

## Case Report

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# Stevens–Johnson syndrome without skin lesions

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In childhood, *Mycoplasma pneumoniae* infections usually present as respiratory tract disease. However, extrapulmonary manifestations can be severe but the association with *M. pneumoniae* might not be considered. Here two adolescents who presented with severe exudative and ulcerative stomatitis accompanied by conjunctivitis and genital erosions are reported on. The skin was unaffected. The diagnosis of an acute *M. pneumoniae* infection was confirmed by serology and PCR. There are only few reports about this clinical entity and its nomenclature is inconsistent. The denomination 'incomplete Stevens–Johnson syndrome' has been suggested.

## Introduction

*Mycoplasma pneumoniae* causes up to 40% of cases of community-acquired pneumonia and is transmitted through aerosols from person to person (Waites & Talkington, 2004). *M. pneumoniae* represents the smallest self-replicating organism in both cellular dimension and genome size, and lacks a rigid cell wall. *M. pneumoniae* is primarily a mucosal pathogen infecting both the upper and the lower human respiratory tract. Infections occur endemically and epidemically in children and adults worldwide. The most common manifestations include sore throat, hoarseness, fever, cough and headache (Waites & Talkington, 2004). In 25% of patients, extrapulmonary manifestations occur before, during or after pulmonary infection, as well as in the complete absence of any respiratory symptoms. Extrapulmonary manifestations include central nervous system, cardiac, haematological and dermatological disorders. Dermatological symptoms are clinically significant complications in up to 25% of patients (Waites & Talkington, 2004). They consist of erythematous maculopapular or vesicular rashes and are usually self-limiting. However, severe forms of Stevens–Johnson syndrome (SJS) with conjunctivitis, ulcerative stomatitis and bullous exanthems have been reported (Waites & Talkington, 2004; Talkington *et al.*, 2001). Of interest, skin lesions may be absent in this condition.

## Case report

### Case 1

A previously healthy 13-year-old female adolescent was referred to us with fever, cough, extensively swollen and

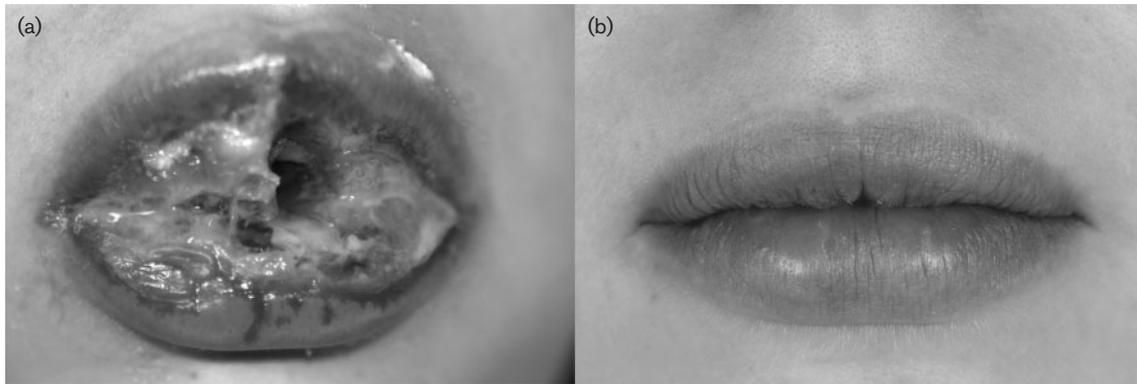
incrusted lips, sore throat and conjunctivitis. The patient had complained of blisters on her lips and oral mucosa as well as photophobia for 3 days. Due to high fever and suspected herpes simplex infection, a systemic aciclovir therapy had been started previously.

On examination, the girl had a high fever of 39.8 °C. She presented with swollen and ulcerative lips covered with yellowish serofibrinous exudates and extensive pseudomembranes. The latter started to fill the complete oral cavity and fixed the mouth in a half-open position (Fig. 1a). Touching the lesions caused significant pain and bleeding. Conjunctivae and sclerae were inflamed. Lung auscultation revealed minor crackles. No other abnormalities were observed on physical and neurological examination. Of note, the skin and the genital mucosa were normal on the day of admission. Chest X-ray revealed an atypical pneumonia (Fig. 2).

Laboratory examinations revealed a significant difference in the erythrocyte sedimentation rate (ESR) when performed in a cold (4 °C) environment (55 mm h<sup>-1</sup>) compared to room temperature (25 mm h<sup>-1</sup>). The C-reactive protein level was 6.3 mg dl<sup>-1</sup>. Complete blood count, serum electrolytes, liver enzymes, blood urea nitrogen and creatinine levels were normal. Serological investigations and PCR for mucotropic viruses (Coxsackie virus A/B, enterovirus, herpes simplex virus 1/2 and Epstein–Barr virus) in blood and from throat swabs were negative at initial assessment and remained negative during follow-up. However, examination of swabs taken from the lesions directly revealed *M. pneumoniae* DNA by PCR and sequencing (Abele-Horn *et al.*, 1998). *M. pneumoniae* serology documented a markedly increased microparticle agglutination assay (MAG) (1:1280) in serum with slightly positive IgM antibodies demonstrated by immunoblotting. IgA and IgG antibodies were negative at initial assessment, suggesting the presence of an acute *M. pneumoniae* infection associated with stomatitis and mucositis. Thus

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Abbreviations: ESR, erythrocyte sedimentation rate; MAG, microparticle agglutination assay; SJS, Stevens–Johnson syndrome.



**Fig. 1.** Extensive pseudomembranous lesions on the lips and in the whole oral cavity in a 13-year-old girl (a) and complete resolution of mucosal lesions 14 days after admission (b).

an antibiotic therapy with clarithromycin (15 mg kg<sup>-1</sup> per day) was started. Additionally, a symptomatic therapy including morphine-based analgesia and meticulous mucous membrane care was initiated. The extensively growing fibrinous pseudomembranes were removed up to four times a day with scissors. Conjunctivitis was treated by local application of erythromycin and colistin, and artificial eye drops. The girl had high fever continuously and was unable to swallow. Therefore, she received intravenous fluids as well as nutritional support via a gastric tube. Due to repeated coughing up of large pieces of membranes followed by oral bleeding, the girl was eventually transferred to the intensive care unit for 2 days since oesophageal involvement could not be excluded. Moreover, the girl developed erosions of the vaginal mucous membranes and dysuria developed. On day 4 of admission, fever ceased. On day 7, gradual oral feeding was possible again. Within 14 days, the patient recovered almost completely. At a 4-week follow-up assessment, a

complete resolution of mucosal erosions and pseudomembranes was documented (Fig. 1b). At this time, serology still revealed a markedly elevated MAG (1:1280). A significantly positive *M. pneumoniae* IgM response and an IgG seroconversion demonstrated by immunoblotting confirmed the diagnosis of an acute *M. pneumoniae* infection. A 3-month follow-up was uneventful.

## Case 2

A previously healthy 11-year-old boy was referred to us with conjunctivitis and swollen, incrustated lips. There was a 3-week history of high fever, cough, headache, malaise and arthralgia. He had developed blisters on his lips and oral mucosa later and had been treated symptomatically. After a short period of recovery, mucosal erosions had aggravated again 5 days prior to admission. Bleeding erosions on the tongue and lips had been noted. He had complained of a sore throat, had been unable to swallow and had lost 4 kg in weight in the past 3 weeks. He had been treated with aciclovir because of a suspected herpes simplex infection.

Physical examination revealed swollen lips with flaccid bullae filled with yellowish 'serosanguinous' exudates. Multiple ulcerations were present at the buccal mucosa and soft palate. Touching these lesions caused pain, and swallowing was almost impossible. Skin and genitalia were unaffected. The boy had a productive cough, a bilateral conjunctivitis, but no fever. No other abnormalities were observed.

Laboratory examinations demonstrated a significant difference in the ESR performed at 4 °C (81 mm h<sup>-1</sup>) compared to that performed at room temperature (23 mm h<sup>-1</sup>). Normal findings included complete blood count, serum electrolytes, liver enzymes, blood urea nitrogen, creatinine and levels of the immunoglobulins A, M and G. The C-reactive protein level was 0.7 mg dl<sup>-1</sup>. Sonographic and radiographic investigations were normal. Serological and PCR investigations for mucotropic viruses (Coxsackie virus A/B, enterovirus, herpes simplex virus 1/2



**Fig. 2.** Chest radiograph showing atypical pneumonia.

and Epstein–Barr virus) in blood and from throat swabs were negative at initial assessment and remained negative during follow-up. A sputum specimen was positive for *M. pneumoniae* DNA. Moreover, *M. pneumoniae* MAG was markedly elevated in serum (1 : 2560). *M. pneumoniae* IgM, IgA and IgG antibodies were present as shown by immunoblotting. Again, the diagnosis of *M. pneumoniae*-associated stomatitis was made.

The therapy consisted of oral clarithromycin (15 mg kg<sup>-1</sup> per day), combined with a symptomatic treatment (local and systemic analgetic therapy, antiseptic treatment of the mouth, and intravenous fluid replacement). Erythromycin and colistin eye drops were applied. Within 2 weeks, the mucous membrane lesions resolved completely. A follow-up assessment 4 weeks after discharge was normal.

## Discussion

Extrapulmonary complications can be observed in about 25% of infections with *M. pneumoniae* at variable time points after onset or even in the absence of respiratory symptoms (Waites & Talkington, 2004). Autoimmune reactions have been suggested to be responsible (Talkington *et al.*, 2001). Dermatological disorders are, by far, the most common clinically significant complications (Waites & Talkington, 2004). Beside harmless erythematous maculopapular or vesicular rashes, severe SJS is a well-known complication of *M. pneumoniae* infection that has been reported in adults as well as in children (Levy & Shear, 1991; Waites & Talkington, 2004). Classic SJS has an incidence of 1.2–6 per million per year and typically presents with fever, conjunctivitis, stomatitis and a generalized, often bullous exanthema (Stevens & Johnson, 1922). Skin lesions are part of the diagnostic criteria but may be absent. The pathophysiology includes a hypersensitivity reaction most commonly due to infections and drugs. According to a retrospective analysis, *M. pneumoniae* seems to be the most frequent infectious cause of SJS in children (Léauté-Labrèze *et al.*, 2000).

We report two cases of severe *M. pneumoniae*-associated exudative stomatitis, bilateral conjunctivitis and partly urogenital affection. Diagnosis was made in accordance with the current guidelines on serological assays including MAG as a screening test and immunoblotting as a confirmation test, as well as on the direct detection of *M. pneumoniae* DNA by PCR (Jacobs, 1993; Daxboeck *et al.*, 2003; Abele-Horn *et al.*, 1998). In paediatric patients, the presence of *M. pneumoniae*-specific IgM in the immunoblot indicates an acute infection (Waites & Talkington, 2004; Daxboeck *et al.*, 2003).

In addition to diagnostic procedures, the clinical courses with preceding fever, malaise, coughing and sore throat in both cases can be easily associated with an *M. pneumoniae* infection. Standard laboratory parameters are hardly of diagnostic use for *M. pneumoniae* infection, with the

exception of the ESR. A difference in ESR, in particular when performed at 4 °C and at room temperature, suggests the presence of cold agglutinins. However, cold agglutinins are not specific indicators for *M. pneumoniae* infections, as they might be present in cases of various bacterial and viral infections as well (Waites & Talkington, 2004; Daxboeck *et al.*, 2003).

With the exception of missing skin affections, the clinical symptoms in the cases described here correspond to the presentation of SJS. However, a denomination as ‘atypical SJS’ is favourable; ‘atypical’, because the syndrome presented without skin lesions. To our knowledge, there are only a few reports of severe *M. pneumoniae*-associated mucositis and stomatitis in the absence of skin affections (Vanfleteren *et al.*, 2003; Kirke & Powell, 2003; Schalock & Dinulos, 2005; Léauté-Labrèze *et al.*, 2000). Nomenclature of this manifestation of *M. pneumoniae* infection is inconsistent. Some authors have referred to it as ‘SJS without skin lesions’; others prefer the more neutral term of ‘*M. pneumoniae*-associated stomatitis’. However, our first case did have oesophageal involvement as a severe complication and other characteristic features of SJS. Thus the alternative diagnostic term ‘*Mycoplasma*-associated stomatitis’ might implicate a less severe clinical course.

We and others observed complete resolution under careful symptomatic and antibiotic treatment in all patients. So far, no lethal cases have been described for this atypical variant of SJS, whereas SJS is associated with a mortality rate of 5–10% (Wolkenstein & Revuz, 1995; Levy & Shear, 1991). However, the limited number of reported patients makes it difficult to judge the mortality risk. Levy and coworkers documented complications of SJS which were less frequent and less severe when *M. pneumoniae* was the causative agent (Levy & Shear, 1991).

In conclusion, patients with severe stomatitis, accompanying fever, cough and malaise most likely benefit from appropriate microbiological diagnostic methods, which should include *M. pneumoniae* serology and PCR, and subsequent antimicrobial therapy.

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