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Case Report

Usefulness of bronchoalveolar lavage in the management of patients presenting with lung infiltrates and suspect COVID-19-associated pneumonia: A case report



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ABSTRACT

Objective: To report a clinical case of a patient with a compatible HRCT scan and two negative SARS-CoV-2 RNA upper respiratory tract specimens but with a confirmed viral infection by BAL (19 days after symptom onset).

Methods: Revision of a patient's clinical charts with COVID-19 admitted at INMI L. Spallanzani Hospital
Results: Two oropharyngeal swab tests of SARS-CoV-2 by qualitative real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay were performed at admission (17 days from symptoms onset) and a day apart and were found negative. BAL fluid collected 19 days after symptoms onset was positive for SARS-CoV-2.

Conclusion: This case highlights importance of clinical suspicion of SARS-CoV-2 infection in diagnosis and infectivity assessment. We suggest collection of BAL fluid when consecutive nasopharyngeal swabs are negative, to confirm or exclude the diagnosis of COVID-19-associated pneumonia. Healthcare workers should perform aerosol-generating procedures in an adequately ventilated room and should wear adequate PPE.

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Introduction

In December 2019, a novel coronavirus infection, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan, Hubei Province, China which the World Health Organization (WHO) has named 2019 novel coronavirus disease (COVID-19) [1]. The clinical spectrum of SARS-CoV-2 infection appears to be wide, encompassing asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with

respiratory failure and even death [2]. It is a highly infectious disease and currently person-to-person transmission is the main source of infection; many unknowns remain regarding the virulence/pathogenicity, the effectiveness of different modes of transmission, the infectivity during the incubation period and during recovery, the impact of individual or population-based preventive measures [3]. The approach to initial management should focus on early recognition of suspect cases, immediate isolation, and institution of infection control measures [4]. Viral nucleic acid detection by reverse transcription PCR (RT-PCR) is regarded as the gold standard technique for the etiological diagnosis of COVID-19 [5]. For initial diagnostic testing for COVID-19, collecting and testing an upper respiratory specimen is recommended. Nasopharyngeal and oropharyngeal swabs are the preferred choice for swab-based SARS-CoV-2 testing. The induction of sputum is not recommended and aspirate or bronchoalveolar lavage sample should be collected and tested only when it is clinically required [6]. Here we report a case with CT

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scan images suggestive for COVID-19-associated pneumonia with negative oropharyngeal swabs test for SARS-CoV-2 RNA at hospital admission and confirmation after BAL positivity.

Case presentation

A 72-year-old female patient was admitted to L. Spallanzani Institute in Rome, compelling a 17-day history of fever (up to 39°C), cough and sore throat. She has been treated with amoxi-clavulanic acid and then with ceftriaxone before admission, with no clinical response. She denied travel to China or to northern Regions of Italy, contacts with symptomatic patients in the past fourteen days before hospitalization. She denied experiencing shortness of breath, chest pain cough and any gastrointestinal symptoms (no nausea, vomiting, or diarrhea). Her past medical history included hypertension, past breast and thyroid cancer with thyroid hormone replacement.

High-resolution computed tomography (HRCT) of the chest documented images of multiple patchy ground glass opacities in bilateral sub pleural areas (Fig. 1). Given chest HRCT findings, suggestive for COVID-19 pneumonia, she was admitted an airborne-isolation room.

On admission, physical examination revealed normal vital signs, with body temperature 38°C and oxygen saturation of 97% in ambient air. Lung auscultation was normal. Arterial blood gas analysis showed mild respiratory impairment with arterial oxygen tension (PaO₂) 67 mmHg in air breathing and oxygenation index (P/F ratio) of 323 mmHg. Her white blood cell count was 8.75×10^9

cell/L, lymphocyte count was 1.15×10^9 cell/L, C-reactive protein level was 13.85 mg/L (normal range <1 mg/L). Liver function, renal function, myocardial enzymes and electrolytes were normal (Annex 1). Legionella and Pneumococcal urinary antigen, Chlamydia and Mycoplasma serology were negative. Two oropharyngeal swab tested negative for SARS-CoV-2 by qualitative real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) at hospital admission (17 days from symptoms onset) and a day apart. According to chest HRCT findings and persistent fever, a Bronchoscopy was performed (19 days from symptoms onset) with RT-PCR for SARS-CoV-2 positive result in BAL fluid. The patient has been treated according to local protocol at that time, with symptomatic and antiviral therapy including lopinavir/ritonavir. Seven days after admission patient's respiratory symptoms improved and she was discharged in community after collection of two negative oropharyngeal swab tests.

Discussion

We describe the case of a patient with a very high index of suspicion for COVID-19-associated pneumonia in whom the research of SARS-CoV-2 RNA was negative in upper respiratory tract specimen, and detectable in BAL fluid. The possibility of COVID-19 should be considered primarily in patients with fever and lower respiratory tract symptoms, who resided in or have recently (within the prior 14 days), traveled to high incidence regions or who have had recent (within the prior 14 days) close contact with a confirmed or suspected case of COVID-19 [4]. Even if pneumonia appears to be the most frequent serious manifestation of infection, patients could be falsely negative if tested only with upper respiratory tract samples [7]. Over the course of the infection, the virus has been identified in respiratory tract specimens 1–2 days before the onset of symptoms and it can persist for 7–12 days in moderate cases and up to 2 weeks in severe cases [8]. Collection of specimens from upper respiratory mucosa by nose and throat swabs is a procedure used for the diagnosis of Covid-19 [9]. Lillie PJ et al reported discordance between nose and throat samples in a UK patient, highlighting the need to sample from both areas [10]. In the presence of a suspicion of COVID-19-associated pneumonia, false-negative results could hinder the prevention and control of the epidemic, particularly when this test plays a key role in deciding the necessity for continued isolated medical observation or discharge. Screening based on symptoms and CT scan, even in the best case scenario, is not sensitive [11]. According to WHO guidelines, in patient with suspected COVID-19-associated pneumonia, negative specimens from the upper respiratory tract do not exclude the diagnosis, and additional lower respiratory tract samples are recommended [12]. Sputum induction demonstrated more helpful than throat swabs for the detection of SARS-CoV-2 RNA in convalescent patients [13]. Although sampling from the lower respiratory tract is recommended by WHO, these procedures potentially generate aerosols with an increased risk of transmission and must be performed with strict airborne precautions, minimizing exposure of health care workers [14]. Here we report the case of a patient with a compatible HRTC scan and two negative SARS-CoV-2 RNA from upper respiratory tract specimens, but with a confirmed viral infection in BAL (19 days after symptom onset). The detection of SARS-CoV-2 RNA in lower respiratory tract samples after two negative nasopharyngeal may reflect SARS-CoV-2 persistence in lower respiratory tract. This case highlights importance of clinical suspicion of SARS-CoV-2 RNA for diagnosis and infectivity assessment. If the patient's travel or exposure history or symptoms and radiological imaging suggest possible COVID-19-associated pneumonia, each effort should be done to achieve etiological diagnosis of the disease, also for infectiousness consequences.

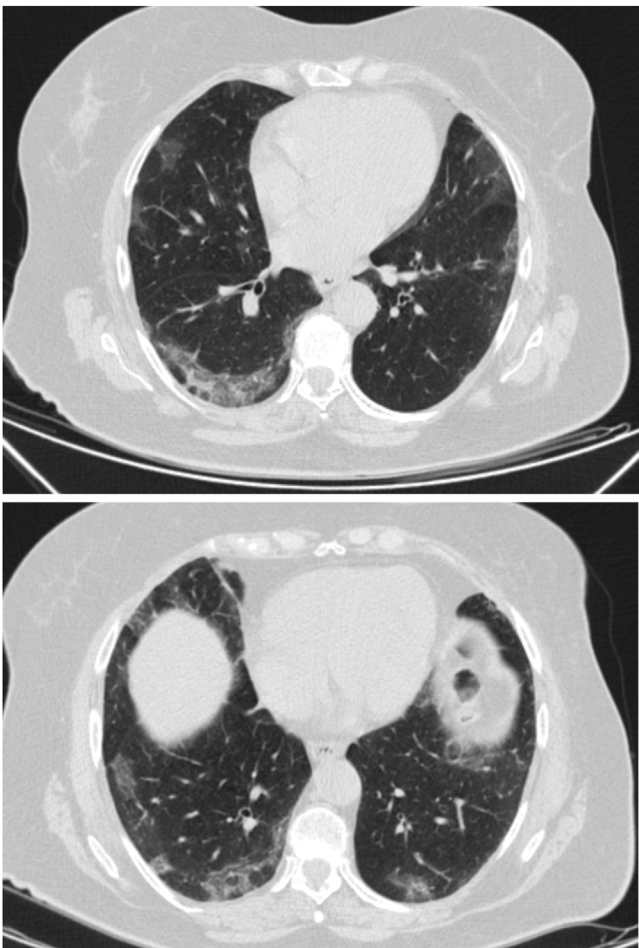


Fig. 1. Chest CT images showing bilateral ground glass opacities.

RT-PCR for SARS-CoV-2 in lower respiratory samples (induced sputum or BAL) may increase sensitivity in cases with clinical and radiological suspicion of COVID-19 pneumonia. During ongoing epidemic in presence of symptoms and radiological findings compatible with suspected COVID-19 pneumonia, negative upper respiratory tract samples does not ever exclude the diagnosis, and additional lower respiratory tract samples are recommended. It should be underlined that bronchoscopy, and induced sputum, are aerosol-generating procedures and have been associated with an increased risk of nosocomial transmission of coronaviruses. Healthcare workers, possibly trained and dedicated personnel, should perform these procedures in an adequately ventilated room and should wear adequate PPE.

Consent for publication

Written informed consent was obtained from patient for this paper to be published. A copy of the written consent is available for review by the Editor of this journal.

Authors contributions

GG and FP conceived the study. MM, GG and FP wrote the paper. MM, SM, PM, PV and MZ supplied the clinical data. GG, MM, SM, PM, MZ, CP, AM and FP evaluated and treated the patients. GI and AZ reviewed the paper.

All authors reviewed and approved the final version of the paper submitted to the journal.

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Ethical approval

The patient provided written informed consent to the utilization of anonymous clinical data for research purpose

Conflicts of Interest

All authors declare no conflict of interest

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ijid.2020.05.027>.

References

- Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* [1];382(8):727–33.
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* [2];395:497–506.
- Eurosurveillance Editorial Team. Updated rapid risk assessment from ECDC on the outbreak of COVID-19: increased transmission globally. *Euro Surveill* [3];25(9), doi:<http://dx.doi.org/10.2807/1560-7917>.
- World Health Organization (WHO). Novel Coronavirus - China. Available from: Geneva: WHO; 2020. <https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/>.
- Centers for Disease Control and Prevention (CDC). Coronavirus Disease 2019 (COVID-19). Available from: Atlanta: CDC; 2020. <https://www.cdc.gov/coronavirus/2019-ncov/about/symptoms.html>.
- Phua J, Weng L, Lowell Ling L, et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. *Lancet Respir Med* [6];30161–2, doi:[http://dx.doi.org/10.1016/S2213-2600\(20\)30161-2](http://dx.doi.org/10.1016/S2213-2600(20)30161-2) Published Online April 6.
- Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology* [7];200642, doi:<http://dx.doi.org/10.1148/radiol.2020200642>.
- Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. *J Med Virol* [8];, doi:<http://dx.doi.org/10.1002/jmv.25748>.
- Loeffelholz Michael J, Tang Yi-Wei. Laboratory Diagnosis of Emerging Human Coronavirus Infections – The State of the Art. *Emerging Microbes & Infections* [9];.
- Lillie PJ, Samson A, Li A, et al. The Airborne Hcid Network. Novel coronavirus disease (Covid-19): The first two patients in the UK with person to person transmission. *J Infect.* [10];80(5):578–606.
- Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* [11]; Feb 7.
- World Health Organization (WHO). Coronavirus disease (COVID-19) technical guidance: early investigation protocol. Available from: Geneva: WHO; 2020. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/early-investigation>.
- Liu Y, Yan LM, Wan L, et al. Viral dynamics in mild and severe cases of COVID-19. *Lancet Infect Dis.* [13];, doi:<http://dx.doi.org/10.1001/jama.2020.1585>.
- Infection prevention and control during health care when COVID-19 is suspected; Interim guidance 19 March 2020 WHO available from <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/infection-prevention-and-control>; accessed at 2nd May 2020.