# Bronchiolitis Obliterans Syndrome After Heart-Lung Transplantation: A Case Report and Review of Literature

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*Bronchiolitis obliterans syndrome (BOS) is regarded as a manifestation of chronic rejection after lung transplantation and remains the major cause of late morbidity and mortality after lung and heart-lung transplantation. The authors, herein, reported the first documented case of a patient who receiving heart-lung transplantation at our institute and developed BOS as a late complication. The patient presented 5 years after received heart-lung transplantation with progressive shortness of breath due to obstructive lung disease. He was diagnosed with BOS by typical clinical presentation, pulmonary function test and radiographic findings and there were no other identified etiologies of airway obstruction. The authors also reviewed the recent update on the diagnosis and management of BO after lung transplantation.*

***Keywords :*** *Bronchiolitis obliterans syndrome*

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Lung and heart-lung transplantation are currently accepted as treatment for selected patients with end stage lung or heart-lung disease. Survival rates have improved markedly in recent years, however the overall outcome and long-term survival of these patients is still hampered by the development of chronic rejection. Bronchiolitis obliterans syndrome (BOS) is regarded as a manifestation of chronic rejection and remains the major cause of late morbidity and mortality after lung and heart-lung transplantation. The authors, herein, reported the case of a patient who received heart-lung transplan-tation at our institute and developed BOS as a late complication. The authors also reviewed the recent update on the diagnosis and management of BOS after lung transplantation.

**Case Report**

A 58-year old gentleman was admitted to King Chulalongkorn Memorial Hospital because of progressive shortness of breath. The patient had a history of diabetes mellitus and severe coronary heart disease. He had coronary artery bypass surgery 10 years prior to this admission, but he developed severe ischemic cardiomyopathy and secondary pulmonary hypertension. Due to a very limited functional capacity, he underwent heart-lung transplantation 5 years prior to this admission. The patient and donor both had positive CMV antibody. He received immunosuppressive regimen with corticosteroids, cyclosporine and azathioprine, which was subsequently switched to mycophenolate due to drug-induced hepatitis. He also received prophylactic treatment with trimetroprim and sulfamethoxazole. His early post transplantation course was uneventful. He had minor rejection episodes in the first few months after transplant, which responded well to an increasing dose of corticosteroids. Follow up post-operative lung function (Table1) and chest x-ray were normal. Routine lung biopsy is not performed as rejection surveillance in our institute. He was otherwise in a normal state of health and able to resume normal daily activities. His recent immunosuppressive regimen was prednisolone 5 mg/day, mycophenolate

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**Table 1.** Spirometry

| | Post transplant | 2 /4/2002 | 3/5/2002 (admission) | 8/8/2002 (3 months)** | 9/10/2002 (4 months)** | 01/02/2003 (8 months)** |
|---|---|---|---|---|---|---|
| $FEV^*_1$ | 2.81(90%) | 2.14(75,9%) | 1.86(66%) | 1.68(62.5%) | 1.70(64%) | 1.64(61%) |
| FVC* | 3.00(85.2%) | 3.00(85.2%) | 2.92(83%) | 2.68(79.3%) | 2.72(80%) | 2.66(78%) |
| $FEV_1$/FVC | 0.94 | 0.71 | 0.64 | 0.63 | 0.625 | 0.62 |
| | No bronchodilator response | | | | | |

* actual number and % of predicted from normal in parenthesis
** Indicates period after adjustment of immunosuppressive medications

1 gm/day and cyclosporine 100 mg/day. He started having increased shortness of breath about 2 months prior to this admission. He experienced a dry cough but denied any fever, chest pain or other systemic symptoms. He also had about 5 kilograms weight loss in the past 2 months. He took his immunosuppressive medication on a regular basis and recent cyclosporine level was in the accepted range (130 ng/ml). At admission, body temperature was 37.2 C, respiration rate was 16/min. The pulse rate was 100 beats/min with regular rhythm. Oxygen saturation on room air was 97%. On examination, the patient was not in acute distress, he was not pale or cyanotic. Jugular vein was not engorged. Heart sound was normal. Chest examination revealed a good bilateral breath sound with end expiratory wheezing bilaterally, no crackles were audible. Liver and spleen were not palpable. There was no pedal edema or abnormal skin lesions.

Initial laboratory tests were performed (Table 2). Chest x-ray at admission was normal without new pulmonary infiltration. The pulmonary function test showed moderate obstructive defect without bronchodilator response (Table 1). Transthoracic echocardiogram showed mild impairment of LV systolic function (EF 40%) with normal pulmonary pressure, which was not changed from the previous examination. High resolution computerized scan of the chest revealed a small area of ground glass opacity at the posterior segment of the right upper lobe, and no evidence of air trapping.

The patient underwent bronchoscopic examination, which revealed a normal upper airway. Tracheal anastomosis and main stem bronchus were normal without any evidence of an endobronchial lesion or obstruction. The appearance of airway mucosa was normal with minimal secretion. Bronchoalveolar lavage was performed at both lower lobes. All staining and cultures for pathogens were negative.

In the context of progressive shortness of breath and airways obstruction in a patient after heart-lung transplantation without other etiology demonstrated, the patient was diagnosed with bronchiolitis obliterans syndrome. He was treated by an augmentation of immunosuppressive regimen. Prednisolone was increased to 30 mg/day and mycophenolate increased to 2 gm/day. His clinical status and pulmonary function test was stabilized after adjustment of medication. Subsequent spirometry 3 and 8 months after the episode showed stabilization of $FEV_1$ and FVC (Table 1) and the patient's overall status was stable.

**Table 2.** Initial laboratory findings on admission

| |
|---|
| CBC: WBC 8,000/$mm^3$ N 69% L 30% Hct 42% Hb 13.9 gm/dl plt 230,000/$mm^3$ |
| BUN 25 mg/dl Cr 1.5 mg/dl Elctrolyte: normal |
| SGOT 56 U/ litre SGPT 35 U/litre alkaline phosphatase 36 U/litre |
| MCV serology CMV DNA (< 400 copies/ml: negative test) |

## Discussion

This is the first documented case of bronchiolitis obliterans syndrome in a patient post heart-lung transplantation in Thailand. The patient presented 5 years after receiving heart-lung transplantation with progressive shortness of breath due to obstructive lung disease. He was diagnosed with BOS by typical clinical presentation, pulmonary function test and radiographic findings and there were no other identifiable etiologies of airway obstruction.

Obliterative bronchiolitis (OB) was first described in 1901 in patients with progressive dyspnea[1]. Pathologic hallmark of this condition is dense submucosal fibrosis involving the respiratory

bronchioles. There can be significant intrabronchiolar or peribronchiolar mononuclear cells infiltration in active cases. These are progressive lesions that can result in total or near total occlusion of bronchiolar lumen. There are many medical conditions associated with OB such as infectious process[2] (respiratory syncytial virus, mycoplasma pneumonia etc.), inhalation of toxic fumes[3] (nitrogen dioxide, ozone), autoimmune diseases[4] and post bone marrow transplantation and lung transplantation.

Bronchiolitis obliterans syndrome (BOS) is the deterioration of graft function after heart-lung transplantation secondary to progressive airway disease that is otherwise unexplained by other factors such as infection, acute rejection, or anastomotic complications[5]. BOS does not necessary require histologic confirmation, but the term obliterative bronchiolitis (OB) is reserved for histologically proven diagnosis[5]. The prevalence of BOS is high in patients surviving lung or heart lung transplantation. The study from Standford identified a prevalence of BOS or histologiccally proven OB of 64.6% after heart-lung transplantation[6]. In the presented patient although there was no tissue diagnosis of OB, the authors ruled out other causes of progressive airway obstruction by bronchoscopic examination, bronchoalveolar lavage and serologic testing to rule out other possible etiologies such as endobronchial lesion, and CMV infection.

Clinical symptoms of BOS are dry cough and increasing shortness of breath with exertion. The onset of symptoms usually is insidious and symptoms progress in a few months. On physical examination, evidence of airflow obstruction, such as prolonged expiration or expiratory rhonchi can be detected. Hypoxemia develops as a late clinical manifestation. Mucopurulent secretion may occur in the presence of superimposed infection with secondary bronchiectasis.

Pulmonary function test is the most sensitive diagnostic tool for BOS. There is a progressive reduction of $FEV_1$ and $FEV_1$/FVC ratio compatible with obstructive defect. $FEF_{25-75\%}$ may decline earlier in the course of disease than $FEV_1$. Airways obstruction rarely responds to bron-chodilator. Percentage predicted $FEV_1$ can be used to stage BOS (Table 3). Bronchoscopic examination help rule out anastomotic complication and bronchoalveolar lavage can help to identify infectious cause. Sensitivity of transbronchial biopsy for tissue diagnosis of OB varies from 17-87%[7]. Chest x-ray findings in BOS are nonspecific. High resolution computerized scan may show clear abnormalities suggestive of OB such as bronchiectasis, air trapping or areas of patchy infiltration[8].

Several risk factors associated with development of BOS in lung transplant patients have been identified. The single most important risk factor for OB is acute rejection. Other factors are CMV infection, HLA mismatches at A locus, noncompliance with immunosuppressive regimen, lymphocytic bronchitis/bronchiolitis[9]. The best way to prevent OB is to prevent and control acute rejection episodes. The natural course of BOS varies between patients. Patients with progressive disease can develop severe airflow obstruction and severe hypoxemia leading to death within a few months. Other patients may have slow deterioration of lung function, which is stabilized after treatment. Hower, OB is the most common cause of death of patients surviving longer than 3 months after lung transplantation. The most common cause of death in patients with OB is severe superimposed infection[5].

The main treatment of BOS in patients receiving lung transplantatoin is enhancing the immunosuppressive regimen. Prednisolone should be increased to 1 mg/kg/day and other immunosuppressive drugs should be increased to the maximum possible dose. Patients with histologiccally proven acute rejection episode should be treated with pulse methylprednisolone or antilymphocyte globulin. In some centers, changing from a conventional regimen to newer immunosuppressive drugs such as substitute tacrolimus for cyclosporine or mycophenolate for azathioprine have resulted in successful treatment[10,11]. However, early diagnosis and management are very important for treatment success. Patients with BOS stage 1 have a much better prognosis than others with stage 2 or 3[5]. Patients will also have increased risks of having secondary infection, so superimposed bacterial or fungal infection need to be treated aggressively. In patients who experienced progressive disease despite

**Table 3.** Staging of BOS (from reference 5)

| | |
|---|---|
| BOS stage 0 | : $FEV_1$: 80% to 100% |
| BOS stage 1 | : $FEV_1$: 65% to 80% |
| BOS stage 2 | : $FEV_1$: 50% to 65% |
| BOS stage 3 | : $FEV_1$ less than 50% of previous best baseline value |

(%$FEV_1$= of best post operative $FEV_1$)

medical treatment, retransplantation remains the last therapeutic option [12]. In the presented patient, he responded to an escalating dose of immunosuppressive drugs with stabilization of clinical status and $FEV_1$ after adjustment of immunosuppressive medications.

**Conclusion**

BOS is a common complication in long-term survivors after lung transplantation. The presented patient developed BOS 5 years after heart-lung transplantation with a typical presentation of BOS. He was treated with augmentation of immunosuppressive regimen and responded well with stabilization of clinical status and lung function.

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## *ภาวะ Bronchiolitis obliterans syndrome (BOS) ในผู้ป่วยที่ได้รับการผ่าตัดเปลี่ยนปอดและหัวใจ: รายงานผู้ป่วย 1 ราย*


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*ภาวะ bronchiolits obliterans syndrome (BOS) เป็นภาวะแทรกซ้อนที่พบได้บ่อยในผู้ป่วยที่ได้รับการผ่าตัดเปลี่ยนปอด หรือ เปลี่ยนหัวใจและปอด และเป็นสาเหตุสำคัญของการเสียชีวิตในผู้ป่วยหลังจากการผ่าตัดดังกล่าว ผู้นิพนธ์ได้รายงานผู้ป่วยชายที่ได้รับการผ่าตัดเปลี่ยนปอดและหัวใจที่โรงพยาบาลจุฬาลงกรณ์ และต่อมา 5 ปีหลังการผ่าตัด ผู้ป่วยเริ่มมีอาการหอบเหนื่อยมากขึ้นและตรวจพบว่ามีอาการอุดกั้นของหลอดลม จากอาการทางคลินิก การตรวจเพิ่มเติมทางห้องปฏิบัติการณ์สามารถให้การวินิจฉัยภาวะ BOS ในผู้ป่วยรายนี้ได้ผู้นิพนธ์ได้ทบทวนวรรณกรรมที่เกี่ยวข้องกับภาวะ BOS ที่เกิดภายหลังการผ่าตัดเปลี่ยนปอดในด้านการวินิจฉัยและการรักษาในปัจจุบัน*


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