Vasculitis Associated with COVID-19 Reinfection in a Fully Vaccinated 66-Year-Old Filipino Male: A Case Report

Bernadette Bergonio Iglesia, MD, MBA[1]
Jacqueline D. Melendres, MD, FPDS[2]

Abstract

COVID-19-associated vasculitis is a term used to describe a genuine vasculitis associated with SARS-CoV-2 infection when all other possible causes of vasculitis have been ruled-out. We report a case of a 66-year-old-male, reinfected by COVID-19 after 5 months, who presented with a 2-week history of multiple petechiae on bilateral anterior legs that gradually evolved into targetoid purpura with central blisters, spreading to the proximal medial thighs and the trunk, associated with pruritus and a warm sensation over the affected areas. The patient also presented with marked periorbital swelling, abdominal and joint pains, and decreased kidney function. Histopathology of the skin biopsy showed leukocytoclastic vasculitis while direct immunofluorescence study came out positive result for fibrinogen but negative for IgA, IgG, IgM and C3. Skin lesions resolved and kidney function improved prior to discharge after treatment with IV antibiotics (azithromycin 500 mg and ceftazidime 1 g) and IV steroids (hydrocortisone 50 mg). Recurrence of the vasculitic skin lesions occurred 2 weeks after being tagged as COVID-recovered but improved after 14 days of treatment with oral prednisone. We highlight the importance of recognizing cutaneous vasculitis as a possible marker of a severe COVID-19 disease which could be in the form of single-organ damage particularly acute kidney injury.

Keywords: *COVID-19-associated vasculitis, SARS-COV-2-associated vasculitis, case report*

INTRODUCTION

Since the start of the COVID-19 pandemic, 232,703,120 cases have been documented globally, including 4,746,620 deaths, as reported by the World Health Organization (As of September 28, 2021)[1]. In the Philippines, cases continue to rise, now totaling to 2,490,858 cases, with over 37,000 deaths [1]. This situation has brought a lot of challenges to the healthcare system of the country as well as to its economy, as the medical, scientific and lay communities continue to battle the disease.[2] Several literatures were already published documenting the vast clinical manifestations of COVID. Commonly, it involves the respiratory system ranging from mild symptoms such as fever and cough, to severe manifestations such as dyspnea secondary to severe COVID pneumonia, some leading to acute respiratory distress, and ultimately, death [3]. Aside from the respiratory system, it has been proven that the virus can affect any organ, including the skin, with cutaneous manifestations frequently being underreported [2].

There are varying theories regarding the dermatologic findings in COVID-19. Most of the published literature describes a myriad of cutaneous manifestations ranging from morbilliform lesions to vasculitis-like skin eruptions [4]. Depending on the skin manifestation, literatures were able to relate it with disease severity [4] and presented theories about their pathophysiology. Some case reports even noted the timing of onset of the dermatologic findings [5], which could be useful in predicting the prognosis of the COVID-19 infection, identify complications that require treatment or may even aid in identifying asymptomatic carriers [6]. One of the most important

[1]*Resident, Department of Dermatology, Rizal Medical Center*
[2]*Consultant, Department of Dermatology, Rizal Medical Center*

skin manifestation that has been linked to poor prognosis and mortality is the presence of cutaneous vasculitis [6]. Some of the skin lesions with features of vasculitis that have been described in the literature range from asymptomatic to fulminant disease, which include rounded, well circumscribed erythematous to violaceous plaques or nodules, necrotic purpura, diffuse digital erythema, and chilblain- like lesions [7]. To date, COVID-19-associated vasculitis is a possible complication that needs further research, especially now that the COVID-19 pandemic is yet to end. As knowledge about the virus continues to grow, it is also of great importance that all doctors, not just dermatologists, be able to identify the disease when faced with patients presenting with cutaneous manifestations such as vasculitis, in the absence of other possible causes.

As such, we report a case of vasculitis associated with COVID-19 reinfection in a fully vaccinated adult male and to our knowledge, this is the first case to be reported in the Philippines.

CASE REPORT

A 66-year-old, Filipino male, previously admitted due to severe COVID five months prior, presented with a 2-week history of multiple petechiae on bilateral anterior legs that gradually evolved into targetoid purpura with central blisters, spreading to the proximal medial thighs, associated with pruritus and a warm sensation over the lesions. In the interim, he complained of intermittent, undocumented fever, abdominal pain, and joint pains. One day prior to admission, he developed periorbital edema which prompted consult at the emergency room. Other pertinent medical history includes uncontrolled hypertension and diabetes, a 46-pack-year history of smoking and completion of 2 doses of COVID-19 vaccine (Sputnik).

At the time of admission, the patient's vital signs were stable and cutaneous examination revealed multiple, well defined, targetoid purpuric lesions some with central hemorrhagic bulla on the extremities, trunk, and pelvic area, predominantly on the anterior legs and the proximal medial thighs, with noted bilateral periorbital swelling (Figures 1, 2,3). Dermoscopic findings showed irregularly shaped, red to violaceous patches with clusters of petechial hemorrhages or ill-defined globular structures with blurred borders (Figure 4). A SARS-COV-2 RT-PCR test via oropharyngeal and nasopharyngeal swab came out positive for COVID-19 infection. Laboratories showed elevated BUN and creatinine, with an eGFR of 26 mL/min/1.73m2 as well as elevated CRP(155.7mg/L) and D-dimers (8,262). Chest radiograph showed suspicious bilateral opacities consistent with COVID-19 pneumonia.

A 4 mm skin punch biopsy on 2 sites was done at the ER for H & E stain and direct immunofluorescence studies. Histopathology showed superficial and deep infiltrates composed of neutrophils and eosinophils, with fibrinoid degeneration of blood vessels, extravasated erythrocytes and swollen blood vessels consistent with a histopathological diagnosis of leukocytoclastic vasculitis (Fig.5). Direct immunofluorescence study came out positive for fibrinogen but negative for IgA, IgG, IgM and C3 . Serum IgA done at day 6 of admission showed normal values (3.550 g/L). Upon admission, the patient was immediately started with intravenous antibiotics (ceftazidime 1 g, azithromycin 500 mg), intravenous steroids (Hydrocortisone 50 mg IV) and cetirizine. Lesions on the trunk were noted to progress to erythematous, annular and edematous plaques and targetoid lesions on the lower extremities were noted to develop multiple vesicles and blisters at the periphery (Fig.6).

During the course of the admission, creatinine was persistently elevated leading to the diagnosis of an acute kidney injury. On the 8th day of admission, creatinine levels started to decrease and skin lesions also started to resolve (Figure 7). Upon completion of his antibiotics and with decreasing trend of creatinine levels, the patient was then cleared for discharge, with strict home quarantine for 2 weeks.

The patient was monitored closely via teledermatology and 2 weeks after discharge, the patient again presented with multiple petechiae on the lower extremities that gradually enlarged into purpura,

but with no noted bullae or blister formation, associated with periorbital swelling. Patient also complained of pruritus and minimal abdominal pain (Figure 8). Repeat laboratories were requested which showed normal results for kidney function tests (BUN, Creatinine) but RBC was noted on urinalysis. Patient was given Prednisone (0.5mg/kg/day) and Cetirizine 10 mg/tab for 14 days, with noted improvement of the lesions (Figure 9 and 10).

DISCUSSION

The SARS-CoV-2 infection, or more commonly known as COVID-19, has been known to affect several organ systems in the body, causing mild to severe manifestations, depending on the host immunity [7]. In a report done by Gottlieb & Long in 2020 about common dermatologic manifestations and complications of COVID-19, they stated that the dermatologic manifestations in the setting of COVID-19 infection could be due to the presence of angiotensin-converting enzyme 2 (ACE2) receptors that can also be found in the skin [6].

COVID-19-associated vasculitis is defined as a genuine vasculitis associated with COVID-19 infection, including cutaneous vasculitis, when all other possible causes of vasculitis have been ruled-out [2]. Features of vasculitis range from asymptomatic to fulminant disease[9], which include rounded, well-circumscribed erythematous to violaceous plaques or nodules, diffuse digital erythema, chilblain-like lesions [10,11], retiform purpura, livedo racemosa, erythema-multiforme like eruption, true acral ischemia [4] and urticarial vasculitis[12]. What is note-worthy about this case is that the patient presented with a mixture of different forms of vasculitis such as retiform purpura, livedo racemosa, erythema-multiforme like eruptions and urticarial vasculitis.

A report by Nasiri, et.al. in 2020 described a case presenting with prominent periorbital edema with annular purpuric rash and urticarial lesions, with associated warm sensation on the lesions after recovering from COVID-19 infection [12]. The authors characterized it as urticarial vasculitis, defined as persistent urticarial lesions, resolving with purpura and hyperpigmentation, with evidence of a leukocytoclastic vasculitis. Clinically, the cutaneous manifestations of this type of vasculitis is the closest when compared to our case, although other forms of vasculitis-like skin eruptions were also found in the patient.

There is conflicting evidence regarding the time of onset of vasculitis-like lesions in COVID-19 infected patients. In one systematic review, they concluded that for vascular patterns, there are differences among its subtypes [5]. Livedoid lesions occurred mainly in the first 2 weeks while purpuric/petechial lesions were equally distributed during the first 4 weeks [5]. In contrast, a review about the rheumatologic complications of COVID reported that cutaneous vasculitis associated with severe respiratory failure and ARDS, manifesting as lower limb purpura, bullous hemorrhagic rash, necrotic lesions and cutaneous vasculitic lesions with gangrene, are late manifestations of COVID-19 infection [14]. However, there are also vascular patterns that do not fall under the subtypes which include erythema multiforme and Kawasaki-like disease [5].In the case of our patient, he was reinfected with COVID-19 after 5 months when the lesions occurred. This may be a rare case because the patient presented with a myriad of vasculitis-like skin eruptions, hence, we cannot entirely conclude that the lesions are complications of the first COVID-19 infection, an acute manifestation of the more recent infection, or both.

Guidelines are not yet available on the laboratory work-up to diagnose COVID-associated vasculitis, however, it is important to rule out other possible differential diagnoses. In a review done by Criado et. Al in 2020, they reported about the characteristics of severe COVID-19 which include an upregulated innate immune response, hypercoagulopathy state, pulmonary tissue damage, neurological and/or gastrointestinal tract involvement, and macrophage activation syndrome which could lead to fatal outcomes due to cytokine storm [13]. Dermatological manifestations can occur with these systemic conditions and abnormalities such as hyperferritinemia, increased levels of D-dimer, lactic dehydrogenase, reactive C-protein and serum A amyloid [13] may aid in the diagnosis.

For the treatment, one systematic review was able to tabulate treatment options per dermatologic manifestation. For purpuric "vasculitic' pattern, the authors suggested topical corticosteroids for mild cases and systemic corticosteroids for severe cases [15].

The importance of knowing the different cutaneous vascular manifestations of COVID-19 lies in its possible use a predictor of the severity of the disease. [4,7]. In a systematic review done by Conforti et.al in 2020, different patterns of vascular lesions were reported which include chilblain-like, non-necrotic purpura, necrotic purpura, retiform purpura, livedo reticularis, livedo racemosa, petechial rash, eruptive cherry angiomas, porcelain- like macules, and dry gangrene. Chilblain-like non-necrotic purpura are more common in the young, while vasculitis like, with necrotic, retiform purpura are more common in the elderly [4]. Majority of the lesions appeared after onset of COVID symptoms, occurring within 2-112 days [4]. In the review, they were able to conclude that chilblain-like lesions appeared in patients with relatively mild COVID-19 disease courses which suggest that the underlying mechanism might be protective, making pernio (chilblain) a marker of a robust, effective host anti-viral response, limiting COVID-19 complications. In contrast, older patients, may have an inadequate or delayed IFN-I response leading to an exacerbated hypercytokinemia which can manifest as purpura. These lesions were associated with subsequent increased morbidity and mortality [4]. However, not all purpura leads to a severe outcome. In the same journal, they mentioned that livedoid/necrotic lesions to older patients are associated with severe disease (10% mortality) whereas fixed livedo racemosa, retiform purpura, and true acral ischemia are related to critical or poor prognosis. Livedo racemosa and retiform purpura are hallmark manifestations of cutaneous thrombosis, appearing due to partial and complete occlusion of cutaneous blood vessels, respectively [4].

In the patient's case, although he presented with mild respiratory symptoms possibly due to the history of previous COVID-19 infection and completed doses of COVID-19 vaccine, the occurrence of decreased kidney function due to acute kidney injury may still be a manifestation of severe disease.

Lastly, one case report also presented a patient who developed a leucocytoclastic vasculitis for COVID-19 with positive SARS-CoV-2 PCR in skin biopsy. it is believed that SARS-CoV-2 antigens may promote the development of antibodies, forming antigen– antibody complexes that target the vascular endothelium of the skin and provoking the appearance of the leucocytoclastic vasculitis. This finding supports a relationship between leucocytoclastic vasculitis and coronavirus instead of relating it with other infections or medications.

This finding is important because it reiterated that further work-ups are needed to clarify if particles detected by PCR in skin tissue, specifically in endothelial cells of small dermal vessels, are viable virions or, more probably, just immune complex with non-viable viral particles. Further studies should also be done if ulcerated skin lesions could be infective.

CONCLUSION

The end of the COVID-19 pandemic remains to be out of sight as cases still continue to rise. Understanding the different pathologic mechanisms of the virus may help in the early diagnosis and treatment of COVID-19 infection. Vascular dysfunction could be one of the indicators of a severe illness and may manifest as cutaneous vasculitis. By recognizing these skin lesions, clinicians may be able to predict the course of the COVID-19 infection. As a recommendation, a PCR test on the skin biopsy sample could be done to show the presence of SARS-CoV-2 in the skin lesions in order to establish causation.

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APPENDICES

Figure 1. Targetoid purpuric lesions on anterior legs and proximal medial thighs

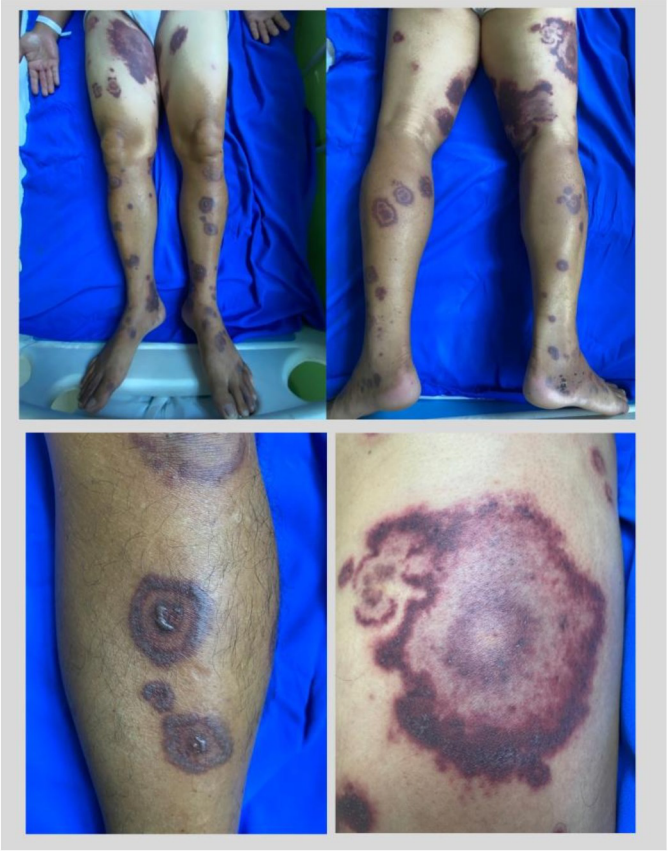

Figure 2. Periorbital swelling and multiple petechiae on the trunk

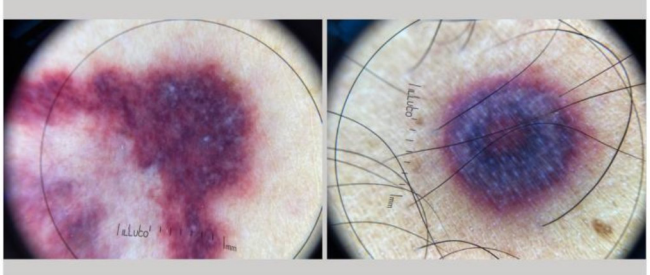

Figure 3. Dermoscopic findings of the lesions

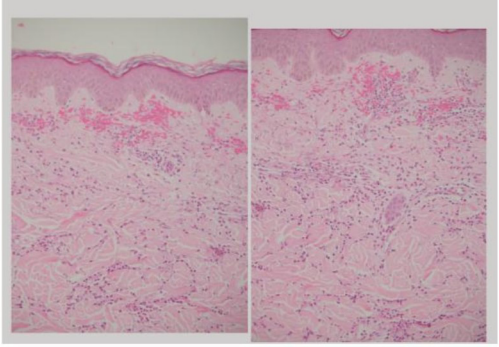

Figure 4. Histopathological findings of leukocytoclastic vasculitis

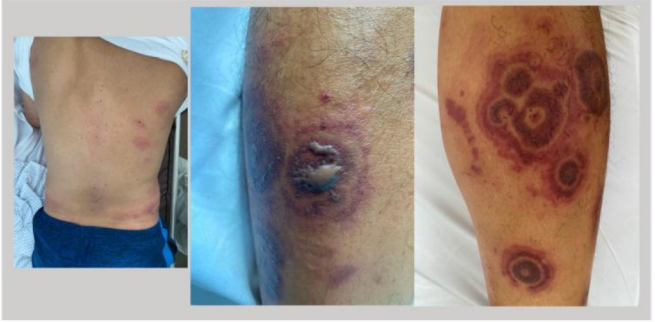

Figure 5. Evolution of the lesions on Day 2 Admission

Figure 6. Resolution of the lesions on Day 8 of admission