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Case report

Bronchoscopic suspect of *Herpesvirus* infection in critically ill COVID-19 patients: two case reports and brief literature review.

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Abstract. Herpesviridae infection in COVID-19 patients has been reported, particularly muco-cutaneous lesions. Little is known about Herpesviridae lung infection in critically ill COVID-19 patients. Typical scattered lesions seen through fiberoptic bronchoscopy in these patients should raise the question as to whether to start empirically acyclovir treatment while a Herpesviridae diagnostics result becomes available. (www.actabiomedica.it)

Key words: herpesvirus, COVID-19, pneumonia, fiberoptic bronchoscopy, critically ill patient, ICU, bronchoalveolar lavage.

Introduction

Herpesviridae is a large family of DNA viruses also named Herpesviruses. These agents can cause latent infection or they may manifest with lytic lesions. There are many types of Herpesviruses, but the most important in humans are Herpes simplex 1 (HSV-1), Herpes simplex-2 (HSV-2), that can both cause labial or genital herpes, Varicella zoster herpes (HSV-3 or ZVZ), that causes chickenpox or herpes zoster, Epstein-Barr Virus (HHV-4 or EBV) causing mononucleosis or some cancers, and finally Human Cytomegalovirus (HHV-5 or CMV) which usually causes an asymptomatic infection (1).

After binding with receptor molecules on the surface of the cell, Herpesviruses release virions inside the infected cells. After this event, viral DNA entering the nucleus can be transcribed into mRNA and the infection begins (2).

Herpesviruses are able to persist in the host cell indefinitely, evading the immune system. When immunosuppression is present, a reactivation of the herpes infection may occur (3).

SARS-CoV2 infection reached pandemic level during 2020, infecting millions of people around the world. At the same time, reports of herpes infection, especially cutaneous manifestations, began to appear (4).

Despite this, Herpes infections in critically ill patients admitted to ICU for COVID-19 pneumonia are still scarce.

In this paper, we describe two cases in which severely critically ill patients developed Herpes reactivation needing antiviral treatment. The antiviral therapy was empirically started after the bronchoscopic vision of tracheo-bronchial lesions suspected to be elicited by *Herpesvirus spp* infection. A rapid literature review about possible lung overinfection by Herpesviruses in critically ill COVID-19 patients will be provided.

Case reports

Case 1

A 73-year-old man (78 kg x 168 cm, BMI 27.6 kg/m^2) with a history of hypertension was admitted

to the Infectious Disease Unit with COVID-19 pneumonia (day 0) 8 days after symptoms onset (fever and dry cough). He was initially treated with intravenous desametasone 6 mg/day, enoxaparin 4000 UI/day and remdesivir (for 5 days). During his stay in the Infectious Disease Unit, he developed SARS-CoV2 severe acute respiratory distress syndrome needing ICU admission (day 5). He was immediately intubated due to worsening dyspnoea and a low P_aO_2/F_IO_2 ratio of 110 mmHg. After an initial improvement as regards oxygenation parameters, the patient's clinical course showed a worsening pulmonary gas exchange needing pronation. On day 6, ceftriaxone 2g/day was started empirically, given the increasing values of C-reactive protein and procalcitonin (CRP 158 mg/dL, PCT 0.9 ng/mL). Before starting ceftriaxone, a bronchoalveolar lavage (BAL), including a viral search for Herpesviruses, blood cultures and urine sample were obtained revealing no bacterial growth. On day 13, antibiotic therapy was upgraded to piperacillin-tazobactam 18g/day because of fever and increasing CRP. He was still lymphopenic (Ly 890/mm^3). Since no satisfying clinical improvement was recorded, on day 17, a fiberoptic bronchoscopy was performed after repeating a CT thorax scan (figure 1).

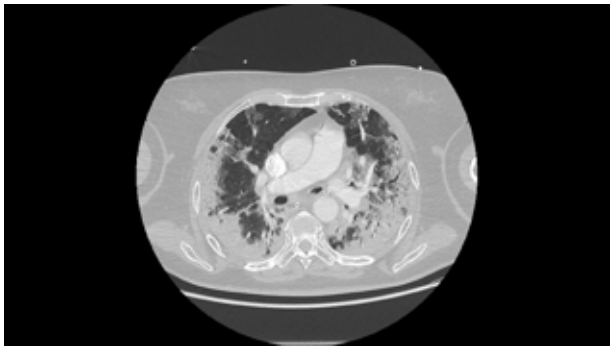

Figure 1. CT thorax scan demonstrating a severe lung involvement of COVID-19 infection. Ground glass, crazy paving and consolidations phenomena occur at the same time.

During the bronchoscopy, an easily bleeding tracheo-bronchial mucosa with suspected whitish vesicles was seen (figure 2 A-B).

Based on these findings, a herpetic infection was suspected, so a real time polymerase chain reaction (RT-PCR) exam was performed. In addition, acyclovir 10 mg/kg every 8 hours was empirically added to the antibiotic therapy. A 6688 copies/mL of HSV-1 DNA were detected in blood samples, but neither HSV-2 nor CMV-DNA were found. After 15 days acyclovir was stopped. The patient stayed in the ICU for

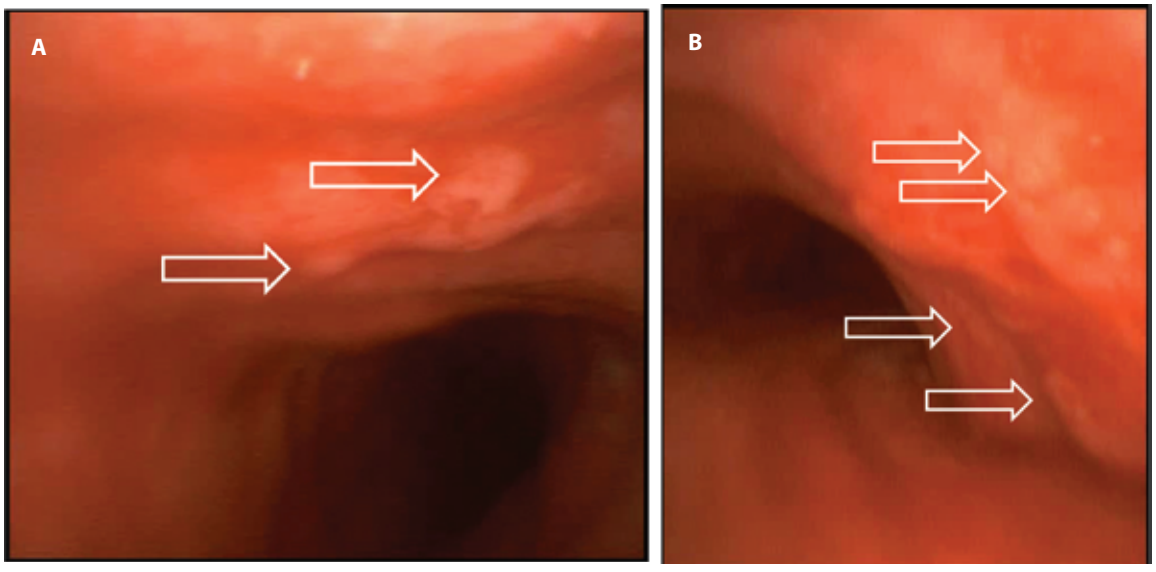

Figure 2 A-B. Bronchoscopic (Ambu® aScope™ 4 Broncho, Ambu® A/S, Ballerup, Denmark) view of suspected Herpes lesions in the tracheo-bronchial tree. Empty arrows show the scattered white lesions surrounded by an easily bleeding mucosa.

40 days, after that he was discharged into a rehabilitation unit in moderate condition, spontaneously breathing through a tracheostomy. On day 29 a BAL was repeated and blood samples were screened for HSV-1/2, EBV and CMV-DNA. Only BAL tested positive for HSV-1 (2024 copies/mL).

Case 2

A 77-year-old woman with a history of hypertension, obesity (88 kg x 159 cm, BMI 35 kg/m^2), combined hyperlipaemia and hypothirodism, was admitted to the Emergency Department due to dyspnoea (day 0). Twenty days before she had tested positive for COVID-19 using a nasal swab (real time PCR method). She was then admitted to the medical ward dedicated to COVID-19 and treated with dexamethasone 6mg/day and enoxaparin 6000 UI daily. Inflammation indices were as follows: CRP 275 mg/dL and PCT 0.29 ng/mL and a levofloxacin 750 mg daily was empirically started. On day 5 she worsened and was intubated due to severe acute respiratory insufficiency with a P_aO_2/F_IO_2 ratio of 60 mmHg. A CT thorax scan demonstrated severe disease related to COVID-19 infection and pulmonary thromboembolism (figure 3).

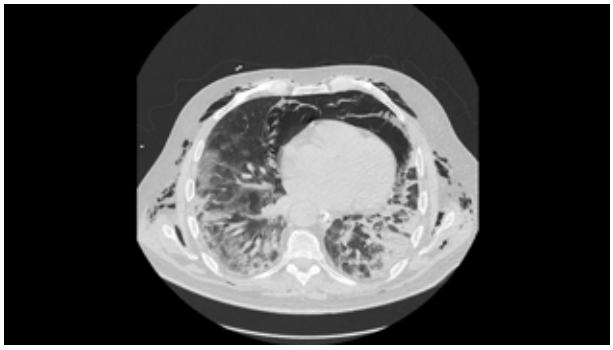

Figure 3. Severe lung involvement with pneumomediastinum and subcutaneous emphysema.

She was pronated without improvement, so inhaled nitric oxide was started to relieve severe hypoxaemia. On day 6 no clinical improvement was noted, and the patient's fever rose to 38.7°C. She still presented lymphopenia (Ly 460/mm^3). Blood and urine samples, with bronchoalveolar fluid lavage were obtained, later revealing no positivity for bacteria. During a bronchoscopy, a bloody tracheal mucosa with white scattered vesicles was also seen in this patient (figure 4 A-B).

Piperacillin-tazobactam 18g/day was started on the same day plus acyclovir 10 mg/kg every 8 hours empirically. On day 9, RT-PCR revealed 94325 copies/mL of HSV-1 in BAL fluid. HSV-2 and CMV DNA tested negative. She continued to receive acyclovir for

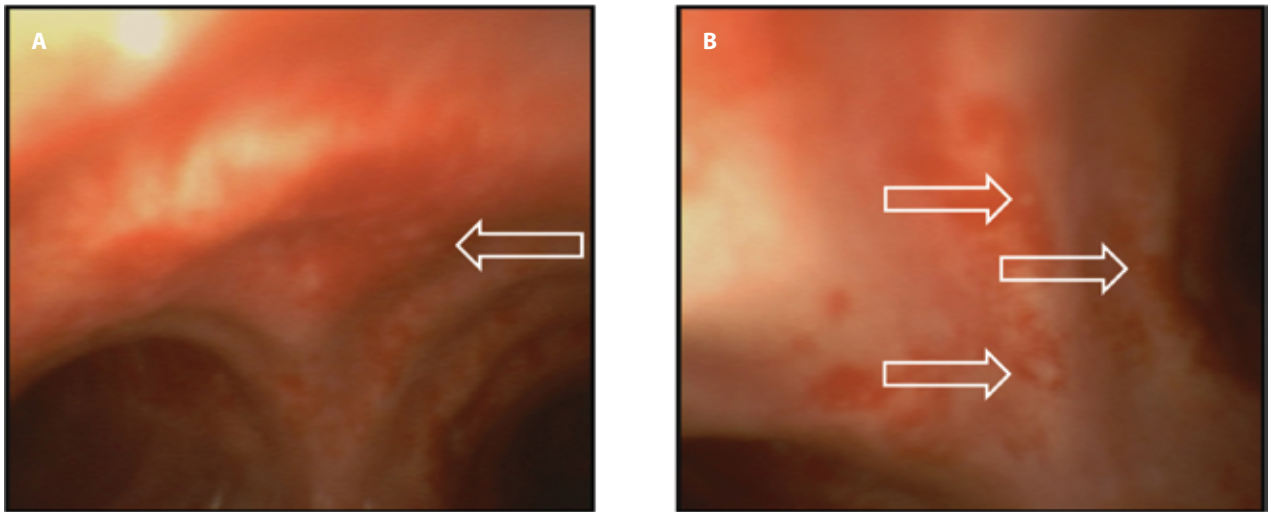

Figure 4 A-B. Bronchoscopic vision of the lesions in near the carina after 24 hours of invasive mechanical ventilation. Due to the short time from intubation and bronchoscopic vision, it is unlikely that the lesions were provoked by suction tube.

14 days after which it was stopped. Clinical improvement was good and the patient was discharged into a medical ward in good clinical condition at day 29.

Case review of the literature

A systematic review of the literature for all relevant articles limited to adult patients was performed using the PubMed and Scopus databases. Articles were limited to those published in the English language and with available abstracts. The search strategy used the keywords and MeSH terms: "COVID-19", "SARS-CoV-2", "herpes infection", "viral pneumonia", "herpetic pneumonia", "acyclovir", "critically ill", "ICU", "fiberoptic bronchoscopy".

Up to the date of submission of the present manuscript, a total of four manuscripts of Herpesviridae lung infections in critically ill COVID-19 patients have been reported whose characteristics are summarized in Table 1.

Discussion

We present herein two cases of Herpesviridae lung infection in COVID-19 critically ill patients with typical scattered lesions seen at bronchoscopy.

Both patients were treated empirically with acyclovir, with clinical improvement noted on the basis of bronchoscopy vision.

Herpesviridae reactivation has also been described in non-immunocompromised critically ill patients undergoing mechanical ventilation in up to 64% of cases. In addition, in these patients, a longer mechanical ventilation (MV) and higher mortality rate have been reported (5).

The diagnosis of Herpes pneumonia remains challenging and is not broadly accepted (6). However, a study by Schurierer demonstrated that acyclovir treatment was associated with a significantly longer time to death in the ICU, reduced hazard ratio for ICU death, and improved circulatory and pulmonary oxygenation function in patients with VAP not responding to antibiotic treatment and with high HSV load (viral load> 10^5 HSV copies/mL) (6). They also suggested testing for HSV in any ventilatory associated pneumonia that does not improve after adequate antibacterial treatment.

Fiberoptic images in our cases were suggestive for herpetic involvement: lesions of the tracheo-bronchial mucosa similar to small vesicles or ulcers were comparable to those described by Xu and colleagues (8).

Le Balc'h and colleagues recently described a higher-than-expected Herpesviridae infection rate among critically ill COVID-19 patients (9).

There are several reasons that could explain these findings: COVID-19 critically ill patients often present with immunosuppression either caused by SARS-CoV2 infection or induced by steroids. A cytokine storm may also induce a sort of immunoparalysis favouring HSV reactivation (10).

In our cases, both tested positive for HSV-1 subtype. This is in line with the higher incidence rate of HSV-1 than HSV-2, with a 54% and 16% seroprevalence rate respectively (11).

Table 1. Summary of studies available regarding *Herpersviridae* lung infection in critically ill COVID-19 patients.

Author	Year	Number	Age	Treatment	Outcome	Reference
Patrucco et al.	2020	10	NA	NA	NA	Respiration. 2020;99(11):970-978.
Le Balc'h et al.	2020	18	64	NA	Higher LOS_{ICU} Mortality 11%	Crit Care. 2020 Aug 28;24(1):530.
Xu et al.	2020	1	73	Acyclovir 500 mg every 8 hours iv	NA	Br J Dermatol. 2020 Dec;183(6):1145-1147.
Franceschini et al.	2021	21	72	Acyclovir 400 mg every 12 h or acyclovir 10 mg/kg every 8 hours iv	Mortality 28.6%	Microorganisms. 2021 Sep 7;9(9):1896

Legend: NA=not applicable, LOS_{ICU}=length of Intensive Care Unit stay, iv=intravenously.

The antiviral therapy with acyclovir in our experience improved clinical condition. There is scarce evidence about the optimal timing of starting acyclovir on suspicion of Herpesviridae infection. We decided to initiate therapy empirically, supported by a strong suspicion for HSV infection based on seeing the lesions during bronchoscopy.

There are many reports describing herpetic skin lesions in COVID-19 patients, including critically ill ones (12). There are also reports of fatal infection by HSV-1 in COVID-19 ICU patients who developed acute liver failure (13). However, there is only one case in the literature that describes the fiberoptic appearance of tracheal lesions caused by Herpesviridae in COVID-19 critically ill patients (8).

We decided to start empirically acyclovir by basing our decision on just the appearance of tracheal mucosa. We suggest that in critically ill patients with worsening pulmonary function despite a supposed adequate therapy, in cases of tracheal lesions similar to the ones described above, it is reasonable to start acyclovir before the definitive herpes result is available. Whether this approach is right or not remains an open and interesting question.

Testing at least once a week for HSV replication in blood samples or lung fluids could be reasonable in severe COVID-19 patients under mechanical ventilation (14).

Also, EBV and CMV infections have been frequently reported in critically ill patients with SARS-Cov-2 infection (15). We note that EBV and CMV are members of Herpesviridae group, and as such they present the same behaviour and risk factors as HSV. However, in these two patients, only HSV-1 viral infection was detected.

Literature about Herpesviridae lung involvement in critically ill COVID-19 patients is very scarce; further studies need to be designed.

Conclusions

We described two cases of critically ill COVID-19 patients with bronchoscopic findings suspected for herpetic infection. Accordingly, we decided to start empirically acyclovir with clinical improvement. Herpesviridae reactivation in critically ill COVID-19 patients is probably underestimated, and further studies should be designed to clearly define its implication for a better clinical practice.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. Yasushi K, Yasuko M, Hiroshi K. Human Herpesviruses. Springer, 1st Edition 2018.
2. Whitley RJ, Roizman B. Herpes simplex virus infections. Lancet 2001; 357:1513–8.
3. Ong DSY, Bonten MJM, Spitoni C, Lunel FMV, Frencken JF, Horn J, et al. Epidemiology of multiple herpes viremia in previously immunocompetent patients with septic shock. Clin Infect Dis. 2017;64(9):1204–10.
4. Marzano AV, Genovese G, Fabbrocini G, et al. Varicella-like exanthem as a specific COVID-19-associated skin manifestation: multicenter case series of 22 patients. J Am Acad Dermatol. 2020;83(1):280-285.
5. Luyt CE, Brechot N, Chastre J. What role do viruses play in nosocomial pneumonia? Curr Opin Infect Dis. 2014; 27:194–9.
6. Saugel B, Jakobus J, Huber W, Hoffmann D, Holzapfel K, Protzer U, et al. Herpes simplex virus in bronchoalveolar lavage fluid of medical intensive care unit patients: association with lung injury and outcome. J Crit Care. 2016; 32:138–44.
7. Schuierer L, Gebhard M, Ruf HG, Jaschinski U, Berghaus TM, Wittmann M, Braun G, Busch DH, Hoffmann R. Impact of acyclovir use on survival of patients with ventilator-associated pneumonia and high load herpes simplex virus replication. Crit Care. 2020 Jan 10;24(1):12.
8. Xu R, Zhou Y, Cai L, Wang L, Han J, Yang X, Chen J, Chen J, Ma C, Shen L. Co-reactivation of the human herpesvirus alpha subfamily (herpes simplex virus-1 and varicella zoster virus) in a critically ill patient with COVID-19. Br J Dermatol. 2020 Dec;183(6):1145-1147.
9. Le Balc'h P, Pinceaux K, Pronier C, Seguin P, Tadié JM, Reizine F. Herpes simplex virus and cytomegalovirus reactivations among severe COVID-19 patients. Crit Care. 2020 Aug 28;24(1):530.
10. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–4.
11. Bradley H, Markowitz LE, Gibson T, McQuillan GM. Seroprevalence of herpes simplex virus types 1 and 2—United States, 1999-2010. J Infect Dis. 2014; 209:325–33.

12. Tartari F, Spadotto A, Zengarini C, Zanoni R, Guglielmo A, Adorno A, Valzania C, Pileri A. Herpes zoster in COVID-19-positive patients. Int J Dermatol. 2020 Aug;59(8):1028-1029. doi: 10.1111/ijd.15001.
13. Busani S, Bedini A, Biagioni E, Serio L, Tonelli R, Meschiari M, Franceschini E, Guaraldi G, Cossarizza A, Clini E, Maiorana A, Gennari W, De Maria N, Luppi M, Mussini C, Girardis M; Modena Covid-19 Working Group (MoCo19). Two fatal cases of acute liver failure due to HSV-1 infection in COVID-19 patients following immunomodulatory therapies. Clin Infect Dis. 2020 Aug 25:ciaa1246.
14. Franceschini E, Cozzi-Lepri A, Santoro A, Bacca E, Lancellotti G, Menozzi M, Gennari W, Meschiari M, Bedini A, Orlando G, Puzzolante C, Digaetano M, Milic J, Codeluppi M, Pecorari M, Carli F, Cuomo G, Alfano G, Corradi L, Tonelli R, De Maria N, Busani S, Biagioni E, Coloretti I, Guaraldi G, Sarti M, Luppi M, Clini E, Girardis M, Gyssens IC, Mussini C. Herpes Simplex Virus Re-Activation in Patients with SARS-CoV-2 Pneumonia: A Prospective, Observational Study. Microorganisms. 2021 Sep 7;9(9):1896. doi: 10.3390/microorganisms9091896. PMID: 34576791; PMCID: PMC8465957.
15. Patrucco F, Albera C, Bellocchia M, Foci V, Gavelli F, Castello LM, Bellan M, Sainaghi PP, Airoldi C, Balbo PE, Solidoro P. SARS-CoV-2 Detection on Bronchoalveolar Lavage: An Italian Multicenter experience. Respiration. 2020;99(11):970-978.

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