Original Article

The Pathology of Severe COVID-19-Related Lung Damage

Mechanistic and Therapeutic Implications

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Summary

Background: The histomorphological changes of lung damage in severe coronavirus disease 2019 (COVID-19) have not yet been adequately characterized. In this article, we describe the sequence of pathological changes in COVID-19 and discuss the implications for approaches to treatment.

Methods: Standardized autopsies were performed on thirteen patients who had died of COVID-19. The findings were analyzed together with clinical data from the patients' medical records.

Results: Most (77%) of the deceased patients were men. Their median age at death was 78 years (range, 41–90). Most of them had major pre-existing chronic diseases, most commonly arterial hypertension. The autopsies revealed characteristic COVID-19-induced pathological changes in the lungs, which were regarded as the cause of death in most patients. The main histological finding was sequential alveolar damage, apparently due in large measure to focal capillary microthrombus formation. Alveolar damage leads to the death of the patient either directly or by the induction of pulmonary parenchymal fibrosis. Diffuse lung damage was seen exclusively in invasively ventilated patients.

Conclusion: Autopsies are crucial for the systematic assessment of new diseases such as COVID-19: they provide a basis for further investigations of disease mechanisms and for the devising of potentially effective modes of treatment. The autopsy findings suggest that focal damage of the microvascular pulmonary circulation is a main mechanism of lethal lung disease due to the SARS-CoV-2 virus. It may also be a cause of persistent lung damage in patients who recover from severe COVID-19.

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Coronaviruses are encapsulated, single-stranded RNA viruses that generally cause mild, cold-like illnesses in human beings (1). They can, however, cause life-threatening diseases such as severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS) (2, 3). Since late 2019, a new virus of this family, SARS-coronavirus-2 (SARS-CoV-2), has caused a global pandemic (4). Persons infected with SARS-CoV-2 can become symptomatic with coronavirus disease 2019 (COVID-19), which usually presents at first with non-specific symptoms such as fever, myalgia, and fatigue. Loss of the sense of taste is a not uncommon accompaniment (5). While most persons infected with the virus (about 80%) have only mild symptoms or none, some develop a clinically relevant disease necessitating hospitalization and, in some patients with respiratory failure, mechanical ventilation. This type of course is associated with high mortality, which, however, displays a wide geographic variation (6). Factors that promote a severe disease course include the following (7, 8):

- advanced age
- male sex
- pre-existing chronic lung disease
- pre-existing chronic heart disease
- obesity
- diabetes mellitus

With no effective vaccine yet available, deciphering the pathophysiology of COVID-19 now has the highest priority so that effective treatments can be developed. In particular, the sequence of pathophysiological processes leading to lethal outcomes of COVID-19 is still inadequately characterized and

understood. Recently published studies have shown that a SARS-CoV-2 infection, like a SARS or MERS infection, can cause progressive lung damage (9, 10). There is increasing evidence that microvascular damage plays a role in the progression of the disease (11–13).

In this article, we describe the spectrum of histological changes that are demonstrable in lethal cases of SARS-CoV-2 infection. These changes were determined with a standardized autopsy technique adapted to the main questions at hand, and they were analyzed in their clinical context. The resulting insights into the pathogenesis of COVID-19 may be of help in the development of therapeutic strategies.

Materials and methods

Patient cohort

All patients who had a SARS-CoV-2 infection and died at University Hospital Heidelberg from 26 March to 23 May 2020 were documented in the hospital's Institute of Pathology. In all cases, the infection was confirmed before or during hospitalization with a reverse transcriptase polymerase chain reaction (RT-PCR) performed on a nasopharyngeal swab sample. The study was approved in advance by the ethics committee of the University of Heidelberg Faculty of Medicine (no. S-242/2020) and carried out in accordance with the Declaration of Helsinki.

Clinicopathological autopsy

All of the autopsies were performed with a standardized technique. All of the necessary organizational and infrastructural precautionary measures to protect the staff and prevent infection were taken during the external and internal portions of each autopsy. To minimize aerosol and dust formation, the cranium was not opened, and no cerebral autopsy was performed, with the single exception of a female patient with clinically relevant neurological manifestations.

All findings were documented in a standardized fashion, and tissue samples were fixed as rapidly as possible with 4% neutral buffered formalin. At least four cardiac tissue samples and one tissue sample from each of the two kidneys, the spleen, the liver, and the adrenal glands were taken. The lungs, after instillation of 4% neutral buffered formalin in the trachea and the major pulmonary vessels, were fixed for at least three days in a formalin-filled container of adequate size. The photographically documented processing of the lungs was carried out in axial sections (slice thickness, 1 cm). Three representative tissue samples were taken from each pulmonary lobe for histological processing. In addition, samples of fresh tissue were snap-frozen in liquid nitrogen and sent to the tissue bank of the German Center for Infection Research (*Deutsches Zentrum für Infektionsforschung,* DZIF).

Histology

After paraffin embedding, histopathological sections of all samples were prepared and stained according to

TABLE 1

Pulmonary pathological findings in the autopsies of 13 patients who were positive for SARS-CoV-2

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
Duration of disease (days)	12	16	7	6	12	22	23	32	27	34	33	40	32
Mechanical ventilation (days)	none	12	none	none	none	7	8	6	20	15	24	31	22
Lung weight (g, both lungs)	1990	2650	2200	2150	2100	2350	650	2100	2350	2400	840	2240	2100
Demonstration of microthrombi	no	yes	yes	yes	no	no	yes	no	yes	no	no	no	yes
Alveolar edema	diffuse	focal	diffuse	focal	patchy	focal	no	no	no	focal	no	focal	diffuse
Alveolar hemorrhage	no	no	focal	focal	no	focal	focal	focal	patchy	focal	focal	focal	no
Hyaline membranes	patchy	focal	patchy	patchy	patchy	patchy	focal	none	focal	focal	patchy	focal	none
Hyperplasia of type II pneumocytes	none	patchy	focal	marked	focal	focal	patchy	patchy	patchy	patchy	patchy	patchy	focal
Squamous metaplasia	no	focal	no	patchy	focal	no	focal	focal	focal	focal	focal	focal	focal
Polynucleated cells	no	yes	no	no	no	yes	yes	no	yes	yes	yes	no	no
Acute inflammation	none	none	patchy	patchy	none	patchy	none	none	patchy	patchy	no	patchy	patchy
Lymphohistiocytic inflammation*	M	PB	PB	PB, I	I	PB, I	PB, I	PB, I	I	I	PB, I	PB, I	PB, I
Interstitial fibrosis	none	mild/focal	none	mild/focal	mild/focal	none	none	mild/focal	marked	marked	marked	mild/ focal	mild/focal

*classification: M, mild; PB, peribronchial aggregates; I, interstitial aggregates

TABLE 2

Clinicopathological features of the autopsy cohort of 13 patients who were positive for SARS-CoV-2

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
Age	41	78	80	81	90	84	79	82	60	71	76	76	72
Sex	m	m	m	f	f	m	m	m	m	m	f	m	m
Body-mass index	29.0	23.4	23.2	30.0	28.2	26.2	26.3	24.4	27.8	24.3	20.7	27.1	36.5
Nicotine abuse	n. b.	Ø	Ø	n. b.	n. b.	n. b.	Ø	Z. n.	n. b.	Ø	n. b.	n. b.	Z. n.
Comorbidity	FLD	Ø	S/p PCA (2004)	AH, COPD, MetS	AH, DM, MetS, CRF	CHD	AH, DM, CHD, DCMP	AH, COPD, CHD	AH, AS	CHD	AH, DM	AH, DM, CHD	AH, DM, CHD, MetS, CRF
Duration of disease (days)	12	16	7	6	12	22	23	32	27	34	33	40	32
Time to diagnosis (days)	11	0	6	4	2	13	14	1	0	3	0	7	10
Length of hospital stay (days)	2	12	1	3	10	9	9	28	27	30	24	33	19
Pathogens revealed by BAL	Ø	Ps. ae.	Ø	Ø	Ø	Ø	Ø	Ps. ae.	Ø	Ø	Ø	Ø	Ps. ae.
Mechanical ventilation (days)	refused	12	Ø	refused	refused	7	8	6	20	15	24	31	22
Drug treatment	AB	AB, IMT, FH	Ø	AB, IMT	AB, IMT	AB, IMT, FH	AB, IMT, FH	AB, IMT, PA	AB, IMT, PA, TNFi	AB, AV, IMT, FH	AB, IMT, FH	AB, AV, IMT, VH	AB, AV, IMT, VH
D-dimers (< 0.5 mg/l)	n.a.	>35	n.a.	>35	6.03	> 35	> 35	1.17	15.3	19.9	5.07	21.6	3.41
Cause of death	CPF	PF	CPF	CPF	CPF	PF	PF	IB	PF	PF	PF	CPF	PF

AB, antibiotics (piperacillin/tazobactam/caspofungin); AH, arterial hypertension; AS, ankylosing spondylitis (Bekhterev's disease); AV, antiviral therapy (aciclovir); BAL, bronchioalveolar lavage; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CPF, cardiopulmonary failure; CRF, chronic renal failure; DCMP, dilated cardiomyopathy; DM, type 2 diabetes mellitus; f, female; FH, full heparinization (1 000 IU heparin/h); FLD, fatty liver disease; IB, intestinal bleed; IMT, immune-modulating treatment (hydroxychloroquine/maraviroc); MetS, metabolic syndrome; m, male; n. a., data not available; PA , prophylactic anticoagulation (enoxaparin 40 mg b.i.d.); PCA , prostatic carcinoma; PF, pulmonary failure; Ps. ae., Pseudomonas aeruginosa; S/p, status post; TNFi,anti-tumor necrosis factor α antibodies (golimumab).

-standard protocols, with hematoxylin and eosin (H&E) staining of all samples, and additional staining of lung and kidney samples with the periodic acid Schiff (PAS) reaction and acid fuchsin orange G (AFOG).

Liver and lung samples were stained for iron, and the liver tissue was also stained with PAS with diastase, as well as with a modified Gomori stain.

Each of the histological sections was viewed under the microscope and assessed by at least four pathologists (FKFK, CS, LT, DJ, TL, PS). Histological changes in lung tissue were evaluated in standardized fashion with the aid of a modified scoring system for the grading of lung damage *(Table 1)* (14).

Results

Cohorts

During the peak of the pandemic COVID-19 wave in Germany, 17 SARS-CoV-2-positive patients died at University Hospital Heidelberg *(eTable)*. A clinicopathological autopsy was performed on 13 of them (76%), including 3 women and 10 men, with a median age of 78 years (mean, 74.6; range, 41–90) and a mean body-mass index of 26.7 kg/m² (range, 20.7–30.0 kg/m²).

All patients were admitted to the hospital because of suspected SARS-CoV-2 infection. The mean duration of hospitalization was 15.9 days (range, 1–33), and the mean interval from symptom onset to death was 21.9 days (range, 6–40).

Bronchoalveolar lavage revealed bacterial (super-)infection with Pseudomonas aeruginosa in three patients. Nine patients were invasively ventilated for a mean duration of 16.1 days (range, 6–31 days). The remaining four patients were treated with non-invasive oxygen administration as needed. Three of the patients who died had refused clinically indicated intubation and invasive ventilation and were treated palliatively. Nine of the patients who died received prophylactic or therapeutic anticoagulation.

Ten of the patients who died had known, clinically relevant pre-existing diseases. The most common of these was arterial hypertension (n = 8), and the others were as follows:

- coronary heart disease (n = 6)
- type 2 diabetes mellitus (n = 5)
- metabolic syndrome (n = 3)
- chronic obstructive pulmonary disease (n = 2)
- chronic renal failure (n = 2)
- dilated cardiomyopathy (n = 1).

One of the patients who died was being treated, at the time he became infected, with an anti-tumor necrosis factor α antibody (golimumab 50 mg daily for four weeks), for ankylosing spondylitis (Bekhterev's disease). The clinical features of the patient cohort studied are summarized in *Table 2*.

Clinicopathological autopsy findings

The autopsies revealed a characteristic pattern of histological changes in the lungs; the pulmonary changes were considered the cause of death, or at least the main cause of death, in twelve patients. When alveolar capillary microthromboses were found along with evidence of right heart failure, a cardiopulmonary cause of death was postulated, i.e., the combined effect of lung damage and acute right heart failure *(Table 2)*.

One patient died independently of COVID-19 three days after being weaned off invasive ventilation, immediately before his planned discharge from the hospital, because of an acute lower intestinal bleed due to diverticulitis. He had refused any further treatment.

Pulmonary parenchymal consolidation was found to a variable degree in all of the patients who died. Histological examination revealed patchy alveolar damage associated with microthrombosis of alveolar capillaries (n=7) and intra-alveolar hemorrhages (n = 9). Patients who died within the first two weeks of the onset of disease, even if they had not been invasively ventilated, displayed patchy microvascular damage with edema and the formation of alveolar hyaline membranes *(Figure 1)*. Patients who died at a later phase of the disease displayed hyperplasia and squamous epithelial metaplasia of the pneumocytes. There were also rare polynucleated cells within the alveoli, as well as more pronounced interstitial infiltration, predominantly lymphocytic *(Figure 2)*.

In patients who had been ill for longer times before they died, there were prominent inflammatory infiltrates and interstitial collagen-fiber deposits *(Figure 3)*. In patients who had undergone invasive ventilation, the hyperplastic and metaplastic changes of the pneumocytes and the interstitial fibrosis were more pronounced and, in some cases, diffuse. The pulmonary pathological changes in the lungs are listed in detail in *Table 1*.

None of the patients whose autopsies we performed had a deep venous thrombosis of the leg or macroscopically evident thromboembolism of the pulmonary arteries. Inflammatory changes or microthrombi were not seen in any other organ; thus, no morphologically discernible extrapulmonary changes were documented that could be specifically attributed to COVID-19.

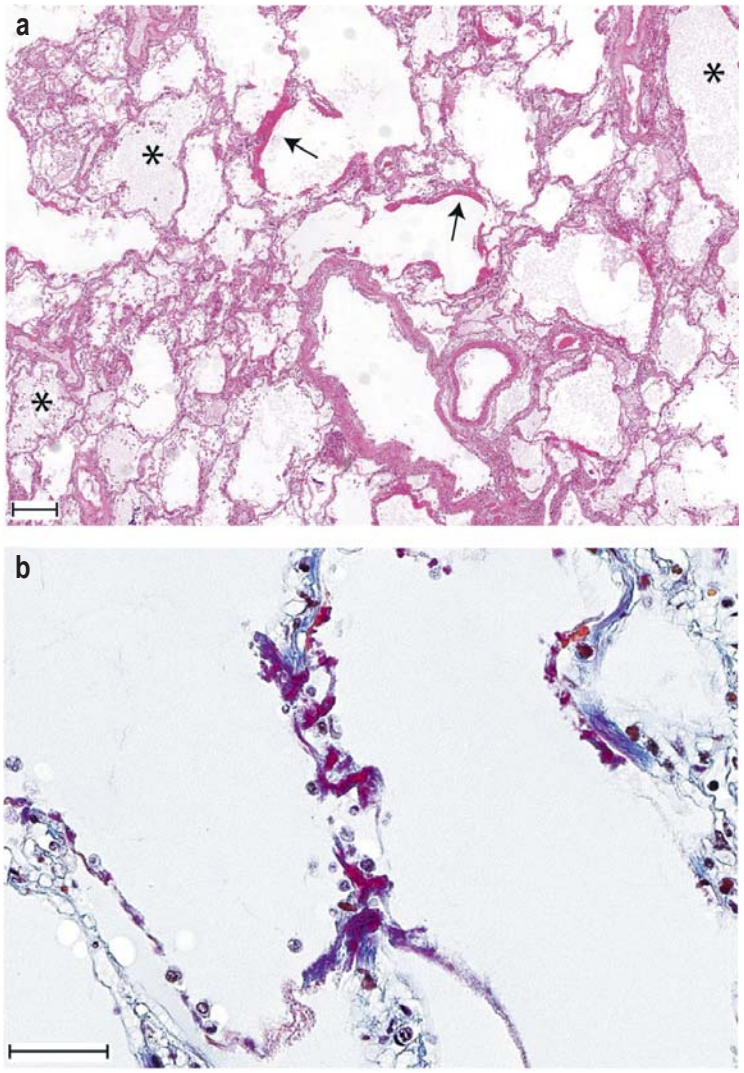

Figure 1: Patient 3 (duration of illness, 7 days; no invasive ventilation):
a) patchy edema (*) and focal formation of alveolar hyaline membranes (arrows); (hematoxylin and eosin stain [H&E], the bar corresponds to 200 µm).
b) alveolar septum with fibrinoid microthrombus (stained with acid fuchsin orange G [AFOG], the bar corresponds to 50 µm)

Discussion

We report the autopsy findings in 13 patients who died as a result of COVID-19. The features of our patient cohort resembled those of the cohorts in other reported case series, as well as the demographic features of patients with severe COVID-19 disease in Germany. One may, therefore, presume that the clinical and pathological findings presented here, despite the low case numbers and the monocentric study design, do indeed accurately reflect the spectrum of COVID-19 manifestations (9, 15, 16).

While twelve of the patients whom we studied died of pulmonary or cardiopulmonary failure directly attributable to COVID-19, one patient had already made a good recovery from a severe clinical course of COVID-19 disease and then died, just before his planned discharge, of a lower gastrointestinal bleed. This may indicate that a small number of symptomatic SARS-CoV-2-positive patients die of causes other than COVID-19 itself.

This study did not reveal any COVID-19-specific changes in any organ besides the lungs. Any possible COVID-19-specific changes in the central nervous

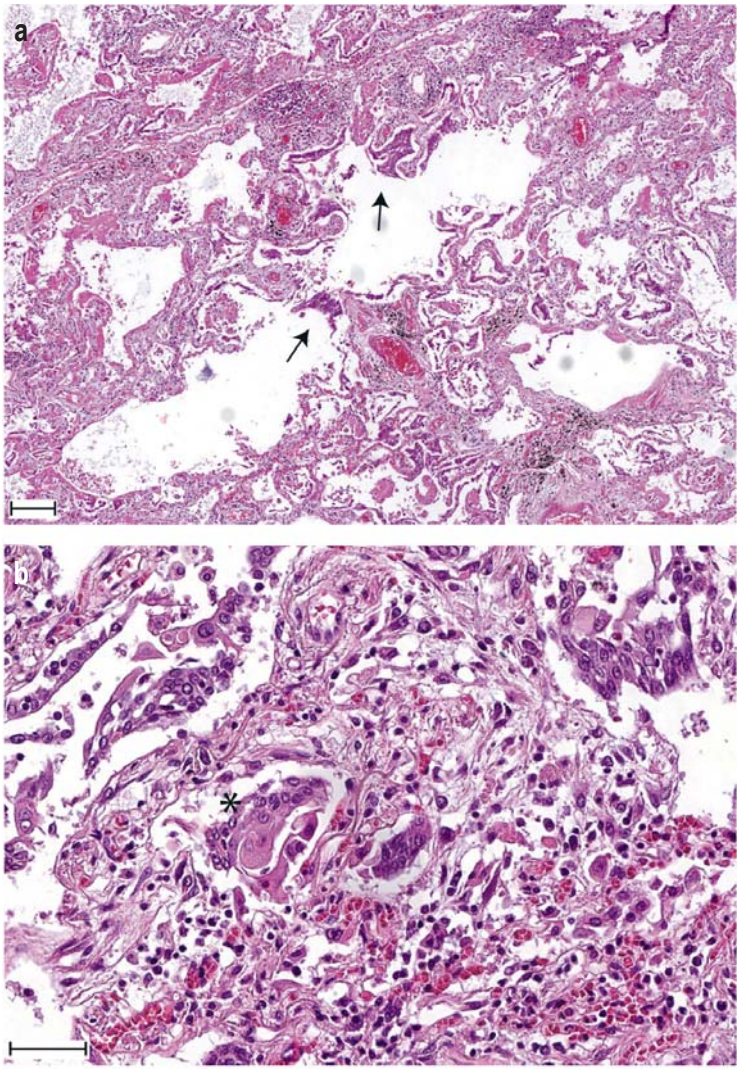

Figure 2: Patient 4 (duration of illness, 6 days; no invasive ventilation):
a) patchy alveolar damage with focally prominent interstitial lymphocytic infiltrates and squamous metaplasia of type II pneumocytes (arrows); (hematoxylin and eosin stain [H&E], the bar corresponds to 200 µm).
b) dystelectatic alveolus with polynucleated cells (*); (hematoxylin and eosin stain [H&E], the bar corresponds to 50 µm).

system could not have been detected, as the relevant tissues were not examined. This study, unlike another recently published study (17), did not reveal any deep venous thromboses of the legs or any macroscopically evident thromboemboli of the pulmonary arteries. It is important to mention in this context that most (n = 9) of the patients in our cohort had been treated with anticoagulant drugs in therapeutic doses.

Severe and potentially life-threatening pre-existing diseases are not a prerequisite for a lethal course of COVID-19, even though most of the patients we studied did, in fact, have them. In addition to the risk factors confirmed in our study, such as advanced age and male sex, it seems conceivable that further factors, e.g., genetic or immunological factors, can predispose to a lethal course of COVID-19 disease.

The histological findings enabled us to determine a specific sequence of severe pathological changes in the lungs in COVID-19. Our standardized sampling and pathomorphological study of pulmonary tissue revealed that early changes in the lung parenchyma manifest themselves in a patchy pattern; this is well correlated with the ante mortem imaging findings (18). These changes consist of microthromboses of alveolar capillaries with associated focal fibrin exudation into the alveoli, developing apparently as the result of microvascular damage. Next, hyaline membranes form in pneumatized alveoli, along with prominent hyperplasia and squamous metaplasia of type II pneumocytes. As the disease progresses, the damage becomes more diffuse and undergoes a transition, within two weeks, to a progressive fibrotic change in the alveolar septa. In this stage, there are pulmonary regions that display acute alveolar damage, hyperplasia, and squamous metaplasia of type II pneumocytes alongside regions with fresh collagen deposits.

These findings suggest that the microvascular pulmonary circulation is damaged early in the course of patients with severe COVID-19 disease, and that this is an important pathophysiological mechanism in the progression to clinically severe disease. The demonstration of coronavirus particles in endothelial cells with associated endotheliitis lends further support to this hypothesis (12). The question remains open, however, whether this microvascular abnormality is a consequence of endothelial-cell damage, of increased thrombogenicity and COVID-19-associated coagulopathy, or both of these factors acting in synergy. In some of the patients that we studied, a predisposition to microvascular endothelial damage in the pulmonary circulation owing to pre-existing disease could not be ruled out: e.g., patient 7 had pre-existing lung damage due to dilated cardiomyopathy, while patients 4 and 8 had chronic obstructive pulmonary disease.

The damage to the pulmonary microcirculation that has been revealed in this study provides a pathophysiological explanation for the reported clinical finding of a low oxygen saturation of the blood early on in the course of the disease, at a time when the lungs still have nearly normal compliance (19). The rigorous administration of drugs to prevent thrombosis therefore seems reasonable, and it may be beneficial even in the early stage of the disease; as seen in our patient cohort, however, anticoagulation cannot reliably prevent microthrombosis. This being the case, one may ask whether further fibrinolytic therapy should be considered in order to prevent progressive lung damage, particularly in patients with increasing D-dimer levels. According to a press release relating to the RECOVERY trial (NCT04381936), low-dose dexamethasone appears to reduce the mortality of severe COVID-19 (20). This may be due to an effect of dexamethasone on blood vessels (21).

Some of the pulmonary changes associated with COVID-19 that were found in our patient cohort, including fibrin exudates, hyaline membranes, and hyperplasia of type II pneumocytes, are also found in patients with other types of virally induced lung damage (e.g., influenza, SARS, MERS) (9, 10). According to our data and other reported studies, alveolar capillary microthromboses are seen much more commonly in COVID-19 than in other viral lung infections (12, 13).

Patients who had been treated with invasive mechanical ventilation had much more severe parenchymal damage. Ventilation for more than ten days was associated with patchy hyperplasia and at least focal squamous metaplasia of type II pneumocytes. Six of these patients also displayed interstitial and alveolar fibrosis, which was more than merely focal in three of the six. The severe lung damage with organizing pathological changes that was seen in these patients might reflect the severity and duration of the disease per se, or, alternatively, it might in fact be due to prolonged invasive ventilation (at times involving high ventilatory pressure, with a high partial pressure of oxygen). This question can only be answered in further studies with adequate control groups. The same holds for the proper roleof extracorporeal membrane oxygenation in the treatment of COVID-19, and for the question whether pulmonary fibrosis in survivors of severe COVID-19 might lead to a persistent, marked impairment of pulmonary function.

Overview

The autopsy findings document a sequence of processes that damage the lungs in patients with lethal COVID-19 disease, with pulmonary microvascular thromboses playing a central role. They have implications for therapeutic approaches that may help to lessen the percentage of patients with COVID-19 who experience a severe clinical course; they also provide a basis for further studies of the pathophysiologic mechanisms that underlie this disease.

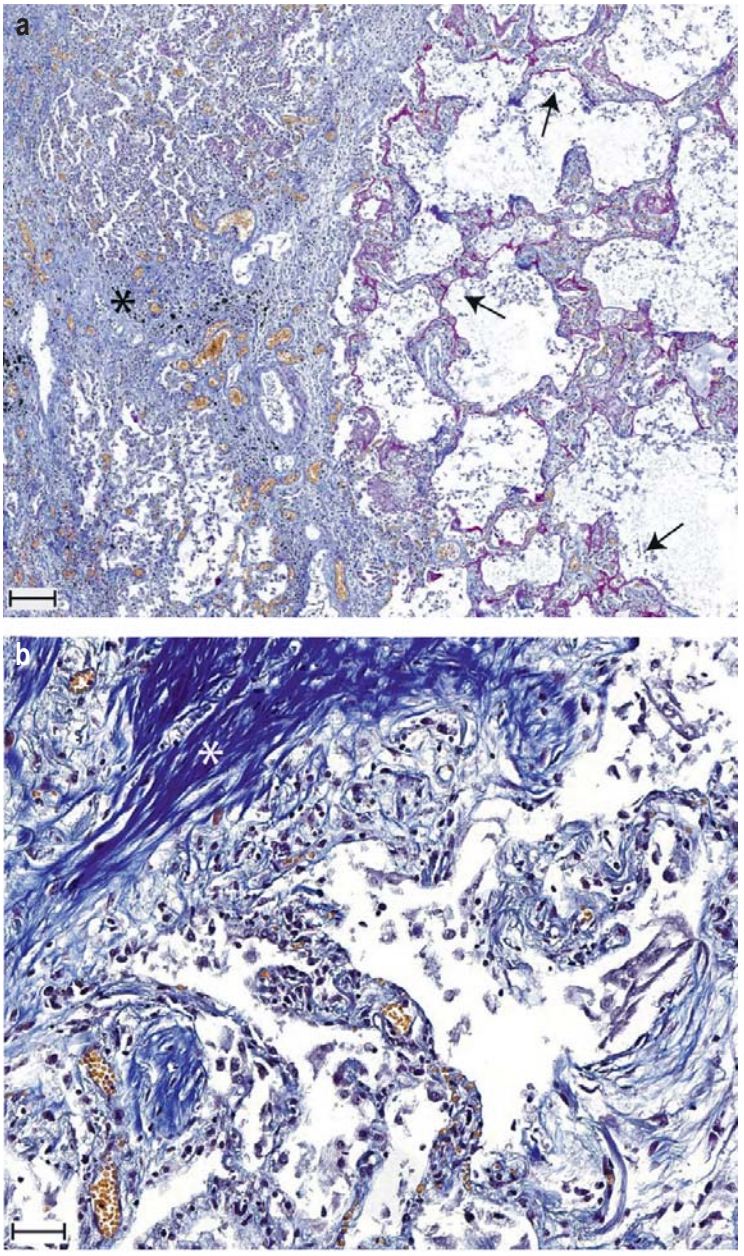

Figure 3: Patient 10 (duration of illness, 34 days; 15 days of invasive ventilation):
a) Acute damage with hyaline membranes (arrows) and adjacent fibrotic transformation (*); (stained with acid fuchsin orange G [AFOG], the bar corresponds to 200 µm).
b) Alveolar septa mainly widened by loose connective tissue; focally (*), there is fibrosis rich in collagen fibers, with few cells (stained with acid fuchsin orange G [AFOG], the bar corresponds to 50 µm).

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Conflict of interest statement
The authors state that they have no conflict of interest.

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Key messages

- Autopsies are of central importance for the systematic assessment of new diseases such as COVID-19 and provide a basis for further studies of pathophysiological mechanisms.
- The pulmonary changes revealed by autopsies of patients who died of severe COVID-19 display a characteristic sequence and distribution of damage.
- Alveolar capillary microthrombi are found in all phases of the course of severe COVID-19.
- The overall histomorphological appearance of lung damage indicates that alveolar capillary damage plays a major role in the progression of disease and contributes to the development of acute respiratory distress syndrome (ARDS).
- The histological changes that have been found in the lungs of patients with COVID-19 explain the clinical finding of an oxygenation disturbance arising early in the course of the disease while the compliance of the lung parenchyma is still normal.

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► **Supplementary material**

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eTABLE

Characteristics of all SARS-CoV-2-positive patients documented at University Hospital Heidelberg* from 26 March to 23 May 2020 (n = 17).

Patient	Age	Sex	Autopsy
1	41	m	yes
2	78	m	yes
3	80	m	yes
4	81	f	yes
5	90	f	yes
6	84	m	yes
7	79	m	yes
8	82	m	yes
9	60	m	yes
10	71	m	yes
11	76	f	yes
12	76	m	yes
13	72	m	yes
14	87	m	no
15	66	m	no
16	84	m	no
17	84	m	no

(* i.e., in the autopsy room of the Institute of Pathology); m, male; f, female.