Recurrent Erythema Multiforme/Stevens-Johnson Syndrome

Response to Mycophenolate Mofetil

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A 26-year-old previously healthy man presented with a 1-month history of progressive mouth sores, eye discomfort, and skin rash. Over the 2 weeks before presentation, he had lost more than 10 kg (22 lb) because of difficulty in swallowing fluids and food, caused by the mouth sores. He had a history of herpes gladiatorum affecting his right shoulder. On physical examination, approximately 90% of his oral mucosa was ulcerated. Bilateral conjunctival hyperemia and targetoid skin macules involving his elbows, palms, upper thighs, and genitalia were observed (Figure 1). Results of 3 separate biopsies of the skin and mucosa were consistent with the clinical impression of erythema multiforme, showing scattered necrotic keratinocytes, basal cell liquefaction, subepidermal and intraepidermal edema, and a chronic inflammatory cell infiltrate (Figure 2). Three direct immunofluorescence studies showed intraepidermal cytoids and vascular staining, which were also consistent with erythema multiforme.

The patient was admitted to the hospital for rehydration. He received oral corticosteroid therapy (prednisone, 1 mg/kg; 80 mg/d) and antiviral therapy (valacyclovir hydrochloride, 1 g twice daily). His condition improved. The prednisone was then decreased to 60 mg/d, and he was discharged from the hospital. Two days later, his mucosal ulcers and skin lesions recurred. The dose of oral prednisone was again increased to 80 mg/d, with a rapid disappearance of his mucosal ulcers and skin lesions within 2 days. Over the following 10 months, each time the dose of oral prednisone was reduced below 80 mg/d, his disabling mouth sores, eye discomfort, and targetoid skin lesions recurred.

The recurrence took place despite continuous antiviral therapy over this period (valacyclovir hydrochloride, 1 g twice daily, taken orally). Repeated cultures and polymerase chain reaction studies of skin and mucosa (both scrub cultures and biopsy material from a total of 17 samples submitted over this time period) were negative for virus, specifically for herpes simplex virus.

Our goal was to institute treatment with a quick-acting corticosteroid-sparing drug that would suppress the disabling mouth sores in this young man and permit tapering and discontinuation from the systemic corticosteroid therapy.
Treatment with mycophenolate mofetil (CellCept; Roche Pharmaceuticals, Nutley, NJ) was prescribed at a dose of 1 g twice daily. Inadvertently, the patient started with a dose of 1 g only once daily, with no effect on the skin lesions. When he began taking 1 g twice daily, his skin and mucosal lesions disappeared completely within 4 to 5 days. He decreased the dose of prednisone gradually: decreasing from 60 mg/d to 40 mg/d after 4 days, further decreasing the dose to 20 mg/d 1 week later, then to 10 mg/d for a week, and then stopping the corticosteroid therapy completely, without recurrence of symptoms.

Two months later, an attempt was made to decrease the dose of mycophenolate mofetil to 1 g once daily, but the mucosal and skin lesions reappeared within a few days. The symptoms disappeared when mycophenolate mofetil (1 g) was again administered twice daily. Three months later, a similar attempt to decrease the mycophenolate mofetil dose was made, with the same result. Treatment continued with mycophenolate mofetil and valacyclovir hydrochloride, each at 1 g twice daily, with no adverse reactions.

One year later, the mycophenolate mofetil dose was decreased to 1 g once daily for a month and then successfully stopped without recurrence of symptoms. The antiviral treatment was stopped 2 months later. After approximately 4 months, the patient again experienced conjunctival hyperemia, incapacitating oral ulcerations, and “target lesions” involving his upper extremities that increased over a 3-day period. These symptoms did not respond to oral corticosteroids in doses as high as 80 mg/d in combination with reintitiation of valacyclovir, but they did respond within 36 hours to reinstatement of mycophenolate mofetil treatment.

Six months later, the valacyclovir and the mycophenolate mofetil treatments were tapered and discontinued. Nine months later, the incapacitating oral ulcerations recurred; they responded to reinstatement of mycophenolate mofetil and valacyclovir. The patient remains on this treatment to the present.

The observed extensive mucosal (mouth, conjunctivae, genitalia) ulcerations suggested 2 possible diagnoses: erythema multiforme and Stevens-Johnson syndrome. The nosology here is controversial and confusing. It has been argued that the terms are synonymous and that the original description by Stevens and Johnson was consistent with erythema multiforme major. We termed this patient’s condition recurrent erythema multiforme/Stevens-Johnson syndrome.

Within the clinical spectrum of erythema multiforme, 2 subgroups have been identified: recurrent erythema multiforme and persistent erythema multiforme. Recurrent erythema multiforme is characterized by multiple interrupted episodes (as were observed in the patient described herein), whereas persistent
Erythema multiforme is a rare condition in which lesions occur without interruption. There is little else to distinguish these forms of erythema multiforme from the sporadic form except that they are recurrent or persistent.

Erythema multiforme/Stevens-Johnson syndrome is difficult to treat. A critical question is whether a precipitating factor can be identified. One of the keys to management is to withdraw the offending drug or to treat the offending infection. In a case-control study, Roujeau et al found that the use of antibacterial sulfonamides, anticonvulsant agents, oxamic nonsteroidal anti-inflammatory drugs, allopurinol, chlorimexanone, and, interestingly, corticosteroids is associated with large increases in the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis.

Meticulous skin care, fluid management, nutritional support, and surveillance for and aggressive treatment of infection are essential. In the patient presented, the results of viral studies were repeatedly negative, and antiviral treatment did not suppress the disease. Nonsteroidal anti-inflammatory drugs (taken for a headache) were thought to be possible culprits. However, the symptoms persisted despite rigorous avoidance of these drugs.

The value of systemic corticosteroids in the treatment of erythema multiforme is hotly debated. Some relief of systemic symptoms is achieved, but there is as yet no convincing evidence that use of corticosteroids improves overall mortality or long-term morbidity. Nevertheless, prednisone is often given for severe symptoms, in adults at a dose of 30 to 60 mg/d. The role of antiviral therapy for erythema multiforme is also debated, with some authors suggesting that long-term prophylactic antiviral treatment is both helpful and justifiable. Control of recurrent erythema multiforme with thalidomide has been reported. There have also been case reports of successful treatment with dapsone, therapeutic plasmapheresis, interferon alfa, and the addition of intravenous immunoglobulin to corticosteroid therapy. In a pilot study for toxic epidermal necrolysis, 10 consecutive individuals with clinically and histologically confirmed toxic epidermal necrolysis were treated with intravenous immunoglobulin; disease progression was rapidly reversed, and the outcome was favorable in all cases.

Although further studies are needed to delineate its role, our experience suggests that mycophenolate mofetil might also be considered as a treatment for persistent erythema multiforme. Mycophenolate mofetil is a morpholino ester of mycophenolic acid, which was shown in the 1970s to be effective in patients with severe psoriasis. Mycophenolate mofetil has increased bioavailability compared with mycophenolic acid and therefore an improved therapeutic window. The drug reversibly and noncompetitively blocks the de novo synthesis of guanine nucleotides required for DNA and RNA synthesis during T- and B-cell proliferation. Because mycophenolate mofetil inhibits the de novo pathway of purine synthesis that is used by lymphocytes, it seems to be more specific for B and T lymphocytes than azathioprine.

Although approved by the US Food and Drug Administration for the prevention of renal allograft rejection only, according to growing evidence mycophenolate mofetil may be useful in the management of lymphocyte-mediated skin diseases. It has been used for the management of chronic graft-vs-host disease, chronic plaque-type psoriasis, therapy-resistant pyoderma gangrenosum, autoimmune skin disorders such as paraneoplastic pemphigus, pemphigus vulgaris, pemphigus foliaceus, cutaneous Crohn disease, and bullous pemphigoid.

The most common reported adverse effect of mycophenolate mofetil therapy is gastrointestinal disturbance with subsequent reversible, dose-related hematologic effects. A slightly increased incidence in viral and bacterial infections during mycophenolate mofetil therapy has also been reported. Because there may be an increased risk of lymphoma in the long term, the patient’s condition should be monitored carefully. The drug does not produce clinically significant nephrotoxicity or liver damage; therefore, it may be of value for patients who cannot take cyclosporine or methotrexate because of kidney or liver dysfunction.

Mycophenolate mofetil is an effective and relatively safe immunosuppressive agent for treatment of autoimmune and inflammatory skin diseases and may be an alternative for corticosteroid-dependent patients with recurrent or persistent erythema multiforme/Stevens-Johnson syndrome.

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REFERENCES


Clinicians, local and regional societies, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Submit 4 double-spaced copies of the manuscript with right margins nonjustified and 4 sets of the illustrations. Photomicrographs and illustrations must be clear and submitted as positive color transparencies (35-mm slides) or black-and-white prints. Do not submit color prints unless accompanied by original transparencies. Material should be accompanied by the required copyright transfer statement, as noted in "Instructions for Authors." Material for this section should be submitted to George J. Hruza, MD, Laser and Dermatologic Surgery Center Inc, 14377 Woodlake Dr, Suite 111, St Louis, MO 63017.

Archives Web Quiz Winner

Congratulations to the winner of our September quiz, Parima Laohadtanaphorn, MD, Boston University Medical Center, Allston, Mass. The correct answer to our September challenge was unilateral laterothoracic exanthem (also known as asymmetric periflexural exanthem of childhood). For a complete discussion of this case, see the Off-Center Fold section in the October Archives (Jhin MH, Eidelman M, Cohen SR, Husain S. Unilateral eruption in a child. Arch Dermatol. 2002;138:1371-1376).

Be sure to visit the Archives of Dermatology World Wide Web site (http://www.archdermatol.com) to try your hand at the Interactive Quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the Archives. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of The Art of JAMA II.