CASE STUDY

COVID-19 and herpes zoster co-infection presenting with trigeminal neuropathy

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Background: Varicella-zoster virus (VZV) is a human neurotropic virus that remains in a latent state within ganglionic neurons throughout the entire neuroaxis after the primary infection. When herpes zoster (HZ) leads to trigeminal involvement, the ophthalmic division is the most implicated. COVID-19 has emerged as a viral cause of severe acute respiratory syndrome that has spread all over the world in the last months. Co-infection with COVID-19 and other viruses has been reported, but sparsely, and involving the respiratory viruses.
Methods: The case of a co-infection of COVID-19 with VZV is reported, and the literature reviewed.
Results: A 39-year-old immunocompetent man presented with oligosymptomatic infection with COVID-19, which evolved to left facial HZ, affecting the three divisions of the trigeminal nerve. The co-infection was remotely registered, being the respiratory viruses, especially influenza, the most commonly cited association. However, the present case illustrates the emergence of a latent virus infection, which might be favored by the inflammatory response to the former agent (COVID-19). This reaction ascended from the nasal cavity, where trigeminal branches are also placed.
Conclusions: The emergence of latent VZV infection in this rare presentation might illustrate an effect, at least locally, of COVID-19. This virus possibly induced a retrograde reactivation of VZV in a young immunocompetent patient.

Introduction

Varicella-zoster virus (VZV) is a human neurotropic virus that migrates to a latent state within ganglionic neurons throughout the entire neuroaxis after the primary infection (chickenpox) [1].

Coronavirus, one of the major pathogens targeting the human respiratory system, has featured in outbreaks of public health threat. After severe acute respiratory syndrome (SARS)-CoV and Middle East respiratory syndrome (MERS)-CoV, we are experiencing the rise of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or COVID-19 [2]. In the present paper, we report a case of co-infection of VZV and COVID-19. Consent for publication was obtained from the participant.

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Case report

On 25 March, a previously healthy 39-year-old man was admitted to our emergency room (ER) presenting with left orofacial herpes zoster (HZ) involving the left three trigeminal divisions, with intraoral mucosal lesions. The patient had had chickenpox during childhood. No history of recurrent or opportunistic infections or use of immunosuppressive drugs was reported.

In the preceding 10 days, he had noticed fatigability and experienced occasional episodes of diarrhoea, followed by left trigeminal neuralgia. On 22 March,

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3 days after the beginning of the neuralgia, he presented low fever episodes, at which point he visited an ER for the first time. He still had no cutaneous lesion and was discharged with symptomatic drugs; however, at the end of that day, a papulovesicular rash emerged. His assistant physician prescribed oral acyclovir and pregabalin, but no improvement was observed; therefore, he returned to the ER unit 2 days later, on 25 March.

During examination, he was fully alert, oriented and had no sign of meningism, vestibular disturbance or facial palsy. He complained of sharp left hemifacial pain, especially during chewing, and hypogeusia for sweetness. He had photosensitivity but no visual acuity impairment. Fundoscopy results were normal.

Blood analysis was normal and showed: white blood cell count $6.0 \times 10^3/\mu l$ (22% of lymphocytes), haemoglobin 14.7 g/dl, platelets $246 \times 10^3/\mu l$, gamma glutamyl transpeptidase19 UI/l, alkaline phosphatase 61 UI/l, alanine aminotransferase 33 UI/l, aspartate aminotransferase 18 UI/l, urea 23 mg/dl, creatinine 1.07 mg/dl, lactic dehydrogenase 166 UI/l and C-reactive protein 0.45 UI/l. Varicella-Zoster IgM serology was positive. A human immunodeficiency virus serology test was negative and immunoglobulin levels were normal. Brain MRI demonstrated left trigeminal nerve enhancement. Intravenous acyclovir 10 mg/kg three times a day was initiated. After 24 hours of treatment, there was a remarkable clinical improvement. On the fifth day, the progression of HZ lesions in the patient had already stopped and he was without fever or respiratory symptoms (Fig. 1).

The patient's medical history showed that he could have been exposed to COVID-19 on two different occasions: during a cruise from the United Arab Emirates that arrived in Brazil on 7 March and during a meeting on 14 March with a friend recently arrived from the USA. Owing to the current pandemic, a nasopharyngeal swab specimen was collected to investigate for COVID-19 infection using RT-PCR, and the result was positive.

Discussion

In December 2019, Wuhan reported the first cases of pneumonia caused by COVID-19 [3]. Since then, COVID-19 has spread all over the world, with major outbreaks in China, South Korea, Italy and Iran [4]. Virus co-infection with COVID-19 has been reported in other respiratory agents, such as influenza [3,4]. In 2020, Wu et al. [3] and Ding et al. [4] reported five cases of influenza among 115 Chinese inpatients positive for COVID-19. This infection concurrency was probably favoured by seasonality. In the USA, co-infection with another respiratory virus, metapneumovirus, was reported [5], but there is still no report involving co-infection with a latent non-respiratory virus.

Varicella-zoster virus tends to remain in a latent state, which is probably related to neuronal resistance to VZV-induced apoptosis [1]. The herpesviruses

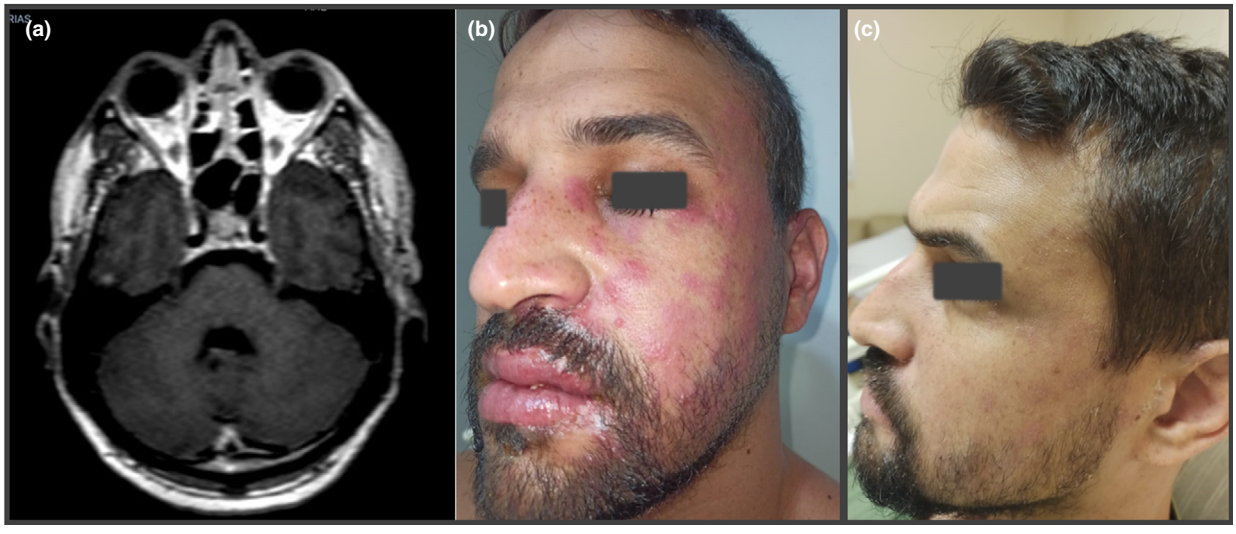

Figure 1 Trigeminal neuropathy due to zoster virus in a COVID-19 positive patient. (a) Admission day, when MRI evinced left trigeminal enhancement (axial CUBE T1WI + contrast sequence). (b) Facial cutaneous lesions in the three divisions of trigeminal nerve. (c) Reduction of vesiculopapular rash and crusted lesions. [Colour figure can be viewed at wileyonlinelibrary.com]

themselves facilitate this escape, for example, by downmodulating the expression of surface ligands that are targeted to natural killer cells. However, these ligands are upregulated following various stress conditions, such as a viral infection [6]. The maintenance of stress conditions, in turn, seems necessary to allow virus reactivation progression [7]. In the present case, the infection by COVID-19 might have been the stress factor.

The reactivation of HZ affects the sensory ganglion and its cutaneous nerve; cranial nerve dermatomes are less affected than truncal ones. For cases involving the trigeminal nerve, the ophthalmic division is the most often implicated [8]. It is rare for the three divisions to be affected, but has been scarcely reported in immunocompetent patients younger than 50 years [9,10].

There is already evidence of a role for COVID-19 in the development of a cytokine storm in a subgroup of patients with severe infection [11]. Even in the present oligosymptomatic case, COVID-19 might have fostered retrograde reactivation of VZV from the nasal cavity, where ophthalmic and maxillary branches of the trigeminal nerve are harboured [12], Hence, COVID-19 might also entailed this rare presentation of HZ.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Data availability statement

Data available on request due to privacy/ethical restrictions.

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