

Recurrent reactive infectious mucocutaneous eruption (RIME) in two adolescents triggered by several distinct pathogens including SARS-CoV-2 and influenza A

Amy Song BA¹  | Cynthia Nicholson MD²  | Sheilagh Maguiness MD² 

¹University of Minnesota Medical School, Minneapolis, MN, USA

²University of Minnesota Department of Dermatology, Minneapolis, MN, USA

Correspondence

Amy Song, University of Minnesota Medical School, 55455 Minneapolis, MN, USA.
Email: songx497@umn.edu

Abstract

Reactive infectious mucocutaneous eruption (RIME) was proposed as new terminology to encompass postinfectious mucocutaneous eruptions. The term includes all postinfectious mucocutaneous eruptions such as the widely reported *Mycoplasma pneumoniae*-induced rash and mucositis (MIRM). Very few reports in the literature regarding recurrent RIME are found. We present two adolescent cases of recurrent RIME that involve SARS-CoV-2 and influenza A where the latter is a newly reported infectious trigger; in both patients, the initial episode was likely triggered by *Mycoplasma pneumoniae* (MP) infection.

KEYWORDS

mucositis, Mycoplasma infection, Mycoplasma-induced rash and mucositis, reactive infectious mucocutaneous eruption

1 | INTRODUCTION

Mycoplasma pneumoniae (MP) is a common cause of pneumonia that can cause mucocutaneous disease in 25%-30% of patients.¹ In 2015, Canavan introduced MIRM to describe the unique set of mucocutaneous eruptions due to MP.² MIRM is an entity distinct from erythema multiforme (EM) and Stevens-Johnson syndrome (SJS) due to its predominance of mucosal involvement and better prognosis than the latter.² In recent years, other infectious etiologies such as *Chlamydia pneumoniae*, influenza B, adenovirus, and group A *Streptococcus* have been described to produce mucocutaneous eruptions indistinguishable from MIRM.³⁻⁸ This has led to the term reactive infectious mucocutaneous eruption (RIME) as a reflection that other infections may stimulate this mucocutaneous eruption. Recurrent episodes are poorly understood. Reports have estimated a recurrence rate ranging from 9% to 38%.⁹ In this report, we describe in detail two cases of recurrent RIME with initial episodes suspected to be triggered by MP. Subsequent episodes were caused by other viral infections including SARS-CoV-2 and influenza A.

2 | CASE 1

A 13-year-old boy was seen by an outside physician for lip blistering preceded by 3 days of dry cough and a runny nose. Limited physical examination and laboratory data regarding this episode are found. The patient was treated with amoxicillin with resolution of oral mucositis after 9 days. Due to subsequent elevated levels of MP IgG levels of 0.35 U/L 9 months later, this initial episode of RIME was thought, in retrospect, to be likely due to MP.

Nine months later, the patient presented with painful bleeding lips with fever, sore throat, and a burn during urination that lasted 2 days. Physical examination demonstrated dried blistering over the lips (Figure 1A). The urethral meatus was clear. A <1 cm circular, hyperpigmented, targetoid papule located on his right arm was found (Figure 1B). Biopsy of a lip lesion showed epidermal necrosis. Laboratory results included a positive Group A *Streptococcus* PCR test from the throat, elevated MP IgG levels, negative MP IgM levels, negative HSV Type 1 and 2 PCR from the lip, negative antibodies to desmoglein-1 and 3. The chest radiograph was negative. The suspected diagnosis was recurrent RIME due to Group A *Streptococcus*.

FIGURE 1 Patient 1 second episode triggered by Group A Streptococcus (A) Dried and crusted plaques overlying hemorrhagic bullae of the lips (B) Right arm with hyperpigmented <1 cm circular targetoid papule along with two dried vesicles



FIGURE 2 Patient 2 initial episode (A) Eroded lips with hemorrhagic crusting along with several vesicles with erythema at base distributed across the face (B) Several pink macules, papules, few with central vesicle, and targetoid appearance across upper back

He was treated with oral amoxicillin 500 mg and clobetasol propionate 0.05% ointment. Lip lesions resolved 12 days later.

One and half years later, he presented with a 5-day history of headaches and malaise without fever or cough and 1 day of oral mucositis with a pinpoint rash on the neck and face. His younger brother had tested

positive for influenza the day before. An influenza test was not performed given recent exposure history, type of symptoms which occurred during peak flu season months, and patient had not received seasonal flu vaccine. Physical examination showed erosions on the lips, erythematous papules on the lateral tongue, and ulcerations on the upper and lower gingival. Laboratory results showed elevated MP IgG and negative MP IgM titers. The suspected diagnosis for this episode was recurrent RIME, presumed to be due to influenza. Patient was given topical 0.05% clobetasol propionate ointment, azithromycin (500 mg \times 2 days, 250 mg \times 4 days), oseltamivir 75 mg, and a tapering course of oral prednisolone (50 mg \times 3 days, 40 mg \times 2 days, 30 mg \times 2 days and 20 mg \times 2 days). The lip lesions were almost completely healed after 10 days.

Eleven months later, the patient presented again with oral mucositis. He reported a cough, fever, and body aches for 3 days preceding the eruption. Physical examination showed oral mucositis with mild desquamation on the lower lip. Hypopigmentation on the upper lip was found. Patient had a positive SARS-CoV-2 PCR test from the nasopharynx the week before the eruption. Given suspected recurrent RIME, no additional laboratory tests were performed. The most likely diagnosis was recurrent RIME, most likely due to SARS-CoV-2. He was treated with a tapering course of oral prednisolone (30 mg \times 3 days, 20 mg \times 3 days, 10 mg \times 5 days), topical 0.05% clobetasol propionate ointment, and petrolatum ointment.

3 | CASE 2

An 18-year-old girl presented with 1 week of cough and fever followed by ocular, oral, and genital ulcerations with a skin rash. Physical examination demonstrated bilateral conjunctival injection, hemorrhages, and drainage. The lips had diffuse ulcerations. Her face had several vesicular lesions (Figure 2A). Pink papules, macules, and several 3-5 mm intact vesicles were noted across the back, chest, and right upper arm (Figure 2B). Her left labia minora had an ulceration. Biopsy of her right posterior shoulder showed interface dermatitis with sub-basilar microvesicle formation. Chest radiograph showed patchy opacities in the left lung. Laboratory results showed negative MP IgG and IgM levels but a positive MP PCR from the sputum. Other test results included negative EBV PCR from EDTA plasma and HSV 1 and 2 PCR from left labia and mouth. The presumed

TABLE 1 Recurrent RIME and its relationship to initial *M. pneumoniae* infection

Condition	<i>M. pneumoniae</i> infection with initial episode?	Persistently elevated <i>M pneumoniae</i> IgG levels post infection?	Publication	Publication type (number of patient cases)
Recurrent RIME	Yes: both cases	Not mentioned	Goyal et al, 2019 ⁶	Case series (2)
Recurrent RIME	Yes	Yes; during 3rd episode; 2nd episode not mentioned	Mazori et al, 2020 ⁸	Case report (1)
Recurrent RIME	Yes: 4 out of 5 cases; one case could not confirm	Not mentioned	Liakos et al, 2020 ⁹	Case series/review (5)
Recurrent RIME	Yes	Not mentioned	Brazel et al, 2020 ¹¹	Case report (1)
Recurrent RIME	Unknown as medical records for 1st episode were not obtained	Not mentioned	Song et al, 2018 ¹²	Case report (1)

diagnosis was RIME due to MP. The patient was treated with 4 doses of 0.5 g/kg IVIG over 5 days, a tapering course of prednisone (90 mg initially, decreasing 10 mg every 3 days), doxycycline 100 mg twice daily, 0.1% triamcinolone ointment, and petrolatum ointment. Clinical course was complicated as patient developed complete bilateral conjunctival epithelial defects which required urgent amniotic membrane transplants. Patient's ocular and oral lesions were resolving after 3 months.

Four years and 9 months later, she presented with mouth and genital sores preceded by 3 weeks of cold-like symptoms. She reported testing positive for influenza A 1 week earlier. Physical examination showed ulcerative lesions in buccal mucosa and lips and clitoral hood with erythematous eroded papules. Laboratory results showed elevated MP IgG (1.08 U/L) and IgM (1.0 U/L), negative MP PCR, negative HSV 1 and 2 PCR. The presumed diagnosis was recurrent RIME due to influenza A. She was treated with 0.5 g/kg IVIG daily for 4 days, intravenous methylprednisolone 500 mg twice daily for 3 days, a tapering course of prednisone (60 mg × 2 days, 40 mg × 2 days, and 20 mg × 2 days), doxycycline 100 mg twice daily and petrolatum ointment. Her lesions were healing well 1 week later.

Eight months later, she presented with 3 weeks of cough and cold symptoms followed by oral ulcers on her lips 2 weeks after the onset of symptoms. Physical examination showed erosions of the lips and buccal mucosa. Laboratory results showed a negative SARS-CoV-2 PCR test; elevated MP IgG and negative IgM; negative MP PCR; PCR negative for HSV1 and 2, adenovirus, coronavirus, rhinovirus, influenza A and B, parainfluenza, RSV, and *Chlamydia pneumoniae*. Chest radiograph revealed hazy left basilar airspace opacities. The presumed diagnosis was recurrent RIME due to an unknown infectious agent. Patient was treated with 0.5g/kg IVIG for 4 days, intravenous methylprednisolone 500 mg twice daily for 3 days, and azithromycin 250 mg daily. Mucosal lesions were healed 2 weeks later.

4 | DISCUSSION

Rash and mucositis due to respiratory infections in pediatric patients has been recently described under the term reactive infectious

mucocutaneous eruption (RIME) since many infectious pathogens have been implicated in the clinical presentation of postinfectious rash and mucositis.³ RIME is distinct from EM and SJS due to its prominent mucositis with sparse cutaneous lesions, association with atypical pneumonia and younger patients as well as a better clinical prognosis than SJS.^{2,10}

In this article, we present two cases of recurrent RIME. In the first case, the first episode was likely due to MP; the second due to group A streptococcus; the third likely due to influenza; and the fourth due to SARS-CoV-2. In the second case, the first was likely due to MP; the second due to influenza A; and the third due to an unknown infectious pathogen. We report episodes of recurrent RIME triggered by SARS-CoV-2 and influenza A, which to our knowledge are the first reports of influenza A triggering RIME. Thus, in cases of rash and mucositis associated with respiratory symptoms in a pediatric patient, we propose the importance of testing broadly for infectious pathogens including seasonal flu and SARS-CoV-2.

In both patients, subsequent recurrent episodes revealed a persistently elevated MP IgG levels which, though expected, may be significant to pathogenesis. We speculate that MP IgG antibodies may predispose to mucositis with repeat exposure to MP or other infectious stimuli. Molecular mimicry due to elevated circulating MP antibodies cross-reacting with the mucous membranes, leading to this reactive phenomenon is a possible etiology. A review of recurrent RIME cases showed that most cases started with an initial MP infection (Table 1).^{6,8,9,11,12} Future studies could investigate whether persistently elevated antibodies from non-MP pathogens could also increase risk of recurrence.

In conclusion, we report two cases of recurrent RIME that introduce influenza A as a new infectious pathogen involved with RIME. We hypothesize that in most recurrent cases the initial pathogen is MP, with subsequent episodes being triggered by a variety of infectious agents.

ORCID

Amy Song  <https://orcid.org/0000-0002-8472-6698>

Cynthia Nicholson  <https://orcid.org/0000-0001-6144-093X>

Sheilagh Maguiness  <https://orcid.org/0000-0002-0033-8285>

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