

Early histologic findings of pulmonary SARS-CoV-2 infection detected in a surgical specimen.

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Case Report

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Abstract

Despite the current pandemic season, reports on pathologic features of Coronavirus disease 19 (COVID-19) are exceedingly rare at the present time. Here we describe the pathologic features of early lung involvement by COVID-19 in a surgical sample resected for carcinoma from a patient who developed SARS-CoV-2 infection soon after surgery.

The main histologic findings observed were pneumocyte damage, alveolar hemorrhages with clustering of macrophages, prominent and diffuse neutrophilic margination within septal vessels and interstitial inflammatory infiltrates, mainly represented by CD8+ T lymphocytes. These features are similar to those previously described in SARS-CoV infection.

Subtle histologic changes suggestive pulmonary involvement by Covid-19 may be accidentally encountered in routine pathology practice, especially when extensive sampling is performed for histology. These findings should be carefully interpreted in light of the clinical context of the patient and could prompt a pharyngeal swab PCR test to rule out the possibility of SARS-CoV-2 infection in asymptomatic patients.

Declarations

Ethics

Compliance with ethical standards. The study complies with ethical standards with both Institutions. The patient *signed the informed consent* for publication of clinical data in anonymous form.

Funding

No industry funds were used.

Conflict of interest

The authors declare that they have no conflict of interest.

Contributions

Pernazza Angelina contributed to the analysis of the pathologic findings and to manuscript writing;

Mancini Massimiliano contributed to the pathologic analysis and to manuscript writing;

Rullo Emma contributed to the analysis of the pathologic findings and to manuscript writing;

Bassi Massimiliano collected and critically analyzed clinical data;

De Giacomo Tiziano collected and critically analyzed clinical data;

Della Rocca Carlo revised the work critically for important intellectual content;

d'Amati Giulia contributed to the analysis of the pathologic findings and to manuscript writing.

Introduction

Coronavirus disease 19 (COVID-19) is a global pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). According to the WHO COVID-19 situation report of March 29th, Italy is the most affected European country, with 92.472 total cases and 10.023 deaths. The virus is transmitted mainly by inhalation of respiratory droplets from both symptomatic and asymptomatic patients. Fever, fatigue and dry cough are the most common symptoms at clinical presentation.

Approximately 13-20% of infected individuals develop severe respiratory symptoms with radiological findings of interstitial involvement, requiring assisted oxygenation [1-3]. A low number of routine autopsies is performed due to the high infectivity of the disease; accordingly, there are only a few reports in medical literature describing the histopathologic findings of SARS-CoV-2 infection [4-5]. More in-depth investigations only come from SARS-Coronavirus outbreaks in the past [6].

Here we describe the histologic features of early lung involvement by COVID-19 in a surgical sample resected for carcinoma from a patient who later developed SARS-CoV-2 infection.

Case Report

A 61 years old male smoker was admitted to our Hospital for surgical treatment of a lung adenocarcinoma, diagnosed on biopsy. His clinical history was positive for a MALT lymphoma diagnosed 6 months before, with complete remission after therapy. According to pre-operative imaging, obtained three weeks before surgery, the lesion was localized in the right inferior lobe, measured 2 cm and showed a solid appearance. There were no ground glass opacities. At admission the patient was in good general conditions, afebrile. A thoracoscopic lobectomy with lymph node dissection (stations 2, 4, 7, 8, 9 and 10) was performed, without intraoperative complications. After surgery, the patient developed progressive lymphopenia (with values ranging between 920 and 340 lymphocytes/ μ L from the first to the fifth post-operative day) and, on the scheduled date for discharge, had an episode of fever (38 °C) in absence of respiratory symptoms. Thus, his antibiotic therapy was changed, with no improvement. A pharyngeal swab PCR test was performed, which confirmed the suspicion of SARS-CoV-2 infection. The patient was immediately transferred to the isolation ward where he developed cough, dyspnea, fatigue and high fever (38-39°C). SpO₂ was stable between 96% and 98%. Both white blood cells (2570/ μ L) and lymphocytes counts were low (280/ μ L). A chest CT-scan, showed post-resection changes and bilateral, peripheral and ill-defined ground-glass opacities, mainly involving the lower lobe, consistent with COVID-19 pneumonia (Fig1a).

Since oxygen saturation had dropped to 35%, he received supplemental oxygen through a CPAP mask. On a second CT scan, performed one week later, the ground-glass opacities were enlarged, with areas of consolidation (Fig 1b). He received a therapy based on antibiotics (Meropenem and Bactrim), antiviral drugs (Acyclovir and Darunavir) and on two recently approved experimental drugs for SARS-CoV-2 infection: Tocilizumab (commonly used for the therapy of rheumatoid arthritis) and chloroquine hydrate (a common antimalarial drug), with an improvement of his conditions and clinical remission in the following weeks.

Histologic examination of the formalin-fixed specimen confirmed the diagnosis of lung adenocarcinoma, with a predominant acinar pattern. The lung parenchyma surrounding the neoplasia showed diffuse hemorrhages and clusters of alveolar macrophages, with occasional multinucleated cells (Fig 2a). At higher magnification there was evidence of both diffuse pneumocyte loss and reactive hyperplasia, with focal pneumocytes showing nuclear inclusions (Fig 3a, b). There were scanty fibrin depositions on the alveolar surfaces, in absence of hyaline membranes (Fig 2c). The interstitium showed edema and a mild inflammatory infiltrate, mainly composed of cytotoxic (CD8 +) T lymphocytes (Fig 3 c-f). Interestingly, there were diffuse aspects of neutrophil margination within small arterioles (Fig 3d). Occasional fibrous plugs were also observed (Fig 3c). Interstitial changes were more marked in the subpleural area, where mild fibrous thickening of alveolar septa was also observed (Fig 2b).

Finally, areas of smoking-related interstitial fibrosis, consistent with the patient's habits, were also present.

Discussion

In this report we provide a detailed analysis of the early histologic changes of pulmonary SARS-CoV-2 infection. Similar to the two previously published cases from China [5] the virus-related alterations were an incidental finding in a surgical sample sent to the Pathology Department for routine diagnostic work-up of lung cancer, before the onset of clear clinical signs and symptoms of Covid-19. As early radiological changes have been demonstrated in the asymptomatic phase of infection [7], we emphasize the importance of recognizing early subtle histological changes in lung surgical specimens.

The main histologic findings herein described are pneumocyte damage, alveolar hemorrhage and clustering of macrophages, and interstitial inflammatory infiltrates, with prominent and diffuse neutrophilic margination within septal vessels. These features are similar to those described in SARS-CoV infection and are consistent with the previously postulated mechanisms underlying pulmonary damage in SARS [8-9]: the interaction between the virus and both pneumocytes and alveolar macrophages triggers a cascade of immunological events, with production of cytokines and chemokines and expression of adhesion molecules by pneumocytes. This in turn drives an inflammatory response with prominent macrophages, neutrophils and T CD8+ lymphocytes, which is responsible for the diffuse alveolar damage observed in the more severe and advanced stage of the disease. Indeed, diffuse alveolar damage (DAD) has been reported as a common autopsy finding in SARS-CoV [10-14]. A recent autopsy

report highlights the finding of diffuse alveolar damage as the major lung feature also in severe SARS-CoV-2 infection [4]. However, the absence of DAD does not rule out the possibility of Covid-19 pneumonia, in the early stage of disease [12].

Interestingly, in our case histologic findings were more marked and diffuse in the subpleural region. This is consistent with the higher frequency of peripheral and subpleural involvement on high-resolution CT scan recently reported in a cohort of 81 patients with Covid 19 pneumonia [3].

Covid-19 has been shown to strike elderly patients with higher frequency and worse clinical outcome especially in presence of comorbidities (e.g. chronic obstructive pulmonary disease and malignancy) [15-16]. A male predilection has also been recognized [15]. We speculate that the rapid disease evolution observed in our patient could be due to pre-existing lung alterations induced by smoking, although there are no evidences supporting a correlation between smoking and severity of the disease [17].

In conclusion, during the current pandemic season, subtle pulmonary histologic changes suggestive of SARS-CoV-2 infection may be accidentally encountered in routine pathology practice, especially if extensive sampling is performed for histology.

These findings should be carefully interpreted in light of the clinical context of the patient and could prompt a pharyngeal swab PCR test to rule out the possibility of SARS-CoV-2 infection in asymptomatic patients.

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Figures

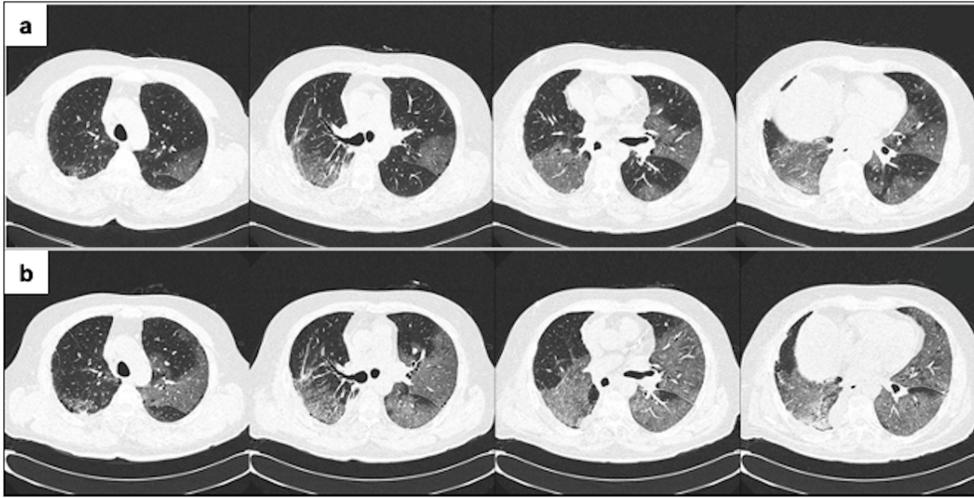


Figure 1

High resolution CT scans performed one (a) and two (b) weeks after surgery, respectively show ground glass bilateral opacities, enlarging with time, with the additional finding of areas of consolidation.

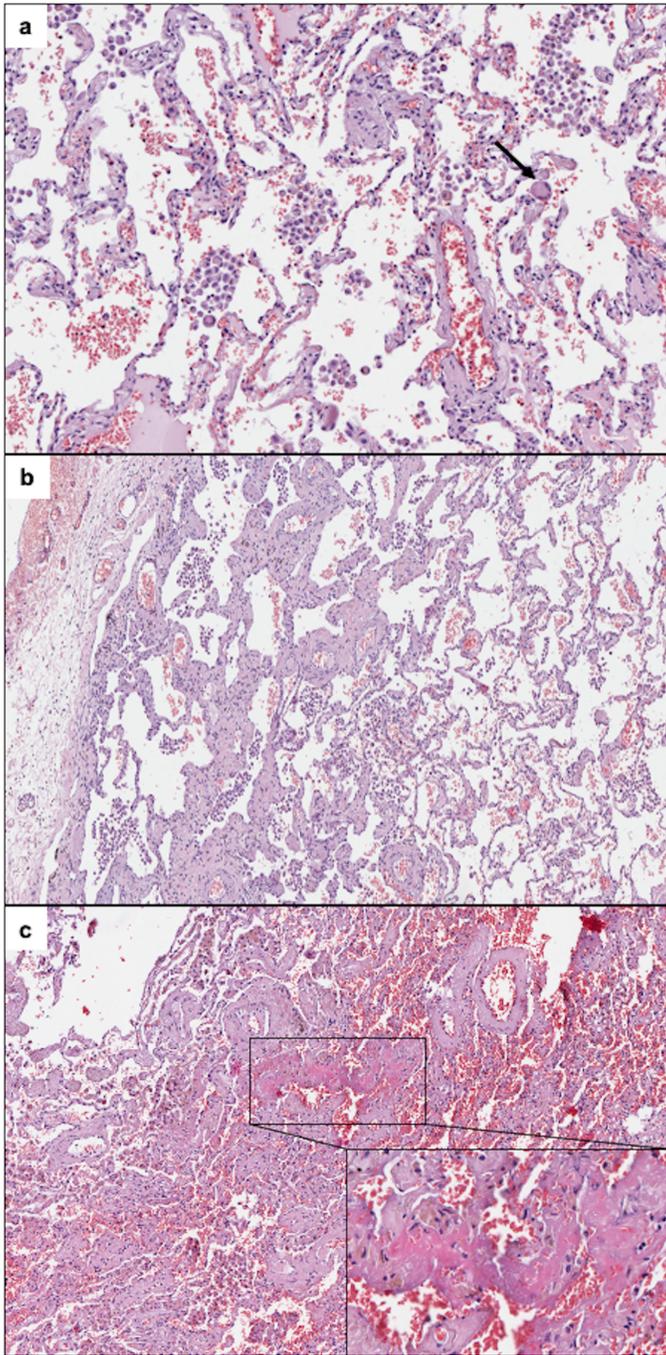


Figure 2

a (20x) Alveolar hemorrhages and clusters of macrophages with occasional giant cells (arrow) b (10x) the alveolar septa show mild fibrous thickening limited to the subpleural area c (10x) fibrin deposits admixed with red blood cells and inflammatory infiltrates (H&E).

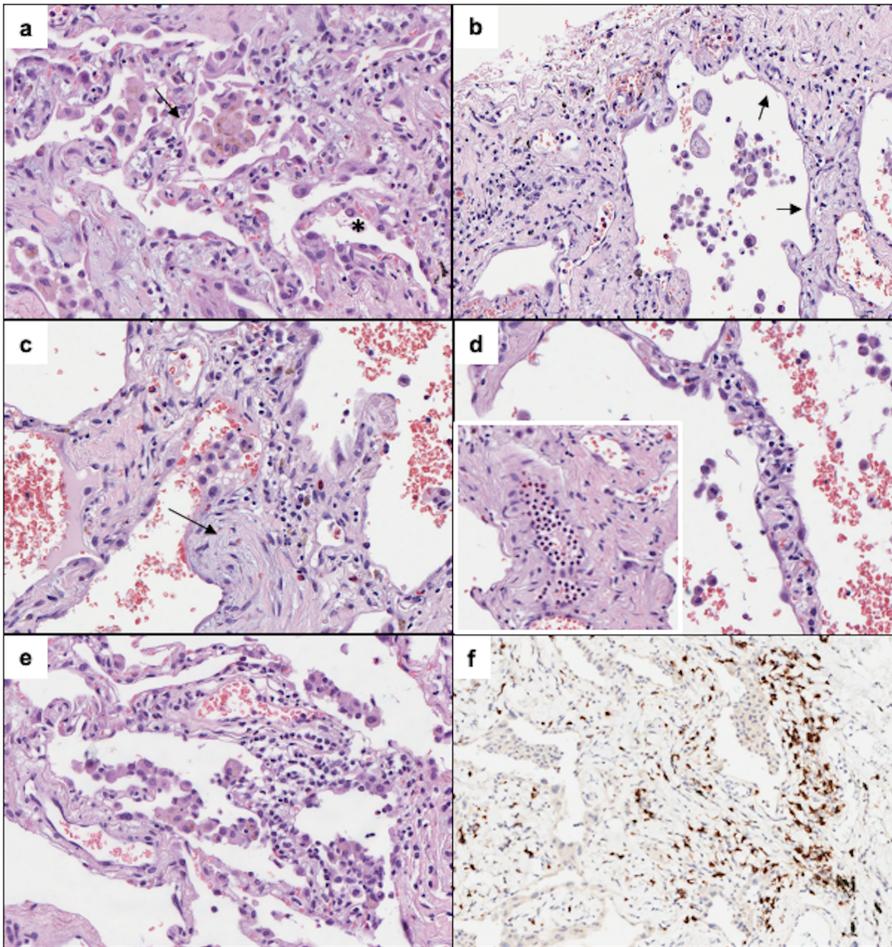


Figure 3

a (40x) Pneumocyte desquamation (arrow) and reactive hyperplasia with focal nuclear inclusion (asterisk). Abundant hemosiderin pigment is present within alveolar macrophages b (40x) diffuse pneumocyte loss (arrows) and alveolar septal thickening c (40x) inflammatory infiltrates and fibrous plugs as those observed in organizing pneumonia (arrow) d (40x) neutrophilic vascular margination and edema of the alveolar wall e diffuse interstitial lymphocytes infiltrate and intra-alveolar macrophages

(H&E) f (20x) CD8 immunostaining shows a prevalence of cytotoxic T lymphocytes (immunoperoxidase stain).