Reactive infectious mucocutaneous eruption following COVID-19 infection in vaccinated patients

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INTRODUCTION
There have been numerous reports of non-respiratory complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),1 including a polymorphic array of cutaneous eruptions.2 While COVID-19 has demonstrated potential for mucosal involvement, a rarely reported manifestation is mucositis.3 Reactive infectious mucocutaneous eruption (RIME) describes postinfectious mucocutaneous eruptions with prominent mucositis and sparse cutaneous lesions following respiratory infections. Formally described as Mycoplasma-induced rash and mucositis because of the high prevalence of mucocutaneous disease following Mycoplasma pneumoniae infection, RIME encompasses a plethora of other infectious respiratory agents which cause clinically indistinguishable mucositis.4 The pathophysiology of RIME is poorly understood with the prevailing theories relating to immune complex activation, complement activation, and molecular mimicry.5 Here we report on 3 young adults and 1 adolescent, who presented with perioral and oral mucositis in keeping with RIME following COVID-19 infection, despite all being vaccinated against COVID-19.

CASES
Case 1
A previously healthy 25-year-old female developed oral erosions and ulcers following a recent COVID-19 infection, confirmed by rapid antigen testing (RAT). She had received 3 doses of the Pfizer-BioNTech Comirnaty COVID-19 vaccine. Complete history revealed initial prodrome of fatigue, fever, and cough followed by onset of painful oral and perioral ulcers 7 days after positive RAT. She reported otalgia, epistaxis, nasal crusting, ophthalmalgia, and odynophagia. The patient did not have any allergies and there were no recent medication changes (Sertraline at baseline). Physical examination revealed sloughing of the buccal mucosa with thick hemorrhagic crusting to the upper and lower lips and nares, as well as several lingual erosions (Fig 1). Palpable mild cervical lymphadenopathy was noted. Her repeat COVID-19 polymerase chain reaction (PCR) was positive; however, throat cultures, plain radiography of the chest, hematologic parameters, and complete metabolic profile were unremarkable.

Abbreviations used:
- BID: twice daily
- COVID-19: coronavirus
- CRP: C-reactive protein
- HSV: herpes simplex virus
- IVIG: intravenous immunoglobin
- PCR: polymerase chain reaction
- PO: by mouth
- Q6h: every 6 hours
- RAT: rapid antigen testing
- RIME: reactive infectious mucocutaneous eruptions
- SARS-CoV-2 virus: severe acute respiratory syndrome coronavirus
The patient had received Valacyclovir by mouth 1000 mg twice a day for 7 days for possible herpes simplex virus (HSV) infection. Dermatology was consulted for persistent and progressive mucositis. A diagnosis of RIME secondary to COVID-19 infection was made based on the constellation of history and clinical findings. The patient was started on a trial of prednisone 50 mg by mouth daily.

Reassessment after 4 days revealed marginal improvement. Given the ongoing erosive plaques and debilitating pain, the patient was switched to oral cyclosporine 4.3 mg/kg twice a day. One week later, there was significant improvement of her ophthalmic, auricular, and nasal symptoms, and partial resolution of her mucositis. Despite resolving erosions and hemorrhagic crusts, there were several foci of remaining reepithelialization on the buccal mucosal and right oral commissure. Cyclosporine was continued for an additional 7 days. She subsequently demonstrated near complete resolution of her symptoms and mucosal lesions.

Case 2

A 34-year-old male with a history of PCR detected SARS-CoV-2 was evaluated for severe oral mucositis. He initially experienced respiratory symptoms and subsequently developed oral erosions and lip crusting 8 days post infection. Additionally, he reported urethral pain and 7 kg weight loss secondary to reduced oral intake from odynophagia. Past medical
history was unremarkable, including no known dermatologic conditions, no allergies, and no medications. The patient had received 3 Pfizer-BioNTech Comirnaty COVID-19 vaccines.

Physical examination revealed hemorrhagic crusting and sloughing of his lips, and ventral and dorsal lingual erosions (Fig 2). Bilateral, non-purulent conjunctivitis and erythematous eruptions to his urethral meatus were also noted. On assessment, he had an elevated c-reactive protein (CRP) of 173 mg/L, a negative throat culture and mononucleosis test, and was otherwise unremarkable for other inflammatory and hematologic markers, and complete metabolic profile. The overall clinical presentation was felt to be consistent with COVID-19 RIME. Initial management by his primary-care physician consisted of oral prednisone 50 mg daily and morphine for oral pain for 4 days without significant improvement. Given persistent mucositis, he was assessed by dermatology and switched to cyclosporine 3.9 mg/kg per day for 7 days. At the 1-week follow-up there was resolution of oral pain and lesions involving the lip and urethral meatus. The erosions of the tongue and buccal mucosa were persistent but improved. The dose of cyclosporine was increased to 4.9 mg/kg/d for an additional 7 days. The patient had complete resolution of his mucositis at 2-week follow-up.

Case 3

A 25-year-old otherwise healthy female presented to the emergency department for 24 hours of progressive swelling and development of a papular and pustular eruption involving the hands, feet, as well as self-reported painful vulvar lesions. She had rhinorrhea and a positive COVID-19 PCR test 7 days prior to the onset of cutaneous symptoms. She was triple-vaccinated for COVID-19 (Moderna Spikevax COVID-19 vaccine × 2 doses, 1 × Pfizer-BioNTech ComirnatyCOVID-19 vaccine). The patient was not taking any medications and had no allergies. Her medical history was notable for coxsackie virus infection during childhood which resolved without sequelae. She was seen by dermatology 8 days after the initial onset of her cutaneous eruption. Physical examination revealed multiple dull pink to violaceous erythematous macules and papules on the volar aspect of both hands and plantar feet bilaterally; a collarette of scale was appreciated within several lesions (Fig 3). Pustules were noted on the distal left phalange. There was marked edema and bright pink erythema, and significant tenderness of the right great toe, which was distinct from other morphology and appeared most consistent with concomitant cellulitis. There was edema, ulceration, and hemorrhagic papules as well as few pustules over the upper and lower lips, with numerous lingual erosions. No genital abnormalities were appreciated at the time of examination.

The major differential diagnosis included RIME following COVID-19 infection and erythema multiforme, with hand-foot-mouth disease and syphilis felt to be less likely. Further investigations revealed a mild neutrophilic leukocytosis but were otherwise unremarkable, including negative rheumatoid factor, CRP, and negative syphilis serology. A biopsy of the most representative lesion of the left hand was obtained for correlation with hematoxylin and eosin stain. Final pathology was nonspecific with mild acanthosis and mild dermal inflammatory infiltrate, felt to be most consistent with a resolving inflammatory dermatosis.

The patient was started empirically on cephalexin 500 mg by mouth every 6 hours for 10 days for suspected bacterial infection of the great toe. At the 1 week follow-up there was complete resolution of
the erythematous patches on her hands and feet, but continued to endorse hand and toe arthralgia and joint swelling. Her lip mucositis was improved with a few remaining white erosions on her tongue. The patient was started on a course of oral prednisone 30 mg per day for 4 days with gradual taper over the next 20 days for treatment of her persistent cutaneous and mucosal findings. The patient was referred to the rheumatology service for further workup of potential autoimmune disease given the persistent arthralgia and localized joint edema.

Case 4

A 12-year-old male developed mucositis 8 days after positive test for SARS-CoV-2 by RAT. His initial symptoms included generalized headache, rhinorrhea, wet cough, fatigue, and fever (38.5 °C). These symptoms resolved 5 days posttest but he acutely developed painful oral mucosal eruption with oral swelling, blisters along the inside of lips, gingival lining, and tongue with fever. Ten days post infection, the patient reported dysuria and an enlarging lesion at the urethral meatus.

The patient’s medical history included remote infantile eczema, recurrent croup, and ADHD managed with methylphenidate. He did not have any known allergies, pertinent medication or social history. His vaccinations were up to date including 2 doses of Pfizer-BioNTech Comirnaty COVID-19. Physical examination revealed hemorrhagic crusting of the lips with white sloughing of the tongue, buccal mucosa, and hard palate (Fig 4). There was a circumferential area of hemorrhagic crusting of the urethral meatus. Cervical lymphadenopathy was noted. Preliminary investigations revealed elevated CRP of 64.3 mg/L but were otherwise unremarkable.
| Patient ID | COVID-19 testing | COVID-19 associated symptoms | Onset of cutaneous symptoms | Distribution of mucositis | Other features | Treatments received | Resolution of mucositis |
|------------|------------------|-----------------------------|-----------------------------|--------------------------|---------------|---------------------|-------------------------|
| 25-year-old female | RAT confirmed Pfizer Vaccine × 3 | Fatigue, fever, cough, otalgia, epistaxis, and odynophagia | Day 7 post-RAT | Buccal mucosa, lips, tongue, and nares | Cervical LAD | Valacyclovir by mouth 1000 mg twice a day × 7d | Day* 22 |
| 34-year-old male | PCR confirmed Pfizer Vaccine × 3 | Shortness of breath, cough, and odynophagia | Day 8 post-PCR | Lips, tongue, and urethral meatus | Bilateral conjunctivitis | Prednisone by mouth 50 mg × 4d Cyclosporine by mouth 4.3 mg/kg twice a day × 14d | Day* 19 |
| 25-year-old female | PCR confirmed Moderna × 2 Pfizer × 1 | Rhinorrhea | Day 9 post-PCR | Lips and tongue | Hands and feet | Cephalexin by mouth 500 mg every 6 hours × 10d Prednisone by mouth 30 mg taper × 24d | Day* 15 |
| 12-year-old male | RAT confirmed Pfizer × 2 | Headache, rhinorrhea, cough, fatigue, and fever | Day 8 post-RAT | Buccal mucosa, lips, tongue, hard palate, and urethral meatus | Cervical LAD | Acyclovir by mouth 330 mg × 1d Prednisone by mouth 25 mg × 7d | Day* 8 |

*ID, Identification; LAD, lymphadenopathy; PCR, polymerase chain reaction; RAT, Rapid Antigen Test.*

*Refers to the number of days following initial onset of mucocutaneous eruption at which complete resolution was noted.*

Table I. Summary of clinical presentations of COVID-19 associated reactive infectious mucocutaneous eruption in 4 cases
Additional infectious workup was negative including negative urinalysis, HSV1/HSV2 PCR, varicella PCR and Mycoplasma pneumoniae PCR, and no clinically relevant growth on mouth and fungal cultures.

He received 2 doses of acyclovir 350 mg empirically while awaiting results of viral panel, as well as oral prednisone 25 mg per day for a total of 7 days. The oral and urethral lesions resolved after the third dose of prednisone. On day 11 post infection, physical exam showed improvement of the lip erosions without hemorrhagic crusting. The patient’s oral pain and dysuria resolved within the next few days.

DISCUSSION

We report on 3 cases of young adults and 1 adolescent who developed severe mucositis with varying mucocutaneous involvement approximately 1-week following COVID-19 infection, summarized in Table I. All patients in this series were healthy, young (between 12 and 35 years of age) and had received multiple doses of mRNA COVID-19 vaccine. The prevailing endemic COVID-19 variant was omicron at the time that these patients presented; however, none of the patients were tested for viral variants. All cases required systemic immunosuppression to achieve clinical resolution, either with prednisone (2 cases) or cyclosporine (2 cases). To the best of our knowledge, this is the first report to describe COVID-19 associated RIME amongst COVID-19 vaccinated patients. A large cohort British study found that the incidence of cutaneous COVID-19 manifestations were unchanged between vaccinated and unvaccinated individuals. As the vaccine does not prevent infection but blunts viral load, it is possible that immunological mechanisms mediating cutaneous reactions represent early or mild symptomology of infection.

COVID-19 infection has been associated with several oral manifestations including aphthous stomatitis, herpetiform lesions, and red and white plaques, which most frequently involve the tongue, labial mucosa, and palate. We identified 7 previous cases of RIME post-COVID-19 infection in the literature. Most patients were male (86%), and most cases involved pediatric patients (71%, aged 14-17). Our cases were also consistent with the reported literature in terms of onset of mucocutaneous findings of COVID-19, which is reported between 3 days and 2 weeks post infection with resolution of COVID-19 mucositis varying from 5 days to 3 months. In our patients, mucositis onset was approximately 1-week post infection and resolution was achieved within 1 to 4 weeks. Our cases present similarly to previous literature, whereby lip involvement appears to be a consistent manifestation, whereas, urogenital involvement and ocular findings are variable.

Among the previous reported cases, most blood work was benign with all patients presenting with normal complete blood counts; however, 80% of patients demonstrated mildly elevated CRP levels. Similarly, 2 of our patients had elevated CRP levels and 1 patient presented with mild neutrophilic leukocytosis.

There is no standardized management of RIME; treatment is typically supportive, and spontaneous complete resolution often occurs within 1 to 3 weeks post-eruption. Approximately 35% of patients have recalcitrant disease requiring systemic corticosteroids, additionally cyclosporine and intravenous immunoglobulin have been used with varying clinical benefit. However, all reports of COVID-19 RIME describe the use of systemic immunomodulators including systemic corticosteroids, cyclosporine, and/or intravenous immunoglobulin to ameliorate symptoms. Similarly, in this series, all patients had progressive or recalcitrant disease requiring systemic immunosuppression. Two of our adult patients failed to respond to high dose prednisone, but experienced resolution of mucositis following 14 days of cyclosporine. This treatment effect is corroborated by a previous case, whereby a steroid resistant patient with COVID-19 RIME improved following cyclosporine. Notably, none of our patients reported any adverse events or long-term COVID-19 complications following immunomodulatory therapy.

This case series adds to a growing body of literature of independent case reports of RIME secondary to COVID-19. There appears to be a trend towards young patients and possibly more resistant disease requiring intervention compared to other infectious RIME. It is possible COVID-19 RIME is an underreported mucocutaneous manifestation. Limitations include publication bias and weak quality of evidence inherent to independent case studies, thus restricting the ability to draw definite conclusions. Moreover, other infectious RIME etiologies cannot be excluded in 3 of the 4 cases as they were not investigated due to clinical suspicion given the temporal relation of mucocutaneous eruptions following COVID-19 infection. To the best of our knowledge, we are reporting on the youngest case of COVID-19 associated RIME (12 years old) and are the first to report on RIME amongst those fully vaccinated against COVID-19. For steroid resistant cases, cyclosporine was found to be effective in achieving complete resolution of mucositis. This case series highlights the importance of ongoing reporting to better understand the clinical characteristics of skin manifestations associated with COVID-19.
Conflict of interest
None disclosed.

REFERENCES
1. Pijls BG, Jolani S, Atherley A, et al. Demographic risk factors for COVID-19 infection, severity, ICU admission and death: a meta-analysis of 59 studies. BMJ Open. 2021;11(1):e044640. https://doi.org/10.1136/bmjopen-2020-044640
2. Polly S, Fernandez AP. Common skin signs of COVID-19 in adults: an update. Cleve Clin J Med. 2022;89(3):161-167. https://doi.org/10.3949/ccjm.89a.21126
3. Bhujel N, Zaheer K, Singh RP. Oral mucosal lesions in patients with COVID-19: a systematic review. Br J Oral Maxillofac Surg. 2021;59(9):1024-1030. https://doi.org/10.1016/j.bjoms.2021.06.011
4. Song A, Nicholson C, Maguiness S. Recurrent reactive infectious mucocutaneous eruption (RIME) in two adolescents triggered by several distinct pathogens including SARS-CoV-2 and influenza A. Pediatr Dermatol. 2021;38(5):1222-1225. https://doi.org/10.1111/pde.14780
5. Canavan TN, Mathes EF, Frieden I, Shinkai K. Mycoplasma pneumoniae-induced rash and mucositis as a syndrome distinct from Stevens-Johnson syndrome and erythema multiiforme: a systematic review. J Am Acad Dermatol. 2015;72(2):239-245. https://doi.org/10.1016/j.jaad.2014.06.026
6. Visconti A, Murray B, Rossi N, et al. Cutaneous manifestations of SARS-CoV-2 infection during the Delta and Omicron waves in 348,691 UK users of the UK ZOE COVID study app. Br J Dermatol. 2022. https://doi.org/10.1111/bjd.21784
7. Iranmanesh B, Khalili M, Amiri R, Zartab H, Aflatoonian M. Oral manifestations of COVID-19 disease: a review article. Dermatol Ther. 2021;34(1):e14578. https://doi.org/10.1111/dth.14578
8. Gimeno E, Morgado-Carrasco D, Moriscot D, Piquero-Casals J. Reactive infectious mucocutaneous eruption triggered by COVID-19 infection in an adult patient. J Eur Acad Dermatol Venereol. 2022;36(9):e673-e674. https://doi.org/10.1111/jdv.18213
9. Holcomb ZE, Hussain S, Huang JT, Delano S. Reactive infectious mucocutaneous eruption associated with SARS-CoV-2 infection. JAMA Dermatol. 2021;157(5):603-605. https://doi.org/10.1001/jamadermatol.2021.0385
10. Bowe S, O’Connor C, Gleeson C, Murphy M. Reactive infectious mucocutaneous eruption in children diagnosed with COVID-19. Pediatr Dermatol. 2021;38(5):1385-1386. https://doi.org/10.1111/pde.14801
11. Ryder CY, Pedersen EA, Mancuso JB. Reactive infectious mucocutaneous eruption secondary to SARS-CoV-2. JAAD Case Rep. 2021;18:103-105. https://doi.org/10.1016/j.jjcr.2021.10.007