Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Is it COVID-19? The value of medicolegal autopsies during the first year of the COVID-19 pandemic

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ABSTRACT

Objectives: We describe the experience of a busy metropolitan medical examiner's office in the United States and share our navigation of the COVID-19 autopsy decision-making process. We describe key gross and microscopic findings that, with appropriate laboratory testing, should direct a pathologist towards a COVID-19-related cause of death.
Material and methods: We performed a retrospective review of 258 suspected and/or confirmed COVID-19 associated deaths that occurred between March 5, 2020, and March 4, 2021.
Results: A total of 62 cases due to fatal COVID-19 were identified; autopsy findings included diffuse alveolar damage, acute bronchopneumonia and lobar pneumonia, and pulmonary thromboemboli. Nine additional decedents had a nasopharyngeal swab positive for SARS-CoV-2 and a cause of death unrelated to COVID-19. Forty-seven cases with COVID-19-like symptoms showed no laboratory or histopathologic evidence of SARS-CoV-2 infection; the most common causes of death in this group were hypertensive or atherosclerotic cardiovascular disease, complications of chronic alcoholism, and pulmonary thromboemboli unrelated to infection.
Conclusions: The clinical findings associated with COVID-19 are not specific; a broad differential diagnosis should be embraced when decedents present with cough or shortness of breath. An autopsy may be indicated to identify a cause of death unrelated to COVID-19.

1. Introduction

At the time of this writing, the novel human coronavirus SARS-CoV-2 (COVID-19) has resulted in the death of 4.5 million people worldwide and 643,706 deaths in the United States alone [1,2]. The toll this has taken on surviving family members, healthcare workers, and government agencies cannot be understated. Prior to the pandemic, the number of autopsies performed declined considerably over the course of several decades, dropping from 19.3% in 1972 to 8.5% in 2007 [3]. Advancements in diagnostic imaging techniques, malpractice concerns, funding and cost control, resource availability, next-of-kin consent, clinician attitudes towards autopsy, forensic pathologist shortages, and the opioid crisis have all played a role in straining autopsy services [4–6]. These factors, aggravated by concerns regarding procedural aerosolization of a novel virus, insufficient personal protective equipment, and often antiquated morgue facilities, resulted in relatively few autopsies of those who died from fatal COVID-19 in the United States [7,8].

Nevertheless, autopsies remain valuable laboratory tests that confirm accurate diagnoses, reveal unknown conditions, illuminate errors, and improve the quality of clinical practice [9]. During a pandemic, autopsies are essential for calculating accurate mortality rates and clinicopathologic characterization of infection. In turn, the data derived from autopsies can and should be used to guide every facet of the global response.

To date, numerous autopsy studies have examined the pathologic findings of patients who have died from confirmed acute COVID-19. Pulmonary findings associated with fatal infection include diffuse alveolar damage with hyaline membrane formation, acute pneumonia, reactive type II pneumocytes, perivascular lymphocytic infiltration, increased megakaryocytes, and thromboemboli [9–14]. There is a dearth of studies that examine diagnostic challenges in

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postmortem identification of COVID-19, especially in the setting of limited resource availability.

Relative to other states, Georgia is ranked sixth in the United States for total SARS-CoV-2 infections and ninth for COVID-related deaths [15]. On March 5, 2020, the first autopsy of a decedent who died of COVID-19 in the state of Georgia occurred at our facility–three days after the first infection in the state was confirmed [16]. Here, we describe our experience in a substantially affected metropolitan area and share our findings to assist medical examiners, clinicians, researchers, and public health officials also navigating the COVID-19 autopsy decision-making process. We hope to empower other agencies to perform full autopsies, rather than rely solely on external examinations and clinical history.

2. Methods

In 2020, our office received a total of 3083 death notifications, which is a 16% increase from the preceding year. We performed a retrospective review of 258 suspected and/or confirmed COVID-19-related deaths that occurred between March 5, 2020, and March 4, 2021. The following variables were examined: age, race, sex, cause of death, other significant conditions/comorbidities, gross findings, histologic findings, ancillary procedures, and investigative/clinical data. All data were maintained in a password-protected electronic database on a secure server. No institutional review board approval was required because all human subjects were deceased.

As specified by Georgia Death Investigation Act (O.C.G.A. 45-16-20), jurisdiction is typically accepted in deaths involving any of ten factors: violence, injury, accidental death, suicide, sudden, suspicious, a child under age 7, unattended by a physician, death penalty executions, state hospital or state, county, or city penal institution inmates, or unconscious hospital admittance followed by death within 24 h without regaining consciousness [17]. Jurisdiction is declined when ample medical history is present and a primary care physician can be located to sign the death certificate. Decedents with medical history sufficient for death certificate completion may be designated for “sign-out”, after appropriate investigation. All external examinations, limited dissections, and full autopsies were performed in accordance with standard operating procedures.

Autopsies were performed in a negative-pressure morgue with recirculating airflow. While an isolated infectious autopsy area and the utilization of HEPA filters are standard protocol for facilities accredited by the National Association of Medical Examiners, the additional precaution of a negative-pressure autopsy suite allowed for proactive containment of potentially infectious viral particles within the immediate environment [18].

Appropriate personal protective equipment was utilized, including an N-95 or KN-95 mask with an overlying surgical mask, face shield, waterproof plastic apron, and two sets of gloves. In accordance with OSHA and CDC guidelines, efforts were taken to limit aerosol-generating procedures [19,20]. Following autopsy completion, the morgue was disinfected using a handheld multi-purpose fogger with aerosolized hospital-grade detergent. When microscopic examination was required, tissue sections were retained in 10% buffered formalin and processed into slides. All findings were reviewed by at least one board-certified forensic pathologist. When indicated, an additional review was performed by expert consultants, including neuropathologists and surgical pathologists. No staff contracted COVID-19 from occupational exposure.

COVID-19 was confirmed by one of the following procedures:

1. Postmortem nasopharyngeal swab positive for SARS-CoV-2 (n = 42).
2. Documentation of recent antemortem laboratory confirmation of COVID-19 (nasopharyngeal swab or rapid test), with postmortem confirmatory testing when possible (n = 24).
3. Positive COVID-19 IgM/IgG antibody screen performed on blood sample in the context of appropriate histology and/or clinical presentation (n = 6).
4. Molecular and immunohistochemical evidence of SARS-CoV-2 identified on paraffin blocks and slides, respectively (n = 1).

Nasopharyngeal swabs were refrigerated at 4 °C and transported to the Microbiology Lab at a local hospital or the Georgia Health Department to undergo real-time reverse transcription-polymerase chain reaction (rRT-PCR) testing within six days of collection. Beginning June 3, 2020, decedents with suspected COVID-19 were concurrently screened for COVID-19 antibodies when resources were available. Antibody screening of whole blood was performed using lateral flow immunoassay through a COVID-19 IgG/IgM Rapid Test Cassette. Whether or not COVID-19 played a role in the cause of death was determined in the context of appropriate clinical history and/or gross and microscopic findings typical of COVID-19.

To exclude a diagnosis of COVID-19 on cases that were examined before the study period, all cases performed between January 1, 2020, and March 4, 2020, with a respiratory cause of death were reviewed to rule out findings suggestive of COVID-19 (n = 15). No diffuse alveolar damage was identified in the aforementioned cases.

3. Results

A total of 250 suspected COVID-19 cases were reported to our office within one year of March 5, 2020. Jurisdiction was accepted for 144 cases; the remaining 106 were declined.

Of cases in which jurisdiction was accepted, 110 decedents (76%) were sent to the autopsy facility for an examination. The remaining 34 decedents were designated as “sign-out” cases after appropriate investigation and released to a funeral home (24%) (Table 1).

Sixty-two decedents with suspected SARS-CoV-2 infection were found to have fatal COVID-19. An additional 9 decedents had a non-COVID-19 cause of death but a nasopharyngeal swab positive for SARS-CoV-2. Demographic features and comorbidities in COVID-19 positive decedents are described in Table 2.

Table 2 Demographics, clinical presentation, comorbidities, and social history in decedents that were sent to the facility for autopsy or external examination and COVID-19 was determined to have caused or contributed to death.

Antibody testing was performed on 26 of the aforementioned decedents. Eight cases were concurrently positive for IgG and IgM antibodies, 14 cases were positive for IgG only, and 1 case was positive for IgM only. See Table 3.

Table 3 Nasopharyngeal swab results and antibody status of decedents with fatal COVID-19.

3.1. Cases in which an autopsy was performed and the cause of death was fatal COVID-19

A total of 32 full or limited autopsies involving a histopathological examination were performed on cases in which the underlying

Table 1
Procedure on suspected COVID-19 decedents.

A. Disposition (n = 250)	
Accepted jurisdiction	**144 (58%)**
Sent to morgue for examination	110
Released to funeral home	34
Declined jurisdiction	**106 (42%)**
B. Procedure (n = 110)	
Full autopsy	26 (24%)
Limited dissection	39 (35%)
External examination	45 (41%)

Table 2
Characteristics of decedents with fatal COVID-19 (n = 62).

Mean Age (range)	58.10 years (18 – 90 years)
Sex	
Male	46 (74%)
Female	16 (26%)
Race/Ethnicity	
African American/Black	31 (50%)
White	23 (37%)
Hispanic	5 (8%)
Asian	3 (5%)
Mean BMI (range)	33.53 kg/m^2 (16.13–74.27 kg/m^2)
Infection length (range)	14.59 days (1–60 days)
Clinical presentation	
Shortness of breath/difficulty breathing	27 (44%)
Cough	22 (35%)
Fever	14 (23%)
Pneumonia	14 (23%)
Acute lethargy	10 (16%)
Diarrhea	9 (15%)
Headache	6 (10%)
Nausea/vomiting	5 (8%)
Chest pain	4 (6%)
Abdominal pain	3 (5%)
Seizure	3 (5%)
Loss of taste/smell	2 (3%)
Muscle ache	2 (3%)
Wheezing	2 (3%)
Associated comorbidities	
Obesity	41 (66%)
Hypertension	40 (65%)
Atherosclerotic cardiovascular disease	23 (37%)
Diabetes mellitus	18 (29%)
Cardiomegaly	16 (26%)
Chronic obstructive pulmonary disease	7 (11%)
Dementia	4 (6%)
Social history	
Tobacco use	12 (19%)
Alcohol use	11 (18%)
Drug use	5 (8%)

Table 3
Test results of antibody-screened decedents with fatal COVID-19 (n = 26).

Nasopharyngeal swab	
Positive	22 (85%)
Negative	4 (15%)
Rapid antibody test	
Positive	**23 (88%)**
IgM only	1 of 23 (4%)
IgM/IgG	8 of 23 (35%)
IgG only	14 of 23 (61%)
Negative	**3 (12%)**

cause of death was fatal COVID-19. Of these decedents, 24 were male (75%) with an average age of 56 years (range: 23 – 90 years).

Gross pulmonary findings associated with COVID-19 included edematous, heavy, beefy-red lungs, multiple areas of parenchymal consolidation, and acute and organizing pulmonary thromboemboli with deep vein thrombi.

Microscopic examination of beefy-red parenchyma revealed acute/exudative diffuse alveolar damage (predominantly hyaline membranes), sometimes with foci of organization in the form squamous metaplasia and fibroblastic activity (n = 18 cases; Fig. 1). In a background of diffuse alveolar damage, acute main and segmental thromboemboli consisting of alternating red blood cells with fibrin and acute inflammatory cells were seen (n = 7 cases; Fig. 2). Accompanying acute thromboemboli were often organized thromboemboli, some with recanalization, and associated wedge-shaped pulmonary infarcts. Leg dissection, when performed, showed deep vein thrombi (n = 3). Examination of consolidated lung tissue showed a total of 6 cases of pneumonia. Of these, 4 cases were identified as acute bronchopneumonia. The remaining 2 cases of lobar pneumonia were likely associated with bacterial coinfection.

Pulmonary edema and reactive type 2 pneumocytes were commonly seen. In 13 cases, megakaryocytes were prominent in the lungs. In 2 cases, they were also present in the kidneys or liver.

Postmortem examination of a 32-year-old male who suffered a witnessed collapse demonstrated SARS-CoV-2 positivity on nasopharyngeal swab and no significant pulmonary histology. A single section of left ventricular myocardium contained lymphocytes, neutrophils, and eosinophils with minimal myocytolysis compatible with multiple foci of acute myocarditis; no gross changes were observed (Fig. 3).

In one case in which COVID-19 was not suspected, clinical presentation suggested the presence of a postoperative bowel obstruction several days after an outpatient surgery. No pulmonary complaints were reported by next of kin. However, diffuse alveolar damage revealed by microscopic examination sparked concern for COVID-19. Too late to perform a nasopharyngeal swab, a postmortem blood sample stored in an EDTA tube was used to perform a COVID-19 antibody screen 15 days after autopsy. Results were positive for IgG, which, in the context of diffuse alveolar damage, supported a diagnosis of fatal COVID-19.

Other gross autopsy findings were associated with underlying natural disease processes, including atherosclerotic cardiovascular disease, hypertensive left ventricular hypertrophy, cardiomegaly, fatty appearing or cirrhotic liver, and granular appearing kidneys. Associated microscopic findings included interstitial fibrosis of the myocardium, hepatic steatosis, hepatic bridging fibrosis with nodule formation, renal arteriosclerosis, and glomerulosclerosis.

Brain examinations were performed in 16 cases. In 14 cases, no neuropathologic findings were identified. One case, which was initially reported as a possible drug overdose, demonstrated petechial and ring hemorrhages in white matter throughout the brain, in a pattern reminiscent of a microangiopathic or acute hemorrhagic leukoencephalitis (AHLE)-like phenomenon, with minimal inflammation and no definitive evidence of demyelination. The lungs showed severe diffuse alveolar damage and acute pneumonia; toxicology results were non-contributory. A second case revealed acute bilateral hemorrhages of the basal ganglia, with evidence of previous ischemic infarcts and severe atherosclerotic cardiovascular disease. The lungs showed acute pneumonia.

Our facility has examined six cases of decedents with postmortem nasopharyngeal swabs positive for SARS-CoV-2 and initial diagnosis of COVID-19 greater than 4 weeks. Pathologic findings in these cases include bacterial superinfections, pulmonary infarcts with organized thromboemboli, acute bronchopneumonia with prominent giant cells, pulmonary edema, and fibrinous pericarditis.

3.2. Cases reported as suspicious for fatal COVID-19 with a non-COVID-19 cause of death

Forty-seven cases initially reported as suspicious for fatal COVID-19 revealed no laboratory evidence of SARS-CoV-2 infection. The most common causes of death in these cases were hypertensive or atherosclerotic cardiovascular disease (n = 19; 41%), acute drug intoxication (n = 4; 9%), complications of chronic alcoholism (n = 4; 9%), and pulmonary thromboemboli due to deep vein thrombosis (n = 3; 7%). One case was due to complications of undiagnosed malignancy and another was due to undiagnosed complications of Acquired Immunodeficiency Syndrome (AIDS).

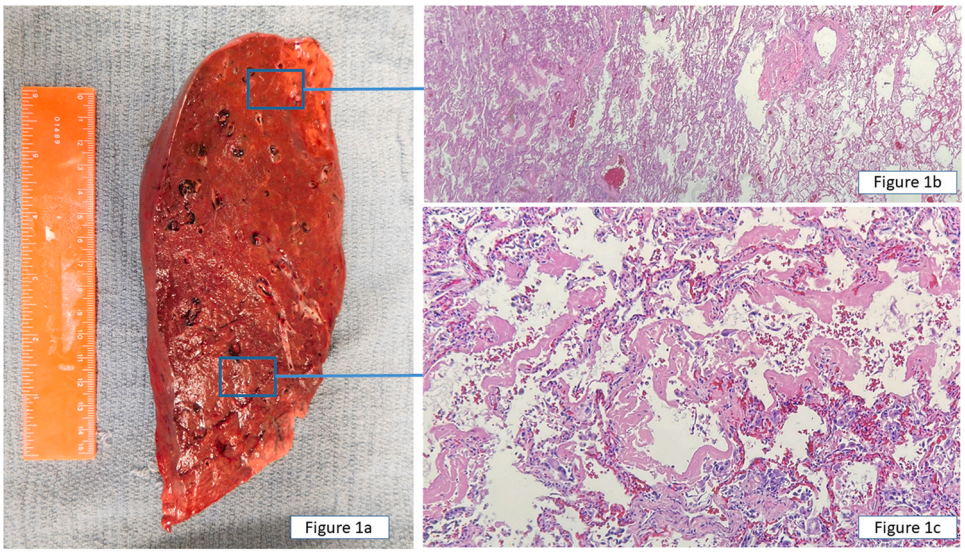

Fig. 1. Gross and microscopic diffuse alveolar damage, clinically Acute Respiratory Distress Syndrome. Fig. 1a: Cross-section of beefy, red lung with diffuse alveolar damage with focal area of sparing; Fig. 1b: Low power photomicrograph depicting diffuse alveolar damage (left side) and relatively spared pulmonary parenchyma (right side); Fig. 1c: Acute diffuse alveolar damage with prominent hyaline membranes.

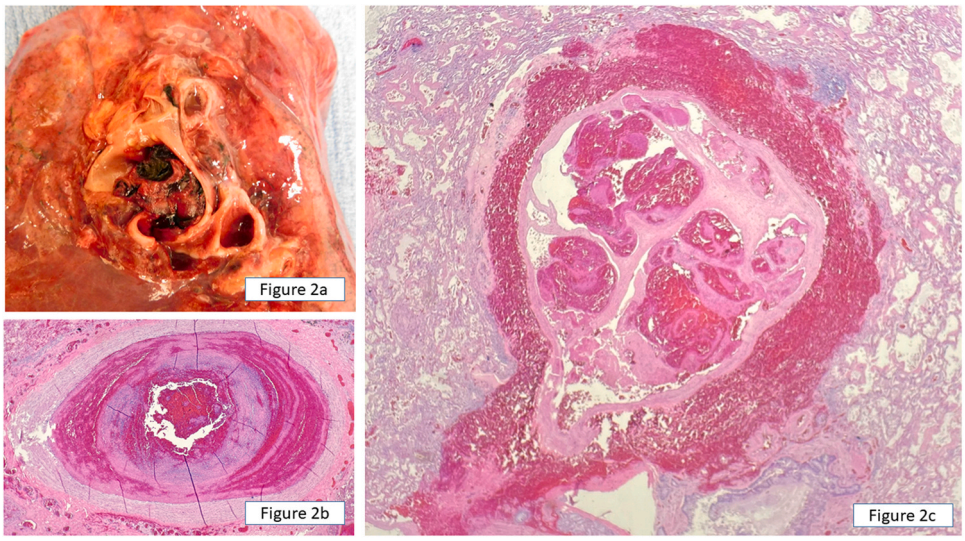

Fig. 2. Gross and microscopic pulmonary emboli; Fig. 2a: Large thromboembolus in the pulmonary artery with acute and organizing features; 2b: Acute pulmonary embolism with alternating red blood cells, fibrin, and acute inflammatory cells (Lines of Zahn); 2c: Organized thromboembolus with recanalization in a background of diffuse alveolar damage.

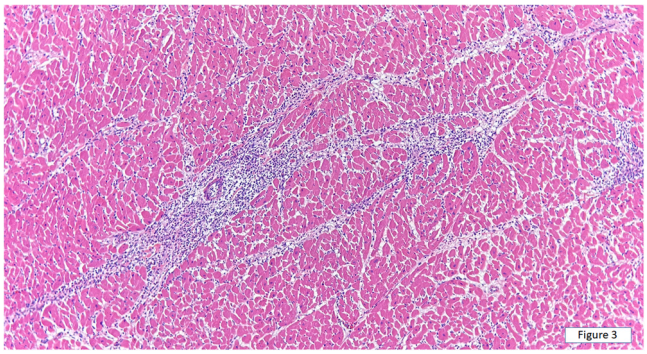

Fig. 3. Lymphocytes, neutrophils, and eosinophils with minimal myocytolysis in a section of left ventricle compatible with multiple foci of acute myocarditis.

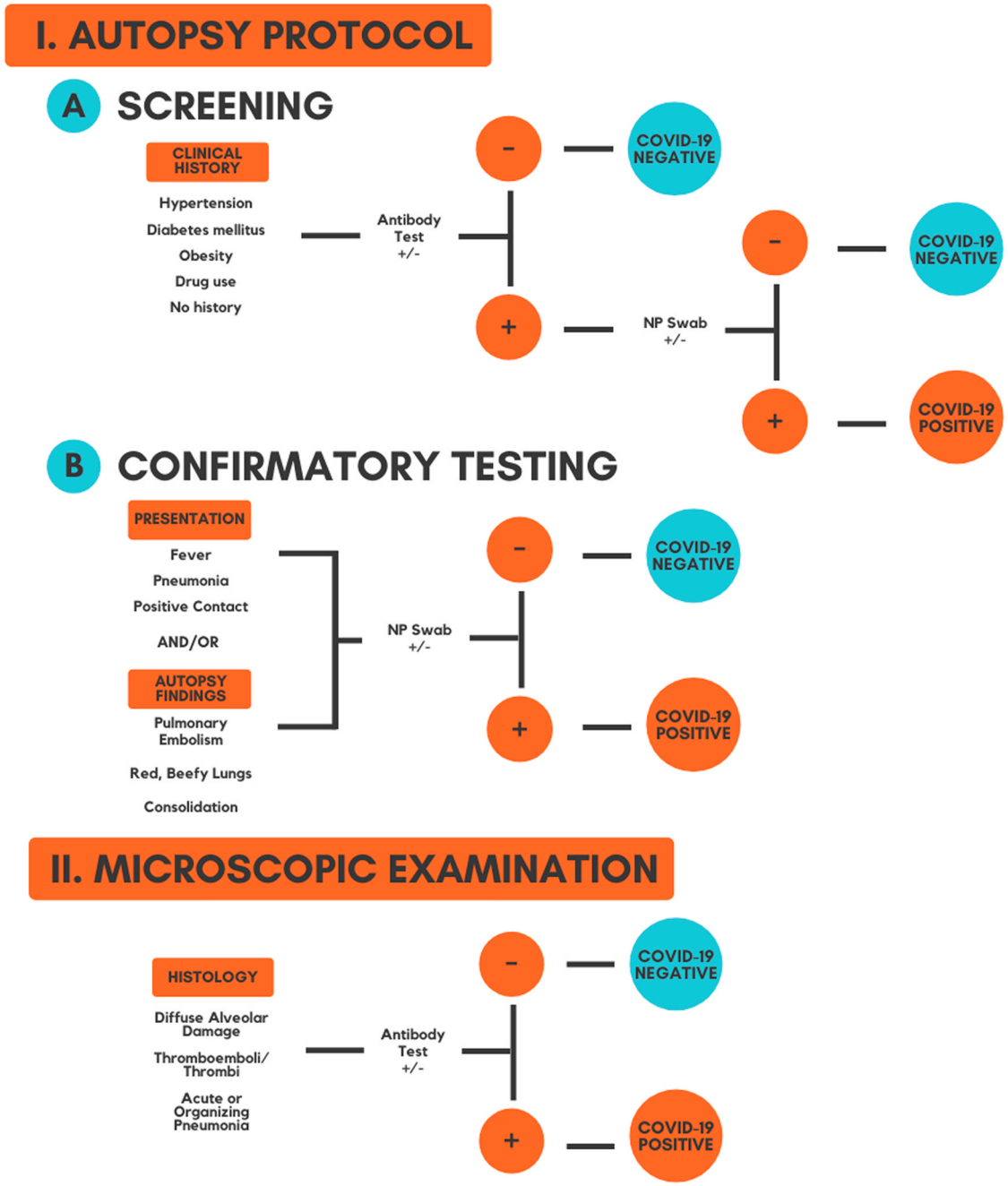

Fig. 4. Protocol for determining COVID-19 status via preliminary screening, during autopsy, and post-autopsy during microscopic examination.

Suspected COVID-19 symptoms included reported flu-like symptoms, fever, shortness of breath, cough, chest pain, pneumonia, acute lethargy, or generally feeling unwell.

Five cases with SARS-CoV-2 positivity on nasopharyngeal swab were determined to have an accidental or suicidal manner due to non-natural causes, including acute drug toxicity and ligature hanging. Investigative findings in these cases included histories of chronic alcoholism, chronic drug use, and cigarette smoking with no mention of COVID-19 like symptoms. Four cases with SARS-CoV-2 positivity on nasopharyngeal swab had a natural cause of death with no histologic findings typical of COVID-19. It is unclear if laboratory results indicate recent infection with viral shedding or asymptomatic infection. In these cases, despite the presence of SARS-CoV-2 positivity, COVID-19 was not listed as a cause of death or other significant condition on the death certificate.

4. Discussion

After performing 110 postmortem examinations on suspected COVID-19 cases, with no autopsy-associated illness, our threshold for examining future infection-related deaths with appropriate precautions is relatively low. Although our procedures adapted to the rapidly evolving pandemic, we were unable to perform nasopharyngeal swabs on all reported cases with an apparent natural or drug-related deaths for much of 2020 due to national testing supply shortages and testing backlogs. However, by screening decedents with an antibody test at the time of examination once these became available, we identified 3 additional cases of fatal COVID-19 and 5 decedents with incidental SARS-CoV-2 infection. As vaccination rates increase, we may explore using other screening methods, such as rapid antigen tests. *Our approach to screening is described in* Fig. 4.

Our study is limited by resource constraints that prevented us from performing complete autopsies with microscopic examination and ancillary testing on every decedent with suspected fatal COVID-19. As a result, some deaths due to fatal COVID-19 were probably attributed to other natural causes based on reported patient history. Such resource constraints included: unfilled physician positions in the setting of a national shortage of forensic pathologists, illness and quarantine-related absences, and the attempt to prudently use limited amounts of personal protective equipment/testing supplies. However, by recognizing common gross findings of fatal COVID-19 in the absence of a supportive clinical history (red firm lungs characteristic of diffuse alveolar damage, foci of pulmonary consolidation suspicious for pneumonia, and pulmonary thromboemboli), we may identify which decedents will most benefit from confirmatory testing. Our findings support previous autopsy studies that show similar postmortem findings [9–14].

While the presence of these aforementioned gross findings are not specific for COVID-19, recognition of such findings should place fatal COVID-19, among other causes of death, into a broad differential diagnosis. Cases reported to our office as suspicious for fatal COVID-19, which ultimately demonstrated no laboratory or pathologic evidence of SARS-CoV-2 infection, most often had common causes of death, including undiagnosed heart disease, drug toxicity, and chronic alcoholism, which have increased in the pandemic setting. These findings mirror increases in the incidence of excess deaths not directly attributed to fatal COVID-19, in the United States [21,22]. Occasionally, less common causes of death (undiagnosed AIDS, undiagnosed malignancy) may present with symptoms similar to those of fatal COVID-19 [23]. It is crucial to remember other causes of COVID-19-like symptoms when deciding how to approach cases, especially when considering whether or not to perform an autopsy, as inaccurate determination of cause of death may have significant implications for next of kin, public health, and public trust [24]. As FEMA has offered financial assistance for COVID-19-related funeral expenses incurred after January 20, 2020, an accurate diagnosis will have additional financial consequences for surviving family members [25].

Studies describe that viral shedding may be seen in respiratory specimens of up to 59–105 days after initial infection in immunocompromised individuals, and as much as 61 days in immunocompetent people [26–28]. Even when its presence suggests this or asymptomatic infection, the identification of previously unknown SARS-CoV-2 at autopsy has significant public health implications. True prevalence may be extrapolated, next-of-kin can be warned of potential exposure, and contact tracing may be initiated. These findings are valuable especially when determining prevalence in marginalized populations, such as alcoholics, people who use drugs, or those with limited access to health care [29,30].

Another limitation of our study is our lack of brain examinations. In accordance with early OSHA/CDC guidelines, we initially performed only rare brain examinations to limit aerosolization. Two of the 16 neuropathology examinations we ultimately performed demonstrated pathologic findings similar to those described in a recent large study from the Mount Sinai team in New York, including AHLE-like pathology and hemorrhagic microinfarcts [31]. Numerous other studies describe microthrombi, cytotoxic T lymphocytic infiltrate, and hemorrhagic white matter lesions, suggestive of microvascular and hypoxic damage [10,32,33]. COVID-19-related brain disease is not uncommon, and more autopsies should include brain examination to accurately discern cause of death.

Multiple sources have suggested lasting post-acute symptoms associated with chronic or “Long COVID.” These include fatigue, dyspnea, cognitive dysfunction, anosmia, sleep disorders, fever, gastrointestinal symptoms, anxiety, and depression [34–36]. The complexities associated with both acute and chronic COVID-19-related illness suggest that a more comprehensive approach is necessary when performing postmortem examinations on positive decedents. In addition to confirming the presence of underlying natural disease, autopsy studies have identified acute extrapulmonary COVID-19-related disease, such as pericarditis/myocarditis or hepatic fibrosis associated with periportal lymphoplasmacytic inflammation, as well as shock-associated organ damage [23,37,38]. More complete autopsies are needed to better understand how acute findings relate to chronic COVID-19 pathology.

As the pandemic continues, numerous variants have emerged. We believe that it is important to identify potential differences in pathology associated with emerging variants to improve clinicoradiologic correlation and treatment. Now, as much as ever, the value of autopsy cannot be understated as we work to elucidate the natural history of the disease and identify possible lasting pathologic effects of this novel virus.

5. Conclusion

Our study highlights the value of the medicolegal autopsy during the COVID-19 pandemic. Aside from providing closure for next-of-kin and recommending medical follow-up when exposed to COVID-19, medicolegal autopsies elucidate pathologic processes that may be used to guide treatment in living individuals. Autopsy and postmortem laboratory testing results reported to the Georgia Department of Public Health in real time were invaluable when calculating the true prevalence of fatal COVID-19 in our county, shaping policy, and providing a foundation for vital statistics.

In the past year, autopsies were essential for confirmation of COVID-19-related death and recognition of non-related deaths. By recognizing pathology associated with COVID-19 in decedents with no laboratory evidence of confirmed infection, often mid-autopsy, we were able to triage ancillary procedures when we had limited resources. Although supplies and resources have increased in the metro Atlanta area, our experience has reinforced our judicious approach and may be of value for physicians who practice in locations where resources remain scarce. In the years to come, we encourage others in both medicolegal and hospital settings to perform complete autopsies to further elucidate acute pathologic findings and explore the chronic effects of SARS-CoV-2 infection.

CRediT authorship contribution statement

Rachel L. Geller, MD Conceptualization, investigation, methodology, resources, visualization, Writing – original draft, Writing – review and editing, **Jenna L. Aungst** Conceptualization, methodology, visualization, Writing – original draft, Writing – review and editing, **Anna Newton-Levins, MPH, PhD** Methodology, Writing – review and editing, **Geoffrey P. Smith, MD** Supervision, resources, conceptualization, **Marina B. Mosunjac, MD** Investigation, **Mario I. Mosunjac, MD** Investigation, **Christy S. Cunningham, DO** Resources, investigation, **Gerald T. Gowitt, MD** Supervision, resources, Writing – review and editing.

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Declaration of interest

None.

Conflict of interest

None.

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