Severe pediatric oral mucositis

We initially suspected primary herpetic gingivostomatitis. But the patient's lab work, persistent fever, and cough led us in a different direction.

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A 12-YEAR-OLD BOY presented to the hospital with a 2-day history of fever, cough, and painful blisters on swollen lips. On examination, he had multiple tense blisters with clear fluid on the buccal mucosa and inner lips (**FIGURE 1A**), as well as multiple discrete ulcers on his posterior pharynx. The patient had no other skin, eye, or urogenital involvement, but he was dehydrated. Respiratory examination was unremarkable. A complete blood count and metabolic panel were normal, as was a C-reactive protein (CRP) test (0.8 mg/L).

The preliminary diagnosis was primary herpetic gingivostomatitis, and treatment was initiated with intravenous (IV) acyclovir (10 mg/kg every 8 hours), IV fluids, and topical lidocaine gel and topical steroids for analgesia. However, the patient's fever persisted over the next 4 days, with his temperature fluctuating between 101.3 °F and 104 °F, and he had a worsening productive cough. The blisters ruptured on Day 6 of illness, leaving hemorrhagic crusting on his lips (**FIGURE 1B**). Herpes simplex virus types 1 and 2 and polymerase chain reaction (PCR) testing were negative.

○ WHAT IS YOUR DIAGNOSIS?

○ HOW WOULD YOU TREAT THIS PATIENT?

FIGURE 1
Painful blisters that ruptured after 3 days

IMAGES COURTESY OF SANJAY WOODHULL, MBBS, MRCP, SUBANG JAYA MEDICAL CENTRE, SELANGOR, MALAYSIA

When the patient presented to the hospital, he had multiple tense blisters on the buccal mucosa and inner lips (**A**). Three days later, the blisters ruptured, resulting in hemorrhagic crusting on the boy's upper and lower lips (**B**).

> **Within 3 days of initiating treatment with IV ceftriaxone, azithromycin, and methylprednisolone, our patient experienced marked improvement of his symptoms.**

Dx: *Mycoplasma pneumoniae*–induced rash and mucositis

Further follow-up on Day 6 of illness revealed bibasilar crepitations along with an elevated CRP level of 40.5 mg/L and a positive mycoplasma antibody serology (titer > 1:1280; normal, < 1:80). The patient was given a diagnosis of pneumonia (due to infection with *Mycoplasma pneumoniae*) and *M pneumoniae*–induced rash and mucositis (MIRM).

❚ **MIRM was first proposed** as a distinct clinical entity in 2015 to distinguish it from Stevens-Johnson syndrome and erythema multiforme.[1] MIRM is seen more commonly in children and young adults, with a male preponderance.[1]

A small longitudinal study found that approximately 22.7% of children who have *M pneumoniae* infections present with mucocutaneous lesions, and of those cases, 6.8% are MIRM.[2] *Chlamydia pneumoniae* is another potential causal organism of mucositis resembling MIRM.[3]

❚ **Pathogenesis.** The commonly accepted mechanism of MIRM is an immune response triggered by a distant infection. This leads to tissue damage via polyclonal B cell proliferation and subsequent immune complex deposition, complement activation, and cytokine overproduction. Molecular mimicry between *M pneumoniae* P1-adhesion molecules and keratinocyte antigens may also contribute to this pathway.

3 criteria to make the diagnosis

Canavan et al[1] have proposed the following criteria for the diagnosis of MIRM:

- Clinical symptoms, such as fever and cough, and laboratory findings of *M pneumoniae* infection (elevated *M pneumoniae* immunoglobulin M antibodies, positive cultures or PCR for *M pneumoniae* from oropharyngeal samples or bullae, and/or serial cold agglutinins) AND
- a rash to the mucosa that usually affects ≥ 2 sites (although rare cases may have fewer than 2 mucosal sites involved) AND
- skin detachment of less than 10% of the body surface area.

The 3 variants of MIRM include:

- **Classic MIRM** has evidence of all 3 diagnostic criteria plus a nonmucosal rash, such as vesiculobullous lesions (77%), scattered target lesions (48%), papules (14%), macules (12%), and morbilliform eruptions (9%).[4]
- **MIRM sine rash** includes all 3 criteria but there is no significant cutaneous, nonmucosal rash. There may be "few fleeting morbilliform lesions or a few vesicles."[4]
- **Severe MIRM** includes the first 2 criteria listed, but the cutaneous rash is extensive, with widespread nonmucosal blisters or flat atypical target lesions.[4]

Our patient had definitive clinical symptoms, laboratory evidence, and severe oral mucositis without significant cutaneous rash, thereby fulfilling the criteria for a diagnosis of MIRM sine rash variant.

These skin conditions were considered in the differential

The differential diagnosis for sudden onset of severe oral mucosal blisters in children includes herpes gingivostomatitis; hand, foot, and mouth disease; erythema multiforme; and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). The presence of pulmonary symptoms and oropharyngeal mucositis, together with the laboratory markers currently proposed as MIRM diagnostic criteria, are important in helping differentiate MIRM from other items in the differential diagnosis.

❚ **Herpes gingivostomatitis** would involve numerous ulcerations of the oral mucosa and tongue, as well as gum hypertrophy.

❚ **Hand, foot, and mouth disease** is characterized by vesicular exanthems of the hands, legs, and buttocks.

❚ **Erythema multiforme** appears as cutaneous target lesions on the limbs that spread in a centripetal manner following herpes simplex virus infection.

❚ **SJS/TEN** manifests with severe mucositis and is commonly triggered by medications (eg, sulphonamides, beta-lactams, nonsteroidal anti-inflammatory drugs, and antiepileptics).

With antibiotics, the prognosis is good

There are no established guidelines for the treatment of MIRM. Antibiotics and supportive care are universally accepted. Immunosuppressive therapy (eg, systemic steroids) is frequently used in patients with MIRM who have extensive mucosal involvement, in an attempt to decrease inflammation and pain; however, evidence for such an approach is lacking. The hyperimmune reactions of the host to *M pneumoniae* infection include cytokine overproduction and T-cell activation, which promote both pulmonary and extrapulmonary manifestations. This forms the basis of immunosuppressive therapy, such as systemic corticosteroids, IV immunoglobulin, and cyclosporin A, particularly when MIRM is associated with pneumonia caused by infection with *M pneumoniae*.[1,5,6]

The overall prognosis of MIRM is good. Recurrence has been reported in up to 8% of cases, the treatment of which remains the same. Mucocutaneous and ocular sequelae (oral or genital synechiae, corneal ulcerations, dry eyes, loss of eye lashes) have been reported in less than 9% of patients.[1] Other rare reported complications following the occurrence of MIRM include persistent cutaneous lesions, B cell lymphopenia, and restrictive lung disease or chronic obliterative bronchitis.

■ **Our patient** was started on IV ceftriaxone (50 mg/kg/d), azithromycin (10 mg/kg/d on the first day, then 5 mg/kg/d on the subsequent 5 days), and methylprednisolone (3 mg/kg/d) on Day 6 of illness. Within 3 days, there was marked improvement of mucositis and respiratory symptoms with resolution of fever. He was discharged on Day 10. At his outpatient follow-up 2 weeks later, the patient had made a complete recovery. **JFP**

REFERENCES

1. Canavan TN, Mathes EF, Frieden I, et al. Mycoplasma pneumoniae-induced rash and mucositis as a syndrome distinct from Stevens-Johnson syndrome and erythema multiforme: a systematic review. *J Am Acad Dermatol* 2015;72:239-245. doi: 10.1016/j.jaad.2014.06.026

2. Sauteur PMM, Theiler M, Buettcher M, et al. Frequency and clinical presentation of mucocutaneous disease due to mycoplasma pneumoniae infection in children with community-acquired pneumonia. *JAMA Dermatol.* 2020;156:144-150. doi: 10.1001/jamadermatol.2019.3602

3. Mayor-Ibarguren A, Feito-Rodriguez M, González-Ramos J, et al. Mucositis secondary to chlamydia pneumoniae infection: expanding the mycoplasma pneumoniae-induced rash and mucositis concept. *Pediatr Dermatol* 2017;34:465-472. doi: 10.1111/pde.13140

4. Frantz GF, McAninch SA. Mycoplasma mucositis. *StatPearls* [Internet]. Updated August 8, 2022. Accessed November 1, 2022. www.ncbi.nlm.nih.gov/books/NBK525960/

5. Yang EA, Kang HM, Rhim JW, et al. Early corticosteroid therapy for *Mycoplasma pneumoniae* pneumonia irrespective of used antibiotics in children. *J Clin Med.* 2019;8:726. doi: 10.3390/jcm8050726

6. Li HOY, Colantonio S, Ramien ML. Treatment of *Mycoplasma pneumoniae*-induced rash and mucositis with cyclosporine. *J Cutan Med Surg.* 2019;23:608-612. doi: 10.1177/1203475419874444

LUNG CANCER SCREENING

mendation on lung cancer screening. Published April 6, 2021. Accessed October 12, 2022. www.aafp.org/news/health-of-the-public/20210406lungcancer.html

10. Mazzone PJ, Silvestri GA, Souter LH, et al. Screening for lung cancer: CHEST Guideline and Expert Panel Report. *CHEST.* 2021;160:E427-E494. doi: 10.1016/j.chest.2021.06.063

11. The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med.* 2011;365:395-409. doi: 10.1056/NEJMoa1102873

12. The National Lung Screening Trial Research Team. Results of initial low-dose computed tomographic screening for lung cancer. *N Engl J Med.* 2013;368:1980-1991. doi: 10.1056/NEJMoa1209120

13. de Koning HJ, van der Aalst CM, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med.* 2020;382:503-513. doi: 10.1056/NEJMoa1911793

14. American Cancer Society. Lung cancer screening guidelines. Accessed October 14, 2022. www.cancer.org/health-care-professionals/american-cancer-society-prevention-early-detection-guidelines/lung-cancer-screening-guidelines.html

15. Pirie K, Peto R, Reeves GK, et al. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. *Lancet.* 2013;381:133-141. doi: 10.1016/S0140-6736(12)61720-6

16. Doll R, Peto R, Boreham J, et al. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ.* 2004;328:1519. doi: 10.1136/bmj.38142.554479.AE

17. O'Keefe LM, Gemma T, Huxley R, et al. Smoking as a risk factor for lung cancer in women and men: a systematic review and meta-analysis. *BMJ Open.* 2018;8:e021611. doi: 10.1136/bmjopen-2018-021611

18. Criss SD, Pianpian C, Bastani M, et al. Cost-effectiveness analysis of lung cancer screening in the United States: a comparative modeling study. *Ann Intern Med.* 2019;171:796-805. doi: 10.7326/M19-0322

19. Lazris A, Roth RA. Lung cancer screening: pros and cons. *Am Fam Physician.* 2019;99:740-742.

20. Ali MU, Miller J, Peirson L, et al. Screening for lung cancer: a systematic review and meta-analysis. *Prev Med.* 2016;89:301-314. doi: 10.1016/j.ypmed.2016.04.015

21. Rampinelli C, De Marco P, Origgi D, et al. Exposure to low dose computed tomography for lung cancer screening and risk of cancer: secondary analysis of trial data and risk-benefit analysis. *BMJ.* 2017;356:j347. doi: 10.1136/bmj.j347

22. Manser RL, Lethaby A, Irving LB, et al. Screening for lung cancer. *Cochrane Database Syst Rev.* 2013;CD001991. doi: 10.1002/14651858.CD001991.pub3

23. Mazzone PJ, Silvestri GA, Patel S, et al. Screening for lung cancer: CHEST guideline and expert panel report. *CHEST.* 2018;153:954-985. doi: 10.1016/j.chest.2018.01.016

24. US Public Health Service Office of the Surgeon General; National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. *Smoking Cessation: A Report of the Surgeon General.* US Department of Health and Human Services; 2020. www.ncbi.nlm.nih.gov/books/NBK555591/

25. Leone FT, Zhang Y, Evers-Casey S, et al, on behalf of the American Thoracic Society Assembly on Clinical Problems. Initiating pharmacologic treatment in tobacco-dependent adults: an official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med.* 2020;202:e5-e31. doi: 10.1164/rccm.202005-1982ST