

Stevens-Johnson Syndrome, Mucositis, or Something Else?

Stevens-Johnson syndrome (SJS) has been described in the literature as a combination of erythematous blistering skin lesions covering <10% of body surface area and ≥ 1 mucous membrane erosion.¹ SJS is usually triggered by a medication or infection. Infectious causes are more common in children, most notably herpes simplex virus (HSV) and *Mycoplasma pneumoniae*. Mucous membrane erosions without significant skin involvement have been classified as “atypical SJS” and mucositis.²

Case: An 18-year-old high school senior presented to his physician with a 2-week history of sore throat and cough, 1-week history of fever, and 1-day history of swollen lips and mucosal ulcerations in his mouth accompanied by pain with swallowing. He was an otherwise healthy adolescent male, with the exception of a PICU admission for anaphylaxis without obvious trigger 8 years ago and attention-deficit/hyperactivity disorder for which he is taking methylphenidate. The treating physician ordered a chest radiograph that demonstrated streaky infiltrates in the right lower lobe and sent serology samples for *Mycoplasma*, immunoglobulin G (IgG) antibodies for HSV type 1 and 2, and HIV testing. The patient was started empirically on azithromycin and acyclovir, with lidocaine viscous for his mouth sores. The following day he developed conjunctival erythema, urethral ulceration, and continued to have poor oral intake; he was therefore admitted to the inpatient pediatric ward for intravenous hydration, pain control, and further observation.

Question: *Does this patient have SJS?*

Discussion: There is disagreement in the literature on the exact definition of SJS. As first described by Stevens and Johnson in 1922, a patient must have a generalized skin eruption in conjunction with mucosal involvement to meet the definition.³ This patient never had a generalized skin eruption and therefore does not meet the classic criteria. He did, however, develop 1 targetoid lesion with a central blister on his glans penis, as well as meatal ulceration (Fig 1). In addition, the patient had bilateral nonexudative conjunctival erythema and oropharyngeal ulcerations seen externally on his lips (Fig 2).

We characterized this illness as mucositis secondary to atypical pneumonia, not meeting the classic diagnosis of SJS due to lack of skin lesions. According to Schalock and Dinulos,⁴ patients with disease limited to the mucous membranes are not at risk for widespread skin involvement and often recover faster than children with skin involvement, making diagnosis important for prognosis.

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KEY WORDS

Chlamydomphila pneumoniae, mucositis, Stevens-Johnson syndrome

ABBREVIATIONS

HSV: herpes simplex virus

IgG: immunoglobulin G

IgM: immunoglobulin M

IVIg: intravenous immunoglobulin

MPAM: *Mycoplasma pneumoniae*-associated mucositis

SJS: Stevens-Johnson syndrome

www.hospitalpediatrics.org

doi:10.1542/hpeds.2013-0052

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HOSPITAL PEDIATRICS (ISSN Numbers: Print, 2154 - 1663; Online, 2154 - 1671).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.



FIGURE 1 Urethral ulceration and targetoid lesion with a central blister on the patient's glans penis.

Question: Does this patient have *M pneumoniae*-associated mucositis?

Discussion: Isolated mucous membrane involvement in patients with *M pneumoniae* infection has been described in the literature on multiple occasions, sometimes called "atypical SJS," "SJS without skin lesions," and "MPAM" (*M pneumoniae*-associated mucositis).⁵ Our patient had a classic clinical course for *M pneumoniae*, with consistent chest radiograph findings and mucositis as described earlier. Empirical therapy for *M pneumoniae* was begun by his treating physician before hospital admission. As part of his diagnostic evaluation, the patient's *M pneumoniae* immunoglobulin M (IgM) and IgG samples were sent for testing. The cold agglutinins test was performed at the bedside; the results were positive, which have been associated with *M pneumoniae* disease in



FIGURE 2 Oropharyngeal ulcerations seen externally on the patient's lips.

30% to 50% of cases.⁶ Given the difficulty in quickly and accurately diagnosing *M pneumoniae* with serology samples alone, *Mycoplasma* polymerase chain reaction analysis was requested as an adjunctive test; however, this test was not available at our laboratory.⁷

Case Continuation: The *M pneumoniae* IgM and IgG test results returned mildly positive (1.07 and 5.15, respectively, with index <0.9 for both). The reflex IgM immunofluorescence assay was negative, suggesting that the patient did not have an acute *M pneumoniae* infection. HSV type 1 and 2 IgG antibodies were both negative. At the request of our consulting infectious disease physicians, we also sent serology samples for *Chlamydia pneumoniae*, which returned a positive finding for IgM (>1:10, with a negative result being <1:10) and a negative finding for IgG (<1:64), suggesting acute infection with *C pneumoniae*. Given the conflicting positive results of the cold agglutinins test and the negative *M pneumoniae* IgM immunofluorescence assay, we sent convalescent titers for both *M pneumoniae* and *C pneumoniae* 4 weeks after the initial serology samples were sent. *M pneumoniae* serology samples returned unchanged (1.21 and 5.49, respectively), whereas the *C pneumoniae* serology samples returned with a significant, more than fourfold increase in IgG (1:256), confirming the diagnosis of *C pneumoniae* with associated mucositis. To the best of our knowledge, the association between *C pneumoniae* and mucositis has not been described in the literature before now.

Question: Is there a role for steroids or intravenous immunoglobulin (IVIg)

in the treatment of SJS? What about in the treatment of mucositis?

Discussion: There is no consensus on the role of steroids and IVIg for the treatment of mucositis or SJS in the literature. The use of corticosteroids is generally not recommended due to earlier studies that showed increased complications and mortality rates in patients with SJS. In 1998, Viard et al⁸ demonstrated in vitro that IVIg administration prevents the apoptotic mechanism of keratinocytes seen in skin lesions with toxic epidermal necrolysis. Although no large randomized controlled clinical trials for the use of IVIg have been conducted to date, case reports in children have shown marked improvement when IVIg is administered in patients with SJS and toxic epidermal necrolysis.⁹ A recent Canadian review of SJS in children found that the use of IVIg and corticosteroids had similar outcomes in terms of infectious complications and length of stay, and that both of these treatments were better when compared with supportive therapy alone.¹⁰ Recently published University of Florida guidelines recommend the routine use of IVIg to treat SJS and recommend against systemic steroids.¹¹ It is important to note, however, that all of these recommendations are based on case reports and retrospective case studies, and IVIg carries with it the risk of transfusion reaction and anaphylaxis.

A literature review of MPAM conducted by Meyer Sauter et al⁵ looked at 32 cases of MPAM (72% ≤18 years of age) and found that 9% of published cases were treated with IVIg, 31% with systemic corticosteroids, and 100% with systemic antibiotics, all with clinical improvement. Schalock et al¹², on

the other hand, recommends only supportive care, antibiotic treatment, and monitoring for MPAM, suggesting that IVIg is not necessary in mucositis without skin lesions.¹³

Further Differential Diagnosis: In addition to SJS and mucositis due to an atypical pneumonia, we also considered less-common etiologies such as systemic lupus erythematosus and Behçet's disease. An antinuclear antibody test was sent on admission, and the result returned positive (1:80). However, the patient did not have at least 4 of the 11 required criteria to meet the diagnosis of systemic lupus erythematosus.¹⁴ Results of a repeat antinuclear antibody test performed several weeks after the acute illness had resolved were negative. There is conflicting evidence regarding the association of *C pneumoniae* with Behçet's disease.^{15,16} Given that this was his first episode of oral ulcerations, and his genital ulcerations involved his urethra rather than his scrotum, he did not meet the criteria for the diagnosis of Behçet's disease either.¹⁷

Case Resolution: We decided to continue the patient's empirical antibiotic therapy with azithromycin for presumed atypical pneumonia with mucositis but did not prescribe steroids or IVIg. Given his lack of skin lesions and overall clinical stability, the risk of steroids and/or IVIg was higher than any possible benefit. The patient was febrile initially, but his fever curve trended down with antibiotic therapy and supportive care alone. He was initially given intravenous fluids to maintain hydration, but this treatment was transitioned to oral liquids and oral nutrition as tolerated by his pain. He applied emollient to his lips multiple times per day and bacitracin

to his urethral meatus. Ophthalmology was consulted, and on eye examination, they found only a nonspecific conjunctivitis. There was no conjunctival ulceration or symblepharon, and the cornea and anterior chamber were uninvolved. Urology and dermatology were also consulted and were in agreement with our conservative treatment measures. The patient was discharged from the hospital after 6 days and after 24 hours of demonstrating that he could meet both his hydration and caloric needs by mouth. On telephone follow-up with the patient and his family several weeks later, he had completely recovered, has no further mucosal lesions, and is back to playing sports as usual. He will be followed up closely by his outpatient provider.

Conclusions: Both *M pneumoniae* and *C pneumoniae* should be considered when an adolescent presents with fever, cough, and mucositis. The diagnosis of both organisms is complex, with rising serial antibody titers over time being the gold standard. Isolated mucositis without skin lesions will often resolve with supportive care alone: fluid and nutrition management, pain management, and lubrication of inflamed mucosa. Immunomodulating agents such as steroids and IVIg are not indicated in the case of isolated mucositis without significant skin or other organ involvement.

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Hospital Pediatrics 2014;4;54

DOI: 10.1542/hpeds.2013-0052

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AN OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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