Radiology

What Are the Long-term Pulmonary Sequelae of COVID-19 Infection?

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The COVID-19 pandemic has been ongoing for 2 years. Over this period, *Radiology* and other peer-reviewed journals have distributed information regarding the nature of the pandemic with unprecedented speed. Based on the extensively documented clinical and imaging manifestations of acute COVID-19 infection, expert thoracic imagers have developed imaging categories that classify patterns according to the likelihood that they represent COVID-19 infection (1).

Acute COVID-19 has a somewhat unique appearance among viral infections on CT scans. It manifests as ground-glass opacity and/or consolidation, often with a strong peripheral distribution. Also, there are CT findings suggesting that organizing pneumonia (OP) is a common pattern of injury. OP is associated with a wide variety of different infections, although it appears particularly common with COVID-19 (2). However, the long-term pulmonary manifestations of COVID-19 pneumonia (part of so-called "long COVID") remain lacking in the literature.

It is important to understand our current knowledge of viral infections and their typical manifestations within the lungs. The long-term sequelae of viral pneumonia, in general, vary depending upon two factors: (*a*) direct injury caused by the viral organisms and *(b)* the host's immune reaction to those organisms. These result in a variety of different patterns of injury, each of which is associated with specific permanent long-term sequelae. The histologic manifestations of acute pulmonary viral infections can be divided broadly into two primary patterns: bronchiolitis and inflammation adjacent to airways, and diffuse alveolar damage (DAD). On images, bronchiolitis and airway inflammation manifest as bronchial wall thickening, centrilobular nodules, and tree-in-bud opacities, whereas DAD manifests as bilateral ground-glass opacity and/or consolidation.

The long-term effects of these two patterns are also characteristic. Inflammation within and around the airways may induce concentric fibrosis around the bronchioles, resulting in airway narrowing or obliteration. This is termed constrictive (or obliterative) bronchiolitis, the development of which may result in persistent dyspnea after resolution of the acute infection, with an associated obstructive defect on pulmonary function tests. Typical CT findings of constrictive bronchiolitis include mosaic attenuation and air trapping, sometimes associated with bronchiectasis. The long-term manifestations of DAD, on the other hand, are quite different. Histologically, fibrosis develops 1–2 weeks after the development of acute symptoms. On images, this is associated with the development of reticulation and traction bronchiectasis. Over time, usually months, the fibrosis may improve; however, residual fibrosis is common (3) and often located in the anterior subpleural lung, which may be associated with restrictive physiology on pulmonary function testing.

OP is particularly common with COVID-19 and its clinical and imaging features have been studied (4), mainly in the setting of cryptogenic (idiopathic) disease. OP is usually a highly steroid-responsive disease with opacities that quickly improve or resolve with treatment, although residual fibrosis may occur. This residual fibrosis often has a pattern that resembles nonspecific interstitial pneumonia with basilar predominant reticulation, traction bronchiectasis, and subpleural sparing (5). It is also important to note that OP and DAD may coexist, with overlapping imaging findings.

Understanding the different patterns of injury associated with viral infections and their long-term sequelae is important for putting the long-term effects of COVID-19 infection in context. Han et al (6) were among the first to describe the persistent CT findings of COVID-19 6 months after the onset of acute symptoms. In their study, more than one-third of patients showed evidence of fibrotic changes.

In this issue of *Radiology*, Cho and colleagues (7) address these long-term pulmonary manifestations in a prospective study of 100 participants with persistent (>30 days) pulmonary symptoms after an acute COVID-19 infection; 106 healthy controls were also evaluated. The particular emphasis of this investigation was on the presence of air trapping on expiratory CT scans. The severity of disease varied among the three study groups, which included participants who were ambulatory, participants who were

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Conflicts of interest are listed at the end of this article.

See also the article by Cho and Villacreses et al in this issue.

hospitalized, and those who required admission to the intensive care unit (ICU). Cho et al discovered that air trapping was present in 58% of participants following COVID-19 infection, with its highest prevalence in the hospitalized group (73%). Using quantitative analysis, air trapping affected a mean of 25%–35% of the lungs in participants, depending on the clinical severity of disease, compared with 7% in the healthy controls ($P < .001$). The authors did not identify obstructive airways disease with spirometry in any of the groups. The lack of obstruction at spirometry in patients with air trapping is not surprising. In a cohort of soldiers deployed to Iraq and Afghanistan with biopsy-proven constrictive bronchiolitis (8), the majority did not have obstruction on pulmonary function tests. Restriction was present at spirometry in the participants with COVID-19 in the study by Cho et al, specifically in the hospitalized and ICU groups. Ground-glass opacity, traction bronchiectasis, and other signs of fibrosis were most frequent in those admitted to the ICU (94%, 69%, and 81%, respectively, compared with 36%, 8%, and 3% of the ambulatory group, respectively).

In summary, the study by Cho et al (7) demonstrates that air trapping on CT scans is common in individuals with persistent symptoms after COVID-19. When considering the long-term pulmonary effects of COVID-19 infection, this is an important finding and may correspond to the development of postviral constrictive bronchiolitis, an entity seen with other viral infections and particularly adenovirus infection. Interestingly, the CT findings of acute COVID-19 are not highly airway-centric. Centrilobular nodules and tree-in-bud opacities, reflecting airway-centric inflammation, are not typical findings of acute COVID-19 infection. Regardless, these results indicate a long-term impact on bronchiolar obstruction. In the study by Cho et al, the presence of ground-glass opacity and/or fibrosis on CT scans was most common in the participants admitted to the ICU and likely corresponds to post-OP and/or post-DAD fibrosis.

It is important to note that not all incidences of pulmonary fibrosis, including those of the airway and of the parenchyma, are permanent. Collagen may be absorbed for months after the acute insult; thus, it is not entirely clear whether the abnormalities seen in the study by Cho et al will be permanent. The median time from COVID-19 diagnosis to the clinic visit for persistent post–COVID-19 symptoms was only 75 days. However, eight of nine participants (of 100 total participants) who underwent imaging more than 200 days from the acute infection had persistent air trapping. Regardless of the imaging findings, the most important question is whether the airways obstruction and/or fibrosis cause clinical symptoms. The results reported by Cho et al suggest that airways obstruction and post-OP and/or post-DAD fibrosis contribute to persistent symptoms after COVID-19 infection, with the contribution of airways disease being greater in the ambulatory group and the contribution of OP and DAD being greater in those admitted to the ICU. Longer-term studies assessing clinical and imaging manifestations 1–2 years after the initial infection are needed to fully ascertain the permanent manifestations of post–COVID-19 fibrosis.

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