Mucosal Respiratory Syndrome: A Systematic Literature Review

Giulia De Luigi, Martina Meoli, Lorenzo Zgraggen, Lisa Kottanattu, Giacomo D. Simonetti, Isabella Terrani, Mario G. Bianchetti, Sebastiano A.G. Lava, Gregorio P. Milani

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

Keywords
Mucosal respiratory syndrome · Fuchs syndrome · Mycoplasma pneumoniae · Chlamydophila pneumoniae · Epstein-Barr virus · Influenzavirus B · COVID-19 · Respiratory infection · Child

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 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 influenza virus B, respectively.

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].
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 *Chlamydia 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 “*Chlamyphila pneumoniae*” OR “*Chlamydiaphila psittaci*” OR “*Coxiella burnetii*” OR “*Francisella tularensis*” OR “*Legionella*” OR “*Mycoplasma pneumoniae*”) AND (“atypical Stevens-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

<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54 (86)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>≤18 years</td>
<td>36 (57)</td>
</tr>
<tr>
<td>&gt;18 years</td>
<td>27 (43)</td>
</tr>
<tr>
<td>Mucosal involvement</td>
<td></td>
</tr>
<tr>
<td>Mouth</td>
<td>63 (100)</td>
</tr>
<tr>
<td>Eyes</td>
<td>60 (95)</td>
</tr>
<tr>
<td>Genital</td>
<td>41 (65)</td>
</tr>
<tr>
<td>Nose</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Ear</td>
<td>3 (4.7)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>3 (4.7)</td>
</tr>
<tr>
<td>Absent respiratory disease</td>
<td>6 (9.5)</td>
</tr>
<tr>
<td>Presumed infectious trigger</td>
<td></td>
</tr>
</tbody>
</table>
| *M. pneumoniae* | 53 (84)%
| *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)%
| 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.
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
De Luca et al. Dermatology

stated that mucosal respiratory syndrome was first re-

have also been employed in the literature. It has also been

-associated isolated mucositis

M. pneumoniae

sions, and

skin lesions, erythema multiforme majus without skin le-

syndrome, Stevens-Johnson syndrome, Stevens-Johnson syndrome without

contrary, an older study found that patients treated with

other hand, these drugs might accelerate the disappear-

in children [70]. Polyclonal

References

DOI: 10.1159/000514815

DOI: 10.1159/000514815

De Luigi et al.
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.”

References


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 Chlamyドフィラ pneumoniae.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The research related to this study did not receive any funding or financial support.

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.

Mucosal Respiratory Syndrome

DOI: 10.1159/000514815


