Paraseptal Emphysema: From the Periphery of the Lobule to the Center of the Stage

Emphysema and small airway disease are pathologic hallmarks of chronic obstructive pulmonary disease (COPD), both contributing to airflow obstruction, the defining feature of this disease. Emphysema and small airway disease are both present in varying degrees in patients with COPD (1, 2). Emphysema is defined as enlargement of airspaces beyond the terminal bronchioles, together with the destruction of alveolar walls. Emphysema was described in autopsies over 300 years ago, but, currently, noninvasive *in vivo* assessment of this feature is typically performed using imaging tools, such as computed tomography (CT) (3). In subjects with COPD, higher-burden emphysema on CT studies has been linked to increased mortality and disease progression, substantiating its clinical relevance (3).

Emphysema can be classified into three types (panlobular, centrilobular, and paraseptal), all of which can coexist. The first is defined as low-attenuation regions involving the entire secondary pulmonary lobule. Panlobular emphysema is linked to alpha-1 antitrypsin deficiency, but it is also seen in smokers, together with the centrilobular type. Centrilobular emphysema is located around the respiratory bronchioles with the coalescence of destroyed lobules in severe cases (4). Brian Heard (5) was one of the first to report the term "paraseptal emphysema." He described that "the periphery of some lobules appears to have been stretched away from the thickened fibrous septa and associated septal veins, leaving thin filaments to bridge the gaps." Paraseptal emphysema is typically upper lobe predominant. CT studies have demonstrated that the prevalence of paraseptal emphysema ranges from 3% in community-dwelling subjects to 15% in smokers with COPD, and men are disproportionately affected compared with women (6, 7). A large quantitative CT study has shown that paraseptal emphysema, measured as the percentage of the total lung area, increases with increasing COPD severity (8). A higher burden of paraseptal emphysema was associated with a higher dyspnea score, more exacerbations, reduced lung function, and decreased exercise capacity. Paraseptal emphysema is also a risk factor for pneumothorax (9).

Although the availability of large-scale studies and state-of-the-art imaging techniques has allowed us to better understand paraseptal emphysema, its pathologic characterization is less understood. In their sophisticated study in this issue of the *Journal*, Tanabe and colleagues (pp. 803–811) present a detailed picture of this entity (10). The authors draw on clinical CT, micro-CT, and histologic techniques to examine the lungs of six COPD subjects who underwent lung transplantation. The lungs were air-inflated, frozen, and imaged with a multidetector CT scanner. Tissue cores were taken from the central and peripheral regions of each lung. Then all of the cores were imaged with micro-CT and used for histologic analyses. Figure 2 of the article provides very illustrative images of paraseptal and centrilobular emphysema. The authors found that airway pathology was different between these two types of emphysema. The number of terminal bronchioles was lower in centrilobular emphysema–dominant regions than in paraseptal emphysema–dominant regions. The bronchiole lumens were narrower, and the wall area percentage was higher in the centrilobular emphysema–dominant regions than in the paraseptal emphysema–dominant regions. These results suggest that the total bronchiolar area would be greater in paraseptal emphysema. Thus, the remodeling process of the remaining terminal bronchioles seems to be less severe in paraseptal emphysema. The authors discussed the link between these structural airway differences and clinical and functional measures of the disease. This is not an easy task, and prior studies have shown conflicting results. Let us take dyspnea and airflow obstruction as examples. Some studies have shown that those with a centrilobular emphysema–dominant pattern report more dyspnea and have more significant airflow obstruction (6). This difference may be explained by more damaged airways in centrilobular emphysema, as the authors have discussed. In contrast, other studies showed that paraseptal emphysema had a more significant effect on dyspnea and FEV_1 than centrilobular emphysema (8). This suggests that factors other than small airway pathology, such as the degree of lung hyperinflation, may explain the differences in FEV_1 and dyspnea between subjects. This work is a significant contribution to study further the clinical and physiologic consequences of COPD's complex lung pathology.

The authors also analyzed the cellular composition of emphysematous regions. The immunohistochemistry demonstrated that although neutrophilic infiltration was greater in paraseptal emphysema–dominant versus centrilobular emphysema–dominant regions, no differences in macrophage, CD4, CD8, or B cells were found between these two types of emphysema. Although it is not possible to determine whether the differential cellular infiltration and airway morphology observed is causing distinct emphysema types or whether it is the consequence of the different small airways' and alveoli's structural changes, this study encourages further work in less severe COPD to disentangle these pathologic events. Regardless of the sequence of the pathologic events, the findings point to a neutrophil-dominant cellular composition in

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paraseptal emphysema. And although neutrophil elastase activity was not measured in this study, it might be speculated that neutrophil elastase might be an important driver of paraseptal emphysema development. A high amount of neutrophil elastase activity has been linked to emphysema in humans and animals (11). Moreover, increased elastase concentrations in sputum are associated with increased risk of exacerbations (12), suggesting that further understanding of the cellular and molecular orchestration leading to emphysema might give insight that ultimately will translate to modifying therapies for many people suffering from COPD.

A question that arises from this work is how paraseptal emphysema develops. The current notion for the pathologic sequence of events from cigarette smoke to centrilobular emphysema development starts with the inflammation of small airway walls occurring in the center of the lobule. This process leads to bronchiolar–alveolar attachments and surrounding alveolar wall destruction. Because paraseptal emphysema occurs adjacent to the pleura and septa and emphysema animal models have marked changes in capillary segments (i.e., a higher number of nonconnecting segments) on the pleural surface (13), disruptions of pulmonary and/or pleural capillaries might also contribute to paraseptal emphysema. It can be speculated that pulmonary perfusion deficiency may lead to misbalanced inflammatory response and tissue damage repair, resulting in paraseptal emphysema.

In conclusion, the authors should be commended for this elegant contribution to pathologic differences in the small airways and cellular composition between paraseptal and centrilobular emphysema. After a long time, this work brings paraseptal emphysema to the center of the stage. ■

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Rewiring the Immune Response in COVID-19

At the time of writing, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues globally, with nearly 15 million documented cases and more than 600,000 deaths worldwide (1). Many countries have recently seen falls in the number of confirmed cases and are beginning to cautiously reopen following lockdown measures, whereas others are experiencing a continued increase, "second waves" of infection, or localized outbreaks following an initial reduction in cases (2, 3).

This pandemic represents the greatest public health, clinical, and scientific challenge of our generation. Containing viral spread has necessitated unprecedented social and economic change as lockdowns only "temporarily" limit morbidity and mortality. Identifying effective therapies and/or a vaccine remain our only long-term solutions. Simply put, research is the only exit strategy (2–5).

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