DR KRISTINE KONOPKA (Orcid ID : 0000-0002-4582-0120)

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Diffuse Alveolar Damage (DAD) from Coronavirus Disease 2019 Infection is Morphologically Indistinguishable from Other Causes of DAD

Running title: Morphology of severe COVID-19-related lung disease

Kristine E. Konopka, Teresa Nguyen,* Jeffrey M. Jentzen, Omar Rayes, Carl J. Schmidt, Allecia M. Wilson, Carol F. Farver, and Jeffrey L. Myers
*Co-first author

All authors affiliated with the Department of Pathology, University of Michigan, Ann Arbor, MI.

Corresponding author: Kristine E. Konopka, MD, Michigan Medicine, Department of Pathology, 2800 Plymouth Rd, Building 35, Ann Arbor, MI 48109; Telephone number: (734)647-3992; Email: krkonopk@med.umich.edu

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Abstract

AIMS

Diffuse alveolar damage (DAD) is a ubiquitous finding in inpatient coronavirus disease 2019 (COVID-19)-related deaths, but recent reports also describe additional atypical findings, including vascular changes. Here, we assess lung autopsy findings in COVID-19 inpatients and untreated, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive individuals who died in the community to understand the relative impact of medical intervention on lung histology. Additionally, we investigate if COVID-19 represents a unique histologic variant of DAD by comparing the pathologic findings to uninfected control patients.

METHODS AND RESULTS

Lung sections from autopsy cases were reviewed by three pulmonary pathologists, including two who were blinded to patient cohort. The cohorts included 4 COVID-19 inpatients, 4 cases with post-mortem SARS-CoV-2 diagnoses who died in the community, and 8 SARS-CoV-2-negative control cases. DAD was present in all but one SARS-CoV-2-positive patient who was asymptomatic and died in the community. Although SARS-CoV-2-positive patients were noted to have more focal perivascular inflammation/endothelialitis than control patients, there were no significant differences in the presence of hyaline membranes, fibrin thrombi, airspace organization, and "acute fibrinous and organizing pneumonia"-like intraalveolar fibrin deposition between the cohorts. Fibrinoid vessel wall necrosis, hemorrhage, and capillaritis were not features of COVID-19-related DAD.

CONCLUSIONS

DAD is the primary histologic manifestation of severe lung disease in COVID-19 patients who die both in the hospital and in the community, suggesting no contribution of hyperoxemic mechanical ventilation to the histologic changes. There are no distinctive morphologic features to confidently differentiate COVID-19-related DAD from DAD due to other causes.

Key words: diffuse alveolar damage; COVID; autopsy

Introduction

As the coronavirus disease 2019 (COVID-19) pandemic sweeps across nations, there has been a general lack of consensus in the rapidly-expanding clinical literature about the extent to which acute respiratory distress syndrome (ARDS) suffered by patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is distinct from ARDS due to other causes. While some patients are described as having typical ARDS, others are thought to have atypical presentations or to represent a new pathobiology altogether. [1-4] Similarly, while the pathologic descriptions of pulmonary changes in patients who suffer from fatal COVID-19 apply the overarching diagnosis of diffuse alveolar damage (DAD), some authors emphasize peculiarities, such as prominent fibrinous airspace exudates, variably conspicuous lymphocytic infiltrates with descriptions of endothelialitis, and a range of other vascular changes that include fibrinoid necrosis of small vessels, hemorrhage and vasculitis, and small vessel and arterial thrombosis.[1,5-9]

To our knowledge, uncontrolled case reports and series of COVID-19-related lung pathology include almost exclusively patients who die in the hospital, often after prolonged supportive care. Since the histologic descriptions of pulmonary changes in COVID-19-related ARDS come largely from inpatient data, it is unknown how or if hyperoxemic mechanical ventilation and other medical interventions may account for some of the histologic findings.

Here, we aim to assess morphologic differences in the lungs of SARS-CoV-2-positive patients who die in the hospital and those who die in the community without pre-mortem diagnoses of COVID-19. Additionally, to better understand if COVID-19 represents a histologic variant of DAD we systematically compare the pathologic findings of SARS-CoV-2-positive patients to uninfected controls.

Materials and Methods

PATIENT SELECTION

This autopsy study is exempt from institutional review board approval. The University of Michigan's Wayne County Medical Examiner Office (WCMEO) performs post-mortem questionnaire screening for COVID-19 on all non-traumatic deaths that occur outside of the hospital. Screening criteria for SARS-CoV-2 testing is based on Centers for Disease Control and Prevention recommendations.[10] Testing may also be pursued when no information surrounding the decedents death is known/available. When testing criteria are met, SARS-CoV-2 nasopharyngeal swabs are collected at the time of autopsy and processed using real-time reverse transcriptase polymerase chain reaction (DiaSorin Molecular Simplexa COVID-19 Direct real-time RT-PCR assay). Complete and limited postmortem examinations are performed by American Board of Pathology-certified forensic pathologists according to standard procedures. Representative sections of tissue, including lung, are submitted for tissue processing and hematoxylin and eosin-stained slides are made.

Four deaths that occurred in the Wayne county community, outside of a hospital setting and without pre-mortem diagnoses of COVID-19 underwent full autopsies at WCMEO and were found to have positive post-mortem SARS-CoV-2 test results. Our database of SARS-CoV-2-positive inpatient autopsies performed at Michigan Medicine's University Hospital was queried to identify a best possible matched cohort by patient demographics to the SARS-CoV-2-positive community death cohort. One patient in our inpatient cohort has been previously reported.[11] Our autopsy databases were then searched from January 1, 2016 through December 31, 2019 for

inpatient and non-hospitalized community cases diagnosed as "diffuse alveolar damage." Since these deaths occurred prior to the first reported case of COVID-19 in the United States,[12] they are considered SARS-CoV-2-negative (further referred to as "control cohort"). Patients were excluded if they were lung transplant recipients or on extracorporeal membrane oxygenation during any part of their hospitalization. Cases with *Pneumocystis* pneumonia were also excluded, since the frothy exudate characteristic of *Pneumocystis* can mimic the appearance of intra-alveolar fibrin deposition. SARS-CoV-2 negative inpatient controls were selected based upon best possible matched ventilator days compared to the SARS-CoV-2-positive inpatient cohort. Only four SARS-CoV-2 negative non-hospitalized community controls were identified that met inclusion criteria and all cases were included. Pertinent patient data was collected for all cases.

HISTOLOGIC ASSESSMENT

All lung slides were independently reviewed by three pulmonary pathologists (KEK, CFF, JLM) without knowledge of the gross findings including lung weights. Two reviewers (CFF, JLM) were blinded to the patient cohorts. Prior to slide review, a reference image bank was circulated for standardization of diagnostic criteria. Reviewers scored the cases on a 0 to 3 scale (0 = absent; 1 = rare/focal; 2 = patchy; 3 = diffuse) for each of the following: hyaline membranes (Figure 1A), fibrin thrombi (Figure 1B), airspace organization (Figure 1C), "acute fibrinous and organizing pneumonia (AFOP)-like" intra-alveolar fibrin deposition (Figure 1D), acute bronchopneumonia (Figure 1E), perivascular inflammation and/or endothelialitis (Figure 1F-G), fibrinoid vessel wall necrosis (Figure 1H), and hemorrhage and/or capillaritis (Figure 1I). Histologic diagnoses were rendered in all cases and other pathologic findings noted.

Results

PATIENT CHARACTERISTICS

Patient characteristics for the SARS-CoV-2-positive inpatient and untreated, community death cohorts are detailed in Tables 1 and 2, respectively. Fever and cough were the most common presenting complaints in the SARS-CoV-2-positive inpatient cohort, while dyspnea was more frequently reported in the SARS-CoV-2-positive community cohort (Table 3). Diabetes, chronic lung disease, and cardiovascular disease represented the most common underlying health conditions in all SARS-CoV-2-positive patients. Obesity was also common with five of eight SARS-CoV-2-positive patients considered obese (body mass index [BMI] ≥30) and of these, two

were severely obese (BMI ≥40). Three decedents in the non-hospitalized community cohort died at home; the fourth died in prison where he reported no symptoms.

The inpatient control cohort was comprised of four females, two black and two white, ranging in age from 22 to 80 years (average 53 years). Ventilator days ranged from 0 to 16. All patients died of clinical ARDS. Two patients had underlying sepsis, including one with polymicrobial bacteremia following acute cholecystitis and one with candidemia. One patient had acute exacerbation of idiopathic bronchiectasis and pneumonia, and one suffered acute intraparenchymal brain hemorrhage. The community death control cohort consisted of two white males, one black female, and one white female, ages 33 to 63 years (average 49 years). All died of natural causes with primary autopsy findings of DAD with or without acute bronchopneumonia.

PATHOLOGIC FINDINGS

An average of 5 sections (range 3 to 7) of lung were submitted at the time of autopsy for SARS-CoV-2-positive inpatients. Inpatient controls averaged 4.8 sections per case (range 4 to 5). Non-hospitalized community cohorts averaged 3.8 sections (range 3 to 5) in SARS-CoV-2-positive cases and 3.5 sections (range 2 to 5) in SARS-CoV-2-negative controls.

Definite DAD was identified in all but one (case #7) of the SARS-CoV-2-positive patients (Table 4). There was overall agreement in confirming the presence of DAD in the control cases. The lung weights for cases with consensus diagnoses of DAD ranged from 620 to 1600 grams for the right lung (normal average 300 to 350 grams) and 640 to 1350 grams for the left lung (normal average 250 to 300 grams). The case without DAD (case #7) had lung weights of 450 grams each for the right and left lungs.

Of all cases reviewed (n = 16), there was unanimity regarding the presence of hyaline membranes for 14 cases and the extent of the hyaline membranes in 9 cases. Of the cases without concordance, the majority of disagreement (n = 5) was due to differences in interpretation of the extent, while 2 cases (#7 and #15) represented lack of agreement on the presence of hyaline membranes. Case #7 was diagnosed as “early DAD” by one reviewer who identified focal hyaline membranes, while the other two reviewers did not see hyaline membranes. Case #15 was complicated by diffuse acute bronchopneumonia. Two reviewers also reported patchy hyaline membranes and diagnosed DAD, while one reviewer only diagnosed acute bronchopneumonia.

Fibrin thrombi, involving small precapillary vessels and/or muscular arteries, were identified by at least one reviewer in 13 cases. Fibrin thrombi were not identified in 1 SARS-CoV-2-positive patient and 2 control cases. There was no difference in the overall extent of fibrin thrombi identified in SARS-CoV-2-positive patients compared to control cases, averaging an extent of 0.9 (on a scale of 0 to 3) in both aggregated SARS-CoV-2-positive and control cohorts.

Histologic evidence of organizing DAD was reported by at least one reviewer as focal (score 1) or patchy (score 2) airspace organization in 3 of 4 SARS-CoV-2-positive inpatients. Airspace organization was scored as present by all three reviewers in only 1 case (#3). In contrast, airspace organization was not identified by any reviewers in SARS-CoV-2-positive community cases.

Inter-observer variability was greatest for AFOP-like intra-alveolar fibrin, which was scored as present by at least one reviewer in all cases. This feature was identified by all three reviewers in 11 cases that were equally distributed across all four cohorts, with unanimity regarding extent in 6 of them. Of the cases where there was not consensus on extent, reviewers scored four cases as either 1 (focal) or 2 (patchy), and one was scored as 2 (patchy) or 3 (diffuse). For 5 cases, spread across all four cohorts, there was lack of agreement on the presence of AFOP-like intra-alveolar fibrin, but when scored as present, it was only a focal finding (score 1). Overall, the extent of fibrin deposition was not appreciably different in aggregated SARS-CoV-2-positive patients (average 0.9) compared to control cases (average 1).

There was more acute bronchopneumonia in SARS-CoV-2-positive inpatients (average 1.5) than SARS-CoV-2-positive community deaths (average 0.8). Perivascular inflammation was a more common finding in SARS-CoV-2-positive cases (average 0.4) compared to controls (average <0.1), but in SARS-CoV-2-positive cohorts, it was a focal finding when identified and only 1 case was scored as having perivascular inflammation by all three reviewers. Fibrinoid vessel wall necrosis, hemorrhage, and/or capillaritis were not features of SARS-CoV-2-positive patients. Viral cytopathic changes were not seen in any SARS-CoV-2-positive cases.

Discussion

To our knowledge, this is the first comparison of autopsy lung findings in SARS-CoV-2-positive medically managed inpatients and untreated, non-hospitalized decedents to uninfected historical control cases of DAD. The main limitation to our study is the small number of cases in each of

the cohorts. Nonetheless, we think our SARS-CoV-2 positive cases are likely representative of the broader COVID-19 patient population, since both hospitalized and non-hospitalized decedents had underlying conditions previously identified as risk factors for severe disease, including diabetes, chronic lung disease, cardiovascular disease,[13] and obesity.[14]

DAD is ubiquitous at autopsy in hospitalized and non-hospitalized COVID-19 patients. DAD was the primary abnormality in all hospitalized COVID-19 patients, as previously reported by others.[5-9,15-16] DAD was also present in nearly all SARS-CoV-2-positive decedents that died without medical intervention. This suggests that COVID-19-related lung disease is a common cause of death not only in hospitalized patients, but also in those who die in the community. The single exception was a case that lacked histomorphologic features clearly diagnostic of DAD. The lung weights were also relatively normal as compared to all other cases in which DAD was present. All reviewers noted a focal AFOP-like airspace exudate similar to previous descriptions of incidental pulmonary findings in patients later diagnosed with COVID-19.[17] This decedent was reportedly asymptomatic prior to being found dead. We conclude that he was either an asymptomatic SARS-CoV-2 carrier or suffered from early pre- or subclinical COVID-19 based upon 1) the absence of significant pulmonary changes and 2) autopsy evidence of hypertensive heart disease which likely accounted for his death.

SARS-CoV-2-positive inpatient and non-hospitalized community cases show no meaningful differences in lung histology at autopsy. DAD is the primary abnormality in both with little to distinguish these two populations. Airspace organization, a finding more typical of the organizing phase of DAD, was seen only in hospitalized COVID-19 patients indicating that they survived longer with their lung disease than their non-hospitalized counterparts. Neither SARS-CoV-2 infected cohort showed fibrinoid vessel wall necrosis, vasculitis/capillaritis, or hemorrhage resembling that previously reported by others.[7-9] We have not observed any of these vascular changes in other hospital-based COVID-19 patient autopsies that were not included in this study. Given the morphologic similarity between treated COVID-19 DAD and non-hospitalized COVID-19 DAD, we conclude that the DAD seen in the inpatient cohort is directly attributable to viral infection rather than medical therapies, including those that may cause hyperoxemic lung injury.

DAD in SARS-CoV-2-positive patients is histologically indistinguishable from DAD due to other causes. While additional clinical correlation is needed to understand if the ARDS

experienced by COVID-19 patients represents a novel subphenotype, our results suggest that the histologic features of COVID-19-related DAD are not specific and indicate that the pathogenesis includes elements common to other causes of DAD. Fibrin thrombi with an average score of at least rare/focal (≥ 1) were seen in 5 of 8 SARS-CoV-2-positive cases and 4 of 8 control cases. Furthermore, we have not observed a greater incidence of thrombi in other COVID-19 inpatient autopsies. These observations underscore original descriptions of DAD, in which fibrin thrombi were common.[18] Indeed, the term *DAD* was coined to emphasize the central role of diffuse injury to the epithelium and endothelium comprising the distal pulmonary acinus. AFOP-like fibrin also occurred with similar frequency in all SARS-CoV-2 infected and uninfected cohorts. At least focal (mean ≥ 1) AFOP-like changes were identified in 5 of 8 SARS-CoV-2-positive patients and in 6 of 8 control cases. This finding was never more than "patchy" in SARS-CoV-2-positive cases as independently assessed by three reviewers including two who were blinded to cohort assignment. AFOP-like fibrin was extensive in only a single non-hospitalized case that preceded the COVID-19 pandemic, supporting this histologic finding as nonspecific in nature. Variably prominent alveolar fibrin deposition was also included in the original description of DAD, [18] further demonstrating that it is not specific to COVID-19 or any other variant of DAD. Perivascular inflammation was noted by at least one reviewer in 5 of 8 SARS-CoV-2-positive cases compared to 1 of 8 COVID-19-negative control cases. When present, this finding was at most focal (mean ≤ 1) and of uncertain significance with regard to the pathogenesis of COVID-19-related lung disease. As a diagnostic clue, it is not specific nor sufficient to reliably separate COVID-19 from other causes of DAD. Similar patterns of inflammation have been described and illustrated using a variety of terms in other viral pneumonias that include coronaviruses as well as human parechovirus, respiratory syncytial virus, human parainfluenza virus 1, and influenza.[19] This finding has also been described in non-viral causes of DAD, further emphasizing its nonspecific nature.[18]

We had relatively high rates of concordance for the presence or absence of most histologic features and discordance usually differed by only a single grade (eg, "absent" versus "rare/focal"). The rates of discordance were randomly distributed across all 4 cohorts and therefore did not significantly impact final comparisons. Finally, since the number of lung sections examined was relatively consistent between cohorts, we think sampling bias is unlikely to explain our results.

In summary, our blinded comparison of SARS-CoV-2 infected decedents affirm previous observations of DAD as the primary histologic manifestation of severe lung disease in hospitalized COVID-19 patients and further establish that this is the primary finding in those who die untreated, in non-hospital settings. We also demonstrate that the histomorphologic findings in SARS-CoV-2 infected patients show substantial overlap with patients who have DAD of other causes, suggesting common elements in their pathogenesis.

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Table 1. SARS-CoV-2-positive inpatient cohort characteristics

Case	Age	Sex	Race	BMI	Medical Conditions	Symptoms at Presentation	Ventilator Days	Treatment
1	37	Male	Black	34.2	Asthma, DM2	Fever, cough, SOB, myalgia, HA	6	Steroids, hydroxyquinoline, empiric antibiotics
2	46	Male	Black	46.6	Asthma, DM2	Fever, cough, SOB, myalgia, HA	8	Hydroxyquinoline, empiric antibiotics
3	79	Female	White	18.5	DM2, renal transplant, bipolar disorder	Fever, cough, myalgia, diarrhea	0*	Tocilizumab, empiric antimicrobials
4	63	Female	Black	28.2	DM2, HTN, CAD	Cough, fever	16	Sarilumab trial†

*Patient had "do not intubate" orders.

†Patient was enrolled in a phase II/III randomized, double-blind, placebo-controlled study assessing efficacy and safety of sarilumab in hospitalized patients with COVID-19. It is unknown whether the patient received sarilumab or placebo.

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; BMI, body mass index; DM2, type II diabetes; HTN, hypertension; CAD, coronary artery disease; SOB, shortness of breath; HA, headache

Table 2. SARS-CoV-2-positive community cohort characteristics

Case	Age	Sex	Race	BMI	Medical Conditions	Pre-mortem Symptoms	Indication(s) for Postmortem SARS-CoV-2 Testing
5	49	Female	Black	33.7	CVD	Myalgia, cough, SOB, nausea/vomiting	Symptomatic, sick contacts, healthcare worker
6	44	Male	Black	48.5	None	Fever, SOB	Symptomatic
7	55	Male	Black	34.9	CVD, DM2, chronic renal failure on HD	None	Sick contacts, prisoner
8	67	Male	Black	21.7	Drug abuse disorder	Unknown	Unknown symptoms, contacts, and travel history

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; BMI, body mass index; CVD, cardiovascular disease; DM2, type II diabetes; HD, hemodialysis

Table 3. Comparison of SARS-CoV-2-positive inpatient and community cohorts

	SARS-CoV-2-positive inpatient cohort (*n* = 4)	**SARS-CoV-2-positive community cohort (*n* = 4)**
Age range (average) years	44-67 (55.5)	37-79 (56.3)
Age < 65 years	3	3
Age ≥ 65 years	1	1
Male : Female	3 : 1	2 : 2
Black : White	4 : 0	3 : 1
BMI range (average)	21.7-48.5 (34.7)	18.5-46.6 (31.9)
	No. (%)	
Presenting/Pre-mortem Symptoms:		
Fever	4 (100)	1 (25)
Cough	4 (100)	1 (25)
Myalgia	3 (75)	1 (25)
Dyspnea	2 (50)	2 (50)
Headache	2 (50)	0 (0)
GI complaints	1 (25)	1 (25)
None/Unknown	0 (0)	2 (25)
Medical conditions:		
Diabetes	4 (100)	1 (25)
Chronic lung disease	2 (50)	0 (0)
Cardiovascular disease	1 (25)	2 (25)

Immunocompromised condition	1 (25)	0 (0)
Chronic renal disease	0 (0)	1 (25)

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; BMI, body mass index

Table 4. Pathologic Findings

Case	Gross lung weights (grams)†	Histologic diagnosis(es)	Scoring of Histologic Features* Mean (Range)								Underlying chronic changes
			Hyaline Membranes	Fibrin Thrombi	Airspace organization	"AFOP-like" fibrin	Acute bronchopneumonia	Perivascular inflammation / endothelialitis	Fibrinoid vessel wall necrosis	Hemorrhage *and/or* capillaritis	
SARS-CoV-2-positive inpatient cohort											
1	R: 1520; L: 1330	DAD	2 (2)	1.7 (1-3)	0 (0)	1 (1)	1.3 (1-2)	0 (0)	0 (0)	0 (0)	
2	R: 1300; L: 1100	DAD	1 (1)	2 (2)	0.7 (0-1)	1.7 (1-2)	1 (0-2)	0.3 (0-1)	0 (0)	0 (0)	
3	R: 750; L: 700	DAD‡	3 (3)	1 (0-2)	1.3 (1-2)	0.7 (0-1)	1 (0-2)	0 (0)	0 (0)	0 (0)	Diffuse alveolar septal amyloidosis
4	R: 840; L: 640	DAD	1.7 (1-2)	0.3 (0-1)	1 (0-2)	1 (1)	0 (0)	0.7 (0-1)	0 (0)	0 (0)	
SARS-CoV-2-positive community cohort											
5	R: 800; L: 700	DAD	3 (3)	1 (1)	0 (0)	0.7 (0-1)	0 (0)	0.3 (0-1)	0 (0)	0 (0)	
6	R: 750; L: 775	DAD	2 (2)	0.7 (0-1)	0 (0)	1 (1)	0.3 (0-1)	1 (1)	0 (0)	0 (0)	
7	R: 450; L: 450	Focal fibrinous pneumonia‡	0.3 (0-1)	1 (1)	0 (0)	1 (1)	0 (0)	0.3 (0-1)	0 (0)	0 (0)	Metastatic calcifications
8	R: 1400; L: 1100	DAD	3 (3)	0 (0)	0 (0)	0.3 (0-1)	1 (1)	0.3 (0-1)	0 (0)	0 (0)	

Control inpatient cohort											
9	R: 980; L: 840	DAD	2 (2)	1.3 (1-2)	0 (0)	0.3 (0-1)	0 (0)	0 (0)	0 (0)	0 (0)	
10	R: 750; L: 750	DAD	2.3 (2-3)	0.3 (0-1)	1.3 (1-3)	1.7 (1-2)	0 (0)	0.3 (0-1)	0 (0)	0 (0)	
11	R: 970; L: 750	DAD	2 (2)	1 (1)	0 (0)	2 (2)	1.7 (1-3)	0 (0)	0 (0)	0 (0)	Bronchiectasis
12	R: 860; L: 510	DAD	1.7 (1-2)	0 (0)	0 (0)	2.7 (2-3)	1 (0-2)	0 (0)	0 (0)	0 (0)	Metastatic spindle cell neoplasm
Control community cohort											
13	R: 620; L: 420	DAD	2.3 (2-3)	0.3 (0-1)	1 (0-3)	0.7 (0-1)	1 (1)	0 (0)	0 (0)	0 (0)	
14	R: 1150; L: 1280	Acute necrotizing BP *and* DAD	1.7 (1-2)	1.3 (1-2)	0 (0)	1.3 (1-2)	3 (3)	0 (0)	0.7 (0-2)	0 (0)	
15	R: 1150; L: 920	Acute BP *and* DAD‡	1.3 (0-2)	3 (3)	0 (0)	1.3 (1-2)	3 (3)	0 (0)	0 (0)	0 (0)	IV drug abuser's lung
16	R: 1600; L: 1350	DAD	2 (2)	0 (0)	2.3 (2-3)	2 (2)	0.3 (0-1)	0 (0)	0 (0)	0 (0)	

*Scoring scale: 0 = absent; 1 = rare/focal; 2 = patchy; 3 = diffuse

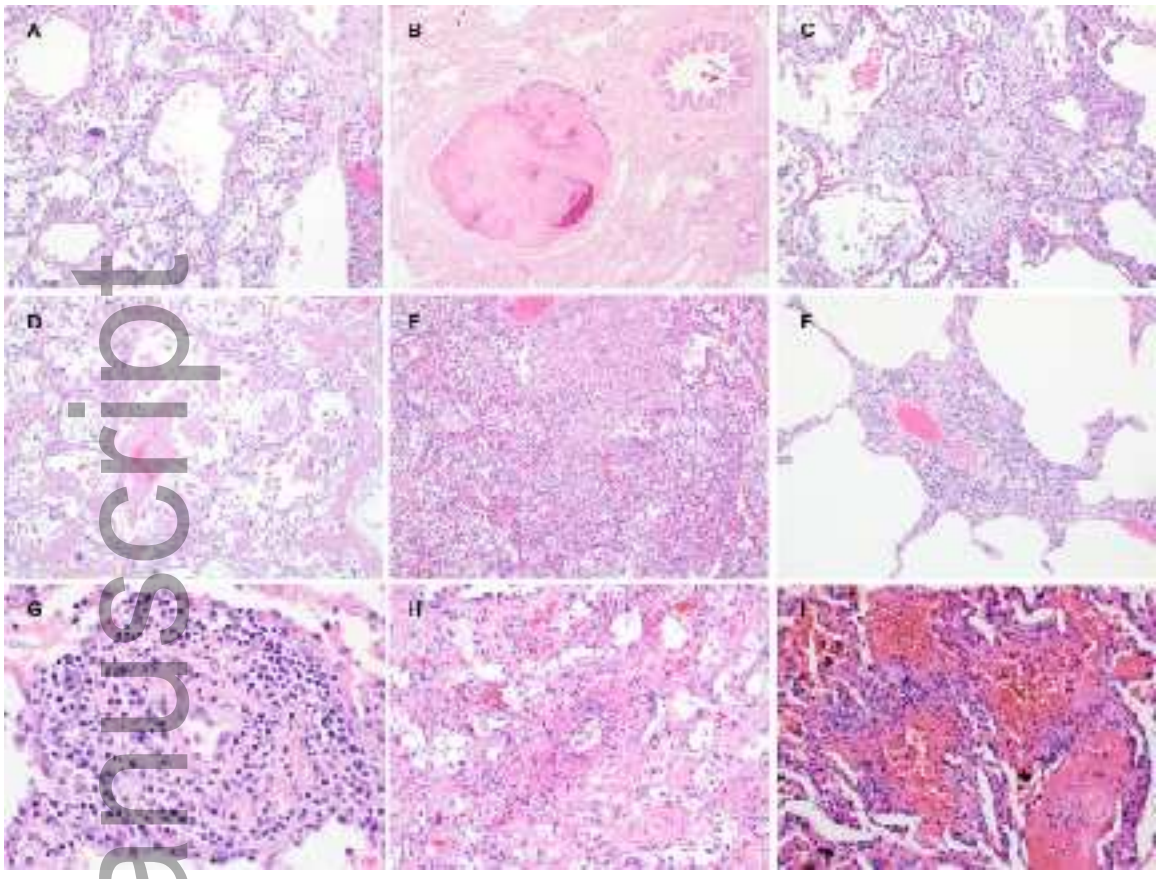
†Normal average adult lung weights: right (R) = 300-350 grams; left (L) = 250-300 grams

‡ Most common histologic diagnosis listed, but no consensus diagnosis

AFOP, acute fibrinous and organizing pneumonia; DAD, diffuse alveolar damage; BP, bronchopneumonia

Figure Legend

Figure 1 Standard reference image bank. **A**, Hyaline membranes. **B**, Fibrin thrombus. **C**, Airspace organization. **D**, "Acute fibrinous and organizing pneumonia"-like intra-alveolar fibrin. **E**, Acute bronchopneumonia. **F**, Perivascular inflammation. **G**, Endothelialitis. **H**, Fibrinoid vessel wall necrosis. **I**, Hemorrhage and capillaritis.



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