Recurrent *Mycoplasma pneumoniae*–associated reactive infectious mucocutaneous eruption responsive to systemic steroids: A case series

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The Pediatric Dermatology Research Alliance has worked toward creating pediatric-specific diagnostic criteria for the spectrum of severe mucocutaneous eruptions, as case definitions are taken from the adult literature without widely accepted pediatric criteria.[1] The proposed reclassification categories are: epidermal necrolysis, which includes Stevens-Johnson syndrome and toxic epidermal necrolysis due to their similar etiology and management; erythema multiforme, without major or minor forms; and a new term, reactive infectious mucocutaneous eruption (RIME), to encompass diverse parainfectious eruptions, including *Mycoplasma*-induced rash and mucositis. Cases that are considered RIME under this categorization are usually characterized by a severe mucositis of 2 or more mucous membranes, with a prodrome that usually includes a cough.[2]

Cases that fall within the RIME category tend to be single occurrences in most patients.[3-6] However, there is a subset of patients with recurrent episodes estimated to be about 8% in a systematic review of cases with *Mycoplasma pneumoniae*–associated mucocutaneous disease.[4] However, recurrent episodes have not been well-characterized, especially among pediatric patients. In this case series, to raise awareness of this unique subset of cases, we describe recurrent cases of RIME due to *M. pneumoniae* in 3 adolescent patients. In the setting of no standard therapy for RIME, we were able to successfully treat the episodes in all 3 cases with systemic steroids.

Abbreviations used:

BSA:	body surface area
CAP:	community-acquired pneumonia
HSV:	herpes simplex virus
RIME:	reactive infectious mucocutaneous eruption
RT-PCR:	reverse transcription–polymerase chain reaction

CASE SERIES

We conducted a retrospective review of 3 patients aged 9 to 18 years who were seen at the Johns Hopkins Children's Center between January 2015 and September 2019. This study was exempt from the institutional review board process because it was based on only 3 retrospective cases in which the patients were de-identified. Clinical and laboratory details are shown in Table I and Fig 1.

Case 1

A 16-year-old female patient had an initial episode of community-acquired pneumonia (CAP) that was associated with conjunctivitis, oral and vulvar lesions, and limited cutaneous involvement, consisting of vesiculobullous and urticarial papules and plaques on <10% of body surface area (BSA). Laboratory results showed elevated levels of *M. pneumoniae* IgM and IgG, with no herpes simplex virus (HSV) detected by reverse transcription–polymerase chain reaction (RT-PCR). She was treated initially with 5 days of azithromycin and 10 days of 60 mg IV methylprednisolone daily, followed by oral prednisone taper (60 mg for 3 days, then 40,

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Table I. Clinical and laboratory characteristics of patients

Age at initial presentation/ sex	Dates of episodes	Clinical presentation	Laboratory results	Treatment
Case 1 16/F	10/2016	Lobar pneumonia with vesiculobullous skin eruptions (<10% BSA), oral mucositis, conjunctivitis, and vulvar blistering lesions	Myco IgM: 3371 (H) Myco IgG: 2.17 (H) HSV: Not detected	5 days of azithromycin, 10 days of 60 mg IV methylprednisolone, with prednisone taper (60 mg for 3 days, then 40, 30, and 20 mg for 4 days each)
	4/2017	Multiple white erosions on buccal mucosa, frenulum, and soft palate. Erythematous throat. Nonproductive cough	Myco IgM: 2619 (H) Myco IgG: 5 (H)	Prednisolone taper (3 mg/mL solution; 20 mL for 3 days, 14 mL for 4 days, 10 mL for 4 days, 7 mL for 4 days)
	2/2018	Breakouts in mouth and vulva reported by telephone		Above prednisolone taper
	8/2018	White erosions on buccal mucosa and soft palate. Small, shallow ulcerations on inner lip (Fig 1, *A*) with gray periphery; similar small ulceration on tonsil	Myco IgM: 1872 (H) Myco IgG: 2.29 (H)	Above prednisolone taper
Case 2 18/M	12/2016	Lip ulcerations with overlying hemorrhagic crusting (with 9-year history of recurrence)	HSV historically negative	Clobetasol 0.05% as needed
	7/2017	Severe erythema and erosions on upper and lower lips; white film on buccal mucosa	Myco IgM: 833 (H) Myco IgG: 1.51 (H) HSV: Not detected	Prednisone taper (40, 30, 20, and 10 mg for 1 week each)
	9/2017	Similar oral mucosal episode reported by telephone		Above prednisone taper
	11/2017	Similar oral mucosal episode reported by telephone		Above prednisone taper
	6/2018	Similar oral mucosal episode reported by telephone		Above prednisone taper
	11/2018	Similar oral mucosal episode, with cough, reported by telephone		Above prednisone taper
	12/2018	Erosions with yellow fibrinous or hemorrhagic crusty base, surrounding erythematous rim on lower lip (Fig 1, *B*), buccal mucosa, tongue, palate, and posterior oropharynx	Myco IgM: 821 (H) Myco IgG: 1.51 (H)	Prednisone taper (40, 30, and 20 mg for 4 days each), then azithromycin (250 mg 3 times a week)
	1/2019	Similar mucosal episode reported by telephone		Prednisone taper (40, 30, 20, and 10 mg for 4 days each)
Case 3 9/F	11/2015	Worsening targetoid and vesiculopustular rash (20% BSA) with prominent oral ulcerations, conjunctivitis, and rectal involvement in the setting of a community-acquired pneumonia	Myco IgM: 4978 (H) Myco IgG: 1.55 (H) HSV: Not detected	Oral azithromycin (5 days of 250 mg daily)

Continued

Table I. Cont'd

Age at initial presentation/ sex	Dates of episodes	Clinical presentation	Laboratory results	Treatment
	3/2018	Recurrent vesiculopustular rash with oral ulcerations	Myco IgM: 2766 (H) Myco IgG: 3.89 (H)	Prednisone taper (40, 30, 20, and 10 mg for 4 days each)
	1/2019	Skin and oral involvement reported by telephone, with images sent showing ulceration on lower lip and blistering plantar foot lesions (Fig 1, *C* and *D*)		Prednisone taper (40, 30, 20, and 10 mg for 4 days each) Azithromycin (250 mg 3 times a week)
	4/2019	Skin involvement reported by telephone; at follow up a few days later, on right knee, left palm, and bilateral arms, multiple patches with rim of hyperpigmentation and perifollicular repigmentation		Above prednisone taper Azithromycin (250 mg 5 times a week for 3 weeks)
	5/2019	Recurrent oral flare reported by telephone		Above prednisone taper Azithromycin (250 mg 5 times a week)
	9/2019	Between May and September, 2 recurrent cases involving skin only reported by telephone		Above prednisone taper Azithromycin (250 mg daily)

BSA, Body surface area; *F*, *female; H*, high; *HSV*, herpes simplex virus; *IV*, intravenous; *Myco*, *Mycoplasma*.

30, and 20 mg for 4 days each). Six months and almost 2 years after the initial CAP episode with mucositis, she presented with 2 episodes of recurrent oral mucositis but no skin nor other mucosal membrane involvement (Fig 1, *A*). She had elevated levels of *M. pneumoniae* IgM and IgG in both episodes. She reported an additional episode over the telephone with lesions in the mouth and vulva that occurred 16 months after her initial presentation. All 3 of her recurrent lesions resolved with prednisolone solution taper (3 mg/mL solution; 20 mL for 3 days, 14 mL for 4 days, 10 mL for 4 days, and 7 mL for 4 days).

Case 2

An 18-year-old male patient with a 9-year history of recurrent lip ulcerations presented to our institution initially with oral mucositis and no skin involvement. He did not have a known history of CAP, and HSV was historically negative. The patient presented again 7 months later with recurrent oral mucositis. Laboratory results at that time showed elevated levels of *M. pneumoniae* IgM and IgG, with no HSV detected by RT-PCR. His lesions resolved with completion of prednisone taper (40, 30, 20, and 10 mg for 1 week each). Over the following year, he reported 4 additional oral mucositis episodes by telephone, which resolved with the above prednisone taper. He returned to clinic 2 years after the initial presentation with recurrent mucositis and no skin involvement (Fig 1, *B*). Laboratory results again showed elevated *M. pneumoniae* IgM and IgG. He was treated with prednisone taper (40, 30, 20, and 10 mg for 4 days each) and azithromycin suppressive therapy (250 mg 3 times a week), but he had another episode of oral mucositis 1 month later, reported by telephone, that was treated successfully with an additional course of prednisone taper.

Case 3

A 9-year-old female patient presented with CAP and skin rash (20% of BSA) with oral, ocular, and rectal mucositis. Laboratory results showed elevated levels of *M. pneumoniae* IgM and IgG, with no HSV detected by RT-PCR. About two years after the initial presentation with CAP and mucositis, she had a recurrent episode with only oral erosions. She was found to have elevated levels of *M. pneumoniae* IgM and IgG again. Four years after the initial episode, she reported 5 additional episodes, 1 with skin and oral involvement, 3 with only skin involvement, and 1 with only oral involvement. During these episodes (Fig 1, *C* and *D*), she was treated with prednisone taper (40, 30, 20, and 10 mg for 4 days each) and azithromycin prophylaxis, which was increased from 250 mg 3 times a week to 5 times a week. Her oral

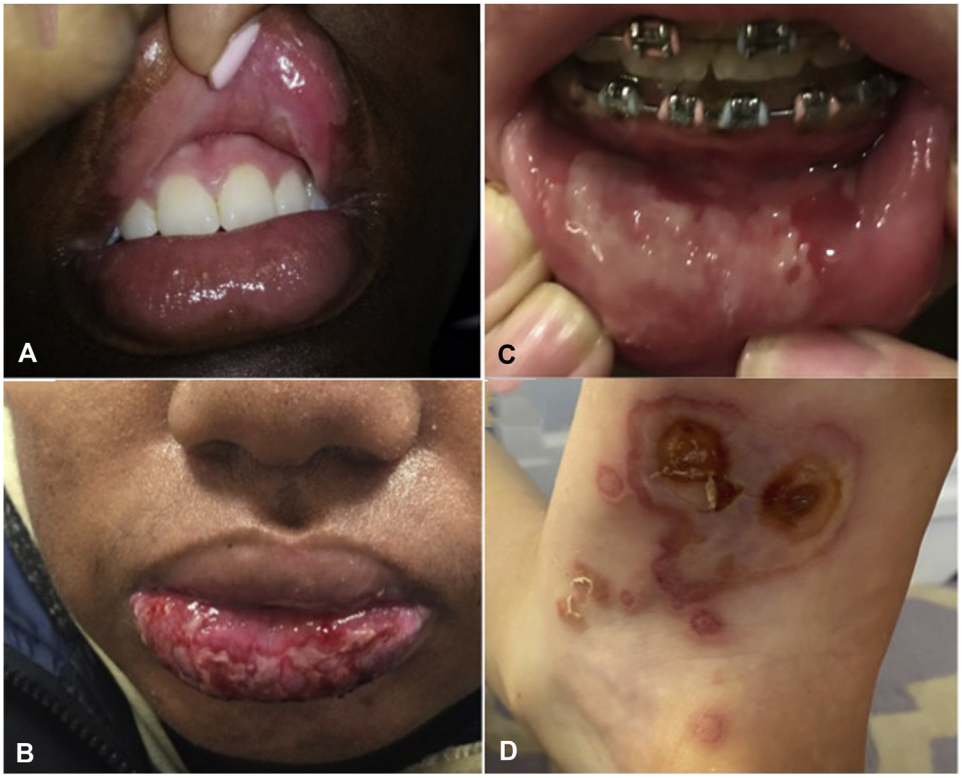

Fig 1. Mucocutaneous lesions. **A**, Case 1, August 2018: ulcerations over inner lip. **B**, Case 2, December 2018: ulcerations with hemorrhagic base over the lower lip. **C** and **D**, Case 3, January 2019: ulceration over the inner lip. On the plantar surface of the foot, atypical targetoid lesions with blistering.

lesions showed improvement within 48 hours of steroid treatment and resolution with completion of the steroid taper, although she had recurrences while on azithromycin prophylaxis, which was increased to 250 mg daily. She had persistent ocular sequelae for several years after her initial episode.

DISCUSSION

We sought to better understand the clinical and laboratory characteristics of 3 adolescent patients with episodes consistent with recurrent RIME due to *M. pneumoniae*. These patients had recurrent lesions associated with laboratory values showing elevated levels of *M. pneumoniae* IgM and IgG on at least 2 occasions over a year apart, with no HSV detected by RT-PCR. There is currently no established standard of care for management of RIME, and treatment is mostly supportive. In all 3 cases, it is notable that we were able to successfully treat each episode with systemic steroid therapy.

Mazori et al[3] recently published a case report of one pediatric patient who presented with 3 episodes of RIME from *Mycoplasma*, group A *Streptococcus*, and influenza B virus. Our case series provides additional important insight into the characteristics of RIME recurrences, in particular those due to *M. pneumoniae*. In our cases and in the case report of Mazori et al, there were many noteworthy similarities. Our patients had subsequent episodes that were less severe than the initial presentation in terms of often just 1 mucous membrane affected, and the recurrent episodes were predominantly oral lesions. In addition, respiratory symptoms were absent in most recurrent episodes. Recurrences were refractory to azithromycin prophylaxis, which could be reflective of macrolide-resistant *M. pneumoniae*, with a prevalence of 90%–100% in Asia and increasing in the United States to an estimated 10%–15%.[7,8]

While oral antiviral therapy is used for recurrent HSV oral mucositis, there has been no preferred treatment for recurrent RIME stemming from *M. pneumoniae* infection, given the small number of recognized cases. Treatments reported in the literature have included antibiotics, systemic steroids, and intravenous immunoglobulin.[4] In all our cases, there was a response to systemic steroids within 48 hours, in which existing lesions and symptoms started to improve, and there was resolution of the lesions with completion of steroid taper in 15 to 30 days.

A limitation of this case series is that it was a retrospective study, and therefore we were restricted to the data that were collected at the time of the visits. We do not have data from physical examination or laboratory studies for a few episodes that were described by telephone, although on some occasions, the parents sent photographs which were reviewed. Although *Mycoplasma* serologic results were collected, RT-PCR for *M. pneumoniae* would have provided further specificity. However, RT-PCR was performed for HSV to rule out the most likely alternative differential diagnosis. Another limitation is that convalescent *Mycoplasma* serologic results were not collected, which would have allowed us to determine whether IgM levels remained persistently elevated between episodes. In our cases, there were documented elevations in IgM levels at least 1 year apart, although IgM levels may remain elevated for longer periods.[3,9]

Of note, all three patients had elevated titers of *M. pneumoniae* IgG on their first evaluation at our institution, suggesting prior primary infection. While cases 1 and 3 presented with CAP, case 2 did not have a known history of prior CAP. None of the patients had respiratory symptoms on the recurrent episodes.

RIME associated with *M. pneumoniae* in particular can result in significant morbidity. It can interfere with oral intake, contributing to weight loss and dehydration, cause ocular complications, as in case 3, and be associated with psychiatric sequelae such as depression among children. Therefore, it is important to recognize RIME quickly and manage it appropriately. Gathering additional cases under the classification of RIME can allow for better recognition and understanding of the best treatment for these patients. While most RIME presentations involve 2 or more mucous membranes, our cases and the case report by Mazori et al[3] have illustrated that recurrent episodes may deivate clinically with involvement of just 1 mucous membrane, often oral. In the setting of no present standard of care for RIME treatment, we were able to successfully treat each episode with systemic steroids. Further research is needed on the prevention of recurrence and alternative treatment options to steroids, along with studies into whether there may be genetic susceptibility to recurrent RIME among certain patients. Parents and patients should be counseled that there is a small risk of recurrence and that earlier presentation and treatment of successive episodes can lead to better outcomes and avoidance of severe sequelae.

Conflicts of interest

None disclosed.

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