Asymptomatic COVID-19 Patient, Occurrence of Fatal Pulmonary Arterial Thrombosis.

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Case Report

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**Abstract**

The induction of hypercoagulability is one of the pathophysiological mechanism in patients with a severe presentation of the SARS-CoV-2 infection that can contribute to death.

A considerable number of SARS-Cov-2 infected individuals could be asymptomatic and they don't need medical treatment. We reported autopic evidences of COVID-19 trombotic fatal lesions in an asymptomatic COVID-19 patient after negative conversion.

This study provides evidences that an appropriate diagnostic screening for thrombotic complications and the early treatment recommendations of antithrombotic drugs could represent an important topic even in asymptomatic individuals.

**Introduction**

A number of recent studies have reported the high risk of hospitalized patients with COVID-19 to develop thrombotic complication (1,2). Here we presented the occurrence of fatal pulmonary arterial thrombosis in an asymptomatic COVID-19 patient.

**Case Presentation**

A 61-year-old woman was referred to an emergency department in Rome (Italy) due to sudden loss of consciousness and cardiac arrest. She could not be resuscitated and was declared dead soon after admission. The patient had contact history with confirmed COVID-19 patients, and 32 days before decease was tested positive for SARS-Cov-2 infection without any symptoms. 5 days before death she tested negative; the test was repeated once more at a distance of 48h, confirming negative results. She had no medical co-morbidities or any cause of immunosupression and presented as healthy individual before SARS-CoV-2 infection, taking no medications. No relevant symptoms have been shown neither at the time of pathogenic test, nor until exitus. To determine the cause of death a complete autopsy was performed.

Whole body complete post-mortem examination was performed at the National Institute for Infectious Diseases Lazzaro Spallanzani-IRCCS Hospital (Rome, Italy) according to guidance for biosafety practices autopsies and collection of specimens and approved by the local Clinical Research Ethics Committee (approval number: n° 9/2020).

Macroscopic inspection of the lung revealed pulmonary edema, massive bilateral congestion and regions of dark-colored haemorrhage (Fig S1A). The pleura was inconspicuous except for fibrous adhesions and pleural effusion was absent. The most striking feature was the presence of a large thrombus occluding the main pulmonary artery at bifurcation (Fig 1A). Lungs were bilaterally extensively sampled for a complete histological evaluation. Microscopic analysis has shown heterogeneous pattern of pathological changes in the lung tissue, as well as different stages of diffuse alveolar damage with edema and
hemorrhagic areas (Fig S1 D). Numerous vascular thrombi were detected (Figs 1B; S1B). Diffuse interstitial fibrosis with fibroblast proliferation was present (Fig 1D), together with inflammatory infiltrate of pulmonary interstitium (Figs 1C; S1D). The alveolar capillaries thickened, and displayed extravasation of erythrocytes into alveolar spaces (Fig S1C). Infiltrating T lymphocytes, both CD4+ (Fig 1E) and CD8+ (Fig S1F), were present into alveolar septa and clustered around capillary vessels, as demonstrated by immunohistochemistry. In addition numerous macrophages (CD68+) were found (Fig 1F). Of note, positivity for CD20 was not detected, indicating the absence of infiltrating B-lymphocytes. Some areas of the lungs appeared not affected and presented no signs of alveolar damage (Fig S1E). Lung samples tested negative for real-time PCR for SARS-Cov-2-infection.

Gross examination of heart revealed decrease in volume and consistency (weight 250 g). Left and right atrium and ventricles appeared dilated. The myocardium was flabby, congested and hemorrhagic (Fig S2A). At histological level myocytes hypertrophy and variable degrees of interstitial and vascular fibrosis were found (Fig S2B). Active myocarditis was characterized predominantly by lymphocytic mononuclear infiltrate, dissociating myocyte fibers (Figs 1G; S2 C,D). The infiltrating cells were mainly represented by CD4+ T lymphocytes (Fig S2E); CD8+ T lymphocytes were instead rare (Fig S2F). CD68+ macrophages were numerous and diffuse (Fig 1H), while B-lymphocytes were not detected.

Other organs analyzed showed some histopathological modifications, as reported in autopic findings of COVID-19 patients: kidneys displayed swelling of the glomerular endothelial cells, the spleen showed white pulp atrophy and congestion of red pulp and macrovesicular steatosis was of the liver observed.

In the final autopsy report, the cause of death was listed as pulmonary arterial thrombosis.

**Discussion**

The induction of hypercoagulability has been recognized as one of the pathophysiological mechanism in patients with a severe presentation of the SARS-CoV-2 infection (3). COVID-19 patients may be susceptible to increased risk for deep vein thrombosis and pulmonary embolism due to hypoxia and immobilization in intensive care unit (4,5). In addition, SARS-CoV-2 infection can affect the coagulation cascade and fibrinolysis either by directly producing vascular dysfunction, by viral effect on endothelial cells, or indirectly, by the exacerbated induction of inflammatory cytokines (e.g., including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) (6). Indeed an exaggerated inflammatory response may induce a condition in which coagulation contributes to pathological arterial thrombotic events (7).

A considerable number of SARS-Cov-2 infected individuals could be asymptomatic, i.e. having viral nucleic acid or antibody testing positive results but without displaying any symptom (8). A multi-center retrospective study, based on 100 individuals with the asymptomatic infection, reported that 60% of cases demonstrated findings of pneumonia during chest CT imaging, including well-recognized features of coronavirus disease, such as ground-glass opacities (9).
To our knowledge, this is the first report describing autopic evidences of COVID-19 trombotic fatal lesions in a case of asymptomatic infection. Sudden death was attributable to pulmonary thrombosis associated with interstitial fibrosis and hemorrhagic destruction of the lung parenchyma. In addition, the inflammation of cardiac interstitium could also have contributed to the unexpected death. Cardiovascular complications, such as heart failure, myocarditis, pericarditis, vasculitis, and cardiac arrhythmias has been reported in COVID-19 in patients without preexisting cardiovascular diseases. Even in some patients who recover, inflammatory cardiomyopathy could persist (10). Our finding demonstrated that also asymptomatic patients can persist with inflammatory cardiomyopathy.

**Conclusion**

Collectively, our study provides evidences that also asymptomatic COVID-19 patients may be at risk to develop trombotic complications. An appropriate diagnostic screening for trombotic complications and to the early treatment recommendations of antithrombotic drugs could represent an important topic.

**Declarations**

**Author contributions**

All authors contributed to the study design and data interpretation. F.D.N. and D.C. collected autopic specimens and performed histopathological analysis. R.N. and L.F. discussed the results and wrote the paper. All authors contributed approved the final version.

**Competing interests**

The authors declare no competing interests.

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Whole body complete post-mortem examination was performed at the National Institute for Infectious Diseases Lazzaro Spallanzani-IRCCS Hospital (Rome, Italy). According to National hospital law, an autopsy in a public hospital is mandatory without requirement of an informed consent by the relatives when the cause of death is unclear, scientific or public interest is present. In this study, autopsy was performed in accordance with the law owing to the unknown cause of death, and to both scientific and public interest in a pandemic novel disease. No informed consent was obtained from the families. All
performed procedures and investigations were in accordance with the ethical standards of the institutional research committee (approval number: n° 9/2020).

References


Figures
Pathological findings. (A) Gross pathological specimen of the thrombus occluding pulmonary artery bilaterally. The specimen consists of an irregular fragment of red-tan hemorrhagic tissue measuring about 1.3 cm in diameter. (B) Light microscopic analysis shows an intravascular thrombus of large vessel (arrow). (C) Lung parenchyma showing inflammatory cells in the pulmonary interstitium (arrows) and in alveolar space. (D) Diffuse interstitial fibrosis is visible (arrow). Numerous CD4+ T lymphocytes (E)
and CD68+ macrophages (F) are sparse into alveolar septa and around vessels (arrows). (G) Heart tissue shows myocarditis characterized by mononuclear, predominantly lymphocytic infiltrate (arrows). (H) Numerous macrophages (CD68+) infiltrates the myocardium (arrows). Scale bars: A = 1 cm; B = 100 μm; C-F = 50 μm; G = 7 μm; H = 14 μm

**Supplementary Files**

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