Review Article

Dermatology

Dermatology
DOI: 10.1159/000506460

Received: September 30, 2019
Accepted after revision: February 12, 2020
Published online: March 27, 2020

Skin and Mucous Membrane Eruptions Associated with *Chlamydophila Pneumoniae* Respiratory Infections: Literature Review

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Keywords
Chlamydophila pneumoniae · Erythema multiforme · Erythema nodosum · Cutaneous vasculitis · Respiratory infection · Child

Abstract
Background: *Mycoplasma pneumoniae* pneumonia is sometimes associated with skin or mucous membrane eruptions. Available reviews do not address the association of *Chlamydophila pneumoniae* pneumonia with skin eruptions. We therefore conducted a systematic review of the literature addressing this issue. The National Library of Medicine, Excerpta Medica, and Web of Science databases were employed. ***Summary:*** In two reports, skin lesions and especially urticaria were more common ($p < 0.05$) in atypical pneumonia caused by *C. pneumoniae* as compared with *M. pneumoniae*. We found 47 patients (<18 years, $n = 16$; ≥18 years, $n = 31$) affected by a *C. pneumoniae* atypical pneumonia, which was associated with erythema nodosum, erythema multiforme minus, erythema multiforme majus, isolated mucositis, or cutaneous vasculitis. We also found the case of a boy with *C. pneumoniae* pneumonia and acute generalized exanthematous pustulosis. We did not find any case of *C. pneumoniae* respiratory infection associated with either Gianotti-Crosti syndrome, pityriasis lichenoides et varioliformis acuta Mucha-Habermann, or varicella-like skin eruptions.

Introduction

Mycoplasma pneumoniae atypical pneumonia is sometimes associated with skin or mucous membrane eruptions [1] such as urticaria and the various forms of erythema multiforme (mostly erythema multiforme majus). More rarely, *M. pneumoniae* has also been associated with varicella-like skin eruptions, vasculitides such as Henoch-Schönlein syndrome, or erythema nodosum [2].

Chlamydophila pneumoniae, known until recently as *Chlamydia pneumoniae*, accounts for approximately 10% of atypical pneumonias [3]. Since available reviews do not address the association of *C. pneumoniae* with skin and mucous membrane eruptions, we reviewed the corresponding literature.

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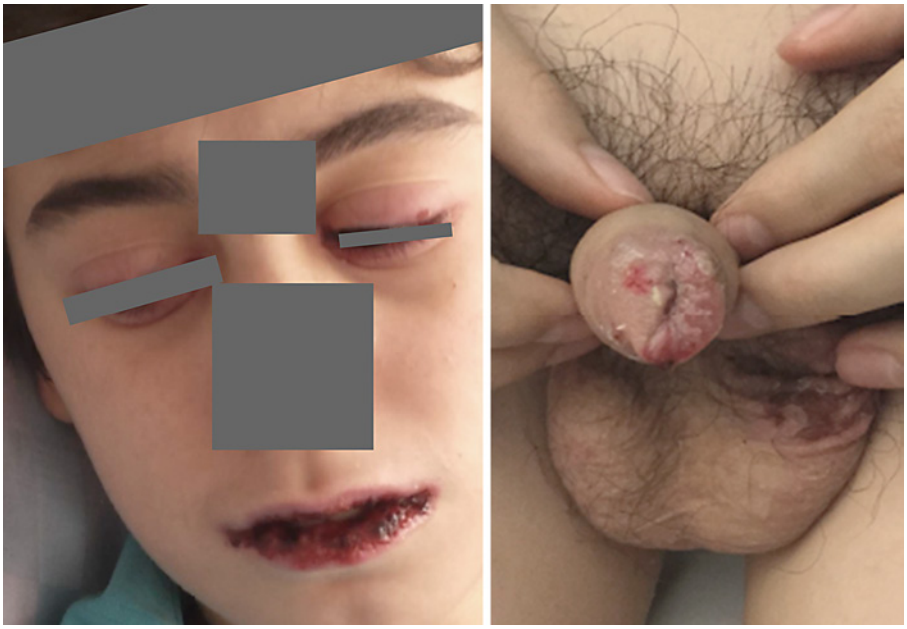

Fig. 1. Non-purulent conjunctivitis, oral mucosal lesions, and penile lesion in a 14-year-old adolescent boy with atypical pneumonia. No skin lesions were noted in the patient. Both the serology and the polymerase chain reaction on sputum were negative for *Mycoplasma pneumoniae* but were instead found to be positive for *Chlamydophila pneumoniae*.

Methods

Search Strategy: Selection Criteria

A computer-based search in the National Library of Medicine, Excerpta Medica, and Web of Science databases was performed. The principles advised by the Economic and Social Research Council guidance on the conduct of narrative synthesis and on the Preferred Reporting Items for Meta-Analyses and Systematic Reviews were used [4]. Articles published after 1970 were considered, which address a possible link between *C. pneumoniae* respiratory infections and erythema multiforme, erythema nodosum, Gianotti-Crosti syndrome, pityriasis lichenoides et varioliformis acuta Mucha-Habermann, urticaria, varicella-like eruptions, and vasculitides with skin involvement. For this purpose, "Chlamydophila pneumoniae" ("Chlamydia pneumoniae") and each of the aforementioned conditions (and their synonyms), skin lesions and eruptions, together with the Boolean operator "AND," were utilized. The literature search was conducted independently by two of the authors (G.D.L. and M.G.B.). Incongruent results were resolved by reaching a consensus. Pertinent secondary references were also screened. Reports published in languages other than Dutch, English, French, German, Italian, Portuguese, or Spanish were excluded.

In the retained cases, the diagnosis of respiratory *C. pneumoniae* infection [3] was based both on characteristic clinical and laboratory features (detection of *C. pneumoniae* in a nasopharyngeal swab, a fourfold rise in titer of a specific immunoglobulin G level, a single immunoglobulin G titer ≥1:512, or a single immunoglobulin M titer ≥1:16). Cases with eruptions possibly due both to *C. pneumoniae* as well as to an already recognized cause (e.g., erythema multiforme with clinical and laboratory findings consistent with both *M. pneumoniae* and *C. pneumoniae* infection) were excluded. Cases with possibly drug-induced skin lesions and cases developing in immunodeficient patients were also excluded.

Furthermore, the diagnosis of erythema multiforme (erythema minus, erythema majus, or isolated mucositis), erythema nodosum, Gianotti-Crosti syndrome, pityriasis lichenoides et varioliformis acuta Mucha-Habermann, urticaria, varicella-like eruption, and vasculitides with skin involvement (such as Henoch-Schönlein syndrome) made in the original reports was reviewed using recognized criteria [2, 5]. Specifically, erythema multiforme was classified as follows: the diagnosis of erythema multiforme minus (or von Hebra syndrome) was made in cases with skin lesions covering 1–10% of body surface area, target lesions, and inflammation of no more than one mucous membrane, cases of erythema multiforme majus (or Stevens-Johnson syndrome) in patients with skin lesions as in erythema multiforme and inflammation of ≥2 mucus membranes, and cases of isolated mucositis (or Fuchs syndrome; Fig. 1) in patients with inflammation of ≥2 mucus membranes and no skin lesions (or lesions covering <1% of body surface area).

Data Extraction: Analysis

From each published case, data were sorted using a piloted form and transcribed into a dedicated database. Attempts were also made to contact authors of original articles to confirm the accuracy of reported data or provide additional missing data. The data extracted from each case meeting the study criteria included demographics and both clinical and laboratory data.

Results are presented either as median and interquartile range (which includes half of the data points) or frequency, as appropriate. The Cohen kappa coefficient was used to assess the agreement between investigators. The Fisher test was used to compare dichotomous variables. Statistical significance was assigned at $p < 0.05$.

Results

Search Results

After reviewing title and abstract, the full text of 41 articles was obtained and assessed in detail (Fig. 2). Ultimately, 26 articles [6–31] published between 1980 and 2019 were retained for analysis: 5 from Japan, 3 from Poland, 3 from Turkey, 3 from the USA, 2 from Spain, 2 from Sweden, and 1 each from the Czech Republic, Finland, France, Italy, Pakistan, Portugal, the UK, and Switzerland. Twenty-three reports were published in English, 2 in French, and 1 in Spanish. The case of a Polish patient with erythema nodosum reported twice [12, 13] in the literature was considered only once. The Cohen kappa coefficient between investigators on the application of exclusion and inclusion criteria was 0.93.

Clinical Data

General Prevalence of Skin or Mucous Membrane Eruptions

The prevalence of skin lesions was addressed in a case series including 300 Polish children [6] with atypical pneumonia caused by either *M. pneumoniae* ($n = 198$) or *C. pneumoniae* ($n = 102$). Skin lesions were observed in 8 (4.5%) cases with *M. pneumoniae* and 9 (8.8%; $p < 0.05$) with *C. pneumoniae*. No further report addressed the prevalence of skin lesions in case series including patients with community-acquired *C. pneumoniae* atypical pneumonia.

Urticaria

The existence of a possible association between *C. pneumoniae* and acute urticaria was addressed in 2 reports [7, 8]. In a case series [7], which included 54 paediatric patients affected by acute urticaria, the most frequently documented infection was urinary tract infection ($n = 7$), followed by serologically determined infections caused by *C. pneumoniae* ($n = 5$), *Helicobacter pylori* ($n = 4$), and *M. pneumoniae* ($n = 1$). Furthermore, *C. pneumoniae* was associated with both a respiratory infection and angioedema in a 13-year-old boy [8].

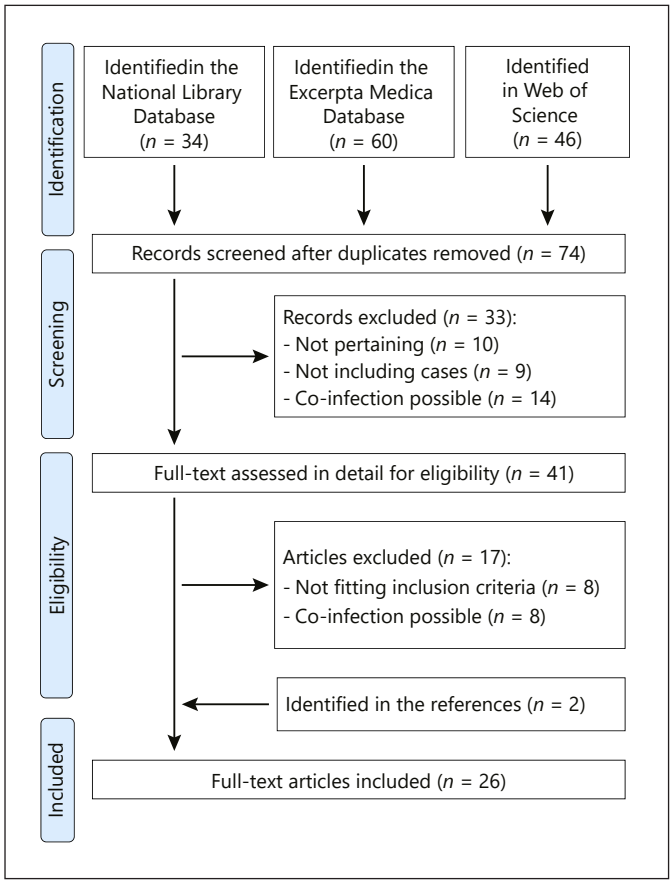

Fig. 2. Skin and mucous membrane eruptions associated with *Chlamydophila pneumoniae* respiratory infections. Flowchart of the literature search process.

Erythema Nodosum, Erythema Multiforme, and Vasculitis

In the literature, we found 47 patients [9–22, 24–30] affected by *C. pneumoniae* atypical pneumonia, which was associated with erythema nodosum [9–14], erythema multiforme [15–24] (either erythema multiforme minus, erythema multiforme majus, or isolated mucositis), or cutaneous vasculitis [25–30], as shown in Table 1.

Finally, a retrospective chart review [23] found 9 children with at least three episodes of erythema multiforme or isolated mucositis that were triggered either by *M.*

Table 1. Characteristics of 47 patients with erythema nodosum, erythema multiforme, or cutaneous vasculitis associated with *Chlamydophila pneumoniae* pneumonia

	All	Erythema nodosum	Erythema multiforme			Cutaneous vasculitis
			minus	majus	isolated mucositis	
Total	47	17	17	3	3	7[a]
Age						
<18 years	16	4	6	1	2	2
≥18 years	31	13	11	2	1	5
Gender						
Female	26	10	12	0	0	4
Male	21	7	5	3	3	3

Data are presented as frequency (*n*). Erythema multiforme: erythema multiforme minus, erythema multiforme majus (Stevens-Johnson syndrome), or isolated mucositis (Fuchs syndrome). [a] Including 3 cases of Henoch-Schönlein syndrome.

pneumoniae or, less frequently, *C. pneumoniae* (testing for herpes simplex virus was negative in these patients).

Further Skin Eruptions

Finally, we found the case of a 14-year-old boy with *C. pneumoniae* pneumonia and acute generalized exanthematous pustulosis [31]. In the literature, we did not find any case of *C. pneumoniae* respiratory infection associated with either Gianotti-Crosti syndrome, pityriasis lichenoides et varioliformis acuta Mucha-Habermann, or varicella-like skin eruptions.

Discussion

More than 55 years ago [32], it was first speculated that *C. pneumoniae* might present with skin or mucous membrane lesions. To our knowledge, this is the first comprehensive review addressing a possible relationship between this germ and skin lesions. The results of this review suggest that *C. pneumoniae*, like *M. pneumoniae*, may cause urticaria, erythema nodosum, erythema multiforme minus, erythema multiforme majus, isolated mucositis, and various cutaneous vasculitides [1, 2].

The results of 2 studies suggest that skin lesions, and especially urticaria, are more common in atypical pneumonia caused by *C. pneumoniae* as compared with *M. pneumoniae*. These findings deserve further confirmation in future research.

It is hard to prove the existence of a causal relationship between *C. pneumoniae* (or *M. pneumoniae*) pneumonia and the occurrence of skin and mucous membrane lesions [1]. With this limitation in mind, two possible mechanisms might underlie the development of these extrapulmonary manifestations [1, 33]. First, skin lesions might develop directly if *C. pneumoniae* is present at the site of inflammation with local inflammatory cytokines induced by the bacterium playing an important pathogenic role. Second, the bacterium might not be present in the skin, but autoimmunity or formation of immune complexes might play the crucial pathogenic role [1, 33]. Physicians' everyday experience that antimicrobials do not shorten the course of skin and mucous membrane eruptions associated with atypical pneumonia supports this latter hypothesis [33].

There are limitations and strengths that should be noted when reading this report. The major limitation relates to the fact that it includes data from a small number of communications published after 1970, whose quality of reporting is variable and sometimes poor. Furthermore, available data do not allow to estimate the prevalence of the reported skin lesions in *C. pneumoniae* pneumonia. Finally, we did not specifically investigate the possible existence of skin and mucous membrane eruptions in patients with pneumonia caused by *Chlamydophila psittaci*, *Coxiella burnetii*, *Francisella tularensis*, or *Legionella* species. The most relevant strength of the study relates to the comprehensive and exhaustive literature search, aiming at surveying the entire literature on this topic.

Conclusion

Every fifth atypical pneumonia patient experiences extra-respiratory symptoms or findings such as headache, mental confusion, meningeal signs, or rash [32]. This re-

view of the literature shows that *C. pneumoniae* pneumonia can be associated with urticaria, erythema multiforme, erythema nodosum, cutaneous vasculitides, and acute generalized exanthematous pustulosis.

Key Message

This review of the literature shows that *Chlamydophila pneumoniae* pneumonia may cause urticaria, erythema multiforme, erythema nodosum, cutaneous vasculitides, and acute generalized exanthematous pustulosis.

Statement of Ethics

Written consent to publish the photographs was obtained from the patient and his guardians.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

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

Author Contributions

Drs. Bianchetti, Lava, and Milani were responsible for the conception and design of the study. Drs. De Luigi and Bianchetti were responsible for literature screening, article selection, and data extraction. Drs. De Luigi, Zgraggen, Kottanattu, Terrani, Vanoni, and Simonetti were responsible for the interpretation of data. Drs. Bianchetti, Lava, and Milani were responsible for statistical analysis. Drs. De Luigi, Bianchetti, Terraneo, and Terrani were responsible for manuscript preparation. Drs. Lava, Milani, and Simonetti critically revised the manuscript. All authors read and approved the final manuscript.

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