A UNIQUE PRESENTATION OF REACTIVE INFECTIOUS MUCOCUTANEOUS ERUPTION (RIME) AND THE IMPORTANCE OF ACUTE DIAGNOSIS

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Keywords Mucous membranes, respiratory tract infections, children.

Abbreviation **RIME** = reactive infectious mucocutaneous eruption.

Case report. A young adolescent male presented to his rural community primary care office with five days of cough, congestion, myalgias, fevers and chills. He was otherwise healthy, with no relevant past medical history. Earlier in life, his gestational course and delivery were uncomplicated. The patient was up to date with all age-appropriate vaccines. He regularly met developmental milestones and was not diagnosed with any childhood illnesses or chronic conditions. There were no prescribed medications, and he was only taking an over-the-counter multivitamin supplement daily. His past surgical history included a remote craniosynostosis repair but was otherwise unremarkable. He did not have any known allergies to medications, food, or the environment. The patient had no recent travel. During a private and confidential interview, he denied a history of sexual intercourse or abuse. The patient resided in a single-family home in a rural community with his parents and siblings. Regarding sick contact exposure, one sibling tested positive for strep pharyngitis the same day that the patient presented to his primary care clinic.

On exam, his vital signs were notable for a tachycardic heart rate of 121 bpm, but were otherwise within normal limits including an afebrile body temperature. At this visit his exam was negative for cutaneous or mucocutaneous lesions, he displayed no tonsillar swelling, non-erythematous tympanic membranes, and clear breath sounds bilaterally.

The patient had negative rapid antigen detection tests for streptococcus, COVID-19, and influenza. However, with his sick contact at home and upper respiratory symptoms, it was decided to empirically treat the patient with a five-day course of oral amoxicillin for a potential strep pharyngitis infection from exposure.

Two days following the initiation of treatment, the patient developed a mucocutaneous eruption of the oral cavity and subsequent poor oral intake of food and liquids due to pain. He returned to his primary care clinic with his parent. His repeat oropharyngeal exam documented a moist, erythematous oropharynx with haemorrhagic bullae and skin sloughing of the buccal and labial epithelium, as well as mildly edematous nasal turbinates. The patient immediately discontinued amoxicillin. At that point, he was believed to have had 4 to 5 doses of amoxicillin. He was discharged home with a combined anaesthetic, antihistamine, and corticosteroid mouth rinse.

The next day, the patient presented to the emergency department for continued poor oral intake due to pain, in addition to a persistent sore throat, cough, and worsening mouth sores. His vital signs were notable for a heart rate of 131 bpm, but vital signs were otherwise within normal limits. On physical exam, marked stomatitis was noted throughout the intraoral cavity and along the soft palate, worsened from previously described. His repeat lung examination was unremarkable. At that time, he received 1 liter of intravenous normal saline and appropriate weight-based dosing of 500 milligrams of intravenous azithromycin. The emergency room physician at that time favored a viral stomatitis, but also

identified RIME as a differential diagnosis for the first time. His tachycardia resolved and he was discharged home with instructions to continue azithromycin and the compounded analgesic mouthwash.

At a follow-up appointment with his primary care physician three days later, the patient was found to have new hemoptysis and dysuria, and his mother reported continued fevers at home. His heart rate at this visit was again tachycardic at 131 bpm, and his temperature was 37.6 °C. He was dehydrated and ill-appearing at this time. His exam noted worsening orolabial sores and new conjunctival injection (Fig. 1) with thick, clear teary discharge and lid edema. On examination of the oropharynx, there was dry appearing mucosa with multiple crusted, hemorrhagic erosions and ulcerations of the lips, buccal mucosa, and tongue, and hard palate petechia (Fig. 2). A genitourinary exam revealed penile ulcerative erosions at the urethral meatus. His pulmonary exam was again unremarkable. Due to his progressively worsening condition, he was directly admitted to his local rural hospital.

Upon admission, the patient denied any history of sexual intercourse or abuse, and there were no further psychosocial concerns noted. There was no evidence of a cutaneous skin rash, and all other systems examinations were unremarkable. Given the severity of the triple-site mucocutaneous eruptions (oral cavity, eyes, and genitals), and growing concern for dermatologic emergency, the patient was promptly transferred to a pediatric tertiary care center.

Initial urinalysis markers, including ketonuria and an increased specific gravity, were present and consistent with physical examination findings of dehydration. Urinalysis was also positive for bilirubinemia and hematuria, which were considered to be contamination from his penile sores. Dehydration was also supported by markers on the comprehensive metabolic panel, which demonstrated an elevated BUN/Creatinine ratio of 33 (normal high = 28). All other findings within the metabolic panel were within normal limits. Urinalysis and the comprehensive metabolic panel were used to help direct immediate management with fluid resuscitation in the hospital. A complete blood count demonstrated elevated neutrophil and monocyte counts as well as an increased mean corpuscular hemoglobin, but was otherwise within normal limits, notably with a normal leukocyte count. A C-reactive protein level was also elevated at 58.4 mg/L (normal high 4.9). Based on these findings, an infectious component of the patient's presentation continued to be considered, though an infectious organism was not yet identified. Urine gonorrhea and chlamydia PCR testing was negative.

To evaluate for infectious agents, a respiratory pathogen panel, expanded respiratory viral panel (including parainfluenzas, human metapneumovirus, adenoviruses, and rhinoviruses), peripheral blood smear, and reticulocyte panel were conducted. However, all results came back negative or normal. A chest x-ray was also completed, which showed no abnormalities. Blood and urine cultures were negative throughout the patient's admission and at 30 days following his discharge. He had negative HIV and hepatitis C testing, as well as a negative RPR study.

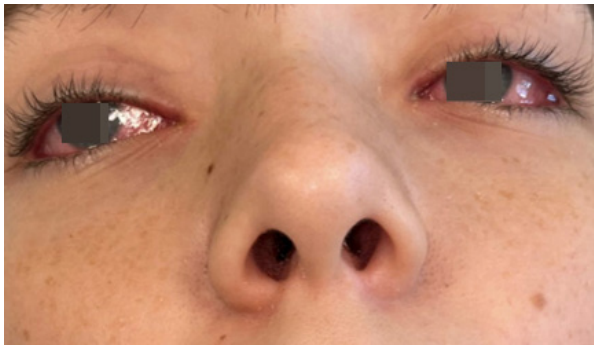

Fig. 1

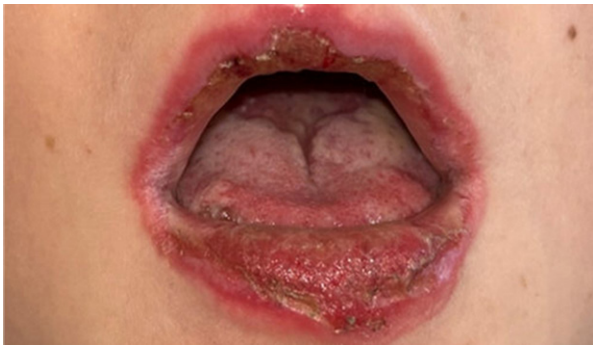

Fig. 2

Fig. 1, 2: Reactive infectious mucocutaneous eruption (RIME). Involvement of the conjunctival (Fig. 1) and oral (Fig. 2) mucosa.

Based on the mucocutaneous eruption with a recent history of antibiotic administration, the differential diagnoses considered for the patient included SJS, DIN, and TEN; however, the lack of cutaneous involvement upon initial presentation or throughout the patient's hospitalization made these diagnoses less likely. Though amoxicillin has been associated with DIN and TEN, it is not a high risk medication, and the patient's symptomatic timeline does not align with the typical course. Kawasaki disease was also considered, though ruled out, also due to the absence of cutaneous findings or extremity edema. Other diagnoses considered, which could present similarly, were MIRM (*Mycoplasma pneumoniae*-Induced Rash and Mucositis) and disseminated gonorrhoea. However, the lack of evidence for either causative agent made these less likely throughout the patient's workup and social history. Viral causes of stomatitis, including Herpes simplex virus, Coxsackie virus, and Varicella-Zoster virus, were initially considered. However, the extent and character of the mucocutaneous involvement did not support these viral causes. The lesions were not vesicular or crusted, but rather ulcerative and bullous in nature. Based on the absence of a cutaneous rash, the lack of known allergies, the preceding coryzal symptoms, and the patient's age group, a final diagnosis of reactive infectious mucocutaneous eruption (RIME) was made.

The patient's treatment was predominantly supportive throughout his outpatient course and hospitalization. Due to evidence of significant dehydration and pain with oral intake, immediate fluid resuscitation with crystalloid solution was initiated upon admission. Adjunctive supportive therapy, such as appropriate pain management with weight-based acetaminophen and ibuprofen dosing, was also used to help with patient comfort.

Ophthalmology was consulted to aid in management of patient's ocular findings and sequelae. This treatment included moxifloxacin ophthalmic drops 0.5% in both eyes every 6 hours, dexamethasone ophthalmic drops 0.1% in both eyes every 6 hours, cyclosporine 0.05% ophthalmic drops in both eyes every 12 hours, tobramycin-dexamethasone ophthalmic ointment in both eyes and eyelid margins every 6 hours, and artificial tears as needed. A dermatology consult was placed to help in management of the mucosal ulcerations, which included dexamethasone oral swish-and-spit solution up to 3 times per day as needed and petrolatum-based ointment to oral and penile lesions as often as desired. These treatment measures continued throughout hospitalization and in the outpatient setting after discharge.

The patient followed up with his primary care physician two days after being discharged from the hospital. He was feeling improved overall, and his mucocutaneous ulcerations were found to be significantly improving. He continued to have dysuria related to urethral meatus ulcerations. He also had pain around the lateral commissures of his lips. He was compliant with his medications at home and continued to apply petrolatum-based ointment to the lesions as directed. His conjunctivitis was noted to have significantly improved following the initial few doses of ophthalmic drops. The patient's vital signs were all within normal limits at this time. After the initial hospital follow-up, he was scheduled for routine well-child visits with his primary care provider and frequent follow-up visits with ophthalmology, starting a few days after discharge.

On follow-up with ophthalmology, he was found to have new bilateral conjunctival epithelial defects. Medical contact lenses, composed of cryopreserved amniotic membrane, were applied for further healing and protection of the corneas. Four days later, he followed up at the eye clinic, the amniotic membrane lenses were removed, and slit lamp examination revealed great improvement in the corneas and conjunctivae. He was seen in the eye clinic frequently over the following 2 months. As the steroid eye drops were tapered, he developed a return of conjunctival injection, so the steroid taper was prolonged. At 5 months post-discharge, the steroid eye drops were able to be weaned completely. At the patient's 6-month follow-up he reported no worsening symptoms and only had dry eyes after prolonged outdoor exposure or swimming. He was able to return fully to activities and school. At this time, he continues to use artificial tears for these symptoms as needed, and reported no further concerns or developments.

Discussion. Upon conducting a literature review, our group was unable to find any previously documented cases of RIME related to antibiotic administration in the absence of an identified microbial or viral infection that also did not meet the diagnostic criteria of drug induced necrolysis. There was also a lack of clarity on the timeline for symptom development and presentation. The most common etiology of this diagnosis is associated with either bacterial or viral etiologies, particularly *M. pneumoniae*. In those diagnosed with MIRM, absent to sparse cutaneous involvement with severe mucositis is used as a differentiating factor from Stevens-Johnson syndrome – SJS – and toxic epidermal necrolysis – TEN – in a pediatric population (3). MIRM and RIME diagnoses also tend to predominate in the pediatric age group compared to SJS and TEN, as mentioned above. Recognizing the differences among these conditions is particularly important when establishing a definitive diagnosis, especially considering the timeline for illness progression in the instance of SJS or TEN vs RIME and MIRM.

To assist clinicians in achieving diagnostic accuracy and establishing diagnostic guidelines for RIME, it may be necessary to highlight a broader range of possible triggers of the disease when a comprehensive infectious workup is negative and the patient meets other diagnostic criteria. While an organism is within the clinical window of being identified, clinicians can quickly act to isolate the organism for management efforts. In cases like ours, that lack a clear infectious etiology but present most consistent with a reactive, infectious mucocutaneous eruption, the lack of an identified infectious source can be confusing for patients and clinicians. Alternatively, if the infectious source was not identified, understanding the timeline for disease progression would support easier acute diagnosis of the condition and allow for more immediate directed therapy.

Given the patient's predominantly ophthalmic complications long term, a review of ocular involvement in the setting of RIME was also conducted. In the setting of MIRM, subsequent ocular pathology has been better documented compared to RIME; yet, it is still scarce. In both, visual outcomes and prognosis are favorable overall. Ocular involvement in RIME and MIRM is frequent, typically manifesting as conjunctivitis, conjunctival ulceration, and pseudomembrane formation. Chronic sequelae such as conjunctival fibrosis and symblepharon (forniceal shortening) have been documented, with rare cases of mild cicatricial changes (7-10). Over 30% of patients may have ocular involvement severe enough to warrant amniotic membrane transfer after attempting treatment with artificial tears, steroids, and antibiotic drops (11). Dry eye symptoms may persist due to conjunctival and adnexal involvement (7-8). However, corneal ulceration, blindness, synechiae, and loss of eyelashes are not reported as typical sequelae in RIME/MIRM; these complications are more characteristic of severe mucocutaneous syndromes such as SJS and TEN (12-14). Although evidence exists investigating the ocular complications of such pathology, our case highlights the need for further studies that address the potential consequences of RIME, with particular emphasis on the ocular sequelae and long-term impacts on visual outcomes.

Conclusion. The current case of RIME was presented to highlight the importance of differential diagnosis from other serious dermatological conditions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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