



## Human Herpesviruses Reactivation in COVID-19

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### Abstract

Since the start of the COVID-19 pandemic, a wide range of clinical pictures have been documented ranging from asymptomatic cases to respiratory failure. Accumulating evidence of co-infection and reactivation of viruses during COVID-19 started to emerge. Herein we report three cases of herpes virus reactivation in severely ill COVID-19 patients. With the presence of herpes virus reactivation, one should think for the possibility to screen simultaneously besides SARS-CoV-2 for other respiratory pathogens, not forgetting HSV reactivation, given its similarity in worsening respiratory functions and similarity in radiologic findings to COVID-19. Missing such diagnosis could worsen the clinical course of COVID-19 patients and worsen the prognosis.

**Keywords:** COVID-19; Human herpesvirus; Pneumonia; Co-Infection; SARS-CoV-2

### Introduction

Since the onset of Coronavirus Disease 2019 (COVID-19) pandemic in December, a wide range of clinical presentations have been reported. Clinical characteristics ranged from asymptomatic cases to respiratory failure and death.

Several case reports documented herpes zoster and herpes simplex activation in the context of infection by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1-3]. Authors proposed that varicella-zoster virus reactivation could be explained by the absolute lymphopenia, especially CD3+ CD8+ lymphocytes noted in COVID-19 patients [4].

Similarly, a retrospective study included 544 with severe COVID-19 pneumonia, 18% of these patients were administered tocilizumab. It was noted in this group when compared to the rest of patients that there was a new episode of infections including four cases of Herpes Simplex Virus (HSV) 1 reactivation [5].

HSV reactivation usually develops in patients with immunosuppression or air way injury. Interestingly most of the patients with HSV pneumonia present radiologically with ground glass opacities and consolidation, which should draw the attention of the clinicians not to miss such associated infection in severely ill COVID-19 patients [6].

Herein we present three cases who were admitted to Misr International Hospital with fatal outcome that tested positive for HSV 1 in tracheal aspirate samples in the context of COVID-19.

### Case Series

#### Case 1

A 79-year-old-male with past medical of type II Diabetes Mellitus, Hypertension, Ischemic cardiomyopathy was admitted on June 19<sup>th</sup> with shortness of breath and hypotension. Chest CT revealed ground glass opacities. The patient tested positive for SARS-CoV-2 Real-Time Polymerase Chain Reaction (RT-PCR). He was started on high flow oxygen for less than 24 h and methylprednisolone 1 mg/kg was administered. The patient remained hypoxic and Tocilizumab 8 mg/kg was started, but he continued to deteriorate and required intubation. He was on Tigecycline, meropenem and voriconazole and his cultures showed no growth. Four days later oxygen saturation started to drop while on FiO<sub>2</sub> 100% and chest X-ray showed diffuse infiltrates so Herpes viruses PCR was ordered from tracheal aspirate and Herpes simplex 1 PCR came back positive and he was started on acyclovir, but he died shortly.

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## Case 2

A 60-year-old-female with past medical history of morbid obesity, type II Diabetes Mellitus, hypertension and ischemic heart disease presented on June 22<sup>nd</sup> with severe respiratory distress. Chest CT showed bilateral ground glass opacities and she was immediately intubated in the emergency room and admitted to ICU and was started on methylprednisolone 1 mg/kg and she received a single dose of tocilizumab at 8 mg/kg. SARS-CoV-2 PCR was positive and cultures were sent and sputum grew *Candida albicans*, *Streptococcus pneumoniae* and coagulase-negative *Staphylococcus* and she remained on meropenem, linezolid and voriconazole without improvement and tracheal aspirate PCR came back positive for Herpes Simplex 1 PCR and she was started on acyclovir but unfortunately she died on June 26<sup>th</sup>.

## Case 3

An 87-year-old-female with no previous medical history who was admitted on June 8<sup>th</sup> following a ground level fall at home and she acquired left femoral neck fracture and multiple rib fractures. She had intraoperative fracture fixation which was complicated by severe bleeding. She remained in the hospital for two days where she developed fever and hypoxemia. Chest CT revealed bilateral ground glass opacities then she was tested for COVID-19 and RT-PCR came back positive. The hypoxemia continued to worsen requiring intubation with vasopressor support and methylprednisolone 2 mg/kg. She then developed left sided pneumothorax that required chest tube placement. During her ICU stay her tracheal aspirate cultures were positive for Carbapenem-resistant *Acinetobacter baumannii* and *C. albicans* and she received fluconazole, meropenem, levofloxacin and tigecycline plus linezolid which was switched to clindamycin following the development of pancytopenia but due to worsening hypoxemia tracheal aspirate PCR for Herpes Viruses was sent and came back positive for Cytomegalovirus, Herpes Simplex Virus 1 and Human Herpesvirus 6 and she was started on intravenous Ganciclovir but she died on July 2<sup>nd</sup> within 24 h of PCR results. Table 1 summarizes the laboratory tests for the three patients on the day of diagnosis of HSV 1 infection.

## Discussion

In a retrospective study conducted in China that included 257 patients viral co-infections represented 81 (31.5%) cases with HSV present in 8 (3.1%) patients but since severe/critical cases represented only 17 (6.6%) of the cohort authors didn't relate HSV to pneumonia in critically ill patients [7].

Guaraldi et al. [5] reported secondary infections in COVID-19 patients including bacteremia, bacterial pneumonia, candidemia, *Pneumocystis jirovecii* pneumonia, invasive aspergillosis, hepatitis B virus reactivation and HSV 1 reactivation.

This accumulating evidence together with our cases should raise the attention of the possibility of co-infection or reactivation of viral infections in patients with COVID-19, as this will increase the difficulty in clinical diagnosis and treatment and eventually worsen

the outcome and prognosis. One should think in such situation to screen simultaneously besides SARS-CoV-2 for other respiratory pathogens, not forgetting HSV reactivation, given its similarity in worsening respiratory functions and similarity in radiologic findings to COVID-19.

Main limitation in our report is the late results of HSV 1 PCR in the clinical course of our patients hence we did not have enough time to improve the outcome. Patient 3 didn't receive tocilizumab, but her age and high dose steroids and subsequent severe lymphopenia may be a cause for reactivation not only for HSV, but also for Cytomegalovirus and Human Herpesvirus 6, which is common in severely immune suppressed patients [8,9]. The protocol in our center was to start voriconazole in all COVID-19 patients before initiating Tocilizumab for prophylaxis against COVID-19 Associated Pulmonary Aspergillosis (CAPA); however, following our results of positive HSV 1 in all tested cases we started adding acyclovir prophylaxis.

We are not sure whether the increased incidence of HSV 1 in our cases was due to lack of antivirals or due to associated immune suppression of COVID-19 or high dose steroids and Tocilizumab. Further research is needed given the new evidence undermining the value of antivirals and supporting the use of steroids which could lead to subsequent increase of incidence of HSV 1 pneumonia.

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