Case Report

Acute Respiratory Distress Syndrome due to *Mycoplasma pneumoniae* Misinterpreted as SARS-CoV-2 Infection

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1. Introduction

A novel coronavirus, SARS-CoV-2, caused a global pandemic with a clinical picture termed COVID-19 and accounted for numerous cases of ARDS in early 2020 [1]. To date, there is no convincing evidence for a specific medical therapy for SARS-CoV-2. Most European hospitals prepared for a surge of these patients. COVID-19 leads to a systemic disease primarily affecting the lung. Approximately 15–42% of COVID-19 patients develop ARDS (CARDS) [1–3]. However, there are still other infectious causes of ARDS that should be considered, especially, as the majority of these pathogens are specifically treatable. The case presented here describes a severe infection with *M. pneumoniae* leading to ARDS in an adult, complicated by a delay in diagnosis and effective therapy as COVID-19 was suspected.

2. Case Presentation

On the 14th of March 2020, a 36-year-old gentleman presented at the emergency unit of a nearby hospital with fever, dry cough, and head and limb aches that started three days earlier. In good physical condition and otherwise healthy, he had completed a half-marathon the week before, but on admission to another hospital, he presented with reduced general condition and shortness of breath. Physical examination revealed crackles in the right upper lobe upon auscultation.
Medical, family, and psychosocial history was completely
unremarkable.

As SARS-CoV-2 was suspected, he was immediately
admitted to the ICU. He received microbiological and
virological sampling as well as chest X-ray and thoracic
CT. A calculated antimicrobial chemotherapy with piper-
acillin/tazobactam (3 x 4.5 g/d.i.v.) and clarithromycin
(2 x 500 mg/d.i.v.) was started. Polymerase chain reaction
(PCR) for SARS-CoV-2 was negative, as were the results for
influenza, Mycobacterium tuberculosis, and Legionella spp.

After 2 days, the antimicrobial regimen was changed to
meropenem (3 x 1.0 g/d.i.v.), linezolid (2 x 600 mg/d.i.v.),
and fosfomycin (3 g/d i.v.) due to persistently elevated
inflammatory parameters and further clinical deterioration.
The assumption of the patient having COVID-19 was main-
tained. Imaging of the lungs revealed a diffuse interstitial
reticular pattern, multilobular patchy ground-glass opacifica-
tion, and consolidation of the right upper lobe.

After a week on high-flow oxygen, he deteriorated and was
intubated at an oxygenation index (P aO2/FiO2 ratio) of
130. Despite priming, he deteriorated further (hypercapnia
with respiratory acidosis and hypoxemia with a P aO2/FiO2
ratio 108), needing higher doses of vasopressors, and our
hospital’s extracorporeal membrane oxygenation (ECMO)
team was called on the 22nd of March 2020 to transfer the
patient. The patient was reported as having COVID-19 and
moderate ARDS with respiratory acidosis.

The ECMO team set out to transfer the patient under
COVID-19 personal protective equipment (PPE). In the
external hospital, after reviewing the laboratory and imaging
findings, as well as the ventilator settings, the team leader
decided against implanting an ECMO on site, and the patient
was transferred under COVID-19 precautionary measures.
Bronchoscopy with bronchoalveolar lavage (BAL) was per-
formed for microbiological sampling and to further elucidate
the hypothesis of an infection with SARS-CoV-2. Additionally,
a naso- and oropharyngeal swab for SARS-CoV-2 was
obtained.

Chest radiographs were reviewed, and a new chest X-ray
was made (Figure 1). Imaging showed mainly right-sided
pneumonia, not typical for COVID-19, and the hypothesis
of COVID-19 was abandoned. Antimicrobial therapy was
changed, as atypical pneumonia was suspected. Meropenem
(then given continuously i.v., monitored by determination
of serum levels) was continued for a total of 7 days, and clar-
ithromycin (2 × 500 mg/d) was added to the antimicrobial
regime again (Table 1). Remarkably, for a young and other-
wise healthy individual, the patient had elevated bilirubin
and LDH levels, with diminished haptoglobin and macro-
cytic hyperregenerative anemia (hemoglobin 5.3 g/dL at a
sO2 of 67%) on admission, demonstrating hemolysis. Coombs’ test revealed cold agglutinins the same day.

Microbiological results from a BAL (March 22nd) were
negative for SARS-CoV-2, Pneumocystis jirovecii, Bordetella
pertussis and B. parapertussis, Chlamydophila pneumoniae,
Haemophilus influenzae, Legionella pneumophila, Moraxella
catarrhalis, and Streptococcus pneumoniae; however, the
patient tested positive for Mycoplasma (M.) pneumoniae.
Thus, a diagnosis of mycoplasma-related ARDS with cold
agglutinin disease was made. The patient was in total
substituted with 4 units of packed red blood cells and
received only warm infusions. Ventilator support was dees-
calated soon after change of the antimicrobial regimen, and
the patient was extubated on March 25th receiving noninva-
sive ventilator support for 4 more days with supplementary
oxygen up to 40%. Meropenem was continued for a total of
7 days, and clarithromycin (2 x 500 mg/d) was added to the
antimicrobial regime again (Table 1). Hemolysis improved
quickly under the antibiotic regime. The patient was dis-
charged from the ICU on March 30th and was discharged
home without supplementary oxygen on April 6th. He had
no health-related complaints in a telephone interview con-
ducted on June 18th.

3. Discussion

Under the impression of a seemingly predominant microor-
ganism at the time of admission, a clinical diagnosis was
established that was questionable according to radiologic
evidence. Additionally, inappropriate management of the
pulmonary infection might have favored clinical deteriora-
tion. Initial antimicrobial therapy was changed early empiri-
cally to a regimen that was much less effective for the
causative microorganism, despite a microbiological workup.
The initial therapy was performed according to current
guidelines [4]. The change was meant to extend the spec-
trum; instead, it missed the causative organism. Furthermore,
at the time antimicrobial therapy was changed, treatment
failure was not proven.

M. pneumoniae is a common cause of community-
acquired pneumonia, particularly in children and young
adults [5]. M. pneumoniae is a very small bacterium without
a peptidoglycan cell wall. It is a common cause of tracheo-
bronchitis and atypical pneumonia mainly because of its
adherence to respiratory cells. Infection of host cells occurs
through special adhesins and an elongated polar attachment
organelle [6]. Usually, the pneumonia caused by M. pneumo-
niae is mild and characterized by a dry cough or self-limiting
pneumonia [7]. The rates of ICU admission ranged between
10% and 16%. With an intense epidemiological background
of COVID-19 as a cause of respiratory disease leading to a
surge of ICU admissions in many countries, the proper diag-
nosis of treatable causes for ARDS is highly important.
Therefore, microbiological testing from respiratory material
(bronchial aspirate) using adequate test methods, such as
loop-mediated isothermal amplification (LAMP) [8] or
quenching probe (QProbe) [9] methods for M. pneumoniae
diagnosis, is highly important, especially as macrolide resis-
tance rates are increasing in M. pneumoniae [10].

Severe ARDS and fatal outcomes due to M. pneumoniae
are rare and may be the result of unclear clinical features,
delayed diagnosis, inappropriate respiratory support, and/or
insufficient initial treatment. If additional diagnostic mea-
sures are not confirming the suspected pathogen, alternative
explanations need to be evaluated. This is especially impor-
tant if a treatable cause is present, as in the case presented
here. However, concomitant cold agglutinin disease is fre-
quently described in the context of M. pneumoniae and
Figure 1: (a) Chest radiograph on the day of admission (March 14, 2020) to an external hospital shows consolidation predominantly in the right upper lobe, vague ill-defined opacities in the right lower lobe and left hilar region, and a diffuse interstitial pattern combined with bronchial wall thickening. (b) Chest X-ray on the day of admission to a tertiary care hospital depicts progressive pneumonia characterized by diffuse reticular and nodular patterns (March 22). (c) Chest X-ray shortly after discharge from the ICU (April 2) shows almost complete regression of previous infiltrations. The patient did not need supplementary oxygen at that time. (d, e) Computed tomography of the chest on March 16th confirms consolidation of the right upper lobe and reveals multifocal, patchy consolidations, ill-defined airspace infiltrates, and ground-glass opacifications. Additional centrilobular nodular appearance and thickening of the bronchovascular structures are present.
usually develops upon generation of polyclonal IgM antibodies directed against I antigens on RBCs. Hemolysis can be severe but is usually self-limiting, while corticosteroids are reported to be barely effective [11].

If severe pneumonia caused by *M. pneumoniae* should be treated with corticosteroids in general remains unclear. While positive effects have been shown in children, there is a lack of prospective studies defining the appropriate dose and duration of steroid administration in fulminant ARDS with *M. pneumoniae* in adults [12].

Antibiotic therapy of *M. pneumoniae* requires agents such as macrolides or fluoroquinolones that do not target the bacterial cell wall and have good intracellular penetration. In our patient, macrolide therapy was started according to guidelines for severe pneumonia but was stopped after 2 days, and the regimen was unintentionally changed to a less effective one. These decisions might have been driven by the assumption that the patient might have an infection with SARS-CoV-2.

The gold standard for the detection of COVID-19 in symptomatic individuals is the detection of viral RNA in naso- or oropharyngeal swabs by reverse-transcriptase polymerase chain reaction (rtPCR) that can be false negative [13].

Radiologic findings alone are often not reliable for differentiating pneumonia. Moreover, coinfection with other bronchopulmonary pathogens is not uncommon. In general, radiographic findings should be used along with clinical and laboratory data to narrow the differential diagnosis. Currently, there is a threat of misinterpreting clinical pictures and lung imaging as SARS-CoV-2-induced disease. It has been suggested only recently that low-dose CT might be of equal sensitivity and specificity as rtPCR testing of nasopharyngeal swabs [14]. However, multiple infectious diseases might produce similar pictures in pulmonary imaging modalities.

At the time, the patient in the present case acquired the infection leading to ARDS, and the prevalence of COVID-19 in Germany, especially in the Federal State of Saarland, was low (2,078 confirmed cases in Germany on March 12]). In contrast, awareness of COVID-19 was high-flying.

If the prevalence of a specific infectious agent is predominant, it is very likely that the radiologic picture in fact happens to be the at the time frequently encountered infectious agent. However, the effective performance of CT for COVID-19 detection critically depends on the pretest probability for the occurrence of a disease, which in turn influences positive and negative predictive values (PPV and NPV). If the prevalence of a disease is truly low, the PPV for the disease will be low. If caregivers overestimate PPV, they might come to the wrong conclusion if no gold standard for the diagnosis of a disease exists or is accepted.

In the present case, treating physicians unintentionally created an unfavorable situation for the patient urged by erroneous assumptions. Unfortunately, the well-intentioned putative escalation of antimicrobial therapy was less effective for the causative organism.

### 4. Conclusion

The case presented here underlines the importance of adhering to established treatment guidelines, scrutinizing treatment modalities, and not forgetting other potential causes of severe pneumonia or ARDS to ensure that critically ill patients are safeguarded from common infections even in times ruled by a predominant pathogen.

### Abbreviations

ARDS: Acute respiratory distress syndrome
CAD: Cold agglutinin disease
ECMO: Extracorporeal membrane oxygenation
NPV: Negative predictive value
PPE: Personal protective equipment
PPV: Positive predictive value

### Data Availability

Data can be provided on request addressed to the corresponding author. All data sharing statements are subject to
conformity with German data protection legislation and rules (Datenschutzgrundverordnung-DGSVO).

Consent
Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Disclosure
A preprint of this report has been uploaded to ResearchSquare (DOI: 10.21203/rs.3.rs-78362/v1). The funders had no role with regard to this study in the design of the study and collection, analysis, and interpretation of data or in writing the manuscript.

Conflicts of Interest
R.B. received funding from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Grifols, Novartis, CSL Behring, German Federal Ministry of Education and Research (BMBF) Competence Network, Sander Stiftung, Dr. Rolf M. Schwiete Foundation, German Cancer help (Krebshilfe), and Mukoviszidose e.V. All other authors have no conflicts of interest to declare.

Authors’ Contributions
C.M., T.R., F.S., S.M., A.B., A.M., S.L.B., C.P., G.D., R.B., and P.M.L. contributed to the collection, review, and/or analysis of the data; C.M. and P.M.L. drafted the manuscript; T.R., A.B., S.M., F.S., S.S., A.M., S.L.B., C.P., B.G., G.D., and R.B. revised the manuscript for important intellectual content. All authors have seen and approved the final version of the manuscript.

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References
[1] G. Grasselli, A. Zangrillo, A. Zanella et al., “Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy,” JAMA, vol. 323, no. 16, pp. 1574–1581, 2020.
[2] Y. Wang, X. Lu, Y. Li et al., “Clinical course and outcomes of 344 intensive care patients with COVID-19,” American Journal of Respiratory and Critical Care Medicine, vol. 201, no. 11, pp. 1430–1434, 2020.
[3] X. Yang, Y. Yu, J. Xu et al., “Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study,” The Lancet Respiratory Medicine, vol. 8, no. 5, pp. 475–481, 2020.
[4] S. Ewig, G. Höffken, W. Kern et al., “Behandlung von erwachsenen Patienten mit ambulant erworbener Pneumonie und Prävention – Update 2016,” Pneumologie, vol. 70, no. 3, pp. 151–200, 2016.
[5] M. W. Boettcher, O. Baetz, and J. Kramer, “Seroprevalence and season variation of Chlamydia pneumoniae and Mycoplasma pneumoniae infection in Germany,” Clinical Microbiology and Infection, vol. 16, p. S6667, 2010.
[6] H. C. Krivan, L. D. Olson, M. F. Barile, V. Ginsburg, and D. D. Roberts, “Adhesion of Mycoplasma pneumoniae to sulfated glycolipids and inhibition by dextran sulfate,” The Journal of Biological Chemistry, vol. 264, no. 16, pp. 9283–9288, 1989.
[7] K. Izumikawa, “Clinical features of severe or fatal Mycoplasma pneumoniae pneumonia,” Frontiers in Microbiology, vol. 7, p. 800, 2016.
[8] T. Notomi, H. Okayama, H. Masubuchi et al., “Loop-mediated isothermal amplification of DNA,” Nucleic Acids Research, vol. 28, no. 12, article E63, pp. 63e–663, 2000.
[9] S. Kurata, T. Kanagawa, K. Yamada et al., “Fluorescent quenching-based quantitative detection of specific DNA/RNA using a BODIPY((R)) FL-labeled probe or primer,” Nucleic Acids Research, vol. 29, no. 6, article E34, pp. 34e–334, 2001.
[10] T. Kakiuchi, I. Miyata, R. Kimura et al., “Clinical evaluation of a novel point-of-care assay to detect Mycoplasma pneumoniae and associated macrolide resistant mutations,” Journal of Clinical Microbiology, 2021.
[11] P. L. Sviejcicki, L. T. Hegerova, and M. A. Gertz, “Cold agglutinin disease,” Blood, vol. 122, no. 7, pp. 1114–1121, 2013.
[12] K. Izumikawa, K. Izumikawa, T. Takazono et al., “Clinical features, risk factors and treatment of fulminant Mycoplasma pneumoniae pneumonia: a review of the Japanese literature,” Journal of Infection and Chemotherapy, vol. 20, no. 3, pp. 181–185, 2014.
[13] S. Woloshin, N. Patel, and A. S. Kesselheim, “False negative tests for SARS-CoV-2 infection-challenges and implications,” The New England Journal of Medicine, vol. 383, no. 6, article e38, 2020.
[14] M. Schulze-Hagen, C. Hübel, M. Meier-Schroers et al., “Low-dose chest CT for the diagnosis of COVID-19,” Deutsches Ärzteblatt International, vol. 117, no. 22-23, pp. 389–395, 2020.