CASE REPORT

Multi-organ failure due to *Mycobacterium tuberculosis* and *Aspergillus flavus* infection after allogeneic bone marrow transplantation

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Abstract *Mycobacterium tuberculosis* (MT) is a serious, but rare infectious complication after allogeneic bone marrow transplantation (BMT). We describe a case of fatal sepsis due to MT and *Aspergillus flavus* after allogeneic BMT for Aplastic Anemia. The diagnosis was made on bone marrow biopsy and asitic fluid culture. Broad-spectrum antituberculous and Amphotericin B therapy was started immediately after diagnosis. The patient developed severe hypoxia and finally died of multi-organ failure. Rapid progression of mycobacterial infection as well as fungal infection should be considered in patients post BMT with unexplained fever, particularly in patients from endemic areas.

Keywords Allogenic BMT · *Mycobacterium tuberculosis* · *Aspergillus flavus*

Introduction

Allogeneic BMT patients have severely impaired cell mediated immunity as a result of their underlying illness, pre-transplant conditioning chemotherapy, and radiation. However, in comparison with solid organ transplant recipients, mycobacterial infection after allogeneic BMT is an uncommon complication. Here we report an interesting case of tuberculosis and aspergilosis in a patient of Aplastic anemia (AA).

Case report

A 37-year-old male was diagnosed as severe AA in October 2006. He was treated with Horse Anti Thymocyte Globulin (ATG) and Cyclosporine (CsA), there was no response after 4 months, and meanwhile HLA identical sibling brother was identified. Peripheral blood stem cell transplantation was done in March 2007. Conditioning consisted of fludarabine, cyclophosphamide and ATG (FLU/Cy/ATG). GVHD prophylaxis was CsA plus methotrexate. He infused 7.1×10^6 /kg of CD34 cell dose. Engraftment was attained on day 10. He developed acute CsA toxicity. CsA was discontinued and put on Mycophenolate Mofetil (MM). His post-transplant course was complicated by chronic GVHD of liver and skin (grade II) which was treated with prednisolone (2 mg/kg bodyweight).

In October 2007 the patient was readmitted with high grade fever and fatigue while he was still being treated with MM and prednisolone. Physical examination was normal; laboratory tests revealed leucopenia with WBC

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of $1.6 \times 10^9 / l$ (94% granulocytes, 3% monocytes and 3% lymphocytes) and elevated liver enzymes. Chest X-ray was normal. Broad-spectrum antibiotics were started because of FUO. The fever resolved, but during treatment the patient became increasingly leukopenic ($0.9 \times 10^9 / l$). Three days later he again developed a fever of $102^\circ F$ and complained of shortness of breath. He had normal breath sounds, but his respiratory rate was increased and an arterial blood gas showed severe hypoxia (pH 7.40, pCO₂ 22.75 mmHg, pO₂ 55.25 mmHg, base excess 1.6 mmol/l, oxygen saturation 88.5%). A high resolution CT revealed multiple small pulmonary nodules and infiltrates involving both the lung fields. Further antibiotics and amphotericin B were added, but his respiratory function worsened dramatically and he developed ascites. A chest X-ray 3 day later showed diffuse bilateral infiltration with bilateral small pleural effusion. CT of abdomen revealed free fluid of abdomen, multiple small splenic abscess. Tissue biopsy was done; send for fungal and tubercular culture. Diagnostic abdominal paracentesis was done and fluid sent for all cultures. A Gram stain and Ziehl–Neelson stain were normal. CMV PCR and pp65 antigen test were negative. BM aspiration and biopsy (BMA & BX) revealed bone marrow necrosis, multiple epithelioid granuloma and Ziehl–Neelson stain showed many acid-fast bacilli (AFB) (Figs. 1 and 2). Therapy with rifampicin, ethambutol, isoniazid, pyrazinamide was started. The bacteria were identified as *Mycobacterium tuberculosis* by successful PCR amplification from ascitic fluid. Despite the anti-tuberculous therapy the patient did not improve. He developed temperatures but repeated blood cultures became negative. He was transferred to the intensive care unit, incubated and ventilated. A BAL was performed and all the tests were normal. Five days later he died of multi-organ failure. Seven days later fungal culture grew *Aspergillus flavus*. Twelve days later the PCR result was confirmed by conventional microbiological methods. Susceptibility testing showed that the strain had been susceptible to all the anti-tuberculous drugs.

Discussions

Mycobacterial infections are common in people with impaired cell-mediated immunity. In a 20-year retrospective review mycobacterial infections were identified in only nine of 1486 allogeneic transplant patients (prevalence 0.6%) [1]. A recent report from India described Tuberculosis was seen in 1.7% of pediatrics transplant patients [2]. Another report from India Tuberculosis was documented in 2.3% of the transplant patients [3]. They can presents with fatal sepsis as reported by Kindler, T et al [4]. Fungal

Fig. 1 Haematoxyline and Eosin stained Bone marrow (BM) biopsy showing BM necrosis and granuloma (40x)

Fig. 2 Ziehl–Neelson stained Bone marrow biopsy showing acid-fast bacilli (100x)

infection with *aspergillus* is common in BMT recipient. The incidence of fungal infection was 15.9% and commonly due to (69.7%) *aspergillus* species [3].

In immuno-compromised patient concurrent tubercular and fungal infections are very fatal. In our patient granulomas and AFB were documented in BX which is very rare finding and very few cases were reported. Early diagnosis of *Mycobacterium tuberculosis* infection and fungal infection in BMT recipients can be difficult, because patients are severely immuno-suppressed and often neutropenic. These factors can mask the febrile response to infection and possibly obscure typical tissue findings such as granulomatous reaction [5]. The patient described here died of fulminant tuberculous and fungal sepsis. Because of his chronic GVHD (grade II) he was receiving immunosuppressive therapy with MM and prednisolone.

In conclusion, rapid progression of mycobacterial infection should be considered early in the differential diagnosis of patients post BMT with unexplained fever, particularly in patients from endemic countries.

References

1. Roy V and Weisdorf D (1997) "Mycobacterial infections following bone marrow transplantation: a 20 year retrospective review." *Bone Marrow Transplant* 19(5): 467–470
2. George BV, Mathews et al (2006) "Infections in children undergoing allogeneic bone marrow transplantation in India." *Pediatr Transplant* 10(1):48–54
3. George BV, Mathews et al (2004) "Infections among allogeneic bone marrow transplant recipients in India." *Bone Marrow Transplant* 33(3):311–315
4. Kindler TC, Schindel et al (2001) "Fatal sepsis due to mycobacterium tuberculosis after allogeneic bone marrow transplantation." *Bone Marrow Transplant* 27(2):217–28
5. Aljurf MM, Gyger et al (1999) "Mycobacterium tuberculosis infection in allogeneic bone marrow transplantation patients." *Bone Marrow Transplant* 24(5):551–554