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# Journal Pre-proof

Response to “Reply to ‘Varicella-like exanthem as a specific COVID-19-associated skin manifestation: multicenter case series of 22 patients’: To consider varicella-like exanthem associated with COVID-19, virus varicella zoster and virus herpes simplex must be ruled out”

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3 manifestation: multicenter case series of 22 patients’: To consider varicella-like exanthem associated  
4 with COVID-19, virus varicella zoster and virus herpes simplex must be ruled out”

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32 We would like to thank Llamas-Velasco *et al.*<sup>1</sup> for their interest in our letter entitled “Varicella-like  
33 exanthem as a specific COVID-19-associated skin manifestation: multicenter case series of 22  
34 patients”.<sup>2</sup> They emphasize the need to use *Herpesviridae* family microarray polymerase chain  
35 reaction (PCR) on the vesicle fluid of COVID-19 patients with papulovesicular eruptions in order to  
36 define the etiology of the exanthem by giving the example of three patients with laboratory-  
37 confirmed COVID-19: PCR demonstrated the presence of herpes simplex virus (HSV)-1, human herpes  
38 virus (HHV)-6 and Epstein-Barr virus (EBV) in case #1, HSV-1 and HHV-7 in case #2, and varicella-  
39 zoster virus (VZV) in case #3.

40 We did not use vesicle fluid *Herpesviridae* family microarray PCR for logistical reasons in the case of  
41 15 patients (six were in our Intensive Care Unit, four in our Infectious Disease Unit, and five were in  
42 isolation at home and evaluated by means of teledermatology). The remaining seven cases were  
43 outpatients who had undergone a skin biopsy, and PCR was not used because true varicella could be  
44 ruled out on the grounds that the vesicles were not umbilicated, were scattered, and were often  
45 seen on the surface of papules; there were no pustules; and usually no itching. Furthermore, all of  
46 our patients had a previous history of varicella infection and, given the similarity of the lesions to  
47 those of varicella, we decided to use the term “varicella-like exanthem”.

48 Lymphopenia was detected in only eight patients, who were affected by more severe SARS-CoV-2  
49 infection and therefore possibly more susceptible to the development of a viral infection other than  
50 COVID-19.

51 In relation to the patients described by Llamas-Velasco *et al.*<sup>1</sup>, case #1 can be diagnosed as having a  
52 classic Kaposi varicelliform eruption (which could be clinically excluded in our patients), and case #3  
53 can be diagnosed as having varicella with a purpuric component that was possibly due to alterations  
54 in the coagulation cascade and/or anticoagulant treatment administered in order to prevent COVID-  
55 19-related thromboembolic complications. We would have liked to have been able to see pictures of  
56 case #2 in order to assess whether there were any similarities to the skin condition of our patients.

57 The detection of different viruses (HSV-1, HSV-2, HHV-6, HHV-7, VZV and EBV) in the patients of  
58 Llamas-Velasco *et al.* raises the question as to whether they had a true viral infection other than  
59 COVID-19 or just a super-infection, because it is possible to speculate that the dysfunctional immune  
60 response associated with COVID-19 acts both systemically and locally in the skin, thus attracting viral  
61 bystanders. This can occur in patients with autoimmune bullous diseases receiving  
62 immunosuppressive treatment as HSV-1 and HSV-2 DNA sequences have been demonstrated by  
63 means of blister fluid PCR.<sup>3,4</sup>

64 Finally, it is important to point out that neither we nor Llamas-Velasco *et al.*<sup>1</sup> assessed SARS-CoV-2  
65 RNA, whereas SARS-CoV-2 RNA and the DNA of *Herpesviridae* family members should both be sought  
66 in COVID-19-associated skin lesions.

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