Reactive Infectious Mucocutaneous Eruptions (RIME) in COVID-19

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ABSTRACT

Reactive infectious mucocutaneous eruptions (RIME) is a relatively novel terminology describing postinfectious mucocutaneous eruptions that usually affect 2 or more mucosal sites. To our knowledge, we describe the first case of RIME secondary to COVID-19 infection in an elderly 64-year-old immunocompetent male patient. This contrasts with previous case reports that have identified cases of RIME post-COVID-19 infection among the pediatric population and young adults. Our patient had characteristic mucosal involvement and required hospitalization and treatment with systemic steroids. This report also reviews the clinical features, treatment modalities, and outcome of RIME secondary to COVID-19 infection in other published case reports. We emphasize the need for further prospective studies to better elucidate the use of steroids in the management of RIME.

INTRODUCTION

A wide array of dermatological and mucocutaneous lesions associated with COVID-19 infection have been described in the literature.[1,2] Dermatological manifestations commonly reported were morbilliform eruptions, pernio-like lesions, and urticaria;[1] while mucocutaneous findings were papillitis, aphthous stomatitis, and mucositis.[2] In addition, a few case studies have highlighted erythema multiforme (EM) or EM-like cutaneous lesions in patients with COVID-19.[3] Recently, reactive infectious mucocutaneous eruption (RIME)—a unique and distinct entity signifying mucocutaneous involvement—also has been described in patients with COVID-19.[3]

RIME is a relatively novel term characterized by the clinical presentation of significant mucositis (oral, ocular, and anogenital) affecting at least 2 mucous membranes, with absent to sparse cutaneous involvement.[4] It has been associated classically with *Mycoplasma pneumoniae* (*Mycoplasma*-induced rash and mucositis). However, RIME also can be triggered by adenovirus, influenza virus, parainfluenza virus, metapneumovirus, enterovirus, rhinovirus, and, lately, SARS-CoV-2.[5]

To date, RIME secondary to COVID-19 infection has been described primarily in children and adolescents.[3,6-11] There are only a few case reports of RIME following COVID-19 in young adults.[4-5,11] In this article, we describe a case of suspected RIME secondary to COVID-19 in a healthy, immunocompetent 64-year-old man.

CASE PRESENTATION

A 64-year-old male patient with a past medical history of coronary artery disease presented with blisters in his mouth and irritation in the eyes for 3 to 4 days. He was diagnosed with COVID-19 via polymerase chain reaction testing a week prior to the presentation when he had a sore throat, myalgia, cough, chills, and diarrhea. Of note, he had not received any COVID-19 immunization. At that time, he was symptomatically managed with rest and hydration. However, he sought an alternative therapy through an online telemedicine consultation and received a single dose of 47 g ivermectin 4 days after his COVID-19 diagnosis. Twenty-four hours after receiving ivermectin, he noticed red eyes with constant tearing, dryness, and

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slightly blurry vision. The next day, he noticed blisters in his mouth, particularly underneath his upper and lower lips. He denied any other cutaneous rashes, headaches, chest pain, or consumption of any new medication except ivermectin. Other than ongoing diarrhea, his COVID-19–related symptoms had subsided.

On admission, the patient was febrile and temperature was 101.5 °F with normal heart rate and blood pressure. He was maintaining an oxygen saturation of greater than 95% on room air. His physical exam was significant for confluent superficial erosions with overlying heme crusting on the upper and lower vermillion lips. There were superficial circular erosions on the hard and soft palate. He also had thick discharge matted on his eyelashes bilaterally and conjunctival injection. His other examinations, including the dilated fundoscopy, corneal exam, penile exam, and detailed skin examination, were unremarkable (Figures 1 and 2). Blood tests, including complete blood cell count, basic metabolic panel, and liver function test, were unremarkable. His platelet counts were normal at 277×109/L; ferritin was 850 ng/mL (normal value 30-400 ng/mL), C-reactive protein (CRP) was 1.04 mg/dL (normal value < 0.50 mg/dL), and erythrocyte sedimentation rate was 17 mm/hr (normal value 0-20 mm/hr). His infectious workup, including rapid plasma reagin screening, nasopharyngeal *Mycoplasma pneumoniae* nucleic acid amplification testing (NAAT), herpes simplex virus (HSV) type 1 and 2 NAAT obtained from buccal mucosal lesions, and extended respiratory panel NAAT (adenovirus, coronavirus 229E, coronavirus HKU1, coronavirus NL63, coronavirus OC43, human metapneumovirus, influenza A, influenza B, parainfluenza virus 1-4, rhinovirus, respiratory syncytial virus, *Bordetella pertussis/parapertussis, Chlamydia pneumonia*) from nasopharyngeal swab were unremarkable, except for SARS-CoV-2 by NAAT. His chest x-ray revealed subtle densities in the bilateral peripheral upper lobes and the right midlung that appeared to be improving compared to a week prior when he was diagnosed with COVID-19.

The patient was diagnosed with suspected RIME secondary to COVID-19 infection and was managed symptomatically with intravenous (IV) hydration, viscous lidocaine, chloraseptic spray, and acetaminophen. He also received topical erythromycin ointment twice daily, along with preservative-free artificial tears for his conjunctival injection. During the hospital course, he had worsening of his mucocutaneous symptoms, including oral pain and difficulty swallowing. He also had low-grade intermittent fever spikes. His subsequent physical exam revealed a slight worsening of his aforementioned oral erosions with interval development of conjunctival pseudomembranes. His inflammatory markers worsened, with ferritin increasing to 1214 ng/mL (from 850 ng/mL) and CRP rising to 26.32 mg/dL (from 1.04 mg/dL). White blood cell count remained within the normal limits without any left shift. Due to his clinical deterioration, he was started on IV methylprednisolone 48 mg daily for 5 days, along with prednisolone acetate 1% eye drops 4 times daily to each eye. He also received IV ketorolac for pain management alongside "magic mouthwash" (lidocaine, Benadryl, dexamethasone) and nystatin. He reported improvement after treatment escalation as above, and once he

Figure 1. Mucositis With Superficial Erosion and Heme Crusting on the Lips and Buccal Mucosa

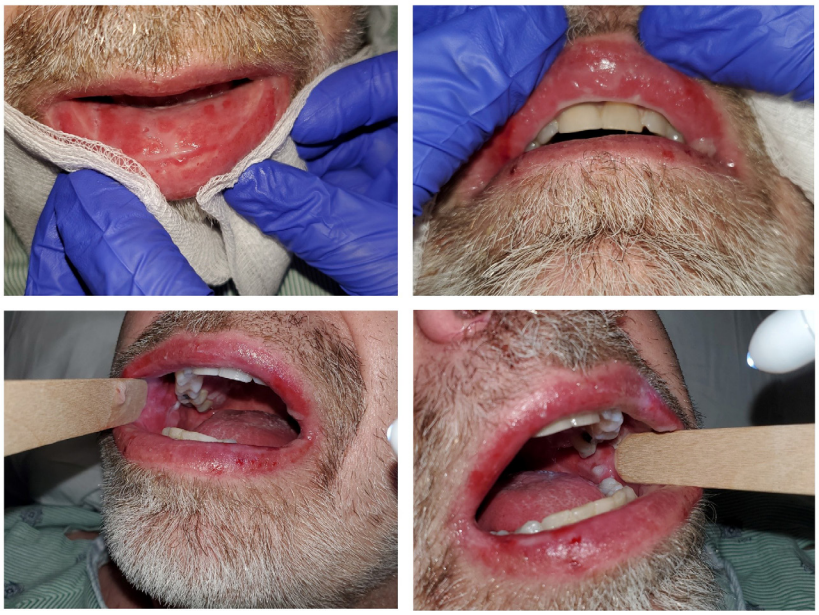
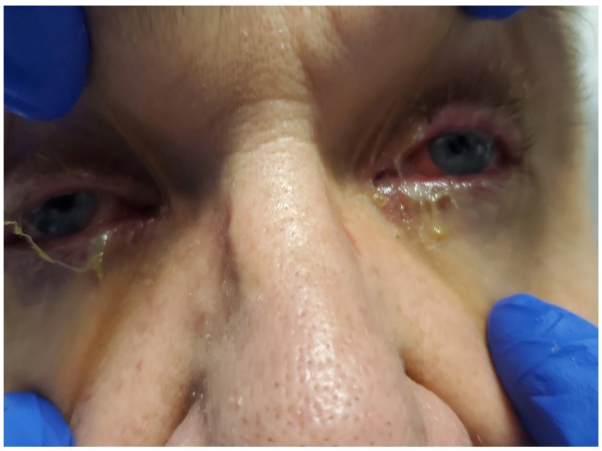


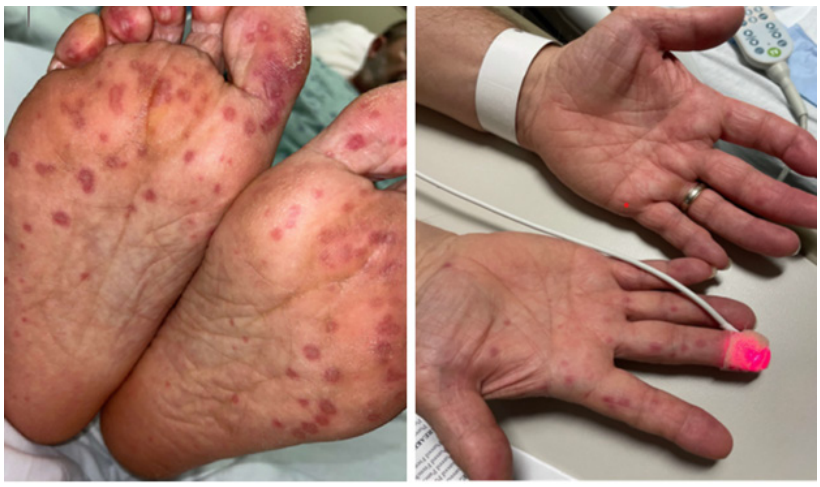
Figure 2. Bilateral Conjunctivitis



was able to tolerate soft food, he was switched from IV methylprednisolone to oral prednisone with the following taper schedule: oral prednisone 60 mg daily for 2 days, followed by 40 mg daily for 4 days, then 30 mg daily for 4 days, 2 mg daily for 4 days, and, finally, 10 mg daily for 4 days.

On day 6 to 7 of admission, he started having nonpruritic and painless maculopapular eruption bilaterally on the hands and feet. It started as a few small macules that increased in size and number and became targetoid lesions of approximately 4 to 5 mm (Figure 3). It later evolved to become papules with central clearing. A few of the papules had even coalesced to form larger plaques. He otherwise felt better with the improvement of his mucocutaneous symptoms. He remained afebrile and his CRP had improved to 8.11 mg/dL. His targetoid lesions were thought to be associated with the diagnosis of RIME, and he was continued on oral steroids as above. His mucocutaneous erosions and acral lesions improved prior to discharge.

Figure 3. Targetoid Macules and Plaques on Bilateral Hands and Feet Occurring on Hospital Day 6 to 7.



At a 2-week follow-up visit, the patient reported significant improvement in his oral symptoms and increased oral intake. In addition, his hands and feet lesions also improved without residual scarring. Unfortunately, he continued to have bilateral eye irritation with conjunctival injection and pseudomembranes. He also was noted to have new punctate epithelial corneal erosions bilaterally. He was continued on prednisolone acetate 1% eye drops 3 times daily, along with erythromycin ointment. After 4 weeks, he had a complete resolution of his ocular symptoms.

DISCUSSION

We report the case of a healthy immunocompetent 64-year-old male patient who was diagnosed with suspected RIME secondary to COVID-19 infection. He had oral mucositis and conjunctivitis, with only sparse cutaneous involvement. His mucositis resolved after the initiation of systemic steroids. No recurrence was noted at the 6-week follow-up visit. To the best of our knowledge, this is the first reported case of RIME secondary to COVID-19 in an older patient. Previous reports have identified cases of RIME post–COVID-19 infection in the pediatric population and young adults from age 13 to 39 years.[3-11]

The diagnosis of RIME can be challenging in patients with COVID-19 due to a wide array of dermatologic and mucocutaneous findings associated with COVID-19 infection.[1,2] In addition, erythema multiforme major (EMM) and EM-like lesions also have been reported in COVID-19,[12] which can be difficult to distinguish from RIME and can pose a diagnostic challenge. The criteria for the diagnosis of RIME include an infectious trigger, erosive mucositis affecting 2 or more sites, vesiculobullous lesions or atypical target lesions affecting less than 10% of the body surface area, noncontributory medication history, and prodromal symptoms.[13] It is distinguished from drug-induced Stevens-Johnson syndrome/toxic epidermal necrolysis and herpes-related EM due to its predominance of mucosal involvement, relatively sparse cutaneous findings, prevalence among younger patients, and its excellent prognosis.[14]

Stevens-Johnson syndrome was a potential differential diagnosis in our patient due to the consumption of 1 dose of 47g ivermectin 24 hours prior to symptom onset. The short latency period of only 24 hours between ivermectin consumption and symptom onset, along with no cutaneous findings on admission, made Stevens-Johnson syndrome unlikely in our patient. Furthermore, the interval development of acral targetoid lesions later in the hospital course was thought to be more likely related to RIME rather than EMM due to the absence of classic target-like lesions, the appearance of rashes while being on steroids, and the negative HSV type 1 and 2 NAAT. The cutaneous findings of papules, plaques, vesicles, and targetoid lesions on extremities including hands and feet also were described in other cases of RIME secondary to COVID-19.[3,4,8,11] Lastly, multisystem inflammatory syndrome in adults (MIS-A) was a potential differential diagnosis in our patient. The Centers for Disease Control and Prevention has postulated criteria for case definition of MIS-A that include presence of fever, severe cardiac illness, rash, new-onset neurologic symptoms, shock, and thrombocytopenia.[15] Our patient did not meet this case definition.

The onset of mucocutaneous findings after acquiring COVID-19 infection can range from 3 days to 2 weeks post-infection, with the resolution of mucositis occurring after 5 days to 3 months.[11] In

our patient, conjunctivitis developed after 4 to 5 days of COVID-19 diagnosis and rapidly progressed to mucositis. It lasted 4 to 6 weeks, with complete resolution occurring after 6 weeks. This timeline of onset and resolution is consistent with the reported literature. Our patient had mucositis involving lips, buccal mucosa, and conjunctiva, with the absence of urogenital involvement. This is also consistent with the reported literature highlighting consistent involvement of lips, with variable ocular findings and urogenital involvement.[11] Lastly, our patient had fever at the onset of his illness, which also is seen commonly in other reported cases of RIME.[3-6,9,11]

As RIME is considered a self-limiting diagnosis, its treatment is usually supportive—with mucosal care, pain management, and hydration[14]—and most patients require hospitalization.[10] The role of immunomodulators, including steroids, is unclear. In most reported cases of RIME secondary to COVID-19 infection, systemic steroids (oral or IV) with variable doses, duration, and tapering schedules were employed.[3-4,6-11] Concomitant IV immunoglobulin (IVIG) with systemic steroids[6] or systemic steroids followed by cyclosporine were utilized in some published cases.[9,11] Antibiotics and antivirals also have been used sparingly.[6,11,14] In the literature, topical therapies commonly administered were hydrocortisone buccal tablet, dexamethasone oral solution, topical corticosteroid ointment, and viscous lidocaine.[3-11] In our case, we initially utilized supportive therapies, including viscous lidocaine, acetaminophen, and IV hydration. Due to worsening symptoms, a systemic steroid with a tapering schedule as mentioned above was initiated. As the complete resolution of mucositis took around 4 to 5 weeks in our case, it is unclear if improvement represents the therapeutic effects of steroids or the natural resolution of the disease process. Further prospective studies are needed in this regard to elucidate the role of steroids in the management of RIME. In addition, it is unclear if COVID-19 vaccinations have any role in mitigating the severity of RIME. Interestingly, in a large retrospective cohort study done in the United Kingdom, the odds of having cutaneous manifestations of COVID-19 were similar between vaccinated and unvaccinated individuals.[16]

CONCLUSIONS

We report a case of RIME secondary to COVID-19 in an older male patient. To the best of our knowledge, this is the first reported case of RIME post–COVID-19 infection in this age group. Due to the wide-ranging mucocutaneous manifestations associated with COVID-19 and challenging differentiation with the EM or EM-like lesions, the identification of RIME can pose a diagnostic challenge. In the context of the recent pandemic, physicians should consider the diagnosis of RIME in patients presenting with predominant mucositis or mucosal involvement after the COVID-19 diagnosis. Most patients usually require hospitalization and treatment with supportive care and systemic steroids. More studies are needed to create a treatment algorithm to aid clinicians in guiding timely therapy. It is unclear if COVID-19 immunizations can have an impact on preventing the development of RIME.

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