Case Communications

Single Lung Transplantation in Refractory Asthma with Irreversible Airflow Obstruction

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Asthma is characterized by airway hyper-reactivity with a tendency of the bronchi to constrict in response to various stimuli. Most patients maintain normal or near-normal lung function over time on appropriate therapy. A small proportion of asthmatics – mostly adults with late-onset, ongoing, poorly controlled disease – develop irreversible airflow obstruction, defined as a failure to achieve normal expiratory flow rates, even on high dose systemic steroids [1]. In rare instances, the degree of IAO is severe. Several therapies have been administered to asthmatics suffering from IAO with inconsistent results [2].

We describe a woman with late-onset asthma complicated by very severe irreversible airflow obstruction. Poor quality of life and recurrent life-threatening attacks despite intensive medical therapy prompted us to perform single lung transplantation.

Patient Description

Our patient was a non-smoking housewife with a history of bronchial asthma from the age of 23. She had no history of allergies, and prick skin test was weakly positive for house-dust mites only. She initially received inhaled steroid via spacer (beclomethasone dipropionate) 1,000-2,000 g/day, bronchodilator on demand, theophylline anhydride 600 mg/day. Nevertheless, she experienced frequent severe asthma attacks that required the administration of oral corticosteroids (30-60 mg/day for 10-14 days) several times a year. Some exacerbations even necessitated hospital admission.

Laboratory examination showed normal blood eosinophils and immunoglobulin E levels. Several pulmonary function tests performed between 1978 and 1992 (Figure A) disclosed extremely basal forced expiratory flow rate values in the first second of 25-50% of predicted, which increased to the normal range following bronchodilating agents (improvement of 150-260%).

From the age of 32 her asthma worsened further, requiring oral steroids on a regular basis. From the age of 44, her FEV₁ values failed to increase above 35% (Figure A). No obvious cause for failure of therapy was found. Compliance with medical treatment and inhaling device techniques were satisfactory. X-ray of the chest was normal. Conditions such as alpha₁ antitripsin deficiency, chronic sinusitis, occupational exposure, gastroesophageal reflux, bronchiectasis, allergic bronchopulmonary aspergilosis and heavy allergen exposure were excluded.

Several alternative anti-inflammatory treatments were tried without improvement. These included high dose intravenous immunoglobulins 1-2 g/kg on 2 consecutive days once a month for 6 months, followed by a 6 month course of methotrexate 7.5 mg/week and then by oral cyclosporin 100 mg b.i.d. for 6 months. The patient remained on prednisone 20 mg/day with gradual deterioration, which included dyspnea during daily activities, poor quality of life, and several life-threatening attacks requiring admission to an intensive care unit. At that point, it was decided to refer the patient for lung transplantation.

At age 48, the patient underwent successful single lung transplantation from a cadaver. The postoperative period was uneventful. On a triple immunosuppressive regime – prednisolone 7.5 mg, Imuran 75 mg and cyclosporine A 225 mg/day – her lung function tests gradually improved. In the last 2 post-transplantation years, her FEV₁ has reached values of 60-65% of predicted (Figure A).

Histologic examination of the resected lung revealed very marked peri-bronchial smooth muscle hyperplasia with the bronchial mucosa thrown up into folds and marked narrowing of the bronchial lumen. Thickening of the basement membrane, some plugging of bronchiolar lumens and peri-bronchial and peri-bronchial inflammatory infiltrates composed of lymphocytes, plasma cells and eosinophils were also revealed, as were mild emphysematous changes in the adjacent lung parenchyma (Figure B).

Comment

The patient, a woman with late-onset brittle asthma, developed irreversible airway obstruction after 21 years of brittle disease, despite adequate therapy. Very
severe irreversible airway obstruction, decreased functional capacity, poor quality of life and recurrent life-threatening attacks led us to perform lung transplantation.

The issue of irreversibility in asthma has been the subject of significant attention over the last decade [2]. It appears that despite apparently optimal therapy, which includes systemic corticosteroids, some adults develop IAO solely from asthma. Because this phenomenon is rare, relevant histologic studies from such cases are scarce. Postmortem studies in asthmatics for whom asthma was not the primary cause of death have shown thickening of bronchial walls and remodeling of the airways more consistently than inflammatory infiltrates throughout the conducting airways [3]. There is sound evidence linking chronic persistent inflammation with airway remodeling, progressive changes in airway anatomy, and IAO.

Histologic sections from the lung removed from our patient during transplantation showed severe bronchiolar wall abnormalities and relatively normal air spaces, a recognized feature of airway remodeling in asthma. Prominent smooth muscle changes, collagen deposition, non-collagenous matrix and mucus plugs, all of which indicate airway remodeling, were present, although to a lesser degree. Typical characteristics of asthma such as eosinophilic inflammation, submucosal desquamation, basement membrane thickening, goblet cell hyperplasia and smooth muscle hypertrophy were also found.

Another diagnostic possibility that needs to be considered is constrictive bronchiolitis. The spectrum of pathologic changes in this set-up varies from bronchiolar inflammation and mild scarring to partial or complete obliteration of the bronchiolar lumen due to submucosal scarring, all of which are associated with evidence of obstructive airway disease [4]. Constrictive bronchiolitis has been described in certain allograft recipients, collagen vascular diseases, after certain pulmonary infections, and after inhalational injuries. Idiopathic constrictive bronchiolitis is a rare, ill-defined entity that overlaps other types of inflammatory bronchiolar lesions, such as asthma. Regardless of the clinical setting, constrictive bronchiolitis is generally associated with significant airflow limitation and has a poor prognosis. A small percentage of patients exhibit significant permanent airflow limitation, as observed in the present case. The amount of peri-bronchiolar scarring in our patient was relatively minimal and, therefore, we feel that the diagnosis of asthma is more reasonable than constrictive bronchiolitis. Uncommon etiologies of IAO such as bronchiolitis obliterans and sarcoidosis were carefully excluded.

The cellular and biochemical events involved in airway remodeling in asthma are not clear. It appears that airway epithelium-derived growth factors act together with myofibroblasts to induce subepithelial collagen deposition with extension to the submucosa and smooth muscle [3]. Administration of anti-inflammatory treatment early in the course of the disease does not necessarily prevent this complication.

Resistance to glucocorticoids, defined as failure to improve the FEV₁ by more than 15% after 2 weeks of oral prednisolone therapy (30-40 mg/day), has been linked to IAO in asthma. This infrequent phenomenon has been related to abnormal glucocorticoid receptor structure and binding affinity, reducing the response to glucocorticoid therapy. Alternative therapies include cyclosporine A, high dose intravenous immunoglobulins, methotrexate and gold.

Lung transplantation as a therapeutic option for patients with end-stage lung disease such as severe obstructive airway disease is rarely performed in asthma because the vast majority of patients respond well to medical therapy. A review of the English literature revealed only one report describing heart-lung transplantation in two asthmatics who remained free of asthmatic symptoms during 3 years of follow-up [5].

Our patient has returned to normal functional capacity, with near-normal FEV₁ values, and does not require bronchodilator therapy. This is somewhat surprising if one considers that her remaining lung is still 'asthmatic'. It could be that this improvement is related to the heavy
immunosuppressive therapy administered after the transplantation. This case report demonstrates that single lung transplantation is another therapeutic option for patients with asthma who suffer from severe IAO that is not responsive to medical therapy.

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**References**


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**Capsule**

**LH in the treatment of infertility**

During the middle part of the mammalian reproductive cycle, a surge of luteinizing hormone (LH) is followed by a series of changes in the ovarian follicle, including resumption of oocyte meiosis and increased gene expression in cells surrounding the oocyte. The endpoint of these changes is follicle rupture and ovulation of a fertilizable egg. It has been unclear how LH participates in this series of events, because the oocyte and surrounding cumulus cells do not respond directly to LH and do not express LH receptors. Park and colleagues show that LH operates via intermediary factors of the epidermal growth factor family to trigger cumulus expansion and oocyte meiotic maturation. Elucidation of LH action on the ovary may be useful in manipulating follicular function in the treatment of infertility.

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**Capsule**

**Eating genetic modified food**

One of the concerns about genetically modified foods is the potential for transfer of foreign genetic material (for instance, antibiotic resistance genes) into either our own cells or those of organisms resident within our bodies, such as intestinal bacteria. Studies of gene transfer from plants to livestock have generally shown that most DNA is destroyed in the harsh conditions of the gut and hence little is found in animal feces. Netherwood et al. carried out a similar test in seven human volunteers who had undergone ileostomy, a procedure in which the last section of the small intestine is removed and the intestinal contents are diverted into a colostomy bag. After a breakfast of a soy burger and milkshake, the levels of the herbicide resistance transgene 5-enolpyruvylshikimate-3-phosphate synthase were measured, with only 3.7% of the initial amount consumed found in one individual’s digesta and much less in the other six people. In a trial of humans with intact gastrointestinal tracts fed the same meal, none of the transgene was detected in their feces, suggesting that DNases produced by flora of the large intestine degrade whatever survives transit through the stomach and small intestine.

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