

# Journal Pre-proof

Varicella-like exanthem as a specific COVID-19-associated skin manifestation:  
multicenter case series of 22 patients

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47 To the Editor:

48 The novel coronavirus disease (COVID-19), an infection due to the severe acute respiratory syndrome  
49 coronavirus 2 (SARS-CoV-2) that may cause interstitial pneumonia and respiratory failure, has  
50 currently taken on pandemic proportions.<sup>1</sup> COVID-19 outbreak has emerged in Wuhan (China) and  
51 has rapidly spread to Europe, particularly to Italy<sup>2</sup>, where, as of to date (April 1, 2020), 80572 people  
52 have tested positive.<sup>3</sup>

53 Two recent publications have brought attention to COVID-19-associated cutaneous manifestations.<sup>4,5</sup>  
54 Joob *et al.* reported on a dengue-like petechial rash in a COVID-19 patient from Thailand.<sup>4</sup> Recalcati  
55 described 18 out of 88 COVID-19 patients hospitalized in the Lecco Hospital (Lombardy region, Italy)  
56 who developed erythematous rash (n=14), widespread urticaria (n=3) or varicella-like vesicles (n=1).<sup>5</sup>  
57 During the Italian outbreak, we have observed a varicella-like papulovesicular exanthem as a rare but  
58 specific COVID-19-associated skin manifestation. Eight Italian Dermatology Units collected clinical  
59 data of patients with COVID-19 (microbiologically proven by nasopharyngeal swab) and no history of  
60 new medications in the previous 15 days who developed varicella-like lesions.

61 Demographic and clinical features of the 22 patients are summarized in Table 1.

62 Male patients were 72.7% (n=16/22) and the median age was 60 years. Most patients (n=17/22;  
63 77.3%) came from Lombardy, currently the worst-hit region in Italy, while the remaining patients  
64 came from Piedmont (n=1), Emilia-Romagna (n=1), Toscana (n=1), Lazio (n=1), and Campania (n=1).  
65 Median latency time from systemic symptoms to exanthem was three days (range from -2 to 12  
66 days). Median duration of skin manifestations was eight days (range= 4 – 15 days). Lesions were  
67 scattered in most cases (n=16; 72.7%), while they were diffuse in six (27.3%) cases. Predominance of  
68 vesicles was observed in 12 (54.5%) patients. No variations in the papulovesicular presentation were  
69 observed in our case series. Trunk was constantly involved, in some cases in association with limbs  
70 (n=4; 18.2%). (Fig. 1a-d) No facial or mucosal involvements were scored. Itching, which was generally  
71 mild, was reported in nine (40.9%) patients. In all the patients who underwent skin biopsy (n=7),  
72 histology was consistent with viral infection. (Fig. 1e-f)

73 Most common systemic symptoms were fever (n=21/22; 95.5%), followed by cough (n=16; 72.7%),  
74 headache (n=11; 50%), weakness (n=11; 50%), coryza (n=10; 45.5%), dyspnea (n=9; 40.9%), hyposmia  
75 (n=4; 18.2%), hypogeusia (n=4; 18.2%), pharyngodynia (n=1; 4.5%), diarrhea (n=1; 4.5%), myalgia  
76 (n=1; 4.5%). Death occurred in three (13.6%) patients.

77 Ours is the first series on this varicella-like exanthem as a specific COVID-19-associated cutaneous  
78 picture, unlike the non-specific cutaneous manifestations such as erythematous rash or urticaria  
79 reported by Recalcati.<sup>5</sup> Its typical features are constant trunk involvement, usually scattered  
80 distribution and mild/absent pruritus, the latter being in line with most viral exanthems but unlike  
81 true varicella. Lesions generally appear 3 days after systemic symptoms and disappear upon 8 days,  
82 without leaving scarring. A limitation of our study was missing histology in some cases. Moreover,  
83 demonstration of SARS-CoV-2 presence by Polymerase Chain Reaction in lesional skin was not  
84 possible due to specific primer unavailability. If further studies validate our findings, this early skin  
85 manifestation will represent a useful clue to suspect COVID-19 in asymptomatic/paucisymptomatic  
86 patients.

87

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109 **LEGENDS AND FIGURES**110 **TABLE 1. Demographic and clinical data of patients with varicella-like exanthem associated with COVID-19**

<b>Id</b>	<b>Sex</b>	<b>Age</b>	<b>Hometo wn</b>	<b>Date of symptoms' onset</b>	<b>Date of nasopharyngeal swab positivization</b>	<b>Skin lesions</b>	<b>Skin symptoms</b>	<b>Latency time (days)</b>	<b>Duration (days)</b>	<b>Localization</b>	<b>Systemic symptoms</b>	<b>Nasopharyngeal swab negativization</b>	<b>Course</b>
1	M	75	Rome	February 19, 2020	March 4, 2020	Diffuse papulovesicular lesions (predominance of papules)	No itching	12	5	Trunk	Fever, asthenia, hypogeusia, hyposmia	Yes	Resolution
2	M	57	Milan	February 20, 2020	February 22, 2020	Diffuse papulovesicular lesions (predominance of vesicles)	Mild itching	5	4	Trunk	Fever, cough, coryza, headache, hyposmia, hypogeusia, weakness	Yes	Resolution
3	M	59	Milan	February 28, 2020	March 2, 2020	Scattered papulovesicular lesions (predominance of papules)	Mild itching	7	15	Trunk	Fever, cough, pharyngodynia, headache, weakness	Yes	Resolution
4	F	56	Brescia	February 28, 2020	March 2, 2020	Scattered papulovesicular lesions (predominance of vesicles)	Pain	3	15	Trunk	Fever, cough, coryza, headache, weakness	Yes	Resolution
5	M	28	Bologna	March 1, 2020	March 10, 2020	Diffuse papulovesicular lesions started (predominance of papules)	Itching	4	7	Trunk	Fever, cough	Yes	Resolution
6	M	45	Biella	March 1, 2020	March 6, 2020	Scattered papulovesicular lesions (predominance of papules)	No itching	6	10	Trunk	Fever, diarrhea, nausea	Yes	Resolution
7	M	72	Brescia	March 1, 2020	March 14, 2020	Scattered papulovesicular lesions (predominance of vesicles)	No itching	Unknown	NA	Trunk, limbs	Fever, cough, coryza, headache, dyspnea	No	Active disease
8	M	83	Cremona	March 2, 2020	March 10, 2020	Scattered papulovesicular lesions (predominance of vesicles)	No itching	2	5	Trunk	Fever, dyspnea	No	Active disease*
9	M	61	Milan	March 2, 2020	March 5, 2020	Diffuse papulovesicular lesions (predominance of vesicles)	Mild itching	2	4	Trunk	Fever, cough, dyspnea, coryza, headache, weakness	//	Death

10	M	29	Brescia	March 3, 2020	March 10, 2020	Scattered papulovesicular lesions (predominance of vesicles)	Mild itching	1	12	Trunk	Fever, cough, weakness	Yes	Resolution
11	M	65	Brescia	March 3, 2020	March 16, 2020	Scattered papulovesicular lesions (predominance of papules)	Burning	2	13	Trunk	Fever, cough, dyspnea, coryza, headache, weakness	No	Active disease
12	M	44	Brescia	March 8, 2020	March 16, 2020	Scattered papulovesicular lesions (predominance of vesicles)	Burning, itching	3	8	Trunk	Fever, cough, coryza, headache, weakness	No	Resolution
13	M	75	Cremona	March 8, 2020	March 16, 2020	Scattered vesicular lesions (predominance of vesicles)	No itching	0	8	Trunk, limbs	Fever, dyspnea	//	Death
14	F	51	Brescia	March 8, 2020	March 17, 2020	Scattered papulovesicular lesions (predominance of vesicles)	Pain	4	8	Trunk	Fever, cough, dyspnea, coryza, headache, weakness	No	Active disease
15	F	62	Brescia	March 9, 2020	March 18, 2020	Scattered papulovesicular lesions (predominance of papules)	Burning	2	11	Trunk	Fever, cough, coryza, headache, weakness	No	Improvement
16	M	25	Siena	March 10, 2020	March 17, 2020	Diffuse papulovesicular lesions (predominance of vesicles)	Itching	5	6	Trunk, limbs	Cough, hyposmia, hypogeusia	No	Resolution
17	F	90	Cremona	March 12, 2020	March 20, 2020	Scattered papulovesicular lesions (predominance of vesicles)	No itching	1	6	Trunk	Fever, cough, dyspnea, coryza, headache, weakness	No	Active disease
18	F	69	Brescia	March 12, 2020	March 20, 2020	Scattered papulovesicular lesions (predominance of papules)	No itching	Unknown	NA	Trunk	Fever, cough, dyspnea, coryza, hyposmia, hypogeusia, headache, weakness	No	Active disease
19	M	65	Naples	March 13, 2020	March 20, 2020	Diffuse papulovesicular lesions (predominance of papules)	Mild Itching	-2	9	Trunk	Fever, cough	No	Improvement
20	M	80	Brescia	March 14, 2020	March 22, 2020	Scattered papulovesicular lesions (predominance of vesicles)	No itching	Unknown	NA	Trunk, limbs	Fever, dyspnea	//	Death
21	M	43	Milan	March 15, 2020	March 23, 2020	Scattered papulovesicular lesions (predominance of vesicles)	Mild itching	0	11	Trunk	Fever, myalgia	No	Active disease

22	F	8	Milan	March 15, 2020	March 24, 2020	Scattered papulovesicular lesions (predominance of papules)	No itching	3	7	Trunk	Fever, cough	No	Resolution
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111 \*, patient with acute respiratory distress symptoms (ARDS) in intensive care unit

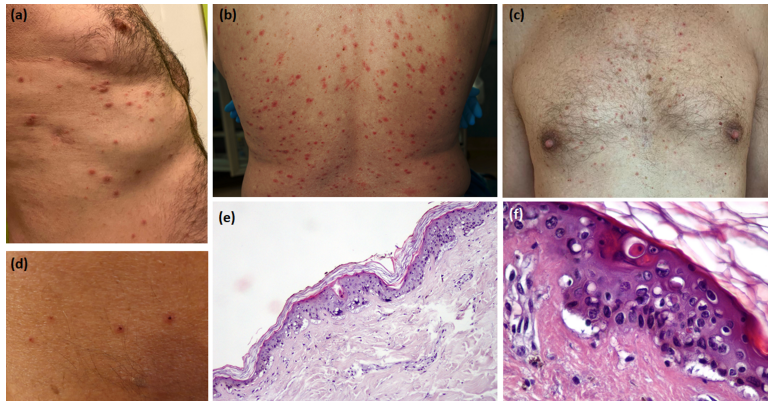
112 NA, not available

113

114 FIGURE 1. **A, B, C, D.** Papulovesicular exanthem on the trunk in four patients with COVID-19. In three patients (A, B and C), predominance of papules is seen.  
 115 In another patient (D) mainly presenting with vesicles, exanthem resolution with crusts is evident; **E,** Basket-wave hyperkeratosis, slightly atrophic  
 116 epidermis, vacuolar degeneration of the basal layer with multinucleate, hyperchromatic keratinocytes and dyskeratotic cells. Note the absence of  
 117 inflammatory infiltrate. Hematoxylin and eosin stain original magnification: x4; **F,** Close-up with atrophic epidermis, vacuolar alteration with disorganized  
 118 keratinocytes lacking orderly maturation, enlarged and multinucleate keratinocytes with dyskeratotic (apoptotic) cells. Hematoxylin and eosin stain, original  
 119 magnification: x20

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