Comment on: "To consider varicella-like exanthem associated with COVID-19, virus varicella zoster and virus herpes simplex must be ruled out. Characterization of herpetic lesions in hospitalized COVID-19 patients"

To the Editor: We have read with great interest the articles by Llamas-Velasco et al[1] and Marzano et al[2] about the current controversy regarding coronavirus disease 2019 (COVID-19) vesicular exanthems and the role of herpesvirus in the etiology of these lesions. Llamas-Velasco et al[1] report 3 cases of vesicular lesions in patients hospitalized with COVID-19, suggesting that complementary tests, such as Tzanck smear, virus culture, polymerase chain reaction (PCR), or skin biopsy should be performed to rule out other viral infections. Marzano and Genovese[2] were not able to perform PCR tests in their previous study of varicella-like exanthem[3] due to logistic reasons but also due to clinical presentation not being suggestive of varicella.

We previously conducted a prospective study of vesicular COVID-19 rashes, all with a positive nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in our hospital from March 1 to April 20, 2020.[4] Of a total of 53 patients, 15 were excluded because of an alternative herpes simplex/zoster clinical diagnosis (clinical data are summarized in Table I). All 15 patients presented typical clinical lesions and symptoms of herpes simplex/zoster. Only 1 patient (6.7%) had a previous history of immunosuppression. Latency time between COVID-19 symptoms and herpetic lesions was variable (median, 16 days; range, 6-32 days). Despite performing PCR tests for SARS-CoV-2 from the content of the vesicles in only 3 patients, all of the results were negative.

Regarding vesicular rashes or varicella-like COVID-19 exanthems,[3] we previously reported 4 cases in which we performed both PCR multiplex for

Table I. Summary of patient clinical data

Patient	Sex	Age, y	Relevant medical history	Chest x-ray	Total number of days since onset of COVID-19 symptoms	Diagnosis	Multiplex herpes PCR/SARS-CoV-2 rt-PCR from the vesicles	Medication
1 (Fig 1, *A*)	Male	69	None	Bilateral interstitial pneumonia (required ICU stay)	16	Recurrent herpes simplex (orolabial)	HSV1/negative	Hydroxychloroquine, azithromycin, ceftriaxone, acyclovir
2	Female	96	Hypertension, chronic kidney disease, hyperuricemia	Bilateral interstitial pneumonia	27	Recurrent herpes simplex (orolabial)	HSV1/negative	Hydroxychloroquine, azithromycin, prednisone
3	Female	77	Primary biliary cholangitis, Alzheimer disease	Bilateral interstitial pneumonia	14	Recurrent herpes simplex (orolabial)	HSV1/not done	Hydroxychloroquine, lopinavir/ritonavir, azithromycin, prednisone
4	Male	65	Hypertension, dyslipidemia	Bilateral interstitial pneumonia (required ICU stay)	32	Recurrent herpes simplex (orolabial)	HSV1/not done	Lopinavir/ritonavir, azithromycin, prednisone, tocilizumab, remdesivir, acyclovir
5	Male	38	Colorectal cancer (on chemotherapy treatment)	Bilateral interstitial pneumonia	9	Recurrent herpes simplex (orolabial)	HSV1/not done	Lopinavir/ritonavir, tocilizumab, remdesivir, prednisone, acyclovir

Continued

Table I. Cont'd

Patient	Sex	Age, y	Relevant medical history	Chest x-ray	Total number of days since onset of COVID-19 symptoms	Diagnosis	Multiplex herpes PCR/SARS-CoV-2 rt-PCR from the vesicles	Medication
6	Male	61	None	Bilateral interstitial pneumonia (required ICU stay)	15	Recurrent herpes simplex (orolabial)	HSV1/not done	Hydroxychloroquine, lopinavir/ritonavir, tocilizumab, prednisone, acyclovir
7	Female	45	None	Bilateral interstitial pneumonia	18	Recurrent herpes simplex (orolabial)	Not done/not done	Hydroxychloroquine
8	Male	76	Hypertension, dyslipidemia	Bilateral interstitial pneumonia	24	Recurrent herpes simplex (orolabial)	Not done/not done	Hydroxychloroquine
9 (Fig 1, *B*)	Female	56	None	Bilateral interstitial pneumonia	22	Localized herpes zoster	HSV3/negative	Hydroxychloroquine, valacyclovir
11	Male	52	None	Normal	14	Localized herpes zoster	HSV3/not done	Valacyclovir
10	Female	63	Hypertension	Normal	26	Localized herpes zoster (ophthalmic)	Not done/not done	Valacyclovir
12	Male	56	dyslipidemia	Normal	26	Localized herpes zoster (ophthalmic)	Not done/not done	Valacyclovir
13	Male	82	Hypertension, diabetes	Bilateral interstitial pneumonia	7	Localized herpes zoster	Not done/not done	Hydroxychloroquine, acyclovir
14	Female	73	Dyslipidemia	Bilateral interstitial pneumonia	12	Localized herpes zoster	Not done/not done	Hydroxychloroquine, prednisone, acyclovir
15	Male	78	Hypertension	Bilateral interstitial pneumonia	6	Localized herpes zoster	Not done/not done	Hydroxychloroquine, acyclovir

COVID-19, Coronavirus disease 2016; *HSV1*, herpes simplex virus 1; *HSV3*, herpes simplex virus 3; *ICU*, intensive care unit; *PCR*, polymerase chain reaction; *rt-PCR*, reverse-transcriptase polymerase chain reaction; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2.

herpesvirus and reverse-transcriptase PCR for SARS-CoV-2 directly from the content of the vesicles. Interestingly, results for both techniques were negative in all 4 cases.[4] This reasonably rules out a role of herpes viruses[3] and a potential infective ability of SARS-CoV-2 through the vesicles.

We agree with the authors that there is a potential role for herpetic viral infections and superinfections in patients with COVID-19. In fact, some presumed COVID-19 vesicular lesions have been later proven to be caused by herpetic infections.[1,5]

In our prospective study,[4] from a total of 96 COVID-19 dermatologic consultations in the reported period, 15.6% corresponded to herpes simplex/zoster diagnoses. However, we cannot categorically affirm that there is an incidence increase of these diagnoses in patients with COVID-19 due to the lack of a control group. In our current experience, the diagnosis of herpesvirus infection in patients with COVID-19 does not usually involve diagnostic doubts, due to the clinical presentation and reported symptoms being

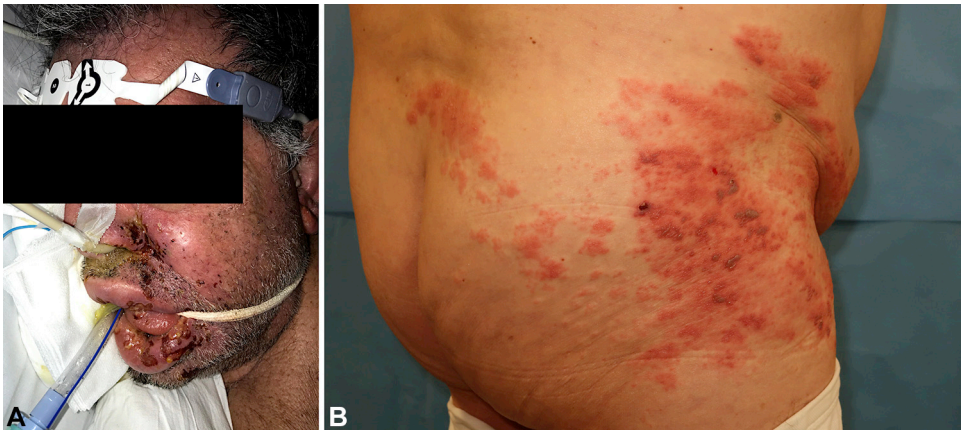

Fig 1. A, A 69-year-old man with COVID-19 pneumonia and extensive orolabial herpes simplex virus 1 reactivation. **B,** A 56-year-old woman with COVID-19 pneumonia and herpes zoster on the trunk.

typical of the disease, even when lesions are extensive (Fig 1).

In conclusion, complementary diagnostic tests for herpesvirus and even SARS-CoV-2 may prove useful for clinical research and should be encouraged if the necessary resources are available. However, we believe that regarding clinical practice, we should reserve these techniques for atypical clinical presentations or cases where therapeutic management would change significantly.

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