Clinical and microbiological characteristics of reactive infectious mucocutaneous eruption: A case series of 5 patients

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INTRODUCTION

The clinical syndrome characterized by an acute mucositis, with variable involvement of the oral, ocular, and genital mucosa and minimal or absent skin involvement, has been described as "atypical Stevens-Johnson syndrome," "Stevens-Johnson syndrome without skin lesions," and "Fuchs syndrome." In the past few years, a new nomenclature was introduced, mostly focused on the etiologic agent, *Mycoplasma pneumoniae*, including terms such as "*Mycoplasma pneumoniae*–associated mucositis"[1,2] and "*Mycoplasma*-induced rash and mucositis"[3]; more recently, the concept of reactive infectious mucocutaneous eruption (RIME) has been proposed to act as an umbrella term including all mucosa-predominant acute parainfectious eruptions.[4] The histopathologic findings of this condition are similar to those found in the Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum, with apoptotic keratinocytes up to a full-thickness epidermal necrosis with subepidermal split, and a sparse superficial inflammatory infiltrate.[3]

Here, we present the clinical records of 5 patients with features of RIME to highlight the key features of this condition that we believe could be helpful in the diagnosis and treatment of this condition in daily practice.

Abbreviations used:

EBV:	Epstein-Barr virus
IgM:	immunoglobulin M
PCR:	polymerase chain reaction
RIME:	reactive infectious mucocutaneous eruption

CASE SERIES

We retrospectively studied patients aged 16 years or older who presented with features consistent with RIME between 2014 and 2020 to the Institute of Dermatology of the Foundation Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo Pavia. The criteria for case selection were an acute occurrence of erosions, ulcers, or vesiculobullous lesions in 2 or more mucosal sites, with minimal (<5% of body surface area) or absent skin involvement and with microbiologic or clinical evidence of active infection. Four adult patients and 1 adolescent were included in the study. The analysis included age, sex, duration of hospital stay, extent of mucocutaneous involvement, presence of prodromic symptoms, results of serologic tests and routine blood tests, occurrence of a relapse or late-term sequela, and drug therapy.

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Mycoplasma pneumoniae was identified in bronchial fluids by polymerase chain reaction (PCR) testing (Respiratory Bacterial ELITe MGB Panel), and evidence of either past or current infection was obtained through the search of immunoglobulin M (IgM) and IgG antibodies (LIAISON *Mycoplasma pneumoniae* IgG and IgM). Active infection by *M pneumoniae* was defined by clinical presentation and a high titer of IgM antibodies. A cultural examination (Mycoplasma IES) was used to determine the presence of *Ureaplasma urealyticum*.

The study was conducted according to the ethical guidelines of the Declaration of Helsinki. The patients gave written informed consent to publication of their case details.

The clinical characteristics of the 5 patients are detailed in Table I. The group was composed of young adults with a median age of 25.8 years and a male predominance (60%). All patients reported prodromic symptoms (median duration, 3.25 days) before the abrupt onset of the mucocutaneous lesions; respiratory symptoms were not a common finding. Oral involvement was present in all cases (100%) (Fig 1, *A* and *B*), resulting in dysphagia to both solids and liquids. Ocular (80%) (Fig 2) and genital (60%) erosions were less frequently reported (Supplementary Fig 1, available via Mendeley at https://doi.org/10.17632/5ppw96s76x.2). Minimal skin lesions with polymorphic appearance were present in 2 patients (40%) (Supplementary Fig 2, available via Mendeley at https://doi.org/10.17632/5ppw96s76x.2). Pulmonary imaging was performed in all patients, but only 2 showed a pathologic pattern of atypical pneumonia, whereas an acute inflammatory state was documented in all cases by a significant increase in the inflammatory markers.

Because *M pneumoniae* infection was suspected in all the patients, the presence of specific IgM and IgG serum antibodies was tested. All but one of the patients tested positive for *M pneumoniae* IgM and IgG. PCR testing was performed on bronchoalveolar lavage fluid in 3 patients and yielded positive results for *M pneumoniae* in patients 4 and 5 and negative results in patient 3; however, in patient 3, a urethral swab showed the presence of *U urealyticum*, which was held responsible for the mucosal lesions. All the patients had serologic evidence of past Epstein-Barr virus (EBV) infection, and 3 patients also showed evidence of past herpes simplex virus 1 infection. PCR testing showed circulating copies of EBV DNA in 1 patient and human herpesvirus 7 DNA in 2 other patients; interestingly, 1 patient (patient 2) showed circulating EBV DNA during an episode of recurrence of the disease, when no *M pneumoniae* reactivation could be demonstrated.

All patients were treated with macrolides and corticosteroids. After administration of the treatment and a median duration of hospitalization of 12.2 days, all patients fully recovered, and only 1 patient (patient 2) had a relapse of the disease. Another patient (patient 5) experienced a postinfectious phimosis as a late-term sequela of the genital erosions.

A biopsy of the oral mucosa was performed in patient 2 after the episode of recurrence. The histopathologic findings showed full-thickness necrosis of the mucosal epithelium and a mixed inflammatory infiltrate with small lymphocytes and neutrophils in the superficial chorion. The results of direct immunofluorescence were negative.

DISCUSSION

RIME is a rare but severe mucositis with limited skin involvement that is generally preceded by nonspecific flulike symptoms. Although this condition is more frequent in otherwise healthy young adults and despite an overall good prognosis, its acute onset can lead to a very painful and disabling mucositis that may require supportive care and pain control in addition to more specific treatments.

RIME is a relatively recent concept, emerging from the need to find a nosologic entity that could encompass all suggested causes of this peculiar acute mucositis, such as *M pneumoniae*, *Chlamydophila pneumoniae*, metapneumovirus, parainfluenzavirus 2, rhinovirus, enterovirus, influenza B virus, and adenovirus.[4,5-8]

The 5 patients here presented showed a similar clinical picture: the appearance of intensely painful mucosal lesions with minimal or absent skin involvement, subsequent to mild flulike symptoms. Upon hospitalization, an *M pneumoniae* infection was detected in 4 patients, whereas 1 patient tested positive only for *U urealyticum* on a genital swab. All patients fully recovered. One patient showed signs of reactivation of EBV infection during an episode of recurrence.

In the literature, the IgM titer for the diagnosis of acute *M pneumoniae* infection is considered of low specificity; however, of the 4 patients in whom we diagnosed this infection, 3 showed evidence of interstitial pneumonia and/or a positive PCR-based assay on bronchoalveolar lavage, whereas the fourth had clear serologic evidence of acute *M pneumoniae* infection. Finally, 1 patient showed evidence of *U urealyticum* infection. Because this infectious agent is part of the Mycoplasmatales order together with *M pneumoniae*, a molecular mimicry-based pathogenic mechanism could be inferred, similar to what has been proposed for *M pneumoniae*.[3]

Table I. Demographic characteristics, clinical presentations, diagnostic tests, treatment, and disease course

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (y)	26	24	23	40	16
Sex	Female	Male	Female	Male	Male
Prodromic symptoms (duration)	Fever, productive cough (4 d)	Fever (not known)	Fever (2 d)	Fever (4 d)	Fever and sore throat (3 d)
Mucosal involvement	Oral and ocular	Oral and ocular	Oral and genital	Oral, ocular, and genital	Oral, ocular, and genital
Minimal skin involvement	Absent	Absent	Absent	Minimal exfoliating lesions on scrotum	Minimal lesions on arms and scrotum
Inflammatory markers (acute phase)	↑ CRP (3 mg/dL) ↑ leukocytes ↑ neutrophils ↑ lymphocytes ↑ monocytes ↑ platelets	↑ CRP (5 mg/dL) ↑ leukocytes ↑ neutrophils ↑ monocytes	↑ CRP (2.8 mg/dL) ↑ leukocytes ↑ neutrophils ↑ monocytes	↑ CRP (6.7 mg/dL) ↑ ESR ↑ leukocytes ↑ neutrophils ↑ monocytes ↑ platelets	↑ CRP (6.3 mg/dL) ↑ leukocytes ↑ neutrophils ↑ lymphocytes ↑ monocytes ↑ platelets
Pulmonary imaging	Interstitial pneumonia on chest x-rays	Negative	Negative	Interstitial pneumonia on chest x-rays and CT scan	Negative
Diagnostic method					
Serology	+ for acute *Mycoplasma pneumoniae* infection (IgM >27, IgG 9 AU/mL) + for past infection with EBV (VCA IgG 205 U/mL, VCA IgM <20 U/mL, EBNA IgG 487 U/mL), and HSV-1	+ for acute *M pneumoniae* infection (IgM >27, IgG 0.0 AU/mL on admission, IgM >27, IgG 85 AU/mL after 4 weeks) + for past infection with EBV (VCA IgG 302 U/mL, VCA IgM <20 U/mL, EBNA IgG 257 U/mL), and HSV-1 (IgG 1.28 index)	− for *M pneumoniae* infection + for past infection with EBV (VCA IgG 121 U/mL, VCA IgM <20 U/mL, EBNA IgG >480 U/mL), HSV-1 (1.4 index), VZV (IgG 18 index)	+ for acute *M pneumoniae* infection (IgM 12, IgG 0 AU/mL) + for past infection with EBV (VCA IgG 145 U/mL, VCA IgM <20 U/mL, EBNA IgG >600 U/mL)	+ for acute *M pneumoniae* infection. (IgM 14, IgG 0 AU/mL on admission, IgM >27, IgG 80 AU/mL after 4 weeks) + for past infection with EBV (VCA IgG 145 U/mL, VCA IgM <20 U/mL, EBNA IgG 540 U/mL)
Molecular testing for virus/bacteria	Not performed	Circulating copies of: EBV DNA 3240 copies/mL (on the second episode) HSV-1, HSV-2, CMV: 0 copies/mL (on the second episode)	Not performed	Circulating copies of HHV-7 DNA: 2160 copies/mL + PCR for *M pneumoniae* on BAL − PCR for *Chlamydia pneumoniae* on BAL	+ PCR for *M pneumoniae* on BAL Circulating copies of HHV-7 DNA: 5310 copies/mL
Other	Not performed	Mucosal biopsy	+ genital swab for *Ureaplasma urealyticum*	Skin biopsy	Not performed

Continued

Table I. Cont'd

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Probable causal agent	*M pneumoniae*	*M pneumoniae*, possible contribution from EBV in recurrence	*U urealyticum*	*M pneumoniae*	*M pneumoniae*
Treatment	Corticosteroids Azithromycin	Corticosteroids Azithromycin	Corticosteroids Clarithromycin	Corticosteroids Azithromycin	Corticosteroids Doxycycline Azithromycin
Relapses	None	One episode	None	None	None
Sequelae	None	None	None	None	Postinfectious phimosis
Outcome	Full recovery	Full recovery	Full recovery	Full recovery	Full recovery

Reference values: VCA IgG (U/mL) <20 negative; VCA IgM (U/mL) <20 negative, >40 positive; EBNA IgG (U/mL) <5 negative, >20 positive; HSV-1 IgG (index) <0.9 negative, >1.1 positive; *M pneumoniae* IgM (index) >1 positive; *M pneumoniae* IgG (AU/mL) <10 negative, >10 positive; VZV IgG (index) <0.9 negative, >1.1 positive.
BAL, Bronchoalveolar lavage; *CMV*, cytomegalovirus; *CRP*, C-reactive protein; *CT*, computed tomography; *EBNA*, Epstein-Barr virus—associated nuclear antigen; *ESR*, erythrocyte sedimentation rate; *HHV-1*, human herpesvirus 1; *HSV-1*, herpes simplex virus 1; *PCR*, polymerase chain reaction; *VCA*, viral capside antigen; *VZV*, varicella-zoster virus.

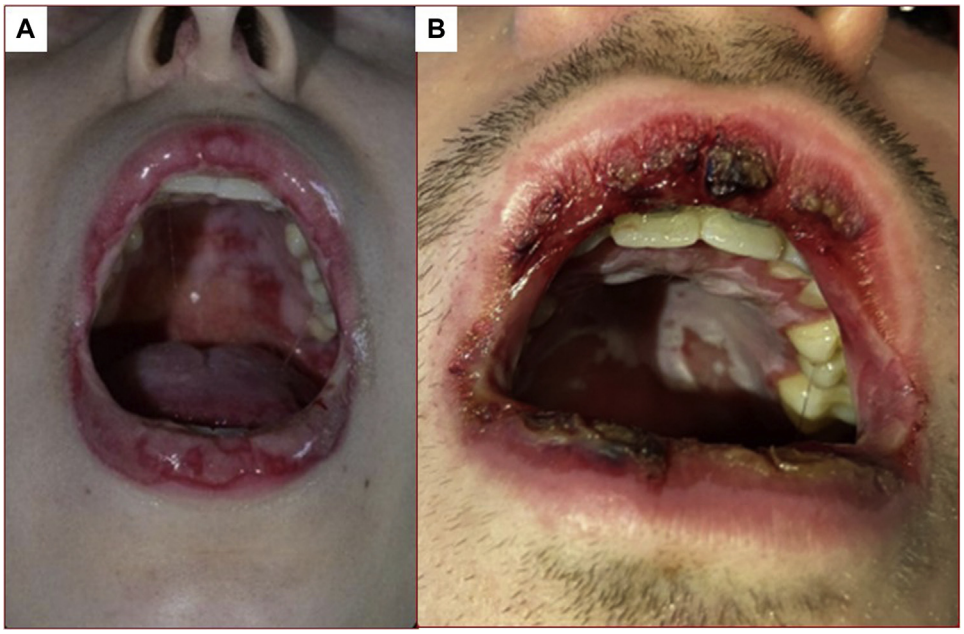

Fig 1. Reactive infectious mucocutaneous eruption. Oral and labial ulcers covered with serofibrinous exudates. **A**, Patient 1. **B**, Patient 5.

The observation of a reactivation of human herpesvirus 7 infection in 2 patients and of EBV infection in another could suggest their potential role as cofactors in RIME pathogenesis, as has been demonstrated in drug-related eosinophilia with systemic symptoms syndrome[9] and graft-versus-host disease.[10] Whereas many eruptions are a direct result of the infection on the skin or mucosa, it is possible that a dermatosis such as RIME could emerge as a parainfectious rash.[11]

In conclusion, we believe that the terms such as "*Mycoplasma pneumoniae*—associated mucositis," "*Mycoplasma*-induced rash and mucositis," and "Fuchs syndrome" should be replaced by RIME, as this definition allows the clinician to include etiologic agents other than *M pneumoniae*. Additional investigations will be needed to elucidate

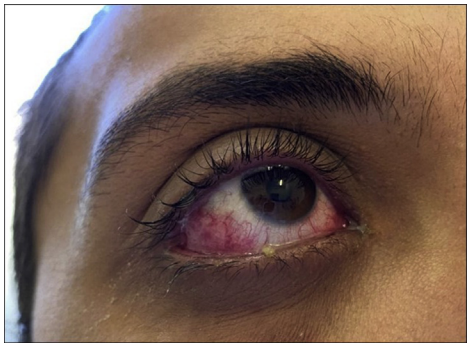

Fig 2. Reactive infectious mucocutaneous eruption. Nonpurulent conjunctivitis in patient 2.

the microbial or host characteristics that could lead to this potentially severe mucositis.

Conflicts of interest

None disclosed.

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