

## Acute respiratory distress syndrome during the COVID-19 pandemic: not only SARS-CoV-2

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### Abstract

A previously healthy 30-year-old woman developed severe ARDS at the beginning of the COVID-19 pandemic. SARS-CoV-2 infection was suspected, but testing was negative. *Mycoplasma pneumoniae* was detected by PCR in bronchoalveolar lavage fluid and blood. This case illustrates that *M. pneumoniae* infection can progress to septicemia and ARDS with severe respiratory failure in young healthy adults.

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**Keywords:** Acute respiratory distress syndrome, extracorporeal membrane oxygenation, *Mycoplasma pneumoniae*, pneumonia, sepsis

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To the Editor,

Severe coronavirus disease 2019 (COVID-19) most commonly manifests as viral pneumonia-induced acute respiratory distress syndrome (ARDS) [1]. At the beginning of the COVID-19 pandemic, a previously healthy 30-year-old woman presented with sore throat, cough, headache and arthralgia for 5 days. She rapidly developed severe multilobar pneumonia with

haemolytic anaemia, septic shock and, ultimately, ARDS [2] with severe respiratory failure requiring mechanical ventilation and venovenous extracorporeal membrane oxygenation (vv-ECMO) 8 days after symptom onset (Fig. 1).

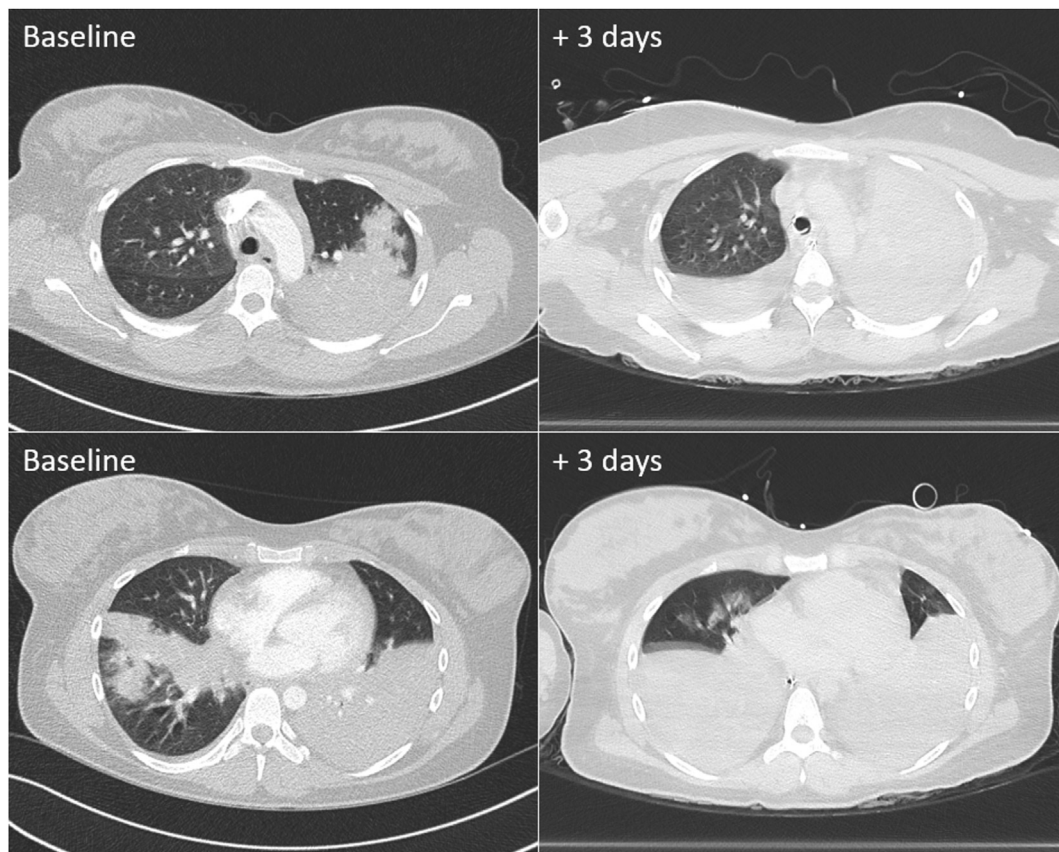
Bacterial, mycobacterial and fungal cultures from blood and bronchoalveolar lavage fluid (BALF), and urinary antigen tests for *Legionella pneumophila* and *Streptococcus pneumoniae* were negative. Polymerase chain reaction on BALF was negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Cobas SARS-CoV-2, Roche Diagnostics, Rotkreuz, Switzerland) and other respiratory viruses and bacteria, but positive for *Mycoplasma pneumoniae* (Unyvero P55 Pneumonia Panel, Curetis AG, Holzgerlingen, Germany). Additionally, *M. pneumoniae* DNA was detected by PCR in blood [3]. The detection of circulating *M. pneumoniae*-specific antibody-secreting cells (ASCs) by enzyme-linked immunospot (ELISpot) assay further confirmed *M. pneumoniae* infection (IgM ASC, 7950 spots; IgG ASC, 430 spots; and IgA ASC, 1030 spots per 10<sup>6</sup> peripheral blood mononuclear cells) [3,4]. Serology for *M. pneumoniae* on blood was also positive (IgM > 150 U/mL, cut-off 17 U/mL; IgG 16 U/mL, cut-off 30 U/mL; Virion \ Serion, Würzburg, Germany).

The patient did not improve with broad-spectrum antibiotics (including amoxicillin-clavulanate, clarithromycin, piperacillin-tazobactam and meropenem), but only upon intravenous doxycycline treatment (100 mg twice daily for 14 days). Serological testing was negative for antinuclear antibodies, anti-neutrophil cytoplasmic antibodies and anti-glomerular basement membrane antibodies. Direct antiglobulin test serology was positive with the detection of cold agglutinins. Human immunodeficiency virus screen was negative. The clinical course was complicated by hypercoagulopathy as a result of disseminated intravascular coagulation, which led to extensive acral necroses requiring debridement.

The patient was finally discharged home after 30 days. At this time-point, anti-SARS-CoV-2 IgM and IgG antibodies were negative (Elecsys Anti-SARS-CoV-2, Roche Diagnostics), but seroconversion could be documented for *M. pneumoniae* (IgM > 150 U/mL; IgG 195 U/mL).

*Mycoplasma pneumoniae* infection is generally mild and self-limiting, but can rarely progress to ARDS [6–10] or septicemia [10–12]. Our case offers a novel illustration of both *M. pneumoniae* septicemia and ARDS with extensive radiological changes leading to severe respiratory failure. Further complications included cold agglutinin-associated haemolytic anaemia, hypercoagulopathy and disseminated intravascular coagulation, which are rarely associated with severe *M. pneumoniae* infection [13].

*Mycoplasma pneumoniae* ARDS occurs mainly in young adults without known underlying disease [6,7,9]. This is in line with



**FIG. 1.** Thoracic computed tomography (CT) scans showing multifocal pneumonia. (Left) Baseline imaging demonstrates acute lung disease with alveolar consolidations in the left upper and right lower lobes and atelectasis of the left lower lobe. (Right) Thoracic CT scan 3 days later reveals disease progression with atelectasis in the left upper lobe and right lower lobe and new ground-glass opacities with alveolar consolidations in the middle lobe.

experimental and clinical data suggesting that an ‘overreacting’ host cell-mediated immune response contributes to *M. pneumoniae* pulmonary disease [13]. The magnitude of the specific T-cell response has been shown to correlate with the severity of pulmonary infiltrates [8,14]. *Mycoplasma pneumoniae* produces a community-acquired respiratory distress syndrome (CARDS) toxin, which can trigger cellular inflammation and mediate organ damage [2,12]. *Mycoplasma pneumoniae* septicaemia in our patient may have triggered massive cell-mediated immune responses resulting in ARDS [12–14].

*Mycoplasma pneumoniae* ARDS manifests after an interval of 1–3 weeks from onset of respiratory symptoms [6,7,9], which coincides with the timing of acquired immunity and further suggests that *M. pneumoniae* ARDS may represent an immune-mediated complication [6–10]. This hypothesis could also be the explanation for the favourable response to corticosteroid treatment observed in some individuals with *M. pneumoniae* ARDS [7–9].

Our case further highlights that in addition to PCR (in BALF and/or blood) the measurement of *M. pneumoniae*-specific ASCs can help to confirm *M. pneumoniae* aetiology in ARDS. *Mycoplasma*

*pneumoniae*-specific ASCs are short-lived and associated with clinical disease [5]. We recently demonstrated that *M. pneumoniae*-specific IgM ASCs measured by ELISpot assay were detectable in children with *M. pneumoniae* community-acquired pneumonia, but not in *M. pneumoniae* carriers suffering from community-acquired pneumonia caused by other pathogens or asymptomatic *M. pneumoniae* carriers [4]. The measurement of specific ASCs in ARDS may be especially useful to determine true *M. pneumoniae* infection in the case of co-detection of *M. pneumoniae* and other respiratory pathogens by PCR and/or serology [4,15]. Establishing an early and rapid diagnosis of *M. pneumoniae* ARDS is essential to stop further disease progression using targeted antimicrobial treatment.

### Authors’ contributions

PMMS, GRK and WCA contributed to patient care and/or diagnostic work up; PMMS and WCA drafted the manuscript; and all authors critically reviewed the manuscript.

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## Conflicts of interest

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None.

## Patient consent

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Informed consent has been obtained in writing.

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