

CASE REPORT

PULMONARY CAPILLARY HEMANGIOMATOSIS INDUCED BY SARS-COV-2 INFECTION. A CASE REPORT

D. Fanni ^{1,7}, R. Demontis ², L. Saba ³, D. Barcellona ⁴, N. Lenigno ², C. Gerosa ^{1,7},
C. Botta ⁵, F. Cau ⁵, G. Faa ^{1,7}, R. Sciot ⁶, E. D'Aloia ²

¹ Department of Pathology, Azienda Ospedaliero Universitaria (AOU) di Cagliari, University Hospital San Giovanni di Dio, Cagliari, Italy

² Forensic Medicine Section, Department of Medical Sciences and Public Health, University of Cagliari, Monserrato, Cagliari, Italy

³ Department of Radiology, Azienda Ospedaliero Universitaria (AOU) di Cagliari, Polo di Monserrato, Cagliari, Italy

⁴ Department of Internal Medicine, Azienda Ospedaliero Universitaria (AOU) di Cagliari, Polo di Monserrato, Cagliari, Italy

⁵ Division of Pathological, San Gavino Hospital, ATS, San Gavino, Italy

⁶ Department of Pathology KU Leuven, University Hospital Gasthuisberg Leuven, Leuven, Belgium

⁷ Department of Biology, College of Science and Technology, Temple University, Philadelphia, PA, USA

CORRESPONDING AUTHOR:

Daniela Fanni

Department of Pathology

Azienda Ospedaliero Universitaria (AOU) di Cagliari

University Hospital San Giovanni di Dio

via Ospedale 54

09100 Cagliari, Italy

Department of Biology

College of Science and Technology

Temple University

1801 N. Broad Street

E-mail: daniela.fanni@unica.it

ORCID: 0000-0003-2797-8343

Doi: 10.48286/aro.2021.18

History

Received: Mar 15, 2021

Accepted: Apr 12, 2021

Published: Jun 1, 2021

ABSTRACT

Human morbidity and mortality associated with the infection SARS-CoV-2 is mainly due to pneumonia. The histological pattern of lungs is characterized by diffuse alveolar damage (DAD) and hyaline membranes. Vascular changes, including endothelial dysfunction in the alveolar septal capil-

laries followed by thrombosis and disseminated intravascular coagulation, are frequently associated. Recently, further microvascular changes leading to new blood vessel growth through intussusceptive angiogenesis and distortion of microvascular architecture have been reported in lungs from patients

died because of COVID-19. Here we report a case of COVID-19 in a 63-year-old patient affected by progressive respiratory failure. At histology, DAD was associated with distinctive vascular changes, including alveolar capillary microthrombi and thrombosis of arterial vessels. Moreover, a marked proliferation of small capillaries extending from the alveolar septa and compressing the adjacent alveoli was observed, allowing the diagnosis of pulmonary capillary hemangiomatosis (PCH). This report of PCH in a patient affected by COVID-19 reinforces the hypothesis of the major role played by endothelial dysfunction, capillary thrombosis and neoangiogenesis in SARS-CoV-2 infection and suggests that new blood vessel growth may evolve toward PCH, ending to the disruption of lung architecture.

oli was observed, allowing the diagnosis of pulmonary capillary hemangiomatosis (PCH). This report of PCH in a patient affected by COVID-19 reinforces the hypothesis of the major role played by endothelial dysfunction, capillary thrombosis and neoangiogenesis in SARS-CoV-2 infection and suggests that new blood vessel growth may evolve toward PCH, ending to the disruption of lung architecture.

KEY WORDS

Pulmonary capillary angiomas; COVID-19; SARS-CoV2.

IMPACT STATEMENT

Endothelial dysfunction, capillary thrombosis and neoangiogenesis with new blood vessel growth induced by SARS-CoV-2 may evolve toward pulmonary capillary hemangiomatosis and lung architecture disruption.

INTRODUCTION

Human morbidity and mortality associated with infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is mainly due to progressive life-threatening pneumonia (1, 2). At imaging assessment, computed tomography (CT) imaging evidences peripheral ground-glass opacities indicative for the diagnosis of acute respiratory distress syndrome (ARDS) (3). The histological pattern of lungs, at autopsy, is characterized by necrosis of alveolar lining cells (type I pneumocytes), hyaline membranes, alveolar and interstitial edema and hemorrhages, *i.e.* the typical features of diffuse alveolar damage (DAD) (4, 5). However, lung pathology in COVID-19 patients is not restricted to alveolar damage: vascular changes are frequently associated with severe SARS-CoV-2 infection. Pulmonary thrombosis and disseminated intravascular coagulation, evidenced at histology by the formation of fibrin thrombi in the alveolar septa capillaries, are frequently detected in COVID-19 lung disease (6, 7). Recently, microvascular changes have been described in lungs from patients died from COVID-19, leading to new blood vessel formation, ending with distortion of the microvascular architecture of the lungs (8). By the use of scanning electron microscopy (SEM), structurally deformed capillaries were found in COVID-19 lungs, whereas transmission electron microscopy (TEM) revealed severe changes in endothelial cells in lungs from patients died from ARDS secondary to SARS-CoV-2 infection (9). All these data taken together, vascular changes, in-

cluding endothelial injury, widespread thrombosis of alveolar capillaries and new vessel growth, have been proposed as distinctive features of DAD due to SARS-CoV-2 infection, being absent in DAD associated with other etiologies (8). A recent proteomic analysis of 144 autopsies in COVID-19 patients evidenced dysregulation in multiple organs of key factors involved in angiogenesis, with 139 angiogenesis-related proteins significantly dysregulated that characterize a multi-organ proteomic landscape typical of COVID-19 (10). Here we report a case of diffuse alveolar damage in a patient died with COVID-19, associated with a marked capillary proliferation leading to a pattern of pulmonary capillary hemangiomatosis (PCH).

Case report

A male patient, aged 63 years, developed a progressive respiratory failure. The patient died at home before medical intervention. Post-mortem molecular tests, performed by nasopharyngeal swabs, revealed SARS-CoV-2 infection. At autopsy, lungs were heavy (right lung 1,100 g; left lung 920 g), reddish in colour, diffusely edematous and showed a firm consistency. Microscopic examination of the lungs evidenced diffuse alveolar damage in the acute stage. Hyaline membranes were associated with marked congestion of larger veins and septal capillaries, alveolar and interstitial edema, fibro-hemorrhagic alveolitis and focal type II pneumocyte hyperplasia (**figure 1**). Lymphocyte and monocyte infiltrations

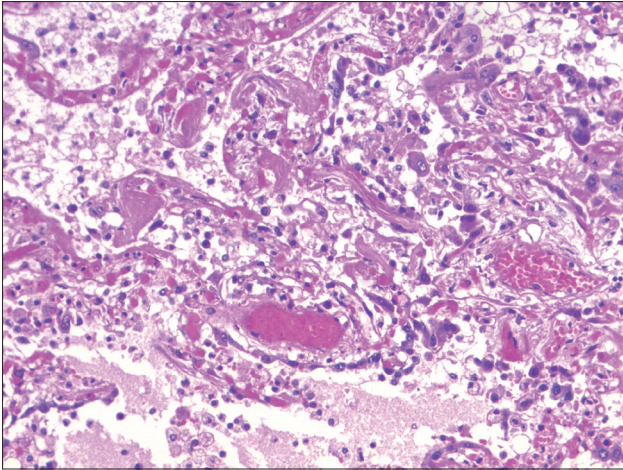


Figure 1. Diffuse alveolar damage. Hyaline membranes, hemorrhagic alveolitis, congestion of septa capillaries, type II pneumocyte hyperplasia.

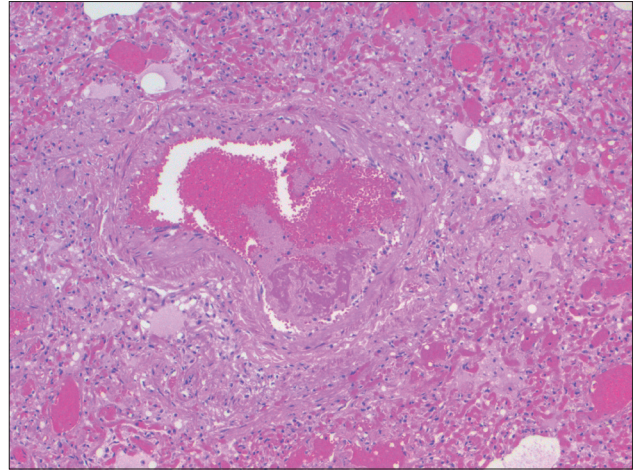


Figure 2. Thrombosis of an arterial vessel surrounded by marked capillary proliferation and alveolar collapse.

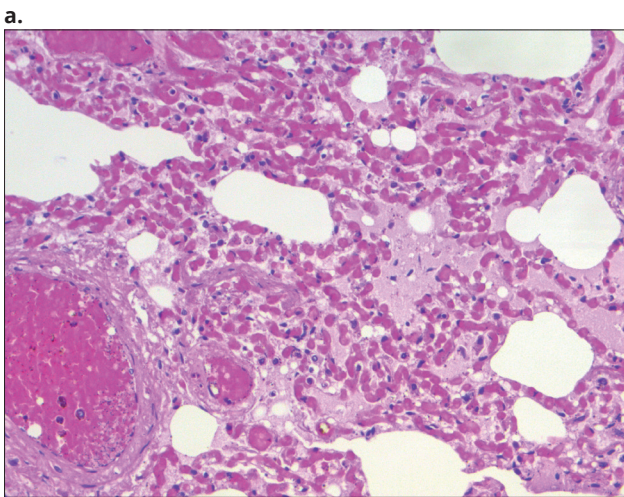


Figure 3. Marked proliferation of capillary vessels, extending from the inter-alveolar septa into the surrounding alveolar and vascular structures.

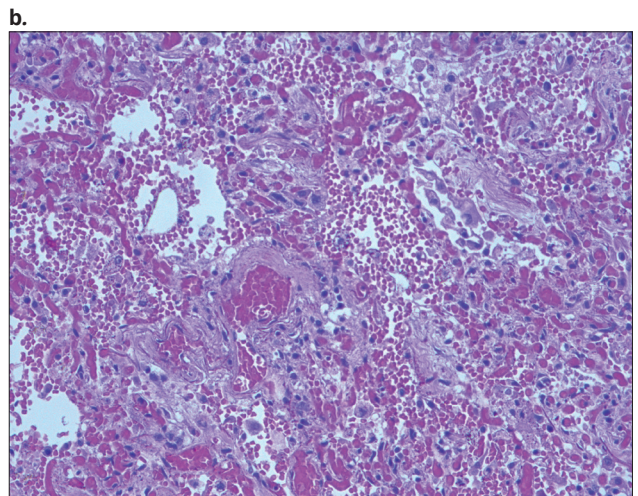
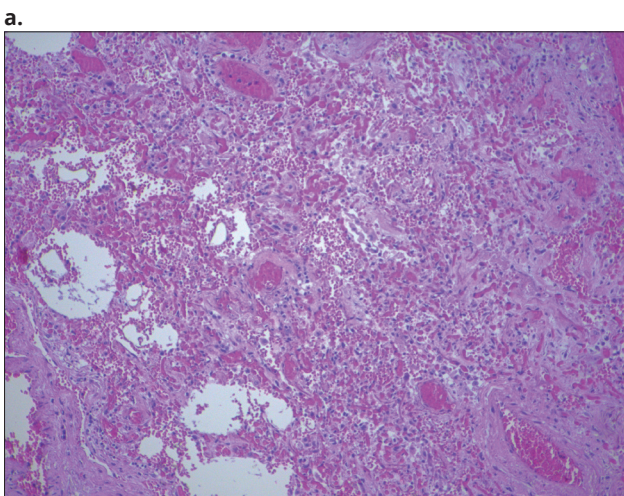
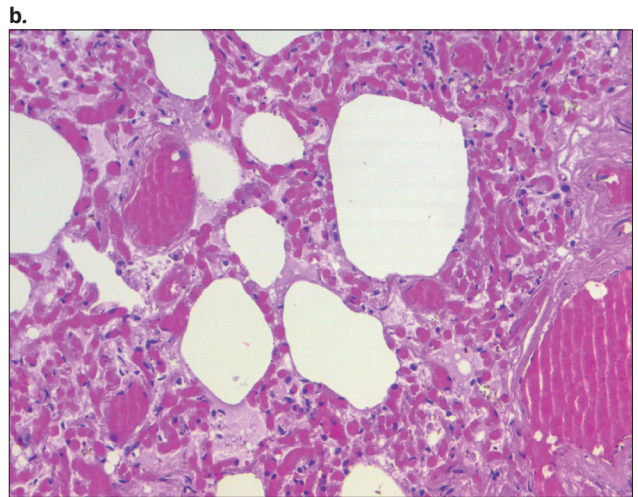


Figure 4. *a.* Residual alveoli surrounded and infiltrated by proliferating capillaries at low power. *b.* At high power.

were mild and patchy. In multiple lung specimens, distinctive vascular changes were also detected, consisting in alveolar capillary microthrombi and

thrombosis of arterial vessels (**figure 2**). Moreover, in some lung specimens we observed a marked proliferation of small capillaries, extending from the

alveolar septa and compressing the adjacent alveolar structures (**figure 3**). The lumen of the proliferating capillaries was occupied by microthrombi. The disordered capillary proliferation irregularly spread, involving pre-existing pulmonary vessels and adjacent airways (**figures 4 a, b**). At immunohistochemistry, proliferating vascular structures showed strong and diffuse immunostaining for CD31, CD34 and focal immunoreactivity for WT1.

DISCUSSION

The complexity of pathological changes observed in the lungs of patients affected by COVID-19 has been recently underlined by multiple reports on the different molecular pathways triggered by SARS-CoV-2 (11). Among them, vascular changes of lung vasculature, including endothelial cell dysfunction, endothelialitis (12), thrombosis of septal capillaries (13) and thrombosis of pulmonary arteries (14) have been proposed as distinguishing elementary lesions of COVID-19 from ARDS due to influenza infection (14). Moreover, previous papers evidenced the occurrence, in lungs from patients infected by SARS-CoV-2, of new vessel growth through a mechanism of intussusceptive angiogenesis (14). Neoangiogenesis was hypothesized to be the consequence of tissue hypoxia, caused by the high degree of endothelial damage and capillary thrombosis due to SARS-CoV-2 infection. In the case reported here, the hypothesis that pulmonary vessels represent one of the main targets for COVID-19 is confirmed by the detection of widespread lesions of endothelium, associated with diffuse intravascular coagulation in all the segments of lung vasculature. Moreover, our findings lay stress on the ability of SARS-CoV-2 to trigger a previously unreported proliferation of lung capillaries. In this case of lung disease due to COVID-19, proliferating vascular structures extended from the alveolar septa, infiltrating the structures of the pulmonary parenchyma, including alveoli, veins, and interstitial structures. These findings were at the basis of the diagnosis of pulmonary capillary hemangiomatosis (PCH), a rare and controversial entity often associated with pulmonary hypertension (15, 16). The underlying pathogenetic mechanisms of PCH are poorly understood. Recently, intussusceptive angiogenesis, a process of dividing pre-existing capillaries by formation of intravascular pillars, has been hypothesized to be involved in the pathogenesis of PCH (17). According to this

hypothesis, venous and capillary occlusion, caused by a widespread thrombosis favoured by SARS-CoV-2 infection, might increase stretching forces in pulmonary capillaries, inducing intersusceptive neoangiogenesis, ending with the insurgence of PCH in COVID-19 pneumonia.

In conclusion, our report of PCH in a patient affected by COVID-19 reinforces previous reports on the major role played by endothelial dysfunction (18), endothelialitis, thrombosis (8) and neoangiogenesis (14) in lung disease due to SARS-CoV-2 infection, and suggests that SARS-CoV-2 induced neoangiogenesis may evolve toward capillary hemangiomatosis, ending with disruption of the lung architecture, a typical feature of PCH.

ETHICS

Fundings

There were no institutional or private fundings for this article.

Conflict of interests

The authors have declared no conflict of interests.

Availability of data and material

All the data supporting the findings of this study are available within the article and can be shared just before a reasonable request to the corresponding author.

Authors' contribution

All the authors contributed equally to conception, data collection, analysis and writing of this paper.

Ethical approval

Studies have been performed according to the Declaration of Helsinki (World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving humansubjects. JAMA 2013 Nov 27;310(20):2191-4. Doi: 10.1001/jama.2013.281053). The procedures have been approved by a local ethics committee (date: 27/02/2021; approval number/code: PG/2021/1531; name of the ethics approving committee: Comitato Etico Indipendente Azienda Ospedaliero Universitaria di Cagliari).

Consent to participate

Informed, written consent has not been obtained because the patient was dead.

REFERENCES

- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395(10223):497–506.
- Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020;395(10223):507–13.
- Raptis CA, Hammer MM, Short RG, et al. Chest CT and Coronavirus Disease (COVID-19): A Critical Review of the Literature to Date. *AJR Am J Roentgenol* 2020;215(4):839–42.
- Barton LM, Duval EJ, Stroberg E, Ghosh S, Mukhopadhyay S. COVID-19 Autopsies, Oklahoma, USA. *Am J Clin Pathol* 2020;153(6):725–33.
- Tian S, Hu W, Niu L, Liu H, Xu H, Xiao S-Y. Pulmonary Pathology of Early-Phase 2019 Novel Coronavirus (COVID-19) Pneumonia in Two Patients With Lung Cancer. *J Thor Oncol* 2020;15(5):700–4.
- Marongiu F, Grandone E, Barcellona D. Pulmonary thrombosis in 2019-nCoV pneumonia? *J Thromb Haemost* 2020. Available at: <http://doi.wiley.com/10.1111/jth.14818>
- Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. *Transl Res* 2020;220:1–13.
- Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med* 2020;383(2):120–8.
- Ackermann M, Mentzer SJ, Jonigk D. Pulmonary Vascular Pathology in Covid-19. Reply. *N Engl J Med* 2020;383(9):888–9.
- Nie X, Qian L, Sun R, et al. Multi-organ Proteomic Landscape of COVID-19 Autopsies. *Cell* 2021;S0092867421000040.
- Saba L, Gerosa C, Fanni D, et al. Molecular pathways triggered by COVID-19 in different organs: ACE2 receptor-expressing cells under attack? A review. *Eur Rev Med Pharmacol Sci* 2020;24(23):12609–22.
- Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;395(10234):1417–8.
- Yao XH, Li TY, He ZC, et al. A pathological report of three COVID-19 cases by minimal invasive autopsies. *Zhonghua Bing Li Xue Za Zhi* 2020;49(5):411–7.
- Ackermann M, Mentzer SJ, Kolb M, Jonigk D. Inflammation and intussusceptive angiogenesis in COVID-19: everything in and out of flow *Eur Respir J* 2020;56(5).
- O'Keefe MC, Post MD. Pulmonary capillary hemangiomatosis: a rare cause of pulmonary hypertension. *Arch Pathol Lab Med* 2015;139(2):274–7.
- Guzman S, Khan MS, Chodakiewitz Y, et al. Pulmonary capillary hemangiomatosis: a lesson learned. *Autops Case Rep* 2019;9(3):e2019111.
- Neubert L, Borchert P, Shin H-O, et al. Comprehensive three-dimensional morphology of neoangiogenesis in pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis. *J Pathol Clin Res* 2019;5(2):108–14.
- Huertas A, Montani D, Savale L, et al. Endothelial cell dysfunction: a major player in SARS-CoV-2 infection (COVID-19)? *Eur Respir J* 2020;56(1).