

Reading COVID-19's signature: lung tissue injury

Anne Paxton

July 2020—Alain Charles Borczuk, MD, began his practice of pathology as a resident 28 years ago and has spent quite a bit of his career doing autopsies. But it is this year, during the pandemic, that he's finding some of the best applications of his autopsy work as he seeks to understand the lung injury patterns in SARS CoV-2, or COVID-19 patients.

"There has not been a period of time in which there's been a greater realization of the absolute critical importance of doing autopsy than right now," says Dr. Borczuk, professor of pathology at Weill Cornell Medical College and vice chair of anatomic pathology at Weill Cornell Medicine.

One reason: "We're not really getting tissue-based samples in the majority of COVID-19 patients during their clinical course, and autopsy gives us a way to learn about the disease that we haven't had before. Everyone has looked at these autopsies and said, 'In looking at these patterns, in talking about what we are seeing, it has resonated with the things we're finding clinically.'"



Dr. Alain Charles Borczuk: "The question I am interested in," he says, "is what is the unique injurious effect on the lung that is resulting in this quite accelerated severe disease with thrombosis."

When asked to discuss COVID-19 and lung tissue injury, Dr. Borczuk cautions that his viewpoint is narrow. From the autopsy suite, his observations relate to COVID patients who don't recover from their illness. "It's a bit of a skewed perspective," he admits. "We are seeing treatment failures, not treatment successes." And as he notes, the majority of hospital admissions for COVID lead to discharge, not death.

The percentage of COVID patients who are intubated is also a figure outside his knowledge. "I find those numbers to be complicated ones that, as pathologists, we don't get to learn. We have an idea of how many patients are in intensive care, we know total patients on ventilators, but we don't actually know how dynamic that is—how many people are coming off the ventilators or never getting on the ventilators to begin with."

"The death rate associated with COVID is a highly controversial number because of the different populations and how much testing is done. So it's difficult to tell, from the perspective of a pathologist, exactly what those numbers are."

Nevertheless, Dr. Borczuk's experience based on patient mortality from COVID offers useful insights into one of the most mystifying elements of COVID: Exactly what does the disease do to the patient's lungs? In his view, it's a question that can be fully answered only with an autopsy.

The decline in the number of autopsies performed in recent years, he says, is partly owing to the improvements in clinical diagnostic testing: imaging, serum testing, noninvasive testing, even biopsies, which are done more easily now than ever before.

"We're able to know a lot more about what is going on in a patient without doing an autopsy. As a result, there is a feeling among the people who consent for autopsy and the clinicians who know the patients and the patients' families that they know everything that happened already and there's no point to an autopsy. And I've heard that said."

Still, "autopsies often reveal severity of disease that was unexpected, and other things that were never detected, often to the surprise of the clinicians when they get the information. But that fact alone hasn't increased the number of autopsies."

With COVID-19, he says, "There is so much uncertainty around this disease. It's new and for the folks who are sick it's a very severe disease. Families are left with a situation where they have a lot of unanswered questions, and so do the physicians. And that combination has led to interest in doing autopsy."

"I can tell you what we find in patients who are acutely ill, who are given respiratory support in a variety of ways including ventilation, but who progress and who pass away." It's an older population and they tend to have comorbid illnesses, which vary quite a bit but include a history of hypertension, of diabetes, of hyperlipidemia, says Dr. Borczuk, who spoke with CAP TODAY on May 1.

Among those patients, "we are seeing a variety of lung injuries. There is often inflammation and even ulcerating lesions in the upper airway, trachea, and bronchus. The patients who have been on ventilators have more of the changes in the lung that we might expect with organization of the lung and recovery steps that are involved in lung healing, meaning the person was supported past that acute period into a more chronic or subacute period, so the lung has a chance to regenerate."

The phase of acute respiratory distress syndrome that he sees is organizing diffuse alveolar damage. "So we see ongoing injury alongside the healing." But he cannot be sure a particular injury might be from the ventilator. "It could be that they've been supported by a ventilator and now have time to heal and then have a new injury on top of that healing. Or it may well be an effect of viral infection. We just don't know."

The injury that is resonating with the clinicians who have taken care of the patient is a lesion of the large airways that is inflammatory, he says. "The clinicians describe a lot of mucus plugging. We haven't seen as much of that, but we certainly have seen a lot of large-airway epithelia injury with some ulceration and inflammation, so it would not surprise me if there is also a lot of mucus production. We just haven't seen a lot of it at autopsy. It may be because they are taking care of the mucus plugging clinically, so it is less dramatic at the time of autopsy."

Both small vessel thrombosis and large vessel thrombosis in the lungs and heart are evident at autopsy. "We've seen that in several cases, and that does resonate with the clinicians who are finding it difficult to control chronic clotting in the patient. There is definitely a blood clot component to the disease, and we are seeing a lot of it in the lungs."

The clotting in the larger vessels includes classical pulmonary emboli and pulmonary thrombosis, he says. "But at autopsy we've also seen some coronary thrombosis." Unlike other diseases, there is a quantity of the smaller clotting in the small vessels of the lung and also in the capillary bed of the lung present in COVID patients. "Although that type of clotting may happen in other acute illnesses, it is particularly prominent in a large subset of our patients."

A second dramatic feature of COVID patients in autopsy is that "the lung weights of these patients are

exceptionally high. That is part of ARDS in general, but it is very notable with COVID and, again, the novelty is the presence of these microthrombi and platelet thrombi in the microcirculation” Dr. Borczuk says.

From the autopsy perspective, “COVID is showing changes that we’ve seen individually in different diseases involving respiratory distress syndrome. But it’s the severity and the combination of all these different injuries—very heavy lungs, platelet microthrombi in the capillary bed, and large airway ulcerating inflammatory lesions— that make COVID unique.”

The existing literature on COVID-19 autopsy supports the same things he has seen, but mostly the thrombotic complications. The large airway lesions have been less noted; he is now planning to collect enough cases to present this aspect of COVID for publication in the coming weeks.

“The question I am interested in is what is the unique injurious effect on the lung that is resulting in this quite accelerated severe disease with thrombosis.” Modern molecular biology techniques, gene and protein expression, looking at protein phosphorylation and pathways of activation in the blood, will likely be able to shed light on this, he says.

Initial observations have been made about what may be causing injury of the vascular bed. “But we need to find out more. What about those epithelial cells—how are they being damaged such that the lungs are more prone to thrombosis? What is the pathway of that thrombosis? Can it be blocked? Can it be blocked through standard anticoagulation or is it going to require a more targeted approach to get us to the cause of the initial injury?”

Autopsy findings on these questions may not immediately change therapy for COVID patients, but they have started to guide thinking about what would be a reasonable therapeutic approach, he says.

Another line of inquiry Dr. Borczuk is pursuing relates to undetected COVID-19. “I’m looking at our autopsy cases going back a couple of months prior to our index case to see whether there are some sudden death cases that we attributed to some other cause or perhaps thought may have been COVID-related.”

“Good tests that work in autopsy material—that is, in situ hybridization and maybe some PCR testing on paraffin tissue—are still in development. When we have a robust assay in that way, and I think we’re getting very close to that, we’ll be able to start interrogating older cases and looking for definitive evidence of COVID infection.”

Dr. Borczuk finds that the autopsy service has worked well with the clinical laboratory in uncovering more details about patients’ COVID-related conditions. “We can do nasal swabs in the postmortem setting if we need to do a confirmatory test, and we have done that. Blood cultures, which we’ve done at autopsy, have been very informative because, again, it may be that patients are developing secondary infections in the hospital and the lung disease may not be due to COVID.

“But while we may have seen one or two patients who definitely have more classical bacterial pneumonias, the ability to have antemortem and postmortem culture has made it possible for us to definitively state which patients had a bacterial infection and which ones didn’t. And, of course, the development of tissue-based PCR tests will be a critical interlaboratory collaboration.”

The need to prepare for future pandemics is also part of what makes answering those questions important. “We need to get answers about the virus as it causes severe lung injury,” he says. “But we need to also start learning what might be the features of this virus in our samples as we move forward,” now that the pandemic lockdown conditions are being eased.

“As we start seeing patients and patient material again, we will need to recognize the complications of this virus in people who perhaps are not as severely ill as the people we have seen so far,” Dr. Borczuk says. In addition, physicians should begin to develop some understanding about whether there will be any long-term sequelae in patients who recover, “especially in the lung, but not exclusively the lung.”

“Then we will want to see if there are any features that may alert us to a new outbreak in the future. As

pathologists who look at tissue and pathologists who do clinical pathology, we will need to have a really good armamentarium of tests that can recognize this disease in its myriad forms and the different ways it causes tissue injuries. But we also need to have robust testing to make sure we are detecting the disease early if there is a future outbreak.”

Anne Paxton is a writer and attorney in Seattle.