

Pathological Lung Lesions of COVID-19 and Opioid Use Disorder: A Post-Mortem Lung and Toxicology Examination of 43 Decedents

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Abstract

The COVID-19 pandemic has continued from 2019 to current times, exacerbating existing epidemics since its beginning. Pathologic lung lesions in acute cases have consisted of hyaline membrane disease and microthrombi. More severe cases have pathologic lesions of alveolar and bronchiolar epithelial necrosis, lymphocytic interstitial infiltrate, and peribronchiolar and perivascular lymphocytic infiltrate. The opioid epidemic is one epidemic exacerbated by COVID-19. Those with opioid use disorder (OUD) are more likely to have compromised lung function, of which infection with the SARS-CoV-2 virus can worsen. The combined symptoms lead to an increased risk of overdose. In addition to anatomical risks, those with OUD require person-to-person contact to obtain opioids. This enhances the spread of COVID-19 and increases the risk of acquiring the disease. Pathological findings in those with chronic OUD can contain fluorescing talc powder with multinucleated giant cells and granulomas in the lung tissue. Twenty-one positive cases and twenty-two negative cases were collected from COVID-19 suspicious decedents in Marion County Coroner's Office. Toxicology screens and COVID-19 RT-PCR tests were run on each of the 43 decedents. Microscopic evaluation was done by hematoxylin and eosin (H & E) and Masson's Trichrome stains. The age range of those collected was 3 to 81 years. The ethnicities were 1 Asian, 8 African American, 1 Cuban, 3 Hispanic, 29 Caucasian, and 1 unknown. The male to female ratio was 3.8:1. The histological features found in this study were alveolar and bronchiolar epithelial necrosis, lymphocytic interstitial infiltrates, perivascular and peribronchiolar lymphocytic infiltrate, fibrosis, microthrombi, and hyaline membrane. Fluorescing talc was seen in 5 cases with granulomas and multinucleated giant cells. Toxicology reports showed 11

drug-related deaths, with cocaine, methamphetamine, alcohol, fentanyl, morphine, acetyl fentanyl, and sertraline as the causative agents.

Keywords

COVID-19, Pathology, Talc, Lung, Opioids

1. Introduction

Since 2019, the novel virus COVID-19 has restructured the daily lives of people throughout the world. From mask mandates to stay-at-home orders, businesses and hospitals have implemented many new rules to keep visitors and employees safe. The chronic disease form has caused death in multiple patients caused by severe alveolar and bronchiolar necrosis with lymphocytic interstitial infiltrate [1] [2] [3] [4] [5]. This damage is caused by the high affinity of SARS-CoV-2 for bronchiole respiratory epithelium on the ACE2 receptor [1] [6] [7] [8]. Patients with the acute form are identified through hyaline membrane disease and microthrombi in the pulmonary vasculature [1] [4] [5].

The pathological findings and transmissibility of the virus have exacerbated the symptoms of the opioid epidemic as well. People with opioid use disorder (OUD) are more likely to develop severe COVID-19 disease and contract the virus [9] [10]. OUD reduces lung function, which causes more exacerbations from COVID-19 and an increased risk of overdose [9] [10]. In addition, people with OUD are more likely to have social contact to acquire opioids [11] [12]. The required social contact increases the spread among those with OUD and subsequent social isolation increases the chance of an overdose not being noticed [13] [14]. Pathological findings in those with OUD may have fluorescing talc in the lung tissue.

This study analyzed the lung pathology of 43 COVID-19 positive and COVID-19 negative decedents from ages 3 to 86 (Table 1). Samples from these patients were collected in partial pulmonary autopsies. Toxicology reports were obtained for each decedent from the Marion County Coroner's Office and logged into the patient's medical history (Table 2 and Table 3). The decedents were not seen in a hospital setting before autopsy in concordance with the study. Pathological analysis was done using H & E and Masson's Trichrome stains.

2. Materials and Methods

The study was run from April 1, 2020, to March 1, 2021, with IRB approval obtained on March 30, 2020. Marian County Coroner's Office investigates deaths meeting the following criteria: "1) sudden death of a healthy child; 2) physician is unable to state cause of death, after careful review of medical chart, or the deceased does not have a physician; 3) known or suspected homicide; 4) known of suspected suicide; 5) related to or following known suspected self-induced or

Table 1. Pathological findings for the 43 COVID-19 positive and COVID-19 negative decedents. “X” marks indicate the presence of the finding for that column.

Patient Number	Pneumonia	Thrombi	Necrosis/Damage	Fibroplasia (Trichrome)	Hyaline Membrane	Talc	Disease Stage	COVID-19 Status
1	MF Interstitial	x	Bronchiole Epithelial, Alveolar				Moderate	Positive
2							Negative	Negative
3	MF Interstitial		Bronchiole Epithelial, Alveolar	x			Severe	Positive
4							Negative	Negative
5							Negative	Negative
6							Negative	Negative
7	MF Interstitial		Bronchiole Epithelial, Alveolar	x			Severe	Positive
8	F Interstitial, MF Bronchiolar		Bronchiole Epithelial, Alveolar	x			Severe	Positive
9	MF/Diffuse Interstitial		Bronchiole Epithelial, Alveolar	x	x		Severe	Positive
10	F Interstitial, F Fibrinous	x	Bronchiole Epithelial, Alveolar	x	x		Negative	Negative
11	F Interstitial	x	Bronchiole Epithelial, Alveolar				Negative	Negative
12			Bronchiole Epithelial, Alveolar	x			Severe	Positive
13			Bronchiole Epithelial, Alveolar			x	Moderate	Positive
14	Bronchopneumonia		Bronchiole Epithelial, Alveolar, General	x	x		Severe	Positive
15		x	Bronchiole Epithelial, Alveolar				Moderate	Positive
16	F Interstitial		Bronchiole Epithelial, Alveolar		x		Negative	Negative
17				x			Negative	Negative
18	F Interstitial	x	Bronchiole Epithelial, Alveolar	x			Severe	Positive
19	F Interstitial		Bronchiole Epithelial, Alveolar			x	Moderate	Positive
20	F Interstitial		Bronchiole Epithelial, Alveolar				Negative	Negative
21			Bronchiole Epithelial, Alveolar	x	x		Severe	Positive

Continued

22		x	Bronchiole Epithelial, Alveolar	x		Severe	Positive
23	Granulomatous		Bronchiole Epithelial, Alveolar	x	x	Negative	Negative
24		x				Negative	Negative
25						Negative	Negative
26						Negative	Negative
27		x				Negative	Negative
28						Negative	Negative
29						Negative	Negative
30			Mild Bronchiole Epithelial, Alveolar			Negative	Negative
31	Diffuse Interstitial		Bronchiole Epithelial, Alveolar	x	x	Severe	Positive
32	Diffuse Interstitial	x	Bronchiole Epithelial, Alveolar	x		Severe	Positive
33						Negative	Negative
34		x			x	Negative	Negative
35			Bronchiole Epithelial, Alveolar		x	Negative	Negative
36		x	Bronchiole Epithelial			Moderate	Positive
37	F bronchiolar	x	Alveolar	x		Severe	Positive
38		x				Moderate	Positive
39	F bronchiolar, F interstitial					Negative	Negative
40	F interstitial, Peribronchiolar	X	Bronchiole epithelial	X		Severe	Positive
41	Focal Interstitial					Moderate	Positive
42		x				Negative	Negative
43			Pulmonary Hemorrhage			Moderate	Positive

Table 2. Table of decedents whose cause of death was drug-related based on toxicology results. Medical history was collected by the Marion County Coroner’s Office from the decedent’s family members. Patients were not seen in the hospital before autopsy.

Patient Number	Age	Decedent Sex	Race	Medical History	Talc	Cause of Death	COVID-19 Status
12	57	Male	White	Shortness of Breath/Cough	White	Acute Cocaine Intoxication	Positive
13	66	Male	White	Flu Symptoms	x	Intoxication Methamphetamine	Positive

Continued

14	63	Male	Black	Tired/Flu Symptoms		Complications Chronic Alcoholism	Positive
15	66	Male	White	Stent Placement		Fentanyl & Morphine	Positive
18	47	Female	White	Kidney Stones		Acetyl fentanyl Intoxication	Positive
20	38	Male	White	Myocardial Infarction		Fentanyl Intoxication	Negative
21	53	Male	Black	Unknown		Fentanyl Intoxication	Positive
24	43	Female	White	Hypertension		Complications Chronic Ethanol	Negative
27	49	Male	White	Fever Symptoms		Complications of Acute Methamphetamine Intoxication	Negative
28	58	Male	Cuban	Diabetes		Toxic Effects Sertraline	Negative
30	32	Male	White	Asymptomatic		Fentanyl and Ethanol Intoxication	Negative

Table 3. Table of decedents whose cause of death was non-drug related based on toxicology results. Medical history was collected by the Marion County Coroner's Office from the decedent's family members. Patients were not seen in the hospital before autopsy.

Patient Number	Age	Decedent Sex	Race	Medical History	Talc	Cause of Death	COVID-19 Status
1	56	Male	Black	Diabetes/Fever		Complications of COVID	Positive
2	46	Male	White	Diabetes/Coughing		Atherosclerotic Heart Disease	Negative
3	28	Male	White	Hypertension/Seizures		Complications of COVID	Positive
4	54	Male	Black	Shortness of Breath		Atherosclerotic Heart Disease	Negative
5	34	Male	White	Diabetes/Vomiting		Diabetes	Negative
6	42	Female	White	Asthma/High Blood Pressure		Hypertensive Heart Disease	Negative
7	76	Female	N/A	Unknown		Complications of COVID	Positive
8	67	Male	White	Shortness of Breath		Complications of COVID	Positive
9	53	Male	White	Flu Symptoms		Complications of COVID	Positive
10	27	Male	Hispanic	Flu Symptoms		Acute Fibrinous Pneumonia	Negative
11	41	Female	White	Flu Symptoms		Interstitial Pneumonia	Negative
16	86	Male	White	Unknown		Acute Pneumonia	Negative
17	64	Male	White	Unknown		Cardiovascular Disease	Negative
19	60	Male	White	Diabetes	x	Organizing Granulomatous Pneumonia	Positive
22	61	Male	Black	Diabetes		Complications of COVID, Diabetes	Positive
23	50	Male	Black	Pneumonia	x	Granulomatous Pneumonia	Negative
25	41	Female	Black	Fever Symptoms		Gastrointestinal Hemorrhage	Negative

Continued

26	16	Male	White	Unknown		Pulmonary Hemorrhage	Negative
29	40	Male	Asian	Flu Symptoms		Ketoacidosis	Negative
31	75	Male	White	Flu Symptoms		Complications of COVID	Positive
32	74	Male	White	Hypertension		Complications of COVID	Positive
33	25	Male	Black	ADHD		Gunshot Wound Head	Negative
34	36	Female	White	Seizure Disorder	x	Hanging	Negative
35	38	Male	Hispanic	Depression	x	Multiple Blunt Force Injuries	Negative
36	64	Male	White	Unknown		Complications of COVID	Positive
37	68	Male	White	Unknown		Complications of COVID	Positive
38	30	Male	White	None		Complications of COVID	Positive
39	40	Male	White	Test positive 3 months prior		Gunshot Wound Head	Negative
40	56	Male	Hispanic	Flu Symptoms		Complications of COVID	Positive
41	3	Female	White	Unknown		Mild Interstitial Pneumonia	Positive
42	27	Female	White	Flu Symptoms		Pending	Negative
43	31	Male	White	Unknown		Gunshot Wound Chest	Positive

criminal abortion; 6) following an accident or injury primary or contributory, either old or recent; 7) accidental poisoning (food, chemical, drug, therapeutic agents); 8) occupational disease or hazard; 9) all deaths of unidentified persons; 10) person in the custody of the state (incarcerated, foster care, adult protective services); 11) has died by casualty” [15] [16]. Of these cases, decedents were chosen for the study if the deputy coroner’s report showed a history of respiratory distress, fever, cough, or viral infection within the past 7 days. This involved 43 cases. Case limits were not set for this study. All cases marked as COVID-19 suspicious were included. Informed consent was collected from the family members of the decedent.

Marion County Coroner’s Office performed partial pulmonary autopsies on decedents marked as COVID-19 positive or COVID-19 suspicious. Blood samples were collected and tested for SARS-CoV-2 by the Indiana Department of Health using RT-PCR methodology. Toxicology screens were run for 30 analytes by Marion County Forensics Department according to their guidelines and used to help determine the cause of death. Lung samples were observed grossly and microscopically. Light microscopic analysis was recorded with H & E and Masson’s Trichrome stains. The pathology read was scored as follows: alveolar and bronchiolar epithelial necrosis, lymphocytic interstitial infiltrates, perivascular and peribronchiolar lymphocytic infiltrate, fibrosis, microthrombi, and hyaline membrane disease, and talc powder.

3. Results

The age range of decedents was 3 to 81 years. The ethnicities were 1 Asian, 8

African American, 1 Cuban, 3 Hispanic, 29 Caucasian, and 1 unknown. The male-to-female ratio was 3.8:1 (**Table 1**). Twenty-one patients tested positive for COVID-19 and twenty-two patients tested negative for COVID-19.

The pathology found in the 21 COVID-19 positive cases mainly consisted of multifocal or diffuse alveolar necrosis and bronchiolar respiratory epithelial necrosis. Lymphocytic infiltration was also seen throughout the lung interstitium, indicating pneumonia (**Figure 1**). In some cases, the lymphocytic infiltration was seen in the peribronchiolar and perivascular interstitium instead (**Figure 1**). Few cases had the alveolar spaces filled with macrophages. Fibroplasia was noted in decedents with severe COVID-19 (**Figure 1**). Six acute cases contained hyaline membrane and microthrombi in multiple pulmonary vasculatures (**Figure 2**). Two cases were found to have granulomatous pneumonia with talc powder characterized by focal granulomas and multinucleated giant cells. The talc powder was positive on polarization (**Figure 3**). One of the cases had plant fiber in the bronchiole surrounded by neutrophils, which was diagnosed as aspiration pneumonia. Other abnormal findings consisted of lymphoid nodules in a three-year-old with COVID-19 and squamous metaplasia in a non-smoker decedent with COVID-19 (**Figure 4**).

The pathology in the 22 negative cases had scattered pulmonary edema and congestion. Five cases had focal interstitial pneumonia with alveolar and bronchiolar damage. One case had granulomatous pneumonia with talc powder characterized by focal granulomas and multinucleated giant cells. The talc powder was positive on polarization. This case was deemed to be a chronic opioid user.

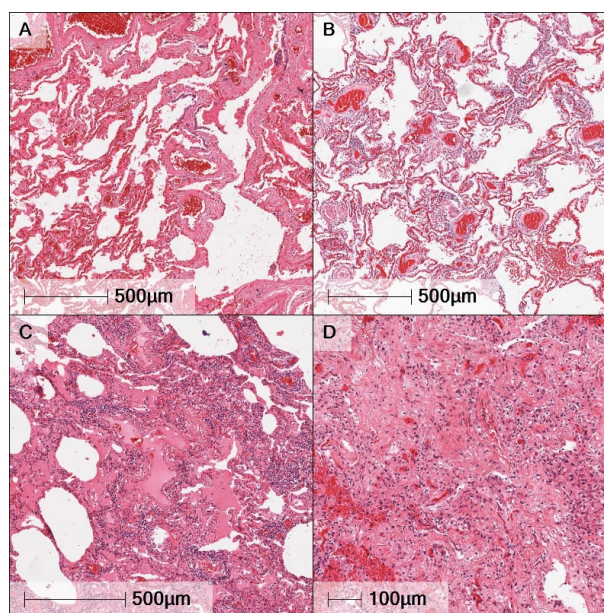


Figure 1. Chronic findings of COVID-19 disease. (A) Bronchiolar epithelial and alveolar necrosis from patient 21, H & E, 5×; (B) Peribronchiolar and perivascular infiltration from patient 19, H & E, 5×; (C) Interstitial pneumonia characterized by lymphocytic infiltrates from patient 1, H & E, 5×; (D) Fibroplasia in the lung from a severe COVID-19 case from patient 8, H & E, 20×.

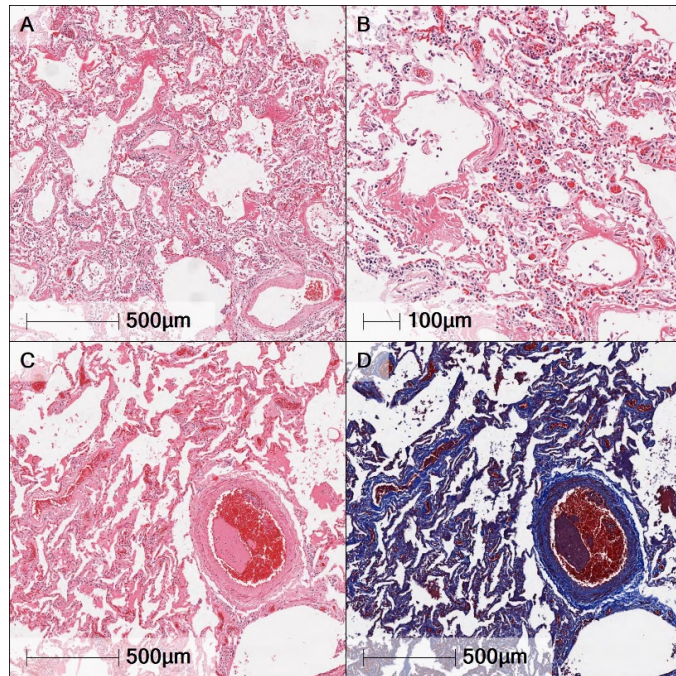


Figure 2. Acute findings of COVID-19 disease. (A) Hyaline membrane disease from patient 9, H & E, 5x; (B) Hyaline membrane disease from patient 9, H & E, 10x; (C) Microthrombi in the pulmonary vasculature from patient 15, H & E, 5x; (D) Microthrombi in the pulmonary vasculature from patient 15, Masson's Trichrome, 5x.

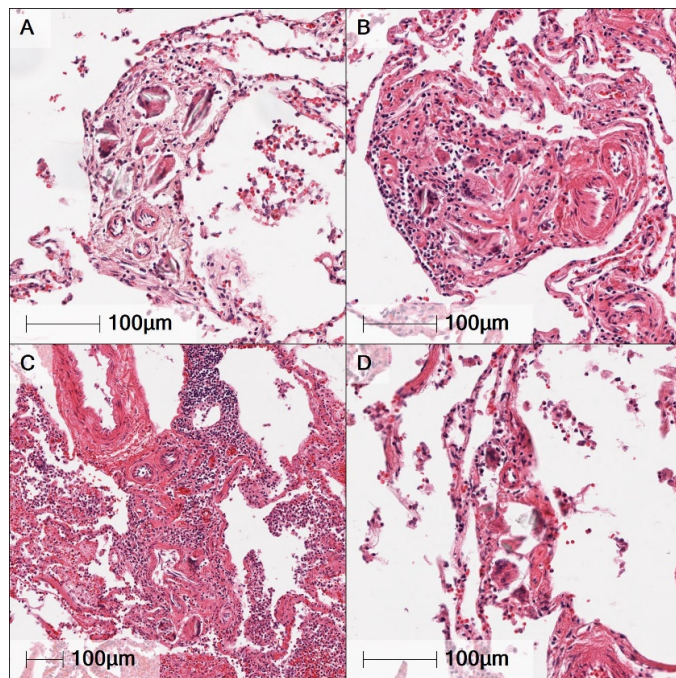


Figure 3. Talc powder, granulomas, and multinucleated giant cells from inhalant drug use. All pictures were taken from patient 13. (A) Talc powder surrounded by multinucleated giant cells and granulomas, H & E, 20x; (B) Talc powder surrounded by a granuloma and multinucleated giant cells, H & E, 20x; (C) Granuloma with talc powder and multinucleated giant cells, H & E, 10x; (D) Talc powder with multinucleated giant cells, H & E, 20x.

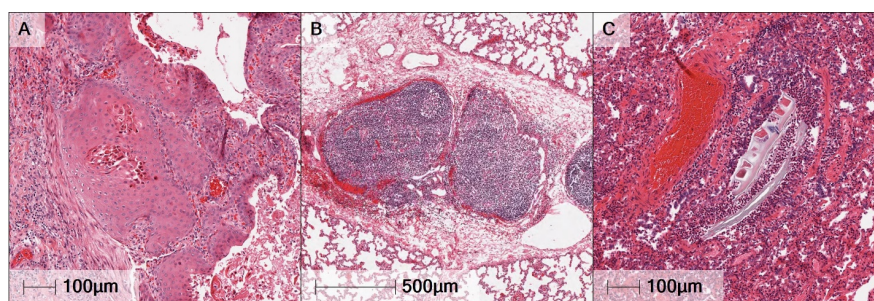


Figure 4. Abnormal findings from the group of decedents. (A) Squamous metaplasia from a non-smoking, COVID-19 positive decedent (patient 32), H & E, 10 \times ; (B) Lymphoid nodules from a 3-year-old decedent that was COVID-19 positive (patient 41), H & E, 5 \times ; (C) Plant fiber surrounded by aspiration pneumonia from patient 3, H & E, 10 \times .

Of all 43 decedents, 11 had the cause of death as drug overdose (**Table 2**). 6 of these 11 were COVID-19 positive, and one case had granulomatous pneumonia with talc powder. The rest of the decedents were determined to have non-drug related causes of death (**Table 3**). Of these non-drug related deaths, 4 were found to have granulomatous pneumonia with talc powder. This is the first study that has a toxicology report with COVID-19 RT-PCR tests.

4. Discussion

In this yearlong study, we enrolled all cases that were deemed COVID-19 suspicious. Twenty-one cases tested COVID-19 positive, and twenty-two cases tested COVID-19 negative.

The consistent pathology change seen in 21 COVID-19 positive decedents was a complete loss of bronchiolar respiratory epithelium and diffuse alveolar damage. These changes were seen in other published papers on COVID-19 lung pathology [1] [2] [3] [4] [17] [18]. In addition to these two, there was severe pulmonary congestion, mild to severe peribronchiolar and perivascular lymphoid infiltration, and focal or multifocal interstitial pneumonia identified by alveolar wall thickening and lymphocytic infiltrate [2] [3] [6] [17] [18]. Four positive cases were diagnosed with hyaline membrane disease, and nine had micro thrombi formations [1] [2] [4] [5] [19].

Many of the negative cases were characterized by pulmonary edema and congestion. These are both signs of cardiovascular disease and respiratory illness. Of the seventeen non-drug related deaths that were COVID-19 negative, nine were found to have one of these as their cause of death.

Eleven cases had causes of death related to drug use based on a forensic toxicology screen. Of these, six cases were COVID-19 positive. Compared to the non-drug related death group, this shows an increasing percentage of COVID-19 positive decedents from 46.8% to 54.5%. This increase could be accounted for by increased person-to-person contact [11] [12]. One of the six positive cases had granulomatous pneumonia with talc powder, which indicates inhalant use of opioids. In addition to this, 4 of the 32 cases with causes of death that were non-drug related had fluorescing talc powder. Out of these four, two died of

granulomatous pneumonia with one being COVID-19 positive. These individuals did not have opioids in their system at their time of death, but the presence of talc powder indicates chronic inhalant use of opioids. Because of this lung damage caused by OUD, COVID-19 positive decedents would have an increased risk of death if they contracted the virus [9] [13]. Of the remaining two, one died of hanging and the other had a history of depression. Mental illness is an indication of any pandemic but can be exacerbated in those affected by the opioid epidemic as well [13] [14]. Finally, the Marion County Coroner's Office's 2019 and 2020 reports show an increase in drug overdoses from 24% to 39% of deaths or 406 to 640 deaths [15] [16].

Overall, approximately 34% of the decedents in this study had either a drug-related death or previous history of opioid use that can be confirmed. This and other statistics stated previously could indicate a greater risk of death during the pandemic for those with OUD overall [10]-[16].

Two limitations were identified for this study. The first was that many cases avoided the coroner's office as hospital confirmed cases that died in the hospital and were sent directly to funeral homes. The second was that medical history could not be collected for many of the patients, due to the patient's lack of a primary care physician.

5. Conclusion

The RT-PCR tests and histological analyses are consistent with the diagnosis of COVID-19 in 22 decedents. In addition, it was found that the COVID-19 pandemic could have multiple ways of exacerbating the opioid epidemic. These included mental health issues, increased social contact, and an increase in drug overdoses in the first year of the pandemic.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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