Importance of sputum and computed tomography assessments of airway neutrophil inflammation and mucus plugging in bronchiectasis management

Naoya Tanabe [1] and Hisako Matsumoto [2]

[1]Department of Respiratory Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan. [2]Department of Respiratory Medicine and Allergology, Kindai University Faculty of Medicine, Osakasayama, Japan.

Corresponding author: Naoya Tanabe (ntana@kuhp.kyoto-u.ac.jp)

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Sputum myeloperoxidase quantification and computed tomography scoring of mucus plugs in central airways deepen understanding of relationships between airway neutrophilic inflammation, mucus plugging and disease severity in patients with bronchiectasis https://bit.ly/3YHP4dF

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Non-cystic fibrosis bronchiectasis is a chronic lung disease characterised by abnormal permanently dilated airways with accumulated mucus in the lumen. The pathogenesis of the disease is now considered on the basis of "vicious vortex" theory: this includes airway dysfunction, such as ciliary dysfunction and mucus hypersecretion, inflammation, infection with pathogenic bacteria, and structural damages, such as airway dilation and lung destruction [1]. Mucus accumulation in the airways and chronic sputum symptoms are the main features of patients with bronchiectasis. Mucus is characterised by higher concentrations of mucins, such as MUC5B and MUC5AC, with greater solidity, which are associated with the severity of bronchiectasis and lower lung function [2]. Mucus plugging causes hypoxic conditions for neighbouring airway epithelium, and chronic airway epithelial hypoxia is associated with MUC5B production [3]. A recent study using a combination of histological and molecular analyses also showed that proximal bronchioles exhibit ectasia with lumen obstruction with mucus plugs. Interestingly, distal bronchioles exhibit few signs of ectasia, but mucus plugs are a main pathology of distal bronchioles, and distal bronchiolar mucus plugs are associated with MUC5B expression in patients with non-cystic fibrosis bronchiectasis [4]. These findings further highlight the importance of the interaction between mucus accumulation and structural changes in specific airway locations in bronchiectasis and bronchioloectasis pathogenesis.

In bacterial infections, neutrophils are recruited to the lungs and activated neutrophils phagocytose bacteria, release neutrophil serine proteases and establish neutrophil extracellular traps (NETs) to capture and eradicate bacteria. NETs are composed of multiple factors including decondensed chromatin, neutrophil elastase and myeloperoxidase (MPO). These functions are appropriately regulated in healthy individuals. In contrast, the abnormal releases of neutrophil serine proteases and NET formation cause chronic airway inflammation in patients with bronchiectasis [5]. A recent review by Long *et al.* [6] proposed that while previous approaches mainly focused on the management of infection using oral and inhaled antibiotics, more focus should be placed on chronic inflammation. Sputum neutrophil elastase activity is associated with the risk of exacerbation and disease severity in patients with bronchiectasis [7]. Inactive neutrophil serine proteases are activated by dipeptidyl peptidase-1 (DPP1) during neutrophil differentiation. The DPP1 inhibitor brensocatib was shown to reduce the frequency of exacerbations in patients with bronchiectasis [8]. Based on the reported association between mucus and bronchiectasis severity, it would be hypothesised that neutrophil activation may be associated with mucus plugging in the airways.

In this issue of *ERJ Open Research*, Kim *et al.* [9] examined mucus plugging on computed tomography (CT) in relation to sputum MPO concentration and disease severity in 78 patients with non-cystic fibrosis

bronchiectasis. By dichotomising the patients into a high mucus plug score group (mucus plugs were observed in ⩾10 bronchopulmonary segments, n=19) and a low mucus plug score group (mucus plugs were observed in <10 bronchopulmonary segments, n=59), they showed that sputum MPO concentration, modified Reiff score and FACED score were higher in the high mucus plug score group than in the low mucus plug score group. Moreover, in a multivariable logistic regression model, higher sputum MPO concentration, lower forced expiratory volume in 1 s (FEV_1) on spirometry, and higher modified Reiff score were independently associated with a high mucus plug score after adjusting for age, body mass index, smoking status, sputum culture findings such as *Pseudomonas aeruginosa*, symptom score, dyspnoea scale, high-sensitivity C-reactive protein and previous history of exacerbations.

The strength of this study is that it examined the associations between airway neutrophilic inflammation, mucus plugging and severity of bronchiectasis using established visual scoring systems for mucus plugging and bronchiectasis on CT. The visual scoring of mucus plugging has been intensively used in previous studies on mucus plugging in the central airways in patients with asthma and COPD [10–12]. In this scoring system, analysts observe all bronchopulmonary segments and manually count the number of bronchopulmonary segments with at least one mucus plug. The mucus plugs score is defined as the total count of bronchopulmonary segments with mucus plugs. Although the cut-off value for defining high mucus plugging was set as 3–5 in patients with asthma and COPD [10–12], this study set the cut-off for the high mucus plugs score as 10 because the area under curve to detect acute exacerbations was the highest when using 10 as the cut-off. Further studies are needed to examine the validity of this cut-off value and to obtain more evidence for the clinical relevance of CT-based scoring of mucus plugging in patients with bronchiectasis.

The findings of this study suggest that increased airway neutrophilic inflammation underlies the development of mucus plugging in the central airways and causes disease progression. While poor lung function and airway structural changes potentially increase the risk of mucus plugging, the observed association of sputum MPO with mucus plugging, independent of lower FEV_1 and higher modified Reiff score, suggests that the process of mucus plug formation by neutrophilic inflammation due to the excess

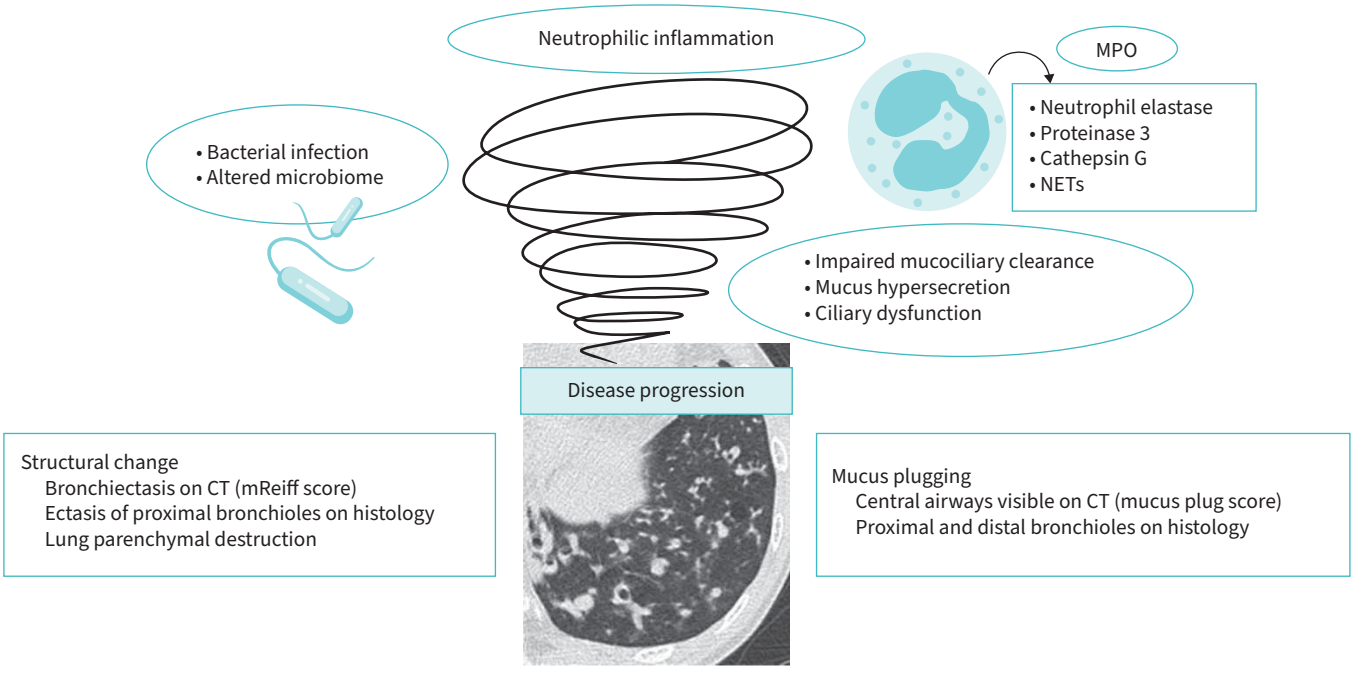

FIGURE 1 Overview of the pathogenesis of bronchiectasis. Chronic airway inflammation (mainly neutrophilic), infection, impaired mucociliary clearance and structural lung damage are involved in the vicious vortex of bronchiectasis. Activated neutrophils release myeloperoxidase, neutrophil elastase and other proteases, and form neutrophil extracellular traps (NETs). The airway inflammation causes mucus hypersecretion and ciliary dysfunction and induces mucus plugging in the central airways visible on computed tomography (CT) and proximal and distal bronchioles on histology. Impaired mucociliary clearance and mucus plugging are associated with chronic bacterial infection, such as *Pseudomonas* colonisation and altered microbiome. These factors interact with each other and induce progression of bronchiectasis. MPO: myeloperoxidase; mReiff score: modified Reiff score.

release of neutrophil serine proteases and NETs formation may occur irrespective of disease severity. Figure 1 conceptualises the pathogenesis of bronchiectasis based on this and previous studies [1, 2, 4, 7]. A recent study showed that high airway interleukin-1β was associated with increased disease severity, caspase-1 activity, neutrophil inflammatory responses, higher relative abundance of Proteobacteria and increased mucus solid contents in patients with bronchiectasis [13]. Neutrophil elastase and other proteases, which are components of NETs, could enhance mucin expression, induce goblet cell hyperplasia and metaplasia and alter ciliary beat frequency [4]. Given that a previous study showed that treatment with brensocatib could suppress neutrophil elastase, proteinase 3, and cathepsin G in the sputum of patients with bronchiectasis [14], future studies should test whether DPP1 inhibitors can improve mucus plugging on CT in these patients.

As mentioned by Kim *et al*. [9], this study had several limitations. Due to the small sample size (n=78), the effect of sputum MPO on mild mucus plugging could not be tested. A future study with a larger sample size is needed to examine whether neutrophilic inflammation could differ between patients with minimum mucus plugging (score 0–2) and those with moderate mucus plugging (score 3–9). Moreover, considering the potential of DPP1 inhibitors to control neutrophilic inflammation, quantification of blood and sputum DPP1 levels may increase our understanding of the activation of airway neutrophilic inflammation in relation to mucus plugging and airway dilation. Additionally, although microbiology was examined using bacterial cultures, in-depth microbiome features were not explored. As the microbiome community may change during disease progression and affect airway inflammation and mucus plugging, microbiome analysis using 16S rRNA sequencing would add to the understanding of bacterial–host interactions in patients with bronchiectasis.

Despite these limitations, Kim *et al*. [9] substantially contributed to further understanding of the importance of airway neutrophilic inflammation in the development of bronchodilation with lumen occlusion by mucus plugging in patients with bronchiectasis. These data support the clinical relevance of CT assessment of mucus plugging in relatively central airways. Because mucus plugging is the main pathology of the distal peripheral airways that cannot be visualised on CT due to limited image resolution [4], future studies should be performed to examine whether an indirect assessment of small airway disease using nonrigid registration of inspiratory and expiratory CT images can reflect mucus plugging in the distal peripheral airways [15]. Moreover, since the visual scoring of mucus plugging is reproducible but time-consuming, technical computational advancements, such as artificial intelligence, should be applied to develop an automatic scoring system for mucus plugging on CT. The present data will stimulate further research on this topic, with the ultimate goal of establishing new interventions to prevent disease progression.

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