Herpes simplex-associated erythema multiforme (HAEM): a clinical therapeutic dilemma

Joseph Katz, DMD Avi Livneh, MD Joshua Shemer, MD Yehuda L. Danon, MD Benjamin Peretz, DMD

Dr. Katz is a senior lecturer, Department of Oral Medicine Oral Diagnosis Oral Radiology, The Hebrew University-Hadassah School of Dental Medicine, Jerusalem, and Israel Defense Force, Dental Medicine Center and Sheba Medical Center, Tel-Hashomer, Israel; Dr. Livneh is a senior lecturer and Dr. Shemer is an associate professor at the Tel Aviv University, Sackler Faculty of Medicine, Department of Internal Medicine F, Sheba Medical Center, Tel Hashomer, Israel; Dr. Danon is a professor, Tel Aviv University, Sackler Faculty of Medicine, and head, Kipper Institute of Immunology and director, Schneider Children's Medical Center of Israel; and Dr. Peretz is a clinical senior lecturer, Department of Pediatric Dentistry, The Hebrew University Hadassah School of Dental Medicine, Jerusalem, Israel.

Abstract

Erythema multiforme of the mouth is an acute vesiculoulcerative lesion, which presents a diagnostic and therapeutic challenge to the clinician. Herpes simplex is described as the most frequent cause of this disease. Controversy exists in the literature as to the definition of oral erythema multiforme and the role of systemic corticosteroids in its treatment. Recent treatment protocols advocate the use of systemic Acyclovir, especially in cases triggered by the herpes simplex virus.

Two cases of successful treatment of oral erythema multiforme with systemic corticosteroids after Acyclovir treatment had failed are presented.(Pediatr Dent 21:359-362, 1999)

Erythema multiforme (EM) is an acute muco-cutaneous disorder which appears mostly as symmetrical papules, later developing into "target" or "iris" lesions with an erythematous periphery and a central zone of necrosis.[1] Other characteristic features include bullae and vesicles.[2] The lesions usually appear bilaterally on the dorsal surfaces of the hands and feet. The mucous membranes of the oral cavity, nose, eyes, and genitalia may also be affected. The oral lesions appear as crusted erosions on the lips or intraoral ulcerations and erosions.[3] EM is defined as minor when only one mucous membrane, usually the mouth, is affected, and major if the extent of mucous membrane involvement is larger.[1]

Drugs, mycoplasma, and herpes simplex virus (HSV) infections were described as the most frequent causes,[4-6] although other causes such as allergy to foodstuffs were also suggested.[7] The disease may appear between one and five times annually.[7] The latter form is defined as recurrent erythema multiforme (REM).

It is now accepted that EM minor and major, as well as Stevens-Johnson syndrome (SJS), fixed drug reaction, and toxic epidermal necrolysis (TEN), are considered parts of a single "EM spectrum",[1, 8] where the various disorders are usually symptoms of the same disease.

Prevalence of oral EM varies from 35% to 65% among patients with skin lesions.[1, 2] However, in patients where EM was diagnosed by oral lesions, prevalence of skin lesions ranged only from 25% to 33%.[9, 10]

Accepted March 11, 1999

The efficacy of steroid treatment in EM is controversial, and has not been proven by controlled clinical trials.[8, 11] The prophylactic and therapeutic use of Acyclovir in cases of herpes-induced EM is now common practice.[12]

Two cases of minor oral herpes-induced EM in children where Acyclovir therapy had failed are presented, and the controversy on the role of systemic corticosteroids in EM therapy is discussed.

Case 1

An eight-year-old boy was admitted to the Department of Pediatrics at the Sheba Medical Center because of purulent ulcers on the lips and oral cavity, dysphagia, and fever of one-week duration. These symptoms were unresponsive to treatment with oral Acyclovir and Amoxycillin combined with Clavulanic acid. The past medical history was significant only for two episodes of herpetic lesions on the lips experienced by the patient during the previous year.

On examination, the patient was pale, with body temperature of 38˚C, respiratory rate of 22/min, and heart rate of 100/min. Jaw opening was limited and a few vesicles and ulcers were present on his upper and lower lips which were markedly edematous (Fig 1). Intraoral examination revealed ulcerations

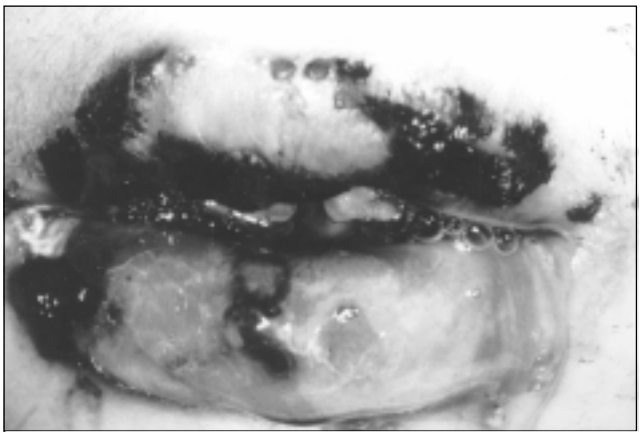

Fig 1. Patient in case 1; severe edema and vesicoloulcerative lesions on the lips.

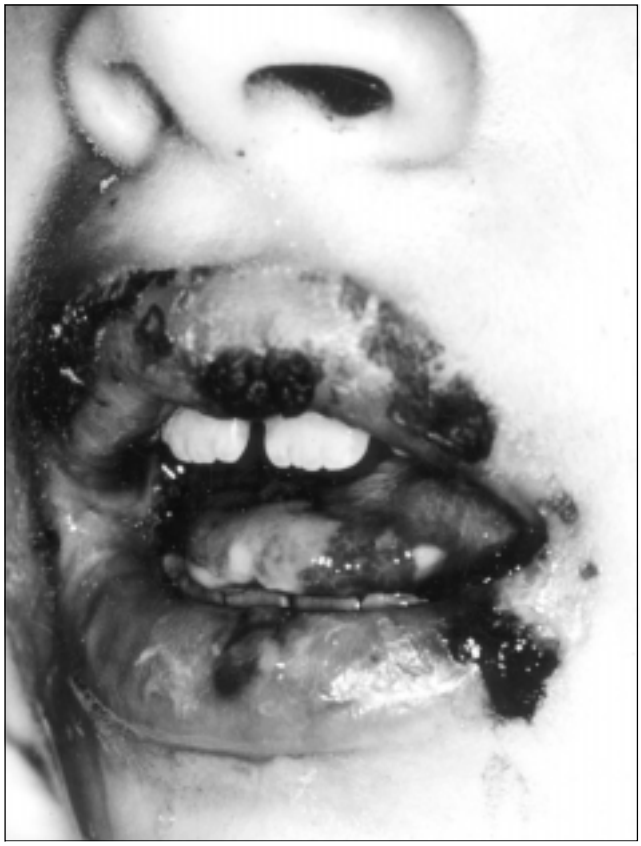

Fig 2. Intra oral view of patient 1; limitation of jaw opening with severe ulcerations on the tongue.

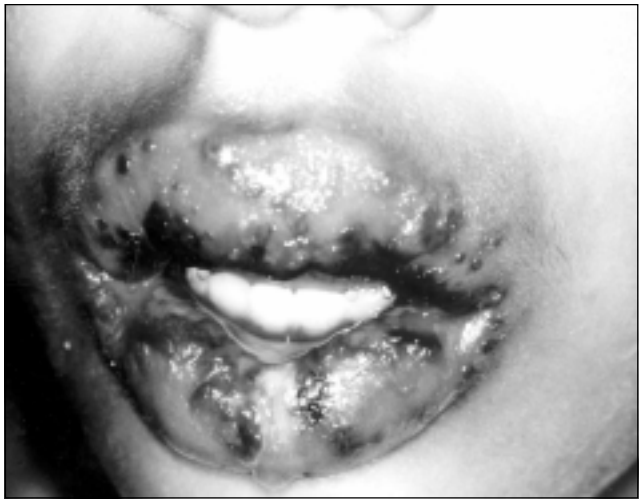

Fig 3. Patient in case 2; edematous and hemorrhagic upper and lower lips with severe ulcerations.

on the tongue, buccal mucosa, and gingivae (Fig 2). Slight submandibular lymphadenitis was noted. The erythrocyte sedimentation rate was 33, white cell count was 4,500 per mcl, hemoglobin was 13.3 g/dcl, hematocrit 34.6, urea values were 32 mg/dcl, glucose values were 92 mg/dcl, K - 4.8 mmol/l, sodium values were 142 mmol/l, and globulin values were 2.7 g/dcl. Liver enzymes and HIV tests were negative. HSV IgM was positive. Complement levels were normal.

A diagnosis of herpetic gingivostomatitis was suggested and the patient received Acyclovir, Penicillin, and Metronidazole intravenously. However, no improvement was noted after ten days of treatment. A consultation with the Oral Medicine Unit was requested. Based on the appearance of the oral lesions, the Acyclovir resistance, and the elevated serum Herpes IgM, a diagnosis of EM, induced by herpes virus, was suggested. Administration of Prednisone (30 mg/day) resulted in substantial improvement within two days of treatment and complete recovery in five days.

Case 2

A ten-year-old girl was admitted to the Department of Pediatrics at the Sheba Medical Center due to multiple painful vesicles on her lips, and oral mucosae with severe dysphagia. Examination showed low fever and malaise. Heart rate was 98/min, and mild cervical lymphadenopathy was noted. The lips were swollen, hemorrhagic and malodorous (Fig. 3), few vesicles appeared on both lips and on the dorsum of the tongue. Laboratory findings showed white cell count of 14,790 cells/mcl with polymorphonuclears of 82%; Hgb was 13.9 g/dcl; glucose values were 90 mg/dcl; urea values were 27mg/dcl. Blood cultures were negative, but viral cultures from the vesicles were positive for herpes type I. Medical history was not contributory and there were no previous episodes of recurrent herpes labialis.

A diagnosis of primary herpetic gingivostomatitis was made and treatment with Acyclovir (PO) and Ampicilline IV was initiated. After one week, this treatment did not relieve the symptoms. After consultation with the Oral Medicine Unit, Ultracorten IV (250 mg/day) was administrated. A dramatic improvement was observed after 24 hours (Fig. 4), and complete resolution of the lesions occured within three days. The patient was discharged from the hospital with no recurrent lesions.

Discussion

EM is an acute, sometimes recurrent, vesiculobullous disorder that is manifested on the skin, mucous membrane, and occasionally in some internal organs. The lesions occur most commonly between the ages of 10-30 years.[13, 14] The etiologic agents documented most conclusively are infection with herpes virus or mycoplasma pneumonia. Recent studies suggest the association of mycoplasma pneumonia infection with SJS, but not with EM. This is a clear separation of these two conditions.[14] In one study, 20%–50% of EM cases were found to be related to herpes virus.[15]

The reported incidence of mucosal lesions varies considerably and appears to depend, in part, on whether the study was based on an oral medicine or a dermatology clinic population.[1, 4, 16] Huft[1] reported that 25% of patients with skin lesions also had oral lesions, but no other mucous membranes were involved. However, Leigh[2] reported that 65% of patients with skin involvement had lesions in the mouth and 35% also had genital lesions. Conversely, in reports about patients with a diagnosis of EM that was based primarily on their oral lesions, the incidence of skin lesions ranged from 25%–33%.[9, 12] A recent multidisciplinary study reported that 70% of EM patients had oral involvement.[17] The oral lesions have predilection for the vermilion border of the lips and the buccal mucosa, generally sparing the gingiva.[6, 8]

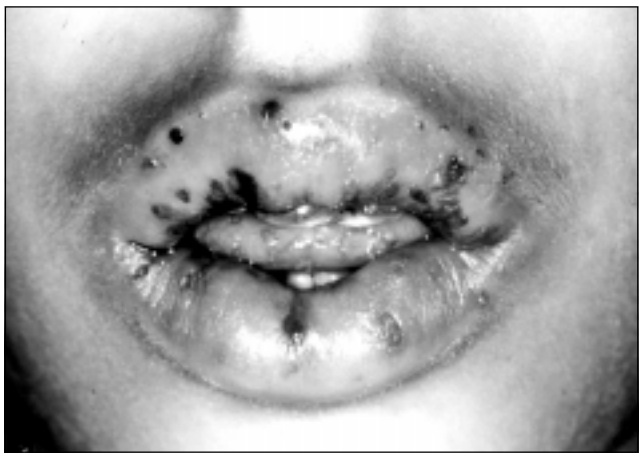

Fig 4. Patient in case 2; twenty-four hours after initiation of corticosteroid therapy.

The differential diagnosis of EM includes another vesiculobulous disease—primary herpetic gingivostomatitis that differs from EM by involving all oral tissues.[8] The distinction is important as corticosteroids may be the treatment of choice in EM, but not in primary herpes simplex infection.[8]

Review of the relevant literature reveals controversies regarding both diagnosis and treatment of this disease. Part of the problem is attributed to the different terminology of some overlapping entities—EM, SJS, and Lyell's syndome. A recent collaborative study has shown the significance of the polymerase chain reaction (PCR) as a diagnostic tool in HSV infection.[18]

More important is the debate on whether corticosteroids should be administered. In an uncontrolled study, Rasmussen[19] found no improvement but increased complications rate following steroid therapy for patients with severe SJS. However, this study appears to be retrospective and possibly selective. In a more comprehensive study, Paterson et al.[20] discussed the different approaches of the dermatologic and pediatric literature concerning the use of corticosteroids in EM. The efficacy of systemic corticosteroids was considered unproved, controversial, or effective only in severe cases, while Acyclovir has been proven to shorten signs and symptoms in children with HSV oral lesions.[21] Particular caution with steroid therapy was advocated in EM associated with HSV of the eyes.

The pediatric literature shows a wide range of recommendations from complete avoidance of steroids,[10] to an early use of these drugs like in case of SJS.[17] Some authors claim that SJS associated with HSV may be prevented by early addition of Prednisone to Acyclovir[22], or Valacylovir.[23]

In a recent retrospective study, it has been shown that childhood HSV-associated EM may be unresponsive to treatment with oral steroids or oral Acyclovir.[11] Another study advocates continuous low-dose Acyclovir with the prompt institution of a regimen of Prednisone and higher dose of Acyclovir.[24] In our cases, the oral lesions appeared in a form that was typical to EM. The presence of elevated serum IgM to HSV, the isolation of the virus from the oral ulcers and the failure of Acyclovir therapy supported the diagnosis of HSV induced EM, despite the negative blood culture. In these cases, steroid therapy proved to be successful, whereas antiviral therapy had failed.

Recurrences of gingivostomatitis are unusual in normal hosts and are most probably caused by immune response to infection. In view of the relatively high seroprevalance of HSV types in adolescents, it is claimed that HSV infection should be studied in all EM patients. [25]

We feel that corticosteroids should still be considered as a mode of treatment in HSV-induced EM especially in cases where a failure to Acyclovir therapy is observed.

References

1. Huff JC, Weston WL. Recurrent erythema multiforme. Medicine 68:133-40, 1989.
2. Leigh IM, Mowbray JF, Levene GM, Sutherland S. Recurrent and continuous erythema multiforme-a clinical and immunological study. Clin Exp Dermatol 10:58-67, 1985.
3. Nesbit SP, Gobbeti JP. Multiple recurrence of oral erythema multiforme after secondary herpes simplex. Report of case and review of the literature. J Am Dent Assoc 112:348-52, 1986.
4. Huff JC, Weston WL, Tonnsen MG. Erythema multiforme: a critical review of characteristics, diagnostic criteria and causes. J Am Acad Dermatol 8:763-65, 1983.
5. Nesbit SP, Gobetti JP. Multiple recurrence of oral erythema multiforme after secondary herpes simplex: report of case and review of literature. J Am Dent Assoc 112:348-52, 1986.
6. American Acadamy of Pediatrics. Herpes simplex: Report of the Comittee on Infectious Diseases. 24 th .Ed. Elk Groove Village , Il. 1997, pp 267-77.
7. Lewis MAO, Forsyth A, Gall J. Recurrent erythema multiforme. A possible role of foodstuffs. Br Dent J 166:371-73, 1989.
8. Lynch M, Brightman VJ, Greenberg MS. Burket' s Oral Medicine 9th Ed. Philadelphia: J B Lippincot Co, 1994, pp 20-3.
9. Brice SL, Huff JC, Weston WL. Erythema multiforme minor in children. Pediatrician 18:188-94, 1991.
10. Lozada-Nur F, Gorsky M, Silverman S. Oral erythema multiforme: clinical observations and treatment of 95 patients. Oral Surg Oral Med Oral Pathol 67:36-40, 1989.
11. Renfro K, Grant-Kels M, Feder HM , Daman LF. Controversy: are systemic steroids indicated in the treatment of erythema multiforme? Pediatr Dermatol 6:43-7, 1989.
12. Tatnall FM, Schofield JK, Leigh IM. A double blind, placebo-controlled trial of continous acyclovir therapy in recurrent erethema multiforme . Br J Dermatol 132:267-70, 1995.
13. Kenneth S. Erythema multiforme affecting the oral cavity. Oral Surg Oral Med Oral Pathol 25:366-73, 1968.
14. Tay YK, Huff JC, Weston WC. Mycoplasma pneumonia infection in association with Stevens-Johnson syndrome and Erythema Multiforme. J Am Acad Dermatol 35:757-60, 1996.
15. Regezi JA, Sciubba J. Oral Pathology. Clinical-Pathologic Correlations. 2nd Ed. Philadelphia: WB Saunders Co, 1993, pp 1-15.
16. Malmstrom M, Ruokonen H, Kenttinnen YT, Bergroth V. Herpes simplex virus antigens and inflammatory cells in oral lesions in recurrent erythema multiforme. Acta Dermatol Venerol 70:405-9, 1990.
17. Farthing PM, Maragou P, Coats M, Tatnall F, Leigh IM, Williams DM. Characteristics of the oral lesions in patients with cutaneous recurrent erythema multiforme. J Oral Pathol Med 24:9-13, 1995.
18. Kimberlin DW, Lakeman FD, Arvin AN, Proler CG, Corey L, Powell DA, Burchett SK, Jacobs RF, Starr SE, Witely RJ. Application of polymerase chain reaction to the diagnosis and

manegement of herpes simplex virus disease. J Infect Dis 174:1162-7, 1996.
19. Rasmussen JE.. Erythema multiforme in children: response to treatment with systemic corticosteroids. Br J Dermatol 95:181-6, 1976.
20. Patterson R, Dykewicz MS , Gonzalzles A, Grammer LC. Eryhema Multiforme and Stevens-Johnson syndrome. Descriptive and therapeutic controversy. Chest 98:331-6, 1990.
21. Amir J, Harel L, Semanta Z, Varsano I. Treatment of herpes simplex gingivostomatitis with acyclovir in children. A randomized, double blind controlled study. Br.Med J 314:1800-3, 1997.
22. Detjen PF, Patterson R, Noskin GA, Phair JP, Loyd SO. Herpes simplex virus associated with recurrent Stevens-Johnson syndrome. Arch Intern Med 56:1513-16, 1992.
23. Smiley ML. Acyclovir and its 1-valyl ester - valacyclovir. Curr Probl Dermatol 24:209-18, 1996.
24. Wetson WL. Morelli JG. Herpes simplex virus-associated erthema multiforme in prepubertal children. Arch Pediatr Adolesc Med 151:1014-6, 1997.
25. Rosenthal SL, Stanberry LR, Biro FM, Slausi M. Seroprevalance of HSV 1 and 2 and CMV in adolescents. Clin Infect Dis 34:135-9, 1997.

ABSTRACT OF THE SCIENTIFIC LITERATURE

CLINICAL EVALUATION OF A NEW METHOD FOR CHEMO-MECHANICAL REMOVAL OF CARIES

The objective of this multi-centered clinical trial was to evaluate the efficacy and safety of the a new chemo-mechanical caries removal system, Carisolv. One hundred and twenty-seven patients ranging in age from 3-85 years were randomly selected for caries removal using customary drilling (20 total patients treated with this technique) or the chemo-mechanical system, Carisolv (100 total patients). The mean time for caries removal was 10.4 (±6.1) minutes using the Carisolv method and 4.4 (±2.2) minutes with drilling. Seventy-four percent of the patients treated with Carisolv reported no discomfort or much less discomfort in comparison to drilling. Approximately 3% of the patients treated with the Carisolv method and 45% of the patients treated with usual drilling techniques required local anesthetic. In conclusion, the new method was as efficacious as conventional drilling in removing caries, but caries removal with the chemo-mechanical system required twice the amount of time as conventional caries removal with a dental handpiece.

Comments: The comparison of treatment time and pain perception, presented in this study, should be interpreted with caution as each patient only received one treatment. PS

Address correspondence to: Dan Ericson, Faculty of Dentistry, Lund University, Malmo, Tandvardshogskolan SE-214 21 Malmo (Sweden)

Clinical Evaluation of Efficacy and Safety of a New Method for Chemo-Mechanical Removal of Caries. Ericson D, Zimmerman M, Raber H, Gotrick B, Bornstein R, Thorell J. Cares Res 33:171-177, 1999.
24 references

ABSTRACT OF THE SCIENTIFIC LITERATURE

CLINICAL APPLICATIONS OF MINERAL TRIOXIDE AGGREGATE

This article reviews several in vivo and in vitro, scientific and clinical reports on Mineral Trioxide Aggregate (MTA). MTA is described as a hydrophilic powder, which becomes a colloidal gel (pH of 12.5) when wet, solidifying to a hard structure in three to four hours. Descriptions of MTA's biocompatibility, ability to prevent microleakage, and to promote pulpal and tissue regeneration are referenced. Clinical applications and procedures are defined for MTA use in pulp capping (for reversible pulpitis), apexification, and repair of accidental and resorptive root perforations. Also, other potential uses for MTA are mentioned as a coronal sealant prior to internal bleaching procedures, a temporary filling material, and as a repair material for vertical fractures.

Comments: MTA seems likely to receive much attention in future research as it seems able to provide a potential treatment option for conditions where previous treatments rendered poor prognosis at best. Several potential applications in pediatric dentistry include MTA use in pulp capping, pulpotomy and apexification protocols as such procedures are described as being appropriate only on teeth with immature apices. Healing during pulp capping is more dependant on a material's capacity to prevent microleakage than on the material itself. RFM

Address correspondence to:Dr. Mahmoud Torabinejad, Department of Endodontics, School of Dentistry, Loma Linda University, Loma Linda, CA 92350.

Clinical Applications of Mineral Trioxide Aggregate. Torabinejad M, Chivian N. J Endondon 25(3):197-205, 1999.
20 (15 by the present author) references