Repeated false-negative tests delayed diagnosis of COVID-19 in a case with granulomatosis with polyangiitis under maintenance therapy with rituximab and concomitant influenza pneumonia

In the pandemic of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease 2019 (COVID-19), patients with immunosuppressive therapies have a potentially more severe course of the disease. While recent data from the registry of the Global Rheumatology Alliance have been reassuring regarding the use of biological disease-modifying antirheumatic drugs (bDMARDs), no definite recommendations can be made regarding specific bDMARDs.[1] In their recent letter, Nuño and coworkers describe a large cohort of 122 patients with rheumatic diseases.[2] Most interestingly, higher hospitalisation rates and more severe and life-threatening cases of COVID-19 have been described with the use of rituximab (RTX).[2–4] To the best of our knowledge, we here describe the first reported case with repeated false-negative tests and a delayed diagnosis of COVID-19 in a patient with granulomatosis with polyangiitis (GPA) under maintenance therapy with RTX and concomitant influenza pneumonia.

An 80-year-old man presented to the emergency department with a 2-week history of productive cough. The patient had received a diagnosis of GPA in 2014 with biopsy-confirmed renal vasculitis and no history of pulmonary manifestation. After remission induction, he received RTX at a dose of 500 mg every 6 months as maintenance therapy. A staging CT of the chest 2 weeks prior to admission had shown only minor orthostatic congestion (figure 1A and B). On admission, chest radiography (CXR) showed mild pulmonary-venous congestion without consolidation (figure 1C). A nasopharyngeal swab was negative for SARS-CoV-2 but positive for influenza A RNA, and antiviral therapy with oseltamivir was initiated. Oxygen and ampicillin/sulbactam for suspected bacterial superinfection were administered and the patient was admitted to a medical ward. Due to progressive respiratory failure, he was transferred to the intermediate care unit and a follow-up CXR showed considerable

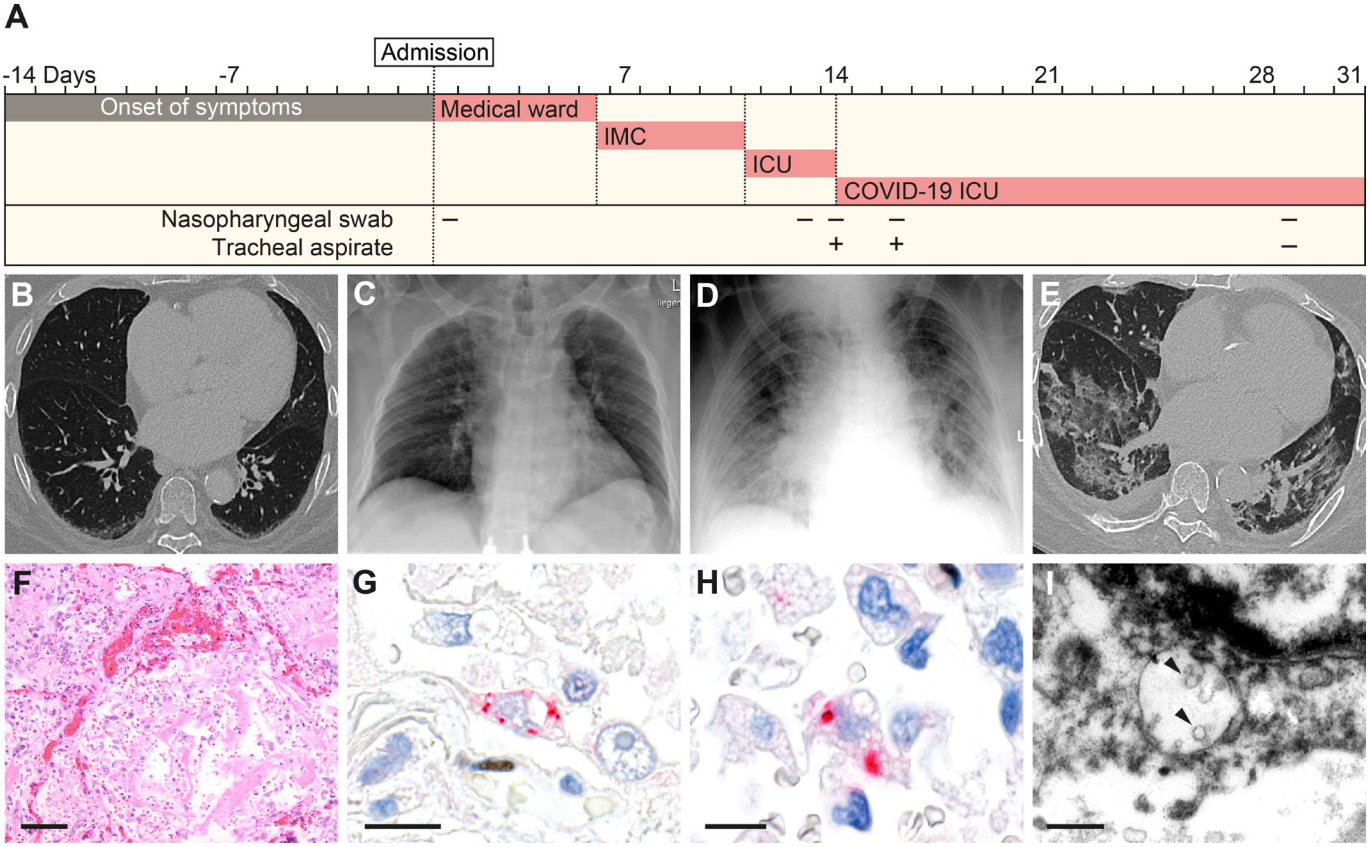

Figure 1 Radiographic and histopathological findings. (A) Timeline of clinical course and SARS-CoV-2 testing. (B) Routine follow-up CT of the lungs 2 weeks prior to admission with no nodular changes, consolidation, ground-glass opacity or significant bronchial wall thickening. Minor orthostatic congestion is noted in the subpleural space of the dependent portion of both lungs. (C) Mobile (supine) CXR upon admission with mild pulmonary venous congestion but no consolidation. (D) Follow-up supine CXR on day 9 at the time of clinical deterioration with considerable congestion as well as multifocal patchy and ill-defined shadowing, consistent with superimposed consolidation. (E) Repeat CT of the lungs on day 12 with bilateral ground-glass opacities as well as extensive and in part streaky consolidation, compatible with COVID-19 or pulmonary haemorrhage. (F) H&E staining of the lung revealing detachment of activated pneumocytes and infiltration of macrophages into the alveolar lumen. Note the hyaline membrane and small foci of haemorrhage. Scale bar represents 100 µm. (G) Immunostaining for SARS spike glycoprotein (red). Scale bar represents 10 µm. (H) Immunostaining for influenza A virus nucleoprotein (red). Scale bar represents 10 µm. (I) Electron microscopy of virus-like particles (arrowheads) in lung pneumocytes fulfilling the criteria of size (diameter: 100 nm), shape and structural features (membrane, surface structures, electron dense material within the particle resembling ribonucleoprotein and cytoplasmic localisation within a membrane compartment, partial attachment to the inner membrane surface). Scale bar represents 500 nm. CXR, chest radiography; ICU, intensive care unit; IMC, intermediate care unit.

congestion and superimposed consolidation (figure 1D). Antibiotic treatment was escalated to piperacillin/tazobactam and clarithromycin. Because of worsening respiratory failure, the patient was transferred to the intensive care unit (ICU) requiring non-invasive-assisted ventilation. Considering his deteriorating renal function, haemoptysis and another negative nasopharyngeal swab for SARS-CoV-2 RNA, a flare-up of GPA was suspected and glucocorticoids with therapeutic plasma exchange were initiated. Consecutive CT scans of the lungs showed bilateral ground-glass opacities and consolidation compatible with COVID-19 or a pulmonary manifestation of GPA (figure 1E). Based on these imaging findings, another nasopharyngeal swab was obtained but returned negative for SARS-CoV-2 RNA. However, tracheal aspirate was found to be positive for COVID-19. Glucocorticoid therapy and plasma exchange were discontinued and the patient was transferred to the dedicated ICU for COVID-19 cases. Subsequently, the patient expired due to multiorgan failure.

In this patient, repeated nasopharyngeal swabs for SARS-CoV-2 RNA yielded negative results, but a tracheal aspirate ultimately confirmed COVID-19. Postmortem analysis of the lungs confirmed COVID-19 and influenza pneumonia with no signs of a GPA flare-up (figure 1F–I). It remains unclear why, although repeatedly performed, nasopharyngeal swabs for SARS-CoV-2 RNA were all negative in our case. A possible explanation is that the patient's immunocompromised state may have contributed and we recommend caution with the use of RTX until more granular data regarding its safety are available. While test availability has been a concern during the COVID-19 pandemic, test accuracy has most recently become an equal matter of debate.[5 6] The difficulties encountered in the differential diagnosis in this case emphasise the need for a clear sense of the performance of SARS-CoV-2 RNA testing in the context of clinical decision-making in cases with multiple causes for respiratory failure and use of bDMARDs in immunocompromised patients.

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Contributors BT conceived the correspondence and wrote the first draft. SH and JF collected pathology specimens and performed histological analysis. JL contributed and interpreted radiology images. PK and MSW provided clinical data. All authors participated in the construction and editing of the manuscript. Compassionate use was approved by our local ethics committee at the University of Göttingen and informed consent for publication was obtained from the patient's family.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Next of kin consent obtained.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Hakroush S, Franz J, Larsen J, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2020-218491

Received 2 July 2020
Accepted 4 July 2020

Ann Rheum Dis 2020;**0**:1–2. doi:10.1136/annrheumdis-2020-218491

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REFERENCES

1 Gianfrancesco M, Hyrich KL, Al-Adely S, *et al*. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 global rheumatology alliance physician-reported registry. *Ann Rheum Dis* 2020;79:859–66.
2 Nuño L, Novella Navarro M, Bonilla G, *et al*. Clinical course, severity and mortality in a cohort of patients with COVID-19 with rheumatic diseases. *Ann Rheum Dis* 2020. doi:10.1136/annrheumdis-2020-218054. [Epub ahead of print: 30 Jun 2020].
3 Monti S, Balduzzi S, Delvino P, *et al*. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. *Ann Rheum Dis* 2020;79:667–8.
4 Schulze-Koops H, Krueger K, Vallbracht I, *et al*. Increased risk for severe COVID-19 in patients with inflammatory rheumatic diseases treated with rituximab. *Ann Rheum Dis* 2020.
5 Woloshin S, Patel N, Kesselheim AS. False Negative Tests for SARS-CoV-2 Infection - Challenges and Implications. *N Engl J Med* 2020. doi:10.1056/NEJMp2015897. [Epub ahead of print: 05 Jun 2020].
6 Watson J, Whiting PF, Brush JE. Interpreting a covid-19 test result. *BMJ* 2020;369:m1808.