

Smoking-Related Small Airway Disease
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Background:

Small airways are defined as airways with an internal diameter of less than 2mm. The small airways are devoid of cartilage and consist of the membranous, terminal and respiratory bronchioles. The small airways consist of simple columnar cells (ciliated and non-ciliated) and rare neuroendocrine cells overlying a thin layer of connective tissue and smooth muscle. Small airways normally contribute little to airway resistance but abnormalities may have a disproportionate effect on lung function.

Overview of small airway disease:

Small airways may be the primary site of pathology or may be affected in association with a wide array of lung diseases including bronchiectasis, asthma, chronic obstructive pulmonary disease (COPD), respiratory bronchiolitis-interstitial lung disease/desquamative interstitial pneumonia (RB-ILD/DIP), hypersensitivity pneumonitis (HSP), cryptogenic organizing pneumonia (COP), Langerhans cell histiocytosis (LCH) and the more recently described airway centered interstitial fibrosis/bronchiolocentric interstitial pneumonia, among others.

Overall, the small airways have not been as extensively studied as the interstitial lung diseases and thus there is no consensus classification for small airway pathology. Further, the histologic findings are largely not specific for a particular etiology and as such, a multi-disciplinary approach is warranted in the evaluation of small airway pathology.

General histologic patterns of small airway disease:

While the focus of this program is on small airway disease related to cigarette smoking, the following is a brief overview of the spectrum of small airway disease in order to provide an appropriate context of COPD in the larger arena of small airway pathology. Smoking related small airway disease may exhibit chronic peribronchiolar inflammation or fibrosis in either a pattern of constrictive bronchiolitis or peribronchiolar metaplasia; patterns which are non-specific by themselves.

Non-specific patterns of small airway disease generally fall into two broad categories-cellular/inflammatory vs fibrotic. The findings may be subtle. The adjacent lung may have foamy macrophage accumulation and/or dilatation of distal bronchioles with mucostasis, which should prompt evaluation of the small airways for pathologic findings. The following represents an overview of histologic patterns of small airway disease and the most commonly associated etiologic agents.

Cellular bronchiolitis may consist of acute (neutrophilic inflammation), acute on chronic (chronic inflammation within the bronchiolar wall and neutrophils within the lumen) or chronic inflammation. The patterns by themselves are not specific and there is much overlap among the potential etiologies for each. In all situations it is important to look for sources of infection, particularly viral inclusions or aspirated material. In all cases it is important to know the clinical distribution of disease, as localized disease may imply association with aspiration or bronchiectasis whereas diffuse disease has differing implications. Acute bronchiolitis typically occurs in association with infection, fume

exposure, aspiration or occasionally Wegener's. Acute or chronic typically occurs in association with infection, inflammatory bowel disease, collagen vascular disease or aspiration. Chronic bronchiolitis may occur distal to bronchiectasis or in association with collagen vascular disease, inflammatory bowel disease or aspiration, among other etiologies.

Fibrotic small airway disease consists of three patterns: Constrictive bronchiolitis, intraluminal fibrosis (bronchiolitis obliterans) and peribronchiolar metaplasia with fibrosis (Lambertosis). An associated inflammatory component may or may not be present. Constrictive bronchiolitis consists of subepithelial collagen deposition with airway narrowing and constriction, and is generally considered to be secondary to chronic airway damage with abnormal healing response. Constrictive bronchiolitis is associated with mosaic air trapping on CT and may be extremely subtle histologically, requiring evaluation of multiple levels or the use of trichrome and elastic stains. Constrictive bronchiolitis may occur secondary to a number of disorders including transplant rejection, fume/toxin exposure, infection, collagen vascular disease, drug reaction, secondary to cigarette smoke or distal to bronchiectasis. Some cases are idiopathic.

The intraluminal pattern (bronchiolitis obliterans) consists of organization of luminal inflammatory exudates evidenced by polypoid plugs of granulation tissue. This pattern rarely occurs as an isolated finding and is more often seen in association with airspace organizing pneumonia as seen in COP or HSP. Isolated bronchiolitis obliterans does occasionally occur and has been reported in association with fume inhalation among other etiologies.

Peribronchiolar metaplasia and fibrosis is a non-specific finding probably representing the end result of a wide range of airway injuries and is frequently seen as incidental findings in resections for lung cancer where it is felt to be likely secondary to chronic smoking. Of note, three groups have described a pattern of interstitial lung disease consisting only of this finding using differing names-bronchiolocentric interstitial pneumonia, peribronchiolar metaplasia-interstitial lung disease and airway centered interstitial fibrosis. Two of the studies report a poor prognosis. The significance of this pattern and its relationship to other lung disease requires further study.

Some patterns of bronchiolitis, while not entirely specific, might point to certain etiologies. These include follicular bronchiolitis, eosinophilic bronchiolitis and granulomatous bronchiolitis. Follicular bronchiolitis consists of lymphoid hyperplasia +/- airway obstruction and may be seen in association with collagen vascular disease, particularly rheumatoid arthritis or secondary to bronchiectasis. Eosinophilic inflammation more typically involves the large airways but may be seen as an extension of asthma, allergic bronchopulmonary aspergillosis or drug reaction. Granulomatous bronchiolitis should suggest infection, sarcoid, hypersensitivity pneumonitis, aspiration, Crohn's disease or drug reaction. Two other rare entities, diffuse panbronchiolitis and diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH) are also specific patterns of disease centered on the small airways.

Small airway disease in the context of smoking-related lung disease:

Described smoking related lung diseases include RB-ILD/DIP, LCH and COPD. More recently, RB-ILD with fibrosis and airspace enlargement with fibrosis have been described, and further study of the significance of these patterns is warranted.

COPD is typically considered to encompass chronic bronchitis and emphysema but in actuality consists of four anatomic lesions, including emphysema and chronic bronchitis as well as small airway remodeling and vascular remodeling/hypertension. While the lesions frequently occur together, the mechanisms for the alterations in each anatomic lesion are thought to differ.

From a clinical standpoint, evaluation of the severity of COPD is based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria which are summarized below:

GOLD Staging System for COPD Severity

Stage	Description	Findings (based on postbronchodilator FEV1)
0	At risk	Risk factors and chronic symptoms but normal spirometry
I	Mild	FEV1/FVC ratio less than 70 percent FEV1 at least 80 percent of predicted value May have symptoms
II	Moderate	FEV1/FVC ratio less than 70 percent FEV1 50 percent to less than 80 percent of predicted value May have chronic symptoms
III	Severe	FEV1/FVC ratio less than 70 percent FEV1 30 percent to less than 50 percent of predicted value May have chronic symptoms
IV	Very severe	FEV1/FVC ratio less than 70 percent FEV1 less than 30 percent of predicted value or FEV1 less than 50 percent of predicted value plus severe chronic symptoms

Direct measurements of pressure and flows within the lung indicate that the small airways are the major site of airway obstruction in COPD. Reduced expiratory flow results from reduction of the lumen by peribronchiolar fibrosis, thickening of small airway walls and occlusion by mucus. Remodeling of small airway wall tissue has been found to correlate more with decreased FEV1 than inflammation

As early as 1957, Leopold and Gould made the observation of inflammation and connective tissue deposition in small airways in association with emphysema, which led to the postulation that extension of the chronic inflammatory process from the terminal into the respiratory bronchioles initiated centrilobular emphysematous destruction. Since that time, most research has focused on emphysema for a variety of reasons, and small airways have only more recently returned as an intense focus of study. Emphysema and small airway disease are typically found in association with one another, and thus a brief review of the mechanisms of emphysema follows for background and comparison. Interestingly, small airway disease appears to be independent of the presence of chronic bronchitis/large airway disease.

The classic theory of emphysema is based on the protease/anti-protease theory, extending from the knowledge that patients with alpha-1-antitrypsin (A1AT) deficiency

develop emphysema. The premise of this theory is that smoke incites an inflammatory reaction which, in turn, results in the release of proteases which overcome the anti-proteolytic defenses and ultimately lead to matrix destruction and emphysema. A variety of proteases have been implicated including serine proteases, metalloproteases and cysteine proteases, although which inflammatory cells and proteases are most critical is complex and controversial. It is generally accepted that smoke invokes an inflammatory response which induces pro-inflammatory cytokines and that smoke induces an increase in expression of chemoattractant and pro-inflammatory mediators, but the precise mechanisms are the subject of much debate. The following represents an overview of some of the more widely studied mediators and is by no means comprehensive. The interested reader is referred to the many excellent reviews on this subject, some of which are referenced below.

Neutrophil elastase is a serine protease that was originally postulated in the development of emphysema. Most studies have supported a role for neutrophils and neutrophil elastase in the development of emphysema. The hypothesis is further supported by lavage studies demonstrating increased neutrophils correlating with increased levels of desmosine and hydroxyproline, which are markers of elastin and collagen breakdown, respectively. Most studies have also demonstrated that tumor necrosis factor-alpha is presumed to be a driver of inflammatory cell influx.

Metalloproteases (MMP) have also been widely studied in regard to the development of emphysema. In mouse models, cigarette smoke increases levels of MMP's 2, 9, 12, 13 and 14. MMP-9 and MMP-12 are of particular interest as they degrade elastin. A link between the original neutrophil elastase theory and metalloproteases exists in that neutrophil elastase activates MMP-12 and decreases tissue inhibitor of metalloprotease-1 (TIMP-1). MMP-12 had also been found to degrade A1AT. Thus, MMP-12 likely has both a signaling role and a direct destructive role. Additionally, MMP inhibition/deletion eliminates development of emphysema in mouse models.

Failure of repair is a key difference between the development of emphysema and small airway remodeling, which generally occurs in association with increased fibrosis. In emphysema, alveolar walls fail to regenerate new matrix. Smoke decreases lysyl oxidase which is critical in the formation of collagen. Smoke also interferes with cell proliferation, chemotaxis, production of matrix components by fibroblasts and increases apoptosis. Why the alveoli and small airways respond differently to the same stimuli has continued to be a puzzle and subject of debate.

Small airway disease has not been as extensively studied as emphysema, but has been assumed to follow similar pathways as emphysema. Hogg, et al (Hogg, *NEJM* 2004), evaluated small airways from 159 surgical specimens and correlated the pathologic findings with the clinical GOLD stage. In this study, progression of COPD correlated with an increase in volume of tissue in the wall, accumulation of mucus exudates, and the percentage of airways containing neutrophils, macrophages, CD4 cells, CD8 cells, the total volume of B-cells and the presence of lymphoid aggregates. Such findings appear to support the role of inflammatory cells in the development of small airway disease. However, Churg, et al (Churg *AJRCCM* 2006), in an elegant study using laser capture microdissection, demonstrated that smoke upregulated gene expression of type 1 pro-collagen and profibrotic cytokines, particularly those related to TGF-beta signaling. Of interest, the elevations were seen at 2 hours following exposure and then decreased, in contrast to BAL inflammatory cells which

increased slowly over 24 hours. Such findings suggest that upregulation of the fibrotic response may be independent of inflammation.

Other studies have demonstrated that upregulation of TGF-beta effects the Smad signaling pathway which results in increased collagen production. A possible role of VEGF and increased microvessel density in small airway remodeling has also been demonstrated but these findings are inconsistent. The role of neutrophils remains uncertain, although some studies suggest that oxidant release from neutrophils and macrophages may potentiate TGF-beta release.

Genetic predisposition

Only 10-20% of heavy cigarette smokers will develop COPD and COPD cases have been observed in familial clusters. Thus, it would appear that COPD develops in genetically susceptible individuals following sufficient exposure to cigarette smoke. Genetic polymorphisms related to levels of antiproteases, metalloproteases, pro-inflammatory and pro-fibrotic cytokines have been reported; however, molecular studies of genetic risk factors predisposing to the development of COPD are still in the infancy stage and will be the subject of much further study.

Future issues and directions:

COPD continues to be a major source of morbidity and mortality. The factors governing matrix destruction in emphysema in contrast to matrix production in small airway remodeling continues to be investigated. Evaluation of molecular targets will hopefully lead to the identification of potential therapeutic targets, although translation of findings in animal models to those in humans has been imperfect. For example, TGF-alpha inhibitors diminish the development of emphysema in mouse models but have not been demonstrated to be clearly efficacious in humans at this time. Genetic factors contributing to the risk of developing COPD will also be an area of further study. The recent description of fibrotic lung disease associated with cigarette smoking in conjunction with emphysema and airspace enlargement also requires further elucidation.

Selected references:

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