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MINIREVIEWS

Tuberculosis and hematopoietic stem cell transplant: Review of a difficult and often underestimated problem

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Abstract

Recipients of solid organ transplants (SOT) and stem cell transplants (SCT) constitute a group of patients at risk for tuberculosis (TB) development. The prevalence of active TB in patients undergoing SOT is higher than in patients undergoing SCT, probably due to the shorter period of immunosuppression in the latter. We reviewed the importance of SCT in individuals with hematological malignancies. Most TB cases occur in transplant patients by reactivation of latent infection after immunosuppression, most often within the first year after transplant, leading to graft loss and in some cases, death. Relevant variables to assess the risk of TB infection in a transplant recipient include the donor's and recipient's medical histories, imaging results, microbiology and tuberculin skin test (TST) and interferon-gamma release assays (IGRA). TST is routinely performed in the donor and recipient before transplantation. If TST is > 5 mm in the recipient or > 10 mm in the donor, it is necessary to exclude active TB (pulmonary and renal). Chemoprophylaxis is recommended in TST (+) recipients and in recipients with recent seroconversion, in donors with a history of untreated TB or in contact with an individual with active TB, if radiological images are suspicious and the IGRA is (+). The drug of choice is isoniazid. These topics are herewith reviewed.

Key words: Tuberculosis; Prophylaxis; Transplant; Solid organ transplantation; Hematopoietic stem cell transplantation

Core tip: This review highlights the importance of stem cells transplant (SCT) in individuals with cancer and hematological malignancies. However, the risk of acquiring tuberculosis (TB) in this way, has received little attention, especially in developing countries. SCT candidates should be screened for TB with a careful medical history and chart review to ascertain any history of prior TB exposure, since immunocompromised individuals are at higher risk of latent TB progression to active disease. Finally, we mention the importance of the immune response, particularly in allogeneic stem cell transplants, because infection by intracellular microorganisms such as Mycobacterium TB, could be inhibited by the process named cell reprogramming.

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INTRODUCTION

Stem cell transplant (SCT), also known as pluripotent

hematopoietic cell transplant, was previously referred to as bone marrow transplantation (BMT) since that was the source from which hematopoietic stem cells (HSC) were preferably obtained. This procedure has become an essential therapeutic tool in modern medical practice. As a results of increasing knowledge on SCT, several dogmas that for years hindered development in this area of medicine, have been set aside. It is now established that: (1) the successful collection of HSC does not require the destruction of the receptor's BM; (2) HSC create their own space in the receptor's marrow via graft-*vs*-host effects; (3) several tumors can be eradicated as a result of a graft-*vs* tumor effect; (4) allogeneic SCT (alloSCT) can be conducted on an out-patient basis[1]; (5) allotransplants can be performed in elderly or frail individuals[2]; (6) allogeneic SCT (alloSCT) can be done without red blood cell or platelet transfusions[3]; and (7) in Mexico and in other emerging countries, allotransplant costs can be significantly diminished. These changes have led to increased availability of SCT to a greater number of patients in Mexico and other emerging countries thus offering, in some cases, a real curative option to patients that until recently had no access to this modern therapeutic modality[4]. Transplant recipients constitute a group of patients at risk of developing tuberculosis (TB) and that face great diagnostic and therapeutic dilemmas; the disease's clinical presentation tends to be atypical and the sensitivity of available diagnostic techniques is low. Moreover, anti-TB drugs are highly toxic and frequently interact with anti-cancer agents, rendering disease management difficult. Most TB cases in patients that have undergone transplantation are due to reactivation of latent infections following immunosuppression[5]. We reviewed the relevance of hematopoietic stem cell transplantation (HSCT) in individuals with hematological malignancies and thus at risk of acquiring TB.

EPIDEMIOLOGY

In the past decades, TB prevention programs in developed countries have decreased its incidence; however, in emerging countries it is still high. In Mexico, the incidence of TB in the general population is 14.5/100000 inhabitants, with important regional differences[6]. Mycobacterial infection was uncommon after BMT in the past and, until recently, was considered to be a rare complication, receiving little attention. In North American studies, incidence rates vary between 0.6% and 1%; however, in countries where it is more endemic, its incidence is higher: 1.6% in Spain, 5% in Hong Kong and in Taiwan[7].

A review of BMT patients in large US centers revealed an incidence rate of 0.49%-1%[8] and the scant data available in countries with a high incidence of TB referred frequencies ranging from < 1% to 5.5%[9] and reaching 16% in Pakistan, according to recent reports[10].

However, since the onset of the AIDS epidemic and the emergence of multidrug-resistant strains of *Mycobacterium tuberculosis* (MTB), there has been an increasing number of reports of mycobacterial infection in SCT recipients[11]. The lack of a significant response after corticosteroids and the initially predominant involvement of the upper lobes should raise the possibility of pulmonary tuberculosis. A high index of suspicion is important in establishing the diagnosis, and prompt and appropriate treatment will invariably improve the disease's outcome[12]. The reported frequency of MTB infection in solid organ transplant recipients varies from 0.2% to15% (mean, 3.7%), which is 6 to 62 times higher than its frequency in the general population (0.01%-0.045%)[13]. The incidence of TB in the general population is the principal predictor of the increased frequency observed in transplant recipients.

STEM CELL TRANSPLANTATION

SCT is a life-sustaining treatment indicated in some individuals with cancer and hematological malignancies[14]. HSCT refers to the infusion of hematopoietic stem cells obtained from a donor into a patient that has been treated with chemotherapy, usually myeloablative. HSCTs are classified as either allogeneic or autologous, depending on the source of the transplanted hematopoietic progenitor cells. HSCT is defined as any transplantation of blood or marrow-derived hematopoietic stem cells, regardless of the type of transplant (allogeneic or autologous) or cell source (bone marrow, peripheral blood, or placental/umbilical cord blood)[15].

The number of transplants performed in the United States has gradually increased over the last 20 years, particularly in older patients (50 years old). According to the Center for International Blood and Marrow Transplant Research summary report, there were 7012 allogeneic and 9778 autologous transplants performed in 2009[16].

SCT provides an increased chance of survival to patients facing hematological and other potentially life-shortening diseases. These malignancies include acute lymphocytic leukemia, chronic lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, aplastic anemia, Hodgkin's and non-Hodgkin's lymphomas, and multiple myeloma. SCT is an expensive treatment and there is wide variation in insurance company coverage, with companies often only paying part of the total expenses. Transplant expenses vary depending on the specifics and type of transplant. A study was conducted between 2000 and 2004 by Saito *et al*[17] at the Dana Farber Cancer Institute/Brigham Women's Hospital, in 376 patients receiving high-dose SCT to estimate costs. The researchers reported median costs of up to $102574 and 36 d of initial hospitalization in a complicated allogeneic SCT.

Hematological disease is frequently accompanied by liver dysfunction. The principal causes of liver injury relating to SCT include: (1) high-dose cytoreductive therapy (chemotherapy and/or radiation) administered prior to transplantation and which may result in veno-occlusive disease (VOD) or nodular regenerative hyperplasia

Table 1 *Mycobacterium Tuberculosis* infections after allogeneic stem cell transplantation

Ref.	Country (period of study)	Patients with TB/No. of HSCT	TB incidence in general population (%)	Site of infection (*n*)
Navari *et al*[20]	United States (1983)	2/682	0.014-0.03	Lung
Kurzrock *et al*[21]	United States (1984)	2/90	0.014-0.03	Lung
Roy *et al*[8]	United States (1974-1994)	11/2241	0.014-0.03	Lung (1), EP (11)
Ip *et al*[22]	Hong Kong (1991-1994)	10/183	5.5	Lung
Aljurf *et al*[23]	Saudi Arabia (1986-1997)	4/641	0.62	Lung, CNS, spine
Budak-Alpdogan *et al*[19]	Turkey (1988-1998)	5/351	1.42	Lung (4), renal (1)
de la Cámara *et al*[11]	Spain (2000)	12/2866	0.41	Lung
Ullah *et al*[24]	Pakistan (2001-2006)	4/154	2.6	Lung (3), EP (1)
George *et al*[25]	India (1986-2001)	9/304	2.3	Lung (2), EP (7)
Lee *et al*[26]	South Korea (1996-2003)	9/295	3.1	Lung (8), EP (1)
Ullah *et al*[27]	Pakistan (2002-2007)	2/37	5.4	Lung
Shima *et al*[28]	Japan (2009)	Case report	-	EP

TB: Tuberculosis; HSCT: Hematopoietic stem cell transplantation; EP: Extrapulmonary; CNS: Central nervous system.

(NRH); (2) liver toxicity due to other drugs used after transplantation; (3) viral and bacterial infections; and (4) acute and chronic graft *vs* host disease (GVHD) in the case of allogeneic transplantation. The differential diagnosis of these complications is guided by knowledge of the timing of their appearance. NRH of the liver is a rare disorder characterized by diffuse micronodular transformation of the hepatic parenchyma, with areas of regenerative activity alternating with areas of atrophy and no fibrous septa between the nodules. Its presentation may be similar to VOD although it is associated with non-cirrhotic portal hypertension and ascites developing after day 100 post-BMT[18].

TB IN ALLOGENEIC STEM CELL TRANSPLANT RECIPIENTS

In general, TB is rarely seen in alloSCT recipients, but this observation has been challenged in developing countries such as Turkey, where TB infection is more prevalent than in Europe and the United States[19]. In this retrospective study, the incidence of TB infections in 351 alloSCT recipients was reported. The frequency of TB in alloSCT recipients after the allograft (5 of 351) was far greater than that in the general population (35.4 per 100000). Among the 351 patients who underwent alloSCT, 77 subjects that received isoniazid (INH) chemoprophylaxis for 6 mo did not develop post-transplant TB. However, 5 of the remaining 274 patients who received no chemoprophylaxis developed TB a median of 12 mo (range, 10-47 mo) after the allograft (Table 1).

In the bone marrow transplant population, despite severe immune suppression, there is a low incidence of mycobacterial infections[29] that contrasts with the experience reported in other immunosuppressed patients (AIDS and renal transplant recipients). This may be due, at least partly, to the more prolonged duration of immunosuppression in AIDS patients and in recipients of solid organ transplants, when compared with the usual BMT patient[30]. Most patients who develop TB after SCT do not have clearly identified risk factors[31]. Most had normal pre-transplant chest radiographs and no direct history of contact with TB. Although most cases of TB have occurred in alloSCT recipients, 20% have developed in autologous recipients. Despite this low rate[32], diagnostic vigilance must be maintained.

TB among transplant recipients may result from reactivation of quiescent M.tb foci, transmission by the graft or contamination by actively infected individuals. Graft transmission has been documented in renal, lung and hepatic transplants, but accounts for less than 5% of all TB cases in transplant recipients. The risk of TB development in transplant recipients is estimated to be 20 to 50 times higher than in the general population even in developed countries, and mortality rates vary between 20% and 40%. Risk factors include pulmonary images suggesting previous TB infection, immunosuppressive treatment with OKT3 or anti-T cell antibodies, diabetes mellitus, chronic liver disease and coexisting infections[33]. In patients undergoing SCT, associated risk factors include chronic GVHD, allogeneic transplant and total body irradiation[22].

Although accurate diagnosis may be difficult, it is currently possible to hypothesize and/or identify a fungal etiology of pneumonia in SCT recipients; however other pathogens such as *Mycoplasma pneumoniae* or MTB may present clinical and radiological pictures resembling mycosis in SCT patients[34].

PATHOGENESIS OF TB IN HSCT RECIPIENTS

TB is transmitted from person to person by respiratory droplets. Although some people develop active TB disease after infection, almost all TB infections are asymptomatic and remain latent. LTB progresses to active disease in approximately 5%-10% of infected individuals. The rate of progression is much greater in HSCT recipients. The risk of TB in transplant recipients is estimated to be 20 to 50 times higher than in general population even in developed countries, and mortality rates vary from 20% to 40%. Risk factors include pulmonary images suggesting previous TB infection, immunosuppressive treatment with OKT3 or anti-T cell antibodies, Diabetes mellitus, chronic liver disease and coexisting infections (Figure 1).

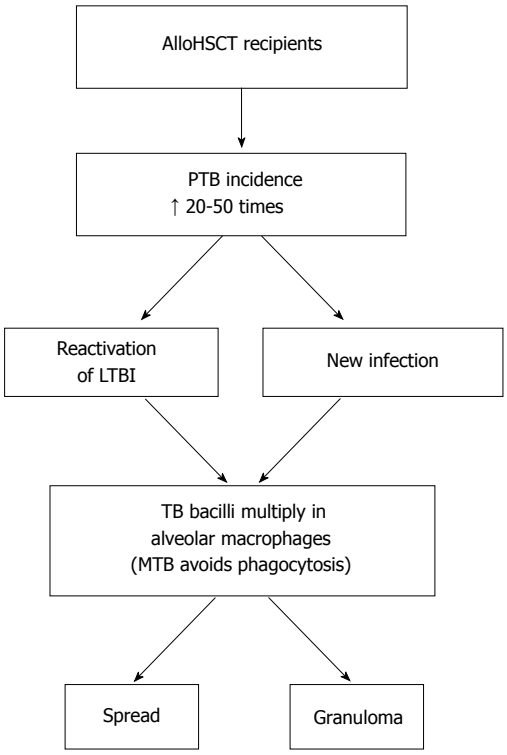

Figure 1 Pathogenesis of tuberculosis in hematopoietic stem cell transplant recipients. AlloHSCT: Allogeneic hematopoietic stem cell transplant; TB: Tuberculosis; PTB: Pulmonary TB; LTBI: Latent TB infection; MTB: *Mycobacterium tuberculosis*.

EVALUATION OF PATIENTS BEFORE SCT

SCT candidates should be screened for TB with a careful medical history and chart review to ascertain any history of prior TB exposure, since immunocompromised individuals have a higher risk of progression of latent TB (LTB) infection to active disease. Also, physicians should apply a tuberculin skin test (TST) using the Mantoux method with five tuberculin units of purified protein derivative or conduct an interferon-gamma release assays (IGRA) The sensitivity and specificity of IGRA testing methods varies according to the used kit type and the study population, and fluctuates between 50% and 100% and 85% and 100% respectively, in different studies (Table 2). Experts disagree on the convenience or benefit of routinely obtaining a TST or IGRA in every transplant candidate. Interpretation of the TST may also be complicated by a history of prior Bacillus Calmette-Guérin (BCG) vaccination, although tuberculin reactivity following BCG tends to wane over time[35]. Any patient with a recent positive TST or IGRA or a history of a positive test and no prior preventive therapy, should be evaluated for active TB. At a minimum, the patient should be asked about symptoms of systemic disease and respiratory symptoms such as cough and shortness of breath, and a chest radiograph should be assessed[36]. Any MTB-mediated disease either in the donor or recipient must be treated until complete microbiological and radiological resolution before considering the possibility of a transplant[37].

Table 2 Salient aspects for diagnosing tuberculosis in a hematopoietic stem cell transplantation recipient

Test	Sensitivity (%)[1]	Specificity (%)[1]	Indicates
TB skin test	72	35	LTBI or active TB
Acid-fast bacillus	50-80	98	Infection
Nucleic acid amplification test	80-98	95-99	Infection
Culture	70-90	98	Active TB
Serology	20-70	47-81	Active TB or infection
Interferon gamma release assays	50-99	85-99	LTBI or active TB
Chest radiography	47-73	76	Probable active TB

[1]These numbers are influenced by the epidemiological situation. LTBI: Latent tuberculosis infection; TB: Tuberculosis.

SCT center personnel should follow guidelines regarding the control of TB in healthcare facilities, including instituting airborne precautions and negative-pressure rooms for patients with suspected or confirmed pulmonary or laryngeal TB. Health care workers should wear N95 respirators, even in isolation rooms, to protect themselves from possible TB transmission from patients with active pulmonary or laryngeal TB, particularly during cough-inducing procedures[38]. SCT candidates and recipients should avoid exposure to persons or environments where there is a substantial risk of respiratory contact with individuals with active TB. It is prudent to advise SCT candidates and recipients that certain occupations (*i.e.*, volunteer work or employment in health care facilities, correctional institutions or homeless shelters) can increase their risk of TB exposure[39].

In SCT patients, a high incidence of TB might be expected due to the complex and severe immunodeficiencies that these patients undergo. Spain has a high incidence of TB (40-45 cases/10^5 inhabitants/year) and a high prevalence of infection (25%-29%) that increases to 56% in individuals > 49 years of age[40], the highest incidence of tuberculosis in Europe after Portugal[41]. It also boasts one of the highest transplant activity in Europe[42]. In a survey of TB after SCT, 20 confirmed cases were found (8 in autologous and 12 in allogeneic transplants) among 8013 patients. TB post-SCT was a late infection (172-324 d), most frequently limited to the lungs (80%) and less frequently, extrapulmonary or disseminated. All SCT patients with TB were symptomatic, fever and cough being the most common symptoms. In allogeneic transplant patients, TB was associated with a high mortality: 25%[11].

INDICATIONS FOR TREATMENT OF LATENT TB INFECTION (LTBI) OR PROPHYLAXIS

Because of the high risk of reactivation or the development of a new infection, prophylaxis should be ad-

Table 3 Clinical manifestations of nontuberculous mycobacterial disease in recipients of hematopoietic stem cell transplant and solid organ transplants

Transplantation type	Mycobacterium species	Types of infection
HSCT	MAC, *M. haemophilum, M. fortuitum, M. Chelonae, M. abscessus*	Catheter-related, pulmonary, cutaneous, disseminated
Kidney	*M. chelonae, M. kansasii, M. haemophilum, M.fortuitum*	Local cutaneous, disseminated, disseminated cutaneous, osteoarticular, pleuro-pulmonary
Heart	*M. kansasii,* MAC, *M. haemophilum, M. scrofulaceum*	Pleuro-pulmonary, disseminated, disseminated cutaneous
Lung	MAC, *M. abscessus, M. haemophilum, M. fortuitum*	Pleuro-pulmonary, local cutaneous, disseminated

HSCT: Hematopoietic stem cell transplant; MAC: *Mycobacterium avium*- intracellulare complex.

ministered to immunocompromised SCT recipients or candidates who: (1) Have been exposed to someone with active, infectious (*i.e.*, sputum-smear positive) pulmonary or laryngeal TB, regardless of the SCT recipient's or candidate's TST or IGRA status; (2) Have a positive TST result-regardless of prior BCG vaccination-without previous treatment and no evidence of active TB disease. A positive TST with a history of BCG vaccination is still considered by the American Thoracic Society as an indication for prophylaxis in patients who "have medical conditions that increase the risk for disease"[36], and which presumably include SCT; and (3) Have a positive IGRA result, without previous treatment and no evidence of active TB.

The report of a high frequency of reactivation of previously treated TB following transplantation, especially in some parts of the world where the endemic TB prevalence is high, suggests that these patients may be at high risk, and therefore, isoniazid (INH) prophylaxis should be considered[26]. LTBI therapy may carry a variable toxicity risk, particularly in the liver and requires strict plasma measurements of immunosuppressive therapy levels. To date, isoniazid is the drug of choice in prophylaxis and has proven effective. The value of prophylaxis in countries with a high rate of LTBI, or in SCT patients from such countries, should be considered at an institutional level.

INH is well tolerated after SCT even with concurrent fluconazole use[43]. Concurrent use of itraconazole is not recommended, and the impact of voriconazole or posaconazole is unknown.

BCG vaccination is contraindicated in SCT candidates. Disseminated BCG infection has been reported among immunocompromised individuals exposed to BCG[44].

Donors who live in or originate from countries where TB is endemic, are at an increased risk of developing TB or LTBI at rates similar to those in their population of origin. There is no known risk in transplanting hematopoietic progenitor cells from an untreated donor with latent or active TB[45].

NONTUBERCULOUS MYCOBACTERIAL INFECTION IN SCT RECIPIENTS

Nontuberculous mycobacteria (NTM) are ubiquitous environmental microorganisms that have generally been considered an uncommon cause of human disease. Before the AIDS epidemic, most cases presented as indolent, cavitating pulmonary infections in patients with other underlying lung diseases, such as chronic obstructive pulmonary disease or previous TB[46]. Mycobacterial infections after transplant have increased in frequency and severity, reflecting both increased exposure and improved diagnostic methods. In countries where TB is endemic, infections due to MTB are more frequent than are infections due to NTM[47].

NTM infections in HSCT recipients have been reported with an incidence ranging between 0.4% and 4.9%[48]. The clinical manifestations of NTM disease in HSCT and solid organ transplant (SOT) recipients are shown in Table 3. The clinical manifestations of disease in HSCT recipients differed from those in SOT recipients. The most common manifestations of NTM disease in HSCT recipients are central venous catheter-related infection, including exit site-related, tunnel-related, and catheter-related blood stream infections. Pulmonary and cutaneous disease is also commonly reported[49].

The most frequently isolated species in HSCT recipients are *mycobacterium avium*-intracellulare complex (MAC) and *M. haemophilum*. Rapidly growing mycobacteria, such as *M. fortuitum* is also common. MAC infection is most often associated with pulmonary or disseminated disease. Rapidly growing isolates have been predominately obtained in catheter-related infections. The presence of *M. haemophilum* has been reported more frequently in SCT recipients than in SOT recipients, usually in association with pulmonary or cutaneous disease but also manifesting as disseminated, osteoarticular, and catheter-related disease.

NTM disease has been reported in recipients of kidney[50], heart[51] and lung transplants[52]. Rapidly growing mycobacteria have been associated with disease in SOT recipients less often than in HSCT recipients.

RELEVANT IMMUNOLOGICAL ASPECTS OF STEM CELLS

Patients receiving transplanted hematopoietic cells undergo a period of immune dysfunction that lasts approximately a year and compromises both cellular and humoral immune mechanisms. This leads to a proclivity to develop infections in the post-transplant period. The

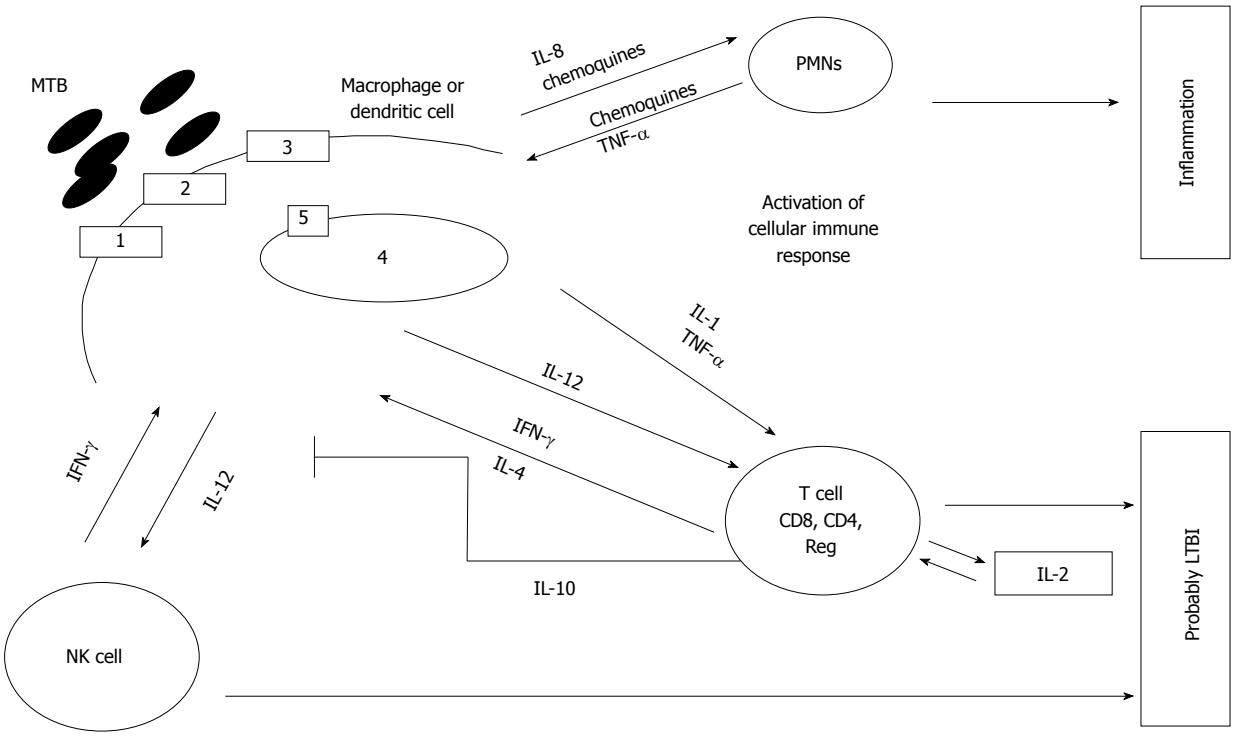

Figure 2 Cellular immune response against tuberculosis. *Mycobacterium tuberculosis* (MTB) recognition by specific receptors and tool like receptors activited signaling pathways that lead to cell activation and cytokine production. The activated macrophages secrete cytokines and chemokines that activate macrophages, T cells and neutrophils, producing inflammation. The T cells and natural killer cells producting gamma interferon with other cytokines that induct activation of macrophages contributing to the elimination of MTB or Latent tuberculosis infection. 1: Complement recepter; 2: Mannose recepter; 3: Scavenger receptor; 4: Phagosome; 5: Toll like receptor. IL: Interleukin; LTBI: Latent tuberculosis infection; NK: Natural killer; TNF-α: Tumor necrosis factor alpha; IFN-γ: Interferon gamma.

conditioning regimen to which patients are subjected destroys normal hematopoiesis and damages different hematological lineages such as neutrophils, monocytes and macrophages as well as mucosal cells, leading to a loss of this barrier's integrity, particularly in the gastrointestinal tract where flora becomes potentially pathogenic.

Recovery of immune function depends on the type of transplant, since in allogeneic transplants the donor's lymphoid cells must learn to recognize an extraneous microenvironment in the absence of a totally functional thymus; this delays immune reconstitution. Another factor affecting the period of immune function recovery is the dosage of cytotoxic therapy in order to allow secondary lymphoid organs to become repopulated. This is applicable in the absence of chronic graft-*vs*-host disease[53].

We must underscore the fact that after hematopoietic stem cell transplant, there is also loss of immune memory in the recipient and the donor's acquired passive immunity unreliably confers long-term immunity[54].

Allogeneic and peripheral blood transplants are associated with a longer immune recovery period than syngeneic and autologous transplants. $CD3^+$ T lymphocytes recover a short time after transplant particularly when more CD34 cells are infused. There is also a prolonged $CD4/CD8$ ratio inversion due to a decrease in $CD4^+$ and an increase in suppressor $CD8^+$ cells[55].

The immunomodulatory capacity of mesenchymal stem cells (MSC), adult multipotent cells, may prevent allogenic rejection by fomenting the avoidance of antigens when interfering with dendritic cell and T lymphocyte function; they thus have a local immunosuppressive effect due to their ability to secrete cytokines. This effect is potentiated when the cells are exposed to an inflammatory milieu or high concentrations of interferon gamma[56,57]. MSC can also inhibit lymphocyte proliferation induced by alloantigens and mitogens such as phytohemagglutinin and concanavalin A or by activation with anti-CD3 and anti-CD28 antibodies. MSC may also inhibit the expression of molecules mediating antigen presentation and in co-culture with peripheral blood mononuclear cells, they increase the proportion of T lymphocyte sub-populations with a regulatory phenotype[58,59].

In hematopoietic stem cell transplants (HSCT), T lymphocyte function remains altered for approximately a year and in allogeneic transplants, the immune repertoire is dominated by donor-derived T cells, particularly effector memory cells[60]. Interleukin-2 (IL-2) production by T Lymphocytes is decreased in response to mitogen stimuli and delayed hypersensitivity reactions are absent and only recover in the absence of Graft-*vs*-Host disease. $CD8^+$ cell cytolytic activity is compromised as underscored by an ineffective response to Epstein-Barr virus[61], a mechanism that may be very similar to that of MTB infection that fundamentally depends on the cellular immune response (Figure 2).

The final phase of cellular immune response recovery hinges on the need for new T lymphocytes from donor pre-thymic precursors in the case of allogeneic transplant.

These cells are processed by the recipient's thymic tissue rendering them tolerant to the allo-environment. There are differences in this lymphocytic "education process" depending on the recipient's age. Children and young patients have a more functional thymus and therefore, an increased recovery in the numbers of T lymphocytes within the first two years after transplantation[62].

In contrast, natural killer cell recovery does not require a functional thymus and develops rapidly within the first weeks after transplant[53]. Although stem cell transplantation is an artificial maneuver, when performed it gears immune mechanisms to take advantage of the stem cells' pluripotent capacity and plasticity; these characteristics are further reflected in organ and tissue regeneration as well as in immune modulation, particularly in immune suppression. Stem cells, particularly MSC, have been shown to inhibit T and B lymphocyte proliferation *in vivo* and *in vitro*, to support the development of regulatory T lymphocytes, to decrease the lytic activity of natural cytotoxic, natural killer and cytotoxic T cells, and to inhibit the risk of infection particularly in the early post-transplant period.

This proclivity to infection particularly in allogeneic stem cell transplants, by intracellular microorganisms such as MTB, could be inhibited by a process named reprogramming in which cells in late differentiation stages reactivate the program of stem cells and recuperate their pluripotentiality.

Tissues can be regenerated by cellular reprogramming and become a treatment strategy for various degenerative disease entities. However, this topic is beyond the scope of this review and is only mentioned because the safety and efficiency of reprogramming methods may represent an alternative, since it imitates the mechanisms used by cells during development; for instance, in cell reprogramming without the introduction of nucleic acids, embryonic fibroblasts have been reprogrammed for the first time with the transduction of the recombinant proteins of transcription factors Oct4, Sox2, Klf-4 and c-myc. However, there are still numerous obstacles to overcome, such as the proteins' short half-lives that require repeated applications and are inherently inefficient[54]. Cellular reprogramming can also be conducted with non-autonomic signals whereby the stem cells destined to a particular organ (multipotent cells) are placed in a similar milieu to that of early embryonic development and are capable of self-reprogramming into a pluripotent state, like embryonic stem cells. Thus, cells from the three embryonic layers (ectoderm, mesoderm, endoderm) can be generated and reflect a state of trans-differentiation[63]. This form of reprogramming is closer to normal cellular ontogenesis mechanisms[64].

CONCLUSION

In summary, transplantation centers should maintain a high level of suspicion of mycobacterial infection during the first 4 mo after transplantation, when mortality due to mycobacterial infections is at its peak. Due to the large numbers of unmatched donors in transplantation programs in countries with high TB prevalences, constant vigilance is required for early detection of mycobacterial infection in SCT recipients. The fact that autologous SCT recipients are immunosuppressed even before transplant, should also be considered.

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