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***Herpesviridae* systemic reactivations in COVID-19 associated ARDS patients**

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Sir,

The clinical spectrum of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection can lead to acute respiratory distress syndrome (ARDS), associated with immune dysfunctions and prolonged duration of mechanical ventilation (1), both responsible for secondary infection acquisition (MV) (2). Along these lines, ARDS and prolonged MV are recognized risk-factors for *herpesviridae* systemic reactivations (HSR) that may affect the outcome of critically ill patients (3,4). However, the burden of these infectious events in severe COVID-19 patients remains poorly explored. Hence, in the present study, we describe the clinical features of HSR in COVID-19 associated ARDS patients.

All consecutive ARDS patients with polymerase chain reaction (PCR) confirmed COVID-19 admitted to the medical Intensive Care Unit (ICU) of Rennes University Hospital between March 12, 2020 and April 16, 2021 were reviewed. We retrospectively analyzed patients that were at least weekly monitored for Herpes Simplex Virus (HSV) and Cytomegalovirus (CMV) systemic replication by quantitative real time (RT) PCR.

HSR were considered when viral DNA was detected by PCR (The lower limits of detection were 119 IU/ml for CMV with Altona RealStar CMV assay and 165 copies/ml for HSV-1 with Altona RealStar HSV assay). Respiratory samples for bacterial, fungal and viral (CMV, HSV and SARS-CoV-2 RT-PCR) examinations were also collected at least weekly. Ventilator associated pneumonia (VAP) were defined in accordance with international guidelines (5).

The Mann-Whitney U test was used for quantitative data and qualitative data were compared using the Chi-square or Fisher-test, as appropriate. All statistical analyses were two-sided, and P values less than 0.05 were considered statistically significant. Analyses were performed using R software version 4.0.4. Our institutional ethical review board approved the study (N 20-56).

Over the study period, 122 patients with COVID-19 associated ARDS were included. Demographic and clinical features are listed in table 1. Patients were mainly male with a median age of 66 years. HSR was observed in 33 patients (27%), 27 patients experienced HSV viremia (21.9%) while 13 patients experienced CMV viremia (10.7%) and seven patients had co-reactivation. Viremia occurred at a median of 12 days following ICU admission (IQR 9-22). As shown in Table 1, among patients experiencing HSR a wide proportion of them also presented herpesviridae respiratory reactivations while such viral respiratory reactivations were observed less often in patients without HSR (87.9% versus 23.6%; $p < 0.001$) (Table 1). Patients with HSR were lymphopenic and experienced positive respiratory RT-PCRs for SARS-CoV-2 for longer durations. As shown in table 1, when analyzing clinical courses, patients with HSR had longer duration of MV and ICU length of stay (LOS). Finally, we also observed higher rates of VAP among these patients.

In this single-center study, 27% of patients admitted to the ICU for COVID-19-associated ARDS developed HSR. Such viral reactivations appeared to be associated with prolonged duration of MV and ICU length of stay, which is consistent with previous studies (3,4). We previously showed that respiratory CMV and HSV reactivations are often observed in critically ill COVID-19 patients (6). Moreover, septic patients, even immunocompetent, are recognized at-risk for developing viral reactivations (7) that may be promoted by sepsis-induced immunosuppression (8). Although associated with immune defects (i.e prolonged lymphopenia and positive respiratory SARS-CoV-2 RT-PCR), there is no clear evidence that viral reactivations have a direct impact on patients' outcomes in ICU. These infectious events could also be considered as a marker for disease severity (7). Furthermore, pathophysiology of systemic reactivations is debated. Lungs are known to be major sites of *herpesviridae* latency. Since here we observed that a wide proportion of patients developing systemic reactivations also experienced previous (or concomitant) respiratory reactivations, we may suppose that respiratory reactivation is the first step before systemic dissemination which may be favored by immunosuppressive mechanisms in patients with sustained SARS-CoV2 infections.

Finally, our results suggest that HSR are common in ARDS COVID-19 patients and may influence the clinical courses of these critical patients. Direct clinical consequences of systemic *herpesviridae* reactivations and treatment of such infections remain to be investigated.

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Table 1. Characteristics of severe COVID 19 patients according to systemic *Herpesviridae* reactivation

	All patients n=122	No Viral Reactivation n=89	Viral Reactivation n=33	p value
Demographic characteristics				
Age (years)	66 (57-73)	64 (55-72)	71 (61-73)	0.044
Male sex	83 (68)	56 (62.9)	27 (81.8)	0.08
Coexisting conditions				
Obesity	48 (39.3)	44 (49.4)	4 (12.1)	<0.001
Hypertension	61 (50)	39 (44.8)	22 (66.7)	0.042
Diabetes	28 (22.9)	17 (19.1)	11 (33.3)	0.16
Previous immunosuppression	27 (22.1)	20 (22.5)	7 (21.2)	>0.99
Clinical and biological baseline features				
Lymphocyte count (10 ⁹ /L)	0.53 (0.39-0.83)	0.55 (0.39-0.79)	0.56 (0.38-0.81)	0.9
CRP (mg/L)	120 (78-167)	116 (76-166)	150 (90-258)	0.2
Ratio of PaO ₂ to FiO ₂ (mmHg)	102 (84-137)	106 (83-139)	100 (86-134)	0.71
SAPS II on day 1	32 (24-41)	32 (23-40)	33 (27-41)	0.36
SOFA score on day 1	4 (3-7)	4 (3-7)	5 (3-7)	0.92
Clinical courses and ICU management				
Corticosteroids use	114 (93.4)	85 (95.5)	29 (87.9)	0.27
ECMO	7 (5.7)	3 (3.4)	4 (12.1)	0.16
Lymphopenia duration (days)	8 (5-13)	7 (4-10)	14 (9-23)	0.001
Positive respiratory SARS-CoV-2 RT-PCR duration (days)	19 (13-27)	16 (11-24)	24 (18-31)	0.013
Ventilated patients with positive respiratory SARS-CoV-2 PCR				
at day 5 (120 patients tested)	99 (81.1)	66/87 (75.7)	33/33 (100)	<0.001
at day 10 (84 patients tested)	65 (77.4)	35/53 (66)	30/32 (93.7)	0.003
at day 15 (58 patients tested)	44 (76)	22/34 (64.7)	22/24 (91.7)	0.02
at day 20 (45 patients tested)	31 (68.9)	15/25 (60)	16/20 (80)	0.2
VAP	26 (21.3)	14 (15.7)	12 (36.4)	0.03
Herpesviridae respiratory reactivations	50 (41)	21 (23.6)	29 (87.9)	<0.001
Duration of mechanical ventilation (days)	13 (8-23)	12 (7-20)	18 (11-31)	0.018
ICU length of stay (days)	16 (10-28)	13 (10-24)	23 (15-33)	0.005
Day-28 Mortality	9 (7.4)	8 (9)	1 (3)	0.44

Data are presented as median (IQR: interquartiles), n (%). P values comparing patients are tested by Mann-Whitney (continuous variables) and Chi2 or Fisher tests (categorical variables).

Abbreviations: CRP: C-Reactive Protein; PaO₂: arterial oxygen tension; FiO₂: Fraction of inspired Oxygen; SAPS II: Simplified Acute Physiology Score II SOFA: Sequential Organ Failure Assessment ECMO: Extracorporeal Membrane Oxygenation; VAP: Ventilator Associated Pneumonia; ICU: Intensive Care Unit

Obesity was defined as BMI>30, lymphopenia as lymphocyte count <1.10⁹/L and previous immunosuppression as immunosuppressive treatments including corticosteroids >0.5 mg/kg/day prednisone-equivalent within 30 days prior to inclusion, severe neutropenia <0.5 G/L of neutrophils, HIV seropositivity, bone marrow or solid organ transplantation.

Declarations section

Ethics approval and consent to participate

Our institutional ethical review board approved the study (N 20-56).

Consent for publication

Not applicable

Availability of supporting data

The datasets from this study are available from the corresponding author on request.

Competing interests

The authors report no conflict of interest related to this work

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Contribution of authors

FR, CL, AM, AG and JMT took care of the patients, performed the literature review and wrote the first draft of the article. CP and VT performed diagnostic tests and raised critical comments on the article.

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