Mycoplasma Pneumoniae Associated Reactive Infectious Mucocutaneous Eruption (RIME). Case Report

Céline De Cuyper [a], Elke de Wachter [b], Martine Grosber [c]

[a] UZ Brussel, Department of Pediatrics, Brussels, Belgium
[b] UZ Brussel, Department of Pediatric Pulmonology and CF Clinic, Brussels, Belgium
[c] UZ Brussel, Department of Dermatology, Brussels, Belgium

celine_de_cuyper@hotmail.com

Keywords

Mycoplasma pneumoniae ; RIME ; rash ; mucocutaneous lesions.

Abstract

Mycoplasma pneumoniae is a well-known cause of community-acquired pneumonia. In a subset of patients, it causes mucocutaneous eruptions with prominent mucositis, termed as "*Mycoplasma pneumoniae* induced rash and mucositis" (MIRM). Recently, "Reactive infectious mucocutaneous eruption" (RIME) has been proposed as the umbrella term for MIRM as other pathogens than *Mycoplasma* species can cause rash and mucositis. In this report, we describe a case of *M. pneumonia*-associated RIME. This article is intended to raise disease awareness and provide diagnostic tools for differentiating *M. pneumoniae*-associated RIME from other, more severe mucocutaneous diseases.

Introduction

Mycoplasma pneumoniae is a common cause of atypical, community-acquired pneumonia in school-aged children. The clinical presentation varies from asymptomatic to multiple extrapulmonary complications. Approximately 25% of patients experience extrapulmonary complications, with mucositis and dermatologic manifestations being the most common (1-5).

For many years, mucocutaneous manifestations associated with *M. pneumoniae* were considered among the spectrum of erythema multiforme (EM) and the potentially life-threatening Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN). EM minor presents with typical target lesions, while EM major includes severe mucosal erosions. In SJS and TEN, skin and mucosae are affected by vesicular and bullous eruptions followed by erosions. In 2014, "*Mycoplasma pneumoniae* induced rash and mucositis" (MIRM) was described as a distinct clinical entity (3, 4, 6-8). Recently, reactive infectious mucocutaneous eruption (RIME) has been proposed as the umbrella term for MIRM as also non-*Mycoplasma pneumoniae* pathogens may cause similar rash and mucositis. RIME emphasizes that mucocutaneous eruptions result from a variety of infectious triggers. Other pathogens reported to cause a similar clinical picture are *Chlamydophila pneumoniae,* human metapneumovirus, human parainfluenza virus 2, rhinovirus, enterovirus, influenza B virus and SARS-CoV-2 (3, 8-11).

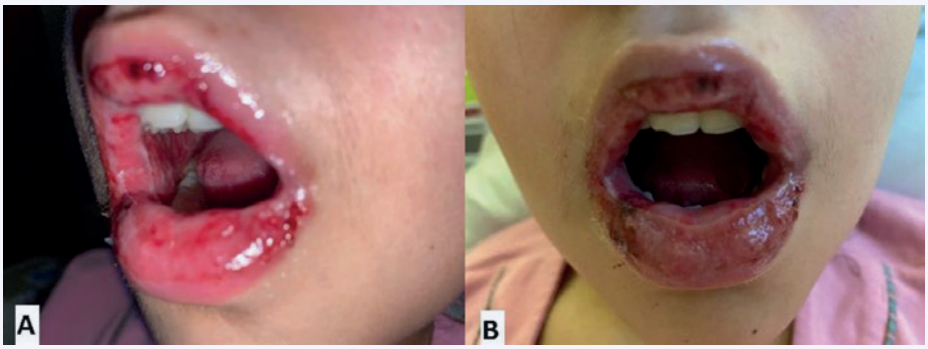
Due to the low incidence of RIME, distinguishing it from SJS/TEN can be challenging. Recognizing RIME as an infection-triggered condition allows for targeted treatment and avoids unnecessary drug restrictions.

Case description

A previously healthy, overweight fourteen-year-old girl (68kg – BMI 26) presented at the emergency department with respiratory problems. She had a sore throat, productive cough, and high fever for five days. Two days before admission, she received oral amoxicillin (500mg TID). After the first dose, she developed painful mucosal ulcerations on her buccal mucosa, palate, and tongue, causing difficulty eating. Blood analysis revealed normal white blood cell (WBC) count (7600 cells/µL; ref. 4300-9640 cells/µL), high C-reactive protein level (CRP 266 mg/l; ref. < 5 mg/l), and normal liver and renal function. Chest X-ray showed bilateral pneumonia. She was treated with intravenous cefuroxime (1,5g TID) and high-flow oxygen (40L 25%). Supportive care, including intravenous hydration and pain management, was provided. Two days later, antibiotic was switched to ceftriaxone (2g BID) and azithromycin (500mg QD) due to persistent fever and a further CRP increase of 403 mg/l. The WBC count was 7800 cells/µL (ref. 4300-9640 cells/µL), with a lymphopenia of 600 cells/µL (ref. 1230-3420 cells/µL). The next day, she developed oral bleeding and macroscopic hematuria. Urine microscopy revealed 277 white blood cells/µL,140 red blood cells/µL and proteinuria of 1.54 g/l. Urine culture was negative. Referral for tertiary care was made.

Upon arrival at our tertiary hospital, she exhibited edema, bleeding, exudation, and hemorrhagic crusts on the lips, with erosions on the buccal mucosa and tongue extending to the pharyngeal cavity (Figure 1a, b). Genitalia were unaffected and no other skin lesions were observed. Ophthalmologic examination was normal. Lung auscultation revealed bilateral crackles and opening snaps. The lymphocytes

FIGURE 1: Erosions on the buccal mucosa and tongue. B: Edema, bleeding and hemorrhagic crusts on the lips.



were normalized. Chest CT showed alveolar opacities with incident bronchiectasis, tree-in-bud configuration in right middle and inferior lobe, and bilateral ground-glass opacification, especially in both inferior lobes (Figure 2). Given its resemblance to granulomatosis with polyangiitis, additional tests were performed, showing positive antinuclear antibody (ANA) (1/1280), negative complement 3 and 4, anti-neutrophil cytoplasmic antibodies (ANCA), and anti-double stranded DNA (dsDNA) antibodies. Polymerase chain reaction (PCR) of a nasopharyngeal swab and a serum immunoglobulin M (IgM) antibody test were positive for *M. pneumoniae*. Tuberculin skin test was negative. Methylprednisolone (40 mg/day) was initiated due to severe oral lesions. High-flow oxygen was replaced by low-flow oxygen for two days. Hematuria and proteinuria resolved, and renal ultrasound was normal. Three days following referral, she became afebrile and resumed eating. Blood cultures remained negative. After five days of ceftriaxone, azithromycin and methylprednisolone, significant improvement in oral lesions and CRP (17 mg/l) was noted. She was discharged with inhaled corticosteroids (ICS) and inhaled long-acting beta 2-agonists (LABA).

Two months post-discharge, auscultation improved with persistent opening snaps and crackles. The cough was absent and pulmonary function remained normal, though prolonged fatigue persisted. A chest CT five months after discharge showed significant improvement with a single bronchiectasis in the lingula and resolution of previous lesions (Figure 3). She had been asymptomatic for weeks without medication. ANA titers decreased (1/320).

Discussion

M. pneumoniae infections are generally mild and self-limiting, with pneumonia being the most common manifestation in school-age children. Extrapulmonary manifestations may occur without respiratory symptoms such as pericarditis, hepatitis, hemolytic anemia, thrombosis, arthritis, glomerulonephritis, mucositis, and varying dermatologic manifestations. MIRM presents with respiratory symptoms such as cough, pharyngitis, malaise, and fever, typically one week before mucocutaneous symptoms. Skin involvement is typically scant, varies from vesiculobullous, to targetoid, macular, papular, or morbilliform and can affect the extremities, trunk, and face. The most affected mucosal areas are oral and ocular, followed by genital and anal mucosa. Mucosal lesions are ulcerative or hemorrhagic and painful. Ocular involvement manifests as bilateral conjunctivitis, photophobia, ulceration, pseudomembrane formation, and eyelid edema (1, 2, 4, 7, 12, 13).

MIRM is associated with prolonged fever, higher CRP level, greater likelihood of hospitalization and oxygen need. Diagnostic criteria include clinical and laboratory evidence of *M. pneumoniae* infection, involvement of at least two mucosal sites, and skin involvement < 10% of body surface area. As in our case, approximately one third of cases present with absent or scarce skin involvement (3-5, 14, 15). The pathological mechanism remains unknown. It is hypothesized that polyclonal B-cell proliferation and antibody production result in skin damage due to immune complex and complement deposition (1, 4, 7, 12, 13).

Detection of *M. pneumoniae* is required to diagnose MIRM. Confirmatory laboratory tests include a PCR of oropharyngeal swabs and measurement of serum-specific immunoglobulin (Ig) G and IgM. The prevalence of *M. pneumoniae* carriage in children is high; up to 56% (2, 14). While PCR is highly sensitive and specific, it cannot distinguish between an acute infection and an asymptomatic carriage. Furthermore, it is unable to differentiate between a past and current infection, as PCR remains positive for up to four months following infection. IgM titers start to increase seven to nine days after infection, reach its peak at three to six weeks and persist for months. IgG titers begin to rise and peak approximately two weeks after IgM titers and persist for years. In the acute phase, both IgM and IgG may be within the normal range. Moreover, there is a significant probability of false positive and false negative results, necessitating repetitive testing (2 to 4 weeks following the acute phase) to document a titer increase for an accurate serologic diagnosis. Once antibiotics are started, the PCR may become negative after 2 days (16).

FIGURE 2: The bronchiectasis (blue arrow), ground-glass opacification (green arrow) and tree-in-bud configuration (red arrow) on chest CT.

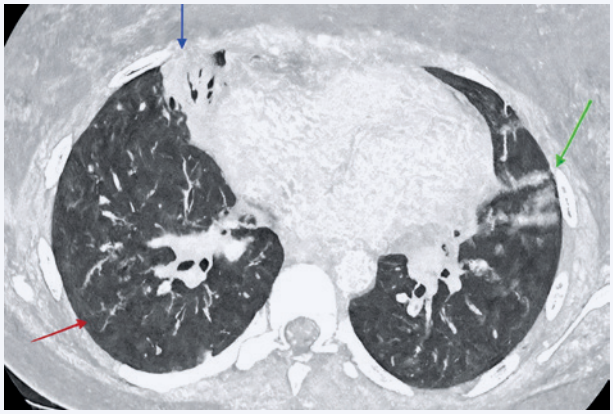
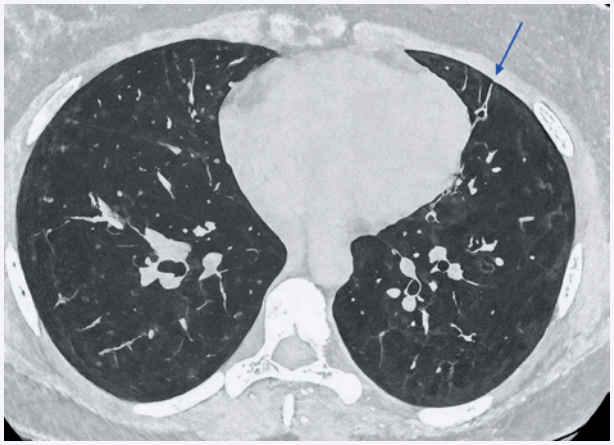


FIGURE 3: One residual bronchiectasis in the lingula (blue arrow) on a control chest CT.



There are no evidence-based guidelines for MIRM treatment. Antibiotics and supportive treatment, which includes pain management, mucosal care and intravenous hydration, appear to be the most universally accepted therapies. Macrolides are the most commonly used antibiotics sharing a combined antibiotic and immunomodulatory effect. While antibiotics reduce pulmonary disease severity, their effect on mucocutaneous symptoms remains unclear. Severe mucocutaneous involvement may require corticosteroids or intravenous immunoglobulin, though strong evidence is lacking (1, 2, 8, 17, 18).

The overall prognosis of *M. pneumoniae*-associated mucositis is good. Long-term sequelae are rare but included mucosal pigmentary changes, orbital complications (corneal ulceration, conjunctival shrinkage, ocular synechiae, xerophthalmia, or blindness), genital adhesions, epiglottitis, and chronic phimosis (1-4, 13). Recurrence of MIRM is usually milder and affects fewer mucosal sites (9, 16). ANA positivity, as observed in this case, have been previously reported as part of the immunological response to *M. pneumoniae* (12). Chest CT abnormalities in this case align with previous reports on MIRM (13, 14). Radiographic findings are variable and nonspecific, including ground glass opacities, air bronchograms, atelectasis, tree-in-bud patterns, peri-bronchial thickening, single or multiple infiltrates, bronchiectasis, pleural effusion, and necrotizing pneumonia. These chest CT abnormalities can persist for months to over a year, despite clinical recovery. In exceptional cases, *M. pneumoniae* infection can lead to bronchiolitis obliterans, characterized by airway obstruction and fibrosis of the bronchioles (19-22).

It is important to differentiate RIME from other mucocutaneous diseases as it requires a less aggressive intervention. A misdiagnosis of SJS/TEN as RIME could result in inadequate and delayed treatment of these potentially life-threatening conditions, that may need immediate withdrawal of the causative drug. TEN is the more severe form of SJS, covering more surface of the body (SJS has skin detachment of < 10%, TEN >30% and 10-30% indicates SJS/TEN overlap). Additional features that help to distinguish between EM/SJS/TEN are patient's age and pathophysiology. Most patients with RIME are young (mean age 12 years). Pathophysiologically, RIME is triggered by an acute infection, whereas SJS/TEN is predominantly triggered by drug exposure. However, the coexistence of both triggers can complicate the diagnostic process. Prominent mucositis, especially oral involvement, with variable though relatively scarce cutaneous involvement is nearly universal for RIME. Nevertheless, prominent mucositis accompanied by minimal cutaneous involvement has been documented in cases of SJS. Similarly, extensive skin detachment as observed in TEN may – though being extremely rare – occur in RIME. SJS and TEN remain important diagnostic considerations (1-4, 6-9, 13).

Conclusion

Children and adolescents suffering from respiratory symptoms accompanied by a prominent mucositis, especially oral involvement, with minimal or absent cutaneous involvement should raise clinical suspicion of RIME/MIRM. Treatment is based on antibiotics and supportive care, with an overall favorable prognosis.

Acknowledgements

We would like to thank the child and her family for providing their consent to publish this case report.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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