CT as a Tool to Depict Pulmonary Fibrosis in Patients With COVID-19: a Radiopathological Correlation

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Abstract

OBJECTIVES

CT findings of COVID-19 infected patients has been well described, but it it's roll in depicting signs of fibrosis in critically ill patients remains unclear. To our knowledge, there are no radiopathological correlations of the pulmonary pathology. Exudative and proliferative diffuse alveolar damage (DAD) are the most commonly reported injury. Few studies describe fibrosis, the last phase of DAD.

Our study correlates post-mortem chest US and CT findings of COVID-19 infected patients with the histopathology from biopsies taken of the lung. It focuses on the role of CT to depict fibrosis.

METHODS

This is a prospective observational study of six consecutive deceased patients infected with COVID-19. Post-mortem chest CTs and US were performed within 24 hours of death. CT and US were used to obtain biopsies of different radiological patterns. Pre-mortem CT examinations were also retrospectively evaluated.

RESULTS

On CT, all patients presented with extensive areas of consolidation and ground-glass opacities affecting most segments of the lung. Pleural effusion was present in all cases. Four of the patients showed signs of fibrosis. On US, subpleural consolidation, pleural thickening, and B-pattern were present.

All patients showed different stages of DAD, mostly proliferative DAD. Four patients presented with fibrotic DAD, all of which had been admitted for over three weeks and correlated with the CT findings of fibrosis.

CONCLUSION

In our study, signs of fibrosis on CT show a histopathological correlation. CT may be useful to identify the group of COVID-infected patients that develop fibrosis as a marker of poor prognosis, in the late stage of the disease.

Introduction

Despite an increasing number of studies describing the radiological findings of COVID-19, there is a lack of post-mortem studies crucial in understanding the pathological changes that occur during the disease. Autopsies of COVID-19 infected patients have not been performed systematically worldwide [1].

Most patients infected with COVID-19 present with respiratory symptoms. Up to 20% of the patients develop severe disease. Some of these will develop an acute respiratory distress syndrome (ARDS) with high mortality rates[2]. CT findings have been described in recent publications[3–7]. Ground-glass opacities

(GGO) with or without consolidation with a peripheral, posterior and lower distribution are commonly seen[3]. These findings are specific in grading the severity of the disease. GGO appear between 0 and 4 days after symptom onset. Areas of GGO become coalescent, and other patterns, including consolidations appear and peak at 6-13 days[8]. Signs of fibrosis has been described at the end-stage of the disease or as a sequalae[9,5].

The use of US of the lung of COVID-19 infected patients has been reported, but its role in the assessment of the disease needs to be fully established. US features include pleural thickening, consolidation, and B-pattern, in a variety of patterns including focal, multifocal, and confluent.[10].

Small series of autopsies report diffuse alveolar damage (DAD) as the fundamental injury in the lung[11–17]. Lung fibrosis is an uncommon feature in these studies, but it has been described as a progression of the disease that can worsen the prognosis[9]. Lung damage in DAD occurs in three phases. The exudative phase, in which hyaline membranes predominate lasts 7 days. The next phase is the proliferative phase, characterized by a thickening of the alveolar septa with proliferation of myofibroblasts and a duration of two weeks. Week three is characterized by the fibrotic phase. Fibroblast activation and collagen formation lead to thickening of the alveolar septa [20,21]

To our knowledge, nothing has been reported on the radiological appearance of post-mortem US or CT. Moreover, there are no studies correlating these radiological findings with tissue samples of the infected lungs.[2]

This study reports the CT and US findings of deceased patients infected with COVID-19. It correlates these findings with pathology samples obtained with US and CT-guided biopsies of different areas of the lung. We hypothesize that CT correlates with pathology findings of pulmonary fibrosis, and therefore could be a tool to depict fibrosis in critically ill patients.

Methods

This is a prospective observational study of six consecutive deceased patients infected with COVID-19 (range 64-100 years, mean age 73.1), who had died as a result of an ARDS. All cases tested positive for COVID-19 by nasopharyngeal swab at time of admission. Patients were recruited from April to June of 2020. The study was approved by the Ethical Committee of the hospital. Oral informed consent was obtained from the relatives in all cases.

Radiological examinations

Post-mortem examinations and biopsies were performed within 24 hours of the death of the patient.

- POST-MORTEM US: US examinations (Esaote^{TM} Mylab70 Vision, Milano It) were performed in the CT room by a single senior radiologist. Patients were examined only in the supine position, so mostly anterior segments of the lung were imaged. We evaluated the following signs and patterns in both

lungs: Normal ventilated lung, B-lines, consolidations, pleural effusion, and nodular pleural thickening.

- POST-MORTEM CT: CTs (OptimaCT660 GE Healthcare, Inc. Boston MA USA) were also performed before the biopsies. We evaluated the presence of: GGO, consolidation, pleural effusion, enlarged lymph nodes, halo and inverted halo sign, crazy paving pattern), consolidation with an organizing cryptogenetic pneumonia pattern, septal thickening, bronchial wall thickening, and pericardial effusion. We defined honey-comb pattern, microcystic pattern, and traction bronchiectasis as signs of fibrosis. All axial and reconstructed CT images were reviewed by two experienced radiologists independently.
- PRE-MORTEM CT: The existing premortem CT examinations performed during admission to rule out pulmonary embolism were compared to the post-mortem examinations.

Post-mortem biopsies

Both CT and US were used to identify areas to be biopsied. 16G needles (Bard ® Magnum Reusable Core System, Arizona USA) were used for all CT guided biopsies. Overall, 15 tissue samples were taken. These included areas of consolidation, of GGO and of parenchymal distortion (honeycomb pattern, microcystic pattern, traction bronchiectasis). We also performed US guided biopsies from aerated lung with B-lines and areas of consolidation. Tissues were fixed in 10% buffered formalin for at least 24 h. They were embedded in paraffin to obtain sections of 3-µm in thickness stained with hematoxylin and eosin (H&E). Immunohistochemical staining was done in selected cases for detection of TTF1 (8G7G2/1), Muscle SpecificActin (HHF35) and CD-68 (KP-1). All antibodies were ready-to-use monoclonal antibodies (Ventana, Roche Diagnostics, Basel, Switzerland). Samples were stained with the BenchMark Ultra IHC/ISH System (Roche, Basel, Switzerland) in accordance with the standard protocols supplied by the manufacturer. Masson trichome staining was applied to characterize collagen deposition and fibrosis. All samples were reviewed by the senior pathologist of the hospital.

Results

The patients were admitted to the hospital between 3 and 10 days after the onset of symptoms. The hospital stays ranged from 9 to 52 days (mean 33,8 days). Five of the patients required mechanical ventilation requiring in the intensive care unit (ICU). Stays ranged from 23 to 45 days (mean of 35.2 days). One patient did not meat criteria for ventilation and admission to the intensive care unit based on age and comorbidities. On average patients died 40.3 days after onset of symptoms, with a range of 19-59 days. All patients died as a result of an ARDS. Table 1 shows the clinical data obtained during the admission.

	NUMBER (if applicable)	PERCENTAGE OR RANGE
AGE (years, range)	65-100	
SEX (men to women ratio)	5:1	
COMORBIDITIES		
High blood pressure	3	50%
Chronic obstructive pulmonary disease	1	16%
Dyslipidemia	2	33,3%
Atrial fibrillation	2	33,3%
Chronic lymphocytic leukemia	1	16%
ANTICOAGULATION during admission	4	66,6%
STEROIDS administered during admission	5	83,3%
Days from onset of symptoms to admission		3-10
Days from admission to death		9-52
Patients in intensive care unit (mechanical ventilation)	5	83%

Table 1 shows the characteristics of the patients included in the study.

Radiological findings

- **Post-mortem US**: Areas of nodular pleural thickening and extensive areas of subpleural consolidation were the most common finding. B-pattern was present in the areas that remained aerated, mostly in the antero-superior segments of the lobes. Two patients showed small areas of normally aerated lung with no pathologic findings. Pleural effusion was depicted in only one patient.
- **Post-mortem CT**: At least 80% of the lung was affected by pathologic changes, including: extensive and bilateral areas of consolidation, GGO with or without crazy paving and bilateral pleural effusion. In all cases, only the anterior and mostly apical segment of the lung remained partially aerated. All patients showed partial collapse of the inferior lower lobes. In 4 patients additional partial collapse of the middle and upper lobes was observed. Signs of fibrosis were seen in 4 cases including: Traction bronchiectasis, honey-comb pattern, and a microcystic pattern, initially with a subpleural distribution (seen in examinations during admission) that became multifocal or patchy in the post-mortem CT (figure 1). Enlarged mediastinal lymph nodes were depicted in 2 patients.

RADIOLOGICAL FINDINGS	Number of patients	Percentage
POST-MORTEM US		
Pleural thickening	6	100%
B-pattern	6	100%
Subpleural consolidation (white lung)	6	100%
Pleural effusion	1	16,6%
Normal lung	1	16,6%
POST-MORTEM CT		
FINDINGS		
GGO	6	100%
Consolidation	6	100%
Septal thickening	5	83,3%
Halo/inverted halo sign	0	0%
Crazy paving	3	50%
Organizing cryptogenetic pneumonia pattern	0	0%
Pleural effusion	6	100%
Signs of fibrosis	4	66,6%
Honeycomb pattern	3	50%
Microcystic pattern	4	66,6%
Traction Bronchiectasis	4	66,6%
Bronchial wall thickening	5	83,3%
Enlarged lymph nodes	2	33,3%
Pericardial effusion	0	0%
DISTRIBUTION		
Unilateral	0	0%
Bilateral	6	100%
focal	0	0%
multifocal	0	0%
diffuse	6	100%
Upper lung predominant	0	0%
Lower lung predominant	6	100%
EXTENT of the lesion >80%	6	100%

Table 2 summarizes the US and CT findings present on post-mortem US and CT.

GGO= Ground glass opacity.

Comparing the post-mortem study and the CT during admission, we observed a progression of the areas of consolidation, collapse, and pleural effusion, as shown in figure 2.

Histopathological findings

We studied 15 lung biopsies from different lung regions of 6 patients. All patients showed proliferative DAD in at least one of the lung samples, in combination with fibrotic DAD in four patients, exudative DAD in one patient, and AFOP in three patients. Only one patient presented a proliferative DAD as the only form of DAD. The rest presented combinations of different patterns of DAD or with AFOP. Only two patients showed microthrombosis. Only one of the patients had a superimposed bacterial pneumonia.

	E DAD	P DAD	F DAD	AFOP	THR	BACT INF	ONSET	ICU	HOSP	FIBROSIS ON CT
P 1		x			x		5	33	33	
P 2	x	x		x		x	10		9	
P 3		x	x				8	33		x
P 4		x	x	x	x		3	45	49	x
P 5		x	x				7	42	52	x
P 6		x	x				3	23	30	x

Table 3. Histopathological findings correlated to key clinical and radiological findings. P= Patient E DAD = Exudative DAD, P DAD = Proliferative DAD, F DAD = Fibrous DAD, AFOP = Acute Fibrinous Organizative Pneumonia, THR = Thrombosis, BACT INF = Bacterial Infection, ONSET = Time to admission in the ICU (in days) from the onset of the symptoms. ICU = Intensive Cure Unit Days, HOSP = Total Hospitalization Days to Death.

The proliferative DAD pattern was characterized by marked type 2 pneumocyte hyperplasia, highlighted by a TTF-1 positive stain. It showed reactive features in the nucleus or even multinucleation, and often cytoplasmic vacuolization. Scaling of pneumocytes into the alveolar lumen and intraalveolar macrophages was a common finding. Alveolar septa were very thickened showing histiocytes and many proliferating of myofibroblasts.CD68 and Alfa-Smooth Muscle Actin tested positive in the most severe cases The inflammatory infiltrates in the septa were scarce or focal consisting mainly of lymphocytes. The fibrotic DAD pattern was characterized by a patchy and irregular distribution. It showed fibroblasts and abundant collagen demonstrated by trichrome staining. Exudative DAD was only present in the patient with the lowest hospital stay (9 days). The biopsy showed hyaline membranes filling the alveolar lumens with a scattered distribution which were accompanied by areas of AFOP and proliferative DAD. The areas of AFOP were characterized by the presence of intraalveolar fibrin and macrophages.

The radiological features and the pathological correlation are shown in table 4.

	E DAD	P DAD	F DAD	AFOP
CONSOLIDATION (US or CT)	1	6		1
GGO on CT/B-lines on US	1	3		1
FIBROSIS on CT			4	

Discussion

The severity of the disease caused by COVID-19 correlates well with the radiological presentations[3]. CT findings have been meticulously described[4]. Initial radiological findings appear to be very specific for COVID-19 in the context of the current pandemic. Very little has been published on the end stage of the disease, as critically ill patients usually do not undergo US or CT examinations unless they show signs of complications (pulmonary embolism or a superimposed bacterial pneumonia). In post-mortem examinations the damage is so extensive that some of the specific findings reported in the literature, such as the halo sign, or the distribution of the opacities are not identifiable. Pleural effusions were present in

all 6 patients. A pleural effusion is an uncommon or nonspecific feature at early stages of COVID, but it has been identified as a sign of bad prognosis if shown[10]. Our findings are consistent with both alveolar and interstitial damage on the subsequent histological studies. Signs of pulmonary fibrosis are rare in patients that fully recover not requiring long hospital stays and/or mechanical ventilation[6]. In our study, there is a perfect correlation between the signs of fibrosis on CT and the subsequent histopathologic study, as discussed below.

The role of US in the management of COVID-19 infected patients has not been fully established. Our study shows a correlation of both US and CT: Areas of pleural thickening were shown as thickened pleura on CT, a B-pattern on ultrasound presented as GGO or crazy paving on CT, and subpleural consolidations as areas of consolidation in contact with the pleura. In our study, US was not as sensitive as CT to detect pleural effusions because examinations only included the anterior segments of the lung.

Our study confirms DAD as the predominant pattern in the lungs of patients infected with COVID-19 virus, most commonly in the proliferative phase. Other publications report exudative DAD as the predominant injury, sometimes associated with the proliferative phase. The presence of the fibrotic phase has been reported by very few groups[14]. In contrast, we demonstrated fibrotic DAD in most patients, always in association of proliferative DAD. Exudative DAD alone was only seen in a severely ill patient that died after nine days of admission. We believe that the differences found with other studies are related to longer courses of the disease of our cohort.. Our patients presented with symptoms for an average of 40,3 days before deceasing, whilst other groups reported symptoms from 16 days until death[17]. What is more, our patients were in the intensive care unit for an average of 35,2 days. Other groups report stays in the ICU for 7 to 30 days with an average of 12,5 days.[17,16,15,23,14] Only Schaller et al. reports a case with areas of fibrotic DAD in a patient with a 26-day disease-to-death course and mechanical ventilation for 21 days[14]. AFOP alone, with no DAD, was the only lesion described by one author[24]. In our study, AFOP was present in two of our cases, but always associated with DAD.

Two patients in our study had been diagnosed with pulmonary embolism during admission, one which had an aortic mural thrombus. Vascular involvement cannot be evaluated on post-mortem CT's. Therefore, radiopathological correlation was not possible. On histology, two patients showed microvascular thrombosis, a common finding in DAD, but not a necessarily specific feature in patients infected with COVID-19.

Our study findings are limited by different factors. First, the number of patients included in our study is very small. Second, whilst the cause of death of these patients was a result of ARDS, other conditions could have contributed to their death, such a bacterial infection, drug toxicity, or barotrauma. Finally, we have no prior history or examinations of the patients. The fact that fibrosis was present in almost all the mechanically ventilated for over 30 days may indicate that it is factor that could worsen the prognosis. However, fibrosis is not necessarily present in patients with a bad prognosis if they die at an early stage of the alveolar damage.

In conclusion, signs of fibrosis on CT correlated with the histopathological findings. Fibrosis in the context of COVID-19 infection may be an indicator of poor prognosis. CT may be a tool to identify the group of patients that develop fibrosis in the late stage of the disease. Further bigger studies are required to examine our observations.

Declarations

Competing interests:

The authors declare no competing interests.

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Figures

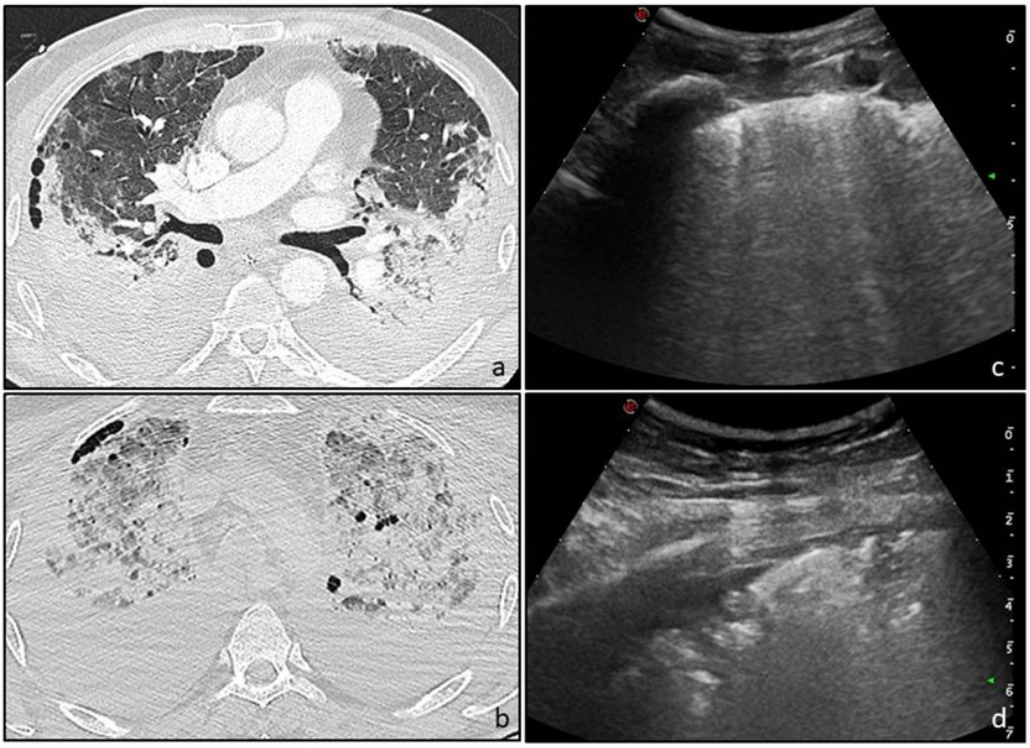

Figure 1

CT and US findings of patient 8 days before and 4 hours after death. a. Axial contrast-enhanced CT in the arterial phase during admission shows postero-basal areas of consolidation, microcystic lesions with a subpleural distribution, areas of GGO, and pleural effusion. b. Post-mortem non-enhanced axial CT shows areas of consolidation affecting most of the lung, with very few remaining aerated areas depictingcrazy paving pattern. Traction bronchiectasis and microcystic lesions had also progressed. A large pleural effusion was present. c and d. Post-mortem US shows a “white lung” as a sign of diffuse consolidation (c) and areas of subpleural nodular thickening (d).

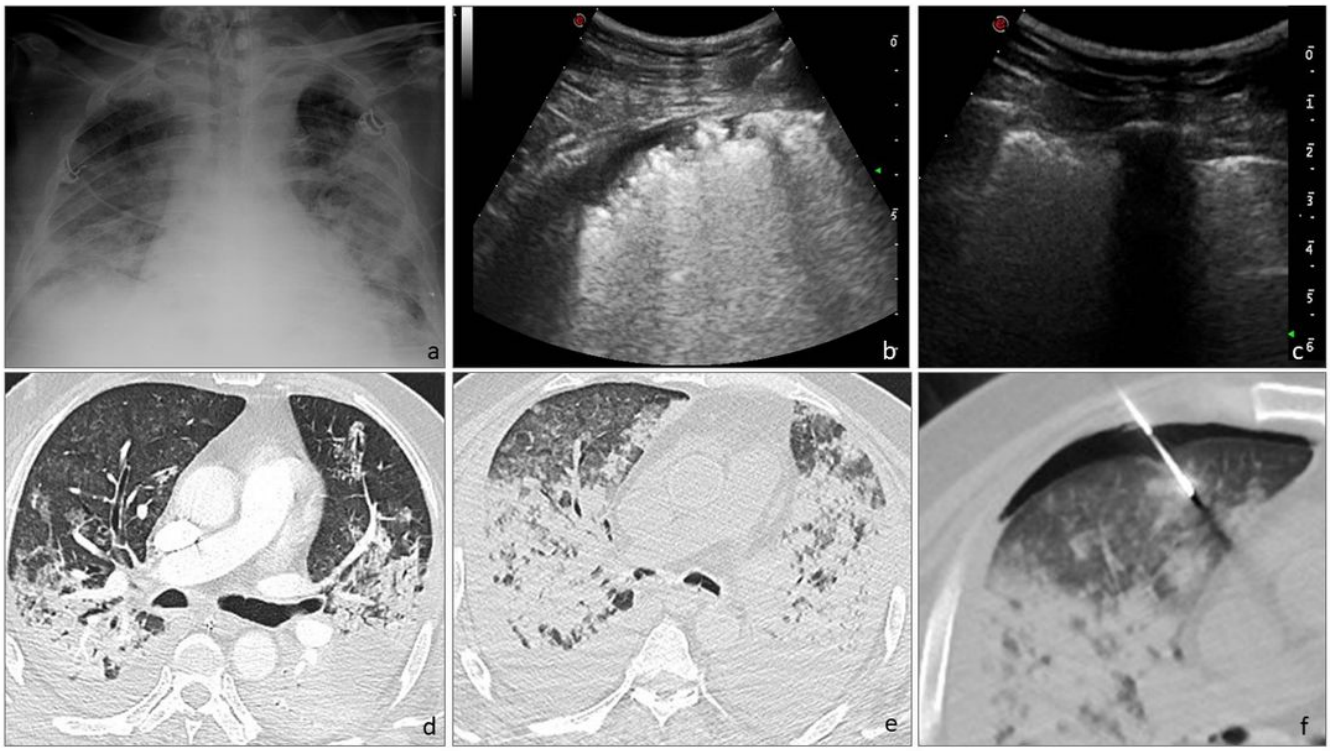

Figure 2

Examinations performed in one of the patients. a. Plain Chest X-ray 2 days before death showing bilateral, predominantly peripheral, and basal opacities. b. Post-mortem US of this patient shows nodular pleural thickening and consolidation, seen as subpleural areas of consolidation on CT. c. US of a ventilated segment shows subpleural B-lines, seen as GGO on CT. d. Axial contrast-enhanced CT in arterial phase 14 days before deceasing to rule out pulmonary embolism shows extensive areas of consolidation affecting the posterior segments of the lower lobes. Nodular opacities, peribronchovascular reticulonodular opacities, and pleural effusion were also present. e. Post-mortem non-enhanced axial CT shows coalescent areas of consolidationaffecting most of the lung and GGO in the remaining ventilated anterior segments. f. CT-guided biopsy of an area of GGO. A small pneumothorax occurred as a result of the procedure.

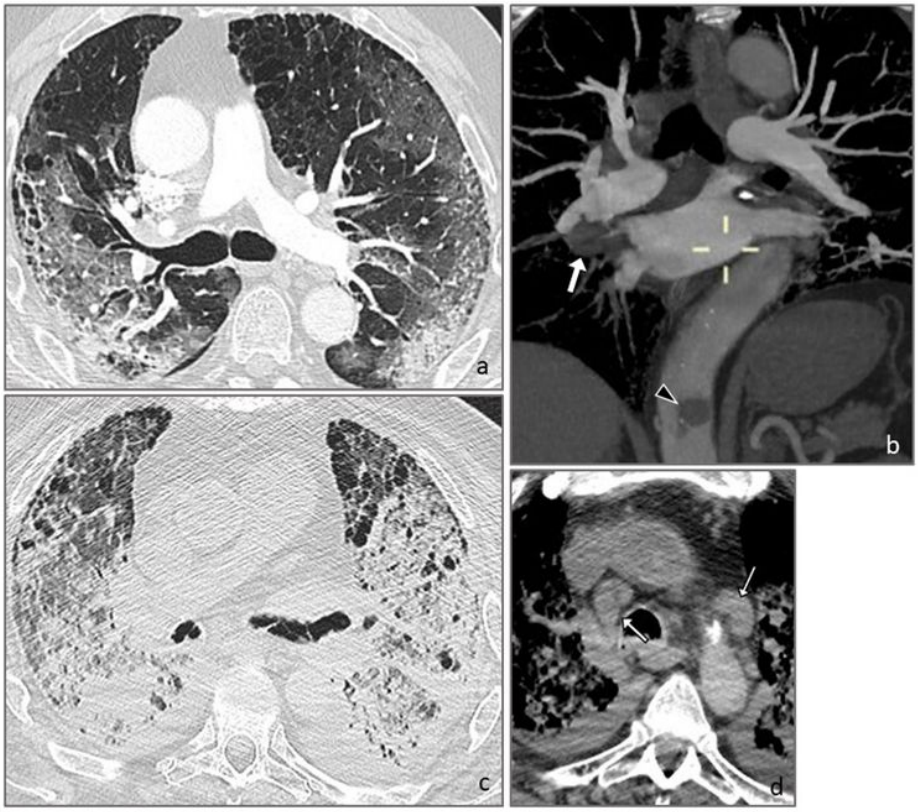

Figure 3

CT examinations of a patient 6 days before (a and b) and 24 hours after death (c and d). a. Axial contrast-enhanced CT in arterial phase before death to rule out pulmonary embolism shows peripheral GGO, crazy paving opacities and posterobasal areas of condensation. Subpleural microcystic lesions as an initial sign of fibrosis were also present. b. Coronal multiplanar reconstruction of the CT in arterial phase shows embolism of the lower right lobe artery (arrow) and a mural thrombus in the thoracic aorta (arrowhead). c. Post-mortem axial non-enhanced CT shows progression of the areas of consolidation, traction bronchiectasis and of the microcystic pattern that becomes diffuse. A small pleural effusion is also present. d. Axial post-mortem on-enhanced CT showing enlarged mediastinal lymph nodes (arrows).

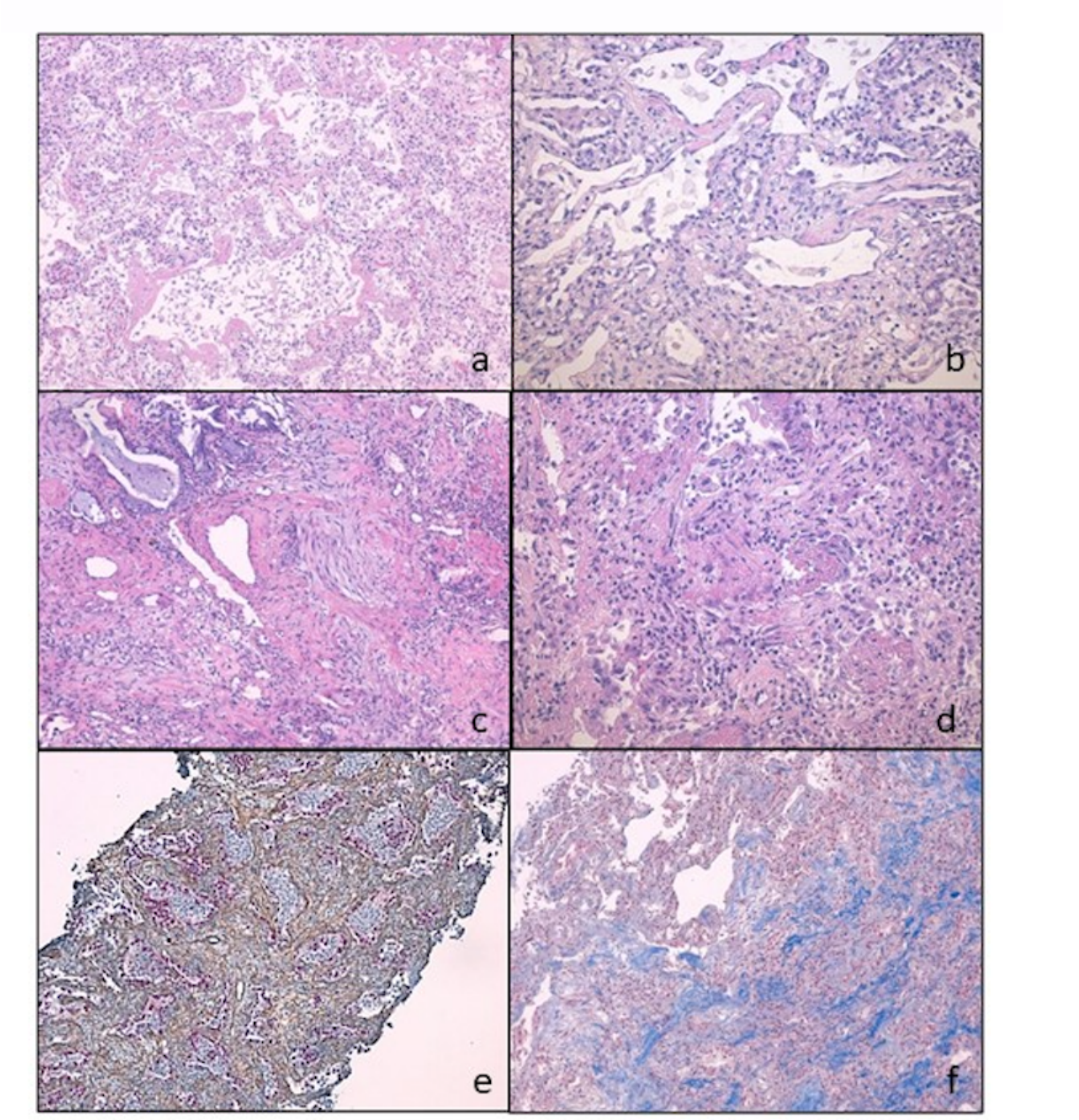

Figure 4

Histologic samples. (A) DAD in exudative phase. (B) DAD in proliferative phase. (C) DAD in fibrotic phase. (D) AFOP. H&E 10X. (E) Proliferative DAD with a positive TTF-1 immunohistochemistry. The hyperplastic nucleus of Pneumocyte type 2 is stained red. The interstitium of the Myofibroblasts is stained in brown by Alfa-Smooth Muscle Actin. (F) The blue trichrome stain highlights the presence of collagen fibers in the interstitium in a case of fibrotic DAD.10X.