Radiology

"ILD" after COVID-19 Infection: A Catalogue of Uncertainties

Manuscript type: Reviews and Commentary

Athol U. Wells [1,2] MD
Anand Devaraj [2,3] MD
Sujal R. Desai [2,3] MD

[1] The Interstitial Lung Disease Unit, Royal Brompton and Harefield NHS Foundation Trust, London, [2] The National Lung & Lung Institute, Imperial College London & [3] Department of Radiology, Royal Brompton and Harefield NHS Foundation Trust, London

Corresponding Author:
Professor Athol U. Wells
Interstitial Lung Disease Unit
Royal Brompton and Harefield NHS Foundation Trust
Sydney Street
London SW3 6NP

E mail: rbhild@rbht.nhs.uk

See also the article by Han et al.

Coronavirus Disease 2019 (COVID-19) has now caused more than a million deaths worldwide. These deaths are often due to severe pulmonary involvement. In fatal cases, features of diffuse alveolar damage are a frequent finding. Many survivors with severe infection have long-term residual abnormalities on their thoracic CT scans. But current studies do not extend follow-up beyond six months. Residual pulmonary disease is sometimes referred to as "post-COVID interstitial lung disease" (ILD).

In this issue of *Radiology*, Han et al report a prospective cohort of 114 patients undergoing CT during hospital admission and six months later **(1)**. In 62% of patients, there were residual CT abnormalities at six months. This included 35% of the total cohort with "fibrotic-like" features (the presence of parenchymal bands, irregular interfaces [bronchovascular, pleural or mediastinal], traction bronchiectasis, honeycombing). The remaining patients with residual abnormalities had ground-glass and interstitial thickening. 26% of patients had reduced gas transfer levels.

Initial features predictive of fibrotic-like abnormalities at six months were also independent predictors in multivariable analysis. These included age, markers of disease severity (tachycardia, duration of hospital stay 17 days or longer, the total extent of disease on CT), the acute respiratory distress syndrome (ARDS), and mechanical ventilation. The linkage between ARDS and fibrotic-like changes at six months was especially striking. ARDS was present in 63% of this patient subgroup but in only 8% of the remaining patients (odds ratio 13.4 in multivariable analysis).

Serial CT evaluation showed an increase in features suggesting underlying fibrosis but a decrease in the total extent of disease on CT and in ground-glass attenuation and consolidation. Fibrotic-like change was present in only two patients at initial CT (i.e. in only 5% of the 40 patients with this CT appearance at six months). The extent of fibrotic-like change was positively correlated at six months with the total extent of disease and the extent of ground-glass attenuation.

In severe COVID-19 infection, histologic information is mostly confined to fatal cases in which ARDS (i.e. histologic features of diffuse alveolar damage) is a prominent feature. This observation is not

directly relevant to residual CT findings at six months. It is important to stress that the current study interprets CT patterns without evaluation of underlying histologic appearances. In general, the term "fibrosis" applies to irreversible disease. The authors are correct to refer to "fibrotic-like" appearances, an important caveat. Similarly, the widespread use of the term "post-COVID ILD" implies something more than the slow regression of abnormalities following the acute episode. It presupposes that residual abnormalities, when clinically significant, will remain so in the longer term. Thus, while the current study provides invaluable CT information at six months, it remains essential that major uncertainties about both the histologic and the long-term clinical significance of the CT observations are clearly understood.

What do the CT patterns mean, in reality? Do the "fibrotic-like" changes truly represent irreversible disease in a post-ARDS setting? It is important to note that in post-SARS disease, CT findings considered to denote fibrosis at initial CT follow-up continue to regress in the longer term **(2)**. In attempting to separate fibrotic and non-fibrotic appearances, one difficulty is the "grey area" in which immature fibrosis ("fibroblastic change"), arising because of diffuse alveolar damage, remodels with time. In the current study, two problems apply to the attempt to separate fibrotic and non-fibrotic CT abnormalities.

First, it is not entirely clear that all the abnormalities grouped as "fibrotic-like" are reliably indicative of irreversible disease in a post-ARDS setting. Bands are especially difficult to interpret. Identical appearances are seen in cryptogenic organizing pneumonia **(3)** and organizing pneumonia-like change is often seen during and following COVID infection, as in the current study. Honeycombing might reasonably represent genuinely irreversible disease. But is this also true of other "fibrotic-like patterns?" Or will these features mostly regress with time and the remodeling of immature fibrosis?

Second, the histologic and clinical significance of the "non-fibrotic" CT patterns is questionable. The authors argue that ground-glass attenuation on CT is likely to reflect inflammatory disease, although they acknowledge the nature of inflammation is not currently understood if this is the case. Despite

partial regression over six months, it is interesting that the extent of ground glass and the total extent of disease at six months were the CT features correlating most strongly with the extent of fibrotic-like abnormalities at six months. Ground-glass attenuation is sometimes indicative of fine interstitial fibrosis that is genuinely irreversible in chronic ILD **(4)**. It is not unreasonable to hypothesize that regression of ground-glass at least partially reflects remodeling of immature fibrosis.

These uncertainties are inescapable as it is unlikely that future histologic studies will evaluate residual disease on CT of patients recovering from serious COVID-19 infection. The authors make reasonable broad separations based on past CT-histologic correlations. But, as discussed above, these may not be accurate in the short-term follow-up of ARDS survivors. It can be argued that the current study lost a major opportunity to examine regional CT linkages between patterns. Each individual CT pattern was examined in isolation, both at six months and with respect to serial change. Ground-glass and fibrotic-like scores were positively correlated at six months, but it is not clear whether fibrotic-like change co-segregated regionally with areas of residual ground glass. Similarly, it is unclear whether features considered to denote fibrosis at six months arose in areas with intense ground-glass or consolidation in the acute scan. In a nutshell, the *evolution* of CT patterns (whether from inflammatory to fibrotic disease, or reflecting partial regression of immature fibrosis with residual disease more overtly fibrotic) was not explored.

This deficiency is important because of the argument that there are twin pathogenetic pathways in severe COVID-19 infection. One pathway involves diffuse alveolar damage as a toxic viral effect, perhaps fueled by ventilator-induced lung injury. The other involves auto-inflammatory pathways contributing to vascular lesions and organizing pneumonia-like change. A small COVID-19 autopsy study recently documented the existence of inflammatory perivascular lesions distant from sites of epithelial injury **(5)**. It is well recognized that viruses can trigger autoimmune disease **(6)** and there are case reports of COVID-19 triggering systemic lupus erythematosus, antiphospholipid syndrome,

Guillain-Barré syndrome, and lupus anti-coagulant positivity. But it is not known whether the CT features, both acutely and at follow-up, represent a pathogenetic continuum, or whether separating diffuse alveolar damage/ventilator-induced lung injury from auto-inflammatory pathways would enhance our understanding of COVID-19 infection. In this regard, future serial CT studies examining inter-relationships between individual patterns and their evolution have much to offer.

Future studies of patients with residual CT abnormalities at six months should consider several additional baseline candidate risk factors. Pulmonary vascular lesions are a major consideration in acute COVID infection and might contribute to residual defects in gas transfer. The current study showed a link between D-dimer levels and the existence of fibrotic-like features at six months. But this link was not retained on multivariable analysis. Dual-energy CT might be harnessed to capture intra-vascular thrombosis in acute COVID-19 **(7)**, in order to identify associations with subsequent CT findings. The impact of ventilator-induced lung injury might best be captured as the duration of high-pressure ventilation, which is linked to residual CT abnormalities at one-year post-ARDS **(8)**. Finally, a baseline variable that may be more difficult to capture is the pre-existence of limited interstitial lung abnormalities (ILA). This variable is present in screening studies in 5-10% of older adults **(9)**, the demographic at greatest risk of COVID-19 mortality. It is conceivable that extensive parenchymal opacification during acute COVID-19 infection might mask limited ILAs and that COVID-19 infection might promote their evolution to apparent residual fibrotic changes post-COVID.

More importantly, future work must pursue a longer-term follow-up of patients — at or beyond a year —to determine whether residual CT abnormalities at six months largely regress, as in past forms of diffuse alveolar damage, or persist. In this regard, it may be important to distinguish between post-ARDS abnormalities (including ventilator-induced injury) and auto-inflammatory/auto-immune pathways triggered by COVID-19 (perhaps giving rise to progressive fibrotic lung disease in a small minority of patients).

In summary, the study of Han et al is an important addition to the literature because it documents the existence of residual CT abnormalities at six months in a large proportion of patients with severe COVID-19 infection. It is helpful for clinicians to know that this outcome is linked separately to ARDS, the use of mechanical ventilation, and extensive disease on CT during the acute episode. But there are many unanswered questions that future works must explore. Areas needing further exploration include the pathogenetic significance of and inter-relationships between individual CT patterns and their longer-term clinical significance. Only time and serial disease behavior will inform us whether the term “post-COVID ILD” is appropriate.

References

1) Han X, Fan Y, Alwalid O, Li N, Jia X, Yuan M, Li Y, Cao Y, Gu J, Wu H, Shi H. Six-month follow-up chest CT findings after severe COVID-19 pneumonia. Radiology (In Press)

2) Wu X, Dong D, Ma D. Thin-Section Computed Tomography Manifestations During Convalescence and Long-Term Follow-Up of Patients with Severe Acute Respiratory Syndrome (SARS). Med Sci Monit 2016; 22:2793-9

3) Murphy JM, Schnyder P, Verschakelen J, Leuenberger P, Flower CDR. Linear opacities on HRCT in bronchiolitis obliterans organizing pneumonia. Eur Radiol 1999; 1; 1813-7.

4) Remy-Jardin M, Giraud F, Remy J, Copin MC, Gosselin B, Duhamel A. Importance of ground-glass attenuation in chronic diffuse infiltrative lung disease: pathologic-CT correlation. Radiology 1993; 189:693-8.

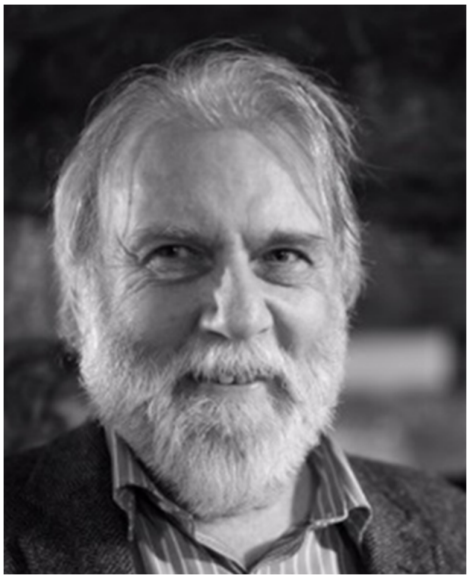
5) Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, Li WW, Li VW, Mentzer SJ, Jonigk D. Pulmonary vascular endothelialitis, thrombosis and angiogenesis in Covid-19. N Engl J Med 2020; 383:120-8.

6) Hussein HM, Rahal EA. The role of viral infections in the development of autoimmune diseases. Crit Rev Microbiol 2019; 45:394-412.

7) Patel BV, Arachchillage DJ, Ridge CA, Bianchi P, Doyle JF, Garfield B, Ledot S, Morgan C, Passariello M, Price S, Singh S, Thakuria L, Trenfield S, Trimlett R, Weaver C, Wort SJ, Xu T, Padley SPG, Devaraj A, Desai SR. Pulmonary angiopathy in severe COVID-19: physiologic, imaging, and hematologic observations. Am J Respir Crit Care Med 2020; 202:690-9.

8) Desai SR, Wells AU, Rubens MB, Evans TW, Hansell DM. Acute respiratory distress syndrome: CT abnormalities at long-term follow-up. Radiology 1999; 210:29-35.

9) Putman RK, Hatabu H, Araki T, Gudmundsson G, Gao W, Nishino M, Okajima Y, Dupuis J, Latourelle JC, Cho MH, et al; for the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators; COPDGene Investigators. Association between interstitial lung abnormalities and all-cause mortality. JAMA. 2016; 315:672–81.



Dr Athol Wells trained, graduated and completed specialty training in New Zealand but found his true home, personally and professionally, in the UK. He is a professor at the Royal Brompton Hospital and affiliated to Imperial College. He specializes in interstitial lung disease. His research focus is clinical science, applied to clinical evaluation, management and translational work. He has over 500 publications and is a member of the Fleischner Society.