Chapter 3

Histopathology of bronchiectasis

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Summary

The clinical presentation of bronchiectasis occurs after initial irreversible damage to the airway has occurred. The clinician then has to control symptoms and limit the progression of the disease. A clearer understanding of the pathogenesis of this disease will enable the development of better treatment strategies.

Bronchiectasis is a multi-factorial disease process in which there are a number of key steps, although they are not always clinically identifiable. There is often an initiator or damaging event such as a viral infection which, in an individual with a predisposing risk such as a degree of immune dysfunction or an impaired mucociliary clearance system, leads to persistent and damaging bacterial infections. These infections go on to provoke an inappropriate and self-damaging inflammatory response in which neutrophil activity leads to progressive tissue damage and a relentless cycle of infection, inflammation and bronchial wall injury. Persistent infection and chronic inflammatory cell infiltration further amplify the local inflammatory milieu and may lead to systemic complications.

Keywords: Aetiology, bronchiectasis, histopathology, inflammation, neutrophils, pathogenesis

Bronchiectasis was first described at the beginning of the 19th century by Laennec [1]. He ascribed the term to the pooling of secretions in the airways leading to wall weakening and dilatation. Whilst the term is often used loosely by radiologists to describe any airway dilatation, pathologically the term is used to describe an irreversible dilatation of the airway often associated with chronic suppuration.

Aetiology and classification

Aetiologically, bronchiectasis may be divided into obstructive and nonobstructive types (table 1). In the obstructive type of bronchiectasis airway dilation may develop from obstruction due to any cause. The disease is confined to the airways distal to the obstruction. Causes of obstruction may be luminal, such as the inhalation of foreign bodies. This is most common in children and shows a
predilection for the right lower lobe and posterior segment of the right upper lobe [2–5]. The risk of developing bronchiectasis following foreign body inhalation has been assessed as 3–16% [6]. However, other causes of obstruction include mucus inspissation in allergic bronchopulmonary aspergillosis (ABPA) [7], with central or upper lobe bronchiectasis, and distal to bronchioles. Tumours may also cause obstruction and bronchiectasis but this is more prevalent in the slower growing often polypoid tumours, such as carcinoid tumours, endobronchial lipomas and chondromas [8]. Extrinsic compression of the bronchus may also lead to obstruction, and typically hilar tuberculous lymphadenopathy can lead to bronchiectasis, particularly of the right middle and lower lobes. The middle lobe, because of its relatively narrow lumen, is at particular risk of compression or obstruction, a condition sometimes referred to as middle lobe syndrome [9].

The pathogenesis of obstructive bronchiectasis is relatively straightforward, as bronchial secretions accumulate distal to the obstruction and become infected producing inflammation and damage to the bronchial wall which becomes weakened and dilated. This was recognised by LAENNEC [1].

There have been several attempts to classify nonobstructive bronchiectasis, which are variably based on a mixture of historic bronchographic and, more recently, high-resolution computed tomography (HRCT), appearances (saccular or cystic, fusiform or cylindric) [10] and histological appearances (follicular) with lymphoid follicles in the wall, as defined by WHITWELL [11]. Nonobstructive bronchiectasis is typically more widespread, affecting more than one lobe and most commonly affecting the basal segments of the lower lobes [11–13]. The left lung is more frequently affected than the right and the disease process typically involves the middle-order bronchi (fourth to ninth generations).

This classification is now probably unsatisfactory and of little pathological significance; although the distribution of changes may provide a clue to the underlying aetiology. Post-infected bronchiectasis is traditionally the most common underlying cause, is most often basal and may be confined to a single lobe. However, nonobstructive bronchiectasis may occur in association with a number of other conditions. In diseases where mucociliary clearance is impaired, bronchiectasis frequently, if not inevitably, develops. In cystic fibrosis [14] and ciliary dysmotility syndromes, such as primary ciliary dyskinesia arising from a defect in the dynein arms [15], bronchiectasis is more widespread, sometimes with upper lobe predominance. The association of bronchiectasis with disturbances in mucociliary clearance mechanisms highlights the importance of local defence mechanisms within the airways in aetiological terms and in terms of the pathogenesis of the disease. There may be primary defects in the immune system with abnormalities of neutrophil function, hypogammaglobulinaemia [16], immunoglobulin (Ig)A and IgG sub-class deficiencies [17], and in ataxia telangiectasia. Bronchiectasis may also be associated with some autoimmune conditions including ulcerative colitis [18], rheumatoid disease [19], Sjögren’s syndrome [20] and ankylosing spondylitis. Bronchiectasis is also associated with several noninflammatory conditions within the lung, such as α1-antitrypsin deficiency, and is reported in some cases of pulmonary fibrosis but in these cases may be due to traction effects of the surrounding fibrosis.

<table>
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<th>Table 1. Causes of bronchiectasis</th>
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<td><strong>Bronchial obstruction</strong></td>
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<td>Foreign bodies</td>
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<td>Mucociliary abnormalities</td>
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<td>Ciliary dysmotility syndromes</td>
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<td>Hypogammaglobulinaemia IgA and IgG sub-class deficiencies</td>
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<td>Neutrophil function abnormalities</td>
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<td>Ataxia telangiectasia</td>
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<td>Rheumatoid arthritis</td>
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<td>Ankylosing spondylitis</td>
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<td>α1-antitrypsin deficiency</td>
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<td>Pulmonary fibrosis</td>
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ABPA: allergic bronchopulmonary aspergillosis; Ig: immunoglobulin.
Of the known causes or associations of bronchiectasis, childhood infection is probably the most common accounting for up to 30% of cases, with immunodeficiencies present in up to 18%. However, in some studies, no underlying abnormality can be detected in >50% of cases.

**Histopathological appearances**

Histopathologically, bronchiectatic airways appear dilated and on examination have a cross-sectional area that is much larger than the accompanying pulmonary artery (fig. 1). The airway lumen is often filled with a mucopurulent exudate with neutrophils and macrophages (figs 2 and 3). The respiratory epithelium lining shows variable changes from a reserve cell hyperplasia to squamous metaplasia (fig. 4) with active inflammation shown by epithelial and mucosal infiltration by neutrophils and in severe exacerbations, ulceration (figs 5 and 6). The bronchial wall is often destroyed due to loss of fibromuscular tissues and the elastic framework, and may show erosion and loss of cartilage [21]. There is usually a reduction in submucosal glands. The wall may be thin but is more often greatly thickened with extensive peribronchial fibrosis extending into the adjacent lung parenchyma (fig. 7) [22]. There is an associated chronic inflammatory cell infiltrate within the wall, predominantly lymphocytes and plasma cells, and in some cases lymphoid follicles with germinal centres may be prominent [23]. The presence of B-cell immune activation through the presence of germinal centres and plasma cells in the walls of bronchiectatic airways, would support the role of antibodies in the immune response to persistent infection. However, bronchiectasis is associated with some autoimmune connective tissue diseases, in particular rheumatoid arthritis [19, 24, 25], and a role for autoimmunity in the destruction of the airway has also been suggested.

Eosinophils may be seen as part of the infiltrate as with any chronic airways inflammation. Whilst non-specific, they raise the possibility of an associated fungal infection such as *Aspergillus*. Although eosinophils are commonly seen in the mucus plugs of ABPA, their presence within the airway wall inflammation is nonspecific. Granulomas and multinucleate giant cells may be seen in the wall and might be a reaction to the inspissated luminal material but the possibility of concomitant fungal or mycobacterial infection should always be considered. In established bronchiectasis, the histological pattern of chronic inflammation within the airway wall with superimposed active inflammation, most likely reacting to concomitant infection, has a fairly uniform appearance and provides little insight into the underlying aetiology or pathogenesis.

The surrounding lung parenchyma may show a number of changes. Where there is distal luminal obliteration of bronchi and bronchioles, the lung parenchyma may
show atelectasis due to absorption and collapse. Obliterative changes in small airways are important in contributing to airflow obstruction in bronchiectasis [10, 11]. Destructive inflammation may lead to the formation of an abscess cavity, although this may be difficult to distinguish from a distended, ulcerated airway. There may be accompanying interstitial pneumonitis, particularly in cases of follicular bronchiectasis, and also changes of an organising pneumonia. Small airway changes, such as bronchiolectasis, may be seen as part of the whole disease process or may be part of an underlying disease leading to more proximal dilatation, as has been seen with small airways disease, such as bronchiolitis [18, 26].

The airways are supplied by the bronchial arteries and the inflammatory destruction and healing processes result in the formation of bronchopulmonary anastomoses, probably due to a mixture of new vessel formation and the re-opening of pre-existing, pre-capillary bronchopulmonary connections (fig. 8). Ulceration of the airways can lead to severe haemorrhage and haemoptysis. The formation of anastomoses and the loss of some of the alveolar capillary bed leads to the development of pulmonary hypertension [27].

Focal proliferations of neuroendocrine cells are also seen and may lead to the formation of multiple tumourlets, small aggregates of neuroendocrine cells in the walls of small airways. These are not specific to bronchiectasis and may be seen in a number of chronic lung conditions [28].

It has also been recognised that the persistent chronic activation of the immune system in the wall of the airway may lead to the development of bronchus-associated lymphoid tissue (BALT), especially in bronchiectasis associated with Sjögren’s syndrome [29]. Increased incidence of BALTomas,
low-grade, B-cell lymphomas, is associated with Sjögren’s syndrome but not specifically related to bronchiectasis [20].

In chronic disease, further complications may arise. Locally, the lung may develop abscesses and even empyema, although this is less common as the pleural space is often obliterated by fibrous adhesions. Bronchiectatic spaces may become colonised by saprophytic fungi, most commonly Aspergillus sp.

Systemic dissemination of infection may lead to abscesses in other organs, notably the brain, and chronic suppuration may be complicated by systemic amyloidosis (type AA). The incidence in bronchiectasis is unclear but in one study of patients with systemic amyloidosis requiring haemodialysis, 40% had underlying bronchiectasis [30].

Pathogenesis

The pathogenesis of bronchiectasis is complex and a number of different mechanisms contribute to the development of a similar morphological appearance and different factors act together to set up a cycle of inflammation and destruction that leads to damage and destruction of the bronchial wall [31].

The initiator to this sequence is usually damage to the bronchial epithelium. This may be due to an external insult or to an intrinsic deficiency within the patient. The most common predisposing factor to the development of bronchiectasis is a severe childhood respiratory infection, which may be viral, such as measles or adenovirus, or bacterial, such as Bordetella pertussis [32–34]. The resultant permanent dilatation of the airways is thought to be due not only to inflammation and destruction of the bronchial wall but also, in part, to a traction effect produced by collapse of the surrounding lung parenchyma. However, the persistence of infection and inflammation are of paramount importance in the progression of the disease.

Whilst an underlying cause is not established in all cases, the number and type of associations for bronchiectasis gives us some indication of what the important underlying pathogenetic mechanisms may be.
In post-infectious causes, the initiating viral infection appears to be transitory and, in the case of adenoviruses, it has not been possible to demonstrate the persistence of the virus within bronchiectasis by in situ hybridisation [35]. However, some respiratory viruses have been shown to lead to abnormalities in ciliary function, which may persist for several weeks [36].

Clinically, it is the recurrence and persistence of bacterial infections in the airways with which most patients present that are of most importance and are linked to the progression of the disease. There is a prevailing view that bacterial infection in the lower respiratory tract provokes an exaggerated and uncontrolled neutrophilic response and that the complex interplay between bacterial infection and airway inflammation, along with the release of tissue damaging substances, leads to the progressive damage which typifies bronchiectasis.

In the early stages of bronchiectasis, the most common bacterial isolate is Haemophilus influenzae, which has the capacity to directly damage the airway epithelium and induce the production of inflammatory mediators [37]. The typical immune response to H. influenzae is a T-helper (Th)1 response. However, some bronchiectasis patients with persistent infection have been found to have a Th2 response with a cytokine profile of interleukin (IL)-4 and IL-10. The release of cytokines contributes to the inflammatory response within the airway and at the same time may also result in a failure of the response to satisfactorily remove the organism [38].

Over time, a number of other organisms have been found to be established within the airways, particularly Streptococcus pneumoniae and Pseudomonas aeruginosa. The initial damage to the epithelium lining allows this secondary bacterial colonisation to occur, which further inhibits ciliary clearance and promotes the persistence of infection and damaging inflammation [39]. The importance of this persistence in bacterial colonisation may be related to the production of heat-labile products by the bacteria, which further damage ciliated cells and inhibit ciliary activity. P. aeruginosa can be a particular problem as it is protected from cellular and humoral attack because it survives in a biofilm on the mucosal surface [40]. Pseudomonas has been shown...
to produce phenazine pigments that can inhibit ciliary action through a mechanism which leads to a reduction in cellular cAMP and ATP. Furthermore, pseudomonal pyocyanin can lead to epithelial disruption and rhamnolipids have a ciliostatic effect [41, 42]. Alveolar macrophages are an important mediator of defence against Pseudomonas and stimulated macrophages secrete cytokines that both recruit and activate neutrophils, thus potentially amplifying both the inflammatory response and the potential for further tissue damage [43, 44].

The resultant inflammatory reaction is an important pathogenic mechanism in the weakening of the bronchial wall. Much of the damage appears to relate to the release of proteolytic enzymes and oxygen free radicals from neutrophils. The severity of an inflammatory response is dependent on the interplay of several cytokines, which may be both pro- and anti-inflammatory [45]. In a well-regulated system, the inflammatory cascade is proportionate to the triggering bacterial stimulation and is switched off. There is evidence that in bronchiectasis the inflammatory response is disproportionate to the infective burden and that the inflammatory response persists [43, 46]. Indeed, in the early phases of bronchiectasis, active airway inflammation has even been reported in the absence of identifiable microbial infection, suggesting a dysregulation of the cytokine network independent of infection [47].

Neutrophils are potent effectors in inflammatory responses and secrete anti-microbial substances, as well as reactive oxygen free radicals [48]. Bronchoalveolar lavage (BAL) studies have demonstrated that neutrophils are consistently present in patients with bronchiectasis, even when sterile and clinically stable, but increase in the presence of potential pathogens [49, 50]. Recruitment and migration of neutrophils in airways is facilitated by the activation of neutrophils and the upregulation of adhesion molecules on endothelial cells [51–53]. These changes are regulated by cytokines, particularly IL-1 and tumour necrosis factor (TNF)-z, as well as lipopolysaccharide (LPS), which have been shown to be increased in the airways of patients with bronchiectasis [54, 55]. Activated neutrophils secrete potentially tissue damaging enzymes such as neutrophil elastase, proteinase 3 and metalloproteinases. Levels of these enzymes in BAL samples have been shown to correlate with neutrophil numbers and markers of disease activity such as 24-hour sputum production [56]. These enzymes can directly damage the structural integrity of the airway via damage to the basement membrane and elastin framework [57–60]. Neutrophils are also an important source of oxygen free radicals. Release of oxygen free radicals are an important part of the defence against infection and are regulated by a protective anti-oxidant system. However, the excessive release of these oxidants can overwhelm the defence mechanisms and cause tissue damage via lipid peroxidation. Furthermore, reactive oxygen species may amplify the inflammatory response through the induction of cytokine and chemokine production by the stimulation of genes regulated by nuclear factor-κB. Studies in bronchiectatic patients have shown increased levels of exhaled H2O2 correlating with neutrophil counts and disease activity [61, 62].

Macrophages also play a role in the disease progression as they secrete TNF-α, which promotes neutrophil recruitment, as well as other inflammatory mediators including IL-8, monocyte chemotactic protein-1 and chemokines [23, 63]. Lymphocytes are also typically present in
bronchial biopsies within the lamina propria and may also infiltrate the overlying epithelium. Studies assessing the relative proportions of CD4+ and CD8+ have produced mixed and, at times, conflicting results. Nonetheless, their presence indicates a cell-mediated immune response contributing to the overall inflammatory process [22].

Whilst the epithelial layer may be seen as a protective barrier through mucociliary clearance and generation of anti-bacterial substances, it also contributes to the inflammatory process through the direct generation of pro-inflammatory cytokines [64]. Exposure to LPS leads to the generation of IL-8 and TNF-α which, as stated previously, are important in neutrophil recruitment. Bronchial epithelial cells are also able to upregulate surface adhesion molecules, such as intracellular adhesion molecule-1, aiding the migration of neutrophils [65, 66].

Thus, a number of pathways lead to the activation and recruitment of neutrophils into the airways which, if not adequately regulated and controlled, results in the destruction of local tissue and the persistence and progression of bronchiectasis. Individual variability in this innate response may help to explain why not all individuals exposed to predisposing triggers will go on to develop bronchiectasis and offers potential targets for therapeutic intervention.

Statement of interest

None declared.

References


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