CASE REPORT

Mycoplasma pneumoniae-Induced Rash and Mucositis: A Management Dilemma

Margarida S. Abreu[1], Ana Luísa Carvalho[1], André Morais[1], Susana Carvalho[1], Arnaldo Cerqueira[2]

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Abstract

Mycoplasma pneumoniae induced rash and mucositis is a recently acknowledged clinical entity; therefore, the effectiveness and utility of therapeutic options are still under investigation. This case report aims to highlight the clinical characteristics of this disease and share a report on its management. Herein is reported a previously healthy 15-year-old male admitted with a high fever, severe oral and ocular mucositis, and scattered bullous lesions with an erythematous halo. The epidemiological context was irrelevant, and laboratory tests revealed elevated inflammatory markers. The patient received complete supportive care and intravenous immunoglobulin; however, there was no clinical or laboratory response. After the etiological investigation supported a *Mycoplasma pneumoniae* infection, treatment with azithromycin and systemic corticotherapy started, which led to favorable outcomes. He was discharged after 24 days with no sequelae.

When *Mycoplasma pneumoniae*-induced rash and mucositis is suspected, extensive testing for mycoplasma infection should be granted and cautiously interpreted. Since disease management lacks robust scientific evidence, case reporting is significantly needed.

Keywords: Adolescent; Exanthema/etiology; Mucositis/etiology; Mycoplasma Infections/complications; Mycoplasma Infections/diagnosis; Mycoplasma Infections/drug therapy; Mycoplasma pneumoniae

Keypoints

What is known:

- *Mycoplasma pneumoniae* induced rash and mucositis is a recently recognized clinical entity with unique epidemiological and mucocutaneous features among clinical conditions.
- In the appropriate clinical setting, confirmatory laboratory tests for *Mycoplasma pneumoniae* should include polymerase chain reaction and measurement of IgM and IgG titers, granting that a positive result should be interpreted cautiously.
- In addition to supportive care, immunomodulator and immunosuppressive therapies are widely used, but the effectiveness and utility of these treatment options remain unclear.

What is added:

- Recent studies have shed some light upon distinguishable pathophysiological aspects, supporting an immune response as the primary cause of tissue damage.
- Systemic corticosteroids are frequently used in patients with extensive mucosal involvement, and this report may support its efficacy in such a scenario, although it is difficult to assess its contribution.
- Although the pathophysiological process is thought to be immunologically based, azithromycin role as an anti-inflammatory agent to trigger attenuation must not be overlooked.

Introduction

Mycoplasma pneumoniae induced rash and mucositis is a recently recognized entity, referred to in the past as part of Stevens-Johnson syndrome / toxic epidermal necrolysis and erythema multiforme spectrum. Apart from the challenging diagnosis of infection by this agent, other clinical and epidemiological aspects of mycoplasma-associated eruptions have further set it apart.[1]

Anamnesis remains a critical cornerstone of diagnosis, allowing the identification of a probable causative effect. History of medication exposure might be a diagnostic clue for Stevens-Johnson syndrome / toxic epidermal necrolysis given the appropriate clinical setting.[2] Infection by other agents, especially *herpes simplex* virus, should raise suspicion for other diagnoses, particularly erythema multiforme.[3]

Regarding *Mycoplasma pneumoniae*-induced rash

1. Pediatric Unit, Hospital de Braga, Braga, Portugal
2. Pediatric Intermediate Care Unit, Hospital de Braga, Braga, Portugal
Corresponding Author
Margarida S. Abreu | E-mail: amargaridasabreu@gmail.com
Address: Rua Engenheiro Vilalobos, 26, 8º esquerdo-trás, 4715-282 Braga, Portugal
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and mucositis mucocutaneous manifestations, and despite its pleomorphic nature, morphological features, such as prominent mucositis with sparse or absent cutaneous involvement, are the most notable and distinctive hallmarks. Lesions are characterized as vesiculobullous, targetoid, atypical targets, or, less frequently, macules, which are scattered sparsely, preferably on the extremities, trunk, and sometimes, on the face.[1] Prominent oral mucositis is nearly universal in *Mycoplasma pneumoniae* induced rash and mucositis, with hemorrhagic crusting of the lips, erosions on the tongue, and buccal mucosa.[4] These complications can lead to the notoriously frequent pulmonary disease caused by the *Mycoplasma pneumoniae* infection itself, as well as severe morbidity, and are an indication for hospitalization. Conversely, hepatic and/or renal dysfunction is relatively rare, when compared to Stevens-Johnson syndrome / toxic epidermal necrolysis, and there are no reports of encephalopathy in this context.[1]
Despite these particularities, *Mycoplasma pneumoniae* induced rash and mucositis is generally a milder disease with much lower overall morbidity and mortality rates, full recovery, and infrequent recurrence,[1] which might be due to the younger average age of patients. Male predominance is observed in *Mycoplasma pneumoniae* induced rash and mucositis and erythema multiforme,[1,5] in contrast to Stevens-Johnson syndrome / toxic epidermal necrolysis.[6]
There is still no solid pathophysiological ground drawing a clear distinction concerning *Mycoplasma pneumoniae* induced rash and mucositis. However, polyclonal B-cell proliferation and antibody production might theoretically result in skin damage from immune complex deposition and complement activation. Even though *Mycoplasma pneumoniae* has been cultured out of blister fluid, there is no data available regarding the incidence of cutaneous infection or virulence factors leading to blister formation.[1] Moreover, histopathologic features unique to *Mycoplasma pneumoniae* induced rash and mucositis remain unclear.
Supportive therapy is needed to alleviate pain and potential complications, but immunosuppressive and immunomodulator therapy might also be useful, if not warranted, in certain circumstances, especially extensive mucosal involvement. However, more investigation is needed. Antibiotic therapy targeted to *Mycoplasma pneumoniae* is usually initiated when there is evidence of atypical pneumonia.
This report describes a case of severe mucositis with scattered skin eruption and evidence of *Mycoplasma pneumoniae* infection, highlighting its clinical characteristics and course, as well as reporting treatment choices and outcomes.

Case Report

A previously healthy 15-year-old male presented at the pediatric emergency department with six days of high fever, myalgias, moderate headache, photophobia with no decreased visual acuity, and prominent oral mucositis progressing since the day before. Furthermore, there was a significantly reduced oral intake, especially concerning solid food, but no history of recent or ongoing respiratory symptoms. Therefore, no relevant epidemiological context was determined. Apart from ibuprofen and acetaminophen for fever management, there was no history of other medication.
Upon admission, physical examination revealed good general condition and hemodynamic stability, mildly dry mucous membranes, hemorrhagic erosion plaques extending from the lips to the tonsils with constant salivation (Fig. 1), bilateral nonexudative tarsal hyperemia with incipient ulceration (Fig. 2), one scrotal bullous lesion, six lesions scattered throughout the dorsal and ventral face of the penis, and one intersecting the penile meatus. Cardiopulmonary auscultation was normal, and he presented no peripheral edema, palpable lymphadenopathy or other organomegaly, or abnormal neurologic findings.

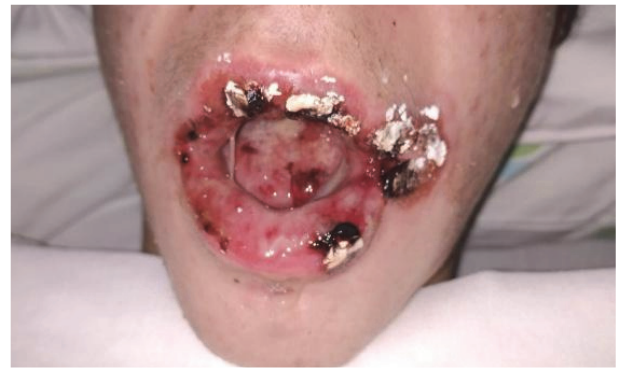

Figure 1. Hemorrhagic erosion plaques and crusting in the lips and oral cavity.

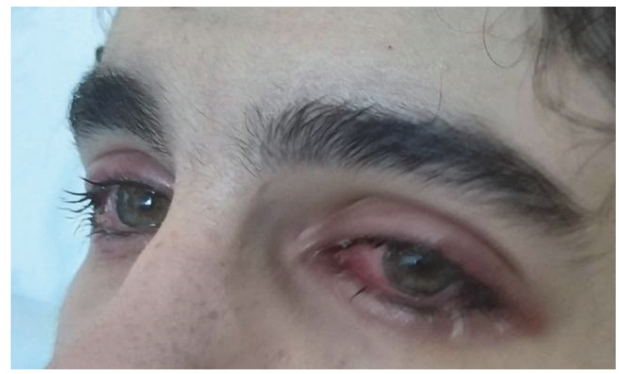

Figure 2. Bilateral nonexudative tarsal hyperemia.

Laboratory work-up results revealed mild leukocytosis (14 200 cells/µL) with neutrophilia (82.3%), normal platelet range, increased C-reactive protein (120 mg/L) and procalcitonin (2.05) ng/mL, elevated creatinine (1.2 mg/dL) with no ionic or acid-base imbalance, and normal liver enzymes values. Serologies for enterovirus, adenovirus, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, hepatitis C, B, and A virus, parvovirus B19, as well as herpes virus 1 and 2 showed no evidence of recent or ongoing infection. Immunoglobulin (Ig) M anti-mycoplasma results were negative (repeated once, 20 days apart), and the chest radiography was normal.

Mucosal erosions and mild superficial detachment were observed on fibroscopy, extending to the hypopharynx and epiglottis. After a multidisciplinary assessment (ophthalmology, otolaryngology, and dermatology), intravenous immune globulin was administered, targeting a possible Stevens-Johnson syndrome / toxic epidermal necrolysis disease spectrum. High fever and elevated inflammatory markers persisted after four days of therapy. At this point, and apart from a few new scattered bullous lesions with an erythematous halo sharing a preferable acral distribution (Fig. 3), physical examination remained unchanged, with no signs or symptoms referred to other systems. Polymerase chain reaction (PCR) for *Mycoplasma pneumoniae* of the pharyngeal swab (non-panel-based) turned out positive; therefore, prednisolone 60 mg/day and intravenous azithromycin 500 mg/day were administered, leading to the cessation of fever in less than 24 hours and the subsequent downward tendency of inflammatory markers values.

Cutaneous lesions were treated with topical dexamethasone and fusidic acid, and mucous membrane lesions with sucralfate. On day two of hospitalization, after the worsening of pain and oral lesions, oral feeding was provided through a nasogastric tube for eight days, in addition to intravenous fluids. Aminocaproic acid was initiated upon detecting abundant hemorrhagic oral secretions and was suspended after 12 days.

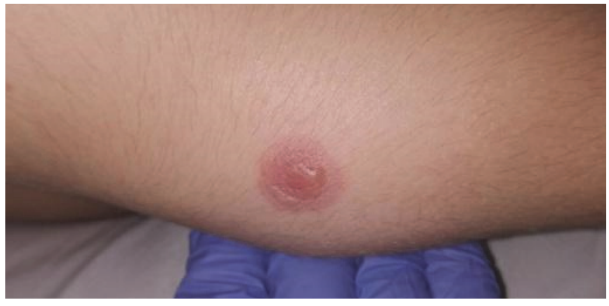

Figure 3. A bullous lesion with an erythematous halo in the posterior face of the right arm.

Progression of ocular lesions halted after ophthalmic oxytetracycline and frequent ocular lubrication, with no corneal ulceration or other sequelae.

Pain control was achieved with paracetamol and topical treatment. Psychological support was also provided due to feelings of sadness, restlessness, transient anhedonia, and loss of appetite, which may have contributed to a slow progression in oral intake and overall recovery.

The patient was discharged after 24 days of hospitalization, having completed five days of intravenous immune globulin, five days of intravenous azithromycin, and six days of corticotherapy. He also presented discrete and healing non-hemorrhagic mucocutaneous lesions. However, he was instructed to maintain sucralfate, ocular lubricant, as well as a combination of ophthalmic steroids and antibacterial. Adequate ambulatory multidisciplinary follow-up was warranted, and complete clinical remission was observed, with no ocular or other mucocutaneous long-term sequelae. Immunological studies revealed no abnormalities, such as leukogram, IgA, IgG, IgM, complement proteins C3 and C4, total complement activity CH50, antinuclear antibodies, and anti-double-stranded deoxyribonucleic acid (DNA). Two years after the above-described episode and one month after being discharged from the outpatient follow-up, he was evaluated for a single 5 mm ulcerated aphthous oral lesion and a few palatal vesicles. There was also eyelid erythema (blepharitis), without the involvement of any other eye structure, as confirmed by a complete ophthalmologic examination. There was no history of fever or other constitutional or respiratory symptoms, either previous or ongoing. Upon investigation, PCR for the herpes virus turned out positive, but serology was compatible with the previous infection. All lesions healed within a few days.

Discussion

Although *Mycoplasma pneumoniae* induced rash and mucositis has been recently recognized as an individualized entity, it is possible to draw a clear distinction between this condition and other mucocutaneous eruptions. It is clinically characterized by distinct lesion morphology with prominent mucositis and, when cutaneous involvement is present, a characteristic sparse vesiculobullous and/or targetoid eruption. A milder disease course is described in most cases, with exceedingly rare mortality and rare long-term sequelae. The following diagnostic criteria remain as a guiding reference for *Mycoplasma pneumoniae* induced rash and mucositis[1]:

- Skin detachment < 10% of body surface area;
- Suggestive lesions of at least two mucosal sites;
- Scattered atypical targets;
- Evidence of *Mycoplasma pneumoniae* infection.

All of the above-described clinical features are present in this case description.

A suggestive clinical context of *Mycoplasma pneumoniae* induced rash and mucositis should thus yield prompt investigation for *Mycoplasma pneumoniae* infection. Confirmatory laboratory tests should include PCR and the measurement of serum-specific IgM and IgG titers, granting that a positive result should be interpreted cautiously. Immunoglobulin M titers start to rise approximately one week after infection, peak between three to six weeks, and persist for months. On the other hand, IgG titers peak approximately two weeks after IgM titers and persist for years.[7] However, IgG mycoplasma is not performed at the hospital under study. Although serodiagnosis based on tests are a cornerstone for *Mycoplasma pneumoniae* diagnosis, they are frequently negative during the acute phase. Despite advances in specificity, the sensitivity of the different tests available, even the most recent ones, remains difficult to improve.[8] The use of convalescent sera might not be helpful in clinical settings because of the time delay that is inevitable when waiting for a titer to increase. Interpretation can also be compromised in immunocompromised patients, which adds to the importance of performing further immunological tests, which turned up normal in this case. As for PCR, albeit being a highly sensitive and specific method, it can remain positive for up to four months after infection.[9] Furthermore, the significant detection rate in asymptomatic children makes it impossible for PCR to differentiate between asymptomatic carriage and infection.[10] This adds to the importance of coupling PCR and serological testing to support this etiology and, most importantly, as shown in the present case, to interpret the results in light of the clinical picture, while taking into consideration the obstacles they present in terms of method, sensitivity, and titers kinetic.

Mycoplasma pneumoniae-specific IgM antibody-secreting cells, which are short-lived and associated with clinical disease, are building up evidence as a promising resource.[11] When and if readily available, they might significantly improve diagnostic accuracy soon.

There is no evidence-based treatment for *Mycoplasma pneumoniae* induced rash and mucositis. Although supportive care in hospital settings with multidisciplinary consultation and severity evaluation is fundamental, adjunctive therapies also play an essential role, sustained by case-documented favorable outcomes.[1] As for this case, antibiotic treatment was initiated with good results. However, simultaneous prescription of corticosteroids may have had an important contribution, making it impossible to determine the real effectiveness of each therapy individually. No high-powered studies have compared efficacy or other related indirect outcomes of treatments for *Mycoplasma pneumoniae* induced rash and mucositis. Both corticosteroids and antibiotics (macrolide, tetracycline, and fluoroquinolone) have been frequently used in these cases, although their applicability in possible clinical variations, such as the extent and site involvement (lung, genital, and ocular), is not yet established.[12] As for azithromycin, its anti-inflammatory properties may bring into question the antibiotic effect in what is thought of as a mainly immunologically-based pathophysiological process, although a trigger attenuation mechanism may take part.[13]

Although the risk of recurrence is low, this possibility should be discussed, and the patients should be instructed to seek medical care early on.[12]

It is fundamental to report cases of *Mycoplasma pneumoniae* induced rash and mucositis addressing its most controversial aspects to consolidate the knowledge gathered so far. In this effort, it is crucial to have more robust scientific evidence and consequently, define the most effective and case-tailored treatment options.

Author Contribuitions

MSA, ALC, AM, SC and AC participated in the study conception or design. MSA, ALC, AM, SC and AC participated in acquisition of data. MSA, ALC, AM, SC and AC participated in the analysis or interpretation of data. MSA, ALC, AM, SC and AC participated in the drafting of the manuscript. MSA, ALC, AM, SC and AC participated in the critical revision of the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this study.

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Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

Consent for publication

Consent for publication was obtained.

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Mucosite e Erupção Cutânea Induzidas por *Mycoplasma pneumoniae:* Um Dilema na Abordagem

Resumo:
A mucosite e exantema associado ao Mycoplasma pneumoniae é uma entidade clínica apenas recentemente reconhecida. A efetividade e utilidade das opções terapêuticas encontram-se ainda em estudo. Este caso pretende salientar as suas características clínicas e fornecer um testemunho de abordagem terapêutica.
Reporta-se o caso clínico de um adolescente de 15 anos previamente saudável, admitido com febre elevada e mucosite oral e ocular severa. Apresentava simultaneamente lesões bolhosas com halo eritematoso. O contexto epidemiológico era irrelevante. Os exames laboratoriais revelaram elevação marcada dos parâmetros inflamatórios. Paralelamente ao tratamento de suporte foi administrada imunoglobulina endovenosa, sem resposta clínica ou laboratorial. Após a investigação etiológica suportar infeção por Mycoplasma pneumoniae, iniciou-se azitromicina e corticoterapia sistémica, com posterior evolução favorável. Teve alta após 24 dias de internamento, sem sequelas. Perante a suspeita de exantema e mucosite associados a Mycoplasma pneumoniae, deve proceder-se a múltiplos testes confirmatórios, que devem ser interpretados cautelosamente. A abordagem terapêutica carece de evidência científica robusta, expondo a importância dos relatos de caso.

Palavras-Chave: Adolescente; Exantema/etiologia; Infecções por Mycoplasma/complicações; Infecções por Mycoplasma/diagnóstico; Infecções por Mycoplasma/tratamento farmacológico; Mucosite/etiologia; Mycoplasma pneumoniae