Mycobacterium tuberculosis pneumonia and bacteremia after allogeneic hematopoietic stem cell transplant: report of an instructive pediatric case

Erika Biral[1], Maura Faraci[1], Edoardo Lanino[1], Giuseppe Morreale[1], Stefano Giardino[1], Cristina Moroni[2], Giuseppe Losurdo[2], Gian Michele Magnano[3], Evelina Senno[4], Elio Castagnola[2]

[1]Hematopoietic Stem Cell Transplant Unit, Hematology-Oncology Department, G. Gaslini Children's Research Institute, Genova, Italy;
[2]Infectious Diseases Unit, Hematology-Oncology Department, G. Gaslini Children's Research Institute, Genova, Italy;
[3]Radiology Service, G. Gaslini Children's Research Institute, Genova, Italy;
[4]Laboratory Medicine, San Martino Hospital, Genova, Italy

SUMMARY

Pulmonary infections often complicate hematopoietic stem cell transplantation (HSCT) outcome. Uncommon aetiologies, like *Mycobacterium tuberculosis*, should be considered when the clinical conditions do not fully improve with standard antimicrobial therapy and microbiological evaluations are repeatedly negative for bacteria and fungi. We describe an interesting pediatric case of miliary lung tuberculosis after HSCT, which was successfully treated after administering the appropriate therapy.

Key words: Mycobacterium tuberculosis, Allogeneic stem cell transplantation, Pulmonary infections.

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INTRODUCTION

Pulmonary infections are an important cause of morbidity and mortality after hematopoietic stem cell transplant (HSCT). Some infections occur during the neutropenic phase following the conditioning regimens, while others complicate HSCT until complete humoral and cellular immunity has been recovered or immunosuppressive treatments have been discontinued.
Although accurate diagnosis may be difficult, it is currently possible to hypothesize and/or identify a fungal etiology of pneumonia in HSCT recipients on the basis of specific clinical findings, radiological imaging (computerized tomography, CT), and laboratory tests such as galactomannan or 1-3-beta-D-glucan assays (De Pauw *et al.*, 2008). However other pathogens, like *Mycoplasma pneumoniae* or *Mycobacterium tuberculosis* may present clinical and radiological pictures resembling mycosis in cancer or HSCT patients (Davis *et al.*, 1993; Banov *et al.*, 2009). The low incidence and the diagnostic difficulties may lead to an underestimation of the frequency of these infections, which are often not considered in the first instance in the differential diagnosis of pneumonias following allogeneic HSCT.
We describe a pediatric case of disseminated infection caused by *Mycobacterium tuberculosis*, which is very rarely reported in the HSCT setting.

Corresponding author
Erika Biral, MD
Hematopoietic Stem Cell Transplant Unit
Hematology-Oncology Department
G. Gaslini Children's Research Institute
Largo G. Gaslini, 5 - 16147 Genova, Italy
E-mail: erika.biral@gmail.com

CASE REPORT

A 10-year-old Ukrainian boy with relapsing acute lymphoblastic leukemia was referred to our Center in April 2006 for HSCT from an alternative donor. During first line and relapse treatment no

major infectious complications were reported, with the exception of HCV infection which was treated with ribavirin and pegylated interferon alpha, and HBV infection that was treated with lamivudine; both viral infections were probably transfusion-acquired, in consideration of the country of origin of the patient.

BCG vaccination was performed according to the Ukrainian schedule (first administration in the first year of life, booster at 7 years of age). Purified Protein Derivate (PPD) skin tests performed on the patient and his mother at the time of our first observation were negative (other family members or prior skin tests performed in Ukraine were not available), though the child was in a condition of immunodepression as a consequence of previous chemotherapies; no lung or mediastinal lesions were observed on the chest CT scan. The patient received myeloablative conditioning regimen including total body irradiation, thiotepa, and cyclophosphamide. Graft versus host disease (GvHD) prophylaxis consisted of rabbit anti-lymphocyte serum, short course methotrexate and cyclosporine. Anti-infective prophylaxis included fluconazole, acyclovir, and low dosage cotrimoxazole. During the pre-engraftment period he developed an *Enterococcus* sp. bacteremia that was treated successfully. The patient then developed skin and gut acute GvHD (overall grade 2), which was successfully treated with methylprednisolone 2 mg/kg/day. He was discharged from the HSCT Unit on day +37 and short tandem repeat analyses performed on peripheral blood and bone marrow showed full donor chimerism.

On day +71, the patient was admitted to the Infectious Diseases Unit because of fever, in the absence of neutropenia, while receiving immunosuppression with cyclosporine and tapering methylprednisolone for acute GvHD. Within a few days his clinical conditions worsened, with the onset of thoracic pain, respiratory distress and renal failure. Chest CT showed presence of pulmonary reticulo-micro-nodular lesions, hilar lymphadenopathy, and bilateral pleural effusion (Figure 1); bronchoalveolar lavage or culture of the pleural fluid were not performed at this time because of the clinical impairment of the patient, and sputum culture resulted negative. Abdominal ultrasound scan showed splenomegaly with a hyperechogenic lesion, which was confirmed by the CT scan. Standard blood cultures and the galactomannan antigen detection test were repeatedly negative. In the absence of microbiological documentation, several empiric anti-infectious treatments were administered in the following sequence: ceftriaxone plus vancomycin for 6 days followed by ceftazidime plus vancomycin plus voriconazole for the following 6 days. But the clinical condition continued to worsen. Therefore, despite the absence of any documented etiology, multidrug therapy including ciprofloxacin, clarithromycin, foscarnet, caspofungin, and linezolid was administered. After these changes, the clinical condition progressively improved and the therapy was administered for 1 month. The patient was then discharged on day +112 from HSCT with a diagnosis of possible disseminated fungal infection according to 2002 criteria (Ascioglu *et al.*, 2002) and oral antifungal therapy with voriconazole.

A chest CT scan performed 15 days after discharge showed the persistence of a left paracardiac infiltrate, possibly with a cavitation process (Figure 2). A few days later the patient was readmitted to the Hospital for a new febrile episode. At this time, specific mycobacterial blood cultures performed during the former hospitalization were available and they disclosed *Mycobacterium tuberculosis*. On this occasion, *M. tuberculosis* was also detected by acid-fast staining in the sputum newly collected; the tu-

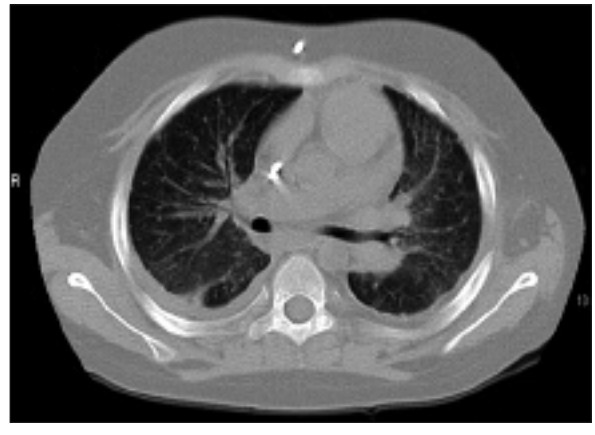

FIGURE 1 - *Chest CT: diffuse reticulo-micro-nodular parenchymal pattern, with increased lymphoadenopathies mainly in the left hilum; a bilateral pleural effusion is also present.*

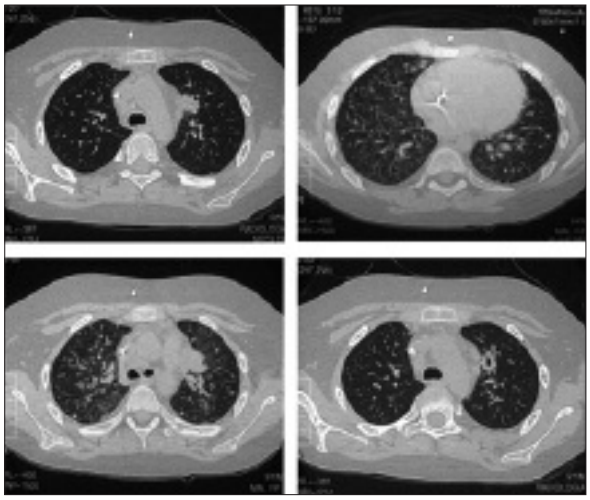

FIGURE 2 - *Chest CT scan shows the persistence of the diffuse reticulo-nodular parenchymal pattern, with a left paracardiac infiltrate: its hypodense core is suggestive for a cavitation process.*

bercular infection was confirmed by both specific cultures and molecular analysis (Polymerase Chain Reaction) performed on the sputum. Chest CT scan showed miliary lung infiltrations and the previous imaging were re-evaluated with identification of this radiological picture also in the scans performed during the previous admission. The patient was then treated with isoniazid, rifampicin, ethambutol, and pyrazinamide. Antibiotic susceptibility test, performed by radiometric assay BACTEC 460, showed 100% bacterial population resistant to isoniazid, and therefore the drug was withdrawn. Moreover, 60% bacterial population was resistant to rifampicin; this drug was later discontinued because of the development of hemolytic anemia, and replaced with rifabutin. Three negative sputum samples by direct microscopy were obtained before discharge; these results were later confirmed by cultures. Four months later, chest CT scan improved, with a decrease in the number of miliary infiltrates, that completely resolved after 14 months of anti-tubercular treatment. Six months after discontinuation of immunosuppressive treatment, and upon reaching $CD4^+$ lymphocyte levels >500/mm^3, anti-tubercular therapy was withdrawn, after a total of 18 months of therapy. At present, 3 years after the end of anti-tubercular treatment, the patient is in good clinical condition and is followed-up on a regular basis. No tubercular reactivation has been seen since the end of the specific treatment.

DISCUSSION

Tuberculosis (TB) is rarely reported after HSCT, but its incidence is considered to be 10-40 times higher compared to the general population (Gasink *et al.*, 2005) and the few data available from countries with high incidence of tuberculosis show frequencies ranging from <1% to 5.5% (Yuen *et al.*, 2002), reaching even 16% in Pakistan according to recent reports (Russo *et al.*, 2010). Patients who undergo HSCT in a country with a high endemicity of TB seem to be at higher risk of infection (Budak-Alpdogan *et al.*, 2000; Akan *et al.*, 2006). However, the prevalence of active TB after allogeneic HSCT has not been reported for patients born in endemic regions who undergo the transplantation procedure in the USA or Western Europe. Onset of disease has been reported between day +11 and +3337 post-HSCT (Gasink *et al.*, 2005), and the lung is the most frequently involved organ (Akan *et al.*, 2006), but fatal sepsis and rapid progressive illness (Kindler *et al.*, 2001) have also been observed. The diagnosis of TB after allogeneic HSCT is difficult due to the absence of typical radiological features (Demirkazik *et al.*, 2008; Jung *et al.*, 2009), and to the frequent incidence of other opportunistic pathogens that may occur after transplant.

We describe a case of disseminated TB in a child receiving allogeneic HSCT from an alternative donor. Since he came from a geographic area with high endemicity, we considered the possibility of latent TB, but chest CT scan was negative and PPD skin test resulted negative both in the patient (even though immunosuppression may have led to a false negative test) and in his mother. Quantiferon assay was not available at this time, and therefore we concluded that TB was absent, at least in the family environment. As a consequence, this diagnosis was not taken into consideration at the beginning of the diagnostic and therapeutic work-up. Primary prophylaxis with isoniazid would have been administered with some clinical or radiological evidence of latent TB, according to local policy, even if there is no consensus in the literature (Russo *et al.*, 2010)

and it is not reported to significantly alter the incidence of TB infection after HSCT (George *et al*., 2004). Because of the rapid worsening of the patient's clinical condition, wide spectrum antibacterial and antifungal therapy was administered, which led to some improvement, and blood cultures for *M. tuberculosis* were performed, but results were only available after a very long time. In the absence of any microbiological documentation and in the presence of a chest CT scan with no specific findings, the clinical picture was considered to be a possible invasive fungal disease according to 2002 diagnostic criteria available at that time (Ascioglu *et al*., 2002) (even though the EORTC/MSG criteria were developed for research and not for clinical purposes), since aspergillosis represents the leading cause of infectious pneumonia following allogeneic HSCT (Afessa *et al*., 2006); the use of 2008 revised definitions of invasive fungal disease (De Pauw *et al*., 2008) might have prevented this misleading diagnosis. Nevertheless, since the patient empirically received ciprofloxacin, clarithromycin and linezolid, which are second-line antitubercular drugs, the "eleventh-hour" treatment probably allowed the patient's survival until a correct diagnosis was made. As recently reported by Lee *et al.* (2011), the timing of TB infection and the delay in the diagnosis can be crucial for the final outcome, because the severe immunosuppression after HSCT may have a negative influence on the response to anti-TB treatment. This issue also emphasizes the critical need to perform a wide microbiological diagnostic work-up in cases of severe pneumonia with an unknown etiology, including the execution of specific cultures for uncommon pathogens, whose isolation may dramatically modify therapy and clinical outcome.

The retrospective re-evaluation of this case, performed after the documentation of *M. tuberculosis* in blood cultures, showed all the pitfalls of this case:

1. EORTC/MSG criteria for clinical evaluation must be applied with caution in everyday practice;
2. CT scan is useful but must always be correlated with the clinical picture;
3. family medical history and PPD skin test only, in a condition of immunodepression, may not suffice to identify which patients are at risk for TB.

In addition, physicians should be concerned that the time required to obtain results from specific microbiological cultures, which represented the only diagnostic method to detect *M. tuberculosis* at the time of our report, can be too long for immunodeficient patients after HSCT as they need prompt therapeutic intervention. Fortunately, in recent years promising diagnostic techniques are being developed like Real Time Polymerase Chain Reaction, which may detect *M. tuberculosis* DNA in a few hours and analyze its pattern of susceptibility by looking for specific gene mutations involved in antibiotic resistance (Hillemann *et al*., 2011). However, this method is currently performed only on some specimens, like pleural fluid and sputum, but is not yet validated on blood samples. This application would be strikingly useful to perform a correct diagnosis in a short time, which can be critical in severely ill HSCT patients.

In the wake of the rising incidence of TB in countries that were previously characterized by a very low prevalence, and the current health migrations, this case report highlights the importance of taking into consideration the possible role of uncommon pathogens in the differential diagnosis of pulmonary infections after HSCT.

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