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Infections post transplant

Tuberculosis among allogeneic bone marrow transplant recipients in India

B George[1], V Mathews[1], V Srivastava[2], A Srivastava[1] and M Chandy[1]

Departments of [1]Hematology and [2]Pathology, Christian Medical College and Hospital, Vellore, Tamil Nadu, India

Summary:

Allogeneic bone marrow transplant recipients have severe impairment of cell-mediated immunity and hence a higher incidence of mycobacterial infections might be expected in regions where tuberculosis is common. We reviewed the case records of 217 patients who underwent allogeneic bone marrow transplantation during the period 1986–1999 at our center in India. Mycobacterial infections were diagnosed in three patients (1.38%). All patients presented with extrapulmonary disease. Two patients had disseminated tuberculosis with one of these being diagnosed on autopsy studies. The third patient had tuberculosis involving the cervical lymph node and dorsal spine. Two patients treated with antituberculous therapy are well. Infection with *Mycobacterium tuberculosis* is not a common problem in allogeneic bone marrow recipients even in an endemic area, but when it occurs, it is usually disseminated with predominantly extrapulmonary involvement.
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Tuberculosis is a major health problem in India with an annual incidence of 250–500 per 100 000 population and a prevalence of 2% of the total population over 10 years of age.[1] Patients who undergo allogeneic bone marrow transplantation (BMT) have severely impaired cell-mediated immunity as a result of their underlying disease, conditioning chemotherapy and radiation, graft-versus-host disease (GVHD) and its treatment.[2] A high incidence of tuberculosis could be expected in such patients especially in areas where tuberculosis is common. Large series from Europe and North America reviewing infections in BMT patients have reported incidences varying <0.1 to 2.2%,[3,4] while reports from areas with a high prevalence of tuberculosis have reported incidences varying from 1.5% to 5%.[5,6] We reviewed the case records of all patients who underwent allogeneic BMT at our center from 1986 to 1999 to study the incidence of tuberculosis in allogeneic bone marrow recipients in India.

Correspondence: Dr B George, Department of Hematology, Christian Medical College and Hospital, Vellore, 632004, Tamil Nadu, India
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Materials and methods

All patients who underwent allogeneic bone marrow transplantation at our center between 1986 and 1999 were included in the analysis. Their case records were reviewed to study the incidence of tuberculosis. The follow-up period ranged from 2 to 120 months post BMT. All patients were nursed in HEPA filtered rooms with positive pressure ventilation during conditioning chemotherapy and in the immediate post-transplant period until the absolute neutrophil count (ANC) was $>500/mm^3$. Antimicrobial prophylaxis given during the period of BMT consisted of fluconazole and acyclovir. Cotrimoxazole was added after the ANC was $>1000/mm^3$ in all recipients. GVHD prophylaxis consisted of cyclosporine and short course methotrexate.[7]

A diagnosis of tuberculosis was made on the basis of: (1) Positive AFB culture for mycobacterium tuberculosis; (2) biopsy showing caseous necrosis with granulomas suggestive of tuberculosis.

Results

Of the 217 patients who underwent allogeneic BMT during the period 1986–1999, three developed tuberculosis.

Their clinical characteristics are shown in Table 1.

UPN 41

A 7-year-old male with ALL in CR2 presented 445 days after allogeneic BMT with pain and swelling in the neck and fever of 3 weeks duration. MRI scan of the spine showed contiguous destruction of C7-D3 spine with anterior wedging and a resultant spinal gibbus deformity at D1. A cervical lymph node biopsy was consistent with tuberculosis. Lymph node samples were positive for AFB bacilli and cultures confirmed the presence of *Mycobacterium tuberculosis*. The patient was given antituberculous therapy (ATT) for 18 months with complete resolution of his symptoms. He is presently 6 years post BMT and in complete remission with no evidence of ALL or tuberculosis.

Table 1 Clinical characteristics

UPN No.	*41*	*123*	*164*
Age/Sex	7/M	3/M	40/M
Diagnosis	ALL	Thalassaemia major	MDS with fibrosis
Conditioning regimen	Bu/Cy	Bu/Cy	Bu/Cy
Acute GVHD and grade	Oral mucosa grade II	Skin and GI tract grade III	Nil
Chronic GVHD	Nil	Nil	Nil
Diagnosis of TB, day post BMT	445	81	13
Therapy at onset of TB	Nil	CSA	CSA
Site of tuberculosis	Cervical spine, lymph node	Liver, bone marrow	Lung, liver, bone marrow, spleen
Diagnosis	Biopsy and culture positive from lymph node	Biopsy positive from liver and bone marrow	Biopsy, post mortem
Resolutions of symptoms	Yes	Yes	Expired

TB = tuberculosis; ATT = anti-tuberculous treatment.

UPN 123

A 3-year-old male with thalassemia major presented 81 days after allogeneic BMT with fever of 2 weeks duration. He had been treated for a primary complex at the age of 1 year with ATT for 6 months. He was receiving cyclosporine for grade III acute GVHD at the time of the fever. He was evaluated and diagnosed to have disseminated tuberculosis on the basis of granulomas in the liver and bone marrow biopsies. He has received 1 year of antituberculous therapy and is well 40 months post BMT.

UPN 164

A 40-year-old male was diagnosed to have myelodysplastic syndrome with fibrosis of the bone marrow, on evaluation for pancytopenia and fever. He was extensively investigated for the cause of the pyrexia, but no etiology could be established. He had received steroids (prednisolone 1 mg/kg) for 4 weeks as therapy for his pancytopenia with a cellular marrow. He had an allogeneic BMT and died on day 13 post BMT with progressive pulmonary infiltrates and jaundice. Autopsy showed multiple necrotizing granulomata with caseous necrosis and Langhan's giant cells in the liver, lung, spleen, hilar lymph nodes and bone marrow, suggestive of tuberculosis along with disseminated aspergillus and candida. AFB cultures were not undertaken, but AFB stains on the autopsy specimens were positive for acid fast bacilli.

All patients had extrapulmonary or disseminated tuberculosis. Both the patients with an antemortem diagnosis of tuberculosis responded well to appropriate therapy with antituberculous drugs with complete resolution of symptoms.

Discussion

There are few reports on the incidence of tuberculosis in BMT recipients. The majority of the studies have reported incidences varying from 0.1 to 2.2%, while only a single study from Hong Kong has reported a much higher incidence of tuberculosis close to 5%.[2–4,8,9] It is generally believed that an immunosuppressed state will magnify the infectious diseases that are endemic in a locality and since Asian countries have a higher incidence of tuberculosis, one would expect the incidence of tuberculosis to be higher in such populations.

Chronic GVHD, immunosuppressive therapy and total body irradiation (TBI) have been shown to be risk factors associated with the development of tuberculosis.[10,11] Patients with chronic GVHD have a marked delay of T cell subset recovery with low numbers of $CD4^+$ cells being present.[12] This period of impairment of T cell function may be indefinite in the presence of chronic GVHD. Immunosuppression results in failure to acquire adoptive immunity, while TBI hampers normal function of alveolar macrophages. Both contribute to an increased predisposition to tuberculosis.[13] The number of patients with tuberculosis is too small in our series to allow any correlation.

The incidence of tuberculosis in our patients of 1.38% is similar to the incidence described in other series, but is lower than figures reported from Hong Kong.[5] One patient (UPN 123) was treated for primary complex at the age of 1 year and had reactivation of tuberculosis, while the other two patients had primary progressive tuberculosis. All the patients had normal chest radiographs prior to BMT. Interestingly, all patients who developed tuberculosis had predominantly extrapulmonary forms of tuberculosis with two patients having disseminated disease and one developing spinal and lymph node involvement. This pattern of infection is analogous to the forms of tuberculosis seen in patients with HIV infection and in renal transplant recipients, where an increased incidence of extrapulmonary forms of tuberculosis has been reported.[14–16] The early reactivation and presentation of tuberculosis in one patient in this series may have been because of the steroids he had received prior to BMT. The other two patients responded very well to long-term antituberculous therapy in spite of extrapulmonary manifestations. One patient (UPN 41) had culture proven *Mycobacterium tuberculosis*, while patient

(UPN 164) had smears positive for acid fast bacilli and the third patient (UPN 123) had necrotizing granulomata in the liver and bone marrow. Although cultures are not available in the other two patients, in a country endemic for tuberculosis presence of acid fast bacilli on a smear is considered to represent *Mycobacterium tuberculosis* only and not to be due to atypical mycobacteria such as *Mycobacterium avium intracellulare* (MAIC) or *Mycobacterium kansasii* (WHO Guidelines for Clinicians in South East Asia).[17] In the patient with disseminated granulomata, there was a good response to four standard anti-tuberculous drugs with complete resolution of symptoms. This is the first report of disseminated tuberculosis occurring in allogeneic bone marrow transplant recipients.

The incidence of tuberculosis in allogeneic bone marrow transplant recipients in this series from India is low. Prophylactic INH does not seem to be warranted in patients undergoing allogeneic BMT in India. Since most patients present with extrapulmonary forms of tuberculosis, a high degree of suspicion and early identification is required to allow antituberculous therapy to be started as soon as possible.

References

1 Annual Report 1997–98. Government of India. DGHS: New Delhi.
2 Wingard JR. Opportunistic infections after blood and bone marrow transplantation. *Transplant Infect Dis* 1999; **1**: 3–20.
3 Navari M, Sullivan KM, Springmeyer SC *et al*. Mycobacterial infections in bone marrow transplant patients. *Transplantation* 1983; **36**: 509–513.
4 Kurzrock R, Zander RA, Vellekoop L *et al*. Mycobacterial pulmonary infections after allogeneic bone marrow transplantation. *Am J Med* 1984; **77**: 35–40.
5 Ip MS, Yuen KY, Chiu EK *et al*. Pulmonary infections in bone marrow transplant transplantation; the Hong Kong experience. *Respiration* 1995; **62**: 80–83.
6 Roy V, Weisdorf D. Mycobacterial infections following BMT: a 20 year retrospective review. *Bone Marrow Transplant* 1997; **19**: 467–470.
7 Storb R, Deeg HJ, Whitehead J *et al*. Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft-versus-host disease after marrow transplantation for leukemia. *New Engl J Med* 1986; **314**: 729–735.
8 Arslan O, Gurman G, Dilek I *et al*. Incidence of tuberculosis after bone marrow transplantation in a single center from Turkey. *Hematologia Budap* 1998; **29**: 59–62.
9 Aljurf M, Gyger M, Alrajhi A *et al*. *Mycobacterium tuberculosis* infection in allogeneic bone marrow transplantation patients. *Bone Marrow Transplant* 1999; **24**: 551–554.
10 Atkinson K. Reconstitution of the hematopoietic and immune systems after marrow transplantation. *Bone Marrow Transplant* 1990; **5**: 209–226.
11 Ip MS, Yuen KY, Woo PC *et al*. Risk factors for pulmonary tuberculosis in bone marrow transplant recipients. *Am J Resp Crit Care Med* 1998; **158**: 1173–1177.
12 Friedrich W, O'Reilly RJ, Koziner B *et al*. T-lymphocyte reconstitution in recipients of bone marrow transplants with or without GVHD: imbalances on T-cell subpopulation having unique regulatory and cognitive function. *Blood* 1982; **59**: 696–701.
13 Lum LG, Seigneuret MC, Orcutt-Thordarson N *et al*. The regulation of immunoglobulin synthesis after HLA identical bone marrow transplantation. *Blood* 1985; **65**: 1422–1433.
14 Barnes PF, Bloch AB, Davidson PT *et al*. Tuberculosis in patients with human immunodeficiency virus infection. *New Engl J Med* 1991; **324**: 1644–1649.
15 Patel R, Roberts GD, Keating MR *et al*. Infections due to nontuberculous mycobacteria in kidney, heart and liver transplant recipients. *Clin Infect Dis* 1994; **19**: 263–273.
16 Delany V, Sumrani N, Hong JH *et al*. Mycobacterial infections in renal allograft recipients. *Transplant Proc* 1993; **25**: 2288–2289.
17 WHO. *TB – A Manual for Clinicians in South East Asia*. Jaypee Brothers: Calcutta, India, 1997.