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Usefulness of bronchoalveolar lavage in suspect COVID-19 repeatedly negative swab test and interstitial lung disease

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1. Introduction

The diagnosis of coronavirus disease 2019 (COVID-19) relies on nasopharyngeal swab, which shows a 20–30% risk of false negativity [1]. Bronchoalveolar lavage (BAL) is reported to be useful in patients with pulmonary interstitial infiltrates on high-resolution computed tomography (HRCT). We investigated the usefulness of BAL in symptomatic patients with positive HRCT and a repeatedly negative swab test ('grey zone').

2. Patients and methods

We performed a retrospective study on 81 consecutive patients (50 male) with HRCT suggestive of COVID-19 interstitial lung disease undergoing BAL. The study was approved by the Ethics Committee of Policlinico Umberto I (Rome, Italy).

All patients showing HRCT findings suggestive of interstitial pneumonia and at least two negative nasopharyngeal swabs were included. When serological test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) became available, patients were also submitted to this test; immunoglobulin G (IgG) and immunoglobulin M (IgM) were assessed using a LIAISON® SARS-CoV-2 S1/S2 IgG test (DiaSorin S.p.A., Italy), with the last 42 consecutive patients (51.9%) being tested.

Fibreoptic bronchoscopy was scheduled within 72 h from the last negative swab. BAL was performed using at least 100 mL of saline delivered in an area of the lung showing interstitial disease on HRCT. The retrieved sample was sent for virological and microbiological examination for SARS-CoV-2, common respiratory bacteria, fungi and mycobacteria, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella* and influenza A and B. Diagnosis of SARS-CoV-2 infection was performed by reverse transcription PCR (RT-PCR) targeting the E

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Table 1
Demographics, clinical and laboratory data of patients.

Characteristics	Overall	SARS-CoV-2-negative BAL	SARS-CoV-2-positive BAL	*P*-value
No. of patients	81 (100)	78 (96.2)	3 (3.7)	–
Age (years)	68.3 ± 16.2	66.9 ± 16.1	62.0 ± 23.3	0.62
Male sex	50 (61.7)	48 (61.5)	2 (66.7)	0.85
Temperature at admission (°C)	37.1 ± 1.0	37.2 ± 1.0	36.8 ± 0.4	0.51
Fever	63 (77.7)	60 (76.9)	3 (100)	0.35
Dyspnoea	38 (46.9)	36 (46.2)	2 (66.7)	0.49
Cough	17 (21.0)	17 (21.8)	0 (0)	0.36
Other symptoms [a]	27 (33.3)	27 (34.6)	0 (0)	0.21
Leukocyte count ($\times 10^9$ cells/L)	10.3 ± 5.5	10.3 ± 5.6	7.8 ± 2.4	0.53
Lymphocyte count ($\times 10^9$ cells/L)	2.1 ± 3.8	2.2 ± 3.9	1.2 ± 1.1	0.61
C-reactive protein (mg/dL)	5.6 ± 6.8	5.8 ± 6.9	1.1 ± 1.2	0.24
Lactate dehydrogenase (UI/L)	291.7 ± 126.8	292.9 ± 128.7	255.5 ± 20.5	0.68
D-dimer (μg/L)	1557.8 ± 1385.6	1551.2 ± 1343.8	1663.0 ± 2355.1	0.89
PaO_2/FiO_2 ratio	343.4 ± 75.3	343.5 ± 76.5	340.5 ± 43.1	0.96
Microbiological findings				
Haemophilus parainfluenzae	4 (4.9)	4 (4.9)	0 (0)	–
Staphylococcus aureus	3 (3.7)	3 (3.7)	0 (0)	–
Pseudomonas aeruginosa	3 (3.7)	3 (3.7)	0 (0)	–
Klebsiella pneumoniae	2 (2.5)	2 (2.5)	0 (0)	–
Enterobacter aerogenes	1 (1.2)	1 (1.2)	0 (0)	–
Enterococcus faecium	1 (1.2)	1 (1.2)	0 (0)	–
Streptococcus pneumoniae	1 (1.2)	1 (1.2)	0 (0)	–
Haemophilus influenzae	1 (1.2)	1 (1.2)	0 (0)	–
Mycobacteria	0 (0)	0 (0)	0 (0)	–
Candida spp. $\geq 10^4$ CFU/mL	3 (3.7)	3 (3.7)	0 (0)	–
Candida spp. $< 10^4$ CFU/mL	5 (7.4)	5 (7.4)	0 (0)	–

NOTE: Data are *n* (%) or mean ± standard deviation.
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; BAL: bronchoalveolar lavage; PaO_2/FiO_2: arterial oxygen partial pressure/fractional inspired oxygen.
[a] Including fatigue, chest pain and diarrhoea.

and S viral genes using a RealStar® SARS-CoV-2 RT-PCR Kit (Altona-Diagnostic GmbH, Hamburg, Germany) after RNA extraction (QIAamp® Viral RNA; QIAGEN).

The χ^2 test and Student's *t*-test were used for analysis of categorical and continuous data, respectively. Sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV) and negative predictive value (NPV) were analysed.

3. Results

The number of pre-BAL negative swabs was 2 in 53/81 patients (65.4%) and 3 in 28/81 (34.6%). At admission, symptoms were fever (>37.5 °C) in 63 patients (77.7%), dyspnoea in 38 patients (46.9%) and cough in 17 patients (21.0%). In addition, 12 patients (14.8%) reported an epidemiological link with COVID-19-positive subjects. All patients were negative for other infections, except for one patient positive for *C. pneumoniae* IgM antibodies. HRCT showed monolateral and bilateral interstitial disease in 7 (8.6%) and 74 (91.4%) patients, respectively.

Three patients (3.7%) were positive for SARS-CoV-2 at BAL, with negative bacterial cultures (Table 1). In all of these patients HRCT showed bilateral interstitial infiltrates. They were transferred to a dedicated COVID-19 ward. They were subsequently confirmed positive at nasopharyngeal swab after 48–72 h. The 42 patients tested were negative for specific antibodies.

Seven patients remained in the 'grey area' despite the negative BAL owing to symptoms and HRCT findings. One of them had a positive swab after 4 days from BAL and was immediately transferred to a COVID-19 dedicated ward. After the positive swab, it was repeated 2, 3 and 5 days later and was negative. During the hospital stay, IgG and IgM antibodies were tested and resulted positive. Among the tested patients, there was no subject with negative BAL but positive for anti-SARS-CoV-2 antibody.

Sensitivity was 75% (3/4), specificity 100% (77/77), PPV 100% (3/3), NPV 98.7% (77/78) and diagnostic accuracy 98.8% (80/81).

4. Discussion

Fast and accurate diagnosis of COVID-19 is mandatory to optimise space and pathways within the hospital. Misdiagnosed cases may lead to dramatic consequences and may appear even after repeated negative nasopharyngeal swabs [1].

BAL is reported to be an effective tool to achieve a diagnosis. The virus might be concealed in the upper respiratory tract in the early period of infection, which represents the time in which BAL is negative while the patient becomes symptomatic [1–3]. This assumption is not fully supported by our observation, with all three BAL-positive patients subsequently becoming swab-positive. This finding supports the suspicion that patients might become positive at BAL before showing a positive swab. This event has been already described [4] and highlights the effectiveness of BAL in the diagnosis of COVID-19 in particular cases.

A high level of suspicion should remain if the epidemiology and clinical status of the patient support the doubt. In this setting, if doubts persist the patient should be kept in the 'grey area' and submitted to other examinations. However, we now tend to discharge home or transfer BAL-negative patients more liberally owing to the high NPV of BAL. Moreover, since we have started to perform BAL in repeatedly swab-negative patients [5], the 'grey area' turnover of patients dramatically increased, reducing the hospital overload and giving the hospital management more possibility to arrange spaces for other patients. We did not have patients with positive antibody and negative BAL but, in that case, the patients would have remained isolated in the 'grey zone' and submitted to swab again. The 'grey zone' was set up to offer a continuous monitoring of general and respiratory function in isolated spaces. Those patients with mild symptoms were discharged home and followed-up by local medical resources. Hospital physicians were not involved in the outpatient recovery but we

had no return to hospital from discharged patients belatedly becoming positive.

In conclusion, BAL has a favourable impact on the management of patients in the 'grey zone'. A high level of suspicion should remain for BAL-negative patients in case of suspicious clinical and epidemiological data.

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Ethical approval

This study was approved by the Ethics Committee of Policlinico Umberto I [protocol no. 109/2020].

Conflict of interests

None declared.

Declaration of Competing Interest

The authors report no declarations of interest.

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