis [3–6]. We report a rare manifestation of tuberculosis in a renal transplant recipient who presented without clinical localizing signs, that had a successful response to treatment.

Case

A 21-year-old female presented to hospital with a 2-day history of fevers to 40°C, sweats, rigors, and fatigue. She complained of no other specific symptoms.

A live related renal transplant donated by her mother had been performed 2 years previously. Her underlying renal failure was secondary to reflux nephropathy and she had received peritoneal dialysis for 2 months prior to transplantation. Both the patient and the donor were CMV IgG negative. There were no post-transplant complications, and immunosuppressive therapy at the time of admission was cyclosporin (225 mg/day in two divided doses), azathioprine (75 mg/day), and prednisolone (5 mg/day). Her serum creatinine on admission was 0.13 mmol/l.

The patient was born in southern England and had immigrated to Australia 10 years previously. She gave no history of contact with tuberculosis, and had not received BCG vaccination. A purified protein derivative (PPD) skin test performed 4 years prior to transplantation (when her serum creatinine was 0.28 mmol/l) was negative. Her mother had no known direct contact with tuberculosis, although a friend of her family had apparently been diagnosed with tuberculosis whilst they lived in England. A PPD skin test had not been performed in the mother prior to kidney donation.

The patient worked in a day-care centre looking after 2–6-year-old children, but was unaware of having recent contact with anyone specifically unwell. There was no recent history of travel, nor of animal contact. Her father had worked in a meatworks factory until 8 months previously.

On admission examination, routine haematology and biochemistry were unremarkable. Empirical antibiotics were given for 2 days and stopped when blood cultures returned negative. Her fevers settled and she was discharged home. Two weeks later she was found to have positive cytomegalovirus (CMV) IgM serology, suggesting that this initial fever may have been due to CMV disease, though culture for CMV (blood, urine, throat) was negative.

The patient’s fevers recurred and ganciclovir was started. After 1 week of treatment her fevers had failed to settle and she was admitted for further investigation.

Examination was significant only for a hectic fever pattern (Figure 1). Her creatinine had increased to 0.19 mmol/l and she underwent a renal biopsy, which showed 25–50% interstitial infiltrate and moderate tubulitis (mild acute rejection in the Banff classification). She was given a 3-day course of 500 mg of methylprednisolone daily. This produced complete defervescence, although the fever recurred within 48 h of its cessation.

Chest X-ray on presentation was normal. Abdominal CT scan revealed two isolated segments of thickened bowel wall but no adenopathy or any other abnormalities. Colonoscopic examination was normal, and random colonic biopsies were histopathologically normal. Bone-marrow examination was unremarkable. No positive bacterial, fungal, or viral cultures were obtained from any specimens. She developed marked hypercalcaemia (corrected serum calcium 3.51 mmol/l, reference range 2.25–2.60 mmol/l; ionized calcium 1.69 mmol/l, reference range 1.16–1.26 mmol/l) in the presence of mildly elevated parathyroid hormone levels (7.2 pmol/l, reference range <5.5 pmol/l), which responded to intravenous pamidronate. Gastroscopy revealed moderate reflux oesophagitis. Serum and urine electrophoresis showed no evidence of a paraprotein. Transthoracic echo showed no evidence of vegetations. Serology was negative for toxoplasmosis, ECHO virus, parvo virus, HHV6, hepatitis C and B, measles,
mumps, rubella, Ross River virus, Coxiella, Brucella, adenovirus, HIV, legionella, mycoplasma, histoplasmosis, and Bartonella. Aspergillus and candida precipitins were negative. The patient’s creatinine plateaued at 0.20 mmol/l and repeat transplant biopsy showed no evidence of ongoing rejection. Thyroid function was normal.

A gallium scan revealed focal uptake within the soft tissues of the right calf (Figure 2). Magnetic resonance imaging of this region demonstrated a contrast-enhancing inflammatory mass deep to the soleus muscle within the intermuscular plane (Figure 3). A biopsy was performed which revealed occasional acid-fast bacilli in the presence of a moderate infiltrate of lymphoid cells, activated macrophages, and neutrophils associated with foci of necrosis.

The patient was initially commenced on therapy for a possible atypical mycobacterial infection (clarithromycin and ciprofloxacin), but this was changed to triple antituberculous chemotherapy with rifampicin (600 mg/day), isoniazid (300 mg/day), and ethambutol (800 mg/day) when she failed to respond. At that stage she was still hypercalcaemic but this improved with further pamidronate. Her fever responded within 72 h of initiation of the new antituberculous regimen.

The chest X-ray subsequently became abnormal, with bilateral fine nodular shadowing, confirmed on a high-resolution CT scan of the chest. Transbronchial lung biopsy revealed epitheliod granulomas with acid-fast bacilli. Cultures taken prior to antituberculous therapy of blood, urine, and bone marrow, as well as biopsy of the calf abscess and lung grew Mycobacterium tuberculosis, which was fully susceptible to all first-line antituberculous chemotherapy agents.

She remained well for the following 2 months until she developed an episode of small-bowel obstruction. At laparotomy, a large constrictive ring of tissue at the ileocaecal junction and several large soft lymph nodes were found. A right hemicolecetomy was performed. Histology of the bowel tissue demonstrated an intense mixed inflammatory cellular infiltrate with loosely formed granulomas and large numbers of acid-fast bacilli. Some of the lymph nodes also contained acid-fast bacilli. Mycobacterium tuberculosis was not grown from any of the specimens. Pyrazinamide (1500 mg/day) was added and cyclosporin ceased in view of concern about disease progression.

She recovered from this operation, and has remained well over the ensuing 4 months. She received 2 months of quadruple antituberculous chemotherapy, and has been maintained on isoniazid and rifampicin.
Tuberculosis in renal transplant recipients usually presents with fevers, cough, dyspnoea, malaise, and weight loss [4]. It is commonly disseminated at the time of diagnosis and extrapulmonary tuberculosis is also more commonly seen than in normal hosts [3]. The mean time to diagnosis of tuberculosis after transplantation is generally between 12 and 20 months [4]. However, up to 40% of cases are diagnosed less than 6 months, and 30% greater than 24 months post-transplant. The chest X-ray is abnormal in greater than 80%, with a miliary pattern in 44%. Positive smears and cultures may be obtained from a variety of specimens, although urine and sputum give the highest yield [4].

Therapy for disseminated tuberculosis in renal transplant recipients does not differ from standard therapy, and although a longer duration is usually advocated, the optimal duration is unknown. Renal transplant candidates should be screened for tuberculosis and this subject has recently been reviewed [7].

Mortality attributed to tuberculosis in renal transplant recipients is significant. A review of 130 reported cases found rates of 11% for pulmonary or localized extrapulmonary disease and 37% for disseminated disease [4]. Several individual series of patients, however, report significantly lower mortality rates [4–6].

Musculoskeletal involvement by tuberculosis occurs in up to 3% of all patients, most commonly affecting the spine or single large weight-bearing joints [8]. Case reports have documented tuberculous bone and joint involvement in renal transplant recipients [9,10]. Soft-tissue (tenosynovium, bursa, muscle, or deep fascia) tuberculosis infection, on the other hand, has been rarely reported, and usually occurs in conjunction with adjacent bone or joint infection [8]. Soft-tissue tuberculosis in renal-transplant recipients has only been reported twice: one patient with isolated pyomyositis involving the erector spinae muscle [11], and one with olecranon bursitis [8].

This patient is of interest for a number of reasons. Firstly, the presentation with protracted fevers but no localizing symptoms, unresponsive to broad-spectrum antibiotics and ganciclovir, but responsive to high-dose methylprednisolone, was very suggestive of either mycobacterial infection or malignancy. The utility of the gallium scan in this situation was highlighted as it detected the clinically silent soft-tissue abscess in the calf. This led to the diagnosis being made several weeks prior to the positive mycobacterial blood and urine cultures and the miliary pattern on the chest X-ray. The hypercalcaemia was partially explained by hyperparathyroidism but is also well described with tuberculous infection thought to be a result of peripheral conversion of 25 hydroxyvitamin D3 to 1,25 dihydroxyvitamin D3 by activated macrophages.

Secondly, our patient demonstrated a rapid and favourable response to triple antituberculous chemotherapy despite continued immunosuppression with cyclosporin (dose adjusted according to serum levels in the presence of rifampicin), azathioprine, and prednisolone (also dose adjusted in the presence of rifampicin).

Thirdly, the small bowel obstruction secondary to a constrictive mass of tissue was of interest. This occurred some 2 months after the initiation of antituberculous chemotherapy, during which time the patient had been afebrile, gaining weight and otherwise symptomatically well. She had been compliant with her drug regimen. Although the sampled tissue contained numerous acid-fast bacilli on histopathological examination, cultures were negative. A pretreatment abdominal CT scan had identified areas of thickened bowel wall, which may have represented tuberculous involvement at that stage. The presence of intense inflammatory infiltration suggests that the mass represented a reactive immune response to tuberculosis at that site, rather than progressive disease. This paradoxical relapse has been described with tuberculous infection of the peritoneum, gut, lymph nodes and meninges.

Fourthly, three possibilities exist for the source of the infection. Our patient was unlikely to have been exposed to tuberculosis early in her life in view of the negative PPD skin test performed 4 years prior to transplantation, the absence of history of tuberculosis exposure, and the normal chest X-ray. It is possible, but unable to be proved, that she was unknowingly exposed in the subsequent pretransplant interval or in the post-transplant period. Similarly, it remains speculative that she obtained the infection from her mother’s donated kidney. Her mother has been subsequently investigated, with a negative PPD skin test and negative urine smears and cultures. Australia has a low incidence of tuberculosis of 5.4 per 100,000 but this falls to 1.7 per 100,000 for those born in the United Kingdom.

In summary, this case represents an unusual presentation of miliary tuberculosis with a clinically silent but radiologically obvious soft-tissue tuberculous abscess in the calf. Successful response was obtained with a multidrug regimen, despite continuing immunosuppression allowing maintenance of renal transplant function.

All prolonged fevers in transplant recipients should arouse suspicion of mycobacterial infection, even in those assessed as at low risk of latent tuberculosis reactivation. All soft-tissue masses should be investigated with smears and cultures for mycobacteria.

References


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