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RESEARCH LETTER

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Mycoplasma pneumoniae-associated mucocutaneous disease in children: A case series with allergy workup in a tertiary care paediatric hospital

To the Editor,

Mycoplasma pneumoniae (MP) infection is a common cause of community-acquired pneumonia in children sometimes associated with intriguing mucocutaneous manifestations variable in severity such as erythema multiforme (EM) or Stevens–Johnson syndrome (SJS).[1] Various papers attempted to distinguish the clinical features of MP-associated diseases, but the topic is still confusing, ending in conflicting classifications.[2–6] A systematic review suggested that they should be considered as distinct entities from the genuine drug-induced SJS, introducing the term '*Mycoplasma*-induced rash and mucositis' (MIRM).[7] Other authors used the expression '*Mycoplasma pneumoniae*-associated mucositis' (MPAM) to distinguish a variant with isolated mucosal involvement without rash.[8] Recently, MIRM have been included in a larger group called RIME (reactive infectious mucocutaneous eruption).[9]

Erythema multiforme is a cutaneous rash characterized by typical target lesions. Moreover, EM major (EMM) involves one or more mucous membrane, thus clinically resembling SJS or the more severe toxic epidermal necrolysis (TEN), where skin and mucosae are affected by vesicular and bullous eruption followed by erosions. EM is mainly related to viral infections, while SJS/TEN shows a different aetiology being mostly drug related, as an expression of type IV delayed hypersensitivity.

There are no studies in the literature investigating a hypersensitivity to the drugs administered in the course of a MP infection with mucocutaneous manifestations. The aim of the present study is to analyse the clinical features of a cohort of children with MP-associated mucocutaneous disease, by performing an allergy workup in order to define whether drugs could have an additional role in the pathogenesis of such diseases plus providing the clinicians with the tools for a correct and complete diagnosis. In fact, in these cases, a concomitant infection can be seldom found, so that cutaneous manifestations are the result of a complex interaction of factors.[10]

Ten children (Nine males and one female) with a cutaneous adverse reaction during a MP infection were retrospectively analysed at Meyer Children's Hospital, from April 2010 to January 2020.

At hospital admission according to the hospital ethic committee form, all the children's parents signed a written informed consent to the processing of clinical data for future research studies. Patients whose parents denied consent were excluded from the study.

All the 10 hospitalized patients suffered from pneumonia with a positive pharyngeal swab for MP detected by real-time polymerase chain reaction. Sex, age at the reaction, type of reaction, list of drugs administered, latency between drug exposure and onset of symptoms, time of resolution and treatment were all recorded.

Five out of 10 patients who had a concomitant drug therapy were referred to our Allergy Unit for further investigations.

In vivo tests (delayed intradermal tests – IDTs -, patch tests – PTs) and in vitro tests (lymphocyte transformation tests – LTT) were performed at least 6 weeks after the recovery and 4 weeks after corticosteroid (CS) cessation (Supporting Information).

Drug provocation test, considered the gold standard for diagnosis of hypersensitivity, was contraindicated in this kind of severe reaction, due to the risk of triggering again a potential similar clinical presentation.

Mean age was 10 years (range 3–13 years). Demographic and clinical characteristics of the study population are shown in Table 1. One patient suffered from two separate episodes of MIRM three years apart (#10a and b). All the children exhibited oral involvement; in 8/10 patients a second mucous membrane was involved, and in 2/10 all the three mucosae (mouth, eye and genitals) were affected. Skin manifestations were present in the majority of patients (7/10): in 5/10 as a cutaneous eruption with blisters or vesicles (resembling SJS), in 2/10 as EM-like with maculopapular exanthema (MPE) and purpuric lesions. Some pictures of our patients are shown in Figure 1A–E.

In Table 1, drugs possibly related to the adverse mucocutaneous event are also reported. β-Lactams (βLs) were used in five patients alone or together with other compounds. Macrolides were suspected in four children and interestingly enough in pt #10 MIRM recurred after being treated with two different molecules of this class. The mean interval between drug exposure and onset of symptoms was short (2.8 days) with a mean time of resolution of 15 days. The most frequent treatment was CS, isolated in 4/11 reactions, associated with IVIg in 4/11. Due to the severity of mucositis with feeding difficulty, three patients needed parenteral nutrition as supportive therapy.

Parronchi and Mori should be considered joint senior author.

TABLE 1 Clinical characteristics of patients and results of in vivo and in vitro tests of the allergy workup

Pt	Age (y)/sex	Clinical picture			Suspected drug	Time interval (d)	Treatment	Resolution time (d)	IDTs	PTs	LTT
		Respiratory symptoms	Mucosae	Skin							
#1	13/M	Symptoms: cough, fever, dyspnoea Chest X-ray: pneumonia O_2 therapy: yes Intubation/ventilation: no	**M** = mucositis, aphthae, blisters cheilitis of the lips **E** = conjunctivitis **G** = mucositis	Vesicular eruption (trunk and limbs)	AMX/CL	1	CS IVIg	16	NEG	NEG	NP
#2	13/F	Symptoms: cough, fever, dyspnoea Chest X-ray: pneumonia O_2 therapy: yes Intubation/ventilation: yes	**M** = gingivostomatitis, cheilitis **E** = conjunctivitis	Rash, blisters, vesicles	AMX/CL	1	IVIg PN	30			
#3	12/M	Symptoms: fever, dyspnoea Chest X-ray: pneumonia O_2 therapy: yes Intubation/ventilation: no	**M** = mucositis, blisters **E** = conjunctivitis	No involvement	CLR	6	CS	10			
#4	3/M	Symptoms: fever, dyspnoea Chest X-ray: pneumonia O_2 therapy: yes Intubation/ventilation: no	**M** = mucositis, erosions	MPE, purpuric lesions	AMP/SUL	2	CS AH	5	NEG	NEG	POS (AMP)
#5	5/M	Symptoms: cough, fever, dyspnoea Chest X-ray: pneumonia O_2 therapy: yes Intubation/ventilation: no	**M** = mucositis, blisters **G** = mucositis	Rash, blisters, vesicles	Paracetamol Ibuprofen AZM	5	CS IVIg	10	NP	NEG NEG NEG	NP
#6	11/M	Symptoms: cough, fever, dyspnoea Chest X-ray: pneumonia O_2 therapy: yes Intubation/ventilation: no	**M** = mucositis, blisters **E** = conjunctivitis	No involvement	AMX/CL Ibuprofen CLR	2	Analgesics PN	20			
#7	10/M	Symptoms: cough, fever, dyspnoea Chest X-ray: pneumonia O_2 therapy: yes Intubation/ventilation: yes	**M** = mucositis, erosions	Rash, blisters, papular exanthema	AMX/CL CTX	2	CS PN	22			
#8	11/M	Symptoms: fever, dyspnoea Chest X-ray: pneumonia O_2 therapy: yes Intubation/ventilation: no	**M** = mucositis, blisters cheilitis of the lips **E** = conjunctivitis **G** = mucositis	Rash, blisters, vesicles	Paracetamol	4	CS IVIg	21			
#9	11/M	Symptoms: Cough Chest X-ray: NP O_2 therapy: no Intubation/ventilation: no	**M** = mucositis, blisters cheilitis of the lips **E** = conjunctivitis	No involvement	Acetylcysteine Carbocysteine	1	Analgesics	10	NP	NEG NEG	NP

(Continues)

TABLE 1 (Continued)

Pt	Age (y)/sex	Clinical picture			Suspected drug	Time interval (d)	Treatment	Resolution time (d)	IDTs	PTs	LTT
		Respiratory symptoms	Mucosae	Skin							
#10/a	11/M	Symptoms: fever, dyspnoea Chest X-ray: pneumonia O_2 therapy: yes Intubation/ventilation: no	**M** = mucositis, aphthae **E** = conjunctivitis	MPE	CLR	1	CS IVIg	20	NEG	NEG	NP
#10/b	14	Symptoms: cough, fever, dyspnoea Chest X-ray: pneumonia O_2 therapy: yes Intubation/ventilation: no	**M** = mucositis, aphthae **E** = conjunctivitis	MPE	AZM	6	CS	2	NEG	NEG	NP

Note: Age (in years) and sex (M, male; F, female) of the 10 patients with pneumonia from Mycoplasma complicated by mucosal (M, mouth; E, eyes; G, genitals) and skin involvement. Patient #10 was affected twice (depicted as /a and /b). Time interval is the period (d, days) between the intake of the suspected drug(s) and the occurrence of mucocutaneous manifestations. The resolution time indicates the days (d) necessary to the complete recovery. Five out of the 10 patients with pneumonia from Mycoplasma complicated by mucosae and skin involvement were tested. Patient #10 was affected twice (depicted as /a and /b).

Abbreviations: AH, anti-histamines; AMP/SUL, ampicillin-sulbactam; AMX/CL, amoxicillin-clavulanic acid; AZM, azithromycin; CLR, clarithromycin; CS, systemic corticosteroids; CTX, ceftriaxone; IDTs, delayed intradermal test; IVIg, intravenous immunoglobulins; LTT, lymphocyte transformation test; MPE, maculopapular exanthema; NP, not performed;PN, parenteral nutrition; PTs, patch tests.

The results of allergy investigations of the 5/10 children evaluated are pictured in Table 1. IDTs were made in four cases with negative results. PTs with the suspected drugs have been done in all the patients resulting negative as well. In a single child reporting a history of ampicillin/sulbactam intake 2 days before MIRM onset, LTT to βLs was performed with positivity towards ampicillin.

The patient cohort described here highlights the variable clinical presentation of MP, even if oral involvement is constantly present in all our patients with classical mucositis, blisters, erosions or aphthae. The skin was also a target of the disease with highly different manifestations ranging from a simple rash to extensive MPE, bullous/vesicular lesions or even purpura. In the literature, the involvement of mucous membranes is reported as predominant in MP-associated SJS, while skin lesions would be more frequently represented in the classical SJS secondary to drug use.[4,5] On this respect, Amode et al.[2] described a large number of adults with EM after *M. pneumoniae* infection (MP-EM) compared to ordinary non-Mycoplasma-associated EM (non-MP-EM) with the finding that they profoundly differ, as multiple mucous membrane involvement was more common in the former while acrally distributed and typical target lesions prevailed in the latter. Similar conclusions were driven from a retrospective study by Olson et al.,[3] where MP-associated SJS led to oropharyngeal mucositis in all the children described, while skin manifestations were fewer and milder than in non-MP-associated SJS. On the contrary, skin lesions were described as predominant by other authors, with bullous lesions as most frequently occurring.[6] In a retrospective study by Langley et al, most of the children included exhibited EMM (14/22), with lower numbers showing EM (4/22) and only one a classical SJS.[4] However, in the same paper 'unspecified' lesions were also reported in 3/22 cases and the finding of a variate skin picture was also noticed by Meyer et al. in a paediatric case series of 10 MP-associated diseases with 5/10 classified as MPE, 3 as MIRM and 2 as urticaria.[1]

The gender male prevalence of our patients was in common with other studies.[2,3] The study of Amode[2] also analysed histopathological characteristics comparing biopsies of MP-ER and non-MP-ER and detecting a 'TEN-like pattern' in the 100% of the MP-ER, with confluent keratinocyte apoptosis to full-thickness epidermal necrosis and detachment.

Of note, in addition to the clinical observation, another point of strength of our study is represented by the address of the potential role of drugs in MIRM. Interestingly, none of the already published papers investigated concomitant drug hypersensitivity during MP infection as usually done in other mucocutaneous manifestations. In our cohort, only one-half of the patients underwent allergy evaluation, but showed negative in vivo tests, thus suggesting that symptoms may depend from the infection itself. However, negative IDTs and PTs cannot fully exclude drug hypersensitivity, due to their quite variable sensitivity, which is heavily determined by drug reaction phenotype (lower in these kinds of blistering/mucocutaneous diseases) and by the drug involved.

However, in one child (pt. #4) treated with ampicillin/sulbactam, circulating ampicillin-specific T lymphocytes could be demonstrated through the LTT. In this only case, we might speculate that the development of mucocutaneous manifestations could be related to T-cell

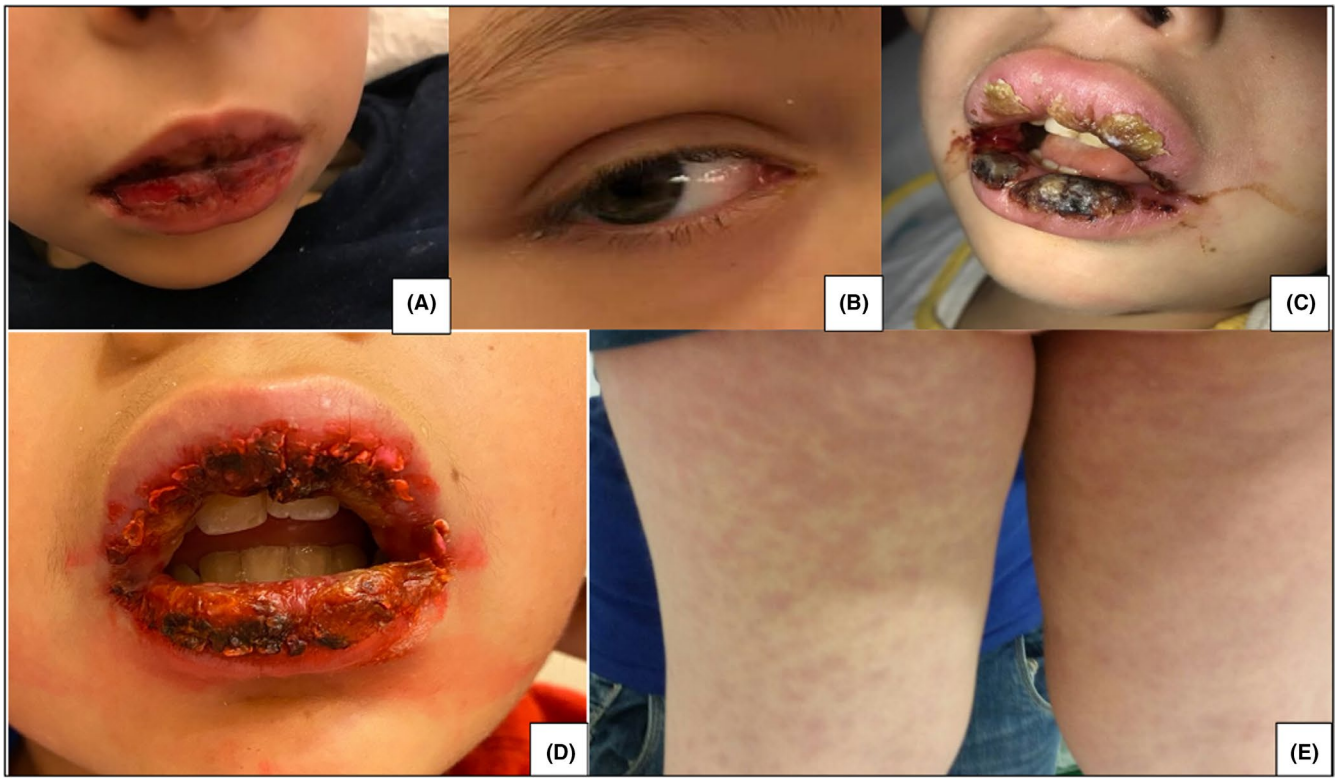

FIGURE 1 Selection of clinical photographs. A, Mucositis with erosions and haemorrhagic crustae. B, Non-purulent conjunctivitis, without corneal lesions. C and D, Mucositis with severe erosions ulcers, denudation and crusting. E, Faint pink morbilliform eruption on the legs of patient #5 at the onset of the clinical manifestation

sensitization towards ampicillin with MP acting as a cofactor. Indeed, it is known that other infections, prevalently of viral origin, characterized by rashes may correlate with hypersensitivity reactions with a still undisclosed cause-and-effect link.[11] Our patient with MP infection and drug hypersensitivity exhibited the involvement of a single mucous membrane (mouth) in addition to a morbilliform eruption closely resembling EM (MPE and purpuric lesions) instead of classic SJS generally associated with adverse drug reactions.

In general, our small number of patients included and the use of drugs not always suitable to be entirely assessed by in vivo or in vitro tests do represent the main limitations of our study. Another limitation could be the lack of skin biopsies and histological examinations.

In conclusion, MP is a common infectious agent in paediatric population and its extrapulmonary complications, and in particular mucocutaneous disease, must be known by paediatricians. The clinical spectrum is so variable that any classification is still controversial, and it is difficult to give a specific nomenclature shared and accepted by all clinicians.

In this study, the mean interval between drug exposure and the onset of clinical manifestations was short (2.8 days) ranging from 1 day to 6. Instead, for the type IV delayed hypersensitivity in SJS/TEN, the latency is typically longer, until several weeks. This point could help clinicians to address patients to allergy evaluation.

Skin biopsies could be a useful tool to differentiate a MP-ER from a non-MP-ER, but, to our knowledge, only a study deepening this aspect was performed.[2] Our experience is based on a limited number of children, and in 1 out of 10 (1/5 investigated), an association with a drug hypersensitivity was found. Thus, even if it does not seem to be mandatory sending to an allergy workup all these patients, it can still be useful to make an allergy evaluation as even a low % detection rate can help patients' management (since test specificity if often close to 100%) in order to give indication about avoiding drugs in the future.

However, more studies are needed to understand the role and the prominence of allergy investigations.

KEYWORDS

children, erythema multiforme, hypersensitivity drug reaction, lymphocyte transformation test, *Mycoplasma pneumoniae*, *Mycoplasma*-induced rash and mucositis, paediatrics, Stevens–Johnson syndrome

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

AUTHOR CONTRIBUTIONS

Liccioli G drafted the work, made substantial contributions to the conception of the work, the acquisition, analysis and interpretation of data. Filippeschi C and Oranges T made substantial contribution to acquisition of photographic documentation and dermatologic consulting. Giovannini M, Sarti L and Barni S, made substantial contribution to the acquisition, analysis and interpretation of data. Capone

M made substantial contribution in making allergy workup and laboratory tests. Parronchi P and Mori F made substantial contribution to the conception of the work, revised it critically for important intellectual content and gave final approval of the version to be published. All authors approved the final version of the manuscript as submitted and agreed to be 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.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.