Case Report

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

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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 mucocutaneous disorder which appears mostly as symmetrical papules, later developing into “target” or “iris” lesions with an erythematous periphery and a central zone of necrosis. Other characteristic features include bullae and vesicles. 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. 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.

Drugs, mycoplasma, and herpes simplex virus (HSV) infections were described as the most frequent causes, although other causes such as allergy to foodstuffs were also suggested. The disease may appear between one and five times annually. 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”, 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. However, in patients where EM was diagnosed by oral lesions, prevalence of skin lesions ranged only from 25% to 33%.

The efficacy of steroid treatment in EM is controversial, and has not been proven by controlled clinical trials. The prophylactic and therapeutic use of Acyclovir in cases of herpes-induced EM is now common practice. 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 on the lips.

Accepted March 11, 1999
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 27 mg/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 administered. A dramatic improvement was observed after 24 hours (Fig. 4), and complete resolution of the lesions occurred 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. 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. In one study, 20%-50% of EM cases were found to be related to herpes virus.

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. Huft reported that 25% of patients with skin lesions also had oral lesions, but no other mucous membranes were involved. However, Leigh 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%. A recent multidisciplinary study reported that 70% of EM patients had oral involvement. The oral lesions have predilection for the vermilion border of the lips and the buccal mucosa, generally sparing the gingiva.
The differential diagnosis of EM includes another vesiculobular disease—primary herpetic gingivostomatitis that differs from EM by involving all oral tissues.\(^6\) The distinction is important as corticosteroids may be the treatment of choice in EM, but not in primary herpes simplex infection.\(^6\)

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 syndrome. 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 to an early use of these drugs like in case of SJS.\(^21\) Some authors claim that SJS associated with HSV may be prevented by early addition of Prednisone to Acyclovir\(^22\), or Valacyclovir.\(^23\)

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.\(^21\) 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 seroprevalence 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


C L INICAL 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

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C LINICAL 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 (±5.1) 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

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20 (15 by the present author) references