No Matter How You Push and Squeeze, Organizing Pneumonia Remains More Than One Disease

Pathologists have long emphasized that the lung demonstrates a fairly stereotypical response to a variety of injuries that cause tissue inflammation. In the instance of pneumococcal pneumonia, Laënnec, over 200 years ago, described 3 phases of pulmonary inflammation. First, congestion develops as air spaces become flooded with inflammatory exudate. Next follows hepatization, with stiffening of the lung due to cellular and matrix infiltration. And finally, resolution occurs, with reabsorption of inflammatory exudates in those patients who survive their pneumonia.

After Laënnec's description, autopsy series demonstrated an additional histopathological pattern in patients who died from pneumonia. Rather than resolving, the inflammatory exudate becomes organized in distal air spaces, with variable degrees of fibrosis.[1] This pattern, termed organizing pneumonia, represents a nonspecific histopathological response to unresolved or partially resolved pulmonary inflammation. It is characterized by intra-alveolar buds (also termed polyps) of granulation tissue composed of myofibroblasts, fibroblasts, and connective matrix within alveoli and alveolar ducts. Many, but not all, lung specimens that demonstrate organizing pneumonia also show accompanying evidence of inflammation in small (1–2-mm diameter) distal airways, which is termed bronchiolitis.

For many years, organizing pneumonia was considered a histopathologic response that was limited to pulmonary infections. When pathologists noted organizing pneumonia on biopsy or autopsy specimens, the rules of parsimony caused them to push and squeeze to label patients with a single disease: infectious pneumonia. Subsequently, however, an increasingly wide variety of respiratory exposures and underlying conditions were associated with organizing pneumonia. These entities include inhalation of toxic fumes, immunologic and connective-tissue disorders, inflammatory bowel disease, human immunodeficiency virus infection, common variable immune deficiency, radiation therapy, myelodysplastic syndrome, drug reactions, malignant diseases, and bone marrow or solid organ transplantation, to name a few. The diverse nature of these conditions that all resulted in the same pathologic response in the lung further advanced the impression that the lung responds stereotypically to a wide variety of injuries.

In the 1980s, reports emerged of patients presenting with respiratory symptoms and radiographic opacities in the absence of any underlying medical conditions, respiratory infections, or exposures to exogenous agents known to cause lung inflammation. Lung biopsy samples demonstrated classic histopathologic features of organizing pneumonia. The clinical range of organizing pneumonia was thereby extended to an idiopathic form of the disease.[2,3]

The common feature that ties all of these conditions together is histopathological evidence of organizing pneumonia, often found in association with bronchiolitis. Consequently, the term bronchiolitis obliterans with organizing pneumonia (BOOP) was adopted to describe the lung-biopsy findings and also the clinical entity of the idiopathic form of organizing pneumonia. Later, it became better recognized that organizing pneumonia was the pathological hallmark of these conditions and evidence of bronchiolitis was variably present or entirely absent in some patients. Also, the term BOOP caused confusion with

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constrictive, proliferative, and other forms of bronchiolitis obliterans, which represent unique forms of lung disease. So we now classify the idiopathic form of BOOP as cryptogenic organizing pneumonia (COP) and the secondary form as secondary organizing pneumonia (SOP). The American Thoracic Society/European Respiratory Society typology for diffuse parenchymal lung disease includes COP under the category of idiopathic interstitial pneumonias.[4] Pathologists maintain use of the term BOOP to describe the histopathologic findings noted in patients with SOP or COP.

With this background, respiratory clinicians may wonder if some patients who present with clinical features of bacterial respiratory infections may actually have COP or non-infectious causes of SOP as a simulator of community-acquired pneumonia. And indeed, this suspicion is valid. Patients with noninfectious SOP and COP often present with cough, fever, chest pain, and other clinical features suggestive of community-acquired pneumonia. So it is important to recognize the clinical features of non-infectious organizing pneumonia that might assist early differentia-

tion of these conditions from community-acquired pneumonia. Also, respiratory symptoms from organizing pneumonia may be the initial presenting manifestations of noninfectious underlying conditions, such as collagen vascular disease. Consequently, evaluation of patients with suspected organizing pneumonia would be assisted if specific presenting clinical features suggested a higher likelihood of SOP rather than COP, considering that suspicion for SOP often warrants additional diagnostic testing to identify the underlying disease.

These considerations highlight the value of the study by Vasu and colleagues in this issue of RESPIRATORY CARE.[5] They review their experience with 33 patients with organizing pneumonia diagnosed via lung biopsy, and report their overall clinical features and those features unique to patients with SOP versus COP. Their report adds to the sparse literature that compares these 2 forms of organizing pneumonia.[6-8]

Vasu and colleagues noted a mean age of 59 years in their patients with organizing pneumonia, and only 6% were current smokers. Previous series report mean ages between 50 and 60 years for COP, and the ages of patients with SOP vary by the distribution of risk factors for organizing pneumonia among the evaluated patient population. Rare reports exist of COP in children[7,9] and patients as old as 92 years.[10] As noted by Vasu and co-workers, other studies confirm that COP is not a disease of smokers.[6] Also, prior studies demonstrate no differences in smoking history between patients with COP or SOP.[8]

The Vasu et al study notes dyspnea, cough, and fever as the most common symptoms reported by patients with organizing pneumonia, with rare patients presenting with chest pain or hemoptysis.[5] These findings correspond with those in the literature, but omit more subtle symptoms previously reported, such as flu-like symptoms with arthralgias, myalgias, and malaise, which may progress to anorexia, night sweats, and weight loss.[11,12] Prominent arthralgias are said to suggest the presence of underlying connective-tissue disease in patients with SOP.[6] Other reports establish that organizing pneumonia may rarely progress to severe dyspnea and respiratory failure.[13] Hemoptysis is uncommon and seldom severe.[14] Pneumothorax and pneumomediastinum are very unusual presentations.[15]

As in prior reports,[16] Vasu and co-workers noted remarkably little in the way of physical findings. Fifty-eight percent of their patients had crackles and none had wheezing.[5] Other studies of patients with COP similarly report only focal and sparse crackles, with many patients having normal chest examinations.[11] Notably, most[6] but not all[7] reports of organizing pneumonia do not note finger clubbing. Perhaps because of the nonspecific symptoms and chest findings, patients in the Vasu et al study were not diagnosed with organizing pneumonia until 6–13 weeks after onset of symptoms, which is similar to previous reports.[6,11] Most patients receive one or more courses of antibiotics for presumed bacterial pneumonia before clinicians consider the possibility of organizing pneumonia.

Previous studies have reported restrictive spirometric findings in organizing pneumonia, which is expected, considering the parenchymal rather than airway location of the disease.[8] The Vasu et al study, interestingly, noted airflow limitation in 24% of patients, restriction in 19%, and mixed findings in 14%. Prior studies that observed airflow limitation in organizing pneumonia noted these findings only in patients with a history of smoking.[17] Vasu and colleagues did not report the distribution of spirometric findings by smoking history but did mention in their discussion that the obstructive ventilatory defect may have occurred because a large proportion of their patients smoked. A stratification of spirometric findings by smoking history, however, was not provided. I suspect the findings of airflow limitation occurred as a result of chronic obstructive pulmonary disease.

Patients with organizing pneumonia demonstrate characteristic radiographic and high-resolution computerized tomography (HRCT) abnormalities, which have been classified into 3 main types: typical, focal, and infiltrative.[18] Typical findings include diffuse, bilateral patchy, ground-glass, or alveolar opacities, often with a peripheral distribution. The densities may range in size from a few centimeters to encompassing an entire lobe, and usually demonstrate air bronchograms in regions of consolidation. Opacities may be migratory, which may confuse clinicians into assuming a response to antibiotic therapy. Focal abnormalities occur as a solitary alveolar opacity that may simulate localized pneumonia or a solitary pulmonary nodule. And the infiltrative pattern is represented by reticulonodular densities, often with radiographic evidence of pulmonary fibrosis. These imaging features are sufficiently characteristic of organizing pneumonia that radiologists may diagnose the condition via HRCT in 79% of patients with a compatible history, which is the highest diagnostic accuracy of HRCT among all patients presenting with idiopathic interstitial pneumonia.[19] Idiopathic chronic eosinophilic pneumonias, low-grade pulmonary lymphomas, alveolar sarcoidosis, and bronchioloalveolar lung carcinoma are in the imaging differential diagnosis.

The spectrum of imaging patterns in organizing pneumonia, however, includes more atypical findings, such as diffuse centrilobular nodules,[20] subtle areas of subpleural fibrosis, mediastinal adenopathy,[21] and crescentic or ring-shaped opacities with a central ground-glass attenuation termed an atoll or reverse halo sign.[20,22] Rare patients may have a perilobular distribution of densities.[23]

Vasu and co-workers noted in their patients the usual radiographic abnormalities of organizing pneumonia, with

consolidation, nodules, and ground-glass opacities, and 29% of their patients demonstrated migratory densities. None of their patients had the reverse halo sign.[5]

Most patients with COP experience a benign clinical course with complete clinical and radiographic response, spontaneously or after the initiation of corticosteroid therapy.[17] The course of SOP depends on the responsiveness of the underlying disease to therapy. Treatment of COP consists of corticosteroids, and there have been some reports of responsiveness to macrolide antibiotics, probably because of their anti-inflammatory rather than antibacterial properties.[8,24] Among all patients with COP, however, patients with the infiltrative form have the worst prognosis.[25] Patients with acute fulminant COP with respiratory failure may also respond poorly to therapy.[13] Relapses occur, with some patients experiencing a seasonal recurrence at the same time of the year.[26] Recurrent catamenial COP has also been reported.[27]

But the important finding from the Vasu et al study is the distribution of various findings between patients with COP and SOP, which might help discriminate between these patients on clinical grounds. Vasu and colleagues report that the COP patients were older, but the difference was not statistically significant.[5] Notably, women more commonly had COP than SOP (67% vs 13%), which differs from the report by Sveinsson and colleagues,[8] who noted similar distribution by sex. This finding may represent the type of underlying conditions among patients with SOP in the Vasu et al report.

Patients with COP in the Vasu et al study had a longer duration of symptoms to diagnosis than did those with SOP (6.2 wk vs 2.8 wk).[5] This finding is not too surprising considering that patients with known underlying conditions would be more likely to undergo a more extensive evaluation of pulmonary opacities than would previously healthy patients with COP, who would initially be treated with antibiotics for a diagnosis of community-acquired pneumonia.

Interestingly, Vasu and colleagues reported that fever occurred at presentation more commonly among patients with SOP (73%) than among those with COP (22%). An asymptomatic presentation was less common with SOP (7%) than COP (33%).[5] These findings are different from previous comparative studies, wherein clinical features of patients with SOP and COP were similar at clinical presentation,[6-8] except for the findings of crackles more commonly detected in patients with SOP in one study.[8] The differences noted in the Vasu et al study may result from the tendency toward more commonly finding consolidation imaging densities in the SOP group and nodular densities in the COP group, considering that nodular densities are more likely to be asymptomatic in patients with organizing pneumonia.[16]

Vasu and colleagues emphasize the potential importance of their finding that 60% of patients with SOP had imaging evidence of pleural effusions, as compared to 0% among patients with COP. They explained this difference by suggesting a different histopathologic response to lung injury in these 2 conditions. The subpleural distribution of airspace densities in COP, however, suggests that the pleura would be affected in a considerable proportion of patients. Although most studies report rare occurrences of pleuritic chest pain in patients with COP, Lohr and colleagues noted pleuritic pain in 23% of their 61 patients.[6] Other studies indicate that up to 50% of patients with COP have pleuritic symptoms when parenchymal densities are adjacent to pleural membranes.[26,28] Moreover, pleural effusions have been reported in 5–35% of patients with COP[3,29,30] and pleural thickening in 23%.[7] The presence of pleural effusions, therefore, may not prove successful in reliably excluding COP.

The present study noted good responsiveness to corticosteroids in short-term follow-up of patients with either COP or SOP. Previous studies noted a higher 5-year survival in patients with COP (73%) than those with SOP (44%), probably as a reflection of the course of the disease underlying SOP.[6]

So what do we conclude from the study by Vasu and colleagues? It appears we are no further along in identifying presenting clinical features that reliably discriminate between SOP and COP. Considering the extensive overlap in clinical and histopathologic expressions between these 2 forms of organizing pneumonia, one might wonder if they actually represent the same clinical entity. Perhaps COP simply represents SOP in instances wherein the etiologic underlying condition or exogenous pro-inflammatory trigger cannot be identified. Our existing typology that separates SOP from COP may represent a helpful system in our present state of limited knowledge but should not establish that these 2 entities represent distinct lung diseases.

But we should note the differences that exist among subsets of patients with different clinical and imaging presentations of organizing pneumonia. As mentioned, patients with infiltrative organizing pneumonia have worse prognoses than other imaging presentations of the disease.[25] Patients with the fulminant form of organizing pneumonia respond less well to corticosteroids.[13] And focal organizing pneumonia appears to have an association with chronic obstructive pulmonary disease and more commonly presents without symptoms.[31] Using our present typology of SOP versus COP, pathologists may be right in squeezing the two into a single disease. But examining organizing pneumonia from the perspective of its distinct subsets of clinical and imaging presentations, no matter how we

push and squeeze, we may be dealing with separate diseases.

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