



# Late histological findings in symptomatic COVID-19 patients

## A case report

Alberto Aiolfi, MD<sup>a,\*</sup>, Barbara Bruni, MD<sup>b</sup>, Tullio Biraghi, MD<sup>a</sup>, Andrea Montisci, MD<sup>c</sup>, Antonio Miceli, MD<sup>c</sup>, Barbara Baronio, MD<sup>c</sup>, Desmond Khor, MD<sup>a</sup>, Silvia Cirri, MD<sup>c</sup>, Francesco Donatelli, MD<sup>d</sup>, Claudio Clemente, MD<sup>b</sup>, Davide Bona, MD<sup>a</sup>

### Abstract

**Rationale:** Although there have been several studies describing clinical and radiographic features about the novel coronavirus (COVID-19) infection, there is a lack of pathologic data conducted on biopsies or autopsies.

**Patient concerns:** A 56-year-old and a 70-year-old men with fever, cough, and respiratory fatigue were admitted to the intensive care unit and intubated for respiratory distress.

**Diagnosis:** The nasopharyngeal swab was positive for COVID-19 and the chest Computed Tomography (CT) scan showed the presence of peripheral and bilateral ground-glass opacities.

**Interventions:** Both patients developed pneumothoraces after intubation and was managed with chest tube. Due to persistent air leak, thoroscopies with blebs resection and pleurectomies were performed on 23rd and 16th days from symptoms onset.

**Outcomes:** The procedures were successful with no evidence of postoperative air-leak, with respiratory improvement. Pathological specimens were analyzed with evidence of diffuse alveolar septum disruption, interstitium thickness, and infiltration of inflammatory cells with diffuse endothelial dysfunction and hemorrhagic thrombosis.

**Lessons:** Despite well-known pulmonary damages induced by the COVID-19, the late-phase histological changes include diffused peripheral vessels endothelial hyperplasia, in toto muscular wall thickening, and intravascular hemorrhagic thrombosis.

**Abbreviations:** COVID-19 = novel coronavirus 2019, CRP = C-reactive protein, CT = Computed Tomography, ICU = Intensive Care Unit, PEEP = positive end-expiratory pressure, WBC = white blood cells.

**Keywords:** COVID-19 pneumonia, novel coronavirus, pathology

## 1. Introduction

The outbreak of the novel coronavirus (COVID-19) infection was first reported in Wuhan, China. The subsequent spread of the disease led to the worldwide diffusion since the World Health Organization declared the pandemic state. Although there have been several studies describing the clinical and radiographic features about the COVID-19 infection,<sup>[1,2]</sup> there is a lack of

pathologic informations conducted on biopsies or autopsies.<sup>[3-5]</sup> A previous study reported data of 2 asymptomatic patients treated for lung adenocarcinoma and retrospectively diagnosed with COVID-19.<sup>[3]</sup> The described pathological features were accidental and likely to be early in asymptomatic patients. Therefore, the histological findings associated with advanced phase of the disease remain unclear. With this report we described

Editor: Maya Saranathan.

Data sharing not applicable to this article as no datasets were generated during the current study.

Written informed consent was obtained from the patients relatives for publication of the case details and accompanying images.

The authors have no funding and conflicts of interests to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

<sup>a</sup> Department of Biomedical Science for Health, Division of General Surgery, Istituto Clinico Sant'Ambrogio, University of Milan, <sup>b</sup> Department of Pathology, I.R.C.C.S. Policlinico San Donato, Milano, <sup>c</sup> Department of Anaesthesia and Intensive Care, Cardiothoracic Center, Istituto Clinico Sant'Ambrogio, University of Milan, <sup>d</sup> Chair of Cardiac Surgery, Department of Cardiothoracic Center, Istituto Clinico Sant'Ambrogio; University of Milan, Milano, Italy.

\* Correspondence: Alberto Aiolfi, Department of Biomedical Science for Health, Division of General Surgery, Istituto Clinico Sant'Ambrogio, University of Milan, Via Luigi Giuseppe Faravelli, 16, Milan 20149, Italy (e-mail: alberto.aiolfi86@gmail.com).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Aiolfi A, Bruni B, Biraghi T, Montisci A, Miceli A, Baronio B, Khor D, Cirri S, Donatelli F, Clemente C, Bona D. Late histological findings in symptomatic COVID-19 patients: a case report. *Medicine* 2020;99:28(e21046).

Received: 16 May 2020 / Received in final form: 28 May 2020 / Accepted: 1 June 2020

<http://dx.doi.org/10.1097/MD.00000000000021046>

the late stage histological findings of 2 symptomatic COVID-19 patients intubated for respiratory insufficiency.

## 2. Case presentation

Written informed consent was obtained from the patients relatives for publication of the case details and accompanying images.

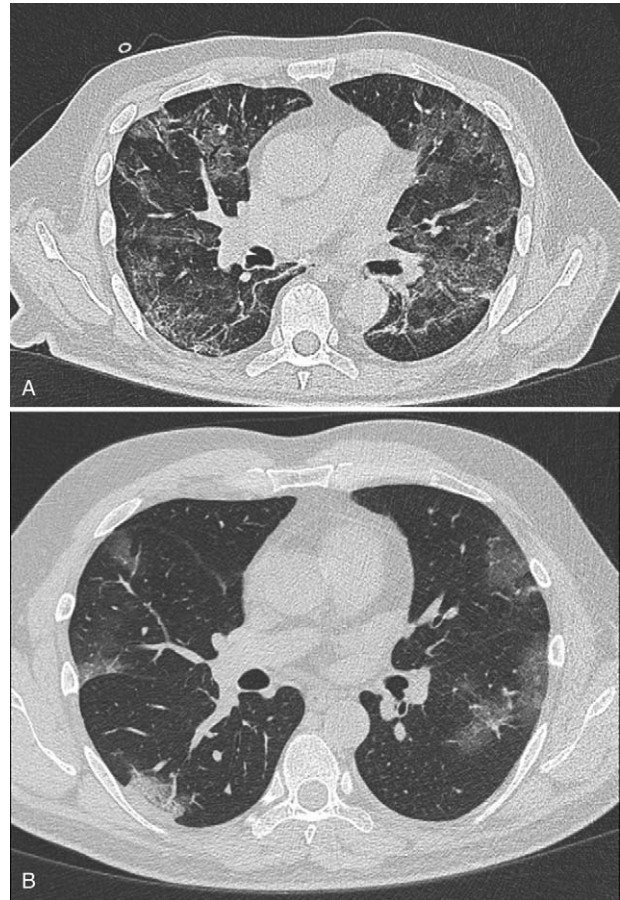
### 2.1. Case #1

A 56-year old man, active smoker, was admitted to our hospital with fever, cough, and respiratory distress. Admission laboratory exams were: WBC: 18.200/mm<sup>3</sup>; neutrophils: 54%; CRP: 21.3 mg/dl, D-dimer: 15.442 µg/L. The nasopharyngeal swab was positive for COVID-19 and the chest Computed Tomography (CT) scan showed presence of peripheral and bilateral ground-glass opacities (Fig. 1A). He was admitted to the Intensive Care Unit (ICU) and later intubated for respiratory insufficiency. Ventilator settings were: tidal volume 6ml/kg and PEEP 10 cmH<sub>2</sub>O. The patient developed post-intubation pneumothorax and was managed with a 28 Fr chest tube. Due to persistent air leak, thoracoscopy (Fig. 2) with blebs resection and pleurectomy was performed on day 23rd after symptoms onset.<sup>[6]</sup>

### 2.2. Cases #2

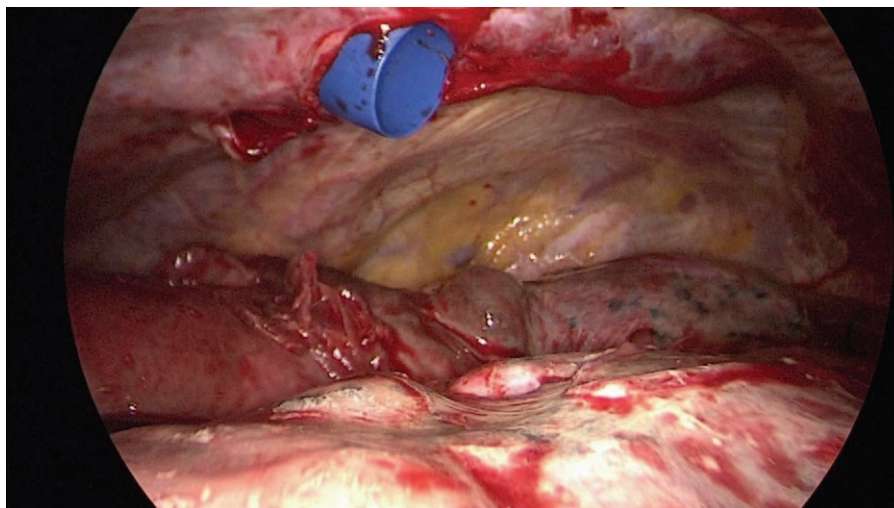
A 70-year old man without comorbidities was admitted to our hospital with fever, fatigue, and respiratory distress. Laboratory exams were: WBC: 14.700/mm<sup>3</sup>; neutrophils: 48%; CRP: 16.1 mg/dl, D-dimer: 12.891 µg/L. Diagnosis of COVID-19 was done with positive nasopharyngeal swab and evidence of bilateral ground-glass opacities was shown on thorax CT scan (Fig. 1B). He was admitted to the ICU and intubated for respiratory insufficiency. Ventilator settings were: tidal volume 6ml/kg and PEEP 8 cmH<sub>2</sub>O. He also developed pneumothorax required the positioning of a 28 Fr chest tube. Again, because of persistent air leak, thoracoscopy with blebs resection and pleurectomy was performed on 16th day from symptoms onset.<sup>[6]</sup>

During the hospital course, both patients received vitamin C, hydroxychloroquine, and azithromycin. The surgical procedures

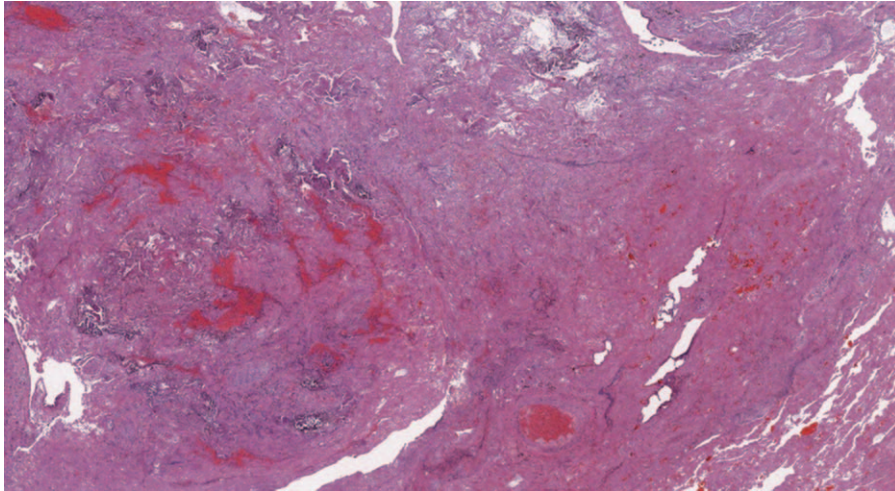


**Figure 1.** A-B. Chest Computed Tomography scan showing bilateral ground glass opacities with multilobar involvement.

were successful in both patients with no evidence of persistent air-leak and respiratory improvement. Drains were removed in both patients on postoperative day 2. Despite the initial respiratory improvement patient#1 passed away 56 days after symptoms



**Figure 2.** The thoracoscopic evaluation showed a stiff, edematous, and congestive lung parenchyma with superficial blebs.



**Figure 3.** Representative hematoxylin and eosin section of the lung (15X) - Massive alveoli damage with hemorrhagic necrosis and interstitial fibrosis.

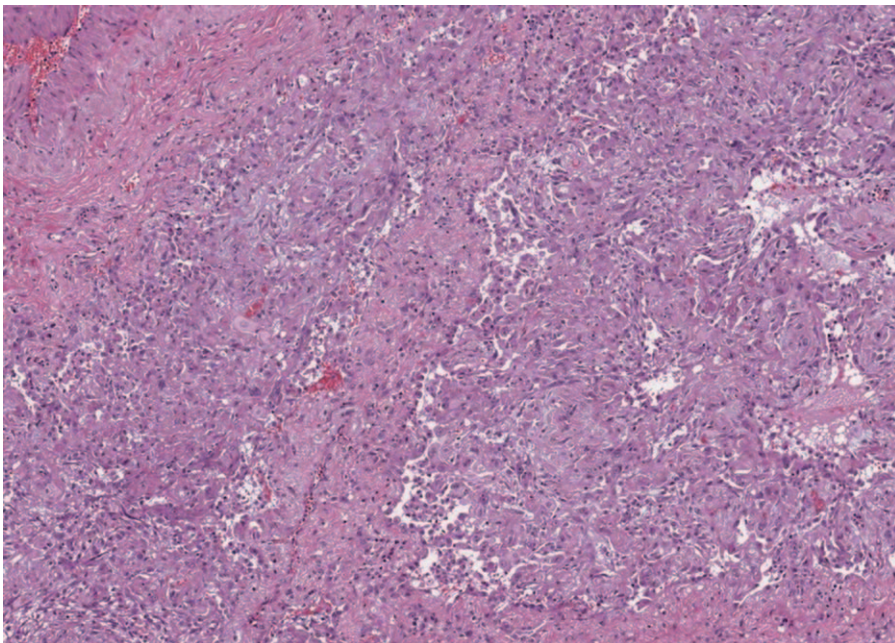
onset because of cardiac failure. Patient #2 was extubated and discharged from the ICU 28 days after symptoms onset.

Specimens were analyzed and pathological findings showed no evidence of pathognomonic lesions. The gross tissue evaluation showed diffuse congestive appearance with edema and hemorrhagic necrosis. The main pathological changes consisted in alveolar damage with septa disruption, desquamation, edema, and proteinaceous exudates (Fig. 3). Alveolar congestion was prominent and contained edema fluid, desquamated epithelial and inflammatory cells. The interstitial tissue was mildly fibrotic and thickened with cells infiltration (monocytes, lymphocytes, plasma cells, and multinucleate giant cells) (Fig. 4). Immunohistochemistry showed positive results for TTF-1, NapsinA, CD3, CD34, CD5, CD8, CD31, CK7, and Collagen Type IV. Peripheral vessels showed diffused endothelial hyperplasia, in

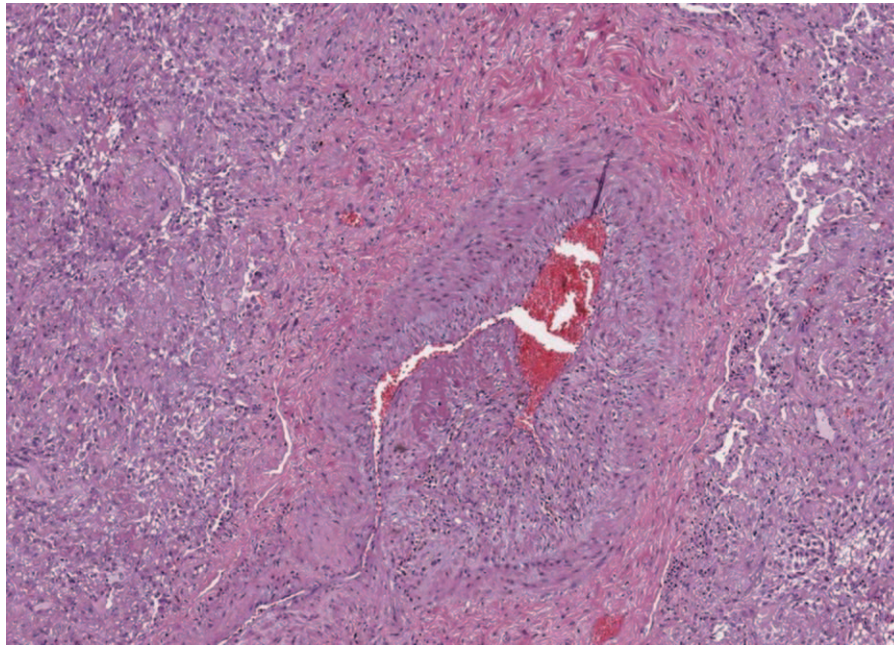
total muscular wall thickening, and massive intravascular hemorrhagic thrombosis (Fig. 5).

### 3. Discussion

The novel coronavirus 2019 (COVID-19), also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, non-segmented positive-sense RNA virus causing severe bilateral pneumonia and acute respiratory distress syndrome (ARDS) in patients. The most commonly reported symptoms are fever, cough, myalgia, and dyspnea.<sup>[7]</sup> Up to 15% of patients may develop severe symptoms and respiratory fatigue requiring mechanical ventilation and intensive care unit management.<sup>[8]</sup> Diagnosis is made with a nasopharyngeal swab,



**Figure 4.** Representative hematoxylin and eosin section of the lung (45X) - alveolar damage with desquamated epithelial cells and inflammatory cells infiltration.



**Figure 5.** Representative hematoxylin and eosin section of the lung (45X) – Intravascular hemorrhagic thrombosis, with in toto muscular wall thickening and endothelial hyperplasia.

immunoglobulin serum tests, and evidence of bilateral and multiple patchy or ground glass appearance at chest CT scan.

Although clinical and radiographic findings in COVID-19 patients have been largely reported, there is a lack of pathologic informations conducted on biopsies or autopsies and the literature is scarce. The early histologic changes of 2 patients that underwent lung lobectomy for adenocarcinoma and retrospectively diagnosed with COVID-19 have been previously described.<sup>[3]</sup> Edema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes with inflammatory cellular infiltration were prominent in the pathological specimens. To our knowledge, this report by Tian and colleagues represents the first description of pulmonary changes induced by COVID-19.<sup>[3]</sup> However, the described tissue alterations were the early-phase changes in asymptomatic subjects and may not be totally accurate for symptomatic patients. Therefore, our study managed to broaden Tian and colleagues report by describing the pathological changes of 2 symptomatic COVID-19 patients intubated for respiratory distress. Bronchiolitis and alveolitis with proliferation, atrophy, and desquamation of alveolar epithelial cells were present confirming the direct tropism of the virus for alveolar cells. This is in accordance with a recently published series describing postmortem findings of firm and severely congested lung parenchyma with concomitant exudative diffuse alveolar damage.<sup>[9]</sup> The selective tropism of the COVID-19 for the angiotensin converting enzyme 2 (ACE2), exposed in type II alveolar cells, results in cells damage and apoptosis with consequent acute alveoli injury, septum disruption, and pulmonary edema. The interstitial tissue is thickened due to sustained fibroblast activation with a significant amount of infiltrated inflammatory cells triggered via the circulating pro-inflammatory “cytokine storm” (i.e. TNF, IL-1 $\beta$ , IL-6, etc.).<sup>[10]</sup> The thickened interstitium correspond to the characteristic radiographic findings of peripheral ground-glass opacity detected by chest computed tomography. Diffuse peripheral vessels involvement,

endothelial thickening, and diffuse intraluminal hemorrhagic thrombosis, consistent with a generalized microvascular injury was found in both cases. ACE2 receptors are expressed by endothelial cells and recent findings showed direct evidence of viral elements within endothelial cytoplasm.<sup>[11]</sup> It is likely that the direct viral and complement-mediated endothelial injury cause a widespread alteration of the endothelial homeostasis with consequent microvascular dysfunction and shift of the vascular equilibrium towards a procoagulant state.<sup>[12]</sup> This further support the recently described findings of capillarostasis, vascular congestion, alveolar capillaries microthrombi, and pulmonary embolism.<sup>[13,14]</sup> These features may correlate with the late phase of disease-induced coagulopathy and consequent increase of lung dead space, presumably cause of respiratory distress necessitating mechanical support.

#### 4. Conclusion

To our knowledge, this is the first report describing the late phase histological findings of 2 symptomatic COVID-19 patients intubated for respiratory distress. Despite the well-known pulmonary damage, the late-phase tissue alterations include diffused peripheral vessels endothelial hyperplasia, in toto muscular wall thickening, and intravascular hemorrhagic thrombosis. These findings may provide new insights into the specific COVID-19 pneumonia pathogenesis, which might be useful for focused and timely therapeutic strategies.

#### Author contributions

Study conception and design: Aiolfi, Biraghi, Bona. Acquisition of data: Aiolfi and Bona. Analysis and interpretation of data: Aiolfi, Bruni, Clemente, Donatelli. Drafting of manuscript: Aiolfi and Khor. Critical revision of manuscript: Aiolfi, Cirri, Miceli, Montisci, Donatelli, Bona.

## References

- [1] Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;doi.org/10.1056/NEJMoa2001017.
- [2] Chung M, Bernheim A, Mei X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). *Radiology* 2020;295:202–7.
- [3] Tian S, Hu W, Niu L, et al. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. *J Thorac Oncol* 2020;pii: S1556-0864(20)30132-5. doi: 10.1016/j.jtho.2020.02.010. [Epub ahead of print].
- [4] Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020;8:420–2. Epub 2020 Feb 18.
- [5] Luo W, Yu H, Gou , et al. Clinical pathology of critical patient with novel coronavirus pneumonia (COVID-19). *Preprints* 2020;2020020407.
- [6] Aiolfi A, Biraghi T, Montisci A, et al. Management of persistent pneumothorax with thoracoscopy and blebs resection in covid-19 patients. *Ann Thorac Surg* 2020;pii: S0003-4975(20)30604-4.
- [7] Wan S, Xiang Y, Fang W, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. *J Med Virol* 2020;1–0. doi:10.1002/jmv.25783.
- [8] Wang Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;doi.org/10.1001/jama.2020.1585.
- [9] Menter T, Haslbauer JD, Nienhold R, et al. Post-mortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings of lungs and other organs suggesting vascular dysfunction. *Histopathology* 2020;doi: 10.1111/his.14134. Online ahead of print.
- [10] Mehta P, McAuley DF, Brown M, et al. HLH across speciality collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395:1033–4. Epub 2020 Mar 16.
- [11] Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;pii: S0140-6736(20)30937-5. doi: 10.1016/S0140-6736(20)30937-5. [Epub ahead of print].
- [12] Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J Am Coll Cardiol* 2020;[PMID: 32311448] doi:10.1016/j.jacc.2020.04.031.
- [13] Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19. *Ann Intern Med* 2020;M20–2003. doi: 10.7326/M20-2003.
- [14] Lax SF, Skok K, Zechner P, et al. Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. *Ann Intern Med* 2020;doi: 10.7326/M20-2566. Online ahead of print.