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

Angelo Valerio Marzano, MD, Giovanni Genovese, MD, Gabriella Fabbrocini, MD, Paolo Pigatto, MD, Giuseppe Monfrecola, MD, Bianca Maria Piraccini, MD, Stefano Veraldi, MD, Pietro Rubegni, MD, Marco Cusini, MD, Valentina Caputo, MD, Franco Rongioletti, MD, Emilio Berti, MD, Piergiacomo Calzavara-Pinton, MD

PII: S0190-9622(20)30657-5
DOI: https://doi.org/10.1016/j.jaad.2020.04.044
Reference: YMJD 14472

To appear in: Journal of the American Academy of Dermatology

Received Date: 2 April 2020
Revised Date: 9 April 2020
Accepted Date: 11 April 2020


This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 by the American Academy of Dermatology, Inc.
Varicella-like exanthem as a specific COVID-19-associated skin manifestation: multicenter case series of 22 patients

Angelo Valerio Marzano, MD1,2, Giovanni Genovese, MD1,2, Gabriella Fabbrocini, MD3, Paolo Pigatto, MD4, Giuseppe Monfrecola, MD3, Bianca Maria Piraccini, MD5, Stefano Veraldi, MD1,2, Pietro Rubegni, MD5, Marco Cusini, MD1, Valentina Caputo, MD7, Franco Rongioletti, MD8, Emilio Berti, MD1,2, Piergiacomo Calzavara-Pinton, MD9

1Dermatology Unit, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy
2Department of Physiopathology and Transplantation, Università degli Studi di Milano, Milan, Italy
3Section of Dermatology, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy
4Clinical Dermatology, IRCCS Istituto Ortopedico Galeazzi, Milan, Italy
5Department of Dermatology, University of Bologna, Bologna, Italy
6Dermatology Unit, Department of Medical, Surgical and Neurosciences, University of Siena, Siena, Italy
7Unit of Pathology, Grande Ospedale Metropolitano Niguarda, Milan, Italy
8Unit of Dermatology, Department of Medical Sciences and Public Health, Cagliari, Italy
9Department of Dermatology, University of Brescia, Brescia, Italy

Corresponding author:
Angelo Valerio Marzano, MD
Dermatology Unit, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico
Via Pace, 9, 20122 – Milano, Italia
E-mail: angelo.marzano@unimi.it
Phone number: +390255035186
Fax number: +390255035236

Funding sources: None
Conflicts of Interest: None declared

IRB approval status: In view of the retrospective nature of the study, only a notification to the Ethical Committee of the Principal Investigator Center (Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy) was requested. All patients gave written informed consent for publishing the clinical images

Reprint requests: Angelo Valerio Marzano

Manuscript word count: 500 words
References: 5
Figures: 1
Supplementary figures: 0
Tables: 1
Supplementary tables: 0

Keywords: COVID-19; SARS-CoV-2; coronavirus; viral exanthem; infection; varicella
To the Editor:

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

Two recent publications have brought attention to COVID-19-associated cutaneous manifestations. Joob et al. reported on a dengue-like petechial rash in a COVID-19 patient from Thailand. Recalcati described 18 out of 88 COVID-19 patients hospitalized in the Lecco Hospital (Lombardy region, Italy) who developed erythematous rash (n=14), widespread urticaria (n=3) or varicella-like vesicles (n=1).

During the Italian outbreak, we have observed a varicella-like papulovesicular exanthem as a rare but specific COVID-19-associated skin manifestation. Eight Italian Dermatology Units collected clinical data of patients with COVID-19 (microbiologically proven by nasopharyngeal swab) and no history of new medications in the previous 15 days who developed varicella-like lesions. Demographic and clinical features of the 22 patients are summarized in Table 1.

Male patients were 72.7% (n=16/22) and the median age was 60 years. Most patients (n=17/22; 77.3%) came from Lombardy, currently the worst-hit region in Italy, while the remaining patients came from Piedmont (n=1), Emilia-Romagna (n=1), Toscana (n=1), Lazio (n=1), and Campania (n=1). Median latency time from systemic symptoms to exanthem was three days (range from -2 to 12 days). Median duration of skin manifestations was eight days (range= 4 – 15 days). Lesions were scattered in most cases (n=16; 72.7%), while they were diffuse in six (27.3%) cases. Predominance of vesicles was observed in 12 (54.5%) patients. No variations in the papulovesicular presentation were observed in our case series. Trunk was constantly involved, in some cases in association with limbs (n=4; 18.2%). (Fig. 1a-d) No facial or mucosal involvements were scored. Itching, which was generally mild, was reported in nine (40.9%) patients. In all the patients who underwent skin biopsy (n=7), histology was consistent with viral infection. (Fig. 1e-f)
Most common systemic symptoms were fever (n=21/22; 95.5%), followed by cough (n=16; 72.7%), headache (n=11; 50%), weakness (n=11; 50%), coryza (n=10; 45.5%), dyspnea (n=9; 40.9%), hyposmia (n=4; 18.2%), hypogeusia (n=4; 18.2%), pharyngodynia (n=1; 4.5%), diarrhea (n=1; 4.5%), myalgia (n=1; 4.5%). Death occurred in three (13.6%) patients.

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

The authors wish to thank the following collaborators for their help in data collection and patients’ management:

Marica Annunziata, Cristiana Colonna, Massimo Ghislanzoni, Raffaele Gianotti, Chiara Moltrasio, Gianluca Nazzaro, Emanuela Passoni, Marina Picca, Gaetano Rizzitelli, Diego Tosi

REFERENCES


### TABLE 1. Demographic and clinical data of patients with varicella-like exanthem associated with COVID-19

<table>
<thead>
<tr>
<th>Id</th>
<th>Sex</th>
<th>Age</th>
<th>Hometown</th>
<th>Date of symptoms' onset</th>
<th>Date of nasopharyngeal swab positivization</th>
<th>Skin lesions</th>
<th>Skin symptoms</th>
<th>Latency time (days)</th>
<th>Duration (days)</th>
<th>Localization</th>
<th>Systemic symptoms</th>
<th>Nasopharyngeal swab negativization</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>75</td>
<td>Rome</td>
<td>February 19, 2020</td>
<td>March 4, 2020</td>
<td>Diffuse papulovesicular lesions (predominance of papules)</td>
<td>No itching</td>
<td>12</td>
<td>5</td>
<td></td>
<td>Trunk</td>
<td>Fever, asthenia, hypogeusia, hyposmia</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>57</td>
<td>Milan</td>
<td>February 20, 2020</td>
<td>February 22, 2020</td>
<td>Diffuse papulovesicular lesions (predominance of vesicles)</td>
<td>Mild itching</td>
<td>5</td>
<td>4</td>
<td></td>
<td>Trunk</td>
<td>Fever, cough, coryza, headache, hyposmia, weakness</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>59</td>
<td>Milan</td>
<td>February 28, 2020</td>
<td>March 2, 2020</td>
<td>Scattered papulovesicular lesions (predominance of papules)</td>
<td>Mild itching</td>
<td>7</td>
<td>15</td>
<td></td>
<td>Trunk</td>
<td>Fever, cough, pharyngodynia, headache, weakness</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>56</td>
<td>Brescia</td>
<td>February 28, 2020</td>
<td>March 2, 2020</td>
<td>Scattered papulovesicular lesions (predominance of vesicles)</td>
<td>Pain</td>
<td>3</td>
<td>15</td>
<td></td>
<td>Trunk</td>
<td>Fever, cough, coryza, headache, weakness</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>28</td>
<td>Bologna</td>
<td>March 1, 2020</td>
<td>March 10, 2020</td>
<td>Diffuse papulovesicular lesions started (predominance of papules)</td>
<td>Itching</td>
<td>4</td>
<td>7</td>
<td></td>
<td>Trunk</td>
<td>Fever, cough</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>45</td>
<td>Biella</td>
<td>March 1, 2020</td>
<td>March 6, 2020</td>
<td>Scattered papulovesicular lesions (predominance of papules)</td>
<td>No itching</td>
<td>6</td>
<td>10</td>
<td></td>
<td>Trunk</td>
<td>Fever, diarrhea, nausea</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>72</td>
<td>Brescia</td>
<td>March 1, 2020</td>
<td>March 14, 2020</td>
<td>Scattered papulovesicular lesions (predominance of vesicles)</td>
<td>No itching</td>
<td>Unknown</td>
<td>NA</td>
<td></td>
<td>Trunk, limbs</td>
<td>Fever, cough, coryza, headache, dyspnea</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>83</td>
<td>Cremona</td>
<td>March 2, 2020</td>
<td>March 10, 2020</td>
<td>Scattered papulovesicular lesions (predominance of vesicles)</td>
<td>No itching</td>
<td>2</td>
<td>5</td>
<td></td>
<td>Trunk</td>
<td>Fever, dyspnea</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>61</td>
<td>Milan</td>
<td>March 2, 2020</td>
<td>March 5, 2020</td>
<td>Diffuse papulovesicular lesions (predominance of vesicles)</td>
<td>Mild itching</td>
<td>2</td>
<td>4</td>
<td></td>
<td>Trunk</td>
<td>Fever, cough, dyspnea, coryza, headache, weakness</td>
<td>//</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>------------</td>
<td>------------</td>
<td>---</td>
<td>--------------------------------------------------</td>
<td>---</td>
<td>--------------------------------------------------</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>29</td>
<td>Brescia</td>
<td>March 3, 2020</td>
<td>March 10, 2020</td>
<td>Scattered papulovesicular lesions (predominance of vesicles)</td>
<td>Mild itching</td>
<td>1</td>
<td>12</td>
<td>Trunk</td>
<td>Yes</td>
<td>Resolution</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>65</td>
<td>Brescia</td>
<td>March 3, 2020</td>
<td>March 16, 2020</td>
<td>Scattered papulovesicular lesions (predominance of vesicles)</td>
<td>Burning</td>
<td>2</td>
<td>13</td>
<td>Trunk</td>
<td>Fever, cough, dyspnea, coryza, headache, weakness</td>
<td>No</td>
<td>Active disease</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>44</td>
<td>Brescia</td>
<td>March 8, 2020</td>
<td>March 16, 2020</td>
<td>Scattered papulovesicular lesions (predominance of vesicles)</td>
<td>Burning, itching</td>
<td>3</td>
<td>8</td>
<td>Trunk</td>
<td>Fever, cough, coryza, headache, weakness</td>
<td>No</td>
<td>Resolution</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>75</td>
<td>Cremona</td>
<td>March 8, 2020</td>
<td>March 16, 2020</td>
<td>Scattered vesicular lesions (predominance of vesicles)</td>
<td>No itching</td>
<td>0</td>
<td>8</td>
<td>Trunk, limbs</td>
<td>Fever, dyspnea</td>
<td>//</td>
<td>Death</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>51</td>
<td>Brescia</td>
<td>March 8, 2020</td>
<td>March 17, 2020</td>
<td>Scattered papulovesicular lesions (predominance of vesicles)</td>
<td>Pain</td>
<td>4</td>
<td>8</td>
<td>Trunk</td>
<td>Fever, cough, dyspnea, coryza, headache, weakness</td>
<td>No</td>
<td>Active disease</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>62</td>
<td>Brescia</td>
<td>March 9, 2020</td>
<td>March 18, 2020</td>
<td>Scattered papulovesicular lesions (predominance of vesicles)</td>
<td>Burning</td>
<td>2</td>
<td>11</td>
<td>Trunk</td>
<td>Fever, cough, coryza, headache, weakness</td>
<td>No</td>
<td>Improvement</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>25</td>
<td>Siena</td>
<td>March 10, 2020</td>
<td>March 17, 2020</td>
<td>Diffuse papulovesicular lesions (predominance of vesicles)</td>
<td>Itching</td>
<td>5</td>
<td>6</td>
<td>Trunk, limbs</td>
<td>Cough, hyposmia, hypogeusia</td>
<td>No</td>
<td>Resolution</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>90</td>
<td>Cremona</td>
<td>March 12, 2020</td>
<td>March 20, 2020</td>
<td>Scattered papulovesicular lesions (predominance of vesicles)</td>
<td>No itching</td>
<td>1</td>
<td>6</td>
<td>Trunk</td>
<td>Fever, cough, dyspnea, coryza, headache, weakness</td>
<td>No</td>
<td>Active disease</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>69</td>
<td>Brescia</td>
<td>March 12, 2020</td>
<td>March 20, 2020</td>
<td>Scattered papulovesicular lesions (predominance of vesicles)</td>
<td>No itching</td>
<td>Unknown</td>
<td>NA</td>
<td>Trunk</td>
<td>Fever, cough, dyspnea, coryza, hyposmia, hypogeusia, headache, weakness</td>
<td>No</td>
<td>Active disease</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>65</td>
<td>Naples</td>
<td>March 13, 2020</td>
<td>March 20, 2020</td>
<td>Diffuse papulovesicular lesions (predominance of papules)</td>
<td>Mild itching</td>
<td>-2</td>
<td>9</td>
<td>Trunk</td>
<td>Fever, cough</td>
<td>No</td>
<td>Improvement</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>80</td>
<td>Brescia</td>
<td>March 14, 2020</td>
<td>March 22, 2020</td>
<td>Scattered papulovesicular lesions (predominance of vesicles)</td>
<td>No itching</td>
<td>Unknown</td>
<td>NA</td>
<td>Trunk, limbs</td>
<td>Fever, dyspnea</td>
<td>//</td>
<td>Death</td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>43</td>
<td>Milan</td>
<td>March 15, 2020</td>
<td>March 23, 2020</td>
<td>Scattered papulovesicular lesions (predominance of vesicles)</td>
<td>Mild itching</td>
<td>0</td>
<td>11</td>
<td>Trunk</td>
<td>Fever, myalgia</td>
<td>No</td>
<td>Active disease</td>
</tr>
</tbody>
</table>
*patient with acute respiratory distress symptoms (ARDS) in intensive care unit

NA, not available

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. In another patient (D) mainly presenting with vesicles, exanthem resolution with crusts is evident; E, Basket-wave hyperkeratosis, slightly atrophic epidermis, vacuolar degeneration of the basal layer with multinucleate, hyperchromatic keratinocytes and dyskeratotic cells. Note the absence of inflammatory infiltrate. Hematoxylin and eosin stain original magnification: x4; F, Close-up with atrophic epidermis, vacuolar alteration with disorganized keratinocytes lacking orderly maturation, enlarged and multinucleate keratinocytes with dyskeratotic (apoptotic) cells. Hematoxylin and eosin stain, original magnification: x20