



Case Report

Tuberculosis in hematopoietic stem cell transplant patients: case report and review of the literature

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ABSTRACT

The literature describing tuberculosis (TB) in hematopoietic stem cell transplant (HSCT) recipients is scant, even in countries where TB is common. We describe a case of pulmonary TB in a patient who underwent HSCT and review the English language literature on this subject. An extensive PubMed and Ovid search was undertaken for the period January 1980 to March 2009; the search terms used were 'Mycobacterium tuberculosis' or 'tuberculosis', in combination with 'hematopoietic stem cell transplantation' or 'bone marrow transplantation'. The patient in the present case report underwent allogeneic transplantation and developed TB 8 days after his HSCT. The patient had received vaccination against TB in childhood. During the year prior to the HSCT he had had contact with a relative who had pulmonary TB. On day 3 of anti-TB treatment he developed pericarditis. The patient received anti-TB treatment for 6 months without major problems. From the literature review, we found 34 related studies, 25 on the clinical manifestations of TB. Most of the reports were from Asia (48%), and the incidence of TB varied from 0.0014% in the USA to 16% in Pakistan. TB occurred at between +21 and +1410 days post-HSCT (257.2 days the median), and the lung was the organ most frequently involved. Mortality varied from 0% to 50% and was higher in allogeneic HSCT. There is no consensus regarding screening with the tuberculin skin test or primary prophylaxis for latent TB, and further research into this is necessary in developing countries with a high prevalence of TB.

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1. Introduction

Hematopoietic stem cell transplant (HSCT) recipients have severe impairment in cell-mediated immunity as a result of the conditioning regimen used, immunosuppressive therapy, and graft-versus-host disease (GVHD).^{1,2} Accordingly, they are susceptible to bacterial, viral, and fungal infections.^{1,2} Mycobacterial infections can also occur in these patients, although the incidence is not high, even in countries where tuberculosis (TB) is common.² Data from the USA show that the incidence of Mycobacterium infection among HSCT recipients ranges from 0.0014% to 3%.^{1,3–5} Countries in which the prevalence of TB in the general population is higher than in the USA have reported incidences varying from 1.6% in Spain⁶ and Turkey,⁷ to 8.57% in Hong Kong and Taiwan and 16% in Pakistan.^{8–11}

We describe herein a case of pulmonary and probable pericarditis TB in a patient who underwent HSCT, and review the English language literature on this subject.

2. Review methodology

2.1. Literature search

An extensive PubMed and Ovid search was performed using the search terms 'Mycobacterium tuberculosis' or 'tuberculosis', in combination with 'hematopoietic stem cell transplantation' or 'bone marrow transplantation', and 'allogeneic and autologous transplant'. A specific search for 'pericarditis due to Mycobacterium tuberculosis' and 'hematopoietic stem cell transplantation' or 'bone marrow transplantation' was performed.

Studies that focused on stem cell transplantation for other diseases, such as autoimmune or solid tumor, were excluded. The search was performed for the period January 1980 to March 2009.

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Figure 1. Computed tomography (CT) scan of the chest showing budding. A new chest CT at 3 days after the onset of pulmonary symptoms, on day 11 post-HSCT, showed pericardial and pleural effusion.

2.2. Study selection

Eligible studies consisted of all those that linked TB with hematological patients who underwent stem cell transplantation and that described a case report or incidence/prevalence of TB in this patient population. There were no requirements for a minimum number of patients or for study design.

3. Case report

During the year 2007, 235 HSCT were performed at the Hospital das Clinicas of the University of São Paulo. Only one case of TB was documented during this period.

A 21-year-old man, born in the northeast of Brazil, who was diagnosed with severe aplastic anemia in August 2007, underwent a sibling human leukocyte antigen (HLA) full matched allogeneic HSCT on September 24, 2007. The patient received busulfan (4 mg/kg) and cyclophosphamide (200 mg/kg) as conditioning treatment, and prophylaxis with acyclovir, fluconazole, and cefepime. The patient developed fever on day 3 following the HSCT. The cefepime was replaced progressively with meropenem, teicoplanin, polymyxin B, and voriconazole. Despite a normal chest X-ray in his HSCT pre-screening, he developed fever and pulmonary symptoms (chest pain, dyspnea and hypoxemia without cough) 8 days after the transplant. A chest computed tomography (CT) scan showed an image suspicious of TB (tree-in-bud), and sputum examination revealed the presence of acid-fast bacilli (AFB; +++/4) (Figure 1). The patient had received vaccination against TB in childhood. During the year prior to the HSCT he had had contact with an aunt who had diagnosed pulmonary TB. The prescribed antibiotics were interrupted and he was started on alternative anti-TB treatment (ATT) with isoniazid, ethambutol, and ofloxacin, because he had a total bilirubin level of 3.0 mg/dl. After 3 days of treatment he developed symptoms of pericarditis, and an electrocardiogram revealed inversion of the T wave. A new chest CT (Figure 1) and an echocardiogram showed pericardial effusion without cardiac tamponade. Since the patient had a low platelet count, the pleural and pericardial fluids could not be examined. Prednisone 40 mg/day was added to his ATT at this time.

On day +16 post-HSCT, his bilirubin level was normal and the alternative ATT was replaced with first-line medication (rifampin, isoniazid, pyrazinamide). After 8 days of this ATT, the patient was afebrile with a significant improvement in his symptoms and was discharged. Despite the positive AFB smear, three mycobacterial cultures remained negative. The patient received the ATT for 6 months without major problems.

4. Results of the review

Thirty-four articles were identified in our literature search. However, only 25 described TB in hematological patients who had

undergone HSCT.^{1,3–5,7–10,18–33} Four studies concerned TB screening with the tuberculin skin test (TST) and prophylaxis,^{12–15} one involved an animal model,¹⁶ and one was on the subject of genetic susceptibility to *Mycobacterium*.¹⁷ Among the 25 studies on TB infection in HSCT recipients, 12 (48%) were from Asia,^{8–10,19,21,22,24,25,27,31–33} five from the USA,^{1,3–5,23} five from Europe,^{6,7,28–30} one from Australia,²⁶ one from the Middle East,¹⁸ and one from Latin America²⁰ (Table 1). The incidence of TB in HSCT ranged from 0.0014% to 16% (Table 1). The time to diagnosis of TB varied from +21 to +1410 days (median 257.2 days) after the HSCT. The lung was the organ most frequently involved (Table 1). There were only two reports of pericarditis.^{19,25} Most of the TB cases were described in relation to allogeneic HSCT, and the mortality in this type of HSCT was high, ranging from 0% to 50% (Table 1).

5. Discussion

The present report describes a case of pulmonary TB and probable pericarditis due to TB that was diagnosed early (8 days) after the allogeneic HSCT. There are few reports of a diagnosis of TB during the first two weeks post-HSCT (Table 1). Most cases of TB described in the literature occurred more than 90 days after HSCT.² The diagnosis of TB in the present report was made only by the positive AFB smear result. Unfortunately, three mycobacterial sputum cultures from our patient remained negative. A positive AFB smear with negative culture could be considered a laboratory failure to isolate *Mycobacterium*.^{35–37} In reports in the literature, positive AFB smear with negative cultures occurs in 0.5% to 25.6% of cases.^{2,35–37} A recently published review of 56 cases of TB among HSCT recipients, showed that only 55% of cases were diagnosed with culture. Histology (20.3%) was the second most common approach for diagnosis, and AFB smear was responsible for 26% of diagnoses.² In this study, molecular techniques were rarely used for diagnosis (3.7%), and were mainly used in conjunction with other diagnostic approaches.² Since the results of mycobacterial culture take 3–4 weeks, the commencement of TB treatment is usually based on the AFB smear or molecular technique results. The positive epidemiology in our patient, his close contact with a relative with TB, his thorax CT scan with an image suspicious of TB (tree-in-bud), his positive AFB smear results, and lastly, his rapid response to the TB treatment, led us to the diagnosis of pulmonary TB.

Another interesting finding in our patient was the development of pericarditis. There are only two cases of pericarditis due TB described in this population of patients, both occurring in allogeneic HSCT.^{19,25} One patient developed symptoms on day +19 post-HSCT.¹⁹ The other case was a patient with previous TB who underwent allogeneic HSCT. The patient developed chronic GVHD and symptoms of pericarditis 30 days after transplant.²⁵ Both patients received ATT for 6 months with cure.^{19,25} Despite the

Table 1
Description of 25 studies regarding TB among HSCT published in the literature between January 1980 and March 2009

Authors (Ref.)	Country (period of study)	Patients with TB/No. of HSCT	Type of HSCT	TB incidence	Time from HSCT to TB (range)	Site of infection (n)	Outcome
Navari et al. (1)	USA (1983)	2/682	2 HSCT	0.0014%	ND	Lung	No death
Kurzrock et al. (5)	USA (1983)	2/90	2 Allogeneic	3%	ND	Lung	ND
Roy and Weisdorf (3) ^a	USA (1974–1984)	11/2241	9 Allogeneic, 2 autologous	0.49%	–180 to +100 days post-HSCT	Lung (1), central venous catheter (4), bone marrow (2), maxillary sinus (1), vertebral (1), bacteremia (3), skin (1), pleural effusion (1)	2 Deaths
Keung et al. (4)	USA (1996)	Case report	Autologous	ND	+10 days post-HSCT	Lung	Death
Ip et al. (8)	Hong Kong (1991–1994)	10/183	Allogeneic	5.5%	+23 to +550 days post-HSCT	Lung	3 Deaths from other complications of BMT
Aljurf et al. (18)	Saudi Arabia (1986–1997)	4/641	Allogeneic	0.62%	+120 to + 600 days post-HSCT	Lung, CNS, spine	2 Deaths before diagnosis
Budak-Alpdogan et al. (7)	Turkey (1988–1998)	5/351	Allogeneic	1.42%	+300 to +1410 days post-HSCT	Lung (80%), renal (20%)	Cure
de la Cámara et al. (6)	Spain (2000)	8/5, 147 Autologous; 12/2, 866 allogeneic	HSCT	0.15%; 0.41%	Median +324 days post-HSCT	Lung (80%)	25% Deaths
Ku et al. (9)	Taiwan (6-year period)	8/350	Allogeneic	2.3%	Median 3.8 months (1–33.5 months) post-HSCT	Lung	4 (50%) Deaths
Ullah et al. (19)	Pakistan (2001–2006)	4/154	Allogeneic	2.6%	+21 to +241 days post-HSCT	Lung (3), mediastinum (1), pericardium (1)	1 Death
Altclas et al. ^b (20)	Argentina (1999)	Case report	Allogeneic	-	+300 days post-HSCT	Lung	Improvement; no relapse
Maeda et al. (21)	Japan (2002–2004)	3/113	Allogeneic, cord blood	2.7%	+34 to +61 days post-HSCT	Disseminated	2 Deaths
Khan et al. (22)	Pakistan (2005)	4/25	Allogeneic	16%	Median 21 weeks	Lung (52%)	ND
Garces Ambrossi et al. (23)	USA (1993–2001)	4/577	Allogeneic	0.69%	+60 to +300 days post-HSCT	Lung (3), lymph node (1)	1 Death, 3 cure
Wang et al. (10)	Taiwan (1995–2001)	3/35	Allogeneic	8.57%	+124 to +605 days post-HSCT	Lung	1 Death
George et al. (24)	India (1986–2001)	9/304	Allogeneic	2.3%	More than 30 days post-HSCT	Disseminated (55%), bone (22%)	Cure
Lee et al. (25)	Korea (1996–2003)	9/295	HSCT	3.1%	+45 to +165 days post-HSCT	Lung (8), pericardium (1)	5 Deaths, 4 cure
Erdstein et al. (26)	Australia (3 years)	4/127	Allogeneic	2.3%	3 to 15 months	Lung	2 Deaths
Yoo et al. (27)	Korea (1998–1999)	242	Allogeneic	3%	<100 to 734 days post-HSCT	ND	Cure
Kerridge et al. (28)	England, 2003	Case report	Allogeneic	-	Day +40	Disseminated	Cure
Kindler et al. (29)	Germany (1999)	Case report	Allogeneic	-	Around 30 days post-HSCT	Disseminated	Death
Campos et al. (30)	Portugal (1995)	Case report	Allogeneic	0.9%	ND	Lung and CNS	Death
		3/310 (previous)					
Ullah et al. (31)	Pakistan (2002–2007)	2/37	Allogeneic	5.4%	ND	Lung	Cure
Kumar et al. (32)	India (2004–2007)	1/40	Allogeneic	2.5%	After day 100	Disseminated	Death
Shima et al. (33)	Japan	Case report	Allogeneic	-	50 days after second HSCT	Disseminated	Death

TB, tuberculosis; HSCT, hematopoietic stem cell transplantation; ND, not described; BMT, bone marrow transplantation; CNS, central nervous system.

^a Mycobacteria isolated: *M. tuberculosis* (2), *M. avium-intracellulare* (2), non-tuberculous mycobacteria (*M. fortuitum* and *M. chelonae*) (7).

^b Case report: *M. tuberculosis* resistant to rifampin, isoniazid, ethambutol, pyrazinamide, streptomycin, ethionamide and rifabutin.

fact that we could not prove that our patient had pericarditis due to TB, his condition improved rapidly with the ATT and steroid use.

The case described in the present study showed a patient with a tree-in-bud appearance on chest CT scan, an image commonly described in pulmonary TB. A recently published study retrospectively analyzed chest radiographic and CT findings of 10 patients who had undergone HSCT and developed TB. It was shown that the most common abnormalities were air-space consolidation (100%) and nodules (80%), and on chest CT scans ($n = 7$), the most common parenchymal lesions were consolidation (100%), nodules (71%), tree-in-bud appearance (43%), and ground-glass opacity (43%).³⁴

TB in HSCT patients is mainly due to reactivation of latent infection.² In countries where TB is endemic, pulmonary TB could be due to a new infection. In the present report, the patient had a relative who had TB in the year before his HSCT. Our hospital does not do screening for TB with TST pre-HSCT. TB screening using TST in HSCT is controversial.^{12–15} T cells play an important role in protective immunity against TB. The question arises as to whether TST-specific memory T cells are transferred from the marrow donor to the recipient and persist in the long-term.¹²

Isoniazid prophylaxis in HSCT recipients with only radiological findings suggestive of past inactive TB infection was not found to significantly alter the incidence of TB infection.²⁴ Tavit et al. evaluated the frequency of TST positivity among 26 patients and their donors, to investigate whether tuberculin positivity of a recipient or donor influences the rate of TB disease or transplant-related events; they also evaluated the effectiveness of isoniazid prophylaxis administered to those with a positive TST.¹⁵ The frequency of TST positivity was 23% ($n = 6$) among recipients and also 23% ($n = 6$) among donors. Two recipients and five donors with a positive TST received isoniazid prophylaxis for 6 months. The transplantation procedure was not postponed for either recipient or donor TST positivity. Despite the high frequency of TB in their country, they did not detect any case of TB at their center, either among the TST screened ($n = 26$) or the non-screened ($n = 128$).¹⁵

The Infectious Diseases Working Party of the European Blood and Marrow Transplant Group conducted a survey to obtain information about the frequency, presentation, and treatment of mycobacterial infection in HSCT recipients.¹¹ Among 29 centers, including one Brazilian hospital, mycobacterial infection was diagnosed in 0.79% of 1513 allogeneic and 0.23% of 3012 autologous HSCT recipients during 1994–1998, a median of 160 days after transplantation. The mean interval between first symptoms and diagnosis was 29 days. The prevalence of mycobacterial infection was highest among those who had received matched unrelated or mismatched HSCT from related donors. The lung was the organ most frequently involved (55% of patients), with cough present in 48%, dyspnea in 32%, and hypoxemia in 29%. Five patients (16%) died, all of whom had received an allogeneic HSCT. Of the participating centers, 51% had a program of vaccination against TB in their country, only 10% systematically screened their patients by TST before transplant, and 51% screened in the case of clinical suspicion.¹¹

The literature review undertaken in the present study showed that most of the reports of TB were from Asia (48%), that the incidence of TB varied from 0.0014% (USA) to 16% (Pakistan), and that the lung was the organ most frequently involved (Table 1). Mortality varied from 0% to 50% and was higher among allogeneic HSCT and patients with disseminated disease (Table 1).

In conclusion, TB is more frequent and has a worse prognosis in allogeneic HSCT, and generally occurs at between +8 and +1410 days after HSCT. The lung is the organ most often involved and pericarditis is rare or under-diagnosed. Risk factors associated with TB in allogeneic HSCT are use of steroid and GVHD. There is no consensus regarding screening with TST or primary prophylaxis for

latent TB, and further research into this is needed in developing countries with a high prevalence of TB.

Conflict of interest: No conflict of interest to declare.

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