



Cutaneous Manifestations Associated with Post COVID-19 Infection: Report of Two Cases

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Abstract

Although COVID-19-associated cutaneous manifestations have been increasingly reported, their exact incidence has yet to be estimated, their pathophysiological mechanisms are largely unknown, and the SARS-CoV-2 role in their pathogenesis is still debated. We describe the clinical and histopathological features of 2 Italian patients with different cutaneous presentations after COVID-19 infection, observed and followed at the P.O. Sandro Pertini ASL Roma2. Both patients had COVID-19 positive serological tests, negative RT-PCR test for COVID-19 virus, negative for other viral and bacterial agents tests suggesting that COVID-19 infection can give rise to cutaneous manifestations through mechanisms that are not known yet, even after the elimination of the virus by the organism. Skin lesions decreased and disappeared after systemic corticosteroid therapy suggesting an immune-mediated inflammatory reaction.

Keywords: COVID-19; Cutaneous manifestations; Skin

Introduction

Various cutaneous manifestations have been observed in patients with COVID-19 infection and in patients after COVID-19 infection. We describe the clinical and histopathological features of 2 Italian patients with different cutaneous presentations after COVID-19 infection, observed and followed at the P.O. Sandro Pertini ASL Roma2.

Case Presentation

Case 1

A 40-year-old man was admitted to the Medical Vascular and Autoimmunity Unit in January 2021. The patient had contracted COVID-19 infection in mid-December 2020 (positive RT-PCR test) with a paucisymptomatic course, and in mid-January 2021 had a second RT-PCR test for COVID-19 virus which was negative. After 13 days since the latter RT-PCR test, the patient developed erythematous crusted violaceous papules focally ulcerated, involving the inferior limbs bilaterally (Figure 1a-1d). Some cutaneous manifestations were confluent, the largest having a diameter of 2 cm on the right leg.

Laboratory tests revealed a normal white blood cells and platelet count (WBC $7.93 \times 10^3/\mu\text{L}$, PLT $250 \times 10^3/\mu\text{L}$), normal liver and kidney function and mild increase in fibrinogen (419 mg/dl), PCR (1.5 mg/dl), Total Bilirubin (1.5 mg/dl), erythrocyte sedimentation rate ESR (32 mm/h), homocysteine (27.4 $\mu\text{mol/L}$) D-Dimer Test (5,308 ng/ml). COVID-19 serological test was positive. Additional laboratory tests were performed as shown in Table 1. Thoracic and abdominal X-ray was negative for thromboembolic disease.

Case 2

A 22-year-old man was admitted to the Vascular Medicine Department in January, 2021. The patient probably had contracted COVID-19 in December 2020 (COVID-19 test were not performed); in January COVID-19 serological test was positive and COVID-19 antigenic tests were negative. This patient developed a diffuse rash in the inferior limbs (Figure 2a-2c), often with coalescent papules. The patient reported that even in December 2020 he showed a petechial rash that went into remission after topical corticosteroid therapy.

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Table 1: Other laboratory tests.

Laboratory analysis	Case 1	Case 2
Lupus anticoagulant Ratio 0.00-120	Negative 1.08	Negative 1.07
Anti-cardiolipin IgG CU<=20.0	Negative 5.1	Negative 3.3
Anti-cardiolipin IgM CU<=20.0	Negative 1.2	Negative 2.4
Anti-beta 2 gp IgG U/ml <=20.0	Negative 5	Positive 34
Anti-beta 2 gp IgM U/ml <=20.0	Negative 0	Negative 0
Complement C3 88 mg/dl-165 mg/dl	Negative 151	Negative 153
Complement C4 10 mg/dl-40 mg/dl	Negative 33	Negative 26
ANA Negative 1:80	Negative 0.097222222222222	Negative 0.097222222222222
ENA CU< 20.0	Negative 4.8	Negative 1.9
Anti-neutrophil antibodies Negative 1:20	Negative 1:20	Negative 1:20
Cytomegalovirus IgG >14 U/ml Positive	Positive 115	Positive 77.5
Cytomegalovirus IgM <18 U/ml Negative	Negative <5,00	Negative <5,00
Herpes type 1 IgG	Positive	Positive
Herpes type 2 IgG	Negative	Negative
Herpes type 1/2 IgM	Negative	Negative
EBV Early Antigen <40 U/ml Negative	Negative <5	Negative <5
EBV IgM <40 U/ml Negative	Negative <10	Negative <10
VCA IgG <20 U/ml Negative	Positive >750	Positive >750
EBNA IgG <20 U/ml Negative	Positive >600	Positive 576
HBsAg	ND	Negative
HCV-Ab	ND	Negative
Urinalysis	Negative	Negative
Pharyngeal swab for streptococcus beta haemolyticus	Negative	Negative



Figure 2: Photographs of Case n°2. A) Biopsy lesion, B) Diffuse rash in the inferior limbs, C) Rash presents coalescent papules.

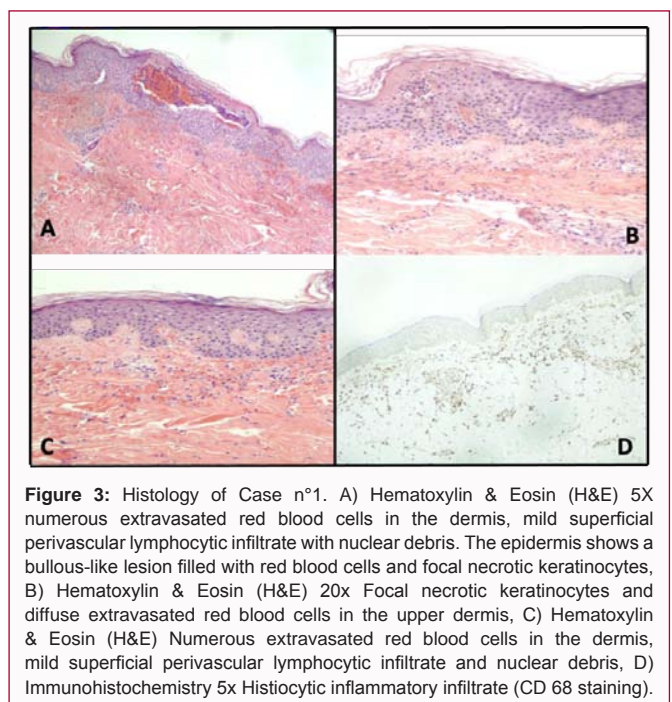


Figure 3: Histology of Case n°1. A) Hematoxylin & Eosin (H&E) 5X numerous extravasated red blood cells in the dermis, mild superficial perivascular lymphocytic infiltrate with nuclear debris. The epidermis shows a bullous-like lesion filled with red blood cells and focal necrotic keratinocytes, B) Hematoxylin & Eosin (H&E) 20x Focal necrotic keratinocytes and diffuse extravasated red blood cells in the upper dermis, C) Hematoxylin & Eosin (H&E) Numerous extravasated red blood cells in the dermis, mild superficial perivascular lymphocytic infiltrate and nuclear debris, D) Immunohistochemistry 5x Histiocytic inflammatory infiltrate (CD 68 staining).



Figure 1: Photographs of Case n°1. A) Biopsy lesion, B) Confluent skin manifestation with a diameter of 2 cm, C) Erythematous crusted violaceous papules focally ulcerated, D) Cutaneous manifestations on the limbs.

Laboratory tests revealed a normal white blood cells and platelet count (WBC $6.82 \times 10^3/\mu\text{L}$, PLT $306 \times 10^3/\mu\text{L}$), normal liver and kidney function and mild increase PCR (0.8 mg/dl), erythrocytation rate ESR (30 mm/h), homocysteine (17.1 $\mu\text{mol/L}$), D-Dimer Test (1.74 mg/L). COVID-19 serological test was positive. Additional laboratory tests were performed as shown in Table 1.

Histopathological Examinations

Both patients underwent skin biopsy. Case 1 showed mild acanthosis of epidermis, small foci of necrotic keratinocytes with cell debris and focally massive intraepidermal extravasation of red blood cells, with a bullous pattern. Numerous extravasated red blood cells were also present in the dermis, associated with mild superficial perivascular infiltrate (Figure 3a-3c) with numerous histiocytes CD68+ (Figure 3d), T lymphocytes CD3-positive and swollen blood vessels.

In Case 2 histological modification were less significant than Case 1, with only a mild increase of extravasated red blood cells in the dermis with a mild lymphocytic infiltrate (Figure 4a, 4b).

Immunohistochemistry revealed that the inflammatory infiltrate consisted mostly of T lymphocytes CD3-positive (Figure 4c, 4d).

Discussion

A few months after the outbreak of the pandemic, many narrative

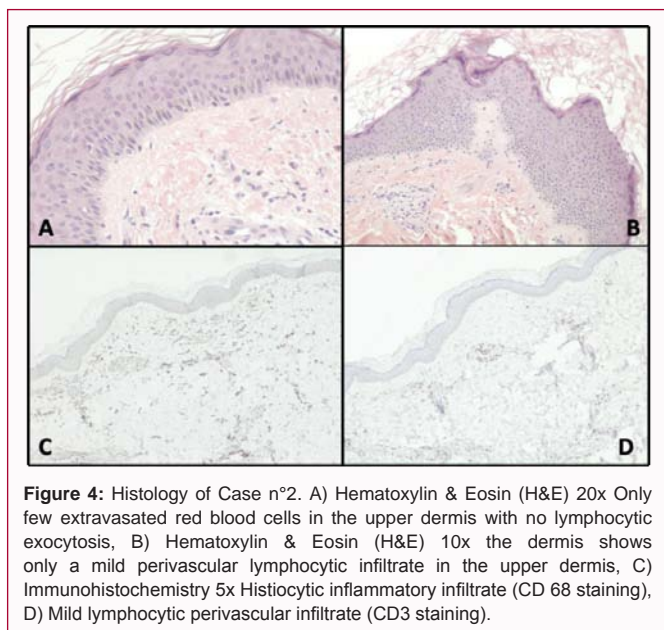


Figure 4: Histology of Case n°2. A) Hematoxylin & Eosin (H&E) 20x Only few extravasated red blood cells in the upper dermis with no lymphocytic exocytosis, B) Hematoxylin & Eosin (H&E) 10x the dermis shows only a mild perivascular lymphocytic infiltrate in the upper dermis, C) Immunohistochemistry 5x Histiocytic inflammatory infiltrate (CD 68 staining), D) Mild lymphocytic perivascular infiltrate (CD3 staining).

and systematic reviews concerning the dermatological manifestations of COVID-19 have been published [1-6]. The clinical and histopathological differential diagnosis of an exanthematous eruption most commonly includes drug eruptions and viral infections. All of our patients were strongly positive to COVID-19 serological tests and negative for other viral and bacterial agent’s tests thus suggesting cutaneous manifestation COVID-19 infection associated. Although COVID-19 is best known for causing fever and respiratory symptoms, it has been reported to be associated also with many extrapulmonary manifestations, including dermatological ones [7]. Whilst the COVID-19-associated cutaneous manifestations have been increasingly reported, their exact incidence has yet to be estimated, their pathophysiological mechanisms are largely unknown, and the SARS-Cov-2 role in their pathogenesis is still debated. Furthermore, evidence is accumulating that skin manifestations associated with COVID-19 infections are extremely polymorphic [8,9]. In this small study we described two cases with late cutaneous lesions COVID-19 associated. Both patients had COVID-19 positive serological tests and the patient in Case 2 had previous skin manifestations.

Cutaneous manifestations of Case 1 were less pronounced and fewer in number than Case 2; however the histological findings in Case 2 were less evident than in Case 1. Both cases presented perivascular lymphocytic infiltrate and extravasated red blood cells. Laboratory tests also showed the presence of an inflammatory picture in both patients, mild increase in PCR, ESR, homocysteine, and D-Dimer Test.

Skin lesions increased in number day by day since the first onset and, after systemic corticosteroid therapy only, they decreased

both in number and severity (Bolos for Three consecutive days, methylprednisolone 40 mg for three day) suggesting an immune-mediated inflammatory reaction affecting the skin. Our hypothesis is that COVID-19 infection can give rise to cutaneous manifestations through mechanisms that are not known yet, even after the elimination of the virus by the organism.

Conclusion

Many cutaneous findings after COVID-19 infections have been increasingly recognized, just as in the case with other viral infections. These two clinical cases describe the skin lesions arising after COVID-19 infection, which also seem to have a worsening trend as these improved following steroid treatment only, suggesting an immune-mediated inflammatory reaction affecting the skin. Furthermore, in order to understand the pathophysiology of the skin damage, in all cases a histological report has to be performed. This is a complex interdisciplinary work in progress, which needs great efforts from both patients and investigators.

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