COVID-19 and Human Herpesviruses Reactivations

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There are several human herpesviruses. A common characteristic of infection by these viruses is latency, by which the virus assumes a non-replicative state, subverting the attentions of the host's immune response. In immunocompetent hosts, herpesviruses are immunologically controlled. In situations where immunological control is lost, herpesviruses can reactivate and produce clinically apparent disease. It is becoming apparent that COVID-19 or exposure to COVID-19 vaccines can exert several effects on the immune system. The pandemic of COVID-19 shows no sign of abating, with new severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) variants continuing to evolve.

COVID-19 SARS-CoV-2 vaccination cytomegalovirus

1. Introduction

COVID-19 (coronavirus disease 2019) is the current World Health Organization-approved term used to describe the clinical syndrome [1][2] associated with infection by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Initially, the most common signs and symptoms included fever, dry cough, and dyspnoea [1][2]. Clinical presentations have ranged from asymptomatic to life-threatening severe acute respiratory syndrome [3][4]. A global pandemic of COVID-19 was declared by the World Health Organization in March 2020 [5] and continues to the present day. Over this period of time, mutations of SARS-CoV-2 have resulted in waves of infection of several variants of the virus [6]. These variants have displayed differing capacities for spread and produced severe disease in both vaccinated and non-vaccinated populations [7][8], particularly as a consequence of new mutations in the SARS-CoV-2 spike receptor-binding domain, potentially enabling evasion of neutralizing antibody responses. SARS-CoV-2 vaccination is a fundamental strategy for reducing COVID-19 and, to date, several vaccines have been licensed for use, while others are in the late stages of development [9]. It is becoming increasingly realised that vaccination will be a long-term measure for controlling the COVID-19 pandemic and, similarly to influenza, regular boosting will be required [10].

Nine human herpesviruses have been described. According to recently updated nomenclature [11], these are *Human alphaherpesvirus 1* (herpes simplex virus type 1), *Human alphaherpesvirus 2* (herpes simplex virus type 2), *Human alphaherpesvirus 3* (varicella-zoster virus), *Human gammaherpesvirus 4* (Epstein–Barr virus), *Human betaherpesvirus 5* (human cytomegalovirus), *Human betaherpesvirus 6A* (human herpesvirus 6A), *Human betaherpesvirus 6B* (human herpesvirus 6B), *Human betaherpesvirus 7* (human herpesvirus 7), and *Human gammaherpesvirus 8* (Kaposi's sarcoma herpesvirus). Throughout this research, historical nomenclature/common

names will be used for the human herpesviruses. A uniform characteristic of human herpesviruses is their capacity to establish long-term or life-long immunopathological relationships with their human hosts [12]. Following primary infection, human herpesviruses are not eradicated by the host's immune response, and virus infection is maintained in various cell types in a mostly non-replicative state (latent infection). Should the host's immune control of virus infection be diminished, for example, by immune senescence or iatrogenic events (e.g., induced immunosuppression for transplantation) or infection by other viruses (e.g., HIV), human herpesviruses can reactivate, potentially causing severe disease (**Table 1**).

Table 1. Clinical presentations and risk factors for severe human herpesviruses infections in immunocompromised/immunodeficient individuals (selected studies).

Human Herpesvirus	Clinical Presentation	Predisposing/Risk Factors
Herpes simplex viruses [13]	Herpes simplex virus encephalitis (type not differentiated)	HIV infection, malignancies, transplantation, immunosuppressive agents for connective tissue disorders
Herpes simplex virus 1 [14]	Stomatitis	Haematopoietic stem cell transplant for acute myeloid leukaemia
Varicella-zoster virus [15]	Herpes zoster/shingles	Autoimmune diseases, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, chronic kidney disease, depression, malignancies
Varicella-zoster Virus [16]	Meningitis/pneumonitis	Transplantation
Cytomegalovirus [17]	Retinitis	HIV infection
Cytomeglovirus [18]	Pneumonitis	Lung transplant
Epstein–Barr Virus [19]	Post-transplant lymphoproliferative disorder	Heart transplant
Epstein–Barr virus [20]	Haemophagocytic lymphohistiocytosis	Chronic active EBV infection
Human herpesvirus 6 (type not differentiated, but most likely 6B) [21]	Encephalitis	Leukaemia requiring haematopoietic stem cell transplant

SARS-CoV-2 infection or vaccination evokes an immune response; the interaction of the virus with the human host is complex and remains to be fully determined [22][23]. Several different pathologies have been identified following SARS-COV-2 infection, e.g., asymptomatic infection [24], acute respiratory distress syndrome with cytokine storm [3][4], and post-acute sequelae of COVID-19 [25], commonly described as "long COVID".

2. COVID-19 and Human Herpesviruses Reactivations

There have been several reports of systemic or pulmonary reactivation of Herpes Simplex Virus (HSV-1) in critically ill COVID-19 patients (**Table 2**). This topic has recently been reviewed by Giacobbe et al. [26], who reviewed seven studies of HSV-1 reactivation in critically ill COVID-19 patients together with relevant immunology and clinical implications. These authors noted that the prevalence of HSV-1 reactivation may be as high as >50%, but with a large heterogeneity across studies that is potentially attributable to a lack of standardization. Specifically, some reports have noted the clinical significance of HSV-1 reactivations to be equivocal; for example, Luyt et al. [27] have reported a 50% rate of HSV lung reactivation in 145 patients with severe COVID-19 pneumonia requiring invasive mechanical ventilation but did not observe any impact on patient outcomes. In an attempt to clarify the association between HSV-1 reactivation and mortality, Meyer et al. [28] conducted an observational study of 153 critically ill COVID-19 patients using prospectively collected data and samples. In this study [28], 26.1% patients had confirmed HSV-1 reactivation, and day-60 mortality was higher in patients with HSV-1 reactivation (57.5%) versus without (33.6%).

There is evidence [29] that herpes zoster due to varicella-zoster virus (VZV) reactivation has increased during the COVID-19 pandemic, which may possibly be related to the lymphopenia commonly associated with SARS-CoV-2 infection [30][31]. Salim Ali Algaadi [30] recently reviewed several case reports of herpes zoster associated with COVID-19, with the conclusion that there is a potential causal relationship between COVID-19 and subsequent herpes zoster. Unfortunately, most of the evidence for this phenomenon is derived from case reports, and there is a need for further epidemiological studies.

Results from a large Italian observational study of COVID-19 patients with moderate to severe acute respiratory distress syndrome [32] have shown cytomegalovirus (CMV) viraemia/reactivation in 20.4% of patients studied (**Table 2**). There have been several reports describing CMV reactivation with gastrointestinal tract involvement [33]. It has been suggested by Alanio et al. [34] that latent CMV infection is associated with an increased risk of COVID-19-related hospitalisation. These authors [34] demonstrated that CMV seropositivity was associated with more than twice the risk of hospitalisation due to SARS-CoV-2 infection. Furthermore, a subset of patients was immune profiled, revealing altered T cell activation profiles potentially indicative of CMV-mediated immune phenomena influencing the outcome and severity of SARS-CoV-2 infection. Other studies—for example, Weber et al. [35]—have also identified CMV seropositivity as a potential novel risk factor for severe COVID-19 (**Table 2**). Finally, Pius-Sadowska et al. [36] reported higher plasma concentrations of chemokines CXCL8 and CCL2, together with CMV-seropositivity, to be potential prognostic factors for severe COVID-19 disease.

Epstein–Barr virus (EBV) reactivation has frequently been detected in COVID-19 patients [37][38], and in some reports [39][40], it has been associated with greater morbidity and mortality. For instance, Chen et al. [39] reported a high incidence of EBV reactivation in COVID-19 patients, which was associated with fever and increased inflammation. In another study, Xie et al. [40] reported 17 (13.3%) of 128 COVID-19 patients to show evidence of EBV reactivation. This group also had higher day-14 and day-28 mortality rates compared to the EBV non-reactivated group. Cases of human herpesvirus-6 reactivation or coinfection have also been reported in association with COVID-19 [41][42]. In both studies [41][42], HHV-6 reactivation was detected, but there was no evidence of an association with COVID-19 disease severity or mortality.

Table 2. Selected studies of herpesviruses reactivations in severely ill COVID-19 patients.

Herpesvirus Reactivation and Study Reference	Total Patients and Clinical Characteristics of Study Group	Results	Conclusions/Comments
HSV-1 Luyt et al. [27]	Retrospective monocentric cohort study of 145 patients with severe COVID-19 pneumonia requiring invasive mechanical ventilation.	Among 145 COVID-19 patients, a total of 50% and 42% had HSV and CMV lung reactivations, respectively, compared to 63% and 28% HSV and CMV lung reactivations in a control group of 89 influenza patients.	HSV and CMV lung reactivations are frequent in COVID-19 patients subject to invasive mechanical ventilation; however, they are no more frequent than in controls with influenza. HSV and CMV reactivations were defined by a positive PCR test result in bronchoalveolar lavage fluid samples or whole blood samples.
HSV Meyer et al. [28]	Observational study using prospectively collected data, as well as HSV-1 blood and respiratory samples from 153 critically ill COVID-19 patients admitted to a regional intensive care unit (ICU) for at least 48 h, from February 2020 to February 2021.	Respiratory and blood samples were tested from 61/153 (39.9%) and 146/153 (95.4%) patients, respectively. On the basis of respiratory sample testing, HSV PCR was positive in 19/61 (31.1%) of patients, and on the basis of blood sample testing, HSV PCR was positive in 36/146 (24.7%) of patients.	Overall, 40/153 (26.1%) patients had an HSV PCR positive sample. HSV reactivation was defined as testing positive by HSV PCR. Day-60 mortality in the whole cohort was 39.9% higher in patients with HSV-1 reactivation (57.5% versus 33.6% in patients without HSV-1 reactivation, $p = 0.001$).
CMV Gatto et al. [32]	Observational study using prospectively collected data of all the patients with moderate to severe acute respiratory distress syndrome admitted to three COVID-19 ICUs at the University Hospital of Modena over the period from 22 February 2020 to 21 July 2021.	A total of 431 patients met the study's inclusion criteria. COVID-19 was confirmed by laboratory detection of SARS-CoV-2. CMV reactivation was evidenced in whole blood samples by CMV PCR with a cut-off of >62 IU/mL.	Blood CMV reactivation was detected in 88/431 (20.4%) patients, with a median onset of 17 days following ICU admission. Patients with CMV reactivation had prolonged hospital stays and a higher mortality rate than patients without reactivation. CMV reactivation was not independently associated with higher mortality.
CMV and HSV Weber et al. [35]	National German COVID-19 bio-sample and data banks were used to retrospectively analyse the CMV and HSV status of patients.	CMV seropositivity was 43.6% in cases of mild COVID-19, 72.3% in cases of moderate COVID-19, and 77.5% in cases of severe to	Patients aged <60 years with severe COVID-19 had a very high prevalence of CMV seropositivity. CMV seropositivity, unlike HSV, might be a strong biomarker for identifying patients <60 years with a higher risk

Herpesvirus Reactivation and Study Reference	Total Patients and Clinical Characteristics of Study Group	Results	Conclusions/Comments
	Serum samples were collected from patients who experienced mild (n = 101), moderate (n = 130), or severe to critical (n = 80) COVID-19.	critical COVID-19. HSV seropositivity was 71.3%, 93.8%, and 96.2%, respectively, in the same groups.	of developing severe COVID-19, particularly in the absence of other co-morbidities.
EBV Chen et al. [39]	A retrospective, single-centre study from 9 January 2020 to 29 February 2020: a total of 188 hospitalised patients were recruited with PCR-confirmed SARS-CoV-2 infection.	EBV serology was available for 78 patients, and 11 failed to meet the study inclusion criteria. Of the remaining 67 patients, 37 (55.2%) had laboratory evidence of EBV reactivation. EBV viral load testing was not undertaken.	Patients with laboratory evidence of EBV reactivation had a 3.09-fold risk of having a fever symptom. C-reactive protein levels were significantly elevated in patients with EBV reactivation.
EBV Xie et al. [40]	Retrospective, single-centre, observational study of ICU admissions over the period from 31 January 2020 to 27 March 2020.	145 critically ill patients with SARS-CoV-2/PCR-confirmed COVID-19 were recruited into the study, and 128 met the study's inclusion criteria. EBV viral load testing (≥500 copies/mL) and serology were used as evidence of EBV reactivation.	Patients with EBV reactivation had higher (29.4%) day-14 and day-28 mortality rates compared to 7.8% and 10.9%, respectively, for patients without EBV reactivation. Patients with evidence of EBV reactivation showed more severe symptoms and received more immunosupportive treatment.
HHV-6 Lino et al. [42]	Retrospective, single-centre study of hospitalised patients with moderate to severe COVID-19	173 patients with suspected COVID-19 were recruited, of which 60 had a positive PCR test for SARS-CoV-2. Of these 60 confirmed cases, 13/60 (21.7%) were also had positive PCR tests for HHV-6.	HHV-6 reactivation did not impact general mortality.

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