Understanding COVID-19 Pathophysiology: What Defines Progress?

The volume of published material related to coronavirus disease (COVID-19) is phenomenal, with more than 185,000 citations on PubMed the time of this writing. To put this into perspective, the number of publications for "pneumonia" between 1990 and 2019 on PubMed is less than 160,000.

Although the number of original research studies is a small subset of the published literature on COVID-19, sorting out the signal from the noise is still a challenge. In the understandable rush to publish, much of what we have seen involves little pieces of a big jigsaw puzzle that has not yet yielded a coherent picture.

In this issue of the *Journal*, Russell and colleagues (pp. 196–205) report on their analysis of tissue samples from 13 autopsy cases of patients who died of COVID-19 (1). As might be expected, the patients were predominantly elderly (mean 80 yr) and overwhelmingly male (12/13), and all had hypoxic respiratory failure with radiological evidence of pneumonitis, although only four received mechanical ventilation.

Proteomic analysis showed that compared with normal lungs, the lungs of the autopsy subjects exhibited a significant decrease in 22 proteins and an increase in 23. Perhaps not surprisingly, a variety of inflammatory proteins, especially related to IFN-1, wound healing, and apoptosis, were increased, and there appeared to be two distinct clusters of profiles based on whether the patients died relatively early with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) still present in the lungs, or later in the illness when the virus was not present. The finding of an early "viral infection" phenotype and a late "post viral immune damage" phenotype is consistent with the findings of an earlier autopsy study by Nienhold and colleagues (2), and also consistent with clinical observations that some patients have ventilatory needs akin to viral pneumonitis, whereas others were more similar to patients with acute respiratory distress syndrome (ARDS) (3).

The extent to which the findings of Russell and colleagues (1) are truly specific to SARS-CoV-2 is more difficult to ascertain. The autopsy samples were not compared with postmortem samples from patients who died of other causes of respiratory infection, or indeed of other causes of ARDS. The IFN-1–related proteins have been shown to be upregulated in patients dying of influenza pneumonia (4). Many of the changes in the late phenotype have also been observed in some of the many studies of lung tissue in patients with ARDS (5). The lack of earlier phenotypic data from blood or lung tissue, understandable given that this is an autopsy study, also give us only a single point in time without providing understanding of when critical changes occurred and when the windows of opportunity for intervention might have existed. As the patients were also relatively old and overwhelmingly male, how well the findings translate to younger or female patients remains open to question. There are clearly significant sex differences in immune responses to SARS-CoV-2 (6), which perhaps is one explanation for the more limited impact of corticosteroid therapy on the outcome of women compared with men (7). The generalizability of the findings by Russell and colleagues across age and sex will need to be assessed by future work.

Regardless of the limitations, there are some key insights from Russell and colleagues (1) that may move us forward. As they point out, dysfunction of pulmonary macrophages appears to be more pronounced in COVID-19 than in other causes of fatal pneumonia. There is some evidence that feedback loops between T cells and macrophages in the lung may be critical to this dysfunction (8). Correlations between granulocyte-macrophage colony stimulating factor (GM-CSF) levels and worse outcome from COVID-19 have led to trials of anti–GM-CSF with very limited impact to date. Exploration of other pathways involved in monocyte and/or macrophage activation and function as suggested by Russell and colleagues (1) may be more productive.

Perhaps the key observation from Russell and colleagues for other investigators is their reconfirmation that there are different patterns of tissue response depending on when patients with COVID-19 are dying (and most likely what they are dying of). The vast majority of COVID-19 studies lump all patients in the same group, especially those looking at biological markers. It is very clear that patients with COVID-19 die as a result of a variety of different pathologies, some of which may be present simultaneously and some of which are not. An intervention designed to modify immune-mediated diffuse alveolar damage and ARDS is not going to affect patients who die of acute viral pneumonitis, pulmonary embolus, myocardial infarction, or stroke. Equally, antiviral strategies are not likely to be helpful if the patient has already cleared SARS-CoV-2 from the lung and is now suffering from immune-mediated lung damage or massive intrapulmonary thrombosis. Therefore, whether the patient is still clearing SARS-CoV-2 from the lung or not may be a critical determinant of whether immunomodulatory therapies will be harmful or helpful.

Moving forward, we need studies that carefully phenotype patients and identify key changes in viral load and immune response that can be used to target individual therapies. Autopsy studies are a great start to understand what might have gone wrong; however, improving patient outcomes will require knowledge of how, when, and by how much to intervene. Russell and colleagues (1) have opened a door that should be explored, but carefully and not by ignoring key issues, including age, sex, the state of viral replication, and the presence or absence of key disease manifestations that drive poor outcome. ■

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