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CLINICAL VIGNETTE

A Case of Erythema Multiforme

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An 18-year-old male presented with a second episode of oral and genital sores. The current oral and genital sores developed soon after he was diagnosed with COVID-19 three weeks before presentation. He developed a dry cough that resolved spontaneously, however, several days after the cough onset, he noted, painful oral and penile sores. The patient also received his third dose of the Pfizer COVID-19 vaccine several days before the diagnosis of COVID-19 infection.

He did not have fevers, chills, shortness of breath, joint pain, swollen glands, nausea, vomiting, or diarrhea. His last sexual intercourse was several months before and had no history of sexually transmitted infections. He had pre-existing chronic left sided chest wall pain, which did not worsen during the infection. At urgent care, he was diagnosed with balanitis and herpes simplex virus and was treated with topical clotrimazole and oral valacyclovir. He did not improve and went to the Emergency Room for further evaluation of the sores. He was given prednisone 50mg daily for a 4-day course, as well as topical lidocaine. His sores had almost fully resolved by the time he came to our office.

Physical exam in the office after completion of treatment included vital signs and no apparent distress. He had anicteric sclerae and no conjunctival injection. No oral ulcerations were seen in the mouth but he had one remaining thin plaque just inferior to the right lower lip. This lesion had no surrounding erythema or warmth to touch and was shallow without crusting. It was minimally tender without discharge. On cardiac exam, he had a regular rate and rhythm without murmurs or gallops. He had mild tenderness to palpation over the intercostal muscles on the left side of the chest between the 4th-6th ribs when twisting to the left. His lungs were clear to auscultation bilaterally. His abdomen was soft and nontender without hepatosplenomegaly or costovertebral angle tenderness. The penile sores had resolved and there were no testicular masses. No cervical or inguinal lymphadenopathy was present on exam. He had no rashes or petechiae elsewhere on his body. He had no edema, erythema or warmth over his fingers or wrists on both hands.

He reported a prior episode of oral and genital sores 2 years prior with more severe symptoms. During the prior episode he had a fever up to 102°F, cough, nasal congestion, and sore throat. He developed sores on his lips and penis after developing a rash on his extremities and chest. He had stopped eating and drinking because of the pain in his mouth and developed

dysuria. He was hospitalized to treat dehydration and assist with pain control. Physical exam during this hospitalization, describes the sores as 0.5-1cm targetoid erythematous papules and plaques which were present on his arms, legs and chest, in addition to the oral and penile mucosal erosions. He also had injection of the lower palpebral conjunctiva.

Labs and Studies

Testing from the hospitalization 2 years ago elevated white blood cell count was elevated at $11.14 \times 10^3/\mu\text{L}$, elevated sedimentation rate at 45mm/hr (reference range <12mm/hr). Chemistries included decreased CO₂ of 19mmol/L with normal creatinine, AST, and ALT. Initial urinalysis showed microscopic hematuria of 657 rbc per μL which may have been due to the bleeding genital ulcerations. Initial respiratory mycoplasma pneumoniae PCR testing and blood cultures returned negative. Mycoplasma IgG later resulted positive at 1.02 U/L (0.33 U/L or higher is considered positive) and mycoplasma IgM was positive at 1.25 U/L (0.96 U/L or higher is considered positive). Parvovirus IgM and EBV-VCA Igm and EBNA-1 IgG were negative. RPR was nonreactive. HIV-1/2 Ag/Ab screen was negative. HSV1 and HSV2 IgG were negative. Gonorrhea and chlamydia PCR tests were negative. Parvovirus IgG was elevated at 5.69 (1.11IV or greater is considered positive). HCV antibody screen was negative.

A right thigh punch biopsy was obtained during his hospital stay. Pathology report, reported thickness confluent epidermal necrosis with clefting at the dermal-epidermal junction. There was superficial perivascular lymphocyte predominant inflammation with rare eosinophils. Gram stain and HSV and VZV testing of the biopsied sample were negative. No vasculitis or malignant cells were noted. Direct immunofluorescence testing was also negative.

Additional laboratory testing from the second episode of oral and genital sores was again negative for HSV 1 specific IgG and HSV 2 specific IgG. Troponin testing was negative. Throat and urine testing for chlamydia and gonorrhea were negative. RPR and HIV testing were negative. Repeat urinalysis was negative for microscopic hematuria.

Treatment Course

During the prior episode 2 years ago, the treating team in the hospital felt that the oral and genital mucositis was likely

secondary to Erythema multiforme major but mycoplasma-induced rash and mucositis (MIRM) was also high on the differential. He had been given only a 2-day treatment of azithromycin which was stopped after negative mycoplasma respiratory testing and serologies had not returned yet. He received intravenous fluid hydration until the pain with eating and drinking improved. He was also given intravenous solumedrol, morphine for pain control, dexamethasone mouthwash, and triamcinolone dental paste.

With the second episode of mucosal erosions, he showed much more rapid improvement with near resolution of his symptoms within a week of starting on treatment. He was treated with valacyclovir, oral prednisone, and topical triamcinolone dental paste.

Discussion

Erythema multiforme (EM) is an immune-mediated condition with acute onset that typically presents with targetoid skin lesions and can in some cases lead to oral, genital or ocular mucosal erosions.¹ The targetoid skin lesions can have three distinct colors with a dusky area in the center, surrounded by a paler pink ring, and then encircled by an erythematous outer ring.² If there is significant mucosal involvement, the condition is called Erythema multiforme major.¹ EM can have a similar presentation to Stevens-Johnson syndrome (SJS) which can also present with targetoid lesions and mucosal involvement. SJS tends to present with macular lesions while EM tends to present with papular lesions.²

Our patient had an acraly distributed targetoid eruption during his first episode along with oral, genital and ocular involvement. During his second episode of possible EM, the targetoid extremity lesions were not seen but he did have oral and genital mucosal involvement. With the lack of the extremity lesions on the 2nd episode, the infectious disease specialist did consider other causes such as herpes simplex virus or Behcet's syndrome. Herpes simplex serology testing was negative during both episodes. His skin biopsy was also negative for herpes simplex virus during the 1st episode.

Approximately 90% of reported cases of EM are caused by infectious agents and 10% or less are secondary to drugs.³ The most common cause is HSV type 1 but HSV type 2 and mycoplasma pneumoniae are also possible triggers.² EM eruptions have been linked to hepatitis C, Epstein-barr virus, and influenza¹ as well as parvovirus, adenovirus, and coxsackie.³ Drugs that have been associated with EM include but are not limited to: nonsteroidal anti-inflammatory medications, sulfonamides, penicillin, erythromycin, nitrofurantoin, tetracyclines, statins, barbiturates, and phenothiazines.²

EM was felt to be the most likely diagnosis during our patient's initial hospitalization when the initial respiratory PCR testing for mycoplasma came back negative. The mycoplasma serum IgM testing later resulted positive and there was some debate if this was truly EM or if the patient had Mycoplasma-induced

rash and mucositis (MIRM). MIRM can have a targetoid eruption as an extrapulmonary manifestation of a mycoplasma infection.⁴ Some treatments used for MIRM include antibiotics, corticosteroids and in more severe cases cyclosporine A and IVIG.⁴ Our patient was treated with azithromycin and intravenous corticosteroids during his hospital stay.

During our patient's second episode of mucosal erosions, he had both an acute COVID-19 infection and a COVID-19 vaccine booster shot within a week before the onset of symptoms. COVID-19 infection has been linked to EM and EM-like skin manifestations.⁵ COVID-19 vaccines have also been linked to EM.⁶ Out of 414 patients who had a dermatologic finding reported after COVID-19 vaccination in the McMahon et al. study (2021), 3 patients in the Moderna group had an EM eruption but no EM lesions were seen in the Pfizer group.⁶ All the individuals in the McMahon et al. study (2021) experienced the EM lesions after the 1st dose.⁶ Our patient had his third Pfizer dose prior to onset of symptoms and had no rashes or mucosal erosions with any of the prior vaccines.

There are diagnostic challenges as can be seen with our patient to both confirm the diagnosis of EM and identify a clear cause. Patients can be categorized as having idiopathic EM when no etiology is found. There have been cases of HSV DNA later being isolated on skin biopsies in individuals categorized as having idiopathic EM.⁷

Acute EM can often be treated with topical steroids, antiseptic medications and oral antihistamines when there is no mucosal involvement.⁷ Antibiotic or antiviral therapy is added on a case by case basis depending on whether or not an infection is isolated.⁷ The offending medication should be stopped if there is a medication trigger for an episode of EM. Mucosal EM, when mild, can be treated with high-potency topical steroid gel.⁷ However, as in our patient's case when it is more severe, intravenous fluids may be needed because of poor oral intake. Systemic glucocorticoids such as prednisone 40-60mg daily can be used and tapered over a 2-4 week period in severe cases.⁷

Fortunately for our patient the severity of the second possible EM episode was much milder and he responded to a 4-day course of oral steroids and triamcinolone dental paste. He also received antiviral medications during this second episode. We hope to see continued progress in both identifying and treating EM early especially as we expand our knowledge of new viral triggers such as COVID-19 that could impact the prevalence of EM in the future.

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