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Achalasia as a Potential Predisposing Factor for Lung Allograft Rejection

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ABSTRACT

Microaspiration secondary to gastroesophageal reflux has been postulated to be a predisposing factor for development of bronchiolitis obliterans syndrome after lung transplantation. Esophageal manometry and ambulatory pH monitoring have been suggested as a screening test in patients with end-stage lung disease. We report a single lung transplant patient who developed allograft rejection presumed to be due to underlying achalasia as the patient's clinical status and lung function improved markedly following the treatment of achalasia.

The potential cause-effect association between esophageal disorder and allograft rejection and the clinical importance of the screening in this group to improve the survival rate after lung transplantation is proposed. (Tanaffos 2008; 7(3): 69-72)

Key words: Lung transplantation, Achalasia, Persistent allograft rejection, Pulmonary fibrosis

INTRODUCTION

Pulmonary fibrosis may result from a broad range of diverse chronic injuries including inhalation of fibrogenic substances, radiation, chemotherapy, chronic aspiration, drug reaction, various immunologic disorders, infection, or preexisting medical illnesses.

Currently, lung transplantation is the only viable therapeutic option with an acceptable survival rate (1). Despite the substantial improvement in surgical techniques, lung preservation, immunosuppression,

and management of post-transplant complications, chronic allograft rejection due to bronchiolitis obliterans syndrome (BOS) remains a major obstacle threatening long-term survival of recipients. BOS is a progressive fibrosis affecting the terminal and respiratory bronchioles which may result in either partial or total obstruction of the lumen. It accounts for more than 30% of all mortalities after the third year following lung transplantation (2).

At present, there is no effective treatment for chronic allograft rejection, and most studies focus on determining predisposing factors, early detection, and finding new therapies for BOS.

Among several potential predisposing factors, gastroesophageal reflux disease (GERD) has been

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shown to be associated with the development of BOS (3-7). It is concluded that, in some patients, the reflux extends into the upper esophagus and causes microaspiration which may lead to development of BOS.

We report a single lung transplant patient who developed allograft rejection presumed to be due to underlying achalasia.

CASE SUMMARIES

A 41-year-old Caucasian man, with a history of dry coughs, progressive exertional dyspnea from childhood and end-stage pulmonary fibrosis with unknown etiology, underwent left single-lung transplantation in August 2006. His open lung biopsy performed when he was 9 years old in England, confirmed pulmonary fibrosis. He had been oxygen dependent for four years before transplantation. His post-operative course was uneventful, and on the 21st post-operative day, the patient was discharged on cyclosporine, mycophenolate mofetil and tapering doses of prednisone. Two months after transplantation, the patient's FEV1 declined and an acute vascular rejection (grade 2-3) was detected on TBLB. Because of severe infection, methyl prednisolone was not administered but there was thick purulent exudate in the transplanted bronchi. His immunosuppressive medication was changed from cyclosporine to tacrolimus with subsequent improvement in FEV1. Bronchoalveolar lavage fluid was positive for *Klebsiella* and *Aspergillus*, treated successfully with broad spectrum antibiotics, itraconazole and inhaled amphotericin.

Forty days later the patient developed tacrolimus-induced hyperglycemia which was reversed by substitution of tacrolimus with cyclosporine and increments of mycophenolate mofetil.

Six months after transplant, the patient developed marked progression of dyspnea. TBLB showed transplant rejection (grade 2-3).

In addition, a dark secretion on bronchoscopy and dilated esophagus on CT-scan were noticed. Upper gastrointestinal (UGI) barium swallow was performed which demonstrated a diffusely dilated esophagus with a "birds-beak" filling defect in the distal part (Figure 1). Achalasia was suspected which was subsequently confirmed by manometric examination showing increased lower esophageal sphincter (LES) pressure. Resting pressure of LES was 7 mmHg and 41.1 mmHg by SPT and RPT analysis, respectively. There was no normal wave. All waves were simultaneous and of low amplitude.



Figure 1. Barium swallow showing beak-like termination of the esophagus.

No change occurred despite medications. Surprisingly, before administration of methyl prednisolone, by dietary regulation and lifestyle modifications (e.g., having more solid foods, sleeping for at least two hours after meals, and sleeping at a 30 degree semi-sitting position) the patient's clinical status and lung function improved markedly (FEV1 rose from 40% to 53%) after only

three weeks and TBLB showed rejection grade 0-1.

Subsequently, pneumatic dilation was performed. The procedure was tolerated well and the patient is now asymptomatic 24 months onward with no decline in lung function.

DISCUSSION

In this case of lung allograft dysfunction, clinical status and lung function improved markedly following treatment of underlying achalasia. A reasonable interpretation of this finding is that achalasia and aspiration contribute to allograft dysfunction and cellular infiltrates.

Achalasia is a neurogenic esophageal motility disorder characterized by lack of normal peristalsis at the lower two third of the esophagus and failure of the lower esophageal sphincter (LES) to relax (8). The symptoms (i.e., dysphagia, weight loss, regurgitation, chest pain, and heartburn) of achalasia are often insidious in onset and gradual in progression. Many patients are treated for other disorders such as GERD before the diagnosis of achalasia is made (9). Accordingly, our patient never had any complaints relative to esophageal disorder.

Previous studies found that no symptoms were sensitive nor specific for diagnosing reflux in patients with end-stage lung diseases (ESLD) (10-12). Sweet et al. showed that 35(33%) patients among 109 patients with ESLD had none of the typical symptoms of GERD (3). They suggested that each patient with ESLD should be screened by esophageal manometry and ambulatory pH monitoring. Our findings in this patient emphasize the clinical importance of esophageal disorder screening of such patients to prevent chronic allograft rejection.

We also speculate that the cause of pulmonary fibrosis in this 41 year-old man was chronic microaspiration secondary to achalasia undiagnosed since childhood. We speculate that this patient may

not have developed lung fibrosis if his esophageal disorder had been diagnosed earlier.

Although the association of GERD and chronic allograft rejection has been demonstrated in several studies (3-7), the cause-effect association of achalasia with vascular rejection of the transplanted lung has not been confirmed.

Because of the impaired cough reflex and mucociliary clearance in transplant recipients, the lungs have no defense against reflux; chronic microaspiration can damage the airway mucosa and deteriorate pulmonary function leading to BOS (7).

On the other hand, it is possible that lung disease preceded GERD (altered respiratory mechanics in patients with ESLD and the bronchodilators' relaxing effects on LES may have contributed to the development of reflux). Moreover, it is not clear whether acid or nonacid reflux also has a role in pathogenesis of BOS (13).

Unfortunately, we did not perform pH assessment or impedance to clarify the type of reflux in our patient. However, it is more likely that nonacid reflux resulted in deterioration of the lung function in this patient, rather than acid reflux as acid reflux has been shown to be associated with a hypotensive LES and is uncommon in achalasia because LES pressure rises to hypertensive levels due to the loss of inhibitory neurons (14).

CONCLUSION

Achalasia may be a predisposing factor for lung inflammation and lung transplant rejection by inducing chronic microaspiration.

Based on our findings in this patient, together with findings from previous studies, we suggest that esophageal disorder (e.g., GERD, achalasia) be screened in patients with end-stage lung disease before lung transplantation and be considered as a predisposing factor for development of allograft rejection.

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