THE INFLAMMATORY PROCESS IN PERIPHERAL AIRWAYS

James C. Hogg, M.D.

Abstract

The inflammatory process consists of an exudative phase where fluid and cells leave the circulation and accumulate in the tissue, and a proliferative or repair phase where connective tissue is deposited to form a scar. When this process occurs in mucus membranes, it is associated with a shedding of epithelial cells and an increase in the amount of mucus that is produced. An inflammatory process in the small airways can show all of the changes that occur as part of this general pattern. For example, in asthma there is marked epithelial shedding leading to increased epithelial cell turnover and thickening of the basement membrane associated with a thick mucus exudate which can occlude the airways. While the smooth muscle in the airway wall tends to proliferate, there is relatively little deposition of collagen in the airway wall and no organization of the exudate in the airway lumen. This contrasts sharply with situations where more severe tissue injury is followed by organization of the exudate in the airway lumen with marked collagen deposition leading to the airway obliteration. Between these two extremes the histological appearance of the inflammatory process can be quite varied and includes epithelial changes such as goblet cell and squamous cell metaplasia, an infiltration of inflammatory cells into the airway wall, hypertrophy and hyperplasia of the airway muscle and less prominent deposition of collagen in the airway wall and lumen. The rather stereotyped nature of this response makes it extremely difficult to associate specific stimuli with a typical response so that a diagnosis of small airways disease may be too non-specific to be helpful. However, it seems likely that a better understanding of the nature of the inflammatory process in the peripheral airways will lead to a clearer concept of the pathogenesis of several obstructive lung diseases.

Introduction

The purpose of this presentation is to review the abnormalities produced in the terminal bronchioles, respiratory bronchioles, alveolar ducts, sacs and alveoli by the inflammatory process. Inflammation begins as a response to the injury of these structures by aerosols such as cigarette smoke, noxious gases, organic and inorganic particulates and following invasion by a wide variety of living agents ranging from viruses to fungi. The changes that are produced by these different types of injury can be very different but as the basic changes associated with the inflammatory process are stereotyped, there are also many similarities. In this lecture I will try to emphasize the principle that the inflammatory process produces predictable changes in the peripheral airways.

General Features of the Inflammatory Response in the Peripheral Airways

The nature of the inflammatory response has been the subject of a great number of studies\textsuperscript{(997).} It seems likely that the changes that occur with an inflammatory response in the airways are similar to those in other lesions and consist of a fluid exudative phase that is followed in turn by a proliferative repair phase. The exudative phase consists of a movement of fluid and then cells out of the vascular space into the tissue and onto the surface of the airway lumen (Fig. 1a). The presence of this exudate causes the airways to become unstable\textsuperscript{6} perhaps by replacing the surfactant normally found there\textsuperscript{69} with fluid that has a much higher surface tension. The source of the mediators responsible for the movement of fluid and cells is probably the same as in other inflammatory responses but has been very little studied in the peripheral airways. In some cases the mediators may come from mast cells\textsuperscript{51} but they may also be generated from the injured epithelial cell membranes\textsuperscript{69} or from the inflammatory cells that migrate from the vascular space to the injured site. In some cases the exudate may continue to accumulate and occlude the airway lumen (Fig. 1b) with a plug of exudate. Although this plug contains mucus produced by both goblet cells and bronchial glands, the fluid protein and cells of the inflammatory exudate may contribute to its substance\textsuperscript{66,97}. The epithelial cells often slough into this exudate\textsuperscript{66,97} and recent studies by Man...
and his associates\textsuperscript{64} suggest that this might occur because water moves quickly out of the lateral surfaces of airway epithelial cells when they are surrounded by even mildly hyperosmotic fluid (Fig. 2). It seems possible that fluid exudation from the bronchial microvasculature into the submucosa might have this effect because the epithelial tight junctions restrict the movement of solute but not fluid so that the osmotic pressure increases in the submucosa. We postulate that this causes the shedding by the mechanism shown in Fig. 2 and ref. 64. After the epithelium is shed, mitotic figures appear (Fig. 1c) and the new epithelium begins to proliferate to repair the defect in the membrane and this new epithelium may be normal or dominated by either goblet or squamous cells.
The ability of the airway epithelium to repair itself completely and reline the lumen is a very important feature of the response to injury. An injury leading to a rapidly turning over epithelium may result in a thickened basement membrane (Fig. 1b) due to collagen deposition in the basal lamina. The features of airway plugging, epithelial shedding and thickened basement membrane are observed frequently in the lungs of patients that die of asthma26)27).

In other cases the cells contained in the inflammatory exudate do not enter the airway lumen but remain in the wall and peribronchiolar tissue (Fig. 1d). Homma and his associates50) have drawn attention to this form of bronchiolitis and reported that it is common in Japan. The cell infiltrate is mononuclear in type with lymphocytes and plasma cells. The precise mechanisms that control which types of cell migrate into the tissue are very poorly understood. Similarly, just why this form of bronchiolitis is associated with less exudate in the lumen is a subject that should be studied.

The repair phase of the inflammatory reaction is associated with an increase in connective tissue in the airways. In some cases this is dominated by hypertrophy and/or hyperplasia of the muscle (Fig. 1e), while in others the accumulation of collagen narrows the lumen as it contracts to form a scar. When the injury to the airway epithelium is very severe so that it is completely disrupted, a necrotic ulcerated surface forms that is covered with an eosinophilic exudate. This exudate can extend down the airway to the second and third order respiratory bronchioles which can be organized into a polypoid mass of fibroblastic granulation tissue that obliterates the airway lumen (Fig. 1g).

Granuloma formation has been shown to be dependent on the fact that macrophages present antigen associated with particulates to sensitized T cells80)8). The fact that the T cells recognize antigens associated with particulates engulfed by macrophages probably accounts for the fact that intracellular parasites such as Tuberculosis and Brucellosis as well as a variety of viral, chlamydial, fungal organisms cause granulomatous inflammation80)8). A granulomatous bronchiolitis (Fig. 1h) can be seen in several pulmonary conditions and is most frequently observed in extrinsic allergic alveolitis where it seems likely that they form because particulate antigens are engulfed by macrophages at that location.

Peripheral Airways Inflammation in Children

Holt48) provided an excellent description of childhood airway disease. He divided acute catarrhal bronchitis into a mild form involving the larger tubes and a more severe form involving the small tubes which he called capillary bronchitis. He recognized that the pathology was one of acute inflammation of the mucus membrane where he described swelling, desquamation of the epithelium and exudation of mucus and pus cells. He described that the lungs were more often inflated than collapsed at autopsy and that there was enlargement of the lymph nodes at the hilum. He also clearly separated this

Fig. 1 Summarizes the changes that occur in the membranous bronchioles as a result of the inflammatory process. Fig. 1a shows an acute inflammatory exudate into the airway wall and on to the airway surface. Fig. 1b shows a chronic inflammatory mucus exudate (MU) from a case of asthma that occludes the airway lumen. Note that the epithelium is disrupted and that the epithelial basement membrane (BL) is quite thick. Fig. 1c: The presence of mitotic fig. (arrows) indicates that a repair process is present in the airway epithelium. Fig. 1d shows a bronchiole where the airway wall has been infiltrated with inflammatory cells but the lumen remains empty. Fig. 1e shows a bronchiole with inflammatory cells infiltrating the wall and prominent bronchial smooth muscle (arrows). Fig. 1f shows a bronchiole with the airway wall thickened by inflammatory cells and the deposition of connective tissue. Fig. 1g shows a bronchiole that has been occluded by an inflammatory exudate that has been organized by fibrous connective tissue (arrows). Fig. 1h shows a peripheral airway involved by chronic granulomatous inflammation (arrows) with granulomas present just below the airway surface (single arrow).
condition from bronchopneumonia where there was an exudate into the airspace.

The development of immunofluorescent techniques and the bedside inoculation of secretions into susceptible cell lines has allowed viral infections of the airways to be studied more carefully in recent years. A number of investigators have shown that this airways disease can be initiated by respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, influenza virus, and mumps virus. Because small bronchi, bronchioles, and respiratory bronchioles are all involved in this condition, the term "peripheral airway inflammation" probably provides a better description than "bronchiolitis".

The importance of respiratory syncytial virus as a cause of life-threatening peripheral airway inflammation in infants and children under the age of two is now widely recognized. Jacobs and his associates found that respiratory syncytial virus accounted for a high percentage of bronchiolitis in this age group and estimated that the disease was fatal in 2—6% of these children. The reason why the disease is life-threatening in young children and relatively mild in older children and adults is incompletely understood. One possibility is that peripheral airways resistance is disproportionately high in younger children so that any further airway narrowing caused by a viral-induced inflammatory reaction interferes with ventilation and gas exchange. A second possibility is that adults are protected by previous exposure to the virus so that they are resistant to infection. A third possibility is that the virus replicates in the upper airways of adults but in both upper and lower airways of children. Whatever the reason, the fact remains that viral disease in the peripheral airways can be severe.

Fig. 2 Shows airway epithelium that has been mounted in chambers (CC=ciliated cell; NCC=non-ciliated cell). (A) is control: (B) hyperosmolar fluid has been placed on the submucosal surface: (C) hyperosmolar fluid has been placed on the luminal surface. The changes in (B) suggest a mechanism for epithelial shedding where the protein but not the fluid in the inflammatory exudate is restricted by the epithelial tight junctions. This would create a hyperosmolar load on the submucosal surface similar to that in (B) where the epithelium is shedding. From Man and his associates with permission of the authors and publishers.

Fig. 3 Shows a resected bronchiectatic lobe of lung of a young adult. The bronchiectasis was produced by the aspiration of the plastic toy (arrow) while the patient was a child. This foreign body was present in the lobe for many years and produced chronic inflammation, obliteration of the peripheral airways, bronchiectasis and hyperplasia of the lymphatics (double arrow).
and life-threatening in children whereas it is usually mild and self-limiting in older children and adults.

Adenovirus infection has been associated with a particularly severe form of peripheral airways disease where up to 60% of proven cases develop long-term complications in the form of obstructive airways disease. In the most severe cases this may take the form of unilateral hyperlucent lung which was first described in children by Swyer and James and in adults by McLeod. Reid and Simon pointed out the probable relationship between bronchiolitis and hyperlucent lung and this relationship has now been confirmed in several studies. In addition to the hyperlucent lung, other complications such as obliterative bronchiolitis and bronchiectasis are frequently reported following adenovirus infection.

**Bronchiectasis**

Laennec first described this condition in 1821. He illustrated this description with the case of a 3-1/2-year-old child who developed severe bronchiectasis after whooping cough, and a 62-year-old woman who had been troubled with cough hemoptysis from early life. The fact that bronchiectasis was a disease that began in childhood was clearly established by Mallory more than a century later.

Bachman and his associates showed that acute airway inflammation could cause the central airways to dilate by performing bronchograms on 60 cases of acute pneumonia where they found large airways dilatation in 25. However, Mallory showed that the presence of inflammation by itself could not explain the ectasia because he found far more severe inflammation in the airways of cases of asthma where no bronchiectasis was observed. The fact that the peripheral airways were obliterated in bronchiectasis was established by the classic studies of Reid who showed that permanent bronchiectasis was associated with obliteration of the peripheral bronchial tree. Whitwell introduced the term "follicular bronchiectasis" by which he meant that he frequently saw follicular hyperplasia of the lymphatic collection in the airways of these cases. It seems likely that repeated episodes of airways inflammation are responsible for both the follicular hyperplasia of the lymphatics and the peripheral airway obliteration. This is illustrated by one of our cases (Fig. 3) which shows a lobe from a patient who aspirated a plastic toy while a child. This foreign body produced chronic airway inflammation, bronchiectasis, obliteration of the peripheral airways and hyperplasia of the lymph nodes.

Lander showed that atelectasis was important in the production of bronchiectasis by introducing mobile gum acacia plugs into the airways of cats which were sucked down into the peripheral airways to produce both atelectasis and dilatation of the proximal bronchi. As the dilated central airways could be returned to normal calibre by causing a pneumothorax, he argued that the bronchi dilated because of increased traction from the partially atelectatic lobe. Alternatively, inflammation of the airways leads to a lengthening of the time required to empty the lung so that the increase in breathing frequency leads to hyperinflation. This also increases the traction on the peribronchial sheath which dilates the central airways. Connective tissue deposition then leads to obliteration of peripheral airways and the formation of bronchiectatic sacs while expansion of the bronchial circulation provides the opportunity for hemoptysis.

**Pulmonary Complications of Fibrocystic Disease**

The presence of bronchiectasis is a common event in the lungs of patients that die from fibrocystic disease of the pancreas. Esterly and Oppenheimer reported 84 autopsies on infants and children with fibrocystic disease of the pancreas and found that bronchiectasis was present in 53. They also found that airways from these patients very frequently showed hypertrophy and hyperplasia of the bronchial mucus gland layer as well as chronic inflammation of bronchial and bronchiolar walls where the inflammation was severe and obliterative in character.

**Chronic Obstructive Pulmonary Disease**

A major problem in describing the pathology of chronic obstructive pulmonary disease is the terminology. The definition of chronic bronchitis is based on the clinical symptoms of cough and sputum production that are thought to be related to mucus hypersecretion. However, the epidemiological studies of Fletcher and his associates have shown that chronic airways obstruction and the chronic cough and sputum production are not related. As most authors seem to agree that the site of airway obstruction is in the peripheral airways, it is incorrect to use the term "severe chronic bronchitis" to describe patients with chronic airways obstruction.

The fact that the lesions in the peripheral airways in COPD are inflammatory in nature has been established by several studies. Although these lesions represent a trivial inflammatory response, experimental studies in animals have shown that minimal lesions such as these can cause airways dysfunction. It seems likely that the reversible airways dysfunction is accounted for by either fluid exudation onto the airways surface or by increased responsiveness of the peripheral airways smooth muscle rather than by permanent structural alteration. However, with severe fixed airway obstruction the deposition of collagen will contract the airway wall and narrow the lumen.

Several authors have suggested that emphysema contributes to peripheral airway obstruction by either decreasing the
infection. In the cases where an immune mechanism can be demonstrated, it occurs as a result of specific IgE binding to
seem to acquire hyperreactivity and asthma in a non-specific fashion very often dating their symptoms to a respiratory
breathing cold air). Where heat and/or water loss are thought to be the factors that precipitate the bronchoconstriction.

Tests. Patients that have hyperresponsive airways are also known to bronchoconstrict to other stimuli such as exercise (or
who have the propensity to develop asthmatic attacks have hyperresponsive airways which can be identified by challenge
procedures. Whether this host factor is genetic or acquired remains to be determined.

Penicillamine as an isolated event following bone marrow transplantation points strongly to a host factor in its
prognosis. In both cases the histology is the same but the changes are diffuse in one case and focal in others.

Results from a diffuse airways injury and that a patchy organizing pneumonia has a similar histology with a much better
prognosis. It seems very likely that severe bronchiolitis obliterans with irreversible airways obstruction
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is that it does not appear to be associated with irreversible airways obstruction and has a much better prognosis. It seems very likely that severe bronchiolitis obliterans with irreversible airways obstruction results from a diffuse airways injury and that a patchy organizing pneumonia has a similar histology with a much better prognosis. In both cases the histology is the same but the changes are diffuse in one case and focal in others.

The occurrence of bronchiolitis obliterans in rheumatologic disease with or without the administration of penicillamine as an isolated event following bone marrow transplantation points strongly to a host factor in its pathogenesis. Whether this host factor is genetic or acquired remains to be determined.

Asthma

This disorder has been difficult to define but is usually thought of in terms of reversible airway obstruction. Those
who have the propensity to develop asthmatic attacks have hyperresponsive airways which can be identified by challenge
tests. Patients that have hyperresponsive airways are also known to bronchoconstrict to other stimuli such as exercise or
breathing cold air where heat and/or water loss are thought to be the factors that precipitate the bronchoconstriction.

It is of interest that relatively few subjects have a clearly established allergic mechanism for their asthma. The majority
seem to acquire hyperreactivity and asthma in a non-specific fashion very often dating their symptoms to a respiratory
infection. In the cases where an immune mechanism can be demonstrated, it occurs as a result of specific IgE binding to
mast cells. The fact that airways hyperreact when a non-specific inflammatory reaction is present has been established in several studies. Airway hyperreactivity induced by such reactions can be induced by specific antigen reacting with IgE on mast cells, with upper respiratory tract infections, non-specific irritants such as cigarette smoke, NO₂ or ozone.

Airway smooth muscle contraction is probably responsible for the cases of asthma that are rapidly reversible by bronchodilator therapy. The increase in severity and decrease in reversibility of asthmatic attacks probably reflect the presence of an inflammatory exudate which thickens the wall and fills the lumen. Smooth muscle constricted in these thickened, mucus-filled airways causes much more severe airway obstruction than the same degree of muscle constriction in a normal airway. When patients with asthma die, the small bronchi and bronchioles are plugged with exudate and the walls are thickened by an edematous exudate rich in eosinophils. The fact that the plugs have a high protein content with much of this protein being albumin suggests that the inflammatory exudate contributes to formation of the mucus plug.

Peripheral Airways Diseases in Hypersensitivity Pneumonitis

A great many antigens have been associated with hypersensitivity pneumonitis. The majority of these are occupational in nature but it has also been described in association with air conditioners, humidified heating systems, and molds growing in floor boards. In every case meticulous history taking is the critical step in establishing a diagnosis. Immunologic study, challenge tests and lung biopsy generally confirm suspicions raised by a careful history. As the materials to which patients are exposed are complex, and contain a multitude of antigenic material, it is very difficult to be certain about which antigen causes the pneumonitis.

The histologic appearance of hypersensitivity pneumonitis is stereotyped in spite of the fact that it can be caused by so many different materials. In general, it is a granulomatous inflammatory lesion that involves the central portion of the lobule including the terminal and respiratory bronchioles. In a careful analysis of 60 cases of farmer's lung, Reyes and his colleagues reported that the common findings were an alveolar interstitial infiltrate consisting of plasma cells, lymphocytes and occasionally eosinophils in 100% of cases; a granulomatous interstitial reaction in 70% of the cases where the granulomas tended to be located in the centre of the lobules. In about 50% of cases a mild form of bronchiolitis obliterans was also observed. Kawanami and his associates provided electron microscopic evidence that the primary cell infiltrating the alveolar wall was the lymphocyte. They also showed that the exudate became organized into buds in regions of extensive epithelial damage which likely represents and early phase of bronchiolitis obliterans.

In summary, the histological manifestations of the inflammatory process in the peripheral airways have been summarized. These changes show a variation in the pattern of response from acute exudation onto the surface of the lumen, plugging of the lumen with a mucus exudate, infiltration of the wall with inflammatory cells, deposition of connective tissue and hypertrophy of muscle in the airway wall, and obliteration of the lumen by organization of the exudate. The pattern of response can be relatively constant in some clinical situations, in that asthma is usually associated with epithelial disruption and repair, thickened basement membrane and plugging of the airways with a mucus exudate that does not become organized. Bronchiectasis on the other hand, is associated with organization of the exudate that forms in the airways so that the peripheral bronchial tree is obliterated. A better understanding of the process responsible for the variation in these patterns will increase our understanding of obstructive airways disease and provide insights into how we should treat the patients that have them.

References


88. Swyer, P.R. & James, G.: Case of unilateral pulmonary emphysema. Thorax, 8: 133, 1953.