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 gene.

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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*                         | 27 (33.3)        | 27 (34.6)               | 0 (0)                   | 0.21    |
| Leukocyte count (<10⁶ cells/L)           | 10.3 ± 5.5       | 10.3 ± 5.6              | 7.8 ± 2.4               | 0.53    |
| Lymphocyte count (<10⁹ 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 (U/L)             | 291.7 ± 126.8    | 292.9 ± 128.7           | 255.5 ± 20.5            | 0.68    |
| D-dimer (µg/L)                           | 1557.8 ± 1385.8  | 1551.2 ± 1343.8         | 1663.0 ± 2355.1         | 0.89    |
| PaO₂/FiO₂ ratio                          | 343.4 ± 75.3     | 343.5 ± 76.5            | 340.5 ± 43.1            | 0.96    |

Microbiological findings

|                              | Overall          | SARS-CoV-2-negative BAL | SARS-CoV-2-positive BAL | P-value |
|------------------------------|------------------|-------------------------|-------------------------|---------|
| *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. ≥ 10⁴ CFU/mL    | 3 (3.7)          | 3 (3.7)                 | 0 (0)                   | –       |
| Candida spp. < 10⁴ 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; PaO₂/FiO₂: arterial oxygen partial pressure/fractional inspired oxygen.
*Including fatigue, chest pain and diarrhoea.

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 epidemiological 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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