Case Report

Pulmonary tuberculosis in allogeneic stem cell transplant recipients

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Abstract

Mycobacterium tuberculosis is a serious, but rare infectious complication after allogeneic bone marrow transplantation. Tuberculosis is a major problem in South East Asia, particularly in India and Pakistan. We describe here infection due to mycobacterium tuberculosis in four patients after allogeneic stem cell transplantation (Allo SCT). The diagnosis was made on the bases of clinical findings, sputum / blood / pleural and pericardial fluids / broncho alveolar lavage (BAL) and tissue biopsy examination. Anti tuberculosis therapy (ATT) was started immediately after diagnosis. Three patients responded to antituberculosis therapy, where as one patient developed severe infective respiratory complications and died at six months post transplant. Mycobacterial infection should be considered in patients post allo SCT with unexplained fever, cough or pleuritic chest pain. These patients at diagnosis should be promptly treated with ATT.

Introduction

Allogeneic Stem Cell Transplantation (Allo SCT) is the most effective treatment for a number of haematological disorders. Opportunistic infections are one of the main causes of morbidity and mortality after SCT and the successful outcome of SCT is largely determined by infectious complications. According to IBMTR data (1996-2000), infections contributed 17% of deaths in allogeneic SCT and 21% in autologous SCT.[1]

In an area where tuberculosis (TB) is endemic, the general population is exposed to the tubercle bacillus for its whole life. However, initial host response can effectively eradicate the bacillus. Bacilli may become dormant without causing clinical disease, such that this is regarded as latent infection manifesting only by a positive tuberculin skin test.[2] This latent infection can become reactivated once host immunity is low. For allo SCT recipients acquiring GVHD, the dysregulation of immune T cells would render these patients immunologically unable to defend themselves against Opportunistic infections including Mycobacterium tuberculosis.[3]

Pulmonary TB should be considered as a significant opportunistic infection post SCT in an endemic area. However, timely diagnosis may be difficult due to the nonspecific presentations of the disease. Therefore, a strict standardized diagnostic and monitoring strategy should be developed for the management of pulmonary TB in allo SCT recipients. A consensus for prophylactic treatment of latent pulmonary TB infection in candidates for and recipients of allo SCT should be set up as soon as possible to improve patient outcomes.[4]

Patient-I

A 40 years old male with Philadelphia chromosome positive CML was evaluated in our hospital for allo SCT in Nov 2001. During pretransplant assessment tuberculin test was found to be strongly positive (20mm). He was treated with antituberculosis treatment for 8 weeks and later on he received allo SCT from his sibling brother in Feb 2002 after conditioning with busulphan 4mg/kg daily for 04 days followed by cyclophosphamide 60mg/kg daily for next two days. Cyclosporine (5mg/kg daily) was used as GvHD prophylaxis and antituberculosis prophylaxis with isoniazid (INH) also continued. Early haematological recovery with ANC > 0.5x109/l was observed on day +12 post SCT. Immuno suppressive prophylaxis with Cyclosporin and prophylaxis against tuberculosis with INH continued for 09 months. Patient had smooth and uneventful post transplant recovery. However, after 01 year post SCT, he started having low grade fever and cough, not responding to broad spectrum antibiotics. Radiological examinations of chest showed opacities in right apical region. Sputum C/S examination revealed the growth of multi drug resistant mycobacterium tuberculosis. He was treated with 2nd line ATT with clarithromycin, amikacin, rifampicin, INH and ethambutal. After 03 months, amikacin was replaced with sparfloxacin and antituberculosis treatment continued for 09 months. At > 4 years post SCT patient is having normal healthy life.

Patient-II

A seventeen years old boy with severe aplastic anaemia received allo SCT from his HLA matched sibling brother in March 2002. During pretransplant assessment ECG was within normal limits. Echocardiogram showed good L.V function with ejection fraction of 80%. He received conditioning with cyclophosphamide 50mg/kg daily for 4 days and Anti thymocyte globulin

(lymphoglobulin - sangstat - Lyon, France) 15mg / kg body weight for 3 days. Patient developed high grade fever (1020F) during conditioning and was treated with Ceftriaxone and Amikacin. Early allogeneic engraftment (ANC >0.5x109/l) started on day +15 post SCT. Patient developed retrosternal chest pain and severe breathlessness on day +19 post SCT. His heart rate was 130 beats /minute and was tachypnoeic (respiratory rate 40/min). Radiological examination of chest revealed right sided pleural effusion. Pleural fluid (500ml) was drained under ultrasound guidance. Echocardiogram revealed moderate degree of pericardial effusion with cardiac temponade. The very next day pericardiocentesis was performed and 300ml of straw coloured fluid was drained. Both Pleural and pericardial fluids examination revealed raised cell counts (> 8000/cmm) with lymphocytosis and presence of acid fast bacilli. Patient was started on ATT. Effusions gradually resolved and on day +45 patient was discharged from hospital with regular follow up in out patient department. ATT continued for next 06 months. Today at >4 years post SCT, patient is enjoying a normal healthy life.

Patient-III

A 5 years old boy with Beta Thalassaemia Major received Allo SCT from his HLA matched sibling sister in April 2002. He was transplanted after conditioning with Busulphan 3.5 mg/kg daily for four days followed by cyclophosphamide 50 mg/kg daily for next 04 days. From day -2 of conditioning he received Cyclosporin (5 mg/kg daily) as prophylaxis against GVHD. Early haematological recovery (ANC >0.5 x 109/l) started on Day + 11 Post SCT. Allogeneic engraftment was confirmed from bone marrow aspiration done on Day + 21. He was discharged from the hospital on D+25 with regular follow-up in out patient department. The patient remained asymptomatic till day + 96 post SCT when he was again admitted with 03 days history of cough and high-grade fever associated with rigors with no focal sign of infection. Patient was started on Inj cefipime and amikacin. Spikes of high-grade fever continued. Repeated blood cultures and peripheral blood smears for malarial parasite were negative. The radiological examination of chest was also normal. However on clinical grounds, he was given a course of antimalarials and amphotericin B was also added in therapeurtic doses (1mg/kg daily). Repeat X-Ray chest revealed widening of mediastinum in the paratracheal region. CT scan chest also confirmed soft tissue density mass in the right paratracheal region in superior mediastinum extending to the middle mediastinum. Mediastinal tissue biopsy by mediastinostomy was carried out under G.A and tissue sent for histopathalogical examination. Sputum for direct AFB microscopy, C/S, and Fast plaque test for AFB along with blood for mycobacterium tuberculosis PCR was sent for analysis. Keeping in view the possibility of tuberculous lymphadenitis, patient was empirically put on ATT. Meanwhile patient also developed right sided pneumonic

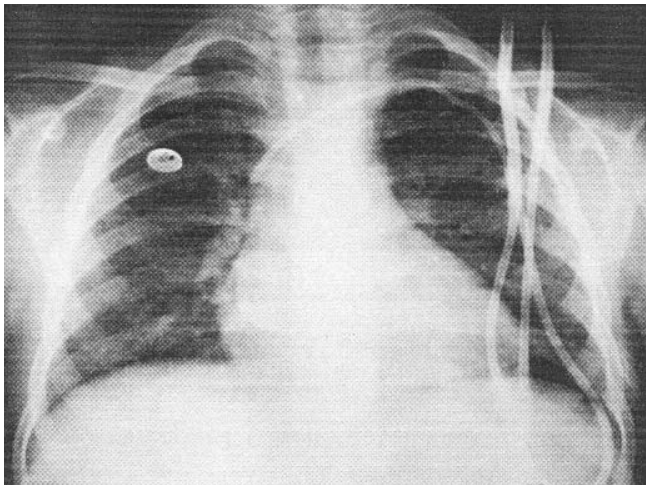

Figure 1. chest radiograph at the time of transplant (hickman line in position).

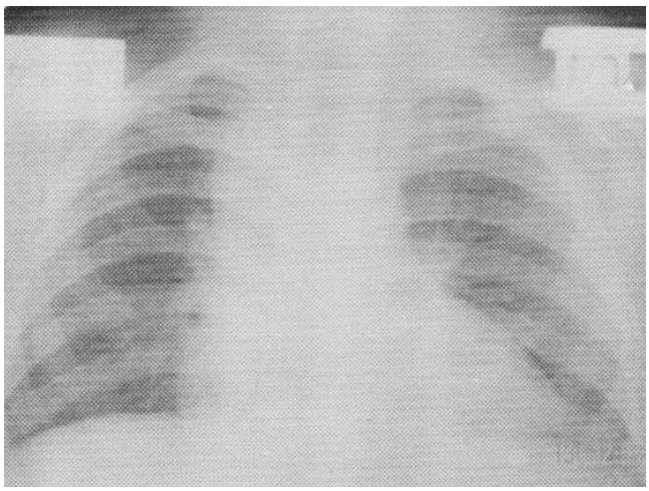

Figure 2. Chest radiograph showing widening of superior mediastinum.

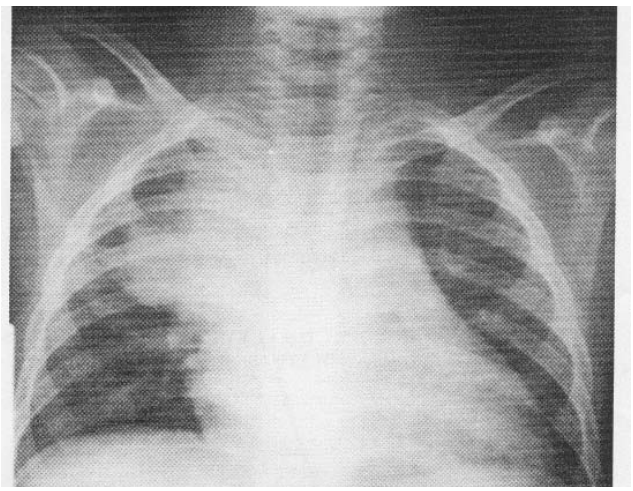

Figure 3. Chest radiograph with wide superior mediastinum and apical opacity right lung.

consolidation. Histopathological examination report of the mediastinal mass revealed chronic caseating granulomas. PCR for mycobacterium tuberculosis DNA was also positive. Patient's condition continued deteriorating despite treatment and died on day + 124 post SCT.

Patient-IV

A 36 years old female with Philadelphia chromosome positive CML received allo SCT from her sibling brother in April 2002 after conditioning with Busulphan 4mg/kg daily for four days and cyclophosphamide 60mg/kg daily for next two days. Early engraftment was observed on Day+15 with ANC>0.5 x109/l. Patient was discharged from hospital on day+21 post SCT with regular follow-up in out patient department. One month later she was admitted with difficulty in breathing, cough and low grade fever. Physical examination revealed decreased breath sounds in right lower chest and radiological examination of chest confirmed the diagnosis of right sided pleural effusion. Diagnostic pleural fluid examination revealed lymphocytosis with raised proteins along with acid fast bacilli on direct microscopy. PCR for mycobacterium tuberculosis DNA was also found positive.

She was put on four drug ATT. She responded very well and pleural effusion resolved completely within next 06 weeks. ATT was continued for 06 months. Thereafter she was given INH prophylaxis for next 06 months. She is now enjoying a healthy life at > 4 years post SCT.

Discussion

Although TB in allogeneic SCT recipients is not a major challenge in developed countries but the situation is different in developing countries due to high prevalence of disease in general population. Every year over eight million people in the world develop active tuberculosis of whom 2 million die, mostly in developing countries. The prevalence of tuberculosis in Pakistan is more than 1% with 0.26 million new cases occurring every year. Allogeneic stem cell transplantation (SCT) is associated with severe immunosuppression and transplant recipients are susceptible to various types of opportunistic infections including tuberculosis (TB) during post transplant period. Patients with impaired cell-mediated immunity are at high risk of severe infectious complications. In a 20 years retrospective review mycobacterial infections were identified in only nine of 1486 allogeneic transplant patients (prevalence 0.6%).[5] Opportunistic infections of varying severity occur in >90% of patient after allogeneic SCT and contribute significantly to morbidity and mortality after engraftment.[6] Fatal opportunistic infections have been reported in 4-15% of related transplant recipients and 12-28% of unrelated transplant recipients.[7]

Tuberculosis following allo SCT has been demonstrated to be a significant problem in endemic countries with an incidence of 0.1-5.5%.4 Incidence of active tuberculosis after allo SCT has been reported in 3.1% patients from Korea.[8] Similarly in Turkey, where tuberculosis is endemic, a 30-40 times higher incidence has been reported in body mass index (BMT) patients compared to general Turkish population.[9] A study from Taiwan shows a trend towards increased risk of having pulmonary tuberculosis in allo SCT as compared to auto SCT (4.8+ 1.8% vs 0).4 In 2001, George B et al from Vellore India reported 1.38% and 2.2% incidence of tuberculosis in transplant recipients. However, updated data from the same centre in 2006 show 1.7% tuberculosis in transplant patients.[10]

Since tuberculosis is prevalent in our country, all patients and donors are screened for tuberculosis and anti tuberculosis prophylaxis is included in our transplant patients which seemed beneficial as only four patients out of 154 who underwent allo SCT. From our experience, we recommend anti-tuberculosis prophylaxis for transplant patients in other centres of our country as well as countries where this disease is prevalent.

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 or with a positive family history.

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