ONLINE EXCLUSIVE

A sheep in wolf's clothing?

Was this a case of Stevens-Johnson syndrome/toxic epidermal necrolysis—or something else?

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A 25-YEAR-OLD COLLEGE STUDENT with no medical history sought care at our hospital for a nonproductive cough, subjective fevers, myalgia, and malaise that he'd developed 10 days earlier. The day before his visit, he'd also developed scratchy red eyes and a sore throat. He said he'd taken an over-the-counter cough suppressant to help with the cough, but his eyes and lips developed further redness and irritation.

On examination, the patient demonstrated conjunctival suffusion, periorbital edema, diffuse oral stomatitis with pseudomembranous crusting, and nasal crusting (**FIGURE 1**). His vital signs were within normal limits, and he had no epithelial skin eruptions or erosions in any other mucosal regions.

The patient was not currently sexually active and had one lifetime female sexual partner. He had no history of sexually transmitted infections or cold sores, and was not taking any medications, herbs, or supplements. During the initial 24 hours of admission, he developed 4 to 5 red targetoid papules on each hand (**FIGURE 2**).

- WHAT IS YOUR DIAGNOSIS?
- HOW WOULD YOU TREAT THIS PATIENT?

FIGURE 1
Periorbital edema and a diffuse oral stomatitis

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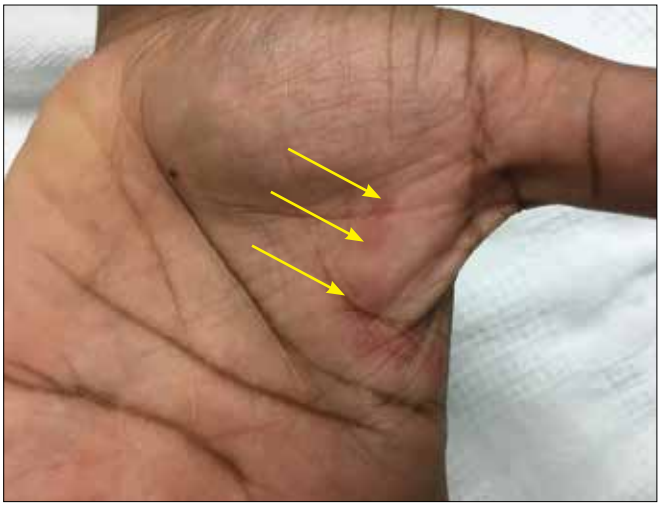
FIGURE 2
Targetoid papules on hands



The degree of mucositis (extensive) compared to the number of targetoid papules on the patient's hands (minimal) suggested *Mycoplasma pneumoniae*-associated mucositis.

Diagnosis: *M pneumoniae*-associated mucositis

The patient was admitted for observation to rule out Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). We felt that the degree of mucositis (extensive) compared to the number of targetoid papules on the hands (minimal) suggested a diagnosis of *Mycoplasma pneumoniae*-associated mucositis (MPAM), a subtype of erythema multiforme (EM) major. The patient's prodrome of fever, cough, and malaise also supported a "walking pneumonia" diagnosis, such as MPAM.

Further testing. The patient had a normal chest x-ray and a negative respiratory virus polymerase chain reaction (PCR), but IgM serologies for *Mycoplasma* were elevated. Although the patient developed targetoid lesions on his hands during his first 24 hours in the hospital, he felt his constitutional symptoms had improved.

Exposure to *Mycoplasma* leads to an immune response

MPAM (also known as Fuchs' syndrome and mycoplasma-associated mucositis with minimal skin manifestations) appears at some point during infection with *M pneumoniae* and causes severe ocular, oral, and sometimes genital symptoms with minimal skin manifestations.

MPAM is primarily seen in young males. In one systemic review of 202 cases, the average age of the patients was 11.9 years and 66% were male.[1] Exposure to *M pneumoniae* is theorized to result in the production of autoantibodies to mycoplasma p1-adhesion molecules and to molecular mimicry of keratinocyte antigens located in the mucosa.[1-3]

Mycoplasma organisms have not been isolated from the cutaneous lesions of patients with MPAM; they have only been isolated from the respiratory tract, supporting the theory that MPAM is the body's immune response to *Mycoplasma,* rather than a direct pathologic effect.[4] This pathogenesis is distinct from that of SJS/TEN, which is thought to involve CD8+ T-cell-mediated keratinocyte apoptosis (programed cell death). In addition, SJS/TEN is almost always drug induced.

First up in the differential: Rule out SJS/TEN

When evaluating a patient like ours with a blistering eruption, the most important diagnosis to exclude is SJS/TEN. This condition is usually triggered by a medication, which was absent in this case. SJS/TEN begins with a host of constitutional symptoms and an erythematous blistering eruption, which may be preceded by atypical targetoid (2-zoned) flat papules along with erosions on 2 or more mucosal surfaces.

Patients with SJS/TEN are usually critically ill and may have a guarded prognosis. Patients with MPAM have a more favorable prognosis and are unlikely to be critically ill—as was the case with our patient.

EM major is often associated with *Mycoplasma* infections. Patients with EM major may have fever and arthralgias, as well as extensive mucous membrane involvement including that of the lips/mouth, eyes, and genitals.

Experts agree that EM is separate from the SJS/TEN continuum, and that patients with EM major, including those with MPAM, are not at risk of developing SJS/TEN.[5] EM is characterized by the presence of the more characteristic 'target' or 'iris' 3-zoned lesion—a central dusky purpura, surrounded by an elevated edematous pale ring, rimmed by a red macular outer ring. EM major is defined as EM along with involvement of one or more mucosal regions.

In this case, the patient had acral target lesions and oral and ocular mucosal involvement characteristic of EM major, without widespread skin erosions or sloughing commonly seen with SJS/TEN.

Kawasaki's disease occurs in young children and presents with conjunctivitis and oral changes. However, patients with Kawasaki's disease generally have a fever for >5 days, a strawberry tongue (not a part of the morphology of EM major or MPAM), and palmoplantar erythema and desquamation that are not common with EM major or MPAM.[1]

Pemphigus vulgaris is uncommon in children and young adults. The disease does not present with diffuse mucositis nor diffuse blistering of the skin, but rather with discrete shallow erosions on the mucosa and the trunk along with flaccid bullae and erosions on the skin.

The morphologies of a fixed drug eruption (round purpuric patch) and toxic shock syndrome (diffuse macular erythema and widespread skin sloughing) are inconsistent with this patient's diffuse mucositis, conjunctivitis, and targetoid lesions.

Confirm exposure to *M pneumoniae*

Testing with the purpose of ruling in MPAM is directed toward proving that the patient has been exposed to *M pneumoniae*. (Of note: *M pneumoniae* cannot be detected via routine commercial blood cultures.)

Serologic testing for elevated IgM antibodies to *Mycoplasma* is the most specific method. Various studies have found it to be positive in 100% of cases, but detection may be delayed for a couple of weeks while the body develops the requisite antibodies.[4]

Respiratory PCR for *Mycoplasma* is rapid and usually appropriately positive, but may be negative in cases where the patient has spontaneously cleared the infection or has been exposed to antibiotics before development of the eruption.[4] An infiltrate on chest imaging is supportive of the diagnosis.

Skin biopsy will demonstrate either mucositis and necrosis of keratinocytes or EM-like necrosis, but does not suggest an etiology.

Strikingly different paths of care

Distinguishing between SJS/TEN and EM major (including MPAM) is crucial to guiding management. Patients with SJS/TEN need critical care, particularly of their eyes and genitourinary and respiratory systems. Specialist consultation is often required.

For EM major, patients require supportive care along with ongoing assurances that the eruption has a benign prognosis. Hospital admission is not mandatory as long as adequate supportive care and symptom control can be provided on an outpatient basis. Early consultation with Ophthalmology, Oral Medicine, and Urology may also be key.

Keep in mind that patients may have severe stomatitis and pain that alter their ability to eat and perform normal activities. Thus, managing pain and ensuring adequate nutrition are crucial for successful support. While antibiotics treat active *Mycoplasma* infection, there is no clear evidence that antibiotics alter the course of the eruption, which is also consistent with the hypothesized pathogenesis.[3,4]

While there is no clear statistical evidence that systemic immune suppression alters the disease course, a large proportion (31%) of patients in a recent systematic review of MPAM were treated with corticosteroids, and a smaller, but noteworthy, percentage (9%) were treated with intravenous immunoglobulins (IVIG).[4] There are reports of severe stomatitis that didn't improve with supportive care, but that showed dramatic improvement with IVIG treatment.[6,7]

Our patient had difficulty controlling secretions and managing the painful mucositis of his mouth; he was initially unable to tolerate solid foods. Topical lidocaine solution for his mucositis caused burning and more discomfort, but acetaminophen-hydrocodone 300 mg-5 mg every 6 hours did relieve his pain. Wound care with a bland emollient and the application of non-stick dressings to his lips at night also helped to relieve some of the pain.

Because the patient's oropharyngeal swelling made it hard for him to swallow, he received oral prednisone 0.5 mg/kg/d, which provided him with relief within 24 hours. The acute inflammation and eruption also subsided within 48 hours and the patient was discharged after 5 days of being hospitalized. He continued to recover as an outpatient, seeing his primary care physician within 2 weeks for final nutrition and wound care support. Two weeks after that, he had a dermatology appointment, and all of his lesions had re-epithelialized. **JFP**

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Patients with erythema multiforme, including those with *Mycoplasma pneumoniae*-associated mucositis, are not at risk of developing Stevens-Johnson syndrome/ toxic epidermal necrolysis.

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