

LETTER TO THE EDITOR**Organizing pneumonia as a manifestation of coronavirus disease 2019**

To the Editor,

Since the arrival of the coronavirus disease 2019 (COVID-19) pandemic, the pathology and clinical literature has been flooded with descriptions of autopsy lung findings in patients who have died of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Diffuse alveolar damage (DAD) is the most commonly reported finding in COVID-19-related deaths and is occasionally accompanied by acute bronchopneumonia. Thrombotic and thromboembolic events are now also recognized as a manifestation of COVID-19.¹ To our knowledge, there are only rare case reports and small case series of COVID-19-related lung pathology in living patients, who did not have DAD and were asymptomatic at the time of surgery.^{2,3} Here, we document the lung findings in a living, symptomatic patient diagnosed with COVID-19-related organizing pneumonia on bronchoscopy.

A 25-year-old woman with past medical history of atypical pemphigus vulgaris in remission and not on immunosuppressive therapy presented to Urgent Care with complaints of cough, dyspnea, myalgias and fever. She was evaluated for possible COVID-19, but a SARS-CoV-2 nasopharyngeal swab was negative and she was given a 5-day course of azithromycin. Despite treatment, her symptoms persisted, she became hypoxemic, and was admitted to the hospital. On admission, computed tomography (CT) of her chest showed bilateral, patchy groundglass opacities (Supplementary Fig. S1a). She was treated with doxycycline and a short course of methylprednisolone, and discharged home on hospital Day 5 following clinical improvement. Her symptoms recurred 1 week later, and she was admitted to our hospital. Broad spectrum intravenous antibiotic therapy was initiated and microbiologic workup was performed, but without identification of a causative pathogen. Serum SARS-CoV-2 immunoglobulin (Ig) G was negative. A repeat CT scan of her chest showed persistent and worsening multifocal opacities (Supplementary Fig. S1b). Bronchoscopy with transbronchial biopsy was performed to further evaluate the etiology of her groundglass opacities. Bronchoalveolar lavage fluid, collected at the time of bronchoscopy, tested positive for SARS-CoV-2 using real-time reverse transcriptase polymerase chain reaction (RT-PCR; Molecular Simplexa COVID-19 Direct real-time RT-PCR assay; DiaSorin, Cypress, CA, USA). Additional laboratory abnormalities included

low serum immunoglobulins with IgG 75 mg/dL (normal, 620–1520 mg/dL), IgM <10 mg/dL (normal, 50–370 mg/dL) and IgA <2 mg/dL (normal, 40–350 mg/dL). Following treatment for COVID-19 pneumonia with convalescent serum and intravenous immunoglobulin (IVIg) for management of her hypogammaglobulinemia, she was discharged home on hospital Day 12 and remained asymptomatic. She continued to receive weekly subcutaneous immunoglobulin for her hypogammaglobulinemia. Three weeks following discharge, a repeat SARS-CoV-2 serologic test for IgG remained negative and follow-up chest CT scan showed resolution of opacities (Supplementary Fig. S1c).

Transbronchial biopsies were obtained from the left lower and upper lobes. Both samples were similar in showing a patchy airspace-filling process, comprised of organizing fibroblasts and myofibroblasts that formed polypoid intraluminal plugs situated within distal airspaces in a pattern characteristic of organizing pneumonia (Fig. 1). Lining pneumocytes were hyperplastic with reactive changes, but viral cytopathic changes were not identified. A focal fibrinous airspace exudate was present, but there were no hyaline membranes. Inflammation was not a conspicuous feature.

Organizing pneumonia is a manifestation of COVID-19 pneumonia, seen here in a patient who did not suffer from acute respiratory distress syndrome and went on to have full resolution of respiratory symptoms. The morphologic findings are typical of organizing pneumonia, characterized by loose plugs of fibromyxoid tissue. In our patient, intraluminal fibrin deposition was only a focal finding. This differs from previous reports of the histologic findings in lungs of patients who were asymptomatic at the time of surgery and later discovered to have COVID-19. Those few anecdotal reports illustrated only a nonspecific inflammatory infiltrate with or without an accompanying fibrinous pneumonia.^{2,3} Additionally, our case did not show prominent perivascular inflammation, which has been described by some in the setting of DAD. While variable degrees of airspace organization have been described in the setting of COVID-19-related DAD (organizing DAD),¹ ours is the first report of biopsy-proven organizing pneumonia as a primary manifestation of COVID-19 lung disease.

Organizing pneumonia is a common manifestation of acute or subacute lung injury that may represent a primary pathologic abnormality or instead be secondary to a variety of underlying conditions. Determining the significance of

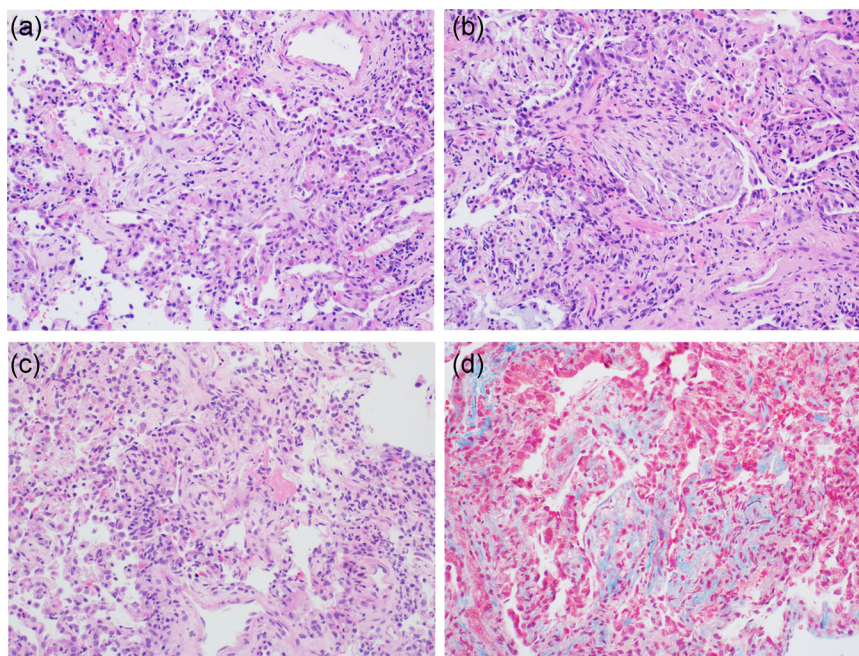


Figure 1 Transbronchial biopsy showed organizing pneumonia, characterized by serpentine (a) and polypoid plugs (b) of fibromyxoid tissue with focal fibrinous airspace exudate (c). A Masson's trichrome special stain highlights the intraluminal fibrosis as pale blue (d).

organizing pneumonia in small, closed lung biopsies is therefore entirely dependent on the clinical context and other supportive laboratory and radiological data. In our patient, organizing pneumonia was the primary pathologic abnormality thought to explain her radiologic findings and was a manifestation of COVID-19 given a positive SARS-CoV-2 bronchoalveolar lavage fluid and no other clinical findings to suggest an alternative etiology.

Nasopharyngeal swab tests for SARS-CoV-2 have a lower sensitivity than bronchoalveolar fluid specimens.⁴ In our patient, she likely had a false negative on initial testing. The patient's persistently negative SARS-CoV-2 IgG serology, following documented COVID-19 is thought to be related to the patient's hypogammaglobulinemia.

The relative contribution of her hypogammaglobulinemia to her clinical presentation and pathologic findings is unclear. Hypogammaglobulinemia has itself been proposed in a couple of case reports as an underlying condition (whether idiopathic or drug-induced) manifesting as organizing pneumonia. Additionally, IVIG has been shown to be an effective therapy in patients with hypogammaglobulinemia and organizing pneumonia,⁵ therefore, it is uncertain the extent to which this therapy may have contributed to her clinical improvement. Finally, in this case, the patient recovered without steroids, a therapy often employed in the management of cryptogenic organizing pneumonia.

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DISCLOSURE STATEMENT

None declared.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to the interpretation of clinical (SE, AJK) and pathologic (KEK) data, participated in the drafting or revision of the work, and have given final approval of the submitted

version.

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REFERENCES

- 1 Borczuk AC, Salvatore SP, Seshan SV *et al.* COVID-19 pulmonary pathology: A multi-institutional autopsy cohort from Italy and New York City. *Mod Pathol* 2020; **33**: 2156–68. <https://doi.org/10.1038/s41379-020-00661-1>.
- 2 Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. *J Thorac Oncol* 2020; **15**: 700–4.
- 3 Zeng Z, Xu L, Xie XY *et al.* Pulmonary pathology in early phase COVID-19 pneumonia in a patient with a benign lung lesion. *Histopathology* 2020; **77**: 823–31. <https://doi.org/10.1111/his.14138>.
- 4 Wang W, Xu Y, Gao R *et al.* Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* 2020; **323**: 1843–4.
- 5 Gamboa PM, Merino JM, Maruri N, Martín-Granizo IF. Hypogammaglobulinemia resembling BOOP. *Allergy* 2000; **55**: 580–81.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.