Mycoplasma Pneumoniae–Induced Rash and Mucositis: A Longitudinal Perspective and Proposed Management Criteria

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• PURPOSE: **To evaluate the natural history and ophthalmologic morbidity of *Mycoplasma pneumoniae*–induced rash and mucositis (MIRM) and propose a treatment algorithm.**
• DESIGN: **Retrospective, interventional case series.**
• METHODS: **Retrospective chart review of all MIRM patients examined by the department of ophthalmology at a tertiary children's hospital. Diagnosis was established clinically concomitant with either positive *Mycoplasma pneumoniae* IgM or PCR testing from January 1, 2010, until December 31, 2019. The main outcome measures were best-corrected visual acuity, long-term ocular sequelae, and duration and type of ophthalmic intervention.**
• RESULTS: **There were 15 patients (10 male and 5 female) aged 10.9 ± 4.2 years who had primary episodes of MIRM; of those, 4 had multiple episodes. All patients required topical steroid treatment, 3 required amniotic membrane transplantation, and 1 patient underwent placement of a sutureless biologic corneal badage device. There were no patients who suffered visual loss, but 1 was left with mild symblephara near the lateral canthus in each eye and 2 others had scarring of the eyelid margins and blepharitis.**
• CONCLUSIONS: **The ocular morbidity is significantly less in MIRM than in other closely related syndromes such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. However, these patients still require close observation and a low threshold for intervention to avoid permanent ophthalmic sequelae and possible blindness. (Am J Ophthalmol 2020;219: 351–356. © 2020 Elsevier Inc. All rights reserved.)**

MYCOPLASMA PNEUMONIAE–INDUCED RASH AND mucositis (MIRM) is a relatively newly described entity. Although MIRM had been described in the literature prior to 2015, it was not until that year that Canavan and associates proposed it as a unique entity apart from both Stevens-Johnson syndrome (SJS) and erythema multiforme (EM).[1,2] Both SJS and EM are well known to cause significant ocular morbidity, blindness, and death.[3] MIRM is a similar disease process that seems to follow a less severe course and have less associated morbidity and mortality. *M. pneumoniae* is a well-known respiratory pathogen that causes "walking pneumonia" or a mild respiratory infection. In up to 25% of patients, however, there are extrapulmonary complications.[4] In terms of mucocutaneous involvement, this can present in numerous disparate phenotypes, from mucositis alone to mucositis with minimal skin involvement to more serious skin complications. Canavan and associates reviewed 95 articles and 202 cases of MIRM and found that there is a significant predilection for ophthalmic involvement, with 82% of patients exhibiting it. They did not go into further detail about ophthalmologic outcomes specifically, but they did note that long-term effects were uncommon. The overall mortality was only 3%, which is much less than SJS or EM.[1]

There is limited data about ophthalmic involvement and outcomes in MIRM. Shah and associates reported 1 case series of 5 patients who were seen over the course of 2 months at a tertiary children's hospital in the United States and concluded that ophthalmic involvement in this disease tended to be mild.[2] Given the paucity of data on the subject, we sought to better characterize ocular involvement in MIRM, its treatment, and long-term visual outcomes.

METHODS

THIS RETROSPECTIVE INTERVENTIONAL CASE SERIES WAS approved by the Institutional Review Board at Boston Children's Hospital and conformed to the requirements of the United States Health Insurance Portability and Accountability Act (HIPAA). The Institutional Review Board waived the need for informed consent. Patients were identified using ICD-9 and ICD-10 codes for mucositis and stomatitis and then were further narrowed by the requirement of having the concurrent diagnosis of a *M. pneumoniae* infection and at least 1 examination by the pediatric ophthalmology consult service. Patients were only included if they had either a positive *M. pneumoniae* IgM level or *M. pneumoniae* PCR. After the cohort of patients was identified, we collected data

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TABLE. Demographic and Illness Characteristics of the Initial and Recurrent Episodes of *Mycoplasma Pneumoniae*–Induced Rash and Mucositis

Characteristic	Number (SD)	Percentage
Patients	15	
Male	10	66.6
Female	5	33.3
Number of events	23	
Primary	15	
Primary events with ophthalmic involvement	13	87
Recurrence	8	
Recurrences with ophthalmic involvement	2	25.0
Age at diagnosis (years)	10.9 (4.2)	
Length of follow-up (months)	13.6 (15.7)	
Treatment type - ophthalmic		
Topical steroid/antibiotic	15	100
Topical cyclosporine	4	26.7
Amniotic membrane transplant	3	20.0
Prokera	1	6.7
Ocular symptoms		
Conjunctival injection/staining	15	100
Lid margin staining	13	87
Corneal involvement (superficial punctate keratitis)	2	14.3
Average time to resolution of symptoms (days)		
Conjunctival	12.1 (6.6)	
Corneal	15.5	
Ocular sequelae		
Lid margin thickening/scarring	1	6.7
Blepharitis	2	13.3
Symblephara	1	6.7
Patients with visual loss	0	

including patient demographics, length of admission, systemic treatment given, episode number, whether it was a recurrence, presence of ocular involvement, and ophthalmic treatments both medical and surgical. We also identified the duration of ophthalmic treatment, the final visual outcome, and any persistent ophthalmic complications. Procedural intervention was either with amniotic membrane transplantation (AmnioGraft; Bio-Tissue, Miami, Florida, USA) or placement of a Prokera Classic device (Bio-Tissue). We used our previously described technique for amniotic membrane transplantation.[5] Statistics were tabulated in Microsoft Excel (Microsoft Corp, Redmond, Washington, USA). Means and standard deviations were calculated for all continuous variables.

RESULTS

THERE WERE 15 PATIENTS (10 MALE AND 5 FEMALE) WHO HAD primary episodes of MIRM. Of those, 4 patients had 8 total recurrences ranging from 1 to 3 further episodes. The average time to recurrence was 1.7 years with a range from 0.25 years to 4.25 years after the most recent event. The average age of patients at their initial episode was 10.9 ± 4.2 years and the length of follow-up for patients with ophthalmic involvement averaged 13.6 ± 15.6 months, with a range from 0.5 to 50 months (Table). Of the 15 primary episodes, 11 were diagnosed with a positive M. *pneumoniae* IgM test, 2 were diagnosed with a positive M. *pneumoniae* PCR test, and 2 were positive for both. Thirteen of the 15 patients (87%) had ophthalmic involvement and 2 did not. In terms of symptoms on presentation, 10 complained of red eye, 4 had mucous discharge, 1 was asymptomatic, and 1 was transferred after being admitted to an outside hospital and there was no record of presenting symptoms. Of those 13 that had ophthalmic involvement, all had fluorescein staining of the lid margin that ranged from minimal to 80%-90%. Lid margin involvement was present on admission for 10 patients and developed within 1 day for the other 3

FIGURE 1. A. External photograph of a 12-year-old boy on the day of diagnosis with significant lid margin involvement, subconjunctival hemorrhage, and conjunctival staining. B. External photograph after bilateral amniotic membrane placement. C. External photograph 5 months after amniotic membrane transplant demonstrating only residual lid margin thickening and scarring.

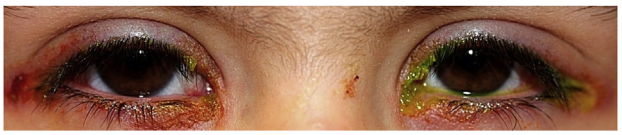

FIGURE 2. External photograph of a 4-year-old girl diagnosed with *Mycoplasma pneumoniae*–induced rash and mucositis on hospital day 2. She was treated with topical antibiotics and steroids and would go on to develop mild bilateral symblephara.

patients. Furthermore, all patients had staining and injection of the bulbar conjunctiva on admission. One patient had a pseudo-membrane removed. The conjunctival findings resolved over an average of 12.1 ± 6.6 days. Only 2 patients had evidence of corneal involvement and it was classified as mild superficial keratitis, which resolved on average over a course of 18 days. Of the 8 total recurrences, 2 had no testing sent, as it was the third and fourth occurrence of the disease and it was not felt to be clinically warranted. Only 2 of the 8 recurrences had ophthalmic involvement. Both patients were diagnosed based on high clinical suspicion. Neither of these patients had ophthalmic involvement on presentation but both developed it during the course of their admission. It took 1 day from admission for the development of conjunctival involvement in both patients. Only 1 of the 2 patients developed lid margin involvement and that occurred 3 days after admission.

Treatment of each patient varied depending on the clinical course. Most patients were managed medically with systemic medications and topical therapy. In terms of systemic treatment, 11 patients received a short (5- to 7-day) course of intravenous (IV) and/or oral steroids. Four of these patients also received a 3- to 4-dose course of IV immunoglobulins and 1 patient received IV immunoglobulins alone. Nine patients received systemic antibiotics (most commonly azithromycin, but doxycycline and levofloxacin were also used). All patients with ophthalmic involvement were started on a topical steroid and antibiotic, most commonly in the form of combination tobramycin and dexamethasone drops. This formulation is commonly used in the pediatric population, as it saves the need for administration of a second medication, which can be difficult in our patient population. Topical therapy averaged 28.6 ± 19.5 days with a range of 6-65 days.

Three episodes (2 primary and 1 recurrent) required bilateral amniotic membrane transplant using AmnioGraft (Bio-Tissue) and 1 primary episode required bilateral Prokera Classic device (Bio-Tissue) placement for worsening conjunctival involvement in the setting of both topical and systemic treatment (Figure 1). The conjunctival examination was felt to be worsening in each of these 4 cases despite topical therapy, and there was concern for permanent sequelae. The average time to procedural intervention was 5.75 (range, 5-6) days from symptom onset and 3.5 (range, 1-5) days from admission. In the 3 episodes that were treated with bilateral amniotic membrane transplant, there was no lid margin involvement at initial presentation. In all 3 episodes, progressive lid margin involvement developed over 48 hours despite topical and systemic therapy. The rapid progression despite medical therapy led to the decision to intervene surgically. The decision was made to use the Prokera device in 1 patient because he had more severe involvement of the palpebral and bulbar conjunctiva, rather than the lid margin, that progressed despite topical therapy over 48 hours. Given that the Prokera device was thought to provide sufficient coverage of the conjunctival areas of concern and the fact that amniotic membrane transplant in children requires placement in the operating room under general anesthesia, it was decided that placement of bilateral Prokera devices at the bedside was in the best interest of the patient.

In terms of ophthalmic sequelae, only 1 patient, who had not been treated with amniotic membrane transplantation, developed bilateral symblephara near the lateral canthi (Figure 2). These were considered very mild. Other ophthalmic complications included 1 patient with scarring/thickening of the lid margins and blepharitis and 1 other with blepharitis thought to be secondary to inflammation. Both patients who developed lid margin thickening and blepharitis had been treated with amniotic membrane transplantation. One of these patients actually had a recurrence 6.5 years after the initial episode that required amniotic membrane transplantation as well. No patients had corneal sequelae. Final visual outcomes were excellent, with best-corrected visual acuity remaining at 20/20 for all patients.

No patients required long-term immune suppression and only 1 developed systemic sequelae, which consisted of stenosis of his urethral meatus that led to urinary retention, requiring placement of a suprapubic catheter. One patient developed a transient intraocular pressure elevation in response to topical steroid use. The maximum intraocular pressure measured by iCare (iCare USA, Raleigh, North Carolina, USA) tonometry was 28 mm Hg in the right eye and 32 mm Hg in the left eye. The elevation required the use of timolol 0.5% for 21 days as the patient was tapered off of topical steroids.

DISCUSSION

MYCOPLASMA PNEUMONIAE–INDUCED RASH AND MUCOSITIS is a disease entity that has had a significant increase in the number of patients diagnosed with it since 2015. As mentioned earlier, it is on the same disease spectrum as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN). SJS and TEN have significant risk of ocular morbidity, as well as overall mortality.[5] These disease processes can lead to damage of the eyelid margin, cicatricial changes to the eyelid itself, permanent corneal damage, and blindness if not treated appropriately.[5] In SJS, it has been shown that in addition to damage sustained in the acute phase, chronic sequelae related to limbal stem cell deficiency can cause late progression from ocular surface failure.[6] More recent studies have demonstrated that an established protocol for the treatment of SJS and TEN that includes aggressive use of amniotic membrane transplant led to significantly better visual outcomes and lower acute and chronic ocular complications.[5]

Given the grave visual consequences of SJS and TEN, it is important to consider how MIRM impacts the eye and how ophthalmologists should be involved in the care of these patients. As mentioned earlier, MIRM was not considered a separate disease entity until 2015, when Canavan and associates performed a meta-analysis of all cases that had been published in the literature up to that point. As with our study, their patients were at the precipice of their teenage years (average age 10.9) and predominately male (66%).[1] Furthermore, they noted ocular involvement in 82% (similar to the 87% of our patients) of patients and a mortality of 3%.[1] Canavan and associates did not provide an in-depth overview of what the ocular and visual sequelae of this new disease entity were. They did note that systemically it seemed to be separate from EM, SJS, and TEN in that it is predominantly a disease of the mucous membranes with less skin involvement, morbidity, and mortality. They also noted infrequent recurrence, which was different from our study, as 4 out of 15 patients had recurrent episodes.[1] Ocular involvement occurred less often in recurrent episodes (25%), though 1 of these episodes was severe enough to require amniotic membrane transplant.

Some papers that have commented on ophthalmic involvement in *M. pneumoniae* related EM, SJS, and TEN merely remarked that it occurred, without further details being included.[7,8] Wetter and Camilleri examined 27 patients with SJS and found 6 to be secondary to *M. pneumoniae*. All 6 of those patients had ocular involvement, but the extent was not described.[9] Kunimi and associates evaluated SJS secondary to *M. pneumoniae* in Japan and they noted that chronic ocular complications occurred in 50% of patients older than 20 and in only 3.7% of patients under 20, but they did not describe in detail what the complications were, how they developed, or what the treatment course was.[10] Stevens and associates described 4 cases of SJS secondary to *M. pneumoniae* and remarked that 1 patient "was left with a severe conjunctival shrinkage syndrome which required a mucous membrane graft."[11]

To our knowledge, Shah and associates have provided the only description of this disease state in the ophthalmic literature as they reported on 5 patients that were seen at a tertiary children's hospital over a 2-month period in 2018.[2] The report included 4 male and 1 female patients with an average age of 11.9 years. They described that all patients developed an acute conjunctivitis with 1 developing conjunctival pseudo-membranes, 2 developing conjunctival epithelial defects, and 3 having lid margin hyperemia. They noted that only 1 patient developed eyelid margin scarring and recommended expeditious treatment with topical steroids and antibiotics. Unlike the current study, none of the patients progressed after the start of aggressive topical therapy and none required amniotic membrane transplant or use of a Prokera device.[2]

The current study adds significantly to the sparse literature that exists surrounding the ophthalmic involvement and morbidity in MIRM. Similar to Shah and associates' study and in contrast to EM, SJS and TEN patients, only 2 of our patients had corneal involvement and it was found to be very mild.[2,12,13] However, the presence of lid margin scarring and symblephara in some of these patients points toward there being a risk for cicatricial conjunctivitis and ocular surface damage, which is a known cause of blindness from the studies of pediatric SJS. We found that there was significant lid margin involvement and scarring in some patients and 3 patients required either amniotic membrane transplantation or Prokera device placement early in the course of their disease. One patient required a second amniotic membrane transplant for a recurrence that happened 6.5 years after the initial event. Even with early treatment, 2 of these 3 patients still developed lid margin scarring and the outcome could have been worse. One patient who did develop a symblephara, albeit mild, was not treated with amniotic membrane grafting. Therefore, we propose that these patients should be followed closely upon initial diagnosis and treated aggressively.

We propose following a modified version of the treatment algorithm for SJS that was outlined in Shanbhag and associates[5] and using the ophthalmic grading criteria proposed by Gregory.[14] For patients without any or with mild ocular involvement, we recommend lubrication, as there can be disease progression and development of ocular involvement after the initial examination. We feel that ocular lubrication is a fairly benign intervention and early intervention may help decrease disease progression and the need for stronger ocular medications. For patients with moderate disease (less than one third of the lid margin staining, conjunctival staining but no corneal involvement), we recommend proceeding with lubrication as well as antibiotic and steroid drops 4 times per day and with steroid ointment at least at bedtime. We tend to prefer tobramycin 0.3% and dexamethasone 0.1% combination drops, as they are better tolerated in the pediatric population givenfewer administrations. For patients with severe (either more than one third of the lid margin on 1 or more lids, a corneal epithelial defect, or greater than 1 centimeter of staining on the conjunctiva) and extremely severe (either more than one third of the lid margin on more than 1 lid, a corneal epithelial defect, or multiple instances of >1 cm of staining on the conjunctiva) disease, we recommend the above medical therapy and very close follow-up for the possibility of amniotic membrane transplant or Prokera device. Unlike the treatment algorithm outlined by Gregory, we do not recommend immediate amniotic membrane transplant unless there has been progression, as MIRM is a different disease than SJS or TEN and the progression of disease tends to be slower. If there is evidence of progression in terms of lid margin involvement after 24 hours of therapy, we advocate for the consideration of amniotic membrane therapy and preparation for intervention within 24 hours of that point if progression continues.

There are some limitations with this current study. Firstly, it is a retrospective review and is dependent on records and documentation dating back 12 years in some cases. Secondly, MIRM has been more frequently diagnosed in recent years owing to increased knowledge of the condition and therefore more cases were seen in the last 5 years than in the 5 years preceding it. This likely has meant that some previous cases were diagnosed as EM, SJS, and TEN rather than MIRM and were not included in our analysis.

Although MIRM is a fairly recently recognized disease, it is being recognized with increased frequency as a cause of mucositis. It is on the same spectrum as SJS and TEN, but systemically it is far milder. Though there is growing literature on the systemic findings, there is a paucity of information on ocular symptoms, sequelae, and treatment. In this study, we present the largest collection of patients formally diagnosed with MIRM and the ocular course of their disease. Although the systemic and ocular morbidity and mortality are lower in this condition than in its counterparts, we would argue that these patients still require close ophthalmologic observation and monitoring. Though there were no patients in our study that suffered vision loss, 2 patients required amniotic membrane transplantation and a third required Prokera device placement in the setting of progressive disease while on topical therapy. One patient who did not receive as aggressive treatment developed mild symblephara. Thus, the potential for serious ocular morbidity remains present with this condition and vigilance is required. We feel that aggressive treatment and close observation contributed to the excellent visual outcomes in our patients.

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