Respir. Med and Res 78 (2020) 100784

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Letter to the Editor

Alveolar lymphocytosis with plasmacytosis in severe COVID-19

ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Pneumonia
Bronchoalveolar lavage fluid
Critical care

To the Editor,

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19) is associated with a pulmonary and systemic 'cytokine storm' [1]. Little is known about the lung immune-inflammatory response in the most severely ill patients. To gain insight into this issue, we report preliminary findings regarding bronchoalveolar lavage fluid (BALF) findings in COVID-19 patients admitted to the intensive care unit (ICU).

We conducted a comprehensive observational monocenter study in the 20-bed ICU of Tenon University Hospital (AP–HP, Paris). During the study period, all consecutive adult patients with laboratory-confirmed COVID-19 were screened, and those having undergone a BAL within ICU stay were included. Data regarding demographics, comorbidities, microbiological investigations and ICU course were collected. Patients were grouped according to their lymphocyte percentage in BALF, with a cut-off of 25% as used previously [2]. Continuous and categorical variables are described as median [interquartile] and number (percentages), respectively, and compared between groups using the non-parametric pairwise Mann and Whitney test and Fisher's exact test, respectively.

From March 17th to April 9th 2020, 84 patients were admitted to the ICU with COVID-19, a median of 8 days [6–11] (median [25th–75th percentiles]) after symptoms onset, and 71 (84.5%) patients received mechanical ventilation. Twenty patients underwent a fiberoptic bronchoscopy with BAL (three 50 mL aliquots of saline) performed for ruling out bacterial pneumonia as well as opportunistic infections, 13 days [8–17] after symptoms onset and 7 days [3–11] after hospital referral. In 3 patients, BAL was performed prior to ICU admission. There were 19 men and one woman, aged 61 [52–68] years, all non-smokers, with a Simplified Acute Physiological Score II (SAPS II) of 31 [24–41] on ICU admission and a Sequential Organ Failure Assessment (SOFA) of 6 [3–7] on the day of BAL. No patient had received high-dose immunosuppressive or immunomodulatory drugs prior to BAL, while 5 were previously immunocompromised (Table 1). The median BALF total cell count was 260 cells/μL [155–470], and the median lymphocyte percentage was 11% [3–31]. Cultures of BALF were positive for bacteria in 7 (35%) patients, among whom 5 with *Staphylococcus aureus*.

One third of the patients had a BALF lymphocyte percentage above 25% (high-Ly_{BALF} group, $n = 6$, median 42.5% [36–47], compared to low-Ly_{BALF} group, $n = 14$, median 6.5% [2–12]). The two groups of patients did not differ in terms of severity, either on ICU admission or on the day of BAL. However, patients in the high-Ly_{BALF} group tended to be younger (52 [45–61] vs. 62 [57–69] years, $P = 0.11$) and to have a longer evolution of the disease (17 [9–19] vs. 12 [8–14] days, $P = 0.14$) and a higher alveolar total cell count (375 [180–640] vs. 215 [140–370] cells/μL, $P = 0.09$). Moreover, in all high-Ly_{BALF} patients, but none low-Ly_{BALF} patient, lymphocytes were mainly activated cells including plasma cells, as assessed by morphology and CD138 positive staining, with only a few small lymphocytes.

Our findings suggest that BAL analysis may be informative particularly in patients with persistent or worsening symptoms, to characterize the immune-inflammatory response in severe COVID-19. A lymphocytic phenotype with plasmacytosis, as recently reported in one case [3], may correspond to a late worsening of the respiratory disease as described by Lescure et al. [4]. Whether this lymphocytic alveolar reaction corresponds to a disease progression towards a COVID-19 organizing pneumonia [5] or to the leakage of the damaged pulmonary vascular endothelium as a consequence of the viral endotheliitis [6] is presently unknown.

This pilot study has several limitations. The cytologic analysis of BALF was rudimentary in the special period of COVID-19 crisis, so both lymphocytic typing and quantification of plasma cells were not available routinely. Similarly, the low availability of RT-PCR test for SARS-CoV-2 RNA detection prevented us to repeat it and assess the viral shedding at time of BAL. Eventually, considering the low number of observations, we did not search for putative associations between BALF lymphocytosis and radiological or laboratory data, or even clinical outcomes.

As far as we know, our study is the first to report data regarding the BAL findings in severe COVID-19. A third of patients displayed a marked lymphocytosis, with mainly activated cells including plasma cells. Additional information on alveolar cellular profiles at different stages of the disease are needed, which may help clinicians to personalize treatments, especially the use of immunomodulatory and/or immunosuppressive agents, in the most severely affected patients.

Author's contribution

GV had full access to all the data and takes responsibility for the integrity of the data. GV drafted the manuscript. AF performed the pathological examination of bronchoalveolar lavage fluids and helped to revise the manuscript. AG and AP performed bronchoalveolar lavages and helped to revise the manuscript. MF

https://doi.org/10.1016/j.resmer.2020.100784

Table 1
Patient characteristics.

Patient	Characteristics of BAL								Outcome
Number/ gender/age	Immuno-suppressive disease	Days from first symptoms	Days from ICU admission	Blood lymphocyte count (G/L)[a]	BALF total cell count (cells/μL)	BALF lymphocyte percentage (%)	BALF macrophage/ neutrophil percentages (%)	Bacterial or viral coinfection	Alive at D28[b]
1/M/52	Renal transplantation	8	−4	0.24	130	14	80/5	*MSSA*	Yes
2/M/62	Renal transplantation	14	−2	0.53	540	12	64/23	*MRSA*	Yes
3/M/68	–	4	−1	0.77	290	8	89/2	*Staphylococcus heamolyticus*	No
4/M/58	–	4	0	0.83	470	12	79/8	No	Yes
5/M/65	HIV	6	1	0.89	20	1	20/79	No	Yes
6/M/69	HIV	11	1	0.65	370	2	41/57	No	Yes
7/M/83	–	8	1	1.69	360	0	7/93	No	No
8/M/69	–	21	1	1.18	240	7	36/53	No	Yes
9/M/42	–	14	1	1.26	490	6	48/46	No	Yes
10/M/71	–	5	1	0.94	280	25	56/18	*MSSA*	Yes
11/M/45	–	9	3	1.83	640	47	46/6	No	Yes
12/F/62	–	9	4	0.23	180	3	13/83	*Streptococcus agalactiae*	No
13/M/63		13	6	0.67	140	3	8/89	*Pseudomonas aeruginosa*	Yes
14/M/74	–	13	6	0.37	120	13	17/68	No	No
15/M/51	–	16	6	0.53	180	41	34/25	No	Yes
16/M/33	Sickle cell disease	19	8	6.78	640	36	50/13	No	Yes
17/M/45	–	17	10	1.71	190	10	49/40	*MSSA*	Yes
18/M/61	–	17	10	0.97	120	54	33/12	HSV-1	Yes
19/M/57	–	20	11	0.99	170	2	5/93	No	Yes
20/M/53	–	22	12	1.78	470	44	48/7	No	Yes

Patients are classified according to the number of days in ICU at the date of BAL; three patients had BAL performed 1,2, and 4 days before ICU admission. BAL: bronchoalveolar lavage; BALF: BAL fluid; F: female; D28: 28th day; HIV: human immunodeficiency virus; ICU: intensive care unit; M: male; MRSA/MSSA: methicillin-resistant/sensible *Staphylococcus aureus*; NA: non available.

[a] At the date of BAL.

[b] D28 means the 28th day following ICU admission.

revised the manuscript. All authors read and approved the final version to be submitted.

Disclosure of interest

The authors declare that they have no competing interest.

Funding

None.

Ethics/Consent for publication

All patients (or next of kin) gave consent for their data to be reported.

Availability of data and material

Data and materials supporting the findings of this study can be entirely shared if asking.

Acknowledgments

None.

References

[1] Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020;71:762–8.

[2] Pelotti V, Cazzato S, Minicuci N, Zompatori M, Burzi M, Schiattone ML. The diagnostic value of bronchoalveolar lavage and transbronchial lung biopsy in cryptogenivc organizing pneumonia. Eur respir J 1996;9(12): 2513–6.

[3] Giani M, Seminati D, Lucchini A, Foti G, Pagni F. Exuberant plasmocytosis in bronchoalveolar lavage specimen of the first patient requiring extracorporeal membrane oxygenation for SARS-CoV-2 in Europe. J Thorac Oncol 2020;15(5):e65–6.

[4] Lescure FX, Bouadma L, Nguyen D, Parisey M, Wicky PH, Behillil S, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. Lancet Infect Dis 2020;20:697–706.

[5] Copin MC, Parmentier E, Duburcq T, Poissy J, Mathieu D. Lille COVID-19 ICU and Anatomopathology Group. Time to consider histologic pattern of lung injury to treat critically ill patients with COVID-19 infection. Intensive Care Med 2020;46(6):1124–6.

[6] Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395(10234).

G. Voiriot [a,*]
A. Fajac [b]
A. Gibelin [a]
A. Parrot [c]
M. Fartoukh [a]

[a] *Service de médecine intensive réanimation, hôpital Tenon, Sorbonne université, Assistance publique–Hôpitaux de Paris, Paris, France*
[b] *Service d'anatomie et cytologie pathologiques, hôpital Tenon, Sorbonne université, Assistance publique–Hôpitaux de Paris, Paris, France*
[c] *Service de pneumologie, hôpital Tenon, Sorbonne université, Assistance publique–Hôpitaux de Paris, Paris, France*

[*] Corresponding author. Hôpital Tenon, 4, rue de la Chine, 75020 Paris, France.
E-mail address: guillaume.voiriot@aphp.fr (G. Voiriot)

Received 4 June 2020

Received in revised form 3 August 2020

Accepted 3 August 2020
Available online 14 August 2020