Diseases of Small Airways of lung

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Abstract
Small airways offer 1/4th of the total airways resistance. Disease of small airways results from exposure to tobacco smoke, mineral dust, air-pollutants, and viral infections. It may also be associated with connective tissue disorders or may follow bone marrow, lung, or heart-lung transplantation. The pulmonary function tests are deranged late in the disease and the damage done is irreversible. Therefore, management lies in preventing exposure to smoke and dust, whether in the form of smoking tobacco or exposure to industrial dusts in the work environment.

Introduction
Disease of the small airways includes the pathological changes in the small airways of the lungs resulting from inflammation and fibrosis. Small airways constitutes the quiet zone between the conducting and the respiratory lung zones, consisting of respiratory bronchioles, having a partially alveolated wall, and of terminal bronchioles that are devoid of cartilage and mucous secreting glands. The diseases of silent zone do affect pulmonary function tests late in the course of the disease. Collectively called small airways disease (SAD), it is a distinct entity as compared to large airways disease and requires a different diagnostic screening strategy.

Aetiology
SAD may be a presenting manifestation in connective tissue disorders such as rheumatoid arthritis. Exposure to tobacco smoke, air borne pollutants, mineral dusts, and viral respiratory infections may result in SAD. It may develop following bone marrow transplantation and in recipients of heart-lung or lung transplantation. Other causes are listed in the table I. Small airways inflammation with structural remodelling may be responsible for recurrent attacks in bronchial asthma. This heterogeneous group of SAD with varied aetiology, has inflammation of small bronchi and bronchioles with minimal emphysema. Clinical presentation includes cough with progressive dyspnoea, and chest X-ray shows a reticular pattern.

Table I : Aetiology of SAD.

1. Tobacco smoke
2. Mineral dust
3. Post-transplant bronchiolitis
4. Constrictive bronchiolitis in rheumatoid arthritis, following inhalation injury, and in post-infective bronchiolitis.
5. Idiopathic bronchiolitis

Pathogenesis
SAD is a pathologic process characterized by inflammation and fibrosis affecting small pulmonary airways. Morphologically it is characterized by inflammation of smallest bronchi and bronchioles with minimal emphysema. Inflammatory cellular infiltration, goblet cell metaplasia, fibrosis, markedly increased thickness of the walls and increased tortuosity in the absence of emphysematous lung destruction bring about changes in airways resistance to produce obstruction in the airways. These are the earliest pulmonary changes in patients with COPD, produced by tobacco inhalation. The presence and severity of these changes of small airways disease, however, do not correlate with the amount of obstruction or emphysema; hence, probably represent a separate entity. This respiratory bronchiolitis involving small airways and surrounding alveolar structures is exclusively found in heavy cigarette smokers. Here, macrophages get accumulated in the respiratory bronchioles. The lesions may contribute to obstruction of airflow as well as to restrictive pulmonary disease. Pulmonary function tests when correlated infer that changes are the result of inflammation and subsequent repair. Whether cessation of smoking can revert the changes in SAD is not clear.
Diagnosis

It is difficult to detect small airways obstruction by the usual pulmonary function tests, since considerable amount of damage has to take place in small airways before dynamic lung functions could become abnormal. However, obstructive disease of the peripheral airways can be demonstrated at low lung volumes during expiration and abnormal distribution of ventilation to peripheral lung units. Abnormality can be detected as limitation to airflow during expiration by forced mid-expiratory flow rate and helium-oxygen flow-volume curves. An abnormal distribution can be demonstrated by frequency dependence of dynamic compliance of ventilation to peripheral lung units and single breath nitrogen washout test.

Tobacco smoke and SAD\textsuperscript{6-8}

Changes in the small airways by tobacco smoke are similar to the earliest changes in the lungs with chronic obstructive pulmonary disease by tobacco smoke. These are produced as a result of inflammation and subsequent repair. Whether the changes in SAD are reversible or not, is not clear as compared to those caused by smoking which would not progress to an irreversible obstructive lung disease if early cessation of smoking is done. Abnormalities in SAD include inflammation with inflammatory cellular infiltration, metaplasia of goblet cells and fibrosis, thus increasing the thickness and tortuosity of walls that would in turn increase airways resistance due to airways obstruction. This produces limitation to airflow during expiration that can be tested by forced mid-expiratory flow rate and helium-oxygen flow-volume curve tests. Abnormal distribution of ventilation to peripheral lung units also occurs that can be tested by frequency dependence of dynamic compliance and single breath nitrogen washout test. However, these tests are not sensitive indicators of SAD.

Mineral dust and SAD\textsuperscript{9-12}

Similar to tobacco smoke, dust induced lesions tend to produce more fibrosis and pigmentation in the membranous and respiratory bronchioles. This parenchymal fibrosis caused by a variety of dusts such as asbestos, coal, silica, talc, mica, aluminium, and iron oxides leads to thickening of small airways with luminal narrowing and ultimately to airflow obstruction. The restrictive ventilatory defect may be produced by interstitial fibrosis (as in asbestosis) or nodular lesions (as in silicosis). It may produce a dust macule which ultimately results into mineral dust induced airways disease because of collagen deposition and distortion of airways, with surrounding emphysema in the late stages. The more are the dust particles, the more is the fibrosis. Abnormal flow volume curves are the initial functional defect.

Post transplant bronchiolitis\textsuperscript{13-15}

Bronchiolitis obliterans may develop in recipients of either single lung or of heart-lung transplants. This is possibly a manifestation of chronic transplant rejection centred around the arrograft airways and mediated by infiltrating T-lymphocytes. Recurrent infections do contribute to it by stimulating class II major histocompatibility complex.

In the initial 3 months and also after the transplantation, there can be acute transplant rejection with peribronchiolar and bronchiolar lymphocytic infiltration accompanied by small airways obstruction. This can be controlled by immuno-suppressive therapy.

Post-transplant bronchiolitis has initial lymphocytic infiltration of bronchiolar walls and epithelium. The airways lumen gets obstructed by fibrosis mixed with fibroblasts, haemosiderin laden macrophages, and inflammatory cells. Submucosal granulation tissue may protrude into the lumen as polypoidal masses, later being replaced by fibrous tissue resulting in scar formation (constrictive bronchiolitis). Bronchiectasis may occur in the proximal airways. The involvement is patchy, therefore, open lung biopsy is a better diagnostic tool over transbronchial biopsy. Progressive dyspnoea, because of hypoxaemia and hypocapnia in these patients, make them ‘Blue puffers’.

A manifestation of chronic graft versus host disease with activated donor T-cells acting on bronchiolar epithelium and repeated infections may produce constrictive bronchiolitis in 20% of bone marrow transplant recipients, within one year of transplantation. The risk of developing bronchiolitis obliterans is enhanced by methotrexate. Patient may present with cough, wheeze, progressive dyspnoea, but without any x-ray abnormality. There is hardly any successful therapy and patient dies from respiratory failure.
Constrictive bronchiolitis and SAD

Constrictive bronchiolitis is a form of bronchiolitis obliterans where bronchiolar inflammation with cellular infiltration of lymphocytes and plasma cells and submucosal fibrosis of small airways is seen histopathologically along with luminal obliteration leading to progressive airflow limitation. Bronchiolitis obliterans with organizing pneumonia may be observed classically when associated with intraluminal polyps extending into alveolar ducts and spaces. The changes in constrictive bronchiolitis are patchy in distribution and irreversible histopathologically. Active inflammatory process may respond to corticosteroids. The condition is uncommon in connective tissue disorders.

Bronchiolitis obliterans may rarely occur in association with connective tissue disorders, exclusively in patients with rheumatoid arthritis and Sjogren’s syndrome, affecting primarily the women. Airways obstruction is progressively increasing, may be aggravated following penicillamine therapy. Prognosis is generally poor.

Constrictive bronchiolitis may occur as a complication of viral chest infections such as influenza, adenovirus, syncytial and mycoplasmal pulmonary involvement. It may occur following exposure to noxious chemicals such as sulphur dioxide, chlorine, ammonia, or phosgene.

Idiopathic bronchiolitis such as cryptogenic obliterative bronchiolitis, adult bronchiolitis, and diffuse pan-bronchiolitis have also been documented, exhibiting small airways disease, but their aetiology has not been clearly established.

Conclusion

The silent zone of the lung can become a seat of inflammation and fibrosis from varied aetiologies leading to distortion and obliteration of small airways, resulting in functional abnormalities. Nevertheless, these functional abnormalities become evident because of increased resistance to airflow at a stage when the condition has become severe or widespread. The situation demands early diagnosis, prevention of causative or aggravating factors by chest physicians to prevent the load of pulmonary disability in the community.

References