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LETTER

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# Successful treatment of a bullous vasculitis with intravenous immunoglobulins in a COVID-19 patient

Dear Editor,

Vasculitides have a large spectrum of phenotypic presentation, causes, and severity, ranging from self-limited, organ-specific disorders to life-threatening systemic involvement. Their causes are numerous, and also many viral infections have been advocated. Accordingly, few cases have been recently associated with COVID-19 infection,[1,2] suggesting the pathogenic role of immune complexes intravascular deposition and cytokine release.[3]

Herein, we report the excellent response to intravenous immunoglobulins (IVIG) treatment of a cutaneous vasculitis diagnosed in a COVID-19 patient.

A 64-year-old Caucasian man was referred for the sudden appearance of cutaneous purpuric macules, papules, and bullae involving his lower extremities with initial aspects of central ulceration and necrosis (Figure 1A), without systemic symptoms. The patient's medical history included ischemic heart disease, congestive heart failure and hyperuricemia, chronically treated with diuretics, acetylsalicylic acid, anti-hypertensives, and allopurinol. Even if an iatrogenic origin of the vasculitis was firstly suspected, due to the onset of slight dyspnea, fever, and blood test abnormalities (lymphocytopenia, neutrophilia), the patient was tested positive for SARS-CoV-2. Chest computed tomography (CT) revealed the presence of bilateral, central and peripheral ground glass opacities; because of the appearance of dyspnea, he required oxygen therapy via nasal cannula. He did not complain of any other COVID-19 symptoms.

The patient's skin condition rapidly deteriorated, with the extension of the lesions beyond the lower limbs (Figure 1B) and despite the prompt treatment with prednisone 1 mg/kg/d, and the suspension of the potentially involved drugs, lesions progressed with the development of multiple necrotic areas in few days. Given the laboratory tests negativity (Table 1) and the absence of response to the steroid therapy, the diagnosis was directed toward viral vasculitis. Based on this suspicion, steroid therapy was rapidly tapered, and treatment with high-dose IVIG (2 g/kg, that is, 400 mg/kg/daily for five consecutive days) was started, together with low-molecular weight heparin, with a rapid improvement of the lung symptoms, and a slight benefit to the cutaneous lesions in 7 days. One month later, the ulcerative and escharotic lesions were completely demarcated with initial re-epithelization (Figure 1C). Unfortunately, the patient died a few weeks later due to a further hearth failure episode.

The novel COVID-19 infection may affect various organs, thus leading to multiple and heterogeneous clinical features. Also, cutaneous manifestations have been described with erythematous rash, widespread urticaria, acroischemia, and, more rarely, vasculitis.[2] Accordingly, a small case series of COVID-19 patients presenting acroischemic lesions associated with the presence of antiphospholipid antibodies has been recently reported.[3] Following the recent attempts

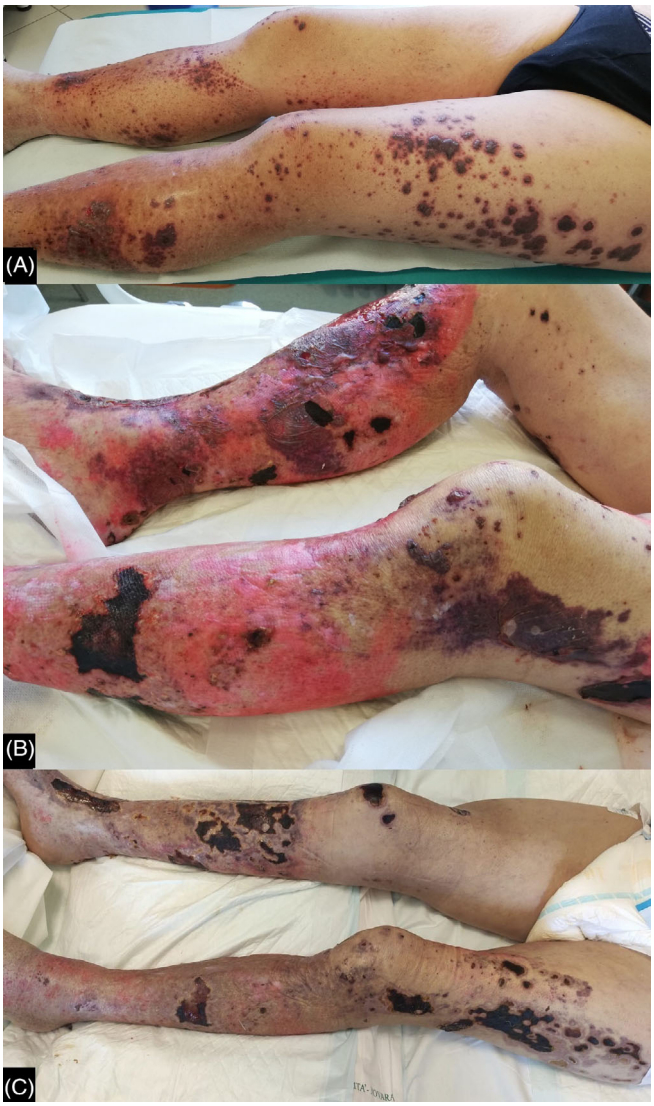


**FIGURE 1** (A) Purpuric macules and papules involving lower extremities, with bullae and initial aspects of central ulceration and necrosis; (B) Extension of the lesions beyond the lower limbs, with diffuse necrotic aspects; (C) Clinical feature 1 month after the disease onset

**TABLE 1** Schematic representation of the laboratory tests performed in the patient

| Laboratory tests | Result | Normal value |
|---|---|---|
| WBCs | 13.05 $10^3$/mm$^3$ | 4.5-11 $10^3$/mm$^3$ |
| Neutrophilis | **94.3%** | 36.9-73.9% |
| Lymphocytes | **2.1%** | 16.8-47.9% |
| Monocytes | 3.4% | 5.3-13% |
| Eosinophils | 0% | 0-8.7% |
| Basophils | 0.2% | 0.2-1.7% |
| RBCs | 4.07 $10^6$/mm$^3$ | 4.5-5.9 $10^6$/mm$^3$ |
| Hb | **12.0 g/dL** | 13.5-17.5 g/dL |
| Hematocrit | 36.7% | 39.8-52.2% |
| PLTs | 239 $10^3$/mm$^3$ | 150-450 $10^3$/mm$^3$ |
| Erythrocyte sedimentation rate (ESR) | 12 mm/h | 10-20 mm/h |
| Serum creatinin | 1.18 mg/dL | 0.9-1.3 mg/dL |
| Serum glucose | 85 mg/dL | 70-100 mg/dL |
| AST | 33 U/L | 10-40 U/L |
| ALT | 35 U/L | 10–40 U/L |
| $Na_+$ | 133 mEq/L | 134-146 mEq/L |
| $K_+$ | 4.2 mEq/L | 3.5-5.5 mEq/L |
| $Ca_{++}$ | 8.7 mg/dL | 8.6-10.0 mg/dL |
| International normalized ratio (PT-INR) | 1.06 | 0.8-1.2 |
| Partial thromboplastin time (PTT) | 30.9 s | 26.0-38.0 s |
| Anti-double stranded DNA | 4.8 UI/mL | 0.0-27.0 UI/mL |
| Antineutrophil cytoplasmic antibodies | Neg | Neg |
| Anti-Beta2-glicoprotein antibodies | IgG 1.1 CU - IgM 0.7 CU | < 20 CU - <20 CU |
| Circulant immune complexes | 1.6 μg/mL | <16 μg/mL |
| Hepatitis B surface antigen | Neg | Neg |
| Hepatitis C antibody | Neg | Neg |
| C reactive protein | **1.25 mg/dL** | 0–1 mg/dL |
| Sideraemia, | **54 μg/dL** | 65-175 μg/dL |
| Lactate dehydrogenase | **543 mU/mL** | 208-450 mU/mL |
| Rheumatoid factor | **63 UI/mL** | <15 UI/mL |

*Note:* The abnormal results are reported in bold; normal values are also reported in the right column.

of classification of cutaneous lesions SARS-CoV-2-related, the present case reports of "livedoid/necrotic lesions" that should be enclosed in the purpuric "vasculitic" pattern.[4,5]

IVIG are currently used in autoimmune diseases resistant to other treatment, thus including vasculitis. Moreover, on the basis of their previous favorable experiences from patients with SARS and MERS,[6,7] IVIG has also been suggested against COVID-19. The rationale for their use is due, given the presence of autoreactive antibodies, to the ability to reduce the inflammatory status, thus promoting the early recovery. Moreover, IVIG therapy has been recently reported to be of help to mitigate the SARS-CoV-2 infection symptoms in a patient complaining of mucosal pemphigoid.[8] Accordingly, IVIG represent the pivotal treatment in Kawasaki disease, whose increased frequency has been recently correlated to COVID-19 infection.

In our case, we cannot affirm that the cutaneous lesions were virus-related, but, on the basis of the existing literature, we could speculate it. Hence, the association between Coronavirus and cutaneous vasculitis has been previously reported, either in human or in veterinary field.[9,10] Accordingly, the detection of autoantibodies against human epithelial and endothelial cell lines has been previously demonstrated in patients affected by SARS-associated Coronavirus infection.[11] Regarding COVID-19, the presence of endothelial damage and endotheliitis virus-related has been recently demonstrated in patients, and this represents a further support to the previously suggested role of the SARS-CoV-2 promoting hypercoagulopathy.[12,13] However, it can be speculated that the same mechanism could be involved in our patient, thus provoking a COVID-19-mediated vasculitis. Furthermore, the concomitant appearance of cutaneous lesions in the course of COVID-19 represents another clue toward such conclusion. Moreover, the plethora of papers reporting vascular damages provoked by SARS-CoV-2, seems to support such hypothesis.

Based on our knowledge, this is the first paper reporting an excellent clinical response to IVIG treatment in a case of necrotizing cutaneous vasculitis during COVID-19.

## CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

## AUTHOR CONTRIBUTIONS

Conceptualization: E.Z., E.C., V.T., P.S.; Data collection: E.Z., E.C., V.T., D.S.; Writing of the manuscript: E.Z., E.C., V.T., P.S.; Manuscript editing and revision: E.Z., E.C., V.T., L.C.G., P.S.

## DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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## REFERENCES

1. Negrini S, Guadagno A, Greco M, Parodi A, Burlando M. An unusual case of bullous hemorrhagic vasculitis in a COVID-19 patient. *J Eur Acad Dermatol Venereol*. 2020;34(11):e675-e676. https://doi.org/10.1111/jdv.16760.
2. Wollina U, Karadağ AS, Rowland-Payne C, Chiriac A, Lotti T. Cutaneous signs in COVID-19 patients: a review. *Dermatol Ther*. 2020;33:e13549. https://doi.org/10.1111/dth.13549.
3. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid19. *N Engl J Med*. 2020;382(17):e38.
4. Galván Casas C, Català A, Carretero Hernández G, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375cases. *Br J Dermatol*. 2020;183(1):71-77.
5. Genovese G, Moltrasio C, Berti E, Marzano AV. Skin manifestations associated with COVID-19: current knowledge and future perspectives. *Dermatology*. 2020;237:1-12. https://doi.org/10.1159/000512932.
6. Wang IT, Sheng WH, Fang CT, et al. Clinical manifestations, laboratory findings, and treatment outcomes of SARS patients. *Emerg Infect Dis*. 2004;10:818-824.
7. Arabi YM, Arifi AA, Balkhy HH, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Ann Intern Med*. 2014;160:389-397.
8. Daneshpazhooh M, Soori T, Isazade A, Noormohammadpour P. Mucous membrane pemphigoid and COVID-19 treated with high-dose intravenous immunoglobulins: a case-report. *J Dermatol Treat*. 2020;31(5):446-447.
9. Chesser H, Chambliss JM, Zwemer E. Acute hemorrhagic edema of infancy after coronavirus infection with recurrent rash. *Case Rep Pediatr*. 2017;2017:5637503.
10. Cannon MJ, Silkstone MA, Kipar AM. Cutaneous lesions associated with coronavirus-induced vasculitis in a cat with feline infectious peritonitis and concurrent feline immunodeficiency virus infection. *J Feline Med Surg*. 2005;7(4):233-236.
11. Yang YH, Huang YH, Chuang YH, et al. Autoantibodies against human epithelial cells and endothelial cells after severe acute respiratory syndrome (SARS)-associated coronavirus infection. *J Med Virol*. 2005;77(1):1-7.
12. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395:1417-1418.
13. Sathishkumar V, Kamaraj S. SARS-CoV-2 and coagulation disorderd in different organs. *Life Sci*. 2020;260:118431.