

A fast and fatal course of bronchiectasis: an unusual rare expression of chronic graft versus host disease. A case report

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Introduction. We report a case of a patient with acute myeloid leukaemia whose treatment with bone marrow transplantation (BMT) was followed by chronic graft versus host disease (GVHD) with lung involvement and bronchiectasis. This report illustrates an unusual course of a fast progression of the bronchiectasis due to BMT.

Case description. A 33-year-old female was diagnosed with acute myeloid leukaemia. An allogeneic BMT was performed. One month after the transplantation, acute GVHD with skin involvement occurred. Treatment with prednisolone and mycophenolate mofetil (MMF) has been started. Nine months later, the patient was examined by a pulmonologist due to progressive dyspnoea. A pulmonary computed tomography (CT) scan showed normal parenchyma of the lungs and no changes to the bronchi. A CT scan performed 7 months later revealed bronchiectasis for the first time. No clinical response was associated with the treatment and the patient's respiratory status progressively deteriorated. During the final hospitalization, a CT scan performed 1 year later revealed huge cystic bronchiectasis in both lungs. Despite the prophylaxis and treatment of GVHD and aggressive antimicrobial therapy, the patient died one year after the diagnosis of bronchiectasis.

Conclusions. This case demonstrates that a fast and fatal course of bronchiectasis, that occurs after BMT, should always be considered as a possible manifestation of chronic graft versus host disease (cGVHD) following allogeneic BMT.

Keywords: bronchiectasis, bone marrow transplantation, chronic graft versus host disease, computed tomography

INTRODUCTION

Bronchiectasis is an uncommon disease, most often secondary to an infection that results in an abnormal and permanent distortion of the conduct-

ing bronchi. There are numerous aetiologies that can contribute to the pathophysiologic processes that may result in bronchiectasis. These include infection, airway obstruction, cystic fibrosis, Young's syndrome, rheumatic and systemic diseases, dyskinetic cilia, allergic bronchopulmonary aspergillosis, cigarette smoking, etc. (1). The prevalence of bronchiectasis varies among different countries. Data from several countries suggests an incidence rate of

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2.7–4.2 per 100,000 people (2). It is estimated that 110,000 individuals in the United States have bronchiectasis (3). The clinical course of bronchiectasis is often chronic and progressive. In most cases, this results in severe lung damage over many years (4).

Bronchiectasis has rarely been reported in association with bone marrow transplantation (BMT) (5). In addition, rapid progression of bronchiectasis is very unusual and only a few cases have been documented. One of the possible aetiological factors for bronchiectasis could be chronic graft versus host disease (GVHD). This report describes a well-documented case of the development of bronchiectasis following bone marrow transplantation, and a fast, irresistible progress of the disease that resulted in the death of a previously healthy female patient.

CASE-REPORT

A 33-year-old female with no significant past medical history was diagnosed with Hodgkin's lymphoma. The patient received eight cycles of an escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, procarbazine) regimen, which resulted in a complete remission.

After three years of remission, the patient returned to our hospital with fever, muscle pain, dizziness, coughing and shortness of breath. Her blood tests revealed pancytopenia, anemia, inflammation, bone marrow aspiration showed that 38% of her marrow comprised blast cells. Her phenotype was characteristic of acute myeloid leukaemia. A chemotherapy protocol with DA (cytarabine and daunorubicin) was started. Two cycles of the DA protocol and two cycles of HD-AraC (high-dose cytarabine) protocols were realized in the next seven months. An allogeneic BMT from an unrelated stem cell donor was performed. Cyclosporin A was administered as a prophylaxis for cGVHD. However, one month after the transplantation, acute GVHD with skin involvement occurred. Treatment with prednisolone and MMF has been started. The patient was examined by a pulmonologist due to progressive dyspnoea nine months after the allogeneic BMT had been performed. Pulmonary function testing (PFT) revealed a severe airway obstruction (FEV_1/FVC was 44% and the FEV_1 was 40%). Inhalations of budesonide and formoterol were administered.

However, shortness of breath gradually increased until the patient was admitted to the Department of Pulmonology and Allergology one month later. A pulmonary CT scan did not show any signs of bronchiectasis (Fig. 1). Based on routine diagnostic criteria, bronchiolitis obliterans syndrome (BOS) was diagnosed (6, 7, 16). The patient was repeatedly hospitalized because of developing respiratory failure and persistent respiratory infections. The most common pathogens detected within her respiratory tract secretions were *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Mycobacteria and fungi were not found. Exacerbations of symptoms became more frequent.

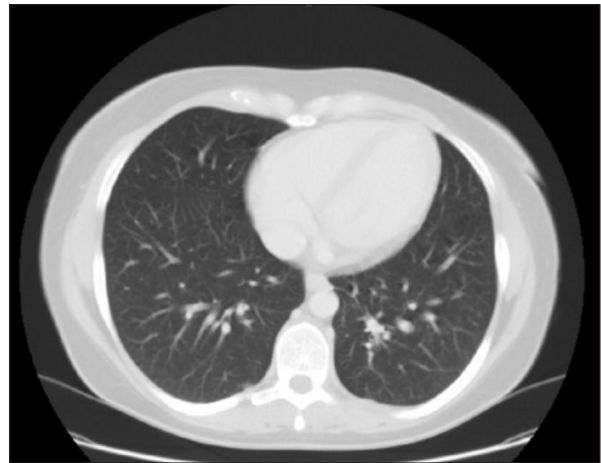


Fig. 1. The first CT scan shows normal parenchyma of the lungs and no changes in the bronchi

Seventeen months after the bone marrow transplantation, a new CT scan revealed bronchiectasis for the first time (Fig. 2). Treatment of cGVHD with MMF and prednisolone was continued. However, the patient's respiratory status progressively deteriorated. PFT indicated progressive airflow obstruction (her FEV_1/FVC was 37% and her FEV_1 was 28%).

During the final hospitalization (30 months after the bone marrow transplantation), the patient's general condition became critical. A CT scan revealed huge cystic and cylindrical bronchiectasis and ground glass zones on both sides of the lungs (Fig. 3). The patient was transferred to the Intensive Care Unit. Despite the aggressive treatment, multiple organ dysfunction syndrome developed, and the patient died one year after bronchiectasis had been diagnosed.



Fig. 2. Performed 17 months after BMT, this CT scan shows scattered ground glass opacities in both lungs with a parenchymal band, interlobular septal thickening and a signet ring appearance in the axial plane

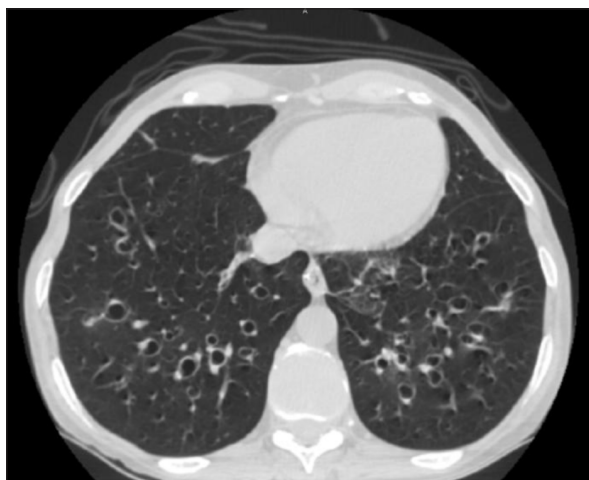


Fig. 3. Performed 29 months after BMT, this CT scan reveals huge cystic and cylindrical bronchiectases and ground glass zones on both sides of the lungs

DISCUSSION

Allogeneic BMT is a part of the treatment for certain serious haematologic and immunologic diseases. cGVHD is the most frequent complication following allogeneic BMT. Approximately 40–60% of the patients who undergo BMT develop pulmonary disease, resulting in a mortality rate of 10–40% (8–10). Severe pulmonary disease associated with cGVHD is a late complication. It usually occurs at least 100 days after BMT (11).

There are many types of pulmonary complications, which can occur following allogeneic BMT. While bronchiectasis may be an under-recognized manifestation of cGVHD, it has already been proven that cGVHD could be one of the possible aetiological factors for bronchiectasis (5, 12–15).

Pulmonary complications account for a significant morbidity and mortality in patients following BMT. The question in our case is whether the lung injury was due to cGVHD that followed allogeneic BMT. As is established by the National Institute of Health report, the diagnosis of cGVHD requires at least one diagnostic manifestation of cGVHD, or at least one distinctive manifestation, with the diagnosis confirmed by a biopsy or a laboratory test (16). BO diagnosed via clinical criteria requires at least one manifestation in a separate organ system in order to establish the diagnosis of cGVHD. In our case, the diagnosis of BOS was documented. Moreover, the temporal relationship between the transplantation and the disease onset, the absence of prior pulmonary function abnormalities and the inability to elucidate another cause suggest cGVHD as a likely aetiology of the patient's pulmonary condition. We cannot rule out the fact that the clinical presentation in our case was not a manifestation of BOS following GVHD and bronchiectasis was not a manifestation of BOS. However, the course of disease was very fast and resulted in a rapid lung function decline and unwanted manifestation of bronchiectasis.

We performed a systematic review of the published literature (including PubMed, Google Scholar and Embase databases) to select cases of bronchiectasis occurring after BMT. We found only 11 such cases of bronchiectasis with a very fast progression (17–23). Analysis of the available data presented in these reports, as well as ours, revealed that bronchiectasis developed 4 to 65 months (median of 13 months) after BMT. Most of the earlier reports describe mild to moderate bronchiectasis in patients following BMT. We describe a case of severe, cystic bronchiectasis, with fast progression of the disorder. The case presented here is unusual because of the rapid progression of bronchiectasis, which was captured on serial CT scans.

Variations in mortality rates of bronchiectasis not related to BMT have been reported in the literature. The survival rates in the studies are 75–84% at nine years and 68–81% at 12–14 years (24–26).

Analysis of the available data for the discussed twelve cases of bronchiectasis following BMT showed that death occurred at two, 12 and 37 months after the initial development of bronchiectasis. One patient was still alive 17 months after developing bronchiectasis. There is no available data regarding the follow-up of the other eight patients.

The pathogenesis of cGVHD-induced bronchiectasis is not yet completely clear. Numerous possible pathogenetic factors that can induce the development of bronchiectasis in patients with cGVHD were examined (5). One hypothesis is that donor T lymphocytes and cytokines attack and damage host bronchial epithelial cells (27). Another hypothesis claims that after some factor induces lung damage, sinopulmonary mucociliary clearance mechanisms are disturbed, which leads to microbial colonisation, such as by *P. aeruginosa* (28), as was seen in our case. Subsequently, the persistent microbial stimulus may produce an inflammatory reaction by the host, resulting in advanced airway damage (28). We believe that this mechanism explains the findings in our presented case, in which both immunological and microbiological pathogenetic mechanisms take part.

In terms of treatment, a combination of cyclosporin A and prednisolone has been the standard front line therapy for cGVHD for almost 20 years (29). The duration of the therapy is usually close to 12 months. In a retrospective series of patients with extensive cGVHD, only 10 to 30% became long-term survivors (30). The pulmonary complications of allogeneic BMT include a broad spectrum of infections. Antimicrobial prophylaxis and/or vaccination is a very important aspect of the treatment of patients after BMT. cGVHD with a lung injury is usually associated with an obstructive ventilatory defect. Bergeron et al. (31) retrospectively analysed a combination of budesonide and formoterol for basic treatment of progressive airflow obstruction. The results showed a durable improvement, both clinically and in PFT, over the follow-up of 12.8 months (5–29 months).

In retrospect, cyclosporin A was administered to our patient as prophylaxis for cGVHD. However, after several months, she returned with a progressive dyspnoea, and a pulmonary function test showed severe obstruction. Our patient also received antibiotics, MMF, oral prednisolone, a combination of inhaled steroids and a long-acting bronchodilator.

Despite the treatment, lung function became worse and recurrent infections led to bronchiectasis.

In summary, bronchiectasis can develop soon after BMT in patients with chronic GVHD and the course of them can be rapid and fatal. This case demonstrates that lung injury and bronchiectasis that occur after BMT should always be considered as a manifestation of cGVHD following allogeneic BMT. Early recognition, improved treatment and prevention of cGVHD-induced bronchiectasis may have a substantial impact on the morbidity and mortality associated with this form of treatment.

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BRONCHEKTAZĖS: GREITA IR MIRTINA EIGA SERGANT TRANSPLANTATO PRIEŠ ŠEIMININKĄ LIGA

Santrauka

Įvadas. Aprašome pacientės, sirgusios ūmine mieloleukemija, klinikinį atvejį, kuriai buvo atlikta kaulų čiulpų (KČ) transplantacija ir išsivystė transplantato prieš šeiminingą ligą (TPŠL) su plaučių pažeidimu. Šis atvejis atspindi greitą bronhektazių progresavimą ir netipinę jų eigą po atliktos KČ transplantacijos.

Atvejo aprašymas. 33 metų moteriai diagnozuota ūminė mieloleukemija, atlikta KČ transplantacija, po kurios praėjus 1 mėn. išsivystė ūminė odos TPŠL. Pradėtas imunosupresinis gydymas prednizolonu ir

mikofenolato mofetiliu. Po 9 mėn. dėl progresuojančio dusulio ligonė konsultuota pulmonologo. Tada krūtinės ląstos kompiuterinėje tomografijoje (KT) plaučių parenchimos ir bronchų pokyčių nebuvo. Praėjus dar 8 mėn. pirmą kartą nustatytos bronhektazės. Skyrus reikiamą gydymą, pacientės būklė blogėjo, ryškėjo kvėpavimo nepakankamumas, o paskutinės hospitalizacijos metu KT stebėtos didelės cistinės bronhektazės abiejuose plaučiuose. Nepaisant profilaktinio TPŠL gydymo, agresyvios antibiotikoterapijos, ligonė mirė praėjus 1 metams po bronhektazių nustatymo.

Išvados. Šis atvejis parodo, kad po atliktos KČ transplantacijos bronhektazių eiga gali būti greita ir mirtina. Tai gali būti lėtinės TPŠL išraiška po atliktos alogeninės KČ transplantacijos.

Raktažodžiai: bronhektazės, kaulų čiulpų transplantacija, lėtinė transplantato prieš šeiminingą ligą, kompiuterinė tomografija