Autopsies show many faces of COVID-19

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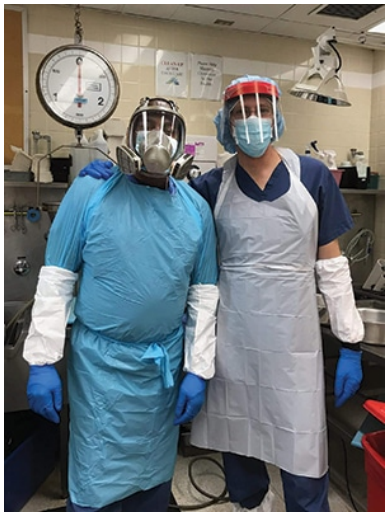
June 2020—"Sudden" and "global" are descriptors that seldom appear in tandem, especially in relation to disease epidemiology. But they both fit the COVID-19 pandemic, which has left the health care world reeling.

"COVID-19 has infected the entire planet pretty much all at once," says Alex K. Williamson, MD, chief of autopsy pathology and director of the regional autopsy service for Northwell Health, the largest health system in New York State. "Never before have I seen a single disease stop the world."

For autopsy services, it has created exceptional challenges, and, in watching the crisis balloon, Dr. Williamson realized that autopsy pathologists would have to cope with a serious information gap. "We were all facing the unknown with how to handle morgue operations and autopsies involving COVID. And we were trying to figure things out in isolation. There's no playbook for what we're going through."

He decided that an ad hoc autopsy pathologist listserv to facilitate group discussion would start to address the problem, so he brought together an international consortium of autopsy pathologists. Its goal: sharing the information that its members have gleaned about COVID-19 from the autopsies they perform. "I thought it would be a good idea to bring everybody together so we could figure out COVID-19 with aggregate, communal knowledge."

The Occupational Safety and Health Administration surprised and baffled many autopsy pathologists by issuing in March a guidance advising against performing autopsies without strong indications to do so, says Dr. Williamson, who spoke with CAP TODAY on April 29. In response, institutions limited the procedures or halted them indefinitely.



Dr. Williamson (right), with Devon Betts, autopsy assistant/morgue attendant. "We can't and shouldn't autopsy every COVID-19 death," Dr. Williamson says, calling it an impossibility and dangerous. "But what we are doing is sampling a subset of patients across the spectrum."

"A really important aspect of this group's coming together," Dr. Williamson says, "was making sense of the ambiguous OSHA guidelines." When the pandemic began, "Everyone was scared. We just didn't know what this

thing is. And as we started talking to each other through forums like the listserv, more and more of us realized that the OSHA guidance was ill-informed."

The guidance has since been retracted. "I was one of the earliest, most outspoken critics of that policy on the listserv," Dr. Williamson says. "And others, through having this forum to share ideas and discuss, realized that if you have the right resources, such as a negative-pressure autopsy suite and appropriate personal protective equipment, and the training and skills to do infectious autopsies, we need to be doing them."

The number of participants on the listserv, which launched in late March, rose to 180 by early May. Dr. Williamson's surveys of participants show that the percentage of people on the listserv responding to the surveys who had done an autopsy on a COVID-19 decedent grew from around 10 percent to nearly 50 percent between March and May.

From a postmortem care standpoint, there are two main aspects to the virus, Dr. Williamson says. "There's the morgue management of an increased death count, and there's the importance of performing autopsy to understand this disease while ensuring the autopsy is done safely."

"Many people who have the disease have diffuse alveolar damage, but in other people COVID-19 forms blood clots. We're also learning on the clinical side, and confirming it by autopsy, that this disease is more aggressive in those with underlying or preexisting conditions," primarily high blood pressure, diabetes mellitus, and obesity.

"In the clinical setting and in autopsy," he says, "I have not yet seen this virus kill a truly healthy individual." Most people who get COVID-19 aren't in the hospital, Dr. Williamson notes. "They definitely aren't on a ventilator and they aren't dying. But we in autopsy pathology and all medical personnel are trying to figure out how to treat those who have a bad course. What is it about that population of people who come into the hospital, go on a ventilator, and then eventually die? What can we learn about that disease process, through autopsy, that can help those who have yet to contract this disease?"

One of the many mysteries yet to be unraveled involves the apparent mismatch of ventilation and blood oxygenation, Dr. Williamson says. So far, he has performed autopsies only on those who had no ventilator support or who had been on a ventilator only for days. "But it's important that we sample patients across the spectrum of duration on a ventilator as well, so that we can learn why there is a 'clinical disconnect' between mechanical ventilation and oxygen levels in the blood," he says. "As is the case with any medical intervention, it's also important to assess if an intervention such as prolonged ventilator support is causing or contributing to tissue injury."

A topic that comes up often on the listserv is how many autopsies should be performed. "We can't and shouldn't autopsy every COVID-19 death," Dr. Williamson says. "That's an impossibility and it's dangerous. But what we are doing is sampling a subset of patients across the spectrum. It's important to examine different ages, different underlying conditions, and different lengths of hospitalization and ventilation." Through that process, "We hope we'll be able to obtain a better understanding of what this disease is, how it affects us, and what we can do to better manage it."

As one example of how the listserv has helped change approaches to maximize the autopsy's usefulness, Dr. Williamson says, "We know that people with COVID-19 have a higher incidence of blood clots, so some who have the training are doing complete exams of the deep leg veins at autopsy to make sure there are no hidden blood clots that we wouldn't see in a normal autopsy approach. That's an example of how we are modifying our autopsy technique to learn more about the disease. It's kind of a feedback loop with the active practitioners, the autopsy pathologists, doing the work, and our experience informing the work we all do moving forward."

At autopsy, pathologists are observing clots filling a vessel that are visible to the naked eye as well as those that require a microscope to be seen. "We are seeing microscopic blood clots in some organs," he says. But they are not as prevalent as initially feared, in his experience. "Early on, there was a report that COVID-19 patients had all these microscopic thrombi forming in the lungs and the kidneys. I haven't seen that in a majority of the cases I've

examined. We're still exploring that as a community, but the microscopic blood clots don't seem to be a salient feature of the disease pathology."

The "cytokine storm," an escalated immune response, is a known feature of some COVID-19 infections. But as a humoral response, circulating in the blood, it cannot be seen at autopsy. "What we can see are the effects of that cytokine storm if they have anatomic manifestations. I may see inflammation of the heart or lung under the microscope, for example. If the cytokine storm sets up a blood clotting state, I will see those blood clots. So autopsy can corroborate the idea of the cytokine storm but it can't visualize the humoral activity of that cytokine storm," he explains.

Using electron microscopes that allow magnification powerful enough to view viruses, autopsy pathologists have been viewing sample tissues removed at autopsy, a survey of the listserv confirms. Dr. Williamson has seen probable virus in the lung of at least one of the decedents he examined, and studies have reported finding virus in various other tissues and organs throughout the body. "It's conceivable that this virus would spread throughout the body during the viremic stage of infection and would deposit in the various tissues," he says. "More definitive results from a larger number of autopsies would confirm this. But we are leaning toward believing that this virus disseminates throughout the body and implants in the colon, in the kidney, in the lung." More clarification of that is needed, he says.

A survey of listserv members found that most people are following the recommended autopsy guidelines of the Centers for Disease Control and Prevention, Dr. Williamson reports—although since testing resources are limited, if a person has a positive antemortem test, such as with a nasopharyngeal swab, a postmortem swab would not add anything and would not necessarily be taken at autopsy.

However, he has found that some pathologists are obtaining postmortem swabs from the lung and collecting tissue to freeze for later analysis. In addition, if someone has suspected COVID-19 and dies but there was no diagnosis in life, "I do think the postmortem nasopharyngeal swab serves an important purpose for epidemiology and for that autopsy."

Most basically, it's important to emphasize, he says, that autopsies are confirming that almost everybody dying with COVID-19—"and I believe probably everybody"—has a preexisting condition that renders them vulnerable to the virus' lethality.

The number of autopsies that NYU Winthrop Hospital conducts each year hovers around 100, says chair of pathology and laboratory medicine and autopsy director Amy Rapkiewicz, MD, who spoke with CAP TODAY on May 5. But when her hospital admitted its first COVID patient March 3, that changed. Based on the OSHA recommendation, "The administration was not in favor of us doing autopsies right from the get-go."

She views a COVID autopsy as no different from an influenza autopsy. "We're board-certified forensic pathologists and our autopsy suites are negative-pressure. We use PPE. But we created a specific COVID protocol and some of it came from talking to Alex and getting great information from other people on the listserv."

After her department re-petitioned the administration, "They allowed us to do two COVID autopsies a week." This agreement came because of the inquiries she and her colleagues received (and kept track of) from the critical care physicians. "We have a good relationship with them, and they were emailing us saying, 'We ventilate the patients but they're still hypoxemic. What are you seeing at autopsy?'"

"So we tried to limit autopsies to patients whose deaths were unexpected or things of that nature. We tried not to do autopsies on patients who had very serious other comorbidities or really advanced age. We have a whole host of patients who were dying in their 90s with dementia and coronary artery disease, diabetes, and hypertension. And they might not be the best candidates because you are going to have so many other mitigating circumstances to sift through in performing the autopsy."

Though few in number, the autopsies they were doing were directly helping with understanding the

pathophysiology of COVID. “After we had about five cases of patients who had very little treatment and died very quickly, we started noticing microvascular thrombosis in these patients. And that was corroborated by the clinicians who would say, ‘We put a central line in and it clotted.’”

She got in touch with one of the translational scientists at NYU, and based on autopsy and clinical information, “they came up with a randomized, controlled trial where they had different arms related to anticoagulation. So even though we may not know the exact reason for that hypercoagulable state, we tried to turn it around quickly to figure out who is going to need that anticoagulation. That was a really important thing the autopsy did for us locally. It confirms there was not only macrovascular thrombosis but also microvascular thrombosis.”

Based on her talks with the critical care physicians, “It seems to me there has to be a relationship between some of the hypoxemia and the microvascular thrombi that are forming. Again, I don’t have a lot of data on this, but the quantity of microvascular thrombi that we’re seeing—and systemically, not just in the lung—is increased in the patients who do very poorly, for the most part.”

Dr. Rapkiewicz, above, says one of the surprising things she has seen is circulating megakaryocytes, which are typically seen outside the bone marrow, in lung or spleen. “But I’m seeing them in many organs, including the heart,” she says. “I have done many, many autopsies, and I have never seen a megakaryocyte in the heart, and there they are.”

“How that’s working, how it may be changing the mechanisms of the red blood cells—it seems like there might be a double layer to that. Potentially there is something about how COVID interreacts with the red blood cells that is either worsening or creating a difficult situation for oxygenation, and patients go on to develop bad respiratory disease.”

Anomalies she cannot yet explain may open up useful lines of inquiry, she says. “One of the surprising things I’ve been seeing is these circulating megakaryocytes. Typically you see them outside of the bone marrow. We may see

them in the lungs or the spleen. But I'm seeing them in many organs, including the heart. I have done many, many autopsies, and I have never seen a megakaryocyte in the heart, and there they are. I don't have an explanation for it at this point." But she called the platelet expert at NYU Langone Health as soon as she saw it.

"He was then able to open his lab, which had been shut because of COVID restrictions, and now he's working on the importance of the platelet in COVID," Dr. Rapkiewicz says. "He's asking: 'Is there a clinical test that we should be looking at? Is the immature platelet fraction, which started back up in the clinical labs, going to be helpful in stratifying risk?'" Along with the group at Langone, she is working on a more formal study of the questions relating to circulating megakaryocytes.

The exchange of information that Dr. Williamson set up has been immensely helpful, she says. "The consortium got everybody online quickly and exchanging useful information and best practices and even things that went badly. And learning from that, it created solidarity around this."

The National Board of Medical Examiners has an active listserv that runs in parallel with Dr. Williamson's, she notes. "But autopsy pathology for natural disease is different from forensics, obviously. Although many people do both, sometimes the pathologists don't cross paths. Sometimes it's a bit of a black hole and you can be isolated from the information that comes out more generally to forensic pathologists through traditional state regulatory routes." There isn't a comparable group in autopsy pathology for natural disease, Dr. Rapkiewicz adds. "We should definitely lobby for one, especially after this pandemic."

The increasing number of patients who are dying at home with COVID is further complicating the ability to gain understanding of COVID through autopsy, she says. "If they are dying at home, they are natural deaths, so the medical examiners are under no obligation to do these cases. And there's the workforce and supply issues too. So we have a whole cohort of patients who are not making it to the hospital to see an autopsy pathologist, and we don't know what the natural history of their disease is as well. So there are going to be a lot of gaps to fill."

"We don't know as much as we should about COVID," Dr. Rapkiewicz continues. "Because most of the elective surgeries were stopped, we aren't getting the 'normal' tissues that you'd be getting from these patients. So one of the big reasons I also wanted to do the autopsies was to secure tissue for researchers to do further studies on."

On a more logistical front, she has found that autopsy pathologists as well as forensic pathologists have useful knowledge about mass fatality planning. "From our friends at different medical examiners' offices, we were able to garner how they are planning, even how to build shelving inside of a body-collection-point refrigerated truck. That was a plan by my carpenter and engineer that we put on the listserv and it was helpful for people to see that."

"We have to lean on every type of way to address the disease process, and I think that autopsy just has to sit at the table with the more—let's call them—'sophisticated' evaluations. Because autopsy has stood the test of time and it has never disappointed in terms of discovering information around the disease process."

With good autopsy practice, Dr. Rapkiewicz says, "we could potentially help with the next round of COVID. If we don't get the tissue now and start to tease out the pathophysiology and natural history of the disease, we're going to be left with the same story next time."

A March 27 virtual meeting of the CAP Autopsy Committee, of which Dr. Williamson is a member, was devoted to a discussion of what individuals were doing and what was happening. "Alex led that discussion. He had the most cases at that time and was one of the few doing cases at all. A lot of us fell into the category of not doing autopsies at that time," says Billie Shawn Fyfe-Kirschner, MD, chair of the committee, who spoke with CAP TODAY on May 6. The committee focused on making sure pathologists knew the CDC-recommended autopsy suite environmental engineering guidelines.

At Rutgers Robert Wood Johnson Medical School in New Jersey, where Dr. Fyfe-Kirschner is director of autopsy pathology, the COVID-19 outbreak limited autopsy service toward the end of March to only those critically indicated clinician-directed examinations on COVID-negative patients. "We limited service for now, except for

critically indicated clinician autopsies, because of limited resources for obtaining PPE and because the work related to decedent management has increased exponentially in New Jersey. It therefore became much more difficult to maintain routine autopsy service."

To support some aspects of postmortem care of COVID-19 patients, Dr. Fyfe-Kirschner has often been able to arrange at least a nasal swab for a COVID test of decedents who haven't had one performed prior to death. "I can then respond to families and discuss the COVID status of their family member and offer at least some insight into probable cause of death after chart review."

Other major teaching institutions in the state had stopped doing autopsies or were doing only non-COVID cases. "The untold story of being inundated with COVID cases here in New Jersey is that it has sometimes impacted the ability of families to get any autopsy performed. That's been an unfortunate downside."

Dr. Fyfe-Kirschner has found the listserv useful. "People are very eager to participate and share knowledge with everyone else so that we can get data together that make more sense than isolated case reports." Dr. Williamson and Jody E. Hooper, MD, director of the autopsy service at Johns Hopkins Hospital and associate professor of pathology, are collecting data from multiple centers and will report their findings in a forthcoming article, she says. "That is going to carry a lot more weight than the single-center reports that have been coming out."

The autopsy is critical in explaining the blood clot pattern associated with COVID-19, Dr. Fyfe-Kirschner says. "The incidence of small-vessel thrombi is probably one of the most important things that autopsy can help us decipher, because you can have organs affected subclinically. Thrombi can mimic other things, so without getting autopsy findings, it's hard to determine the extent of thrombotic disease, the organs most affected, the sequelae."

The Autopsy Committee had previously developed a standardized template for reporting gross autopsy findings that may help standardize reporting, Dr. Fyfe-Kirschner says, and it may be particularly helpful for multi-institutional studies in COVID cases. "I am working with the committee to come out with a consensus guideline for how to do a COVID autopsy to gain the most useful knowledge—such as documenting comorbidities, standardizing the clinical data we receive, standardizing how we report and how we collect tissues. With that guideline, based on our experiences as autopsy pathologists," she says, "we can help people perform the most comprehensive, information-generating autopsies possible."

"And sharing of data in the appropriate way is basically helping support the health of the world."

Anne Paxton is a writer and attorney in Seattle.