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A Case of Late Ulceration of Infantile Hemangioma in the Setting of SARS-CoV2 infection

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Title: A Case of Late Ulceration of Infantile Hemangioma in the Setting of SARS-CoV2 infection

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Introduction:

Infantile hemangiomas (IH) are the most frequent pediatric vascular tumor affecting 5-10% of children in their first few weeks.[1] Ulceration is the most frequent complication reported in IH, with an incidence rate ranging from 10%-30%.[1,2] Often found during the height of the proliferative phase (fastest growth rate at week five to eight weeks)[3] by four 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 an excellent treatment option and has been the drug of choice since 2008.[1,4] Ulceration beyond two 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]

This case highlights the possibility of late ulceration of infantile hemangiomas 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 infantile hemangioma (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 ten weeks of age, soon after propranolol was started. This ulcer healed within three weeks, and the hemangioma gradually involuted during just over a year of treatment. At 16 months of age, she was successfully tapered off propranolol without any significant rebound growth (Figure 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 one week, but she continued to test positive on repeat home antigen tests for almost three weeks.

Examination in clinic showed a 1x3 cm dull erythematous plaque with discrete, shallow ulceration at the inferior portion of the lesion (Figure 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 four 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 (FGF) and vascular endothelial growth factor (VEGF) secondary to intrauterine hypoxia, as with preeclampsia or placental insufficiency.[2,3] More recent studies suggest a critical role of the renin-angiotensin system (RAS) in IH development. Significant increases in serum levels of renin, angiotensin-converting enzyme (ACE), angiotensinogen II (AngII), and VEGF are 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 ten 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 two 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 re-ulceration 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 AngII, 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]

While reports of SARS-CoV-2-related re-ulceration 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, lower lip)[2] in the immediate aftermath of SARS-CoV-2 infection, given the possibility of re-ulceration.

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

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Figure Legends:

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

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

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