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# Unusual Eruptions Associated with *Mycoplasma pneumoniae* Respiratory Infections: Review of the Literature

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Giacomo D. Simonetti<sup>a</sup> Mario G. Bianchetti<sup>a</sup> Gregorio P. Milani<sup>c</sup><sup>a</sup>Pediatric Department of Southern Switzerland, Bellinzona, and <sup>b</sup>University Children's Hospital Bern and University of Bern, Bern, Switzerland; <sup>c</sup>Foundation IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Pediatric Emergency Department, Milan, Italy**Key Words**Erythema nodosum · Gianotti-Crosti syndrome · Henoch-Schönlein syndrome · Mucositis · *Mycoplasma pneumoniae* · Papular acrodermatitis · Pityriasis lichenoides et varioliformis acuta Mucha-Habermann · Pityriasis rosea Gibert · Varicella-like eruption**Abstract****Background:** Maculopapular or urticarial eruptions and erythema multiforme sometimes occur in patients affected with *Mycoplasma pneumoniae* respiratory infections. Further eruptions have also been reported. **Objective:** To review the literature addressing *M. pneumoniae* respiratory infection and rather unusual eruptions. **Methods:** Computer-based search in the US National Library of Medicine database as well as in the search engine Google. **Results:** We found a possible relationship between *M. pneumoniae* infection and Fuchs' syndrome (n = 37), varicella-like eruptions (n = 8), Henoch-Schönlein syndrome and further leukocytoclastic vasculitides (n = 21) and erythema nodosum (n = 11). A temporal relationship was also observed with 2 cases of Gianotti-Crosti syndrome. Finally, there exists reasonable evidence that pityriasis rosea Gibert and pityriasis lichenoides et varioliformis acuta Mucha-Habermann are not associated with*Mycoplasma pneumoniae* infections. **Conclusion:** This review implies that *M. pneumoniae* may cause, in addition to erythematous maculopapular (or urticarial) eruptions and erythema multiforme, Fuchs' syndrome and varicella-like eruptions. Furthermore, there is an intriguing link with leukocytoclastic vasculitides or erythema nodosum that deserves further investigation.

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**Introduction**Skin eruptions sometimes occur in patients affected with *Mycoplasma pneumoniae* respiratory infections [1]. The most usual eruption is a mild erythematous maculopapular (or urticarial) rash. Targetoid lesions, the hallmark of erythema multiforme, mostly associated with erosions or bullae involving the oral, ocular or anogenital mucosae, are a further common manifestation [2]. Obviously, similar eruptions can also be caused by the antimicrobials prescribed to treat this infection.Further eruptions have also been observed in patients with *M. pneumoniae* respiratory infections. Since textbooks and reviews only marginally mention these unusual associations, we analyzed the available literature.

## Data Assessment

Between October and December 2014, we performed a computer-based search in the National Library of Medicine database as well as in the search engine Google. Articles published after 1960 were considered, which address a possible link between *M. pneumoniae* respiratory infections and erythema nodosum, Fuchs' syndrome, Gianotti-Crosti syndrome, Henoch-Schönlein syndrome, pityriasis lichenoides et varioliformis acuta Mucha-Habermann, pityriasis rosea Gibert or varicella-like eruptions. For this purpose 'Mycoplasma pneumoniae' and each of the aforementioned conditions (and their synonyms) together with the Boolean operator 'AND' were utilized. Pertinent secondary references were also selected. Reports published in languages other than English, French, German, Italian, Portuguese, or Spanish were not included. Exclusively cases other than erythematous maculopapular and urticarial eruptions or classical erythema multiforme associated with *M. pneumoniae* infections were considered for the analysis. In retained cases, diagnosis of respiratory *M. pneumoniae* infection was based both on a distinctive clinical presentation and an appropriate laboratory testing [3]. Cases with eruptions possibly due both to Mycoplasma as well as to an already recognized cause (e.g. erythema nodosum with clinical and laboratory findings consistent with both a streptococcal and a *M. pneumoniae* infection) were excluded [4].

Furthermore, to address their possible quantitative relationship with *M. pneumoniae* infections, case series dealing with Henoch-Schönlein syndrome, erythema nodosum or Gianotti-Crosti syndrome published in English after 1980 were also reviewed.

Using the described strategy, 94 reports were retained for the final analysis [4–97]: 1 in German [23], 1 in Italian [38], 3 in French [46, 51, 92], 4 in Spanish [20, 24, 50, 81] and the remaining 85 in English.

The Fisher test was used to compare dichotomous variables. Statistical significance was assigned at  $p < 0.05$ .

## Results

The characteristics of 77 patients with Fuchs' syndrome, varicella-like eruption, vasculitis and erythema nodosum associated with *M. pneumoniae* respiratory infection appear in table 1. Fuchs' syndrome (and varicella-like eruption) more frequently affected male subjects than erythema nodosum.

### *Fuchs' Syndrome (Atypical Erythema Multiforme Major)*

The characteristics of erythema multiforme major, sometimes referred to as Stevens-Johnson syndrome, comprise both targetoid cutaneous eruptions and mucosal erythema, erosions or ulcers involving  $\geq 2$  different sites, including the oral region. Erythema multiforme major sometimes presents exclusively with mucosal involvement and is termed atypical erythema multiforme major or Fuchs' syndrome, because this German author

**Table 1.** Characteristics of patients with Fuchs' syndrome, varicella-like eruption, vasculitis and erythema nodosum associated with *M. pneumoniae* respiratory infection

	Fuchs' syndrome	Varicella-like eruption	Vasculitis	Erythema nodosum
Patients, n	37	8	21	11
Age, years				
Childhood	21	5	14	8
Adulthood	16	3	7	3
Gender				
Male	32 <sup>a</sup>	6 <sup>a</sup>	12	2 <sup>b</sup>
Female	5 <sup>a</sup>	2 <sup>a</sup>	9	7 <sup>b</sup>

Number of patients.

<sup>a</sup>  $p < 0.01$  vs. patients with erythema nodosum.

<sup>b</sup> Information not available in 2 cases.

first reported the condition as 'herpes oris conjunctivae' approximately 150 years ago [98]. Our review disclosed 37 patients affected with Mycoplasma respiratory infection and oral mucositis [5–35]. In addition, ocular involvement was noted in 36, genital in 26 (22 male and 4 female subjects) and anal in 3 cases.

### *Varicella-Like Eruption*

Eight cases of Mycoplasma infection developed vesicular lesions surrounded by an erythematous halo resembling varicella [36–41]. In these patients, the Tzanck preparation or the virus culture had been used to exclude varicella. Like in patients with atypical erythema multiforme major, lesions of the oral and ocular mucosae were noted in 5 of the 8 cases. Genital lesions were observed uniquely in 2 males.

### *Henoch-Schönlein Syndrome and Further Vasculitides*

Leukocytoclastic vasculitides classically present as palpable purpura in the context of Henoch-Schönlein syndrome. Less commonly, they present with targetoid lesions and nonpitting edema in the context of acute hemorrhagic edema of young children, which is considered the infantile variant of Henoch-Schönlein syndrome, or with urticarial plaques in the context of urticarial vasculitis. Our review disclosed 21 cases of leukocytoclastic vasculitides associated with *M. pneumoniae* infection: 18 cases of Henoch-Schönlein syndrome, 1 case of acute hemorrhagic edema and 2 cases of urticarial vasculitis [42–62].

We found 14 case series addressing Henoch-Schönlein syndrome in a total of 2,186 cases published in English-

language journals between 1984 and 2014 [63–76]. None of the reports included cases associated with *M. pneumoniae* respiratory infection. It is true, however, that none of the articles specifically investigated this association. A systematic review dealing with acute hemorrhagic edema of young children published a few years ago did not find any further association with infections caused by *M. pneumoniae* [77].

### *Erythema Nodosum*

Erythema nodosum is characterized by painful erythematous nodules located on the anterior surface of the legs. Our review disclosed 11 erythema nodosum cases associated with *M. pneumoniae* infection [4, 54, 58, 78–83]. No more than 1 case of erythema nodosum associated with *M. pneumoniae* respiratory infection was noted in 9 case series [4, 79, 84–90] including a total of 654 erythema nodosum cases not addressing this possible association. However, 4 cases were noted in 3 case series [79, 80, 91] addressing the mentioned association in a total of 77 erythema nodosum cases.

### *Other Possible Associations*

Papular acrodermatitis Gianotti-Crosti presents with acral papular eruptions and usually occurs in association with a viral illness, most commonly hepatitis B virus, Epstein-Barr virus or picornaviruses. The association between Gianotti-Crosti syndrome and *M. pneumoniae* infection was observed in a 4-year-old girl [92] and in a 44-year-old woman [93]. A systematic review of the infections underlying this condition did not disclose any further case of Mycoplasma infection associated with Gianotti-Crosti syndrome [94].

Finally, there exists reasonable evidence that pityriasis rosea Gibert [95, 96] and pityriasis lichenoides et varioliformis acuta Mucha-Habermann [97] are not associated with Mycoplasma infections.

## Discussion

There is a recognized causal relationship between *M. pneumoniae* respiratory infections and erythematous maculopapular (or urticarial) eruptions or erythema multiforme major [2]. To our knowledge, this is the first comprehensive review addressing a possible relationship with further skin eruptions. The survey focused on a possible relationship between *M. pneumoniae* infections and erythema nodosum, Fuchs' syndrome, Gianotti-Crosti syndrome, vasculitides such as Henoch-Schönlein syn-

**Table 2.** Skin lesions that have been associated with *M. pneumoniae* respiratory infections in the literature

Recognized causal relationship
– Erythematous maculopapular (or urticarial) lesions
– Erythema multiforme (both minor and major form)
– Fuchs' syndrome
– Varicella-like skin eruptions
Not well recognized causal relationship
– Vasculitides (most frequently Henoch-Schönlein syndrome)
– Erythema nodosum

drome, pityriasis rosea Gibert, pityriasis lichenoides et varioliformis acuta Mucha-Habermann and varicella-like eruptions (table 2).

Fuchs' syndrome is a rare form of erythema multiforme major that presents exclusively with mucosal involvement. Likewise, in patients with *M. pneumoniae* infections, varicella-like eruptions are usually associated with a mucous membrane involvement that resembles Fuchs' syndrome. These observations suggest that, like for classical erythema multiforme [2], the correlation between Mycoplasma and Fuchs' syndrome or varicella-like eruptions is causal.

Many cases of Henoch-Schönlein syndrome are preceded by a respiratory illness [99]. In this survey, a relationship between Mycoplasma infection and Henoch-Schönlein syndrome or other leukocytoclastic vasculitides was documented in no more than 21 cases. Erythema nodosum is traditionally associated with inflammatory bowel disease and with mycobacterial and streptococcal infections [100]. However, most cases are caused by different respiratory infections. Our survey shows a possible relationship between erythema nodosum and *M. pneumoniae* infection in 11 cases. Many cases of Henoch-Schönlein syndrome or erythema nodosum are preceded by symptoms and signs consistent with a mycoplasmal infection [99, 100]. Nonetheless, testing for *M. pneumoniae* is usually performed neither in Henoch-Schönlein syndrome nor in erythema nodosum. It is therefore concluded that these possible associations deserve further inquiry.

Gianotti-Crosti syndrome is usually associated with viral infections such as hepatitis B or infectious mononucleosis. Since a relationship between Mycoplasma infection and this condition has been documented exclusively in 2 cases, we assume that the association is accidental. A possible relationship between Mycoplasma infections and pityriasis rosea Gibert or pityriasis liche-

noides et varioliformis acuta Mucha-Habermann has previously been debated, but recent evidence strongly argues against such an association.

The link between *M. pneumoniae* and skin lesions deserves some discussion. *M. pneumoniae* has sometimes been isolated from targetoid lesions, suggesting that in some instances they represent extrapulmonary spread of the infection [2]. Alternatively, skin lesions result from similarities shared between macromolecules found on *Mycoplasma* and in host tissue that trigger an immune response [2].

It is traditionally assumed that macrolides, tetracyclines or fluoroquinolones speed recovery in *Mycoplasma* respiratory infection but do not shorten the course of mucocutaneous manifestations [2, 3]. Recent data indicate that there is no clear evidence that antibiotic treatment of mycoplasmal pneumonia is effective [101].

The results of our review must be viewed with an understanding of the inherent limitations of the analysis, which is based on the scanty available literature.

In conclusion, this review of the literature implies that *M. pneumoniae* may cause, in addition to erythematous maculopapular (or urticarial) eruptions and erythema multiforme, Fuchs' syndrome and varicella-like eruptions. Furthermore, the link between this microorganism and vasculitides or erythema nodosum is intriguing and needs further investigations.

## Disclosure Statement

The authors have no conflict of interest to declare.

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