

Recurrent Pneumomediastinum and Subcutaneous Emphysema Complicating Chronic Graft versus Host Disease after Allogeneic Bone Marrow Transplantation

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Several noninfectious pulmonary complications can be associated with chronic graft versus host disease (GVHD). Obstructive airway disease can be a clinical feature of chronic GVHD and the histopathology reveals characteristic lesions of bronchiolitis obliterans. Bronchiolitis obliterans is an obstructive pulmonary disorder affecting the small airways, and it was first described as a late complication of allogeneic bone marrow transplantation (BMT). Spontaneous pneumomediastinum and subcutaneous emphysema can occur in the setting of severe bronchiolitis obliterans and only rarely are they the first sign of such disease. We describe here a case of a 27-year old woman who developed recurrent pneumomediastinum and subcutaneous emphysema that were secondary to the bronchiolitis obliterans that complicated chronic GVHD after allogeneic BMT. (*Korean J Hematol* 2006;41:61-65.)

Key Words: Pneumomediastinum, Subcutaneous emphysema, Bronchiolitis obliterans, Chronic graft versus host disease, Allogeneic bone marrow transplantation

INTRODUCTION

Half of all patients who undergo allogeneic bone marrow transplantation (BMT) achieve long-term disease free survival, but a similar number develop significant complications. Pulmonary complications remain frequent cause of post-transplantation mortality.^{1,2)}

Bronchiolitis obliterans (BO), a nonspecific inflammatory injury affecting the small airways primarily, has been reported to occur between 5~11% in long term survivors of BMT with chronic

graft versus host disease (GVHD).³⁾ It can comprise a spectrum of pathology ranging from mild histological changes to severe pulmonary function abnormalities and crippling airway obstruction leading to death. Pneumothorax, pneumomediastinum, and subcutaneous emphysema are considered as rare complications of BO.⁴⁾

Here we describe a patient with BO presenting with recurrent spontaneous pneumomediastinum, and subcutaneous and emphysema complicating chronic GVHD after allogeneic BMT.

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CASE REPORT

A 27-year old woman underwent related allogeneic BMT for chronic phase of chronic myeloid leukemia in October 2003. She was diagnosed with chronic phase of chronic myeloid leukemia three months before, when she was presented with abdominal discomfort and headache. She was initially treated with imatinib mesylate for two months. She underwent allogeneic BMT from her brother (HLA full matched) after conditioning with intravenous busulfan (from days -7 to -4; 0.8mg/kg q 6hours per day) and cyclophosphamide (from days -3 to -2; 60mg/kg per day). Post-transplant GVHD prophylaxis was treated with cyclosporine and short-course methotrexate. Pulmonary function tests that were made as a routine before the transplantation showed normal test parameters including spirometry, lung volumes, diffusion, and airway resistance. The course of the transplantation was uneventful, with good engraftment, and the patient was sent home after three weeks of hospitalization. Five weeks after

BMT, she developed jaundice and skin rash on her face and trunk which was proven as acute GVHD and were treated high dose steroids. Since then, she continued to have chronic GVHD involving skin, gut, liver and was treated steroids, cyclosporine and PUVA. Five months after BMT, she developed dyspnea, nonproductive cough and chest pain abruptly. Physical examination at that times showed crepitus involving the neck and anterior chest due to subcutaneous emphysema. Pulmonary function tests showed severe obstructive pattern of small airway. Chest radiographs demonstrated subcutaneous emphysema and pneumomediastinum (Fig. 1). A High resolution CT scan of the chest demonstrated pneumomediastinum and subcutaneous emphysema (Fig. 2). We could not find other causes of air-leak syndrome and the diagnosis of BO was made. Further more, chronic GVHD of the skin continued. Subsequently she was added mycophenolate mofetil and treated conservatively including high-flow oxygen. Subcutaneous emphysema and pneumomediastinum was near completely resolved. After three weeks, subcutaneous emphysema and pneumomediastinum was relapsed more extensively (Fig. 3). She was treated with tacrolimus instead

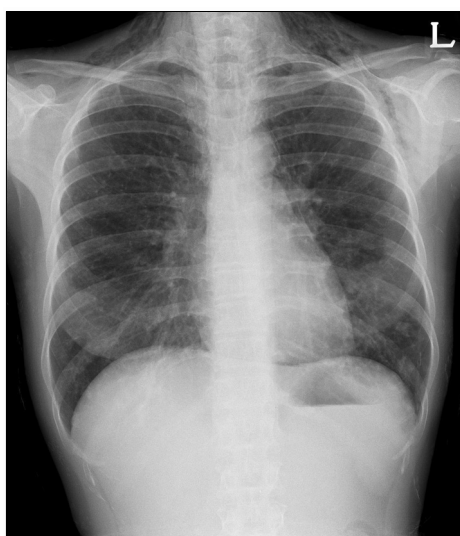


Fig. 1. Plain chest radiograph showing subcutaneous emphysema in the neck and upper trunk and pneumomediastinum.

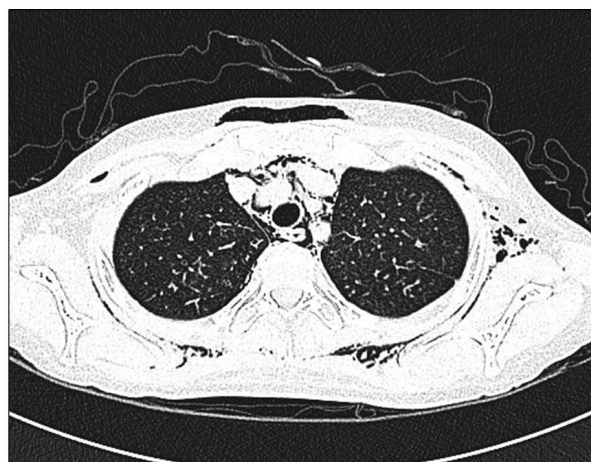


Fig. 2. High resolution CT of the chest showing the subcutaneous emphysema and pneumomediastinum at first event.

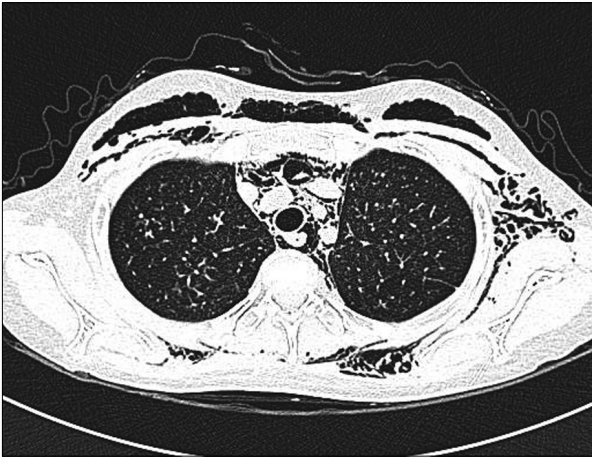


Fig. 3. High resolution CT of the chest showing the recurrent subcutaneous emphysema and pneumomediastinum.

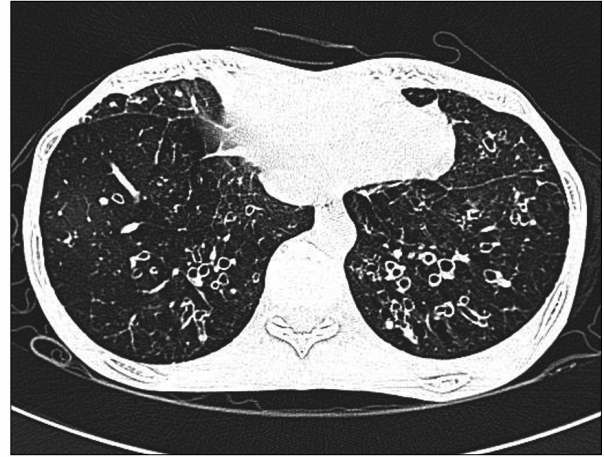


Fig. 4. High resolution CT of the chest showing bronchial wall thickening and dilatation in the both lung field at one year later.

of cyclosporine. After two weeks, her pulmonary condition was improved and subcutaneous emphysema and pneumomediastinum was completely resolved. Her pulmonary condition continued to mildly worsen with immunosuppressive therapy but air leak syndrome did not recur during a follow-up period. One year later, following a high resolution CT scan of the chest demonstrated typical pattern of BO; There was striking dilatation of subsegmental airways in mainly both lower lung field (Fig. 4). She died at home due to sudden respiratory arrest approximately 21 months after transplantation.

DISCUSSION

Chronic airflow obstruction is the most common late complication of allogeneic hematopoietic stem cell transplantation, typically occurring beyond the third month and associated with underlying chronic GVHD in the majority of cases.^{5,6} The incidence in the allogeneic population varies between 6 and 26% in published series. The underlying process accounting for airflow obstruction in the majority of cases is BO.⁶

BO was first recognized in 1982 by Roca et al.,

who described a patient with chronic GVHD after allogeneic BMT for aplastic anemia, and who died of BO.⁷ In addition to chronic GVHD, risk factors for development of OB include recipient old age, low serum immunoglobulin levels, use of methotrexate, and history of a respiratory viral infection within the first 100 days.^{2,5} The etiology remains obscure. However, the strong association with chronic GVHD and the presence of underlying BO suggests that the bronchial epithelium may be the target of immune mediated injury induced by donor cytotoxic T cells.⁸

The onset of OB is often insidious. Presenting symptoms include nonproductive cough, dyspnea, and wheezing. Pulmonary function tests often reveal a moderate to severe airway obstruction as indicated by FEV1/FVC ratios close to 50%.⁹ The chest radiograph is commonly normal, but high-resolution CT often demonstrates evidence of air trapping, hypoattenuation, florid bronchial wall thickening and dilatation.¹⁰ The diagnosis is established by demonstration of persistent airflow obstruction on simple spirometry and exclusion of other causes. The yield of transbronchial biopsies is low and the utility of bronchoscopy is limited to its role in excluding infectious causes. Surgical lung biopsy is rarely indicated.

Disease progression is variable, so some patients experience a rapid decline in lung function whereas others have a more protracted course. In the study by Clark et al., overall mortality was 65% in patients with obstructive lung disease at 3 years after transplantation. There is no standardized approach for the treatment of BO in post BMT patients. The treatment has traditionally involved increased immunosuppression. Increased immunosuppression with cyclosporine or prednisone has been shown to produce stabilization of the clinical condition in several studies.¹¹⁾ A number of other therapies have been suggested, such as antithymocyte globulin, extracorporeal photophoresis, hydroxychloroquine, mycophenylate, thalidomide and rapamycin.^{6,11)} Lung transplantation is an option for select patients with severe BO who are free of other significant comorbid conditions.¹²⁾

Spontaneous pneumomediastinum and subcutaneous emphysema secondary to BO are unusual complications after allogeneic BMT. Multiple pleural bullae have been observed in some of these patients.¹³⁾ Severe obstruction of the terminal bronchioles can lead to air trapping and development of the bullae. Infectious origin should be also considered on the differential diagnosis of those air leak syndromes.¹⁴⁾

Here we describe a patient with BO presenting with recurrent spontaneous pneumomediastinum, subcutaneous emphysema complicating chronic GVHD after allogeneic BMT for chronic phase of chronic myeloid leukemia. Unlikely the majority of patients presenting with BO, her symptomatic onset is abrupt and air leak syndrome is recurrent in spite of additional immunosuppressive therapy. This case again highlights the irreversible nature of this disease and the poor response to conventional therapy. Avoidance of risk factors and the development of new modalities of therapy associated with OB after allogeneic BMT would help to decrease morbidity and mortality.

요 약

저자들은 만성골수성백혈병으로 동종골수이식을 시행받은 환자에서 만성이식편대숙주질환에 합병해 발생한 재발성 자발성 기종격동과 피하기종으로 인해 병발한 폐색성 세기관지염을 진단했던 드문 1예를 경험하여 보고하는 바이다.

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