Mucosal Respiratory Syndrome: A Systematic Literature Review

Giulia De Luigi[a]   Martina Meoli[a]   Lorenzo Zgraggen[a]   Lisa Kottanattu[a, b]

Giacomo D. Simonetti[a, b]   Isabella Terrani[c]   Mario G. Bianchetti[a]

Sebastiano A.G. Lava[d]   Gregorio P. Milani[b, e, f]

[a]Università della Svizzera Italiana, Lugano, Switzerland; [b]Pediatric Institute of Southern Switzerland, Ospedale San Giovanni, Bellinzona, Switzerland; [c]Department of Dermatology Ente Ospedaliero Cantonale, Ospedale Regionale di Lugano, Lugano, Switzerland; [d]Pediatric Cardiology Unit, Department of Pediatrics, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland; [e]Pediatric Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [f]Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy

Abstract

Background: *Mycoplasma pneumoniae* atypical pneumonia is frequently associated with erythema multiforme. Occasionally, a mycoplasma infection does not trigger any cutaneous but exclusively mucosal lesions. The term mucosal respiratory syndrome is employed to denote the latter condition. Available reviews do not address the possible association of mucosal respiratory syndrome with further atypical bacterial pathogens such as *Chlamydophila pneumoniae*, *Chlamydophila psittaci*, *Coxiella burnetii*, *Francisella tularensis*, or *Legionella* species. We therefore performed a systematic review of the literature addressing this issue in the National Library of Medicine, Excerpta Medica, and Web of Science databases. ***Summary:*** We found 63 patients (≤18 years, *n* = 36; >18 years, *n* = 27; 54 males and 9 females) affected by a mucosal respiratory syndrome. Fifty-three cases were temporally associated with a *M. pneumoniae* and 5 with a *C. pneumoniae* infection. No cases temporally associated with *C. psittaci*, *C. burnetii*, *F. tularensis*, or *Legionella* species infection were found. Two cases were temporally associated with Epstein-Barr virus or influenzavirus B, respectively.

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Introduction

Erythema multiforme is an acute skin disease, which is characterized by the onset of symmetrical fixed red lesions, some of which evolve into distinctive papular "target" lesions. Mucosal lesions, which frequently develop a few days after the rash begins, divide this disease into 2 types: in erythema multiforme minus there is not more than 1 mucous membrane involvement, while in erythema multiforme majus 2 or more mucous membranes are involved [1–3]. Erythema multiforme predominantly occurs in pre-adolescents, adolescents, and young adults [1–3]. Several drugs are known to induce erythema multiforme. Approximately 90% of cases, however, occur in individuals affected by a *Herpes* simplex virus or *Mycoplasma pneumoniae* infection [4].

Sebastiano A.G. Lava
Pediatric Cardiology Unit, Department of Pediatrics
Centre Hospitalier Universitaire Vaudois (CHUV)
CH–1011 Lausanne (Switzerland)
webmaster @ sebastianolava.ch

Occasionally, a mycoplasma infection does not trigger any cutaneous but exclusively mucosal lesions. To the best of our knowledge, this association was first reported in 1945 [5] as mucosal respiratory syndrome and is currently known as *M. pneumoniae*-associated isolated mucositis. The condition has also been termed "atypical Stevens-Johnson syndrome," "Stevens-Johnson syndrome without skin lesions," "erythema multiforme majus without skin lesions," and, in German-speaking regions, "Fuchs syndrome" [1–3].

We recently managed an adolescent presenting with atypical pneumonia and extensive mucositis precipitated by *Chlamydophila pneumoniae*, a further atypical bacterial pathogen [6]. Since textbooks and reviews exclusively refer to the association of mucosal respiratory syndrome with *M. pneumoniae*, we systematically analyzed the available literature.

Methods

Search Strategy

A search of the literature with no date and language [7] limits was performed on the National Library of Medicine, Excerpta Medica, and Web of Science databases following the Preferred Reporting of Systematic Reviews and Meta-Analyses guidelines [8]. The search terms included ("atypical pneumonia" OR *Chlamydia pneumoniae* OR *Chlamydia psittaci* OR *Chlamydophila pneumoniae* OR *Chlamydophila psittaci* OR *Coxiella burnetii* OR *Francisella tularensis* OR *Legionella* OR *Mycoplasma pneumoniae*) AND ("atypical Steven-Johnson syndrome" OR "Fuchs syndrome" OR "herpes oris conjunctivae" OR "mucosal respiratory syndrome" OR *Mycoplasma pneumoniae*-associated isolated mucositis" OR "Stevens-Johnson syndrome"). The search was conducted on January 31, 2020 and updated on June 30, 2020. References of selected publications and personal files were also reviewed for eligible reports. The literature search and the data extraction were carried out independently by 2 investigators (G.D.L. and M.M.). Conflicts were resolved by consensus or by an adjudicator (M.G.B.).

Selection Criteria: Data Extraction

Previously healthy subjects without any pre-existing chronic condition were included. We retained the diagnosis of mucosal respiratory syndrome in subjects presenting with the following 2 criteria: (a) a mucositis affecting at least 2 mucous membranes (including the oral region), which was isolated, that is without skin involvement (or with lesions affecting <0.5% of the skin surface and without any cutaneous target lesion); (b) temporally associated (≤7 days) with a symptomatic respiratory infection or with positive microbiological testing for *M. pneumoniae*, *C. pneumoniae*, *C. psittaci*, *C. burnetii*, *F. tularensis*, or *Legionella* species. Cases of mucosal respiratory syndrome possibly precipitated by *M. pneumoniae* and by a further microorganism (or a pharmacological co-trigger) were considered to be due to *Mycoplasma*.

Table 1. Characteristics of 63 patients aged 3–46 years affected by an acute isolated mucositis involving at least 2 foci

Demographics	
Gender	
Male	54 (86)
Female	9 (14)
Age	
≤18 years	36 (57)
>18 years	27 (43)
Mucosal involvement	
Mouth	63 (100)
Eyes	60 (95)
Genital	41 (65)
Nose	10 (16)
Ear	3 (4.7)
Gastrointestinal	3 (4.7)
Absent respiratory disease	6 (9.5)
Presumed infectious trigger	
M. pneumoniae	53 (84)[1]
C. pneumoniae	5 (7.9)
Epstein-Barr virus	1 (1.6)
Influenzavirus B	1 (1.6)
Microorganism unknown	3 (4.8)
Possible pharmacological co-trigger	2 (3.2)[2]
Immunomodulatory drug treatment	
Systemic corticosteroids	27 (43)
Intravenous immunoglobulins	3 (4.8)

Data are presented as *n* (%).
[1] Respiratory syncytial virus was also isolated in 1 of the 53 cases.
[2] Duloxetine (*n* = 1), diclofenac (*n* = 1).

From each retained case, data were extracted using a piloted form and transcribed into a dedicated worksheet. The data sorted from each case meeting the study criteria included demographics and both clinical and laboratory data.

Completeness of Reporting

For each published case, reporting completeness was assessed using 3 items: (1) description of clinical features including imaging studies; (2) testing for infectious agents possibly associated with mucosal respiratory syndrome, and (3) management. Each component was rated as 0, 1, or 2 and the reporting quality was graded according to the sum of each item as high (score ≥4), satisfactory (score 3), or low (score ≤2).

Analysis

Results are presented either as median with interquartile range or frequency, as appropriate. The kappa coefficient was used to evaluate the agreement between investigators in the literature search. The Fisher test was used to compare dichotomous variables. Statistical significance was set at *p* < 0.05.
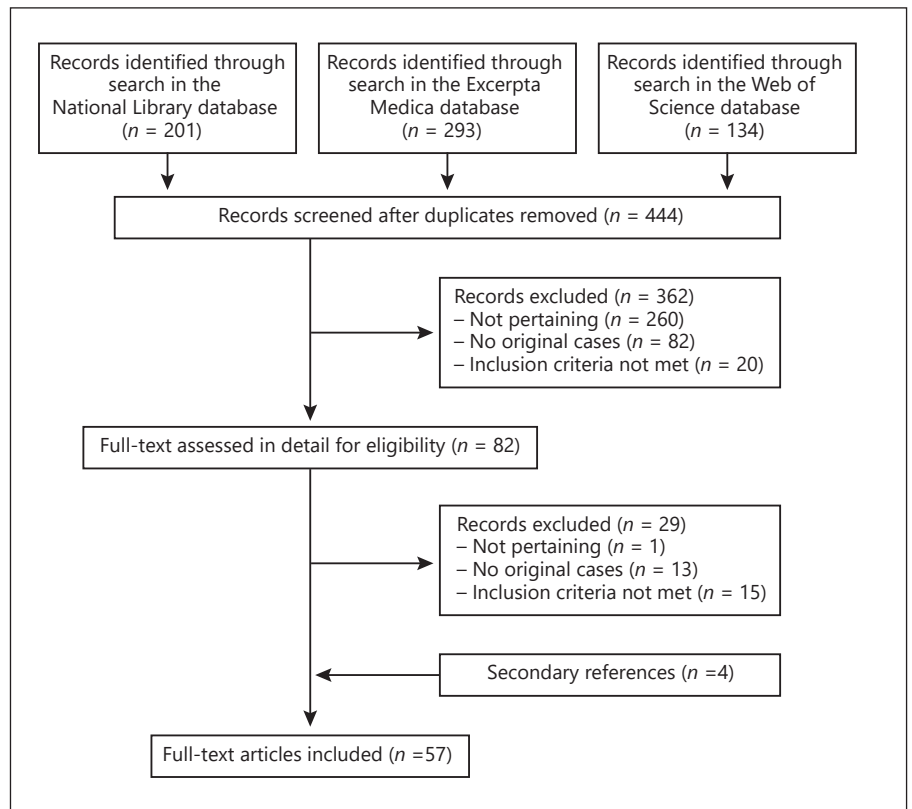
Fig. 1. Mucosal respiratory syndrome – flowchart of the literature search process.

The flowchart contents:

- Records identified through search in the National Library database (*n* = 201)
- Records identified through search in the Excerpta Medica database (*n* = 293)
- Records identified through search in the Web of Science database (*n* = 134)
- Records screened after duplicates removed (*n* = 444)
- Records excluded (*n* = 362)
  - Not pertaining (*n* = 260)
  - No original cases (*n* = 82)
  - Inclusion criteria not met (*n* = 20)
- Full-text assessed in detail for eligibility (*n* = 82)
- Records excluded (*n* = 29)
  - Not pertaining (*n* = 1)
  - No original cases (*n* = 13)
  - Inclusion criteria not met (*n* = 15)
- Secondary references (*n* = 4)
- Full-text articles included (*n* = 57)

Results

Search Results

The literature search returned 444 potentially relevant records (Fig. 1). After the exclusion of 362 non-significant records, 82 potentially eligible reports were considered. The kappa coefficient between the 2 investigators on the application of exclusion and inclusion criteria was 0.91. Fifteen reports detailing 16 cases were excluded because mucositis was associated with skin lesions covering more than 1% of the skin surface or with target skin lesions. Ultimately, 57 articles were retained for analysis [5, 6, 9–63]. They had been published between 1945 and 2020 in English (*n* = 50), Spanish (*n* = 3), Danish (*n* = 2), French (*n* = 1), and Italian (*n* = 1). They had been reported from the following continents: 25 from Europe (Germany, *n* = 3; Spain, *n* = 3; Switzerland, *n* = 3; UK, *n* = 3; Denmark, *n* = 2; France, *n* = 2; the Netherlands, *n* = 2; Austria, *n* = 1; Belgium, *n* = 1; Czech Republic, *n* = 1; Ireland, *n* = 1; Italy, *n* = 1; Poland, *n* = 1; Portugal, *n* = 1), 23 from America (USA, *n* = 19; Canada, *n* = 1; Argentina, *n* = 1; Chile, *n* = 1; Mexico, *n* = 1), 6 from Asia (Japan,

n = 3; Bahrain, *n* = 1; India, *n* = 1; South Korea, *n* = 1), and 3 from Oceania (all from New Zealand).

Findings

The aforementioned articles included 63 patients (54 males and 9 females, aged 3–46 years, median age 17 years), as shown in Table 1. Reporting completeness was high in 54 and satisfactory in the remaining 9 cases. In addition to oral mucositis in all cases, an ocular and a genital mucositis were reported in the vast majority of cases. Furthermore, a colorectal involvement was reported in 3 cases. Interestingly, 6 cases were not associated with respiratory symptoms or signs but uniquely with laboratory features consistent with either a *M. pneumoniae* (*n* = 5) or *C. pneumoniae* (*n* = 1) infection.

The laboratory diagnosis of *M. pneumoniae* infection was made in 53 and that of *C. pneumoniae* infection in 5 cases [6, 41, 55, 62, 63]. The diagnosis of *M. pneumoniae* infection (*n* = 53) was made by means of a relevant rise in immunoglobulin G titer in paired blood samples (*n* = 26), a positive mycoplasma testing in a respiratory tract sample (*n* = 15), or both a relevant rise in immunoglobulin G

titer and a positive mycoplasma testing (*n* = 10). No detailed information was available for the 2 remaining mycoplasma cases. The diagnosis of *C. pneumoniae* (*n* = 5), respiratory syncytial virus (*n* = 1), or influenzavirus B (*n* = 1) infection was made by means of a positive testing for the microorganism in a respiratory tract sample. Immunoglobulin M antibodies directed against the Epstein-Barr viral capsid antigen were detected in the case with the diagnosis of Epstein-Barr virus infection. No case temporally associated with *C. psittaci*, *C. burnetii*, *F. tularensis*, or *Legionella* species infection was reported.

Two cases were temporally associated with Epstein-Barr virus [45] or influenzavirus B, respectively [46]. In 1 of the aforementioned 53 mycoplasma cases, laboratory testing was positive also for respiratory syncytial virus [22]. The microorganism underlying mucosal respiratory syndrome remained unclear in the 3 patients who presented with mucositis and pneumonia before 1953 [5, 9, 10]. In 2 cases, the authors ascribed the mucositis both to the associated infection and to medication with diclofenac or duloxetine, respectively [36, 50].

Apart from antimicrobials and local measures, systemic glucocorticoids or polyclonal intravenous immunoglobulins were prescribed in many cases.

The patient reported in 1945 died [5]. The time to recovery, which was not reported in 9 of the 63 cases, was ≥4 weeks in 16 cases.

Discussion

This careful literature review confirms that, in the vast majority of cases, mucosal respiratory syndrome is precipitated by a *M. pneumoniae* infection and demonstrates for the first time that approximately 10% of cases are associated with *C. pneumoniae*, a further atypical bacterial pathogen. However, the literature review did not disclose cases of mucosal respiratory syndrome possibly associated with *C. psittaci*, *C. burnetii*, *F. tularensis*, or *Legionella* species infection. Finally, a possible association with Epstein-Barr virus or respiratory syncytial virus infection was also noted.

In addition to the so far rather uncommon but descriptively appropriate and convenient term mucosal respiratory syndrome, further terms such as atypical Stevens-Johnson syndrome, Stevens-Johnson syndrome without skin lesions, erythema multiforme majus without skin lesions, and *M. pneumoniae*-associated isolated mucositis have also been employed in the literature. It has also been stated that mucosal respiratory syndrome was first reported in Vienna [64] by the ophthalmologist Ernst Fuchs (1851–1930). Hence, the designation "herpes oris (et) conjunctivae Fuchs" is also sometimes used. However, we were not able to find any original communication in support of this assumption.

The mechanisms underlying the development of mucosal respiratory syndrome related to atypical bacterial pathogens such as *M. pneumoniae* are poorly understood. The clinical features and the histology of erythema multiforme precipitated by *M. pneumoniae* are more similar to drug-induced erythema multiforme than to herpes-associated erythema multiforme. Furthermore, studies investigating the presence of *Mycoplasma* pneumonia deoxyribonucleic acid were negative. Therefore, it is currently supposed that the pathogenesis of *M. pneumoniae*-associated erythema multiforme is mostly indirect and immune mediated [65, 66].

Interestingly, the diagnosis of isolated mucositis likely brought on by cotrimoxazole allergy was made in a 25-year-old Black American presenting with oral and conjunctival mucositis but without any respiratory symptom or laboratory evidence of *Mycoplasma* or *Chlamydophila* infection [67].

Two thirds of patients with *M. pneumoniae*-associated erythema multiforme are pre-adolescents, adolescents, or young adults of male sex [65, 66]. Similarly, the mucosal respiratory syndrome almost exclusively (87%) occurred in male subjects. Interestingly, however, 11 cases of isolated *Mycoplasma* species-associated vulvar mucositis have been reported in the literature, as recently reviewed [68].

It is widely held that antimicrobials, which speed recovery of atypical pneumonia, do not shorten the course of mucocutaneous manifestations [69]. The management is supportive and guided by clinical presentation and severity [70]. Mild cases can be treated with topical corticosteroids. Adequate fluid intake and pain control should also be considered in cases with extensive mucosal involvement. Severe cases are best managed by a multidisciplinary team coordinated by a dermatologist. It is currently impossible to issue recommendations for any systemic therapy. There is no clear-cut evidence that systemic corticosteroids provide any advantage. On the contrary, an older study found that patients treated with systemic corticosteroids took longer to heal than individuals who only received supportive management. On the other hand, these drugs might accelerate the disappearance of symptoms and signs in children [70]. Polyclonal intravenous immunoglobulins are another option, but their use is controversial. Based on a meta-analysis, early

administration of high-dose intravenous immunoglobulins (2.0 g/kg body weight) may be considered in very severe cases. However, an increasing number of reports suggest that, at least in adulthood, intravenous immunoglobulins have hardly any effect on mortality [70].

Skin lesions resembling erythema multiforme have been noted in patients affected with coronavirus disease 2019 [71]. Hence, the latter condition deserves consideration in febrile subjects with mucosal respiratory syndrome. The results of this report must be seen with an understanding of the inherent limitations of the analysis process, which is based on the scanty literature available.

Conclusion

The results of the present analysis indicate that erythema multiforme precipitated by *M. pneumoniae* and *C. pneumoniae* may be characterized by a phenotype of mucous membrane involvement without cutaneous lesions. It has been proposed to reclassify the mucocutaneous diseases associated with *M. pneumoniae* by replacing the designation erythema multiforme with that of "mycoplasma-induced rash and mucositis" [65]. The results of this analysis prompt us to consider the designation "rash and mucositis associated with atypical respiratory pathogens."

Key Message

This literature review confirms that, in the vast majority of cases, mucosal respiratory syndrome is precipitated by a *Mycoplasma pneumoniae* infection, and demonstrates for the first time that approximately 10% of cases are associated with *Chlamydophila pneumoniae*.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.G.B., S.A.G.L., and G.P.M. were responsible for the conception and design of the study. M.G.B., G.D.L., and M.M. were responsible for the literature screening, article selection, and data extraction. G.D.L., L.K., G.D.S., I.T., and L.Z. were responsible for the interpretation of data. M.G.B., S.A.G.L., and G.P.M. were responsible for statistical analysis. M.G.B., G.D.L., and M.M. were responsible for manuscript preparation. M.G.B., S.A.G.L., and G.P.M. critically revised the manuscript. All authors read and approved the final manuscript.

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