CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 23-2020: A 76-Year-Old Woman Who Died from Covid-19

James R. Stone, M.D., Ph.D., Kathy M. Tran, M.D., John Conklin, M.D., and Mari Mino-Kenudson, M.D.

PRESENTATION OF CASE

Dr. Kathy M. Tran: A 76-year-old woman was admitted to this hospital because of confusion and hypoxemia during the pandemic of coronavirus disease 2019 (Covid-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

The patient had been well until 6 days before this admission, when nasal congestion developed, with no fever or cough. One day before this admission, she called her primary care physician, who recommended fluticasone nasal spray and nasal rinses and asked her to follow up by telephone in 2 days. However, the next day, the patient's son visited the patient and found her to be confused and incontinent of urine and stool. Emergency medical services were called, and when they arrived at the patient's home, the oxygen saturation was 87% while she was breathing ambient air. The patient was transported by ambulance to this hospital.

In the emergency department, the patient reported chills but no fever, cough, shortness of breath, sore throat, chest pain, or dysuria. Additional information was obtained from the patient's daughter and son by telephone. There was a history of asthma, diabetes, hypertension, hyperlipidemia, osteoporosis, and psoriasis. Medications included atorvastatin, aspirin, hydrochlorothiazide, losartan, insulin, metformin, glipizide, citalopram, acetaminophen, cholecalciferol, folate, fluticasone nasal spray, and topical betamethasone and fluocinonide. Lisinopril had caused a cough; penicillin and sulfa drugs had caused hives. The patient was widowed and lived in an assisted-living facility where multiple residents had recently received a diagnosis of Covid-19. She did not smoke tobacco or use electronic cigarettes, alcohol, or illicit drugs. Her family history included diabetes and cancer in both her father and her brother; her daughter and son were well.

The temperature was 38.8°C, the heart rate 94 beats per minute, the blood pressure 176/55 mm Hg, the respiratory rate 24 breaths per minute, and the oxygen saturation 94% while the patient was receiving supplemental oxygen through a nasal cannula at a rate of 2 liters per minute. On examination, the patient ap-

From the Departments of Pathology (J.R.S., M.M.-K.), Medicine (K.M.T.), and Radiology (J.C.), Massachusetts General Hospital, and the Departments of Pathology (J.R.S., M.M.-K.), Medicine (K.M.T.), and Radiology (J.C.), Harvard Medical School — both in Boston.

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Table 1. Laboratory Data.*

Variable	Reference Range†	On Admission
Hemoglobin (g/dl)	12.0–16.0	13.9
Hematocrit (%)	36.0–46.0	43.2
White-cell count (per μl)	4500–11,000	7690
Differential count (per μl)		
Neutrophils	1800–7700	6150
Lymphocytes	1000–4800	1270
Monocytes	200–1200	200
Basophils	0–300	70
Platelet count (per μl)	150,000–400,000	149,000
Sodium (mmol/liter)	135–145	136
Potassium (mmol/liter)	3.4–5.0	4.2
Chloride (mmol/liter)	98–108	94
Carbon dioxide (mmol/liter)	23–32	22
Anion gap (mmol/liter)	3–17	20
Urea nitrogen (mg/dl)	8–25	13
Creatinine (mg/dl)	0.60–1.50	0.65
Glucose (mg/dl)	70–110	366
Alanine aminotransferase (U/liter)	7–33	27
Aspartate aminotransferase (U/liter)	9–32	35
Alkaline phosphatase (U/liter)	30–100	54
Creatine kinase (U/liter)	40–150	363
Lactate dehydrogenase (U/liter)	110–210	289
Ferritin (μg/liter)	10–200	675
D-dimer (ng/ml)	<500	3592

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

peared ill and was lethargic. She was alert and oriented but unable to recall events from earlier in the day. The lungs were clear on auscultation. The white-cell count was 7690 per microliter (reference range, 4500 to 11,000); the blood D-dimer level was 3592 ng per milliliter (reference range, <500). Urinalysis results were normal. Nucleic acid testing of a nasopharyngeal swab was negative for influenza A and B viruses and respiratory syncytial virus but was positive for SARS-CoV-2. Other test results are shown in Table 1.

Dr. John Conklin: On radiography of the chest (Fig. 1A), patchy airspace opacities were present in the left upper lobe and surrounding the hilum. On computed tomographic (CT) pulmonary angiography of the chest (Fig. 1B, 1C, and 1D), performed after the administration of intravenous contrast material, multifocal consolidative and ground-glass opacities, including some with rounded morphologic features, were present in both lungs. These findings have been commonly reported with Covid-19 pneumonia, although other processes, such as influenza pneumonia and organizing pneumonia, may have a similar appearance on imaging.[1] There was no evidence of pulmonary embolism.

Dr. Tran: Acetaminophen and empirical ceftriaxone, azithromycin, and hydroxychloroquine were administered. Because the patient had acute respiratory failure and Covid-19, goals of care were discussed with her adult children by telephone; the patient was unable to participate meaningfully in the discussion because of confusion. She had recently expressed to her primary care doctor that she would "not want to be on a breathing machine if something were irreversible." A status of "do not resuscitate and do not intubate" was assigned.

During the next day, intermittent episodes of fever occurred, with temperatures as high as 40.3°C, and delirium and hypoxemia worsened. On the third hospital day, new atrial fibrillation with a rapid ventricular response developed, and metoprolol and furosemide were administered.

On the fourth hospital day, the respiratory rate was 36 breaths per minute and the oxygen saturation was 90% while the patient was receiving supplemental oxygen through a nonrebreather mask at a rate of 15 liters per minute. She appeared to be in distress, with increased work of breathing. Goals of care were again discussed with the patient's family, and a status of "comfort measures only" was assigned. The patient died 36 hours later. After discussion with the family, an autopsy was performed.

CLINICAL DIAGNOSIS

Acute respiratory distress syndrome due to coronavirus disease 2019 (Covid-19).

CONVERSATION ABOUT AUTOPSY

Dr. Tran: I was involved in the care of this patient and discussed autopsy with her family.

In the 1970s, autopsy was performed after

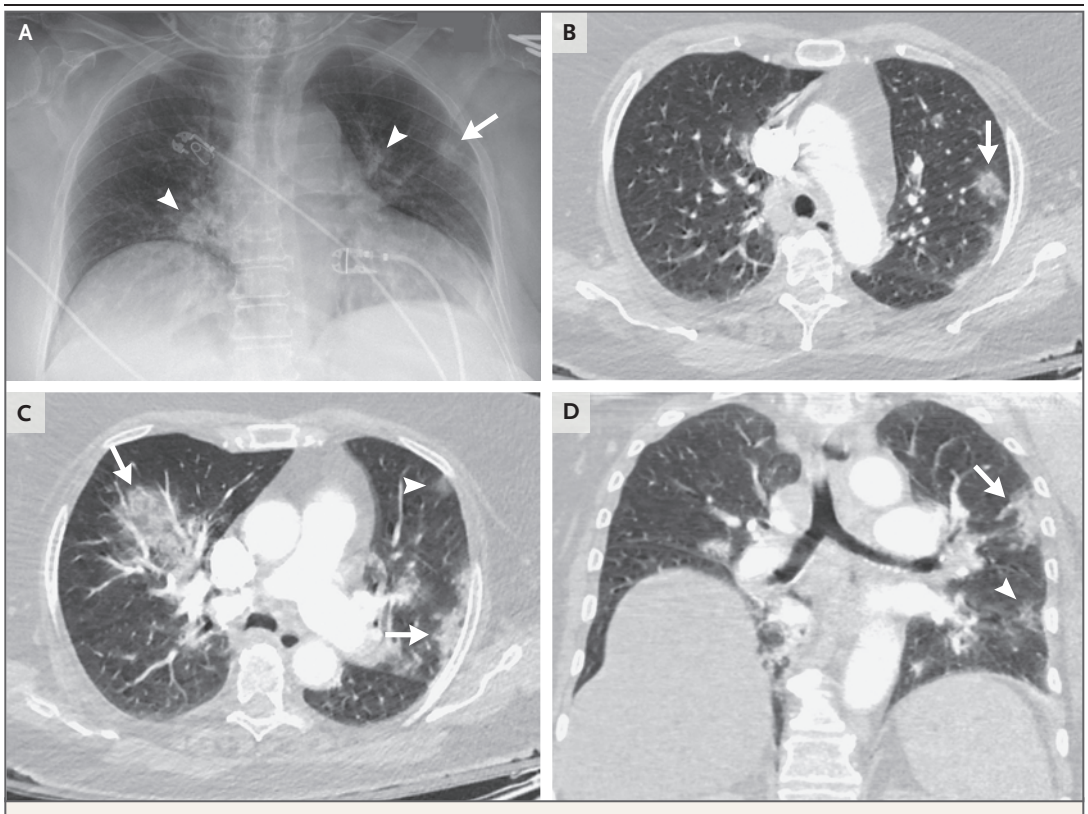

Figure 1. Chest Imaging Studies Obtained on Admission.

A radiograph (Panel A) shows patchy opacities with rounded contours in the peripheral left upper lobe (arrow) and perihilar patchy opacities (arrowheads), along with evidence of mild cardiomegaly. Axial (Panels B and C) and coronal (Panel D) CT pulmonary angiographic images show multifocal consolidative opacities (arrows) and ground-glass opacities (arrowheads), including some with rounded morphologic features, in both lungs. The distribution of these findings is predominantly peripheral and peribronchial.

approximately 1 in 5 deaths, but now, it is performed after fewer than 1 in 10.[2] Among the many factors contributing to this trend is the reluctance of clinicians to discuss autopsy with families and patients.[3-5] Some conversations about autopsy happen in a cursory way out of obligation or do not happen at all. Clinicians may think that they do not have a sufficient rapport with the family to discuss this sensitive topic, or they may show a "hidden paternalism" by avoiding the conversation in order to protect the family from further emotional distress during a time of grief.[4] These sentiments have been particularly pertinent during the Covid-19 pandemic, when relationships and conversations with families have often occurred by telephone or online. Furthermore, clinicians may feel uncomfortable discussing autopsy because of inadequate training or experience. More than 25% of medical students never witness an autopsy,[3] so when these students become physicians, they do not feel equipped to discuss autopsy or answer logistical questions about it.[6]

Usually, the clinician will approach the family about autopsy. However, in this case, during discussions that occurred before the patient's death, the daughter expressed sadness that her mother had become a casualty of the Covid-19 pandemic and initiated the conversation about autopsy.

Like other difficult conversations in medicine — such as those in which bad news is delivered or sexual history is obtained — conversations about autopsy must be approached in a manner that is learned and practiced. Otherwise, the more infrequently they occur, the more challenging they become. During a conversation about autopsy, the clinician should be sensitive to the family's emotional state, as well as to cultural and religious issues, without making any as-

sumptions about the family or patient.[4,6] The conversation with the family can occur either before or after the patient's death; sometimes, it can be appropriate to involve the patient in the conversation. The setting should be quiet, and there should be ample time for discussion, questions, and answers. During the Covid-19 pandemic, conversations about autopsy commonly occur by telephone or video call to limit person-to-person contact and decrease the likelihood of viral spread. However, in this case, an exception to hospital visitor restrictions was made because of the patient's imminent death, and I was able to discuss autopsy with the family in person and in the presence of the patient's nurse.

In discussions about autopsy, the words "consent," "permission," and "request" have traditionally been used, but this language may imply that the benefit of autopsy is for clinicians and institutions, rather than patients and families. It may be more appropriate to use the word "offer" to indicate that the family is being informed of their right to an autopsy. In fact, families are occasionally surprised when an autopsy is offered[5]; some families, as well as some clinicians, do not recognize that there are more indications for autopsy than determining the cause of death. For example, many families seek autopsy in order to absolve feelings of guilt about not recognizing symptoms or to find reassurance about end-of-life decisions that were made for their loved one.[3,4] In this case, during the conversation about autopsy, the patient's daughter shared her family's reason for proceeding with autopsy, which was a desire to further medical research and education. She stated that her mother would want her body to be "one last gift to science" so that more could be learned about Covid-19 during the pandemic.

In conversations about autopsy, the procedure should be described to the family. Autopsy may be described as an operation in which the body is opened and the internal organs are examined by a medical doctor with specialty training. The clinician may feel uncomfortable sharing this level of detail, with concerns that the family will think autopsy causes a disturbance to the body that results in disfiguration and mutilation. However, in interviews conducted with families that focused on their experiences with autopsy, the vast majority of families expressed that they were dissatisfied with the explanation of the procedure and wished that more description had been provided.[5] Although the family may become concerned about the appearance of the body after autopsy, they deserve to know how their loved one would be treated. Clinicians should reassure the family that in an autopsy, as in an operation, bodies are handled with utmost respect and every attempt is made to minimize visual signs of the procedure.

To provide clarity for the family and direction for pathologists, specific decisions should be made during conversations about autopsy. It is important to determine whether a complete or limited examination will be performed, as well as to establish instructions for organ retention for examination and to decide the fate of retained organs. Families frequently appreciate guidance from clinicians in making these decisions, but family preference should be elicited and prioritized.

In this case, the patient's daughter asked about postautopsy care, which is a common concern for families. She was told that a local funeral home of her choice would transport her mother's body from the hospital after completion of the autopsy and that the timing of burial or cremation would not be delayed because of the procedure.

After the results of the autopsy are final, an appointment is typically made with the family to share and discuss the relevant findings. This discussion would be organized by either the clinician who had initially discussed autopsy with the family or another clinician who had been involved in the patient's care, such as the primary care physician. Families are typically understanding of the fact that it can take an extended period of time to receive autopsy results as long as they know that communication will occur in the future.[5]

PATHOLOGICAL DISCUSSION OF AUTOPSY FINDINGS

GROSS PATHOLOGICAL EXAMINATION

Dr. James R. Stone: In this case, owing to the implementation of specific infection-control measures to mitigate the transmission of SARS-CoV-2 during the autopsy, only the heart and lungs were examined grossly. The lungs showed consolidation. The heart showed enlargement and

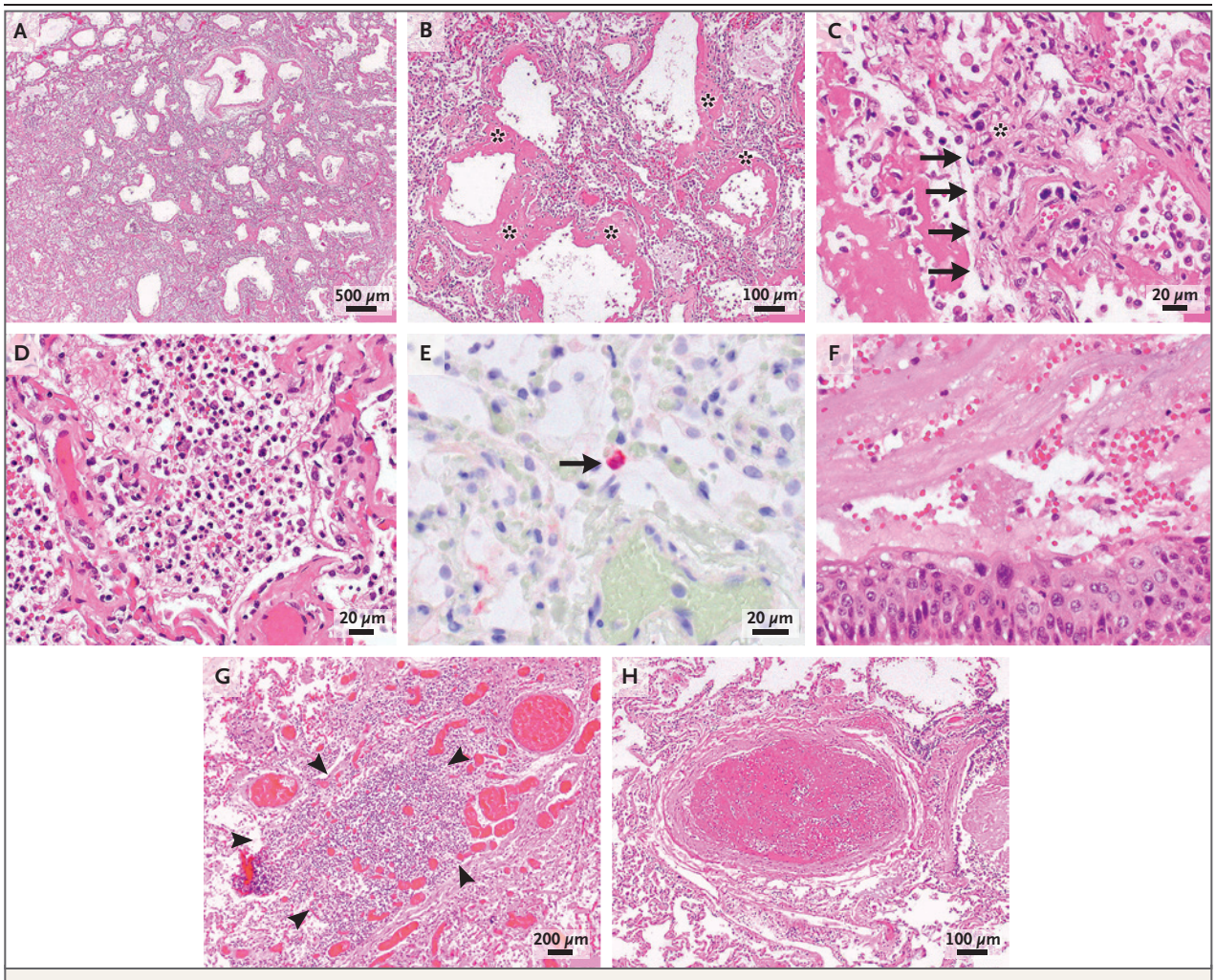

Figure 2. Lung Autopsy Specimens.

On hematoxylin and eosin staining, both lungs show architecturally preserved alveolar parenchyma (Panel A) with thick hyaline membranes (Panel B, asterisks) associated with pneumocyte denudation (Panel C, arrows). In some areas, alveolar walls show increased cellularity with some spindled fibroblast-like cells (Panel C, asterisk). These findings are consistent with an exudative to early proliferative phase of diffuse alveolar damage. There are also rare foci with neutrophilic and histiocytic infiltrates in alveolar spaces (Panel D), features suggestive of a focal pneumonic process. Immunohistochemical staining for SARS nucleocapsid protein highlights scattered pneumocytes (Panel E, arrow) and alveolar macrophages, findings supportive of a diagnosis of SARS-CoV-2 infection in the lungs. Thick mucin and epithelial denudation are seen in the majority of bronchi, and squamous metaplasia with reactive changes is focally replacing the denuded lining (Panel F). Only a few scattered perivascular chronic inflammatory aggregates (Panel G, arrowheads) and rare fibrin thrombi in small pulmonary arteries (Panel H) are present in this case.

left ventricular hypertrophy and dilatation, findings consistent with the patient's history of hypertension. There was mild atherosclerosis in the coronary arteries.

PATHOLOGICAL EXAMINATION OF THE LUNGS

Dr. Mari Mino-Kenudson: Microscopic examination of the lungs showed a broad area of architecturally preserved alveolar parenchyma with thick hyaline membranes associated with focal epithelial denudation and capillary congestion (Fig. 2A, 2B, and 2C). In some areas, alveolar walls showed increased cellularity with some spindled fibroblast-like cells (Fig. 2C). These findings are consistent with an exudative to early proliferative phase of diffuse alveolar damage. In addi-

tion, there were rare foci with neutrophilic infiltrate along with histiocytes in alveolar spaces, features suggestive of a focal pneumonic process (Fig. 2D). There were no definitive viral cytopathic changes in the examined sections; however, rare multinucleated giant cells were identified, and immunohistochemical staining for SARS nucleocapsid protein (shared by SARS-CoV-1 and SARS-CoV-2) highlighted scattered pneumocytes and alveolar macrophages, findings supportive of a diagnosis of SARS-CoV-2 infection in the lungs (Fig. 2E).

In the airways, thick mucin and epithelial denudation were seen in the majority of bronchi, and squamous metaplasia with reactive changes focally replaced the residual epithelial lining (Fig. 2F). These features, along with the aforementioned focal pneumonic process, are consistent with superimposed bronchopneumonia. A few scattered perivascular chronic inflammatory aggregates were present, but pathologically significant inflammation was not present and fibrin thrombi were rare in this case (Fig. 2G and 2H).

Most pathological features seen in this case are in accordance with those described in recent Covid-19 autopsy reports.[7,8] In most cases, autopsy of lungs from patients with Covid-19 has shown features consistent with an exudative phase of diffuse alveolar damage with rare viral cytopathic changes, often with evidence of superimposed bronchopneumonia in a focal or diffuse distribution. Features of a proliferative phase of diffuse alveolar damage have also been described. Some cases have shown evidence of severe tracheitis or tracheobronchitis with mucus production, but lung parenchymal inflammation is relatively limited, as would be expected in an exudative phase of diffuse alveolar damage. In addition, the majority of Covid-19 autopsy reports describe capillary congestion and multifocal microthrombotic disease in capillaries and small vessels.[7,8] Although microthrombotic disease is usually seen in the context of diffuse alveolar damage, it has been reported as the main cause of lung injury in some cases of Covid-19.[9]

PATHOLOGICAL EXAMINATION OF THE HEART

Dr. Stone: In the myocardium, there was relatively diffuse infiltration by CD68+ macrophages (Fig. 3A), which was not associated with myocyte injury. Such infiltration of the myocardium by macrophages is not entirely specific but has been reported in patients with SARS-CoV-1 infection and has been associated with the presence of virus in the myocardium.[10] In this case, there was also focal infiltration of the myocardium by CD3+ T lymphocytes (Fig. 3B), which was not associated with myocyte injury and thus did not meet full criteria for myocarditis.[11] This degree of myocardial lymphocytic infiltrate was not described in a few recent case reports with autopsy and endomyocardial biopsy results from patients with Covid-19,[12-17] but many of those cases involved only limited sampling of the heart. Of note, SARS-CoV-1 infection is not associated with increased lymphocytes in the myocardium, so SARS-CoV-2 may have a greater potential to cause myocarditis than SARS-CoV-1.

ROLE OF AUTOPSY

Dr. Stone: Autopsies can be very important in establishing the cause of death. Even in an era with routine use of high-resolution imaging, published studies have shown that approximately 50% of autopsies reveal findings that were not suspected before death and 20% of autopsies lead to the diagnosis of a primary cause of death that was not established clinically.[18,19] In the absence of an autopsy, the likelihood that a death certificate will be inaccurate is at least one in three.

In addition to establishing the cause of death, autopsies are of tremendous value in furthering our understanding of diseases.[20] They allow us to understand the systematic nature of a disease, given that, for some organ systems, involvement by the disease process may be subclinical and otherwise not readily discernible. Also, autopsies allow us to understand disease processes that suddenly claim the lives of people who do not make it to the hospital in time for a full clinical evaluation. In effect, autopsies play an extremely important role during a pandemic. Just over 100 years ago, during the 1918 influenza pandemic, autopsies facilitated our understanding that the majority of deaths that occurred during that time were due to bacterial pneumonia.[21] Likewise, autopsy studies have

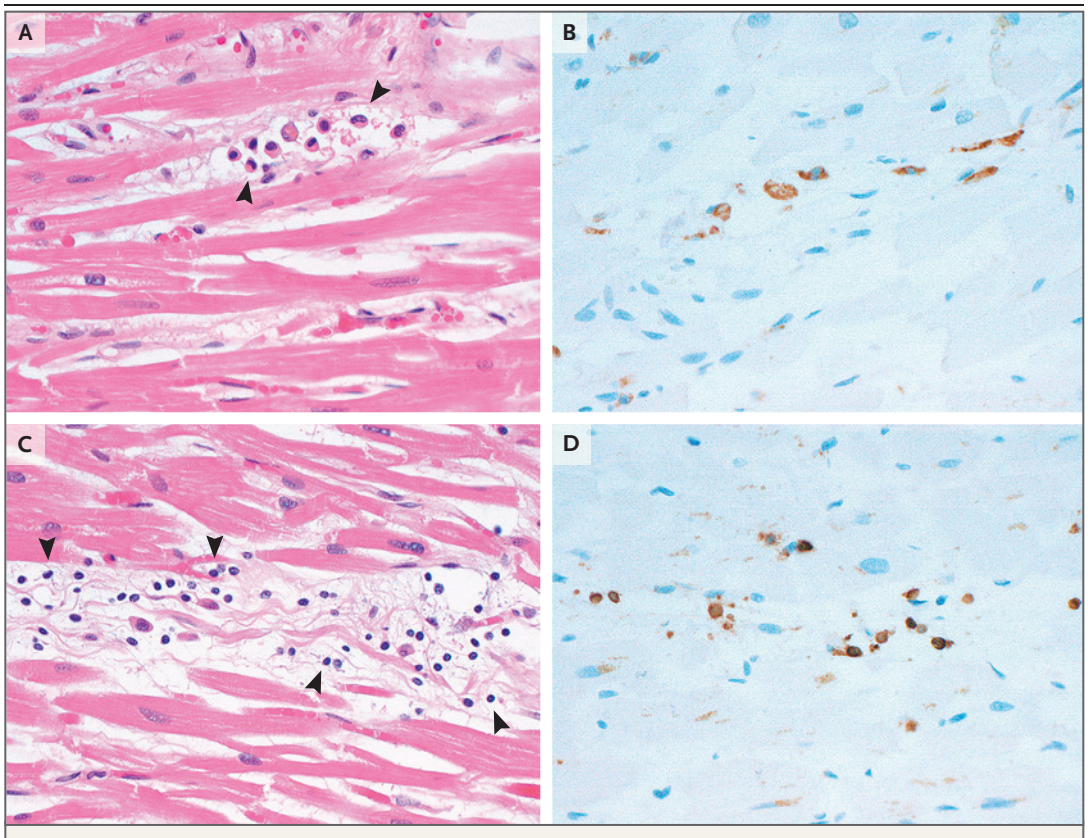

Figure 3. Heart Autopsy Specimens.

On hematoxylin and eosin staining, there is increased infiltration of the myocardium by macrophages (Panel A, arrowheads); on immunohistochemical staining, the macrophages express the marker CD68 (Panel B, in brown). There is also focal infiltration of the myocardium by lymphocytes (Panel C, arrowheads), which express the marker CD3 (Panel D, in brown). These findings are not associated with myocyte injury.

highlighted the role of tuberculosis in the death of patients with human immunodeficiency virus type 1 infection.[22]

During the Covid-19 pandemic, autopsies are critical to our understanding of the full spectrum of pulmonary changes that can occur in this disease, the mechanisms of healing and long-term pathological consequences of the disease, and the extent and nature of the involvement of different organs by the virus. For example, in this case, although diffuse alveolar damage was the predominant pathological finding in the lungs, there were also focal features of a superimposed pneumonic process. In addition, although the patient did not meet full pathological criteria for the diagnosis of myocarditis, she had inflammation in the heart, and elevated serum troponin levels are often seen in patients with Covid-19.[23] Finally, during the Covid-19 pandemic, autopsies are providing critical material for in-depth studies, which are revealing the precise pathological mechanisms involved in this disorder, so that we can better treat people who have this condition.

FOLLOW-UP

Dr. Tran: I shared the findings of this patient's autopsy with her family by telephone. The results helped to relieve the guilt that her son felt because he had discovered his mother was ill only just before hospital admission. I also had the opportunity to reassure the patient's son and daughter that the end-of-life decisions they had made on behalf of their mother preserved her comfort near the time of death.

Perhaps the performance of the autopsy itself was more emotionally beneficial to this patient's family than the autopsy results. In our conversation, the patient's daughter reflected on the helplessness she had felt during her mother's illness and death, as well as more broadly during the Covid-19 pandemic. However, she felt uplifted that her mother's autopsy made the experience "part of something bigger."

ANATOMICAL DIAGNOSIS

Diffuse alveolar damage due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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