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Late histopathologic characteristics of critically ill COVID-19 patients: Different phenotypes without evidence of invasive aspergillosis, a case series

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ABSTRACT

Purpose: Pathological data of critical ill COVID-19 patients is essential in the search for optimal treatment options. **Material and methods:** We performed postmortem needle core lung biopsies in seven patients with COVID-19 related ARDS. Clinical, radiological and microbiological characteristics are reported together with histopathological findings.

Measurement and main results: Patients age ranged from 58 to 83 years, five males and two females were included. Time from hospital admission to death ranged from 12 to 36 days, with a mean of 20 ventilated days. ICU stay was complicated by pulmonary embolism in five patients and positive galactomannan on bronchoalveolar lavage fluid in six patients, suggesting COVID-19 associated pulmonary aspergillosis. Chest CT in all patients showed ground glass opacities, commonly progressing to nondependent consolidations. We observed four distinct histopathological patterns: acute fibrinous and organizing pneumonia, diffuse alveolar damage, fibrosis and, in four out of seven patients an organizing pneumonia. None of the biopsy specimens showed any signs of invasive aspergillosis.

Conclusions: In this case series common late histopathology in critically ill COVID patients is not classic DAD but heterogeneous with predominant pattern of organizing pneumonia. Postmortem biopsy investigations in critically ill COVID-19 patients with probable COVID-19 associated pulmonary aspergillosis obtained no evidence for invasive aspergillosis.

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1. Introduction

Up to 20% of hospitalized coronavirus disease 2019 (COVID-19) patients are admitted to the intensive care unit (ICU) because of acute hypoxemic respiratory failure. [1–4] These patients usually present with bilateral patchy ground glass opacities on computed tomography (CT) thorax fulfilling the definition for acute respiratory distress syndrome (ARDS). Often an atypical high compliance phenotype (L-type) is observed during mechanical ventilation in COVID-19 patients in contrast to mechanical ventilation characteristics typically seen in ARDS with low lung compliance phenotype (H-type). [5,6] During ICU stay the radiologic presentation of bilateral patchy ground glass opacities as present at admission often progress to consolidations with or without

fibrotic characteristics [7]. Two earlier observed features may play a critical role in the severity of this disease: thromboembolic complications and early onset aspergillosis. The cumulative incidence of venous thromboembolism reported was 49% in COVID-19 patients admitted to the ICU [8]. Presumed pulmonary aspergillosis may be present in as much as 19% of ICU COVID-19 patients [9]. Since the physiology in COVID-19 related ARDS as well as its complications seems to differ from “typical” ARDS, an insight into the pulmonary tissue pathology of this new infectious disease is of the utmost importance. The scarcely available pathological data in COVID-19 patients show diffuse alveolar damage, closely related to ARDS [10–12]. The clinical relevance of COVID-19-associated pulmonary aspergillosis (CAPA) as well as survival benefit with antifungal treatment and associated mortality are under debate since histopathological evidence of CAPA is not obtained [13]. We examined postmortem obtained lung tissue in seven patients, with COVID related ARDS who needed mechanical ventilation. The histopathologic findings, together with clinical features, radiological and

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Table 1
Patient characteristics and clinical course.

Case	Sex, age (years)	Medical history	Total hospital days	Total ventilated days	Berlin classification of ARDS	Compliance phenotype	PE	BAL fluid GM and culture (days post hospital admission)	CAPA	Chloroquine	Prednisolone use during hospital admission	Duration of prednisolone treatment
1	M, 77	None	12	10	Severe	Low	Yes	GM negative	No	Yes	No	
2	F, 73	None	20	16	Severe	High	Yes	GM index 4.4 (day 19) <i>Aspergillus fumigatus</i>	Probable	No	Yes	8 days
3	F, 58	None	30	26	Severe	Low	Yes	GM index 3.4 (day 20)	Probable	Yes	Yes	5 days
4	M, 68	None	21	21	Moderate	Low	Yes	GM index 5.7 (day 1) <i>Aspergillus fumigatus</i> <i>Enterococcus faecium</i>	Probable	Yes	No	
5	M, 78	HT, CKI	22	21	Moderate	Low	No	GM index 4.3 (day 20) <i>Enterococcus faecium</i>	Probable	Yes	Yes	2 days
6	M, 83	HT, DM	13	9	Moderate	Low	No	GM index 1.7 (day 11)	Probable	Yes	No	
7	M, 74	None	36	36	Severe	Low	Yes	GM index 4.4 (day 24) <i>Enterococcus faecalis</i>	Probable	Yes	Yes	4 days

ARDS acute respiratory distress syndrome; BAL broncho-alveolar lavage; CAPA, COVID-19 associated pulmonary aspergillosis; CKI, chronic kidney injury; DM, diabetes mellitus; GM, galactomannan; HT, hypertension; PE pulmonary embolism.

microbiological findings are reported here. This report may contribute to new insights in the pathogenesis of COVID-19 as well as suggestions for treatment strategy.

2. Methods

2.1. Study population and design

All patients with laboratory confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) admitted to the ICU due to acute hypoxemic respiratory failure between 22 March 2020 and 30 April 2020 and with available postmortem needle core biopsy of the lung were eligible for inclusion in this case series. SARS-CoV-2 was diagnosed using real-time reverse transcription polymerase chain reaction (RT-PCR) on sputum and/or bronchial aspirates. Routine ICU management included, among other things, selective digestive tract decontamination (SDD), chloroquine until the Dutch National Institute for Public Health and Environment advised against its use at the end of March 2020, and high dose anticoagulation with low-molecular-weight heparin (LMWH) (nadroparin 87 IE/kg twice daily). Bronchoscopy, with or without lavage, and testing for pulmonary aspergillosis were performed at the discretion of the attending physician. Pulmonary aspergillosis was diagnosed using clinical, radiological and mycological data and included galactomannan (serum and sputum), tracheal or bronchial culture. For galactomannan (GM) testing from bronchoalveolar lavage (BAL) fluid Platelia Aspergillus antigen ELISA (Biorad) was used. Recently, a case definition for influenza associated pulmonary aspergillosis (IAPA) was proposed by an expert panel, which could be used to classify patients with CAPA [14]. Diagnostic criteria include proven infection with clinical symptoms and a GM index of ≥ 1 on BAL or of ≥ 0.5 on serum; or *Aspergillus* spp. cultured from BAL.

2.2. Postmortem needle core biopsy of the lung

With permission from the patients' families, postmortem core needle biopsies were performed on both lungs within an hour after death. Lung biopsies were ultrasound and CT guided and combined with surface anatomic landmarks as a reference. A minimum of three histologic 14 gauge true cut needle biopsies were performed in both lungs. Biopsy specimens were fixed in formalin, embedded in paraffin, and cut into 3 μ m sections. Hematoxylin and eosin (H&E), and periodic acid–Schiff with diastase (PAS-D) stains were applied according to routine procedures.

2.3. Statistical analysis

Descriptive statistics were used to describe patient characteristics. For statistical analysis IBM SPSS version 25.0 was used.

The local Medical Ethics Committee (Medical Research Committees United) approved the study.

3. Results

3.1. Clinical features

During the study period, seven patients underwent postmortem needle core biopsy of the lungs. Patients age ranged from 58 to 83 years (median 74 year) and five patients were male. None of the patients had a history of (chronic) pulmonary disease. One patient used immunosuppressive medication before hospital admission, in this case a short course of prednisolone. Median time from hospital to ICU admission was 0 days (interquartile range 0–4). Time from hospital admission to death ranged from 12 to 36 days. Patients deceased at median of 21 (range 9–36) ventilated days. In five out of seven patients ICU stay was complicated by pulmonary embolism. Adopting the proposed definition of CAPA by van Arkel et al. [9], six patients were classified as having probable CAPA (Table 1), based on a positive GM on BAL fluid. In those patients, combination antifungal therapy with voriconazole and anidulafungin was started. Three out of six patients were on corticosteroids (60 mg prednisolone daily) at the time of CAPA diagnosis and corticosteroid treatment was terminated. Indication for steroid treatment in these patients was a suspicion of an organizing pneumonia on chest CT or signs of progression to fibrosis. Nosocomial infections including signs for pulmonary aspergillosis were excluded by bronchoscopy with BAL before steroid treatment was started. Radiologic findings of chest CT and histologic results of the lungs biopsies of all seven patients are shown in Table 2.

To further investigate histopathologic findings we now present the detailed clinical course of four patients with four different histopathological characteristics. Because of complexity and importance of the distinct patterns and their relation with radiologic findings and treatment, we preferred to discuss them separately in more detail. Chest CT imaging of the four discussed patients are shown in Fig. 1.

3.2. Case 1 – Organizing pneumonia

A 77-year old male without significant medical history was evaluated in our emergency department (ED) with complaints of general

Table 2
Radiological Chest CT scan and histological findings.

Case	Radiological findings	Histological findings description	Diagnosis
1	GGO, crazy paving, non-dependent consolidation, subpleural sparing, segmental and subsegmental PE	Intra-alveolar fibromyxoid/fibroblastic bodies (25%), micro-thrombi, thrombi in larger vessels, hyperplasia with atypia, multinucleated giant cell, intranuclear inclusion bodies, no hyphae	OP
2	GGO, crazy paving, resolving consolidation, bronchiectasis, segmental and subsegmental PE	Extensive fibrosis with destruction of alveolar structures, hyperplasia with atypia, multinucleated giant cell, intranuclear inclusion bodies, no hyphae	Fibrosis
3	GGO, large dependent consolidation, bronchiectasis, subsegmental PE	Inflammatory infiltrate, hyaline membranes, sporadic intra-alveolar fibroblastic plug, micro-thrombi, hyperplasia with atypia, multinucleated giant cell, intranuclear inclusion bodies, no hyphae	DAD
4	GGO, crazy paving, non-dependent consolidation, bronchiectasis, segmental and subsegmental PE	Intra-alveolar fibroblastic tissue, with a diffuse component of fibrinous exudate, widening of alveolar septa, micro-thrombi, hyperplasia with atypia, multinucleated giant cell, intranuclear inclusion bodies, no hyphae	AFOP
5	GGO, consolidation	Intra-alveolar fibromyxoid/fibroblastic bodies (32%), micro-thrombi, hyperplasia with atypia, multinucleated giant cell, intranuclear inclusion bodies, no hyphae	OP
6	GGO, consolidation	Intra-alveolar fibromyxoid/fibroblastic bodies (80%), widening of alveolar septa, micro-thrombi, hyperplasia with atypia, multinucleated giant cell, intranuclear inclusion bodies, no hyphae	OP
7	GGO, crazy paving, consolidation, bronchiectasis, subsegmental PE	Intra-alveolar fibromyxoid/fibroblastic bodies (27%), mild widening of alveolar septa, micro-thrombi, hyperplasia with atypia, multinucleated giant cell, intranuclear inclusion bodies, no hyphae	OP

AFOP acute fibrinous and organizing pneumonia, DAD diffuse alveolar damage, GGO, ground glass opacities; OP organizing pneumonia; PE pulmonary embolism.

weakness, fever and dyspnoea. Initial chest CT showed extensive bilateral areas of ground-glass opacity with both central and peripheral distribution, patchy subpleural non-dependant consolidations and areas with subpleural sparing (Fig. 1-1A). Soon after admission patient was in need of mechanical ventilatory support and developed acute renal failure for which renal replacement therapy was initiated. After six days of mechanical ventilation chest CT-angiography showed pulmonary emboli along with new areas of ground-glass opacity and progression of dens subpleural consolidations with air-bronchograms (Fig. 1-1B). A nosocomial infection was ruled out by bronchial culture. Patient's neurologic status deteriorated and CT head revealed brain ischemia due to infarction of the area supplied by the left and right posterior cerebral artery. The patient died 12 days after admission.

Postmortem pathologic examination revealed that the overall architecture of the lung tissue remained intact. However, a prominent amount of fibromyxoid or fibroblastic bodies was present in the alveoli with surrounding histiocytes (Fig. 2A). The extent of involved lung tissue was estimated at around 25% (Table 2). No remnants of hyaline membranes or prominent alveolar fibrinous exudate were found. Microthrombi in small blood vessels of the alveolar septa were seen, as well as an organizing thrombus in a larger sized vessel (Fig. 2E). The histologic findings in this case point towards an epithelial, and vascular phenotype of a SARS-CoV2 infection. No fungi were present in de PAS-D stain. This histologic pattern is characteristic for an organizing pneumonia.

3.3. Case 2 – Fibrosis

A 73-year old female was transferred to our ICU due to shortage of ICU beds in a nearby hospital. Prior to ICU admission, she was healthy but complained of diarrhoea and shortness of breath. Non-contrast chest CT at initial hospital admission showed multiple bilateral areas of ground-glass opacity along the bronchovascular bundles and periphery. There were some small areas of consolidation in the upper lobes. Subtle bronchiectasis were present in affected areas (Fig. 1-2A). Her respiratory condition required mechanical ventilation in prone position due to ARDS. After seven days, prednisolone treatment was started because of lack of improvement. Repeat chest CT-angiography showed segmental pulmonary emboli in the right lung. Ground-glass opacities persisted while the consolidations had disappeared. A reticular pattern combined with GGO was more pronounced with increasing traction bronchiectasis (Fig. 1-2B). BAL was performed twice, but GM and culture showed no signs of additional fungal infection. After one week of high dose glucocorticoid therapy BAL was repeated with a GM index 4.4. Fungal cultures showed growth of *Aspergillus fumigatus*. Therefore,

prednisolone treatment was discontinued and antifungal treatment initiated. CT head was performed because of the development of an epileptic insult and showed small foci of haemorrhage in both frontal lobes. Neurologic condition worsened and progressive cerebral haemorrhage on follow up CT head was seen with poor prognosis. Palliative treatment was started and the patient deceased 27 days after onset of symptoms. Microscopic examination of lung tissue of this case showed an almost complete loss of normal lung architecture. Alveolar structures were unrecognizable and replaced by extensive fibrosis (Fig. 2B). What remained were several foci of pneumocytes, bronchial epithelium, and blood vessels without thrombi. In the PAS-D stain no fungi were observed. The prominent pattern in this patient is pulmonary fibrosis.

3.4. Case 3 – Diffuse alveolar damage

A 58-year old female was admitted to the ICU and needed mechanical ventilation due to severe hypoxemia. Chest CT-angiography showed dubious unilateral sub-segmental pulmonary emboli and diffuse bilateral ground-glass opacities with anteroposterior gradient along with large dependant consolidations (Fig. 1-3A). On the 8th day of mechanical ventilation, BAL was performed and CT-scan was repeated because of deteriorating pulmonary condition with increasing inflammatory parameters. Chest CT-angiography showed bilateral sub-segmental pulmonary emboli, persistent ground-glass opacities and consolidation. Newly formed coarse cyst-like lesions in the middle and ventral regions (non-dependant regions) were noted, probably due to ventilator induced lung injury (Fig. 1-3B). Considering lack of respiratory improvement and progression of fibrosis on radiological imaging prednisolone was started. After five days prednisolone was stopped because of a positive GM index of 3.4 from repeated BAL fluid. Fungal culture remained negative though. Her respiratory status stabilised but remained critical. After pausing the sedation, the patient remained unresponsive and CT head showed ischemia with small areas of haemorrhage. In light of her poor neurologic and respiratory prognosis, treatment was ended and patient expired after 26 days on ventilator support.

In the core needle biopsy specimens the lung tissue largely preserved its preexisting architecture. Histologic findings included an inflammatory infiltrate consisting of neutrophils and lymphocytes, and only a sporadic intra-alveolar fibroblastic plug. The striking, distinctive feature of this case was the presence of thin, delicate hyaline membranes along the alveolar wall (Fig. 2C). Again, micro thrombi were observed in this case. No fungi could be demonstrated in the PAS-D stain. Together with the clinical characteristics, these histologic findings were suggestive of diffuse alveolar damage.

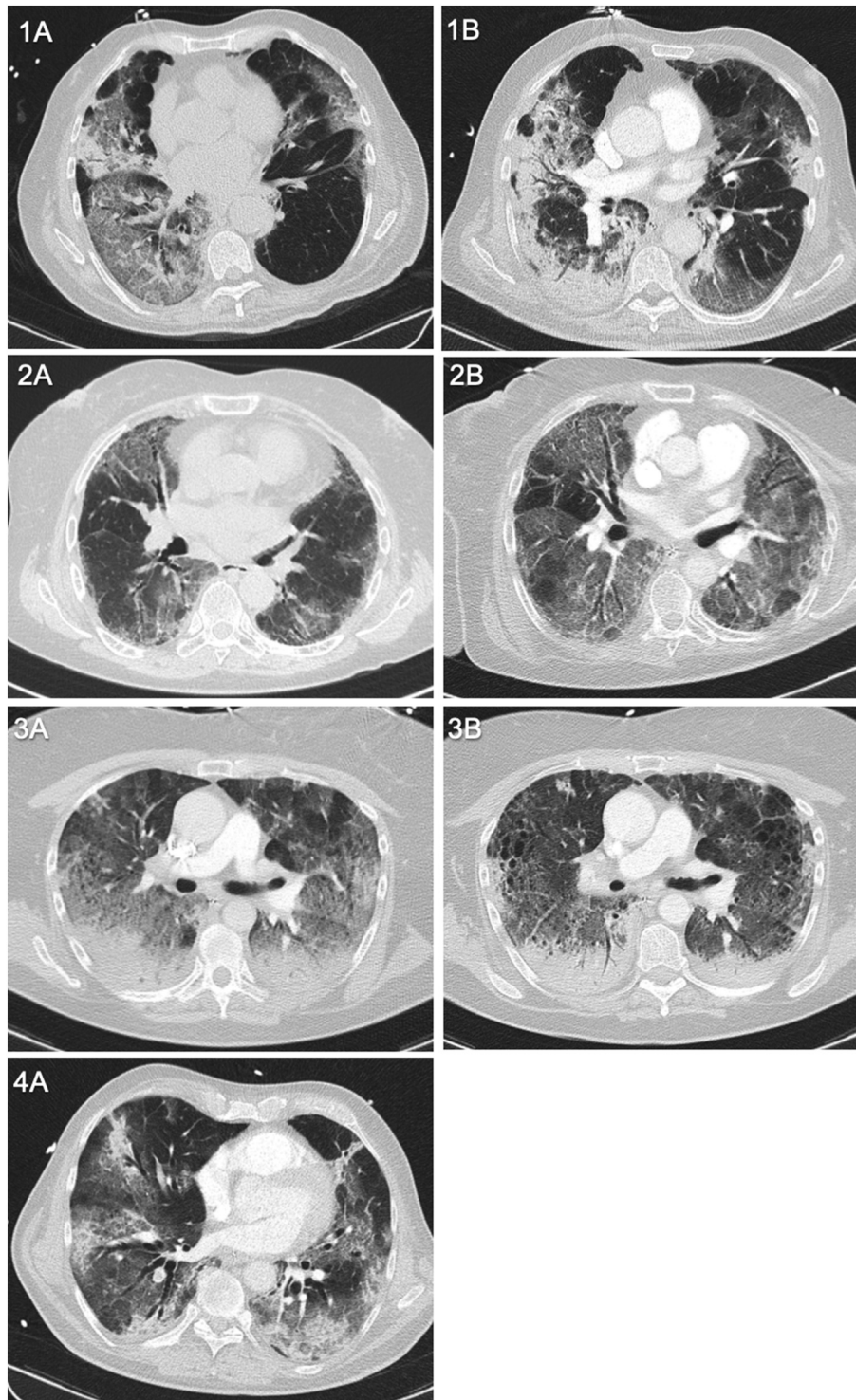


Fig. 1. Chest CT scans of case 1–4. For each patient image A represents chest CT at hospital admission, image B follow up CT-scan (note: chest CT of case 4 was not repeated). 1A: bilateral areas of GGO, patchy subpleural non-dependant consolidations 1B: progression of dens subpleural consolidations with air-bronchograms. 2A GGO in both lungs, combined with crazy-paving pattern, subtle bronchiectasis are present in affected areas. 2B GGO persisted, without progression to consolidations, more pronounced fibrotic reticulation with traction bronchiectasis. 3A diffuse bilateral GGO with large gravity dependant consolidations. 3B persistent GGO and consolidation, newly formed cyst-like lesions in middle and ventral regions. 4A bilateral areas of GGO, patchy non-dependant peripheral consolidations with mild bronchiectasis.

3.5. Case 4 – Acute fibrinous and organizing pneumonia

A 68-year old male without medical history of cardiopulmonary disease, was presented at the ED in a critical condition with fever and dyspnoea. Patient was in need of endotracheal intubation and mechanical ventilation in prone position to improve his oxygenation. To exclude

secondary infection, BAL was performed and revealed a positive GM and cultured *Aspergillus fumigatus* and *Enterococcus faecium*. Antifungal therapy was added to his treatment regimen. Chest CT-angiography showed segmental pulmonary emboli along with extensive bilateral areas of ground-glass opacity with reticulation and multiple patchy non-dependant peripheral consolidations. In contrast to normal areas,

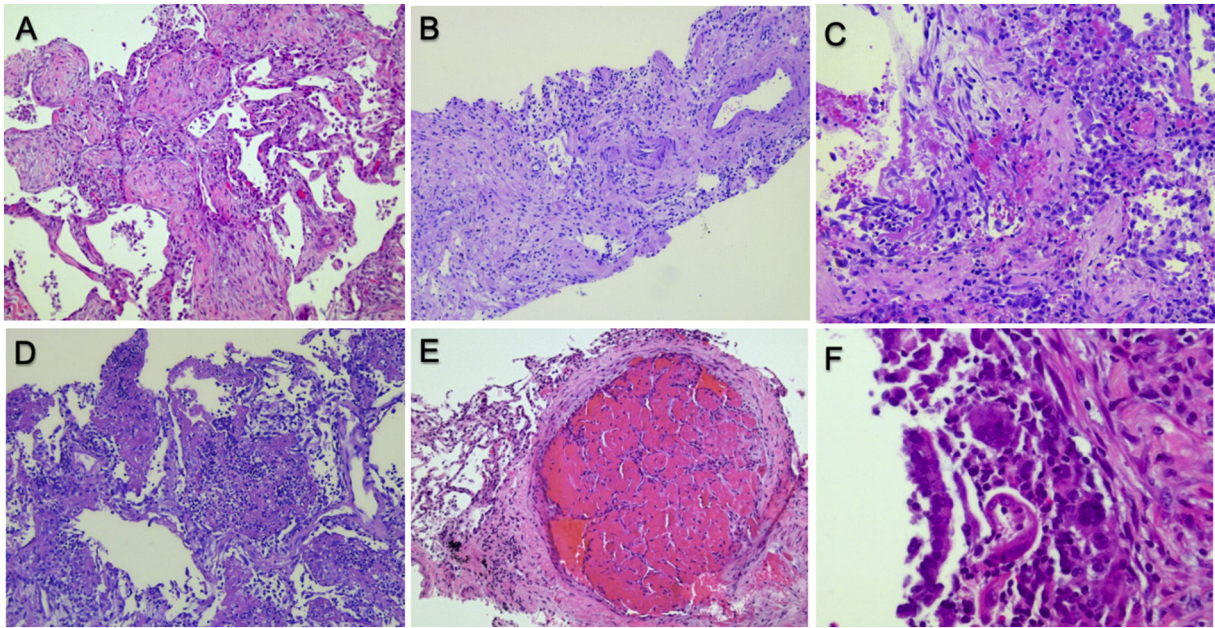


Fig. 2. Microscopic lung findings. A, case 1: intra-alveolar fibroblastic bodies, consistent with organizing pneumonia, (H&E, 10 \times) B, case 2: loss of alveolar architecture with extensive fibrosis (H&E; 10 \times) C, case 3: inflammatory infiltrate with neutrophils and lymphocytes, note the hyaline membranes (arrows), suggestive for diffuse alveolar damage. (H&E, 20 \times) D, case 4: prominent fibrinous exudate in alveoli as seen in AFOP (H&E; 10 \times) E: thrombus in larger vessel (H&E, 5 \times) F: cytopathogenic changes in pneumocytes due to viral infection seen in all cases: hyperplasia, multinucleated giant cells (asterisks), intranuclear inclusion bodies (H&E, 40 \times).

the abnormal areas showed mild bronchiectasis (Fig. 1-4A). The patient remained unresponsive after cessation of sedative medication. CT head showed extensive bilateral cerebellar ischemia with small haemorrhagic components. After three weeks of mechanical ventilation his respiratory status worsened and treatment was ended due to poor prognosis. The patient passed away 21 days after hospital admission.

Biopsy specimens showed a pattern of lung injury, that was partially identical to that of case 1. Intra-alveolar depositions of fibroblastic tissue were found, consistent with organizing pneumonia. However, a predominant, diffuse component of fibrinous exudate in the alveoli was present, which was not the case in the aforementioned case with organizing pneumonia. Other histologic findings were a chronic inflammatory infiltrate, and mild interstitial changes, including widening of alveolar septa. Microthrombi in small septal blood vessels were also observed. Neither remnants hyaline membranes nor prominent eosinophils were present. Additional PAS-D stain did not show any fungi. The overall histologic pattern of this case was classified as acute fibrous and organizing pneumonia (AFOP), Fig. 2D.

4. Discussion

We report pathology in deceased critically ill ICU COVID patient in the late phase of disease to be heterogeneous. Histopathologically, we observed four distinct histopathological patterns: AFOP, DAD, fibrosis and, in four out of seven patients an organizing pneumonia (OP). Interestingly, our findings are in contrast to previously reported postmortem studies in COVID-19 patients in which DAD is the most common predominant pattern [10–12,15–19]. In two recent autopsy studies of 21 and 12 deceased COVID-19 patients, prevalence of DAD was 76% and 67% respectively. None of the patients had the postmortem diagnosis of organizing pneumonia [10,11]. In the study of Ackermann and colleagues, pulmonary histology of all seven studied patients showed DAD [19]. Although the organizing stage of DAD may overlap with the histopathological features of OP in lung biopsy, the histologic hallmark of DAD, namely remnants of hyaline membranes were not present in our four OP cases.

Most plausible explanation for the more common pattern of OP in our study population when compared to previous mentioned studies is the difference in length of hospital and ICU stay correlating with more advanced disease and longer treatment with mechanical ventilation. In the studies mentioned above the mean hospital stay was six days or less and most of the patients did not receive mechanical ventilatory support. In our present series mean hospital stay of 22 days is significant longer and all patients died in the ICU with a mean of 20 days on mechanical ventilation. Secondary OP can be seen in association with many types of non-specific lung injury, including viral infections and drug reactions. OP is reported following severe influenza infections [20–24] and Middle East Respiratory Syndrome [25]. Most recently, Copin et al. reported postmortem biopsies on six patients with COVID and reported in five patients with phenotype H and AFOP histology in contrast to their patient with DAD [26]. Estimated elapsed disease time in the AFOP group was 20 days versus 6 days in the DAD patients. In our opinion this supports the theory that pathology changes over time.

Although the exact pathogenesis of OP remains unknown, it is thought that OP is a consequence of alveolar epithelial injury. This initial epithelial injury is followed by leakage of plasma proteins, leading to a cascade of host responses with hyperinflammation [27,28]. Subsequent fibroblast recruitment and connective tissue and fibroblast organisation is seen within the alveolar space. Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) play a central role in organizing pneumonia and are highly expressed in intraluminal fibromyxoid lesion in organizing pneumonia [29]. Interestingly, binding to ACE2 receptor is recognized as a critical initial step for SARS-CoV-2 to entry alveolar type II cells, resulting in loss of ACE2 at the membrane. ACE 2 is a negative regulator of the renin-angiotensin system (RAS) and this depletion of ACE2 upregulates the RAS [30]. An activated RAS can induce Fibroblastic Growth Factor. ACE2 also plays a role in regulating the effect of VEGF [31]. Therefore, depletion of ACE2 due to the high affinity of SARS-CoV-2 to ACE2 might play a role in the pathogenesis of COVID19 related organizing pneumonia.

Being aware that medication can be the cause of OP it is notable is that in our study six out of seven patients received chloroquine, at

that time the advised treatment by the Dutch National Institute for Public Health and Environment. Although chloroquine use is associated with cardiovascular disorders, pulmonary side effects, i.e. drug induced interstitial lung disease, are not described before, and therefore an unlikely cause of the observed histologic OP. We found no studies reporting possible relations between antifungal therapy and OP.

In retrospect, chest CT scans of each of the patients showed a different development during hospital admission, concordant with the histopathological diagnosis (Table 2). Development of peripheral nondependent consolidations warrant further investigation in the presence of an organizing pneumonia. Excluding nosocomial infections in such cases is essential. The diversity in histopathological findings correlating with radiological findings is interesting considering possible therapeutic implications and should be subject for further research. Although steroids are not routinely recommended to be used in the early phase of SARS-CoV-2 pneumonia, they might have a role in the late phase of COVID-19 when an organizing pneumonia is suspected [32].

Recently there is increasing awareness and concern for development of secondary infection in COVID patients e.g. invasive aspergillus coinfection, a contra-indication for (long-term) systemic steroid therapy. Criteria and risk factors for invasive pulmonary aspergillosis are well defined in immunocompromised populations. Furthermore it is a well known complication of severe influenza pneumonia with reported incidences of 19% in ICU patients admitted for influenza related acute respiratory failure with high mortality rates [33]. In COVID-19 associated pulmonary aspergillosis (CAPA) case definition is absent, although recently an expert panel proposed a classification for IAPA, which was used to classify CAPA [14]. Pathophysiology of CAPA consists of lung damage with bilateral alveolar-interstitial damage due to viral replication and cytokine storm in combination with marked low T-lymphocytes CD4 + T and CD8 + T cells [27]. Secondary infection due to lung tissue damage develop within a median of 17 days [34]. CAPA data are scarce but increasingly reported, although histological confirmation is still absent [9,13,35,36]. Of the first 31 COVID-19 patients admitted to our ICU, six were highly suspected for COVID-19 associated pulmonary aspergillosis (CAPA) [9]. In this case series, BAL fluid galactomannan was positive in six out of the seven cases, concluding in the clinical diagnosis of probable CAPA.

To our surprise, none of the lung biopsies showed any presence of invasive aspergillosis. Lack of evidence for invasive pulmonary aspergillosis in our patients with probable CAPA raises the question whether patients with suspected CAPA truly develop invasive aspergillosis and require antifungal therapy. For instance, the three deaths in the CAPA report from France were attributed to bacterial septic shock, and not to aspergillosis. Although in our patients adequate antifungal treatment could be an explanation for the absence of histologic fungal features, we find this improbable as respiratory conditions deteriorated despite treatment. Further research on the presence of CAPA, its case definition and the necessity for antifungal treatment and (relative) contraindication for steroid treatment is needed.

We acknowledge the limitations of this report and realize that due to limited sample size of pulmonary tissue, a sampling error in our histologic findings cannot be excluded. Although conventional autopsy might be the preferred postmortem examination, postmortem ultrasound guided lung biopsies are a safe and valuable alternative, with an 83% concordance rate with conventional autopsy [37]. Especially in times of new emerging diseases, like COVID-19, histopathological investigation is essential in understanding the pathogenesis of SARS-CoV-2 infection and thereby providing information leading to possible new therapeutic options.

5. Conclusion

We report late pulmonary pathological findings of COVID-19 ARDS to be heterogeneous and non-typical when compared to non-COVID-19 ARDS patients. The predominant histologic pattern in our case series

mainly consists of OP and not DAD. A concordance with specific findings on chest CT is suggested. The absence of histology proven aspergillosis provides further discussion on the presence of CAPA. Based on these late postmortem histopathologic findings, we suggest that the empiric use of corticosteroid therapy in COVID-19 related ARDS should be reconsidered in selected patients. Further research on the late phase of COVID-19 in relation to the presence of different histologic patterns, its concordance with radiology and the presence of COVID-19 associated pulmonary aspergillosis is warranted.

Author's contributions

A.W.F., M.K.M.K., M.J.J.H.G., D.C.Y.Y. and A.W.F.M. drafted the manuscript. N.J.M.M. and T.C.D.R. critically revised the manuscript and approved the final version for publication. All the authors reviewed the final draft of the manuscript and agreed on submitting it to Journal of Critical Care.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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