CASE REPORT

A case of late ulceration of infantile hemangioma in the setting of SARS-CoV2 infection

Chiamaka L. Okorie, BSc,[a] Iman Salem, MD, MS,[b] Matthew J. Davis, MD,[b] and Julianne A. Mann, MD[a,b]

Key words: hemangioma; late ulceration; mixed subtype infantile hemangioma; re-ulceration; SARS-CoV2; vascular anomalies.

INTRODUCTION

Infantile hemangiomas (IH) are the most frequent pediatric vascular tumors affecting 5% to 10% of children in their first few weeks.[1] Ulceration is the most frequent complication reported in IH, with an incidence rate ranging from 10% to 30%.[1,2] Often found during the height of the proliferative phase (fastest growth rate at week 5-8 weeks)[3] by 4 months of age.[2] Risk factors for ulceration include large size, segmental orientation, mixed morphology, and flexural locations. Propranolol, with its effect on vascular tone, angiogenesis, and apoptosis, has proven to be an excellent treatment option and has been the drug of choice since 2008.[1,4] Ulceration beyond 2 years of age, particularly when the hemangioma had been fully treated and was quiescent off of treatment, is very unusual.

Since its declaration as a global pandemic by the World Health Organization in March 2020, SARS-CoV-2 virus, also known as COVID-19, has significantly impacted most medical fields. For the dermatologist, cutaneous complications related to SARS-CoV-2 virus infection have steadily increased. Commonly described manifestations include urticaria, maculopapular exanthemas, vesicular eruption, and acral vasculopathic rash similar to chilblains lesions and referred to as "COVID toe."[5,6] Mucocutaneous ulcerations are rarely recorded in association with the infection and are mainly limited to genital or oral ulcers.[7]

Abbreviations used:

ACE:	angiotensin-converting enzyme
AngII:	angiotensinogen II
FGF:	fibroblast growth factor
IH:	infantile hemangiomas
RAS:	renin-angiotensin system
VEGF:	vascular endothelial growth factor

This case highlights the possibility of late ulceration of IH among children who become infected with SARS-CoV2. We aim through this report to shed light on possible mechanisms of SARS-CoV2 mediated skin ulcerations. We also emphasize the importance of recording SARS-CoV-2-related adverse events to better understand the immune mechanisms comprising these reactions.

CASE PRESENTATION

A 2-year-old otherwise healthy female with a history of mixed subtype IH on the right neck presented to the pediatric dermatology clinic with recent ulceration of her hemangioma. Her hemangioma had previously been treated with oral propranolol from 7 weeks of age to 16 months of age. The hemangioma had briefly ulcerated at 10 weeks of age, soon after propranolol was started. This ulcer healed within 3 weeks, and the hemangioma gradually involuted during just over a year of treatment. At 16 months of age, she was successfully tapered off

From the Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire[a]; and Department of Dermatology and Pediatrics, Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire.[b]

Funding sources: None.

IRB approval status: Not applicable.

Correspondence to: Julianne A. Mann, MD, Associate Professor, Dermatology and Pediatrics, Department of Dermatology, Dartmouth Hitchcock Medical Center, 1 Medical Center Dr, Lebanon, NH 03756. E-mail: Julianne.A.Mann@Hitchcock.org.

JAAD Case Reports 2023;31:109-11.

2352-5126

https://doi.org/10.1016/j.jdcr.2022.10.037

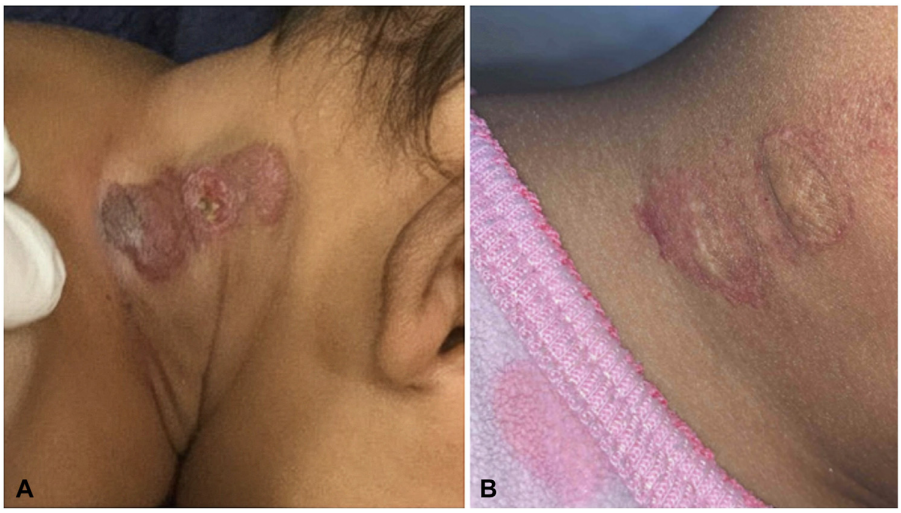

Fig 1. A, 10 weeks of age: initial ulceration of hamngioma (*left*). **B,** 16 months of age: Quiescent, involuted hemangioma following discontinuation of propranolol (*right*).

propranolol without any significant rebound growth (Fig 1). The hemangioma had been completely quiescent for over a year when the patient's mother reported that her entire hemangioma had become more red and indurated, and a portion of it was ulcerated. Three weeks prior to the clinic visit, the patient developed a runny nose, cough, malaise, and fever and tested positive for SARS-CoV2 with a rapid home test. Her respiratory symptoms resolved within 1 week, but she continued to test positive on repeat home antigen tests for almost 3 weeks.

Examination in clinic showed a 1 × 3 cm dull erythematous plaque with discrete, shallow ulceration at the inferior portion of the lesion (Fig 2). There was no history of trauma. Infection was felt to be extremely unlikely as there was no purulence, surrounding cellulitis, or odor. Topical timolol 0.5% gel was prescribed, and there was complete resolution of the ulcerations within 4 weeks. The child made an uneventful recovery from her SARS-CoV2 infection.

DISCUSSION

Despite being the most common infantile tumor, the precise mechanisms dictating IH proliferation and involution are still not fully understood. Evidence supports the role of hypoxia in the development and proliferation of these lesions.[2,3] Pathogenesis was thought to center on aberrant overexpression of fibroblast growth factor and vascular endothelial growth factor secondary to intrauterine hypoxia, as with preeclampsia or placental insufficiency.[2,3] More recent studies suggest a critical role of the renin-angiotensin system in IH development. Significant increases in serum levels of renin, angiotensin-converting enzyme (ACE), angiotensinogen II, and vascular endothelial growth factor were observed in patients with infantile hemangioma compared to unaffected controls.[2,3]

In our case, the first ulceration was noticed, as expected, around the peak growth period at 10 weeks of age. Ulceration is postulated to be due to the rapidly expanding hemangioma outpacing its blood supply and resulting in skin necrosis.[2] The appearance soon after SARS-CoV-2 infection of a second ulcer after over a year of quiescence and after 2 years of age is an unexpected observation that warranted further explanation. In this context, we submit both vascular and immune theories to explain the possible connection of reulceration to SARS-CoV-2.

SARS-CoV2 infection causing a variety of peripheral cutaneous vascular sequelae and purpuric ulcerations have been reported.[6] Onset of these lesions and their timeframe to resolution may vary from days to several weeks after infection.[8] ACE2, the functional receptor of SARS-CoV-2, is highly expressed on endothelial cells of the nasopharynx, oropharynx, and lungs along with arterial smooth muscle cells and microcirculation pericytes, granting it critical influence on vascular homeostasis. The binding of SARS-CoV-2 to ACE2 upregulates the levels of angiotensinogen II, which, in addition to being a strong vasoconstrictor, is also a potent pro-inflammatory molecule known to generate excess free radicals causing a cascade of oxidative stress, endothelial cell damage, and thrombosis which can interrupt blood supply and cause ulceration.[9]

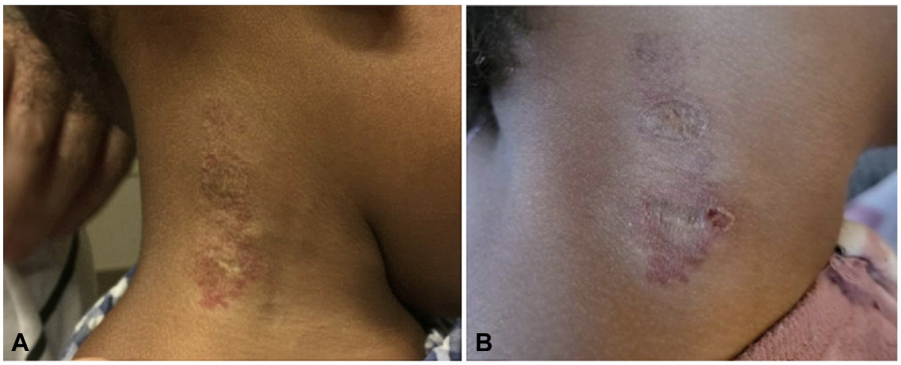

Fig 2. A, 21 months of age: Quiescent hemangioma (*left*). **B,** 30 months of age: ulceration at inferior anterior border of involuted hemangioma, 3 weeks after confirmation of SARS-CoV2 infection via home antigen tests (*right*).

While reports of SARS-CoV-2-related reulceration of infantile hemangioma are scarce, aphthous and genital ulceration have been previously described in association with viral infections.[7] This observation of viral infections and ulcerations could be explained by type III hypersensitivity reaction to circulating viral-antibody immune complex resulting in microthrombosis and vascular occlusion. Another alternative hypothesis could be virus-mediated cytolysis after viral hematological spread or autoinoculation in the skin.

As we continue learning about the various effects SARS-Cov-2 has on our systems and how our body reacts to the infection, it is essential to report unusual presentations, as in our case, so we might better understand the mechanisms of these interactions. Pediatric dermatologists should consider parental counseling and close clinical monitoring of patients with hemangiomas that are large, segmental, or in locations that are higher risk for ulceration (neck, anogenital area, and lower lip)[2] in the immediate aftermath of SARS-CoV-2 infection, given the possibility of reulceration.

Conflicts of interest

None disclosed.

REFERENCES

1. Leung AKC, Lam JM, Leong KF, Hon KL. Infantile hemangioma: an updated review. *Curr Pediatr Rev*. 2020;17(1):55-69. https://doi.org/10.2174/1573396316666200508100038
2. Rodríguez Bandera AI, Sebaratnam DF, Wargon O, Wong LCF. Infantile hemangioma. Part 1: epidemiology, pathogenesis, clinical presentation and assessment. *J Am Acad Dermatol*. 2021;85(6):1379-1392. https://doi.org/10.1016/J.JAAD.2021.08.019
3. Kowalska M, Dębek W, Matuszczak E. Infantile hemangiomas: an update on pathogenesis and treatment. *J Clin Med*. 2021;10(20):4631. https://doi.org/10.3390/JCM10204631
4. Cheng CE, Friedlander SF. Infantile hemangiomas, complications and treatments. *Semin Cutan Med Surg*. 2016;35(3):108-116. https://doi.org/10.12788/J.SDER.2016.050
5. Magro C, Mulvey J, Laurence J, et al. The differing pathophysiologies that underlie COVID-19-associated perniosis and thrombotic retiform purpura: a case series Conflicts of interest. *Br J Dermatol*. 2021;184:11-12. https://doi.org/10.1111/bjd.19415
6. Acharya Y, Alameer A, Calpin G, Alkhattab M, Sultan S. A comprehensive review of vascular complications in COVID-19. *J Thromb Thrombolysis*. 2022;53(3):586-593. https://doi.org/10.1007/s11239-021-02593-2
7. Krapf JM, Casey RK, Goldstein AT. Reactive non-sexually related acute genital ulcers associated with COVID-19. *BMJ Case Rep*. 2021;14(5):e242653. https://doi.org/10.1136/BCR-2021-242653
8. Brandão MGSA, Barros LM, de Aquino Mendonça J, de Oliveira AR, de Araújo TM, Veras VS. Clinical and histopathological findings of cutaneous manifestations of COVID-19 patients. *Dermatol Ther*. 2020;33(6):e13926. https://doi.org/10.1111/DTH.13926
9. Beacon TH, Delcuve GP, Davie JR. Epigenetic regulation of ACE2, the receptor of the SARS-CoV-2 virus 1. *Genome*. 2021;64(4):386-399. https://doi.org/10.1139/GEN-2020-0124