SHORT REPORT

Mycoplasma pneumoniae-associated mucositis – case report and systematic review of literature

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Abstract

Background *Mycoplasma pneumoniae,* a bacterium known to be a common cause of pneumonia, has been documented to cause complications such as debilitating mucositis previously described as an atypical Stevens–Johnson syndrome without skin lesions. However, in the spectrum of epidermal dermatopathies, the condition is increasingly recognized as a separate entity, now termed *M. pneumoniae*-associated mucositis (MPAM).

Objectives We present a case of MPAM and systemically review the literature to discuss diagnostic and therapeutic options.

Methods A systematic literature search was performed to find studies reporting MPAM in adults. We extracted and analysed patient demographics, disease symptomatology, diagnostic testing and treatment.

Results Eleven articles, describing 12 patients and our own patient met the predefined criteria and were analysed. Respiratory, ocular and oral symptoms were present in all patients. Therapies predominantly included antibiotics (10 of 13) and immunosuppressive treatment (9 of 13) leading to complete resolution of symptoms in all patients.

Conclusion Our findings highlight that MPAM should be recognized as a distinct disease entity within the spectrum of epidermal dermatopathies. We discuss and show in our patient why *M. pneumoniae* IgA serum levels could prove to be more reliable diagnostic tools in the MPAM diagnosis than the widely used IgG and IgM titre levels.

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Conflicts of interest

None declared.

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Case report

A 23-year-old otherwise healthy male was admitted with fever (39°C), cough, oral ulcerations and conjunctivitis. He reported a 10-day history of malaise, fever and non-productive cough, and had been treated for a suspected pneumonia with amoxicillin and mefenamic acid for 7 days. One day prior to admission, he developed severe bilateral conjunctivitis and painful oral ulcers which severely limited oral intake. He took no other medications, and his medical history was otherwise unrevealing with no recent sexual contacts.

On examination, painful ulcers covered with yellowish serofibrinous exudates on the oral mucosa, lips and tip of the tongue were found. Flexible video laryngoscopy showed lesions extending to the oro- and laryngopharynx but sparing the vocal cords. In addition, a non-purulent bilateral conjunctivitis was identified (Fig. 1a,b). Genitalia were unaffected, and no other skin lesions were found.

Cardiovascular and functional respiratory examinations were within normal range. A chest radiograph showed an ill-defined opacity in the left lower lobe consistent with atypical pneumonia. Ultrasound examinations did not reveal abnormalities of inner organs or lymph nodes. Blood examinations showed leucocytosis (13; norm 4–9 g/L), neutrophilia (7.94; norm 1.4–6.6 g/L) and elevated C-reactive protein levels (49 mg/L; norm 0–5 mg/L).

An acute herpes infection was excluded by a negative Tzank test, negative herpes simplex virus (HSV) polymerase

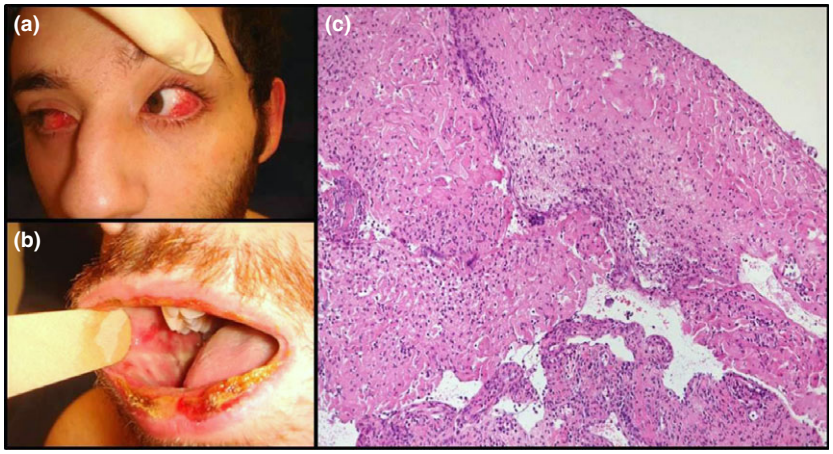

Figure 1 (a) Bilateral, non-purulent conjunctivitis; (b) Oral ulcers covered with serofibrinous exudates; (c) Inner lip biopsy (H&E ×100) – Necrotic mucosa with an extensive inflammatory infiltrate.

chain reaction of oral and conjunctival smears, as well as negative HSV IgM titres. Bacterial cultures showed a normal oral flora. Serologies for HIV, Epstein–Barr virus, *Treponema pallidum* and *Chlamydia spp*. were also negative.

While the clinical presentation reminded of mucosal lesions seen in Stevens–Johnson syndrome (SJS) the skin was not affected, as previously described in a rare disease entity called *Mycoplasma pneumoniae*-associated mucositis (MPAM).

The serum enzyme immunoassay revealed *M. pneumoniae* IgA, IgG and IgM antibodies, of which initial measurements and their progression are presented in Table 1.

Oral mucosa biopsies revealed a highly necrotic mucosa with an extensive inflammatory infiltrate (Fig. 1c) consistent with SJS or toxic epidermal necrolysis (TEN), while we could not identify any significant findings with immunofluorescence.

Based on the clinical presentation, serology and histology, the diagnosis of MPAM was made. Thus, treatment with doxycycline (100 mg IV twice daily) and tapered prednisolone (starting with 500 mg IV daily) was initiated. The patient showed a remarkably fast recovery and was discharged 7 days later. The patient remained symptom free in several follow-up examinations.

Systemic literature review

Introduction

The spectrum of acute epidermolytic dermopathies includes TEN, SJS and bullous erythema exsudativum multiforme, all characterized by cell death with subsequent separation of the epidermis from the dermis.[1] Current pathophysiological causative theories focus on immunological/hypersensitivity responses triggered by medications or pathogens.[2] *M. pneumoniae*, a common cause of pneumonia, can cause a spectrum of extrapulmonary complications, including various skin manifestations ranging from Raynaud's disease, erythema nodosum and Kawasaki disease to life-threatening epidermolytic syndromes such as SJS.[3–5]

Table 1 *Mycoplasma pneumoniae* antibody measurements (U/L) in a 23-year-old patient with *M. pneumoniae*-associated mucositis and their progression over time

M. pneumoniae antibody	Level on admission	Level after 7 days	Level after 2 months
IgA (pos. > 14)	86	80	37
IgG (pos. > 30)	197	>200	>200
IgM (pos. > 17)	18	26	18

Several cases with clinical symptoms consistent with SJS, but without skin lesions, preceded by a *M. pneumoniae* infection, were described previously. They were found to affect predominantly children, but only rarely adults.[6] This type of presentation was termed 'atypical', 'without skin lesions' or 'incomplete SJS' secondary to a lack of skin changes.[4,7,8] Recently, the terms 'Fuchs syndrome' or 'MPAM' seem to have gained popularity, and authors emphasize that mucosal changes observed during the infection can be considered a separate entity from SJS but clinically seem to remain in the same spectrum of epidermolytic dermatopathies.[6,9]

To support our understanding that MPAM shall be recognized as a unique disease in the category of epidermolytic dermatopathies, we performed a systemic literature review to further characterize clinical presentation, histology, changes in laboratory parameters and therapeutic approaches in patients with MPAM.

Methods

We performed a systemic electronic literature search, following the PRISMA statement (www.prisma-statment.org). The last search was performed on 16 December 2013; results were limited to English language. We used the databases Ovid MEDLINE, PubMed and EMBASE with the following search terms: *Stevens Johnson syndrome without skin lesions*, *atypical Stevens Johnson syndrome*, *incomplete Stevens Johnson Syndrome*, *Fuchs syndrome* and *MPAM* to find and compare reports of adult cases of

MPAM. Patients were defined as having MPAM and included in our final review if all four of the following criteria were met: (i) symptoms associated with *M. pneumoniae* infection; (ii) oral ulcerations; (iii) *M. pneumoniae*-positive serology and (iv) lack of skin lesions.

Data abstraction

We reviewed all 818 articles yielded by our initial search, and excluded 790 of them after title and abstract review. After a full text review of the remaining 28 articles, 11 articles, describing 12 patients met our predefined criteria. Including our own patient we analysed a total of 13 MPAM patients (Fig. 2).

Results

The clinical characteristics of the 13 patients included in our study are summarized in Table 2.

Discussion

All cases identified in our review affected young adults (median age 24.9; range 18–38 years). Respiratory symptoms, congruent with a *M. pneumoniae* infection, preceded oral and ocular lesions in all of them by a few days up to a week. Histology was performed in five of 13 cases (including our own case), showing necrosis and inflammation, which are consistent with SJS or TEN.

M. pneumoniae IgM and IgG serum antibodies, part of the inclusion criteria of our review, were reported positive in all MPAM cases found. IgM is typically produced within a week of initial infection with a peak at 3–6 weeks and decline shortly thereafter. High IgM levels are known to be significant in children who have a lower probability of previous infection. In contrast, a direct IgG response is more likely and indicative in adult patients with a reinfection. Therefore, a negative IgM does not exclude the presence of an acute infection. In some cases, a reinfection can lead to a persistent elevation of serum IgM levels lasting up to a year.[4] Therefore, the *M. pneumoniae* IgM titre is not the most reliable marker of a recent infection. Acute infections with low IgM levels might be missed and persistent high IgM can be found in patients who do not have an acute infection.

Interestingly, IgA has been previously suggested as an excellent indicator of an acute *M. pneumoniae* infection, regardless of age group.[4] The usefulness of IgA relies on the fact that it is produced early, peaks quickly, and declines earlier than IgM or

Table 2 Demographic characteristics, clinical presentations, diagnostic tests, histology results and therapies[7,10–19]

Gender	Male	10 of 13
	Female	3 of 13
Median age	24.9 (18–38)	
Clinical presentation	Respiratory symptoms	13 of 13
	Painful oral lesions	13 of 13
	Ocular involvement	13 of 13
	Genital involvement	9 of 13
Diagnostic tests	*M. pneumoniae* serology	13 of 13
	Cold agglutinins reported	2 of 13
	Positive chest X ray	6 of 13
	Inflammatory markers	7 of 13
Histology	Necrosis and inflammation	4 of 6
Therapy	Immunosuppressive treatment	9 of 13
	Corticosteroids	8 of 13
	Cyclosporine A	1 of 13
	Antibiotics general	10 of 13
	Macrolides	4
	Fluoroquinolones	4
	Tetracyclins	2
	Supportive nutritional treatment	4 of 13

Figure 2 Flowchart of literature search.

IgG.[4] The titre changes of IgM, IgG as well as IgA levels in our patient are listed in Table 1. Our findings show IgA levels tapering a week after initial presentation and with significantly lower titres at 2 months. Therefore, we propose to utilize measurements of *M. pneumoniae* IgA levels as an additional diagnostic marker in patients with suspected MPAM.

We and others believe that MPAM should be considered as a separate disease entity in the spectrum of epidermolytic dermopathies.[3] Even though the precise pathomechanism is still unknown, this hypothesis is supported by the observation that mucous membranes are solely affected, which sets the disease apart from typical SJS symptoms. Indeed, all reported cases showed severe mouth mucosa involvement and conjunctivitis and most of the cases showed additional genital mucosa lesions (9 of 13).

Antibiotics were given to 10 and immunosuppressive treatment to 9 of 13 patients. Although all patients recovered in few weeks with or without antibiotics and/or immunosuppression, all cases indicated disease severity meriting hospitalization. We believe that antibiotic treatment, targeting *M. pneumoniae* and thus eliminating the causative agent, could limit the disease duration and severity.

In conclusion, we suggest that MPAM should be considered, alongside TEN, SJS, SJS-TEN overlap syndrome and bullous erythema multiforme, as a separate entity in the spectrum of epidermolytic dermopathies. Furthermore, we recommend that IgA should be granted further interest as a diagnostic marker of *M. pneumoniae* infection when MPAM is suspected.

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