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APPROACH TO DIAGNOSIS AND MANAGEMENT OF REACTIVE INFECTIOUS MUCOSAL ERUPTION (RIME)

Background

Mycoplasma pneumoniae (MP) induced rash and mucositis (MIRM), also known as reactive infectious mucosal eruption (RIME), was first described as a distinct entity in 2015.[1] This condition has historically been under the diagnostic umbrella of erythema multiforme, and within the spectrum of Steven's Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). RIME/MIRM is, however, a separate entity with distinct clinical features requiring a specific approach to providing accurate diagnosis, treatment and optimize patient outcomes.

Mycoplasma pneumoniae is a bacterial infection that is a common cause of community acquired pneumonia in children over 5 years of age and adolescents.[2,3] In addition to respiratory findings, MP is also known to have a number of extra-pulmonary manifestations and has been identified as a cause of significant mucositis and cutaneous rash in the pediatric population and less commonly in adults.[4] Other infectious triggers have also been identified in cases of RIME and include *Chlamydophila pneumonia*, Influenza B, and a number of other respiratory viruses.

Clinical Presentation

A systematic review by Canavan et al. (2015) noted the average age of patients presenting with RIME/MIRM was 11.9 +/- 8.8 years and the majority were male (66%). As well, prodromal symptoms such as cough, fever and malaise were seen in almost all patients and typically presented one week before the onset of the cutaneous eruption.[1] Mucosal involvement is seen in almost all patients with suspected RIME/MIRM. The oral mucosa is most often involved (94% of patients), followed by the ocular mucosa (82% of patients), and urogenital mucosa (63% of patients).[1] Oral mucosal lesions include erosions, ulcers, vesiculobullous lesions and erosive sloughing of the entire buccal mucosa. Ocular lesions were found to include purulent bilateral

conjunctivitis, photophobia and eyelid edema. The urogenital mucosa was noted to include lesions that were vesiculobullous as well as erosions and ulcerations of the meatus, penile shaft, scrotum, vulva and vagina.[1]

Skin lesions in RIME/MIRM patients are polymorphic. In the review by Canavan et al., the authors found that vesiculobullous lesions were most frequently seen (77% of patients), followed by targetoid lesions (48% of patients), papules (14% of patients), macules (12% of patients) and a morbilliform eruption (9% of patients).[1] In contrast to those presenting with SJS, cutaneous lesions in RIME/MIRM are generally sparser with only a few scattered lesions. The most common distribution was acral (46% of cases), followed by generalized (31% of cases) and truncal (23% of cases).[1] This is another differentiating feature from SJS. Typically, SJS skin lesions will begin centrally on the trunk and spread distally with progression of the disease.

Diagnosis of RIME/MIRM

Clinical suspicion for RIME/MIRM should be high in pediatric patients presenting with a prodrome of cough, fever and malaise along with mucosal erosions and ulcerations and sparse acral skin lesions. Depending on clinical presentation, baseline blood work may be indicated. This could include routine blood tests (such as complete blood count, liver and renal function and inflammatory markers such as ESR or CRP) but other tests may be required depending on clinical presentation and therapeutic considerations.[4] Nasopharyngeal or oropharyngeal swabs for *Mycoplasma pneumoniae, Chlamydophila pneumoniae* and respiratory viruses should be performed. Polymerase chain reaction (PCR) testing is generally preferred for these swabs given the rapid turnaround time as well as the test's high sensitivity and specificity.[4] Consideration can be given to a chest x-ray as well but radiographic findings of *Mycoplasma pneumoniae* infection can be variable and can resemble findings seen in children with other viral respiratory infections. Focal reticulonodular opacities confined to one lobe is typically the most common finding in *Mycoplasma* pneumonia.[5] Punch biopsy of the skin can be performed to help rule out other conditions that may be on the differential diagnosis such as pemphigus vulgaris, but histologic findings in MIRM/RIME would be similar to SJS and TEN and would most likely not aide in differentiating between drug or infectious triggered epidermal necrolysis.

Diagnosis of RIME
Consider RIME in patients with cough, fever, malaise and erosive mucosal disease with sparse cutaneous involvement
Oral mucosa is most often involved followed by ocular and genital mucosa, respectively
Lesion morphology and absence of medication exposure helps differentiate from erythema multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis

Management of RIME/MIRM

Given the extent of mucosal involvement, many patients with RIME/MIRM require admission for pain management and nutritional support, in addition to treatments directed at the underlying condition. A recent review by Dr. Michele Ramien contains a comprehensive approach to managing patients with RIME/MIRM and includes a broad overview containing the following recommendations listed below.[4]

Upon diagnosis of RIME/MIRM, patients should be assessed as to whether they require admission to hospital. Generally, these patients can be managed on a pediatric medical unit but may need contact and droplet precautions if *Mycoplasma pneumoniae* is suspected. These patients should receive supportive care including a bland, soft food diet along with pain control, which may include acetaminophen, NSAIDs and occasionally opioids. Cases with significant mucosal involvement should also be consulted to appropriate services such as ophthalmology, urology or gynecology to avoid potential long-term complications such as mucosal synechiae.[1]

Workup of RIME
Test for respiratory infections including *Mycoplasma pneumoniae* in patients with suspected RIME
PCR testing is preferred given rapid turn-around and high sensitivity and specificity
Consider chest x-ray in patients with suspected *Mycoplasma pneumoniae* infection

Medical therapies aimed at treating mucosal lesions may include "magic mouthwash" (a compounded rinse with ingredients such as analgesics, anti-inflammatories and antimicrobials), chlorhexidine rinses or topical corticosteroids such as clobetasol for oral and urogenital lesions. In patients with ocular involvement, topical therapies such as artificial tears, dexamethasone or antimicrobial eyedrops (such as moxifloxacin) can be initiated.[4]

Therapies directed at the infectious trigger, typically *Mycoplasma pneumoniae*, should also be initiated promptly if there is suspicion of underlying infection. First line treatment for MP includes macrolide antibiotics such as azithromycin. Other possible antimicrobial options include tetracyclines or fluroquinolones. Doxycycline is typically avoided in patients less than 8 years of age due to the potential for tooth discoloration, but this is considered to be a low-risk adverse event with short-term use.[6] Typical treatment duration varies by antibiotic but is usually 5 days for azithromycin, with usual dosing, and 7-10 days for alternatives.

There are currently no guidelines regarding treatment of active RIME/MIRM as there have been few studies published on optimal management of this condition. Treatment has historically been similar to the treatment of SJS/TEN. Therapies that have been used include systemic corticosteroids, intravenous immunoglobulin (IVIG), cyclosporine and anti-TNF biologic agents such as etanercept or infliximab. According to previous studies, systemic corticosteroids have been used in approximately 31% of cases and IVIG in 9% of cases.[1,7] Corticosteroids have been shown to not only treat the inflammation associated with RIME/MIRM, but also to provide benefit at treating the underlying pneumonia.[8] A case series by Li et al. (2019) showed that early initiation of cyclosporine may reduce duration of hospital admission to 5-7 days compared to approximately 14 days in patients treated with systemic corticosteroids and IVIG. Dosing of cyclosporine in these cases was 3-5mg/kg/day and was given on average for 7-10 days in total.[4,9]

Treatment of RIME
Many patients with RIME require admission for pain control and nutritional support
Treat for *Mycoplasma pneumoniae* if there is suspicion of underlying infection
Corticosteroids, cyclosporine, IVIG, and anti-TNFα agents have been used to treat RIME with variable success

Prognosis of RIME/MIRM

In general, most patients recover completely with no long-term sequelae.[1] Recurrences of RIME/MIRM are infrequent but are estimated to occur in 8-38% of cases.[1,10] A recent publication by Liakos et al. noted that recurrences of RIME/MIRM tended to be less severe with regards to both skin and mucosal findings, which corresponded to lower rate of admission to hospital or shorter duration of hospital stay.[10] Ocular mucosal synechiae and mucocutaneous dyschromia are the most commonly observed complication. Severe complications, similar to those seen in SJS/TEN, are very rare. As well, in contrast to SJS/TEN, mortality is much lower and estimated at 3%, but these numbers may be an overestimate as this was observed in studies published prior to widespread use of antibiotics for *Mycoplasma pneumoniae*.[1]

Conclusion

Reactive infectious mucosal eruption in the pediatric population is characterized by a prodrome of cough, fever and malaise followed by erosive mucosal disease and polymorphic cutaneous lesions. Mucosal involvement can be severe and hospitalization is frequently needed for nutritional support and pain control. Patients should be screened for *Mycoplasma pneumoniae* infection by PCR testing of nasopharyngeal or oropharyngeal swabs, and therapies directed at mucosal and skin care should be initiated. In some cases, systemic medications such as cyclosporine, corticosteroids or IVIG can be used. Specifically, cyclosporine has shown promising results at reducing duration of disease and length of admission in hospital.

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