ERYTHEMA MULTIFORME

FRANCINA LOZADA, D.D.S., M.S.
and
SOL SILVERMAN, Jr., M.A., D.D.S.
San Francisco, Calif.
University of California School of Dentistry

Reprinted from
ORAL SURGERY, ORAL MEDICINE,
ORAL PATHOLOGY
St. Louis

Vol. 46, No. 5, pp. 628-636, November, 1978
(Copyright © 1978 by The C. V. Mosby Company)
(Printed in the U. S. A.)
Erythema multiforme

Clinical characteristics and natural history in fifty patients

San Francisco, Calif.

UNIVERSITY OF CALIFORNIA SCHOOL OF DENTISTRY

Erythema multiforme is a chronic mucocutaneous inflammatory disease with a variable recurrent pattern. Thirty female and twenty male patients, ranging in age from 11 to 75 years, were studied. Twelve patients had oral lesions only, nineteen had oral and lip changes, and nineteen had oral, lip, and skin involvements. Most of the patients had a noncyclical pattern of attacks which required systemic corticosteroid therapy. When the disease attacks electively were not treated, healing would vary between 2 and 24 weeks. This study confirmed the idiopathic nature and extremely variable features of erythema multiforme. Frequency, location, duration, and severity of attacks did not shed any clues as to trigger mechanisms (etiology), persons who might be predisposed to such attacks, treatment responses, or prognosis.

* Lecturer, Department of Oral Medicine and Hospital Dentistry.
** Professor and Chairman, Department of Oral Medicine and Hospital Dentistry.
The purpose of this prospective study was to collect and examine data from patients with erythema multiforme in order to achieve a better understanding of the causative factors, diagnostic criteria, and therapeutic approaches. In this first of three reports, the clinical characteristics and natural history of patients with erythema multiforme will be described.

REVIEW OF THE LITERATURE

The literature on erythema multiforme (EM) has been scanty. This may be due to the fact that the signs and symptoms of this condition are quite variable and the less severe forms have not been well described. Therefore, retrospective and prospective series have been minimal and poorly documented. The most recent review by Al-Ubaidy and Nally\(^1\) in 1976 consisted of twenty-six cases. The patients demonstrated the variable clinical manifestations of this condition and its enigmatic etiology, and when the condition was not self-limiting the most effective form of treatment entailed the use of prednisone.

Relative to causation, much of the literature has cited the possibility of a complex interaction of factors that may initiate the signs and symptoms. These included viruses, infections, tumors, foods, drugs, alcohol, systemic disease, and immunologic factors.
Viruses

The factor most commonly associated with EM has been previous herpes simplex virus (HSV) infection. In 1933, Urbach reported the occurrence of EM following herpes labialis. In 1934, Forman and Whitewell, studying a series of thirteen patients, found that the signs and symptoms of EM followed attacks of herpes labialis in ten patients. This association was also reported in 1945 by Anderson. Al-Ubaidy and Nally also recorded that two of their patients initially had acute primary herpes simplex stomatitis.

In an attempt to assess the role of HSV in EM, many authors tried to combine clinical and laboratory data. Soltz-Szots, in 1963, induced clinical EM after challenging patients with HSV vaccine, which they were using to treat recurrent viral infections. This finding was later confirmed by Shelley. Many investigators attempted to isolate HSV in patients with EM; however, the only positive observations were found in cultures obtained from the throat, genitals, and skin lesions clinically diagnosed as herpetic lesions and not from nonspecific ulcerations identified clinically as EM.

The largest group of patients with postherpetic EM was reported by Nasemann in 1964. He stated that in a series of 405 patients with erythema multiforme there was a relationship with HSV infection in 15 percent of the cases. In all the reported studies, biopsies of the EM lesions have never demonstrated HSV or virus-like particles. Increased complement-fixing antibody titers to HSV (Types I and II) have been reported.

Drugs

Drugs have commonly been implicated as a causative factor of EM. The most commonly reported compounds have been barbiturates, phenylbutazone, digitalis, gold salts, hydralazine, iodides, mercurials, penicillins, salicylates, sulfonamides, and birth control pills.

Other diseases

Crohn’s disease, ulcerative colitis, and leiomyoma, as well as many infectious diseases, such as mononucleosis, vibrio parahemolyticus septicemia, and mycoplasma pneumoniae, have been associated with the occurrence of EM. In 1972 Nawalkha and associates postulated that the EM reactions seen in their patients who were undergoing irradiation might have been induced by substances liberated from malignant or normal cells that were being altered by irradiation or the malignant process. However, like most of the case histories reported over the years, clinical proof through adequate testing or follow-up has been inadequate to confirm the significance of these postulated associations.

Immunologic factors

There are no sound prospective studies assessing the immunologic aspects of patients with EM. As a screening procedure, immunoglobulins, lymphocyte transformation, and skin testing were performed in three patients. No obvious immunodeficiencies were apparent. In 1976, Krueger and colleagues reported that in two of four patients with EM they were able to show an increase of macrophage aggregation activity. In 1977, Safai and co-authors postulated that an immunologic mechanism may be involved in the pathogenesis of EM, suggesting the presence in blister fluid of immune complexes activated by complement components via the classic pathway.
Table I. Characteristics of fifty patients with erythema multiforme

<table>
<thead>
<tr>
<th>Lesion site(s)</th>
<th>Sex</th>
<th>Age at onset of disease (range in yrs.)</th>
<th>Duration of disease (range in yrs.)</th>
<th>Nature of attacks</th>
<th>Duration of attacks without treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td></td>
<td>Noncyclical*</td>
<td>Cyclical</td>
</tr>
<tr>
<td>Oral</td>
<td>9</td>
<td>3</td>
<td>21-65</td>
<td>2-25</td>
<td></td>
</tr>
<tr>
<td>Oral, lip</td>
<td>13</td>
<td>6</td>
<td>11-75</td>
<td>1-10</td>
<td>16</td>
</tr>
<tr>
<td>Oral, lip, skin</td>
<td>8</td>
<td>11</td>
<td>11-64</td>
<td>1-12</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>20</td>
<td>11-75</td>
<td>1-25**</td>
<td>40</td>
</tr>
</tbody>
</table>

*Patients in whom the signs of disease had persisted at least one month without any evidence of remission prior to treatment.

**Mean = 3 years; average = 4 years.

MATERIALS AND METHODS

The study group comprised fifty consecutive patients with erythema multiforme seen at the Oral Medicine Clinic of the University of California in San Francisco, for whom follow-up visits were possible. There were thirty female and twenty male patients, ranging in age from 11 to 75 years. The following criteria were used for establishing the diagnosis:

1. A history of persistent or recurrent oral ulcerations with or without lip and skin lesions.
2. Clinical findings as follows: diffuse oral erythema and irregular ulcerations frequently covered by pseudomembranes; ulceration and crusting of lips; skin macules and papules, often with crusting (Figs. 1 to 11).
3. A biopsy which rules out other oral mucocutaneous ulcerative diseases and often showed a perivascular lymphocytic cellular infiltrate.

Each patient was evaluated with a complete medical history and physical examination. Oral and skin lesions were photographed.

Laboratory examination included complete blood counts, direct culture for herpes virus, and biopsies of representative lesions. Ten biopsy specimens were processed for direct immunofluorescence.

The patients were followed and treated from 1 to 25 years, with a mean of 3 years and an average of 4 years. During this follow-up period, in most patients the pattern of attacks remained the same.

RESULTS

Patient characteristics

Table I illustrates the wide diversity of characteristics found among the patients. Variations in the duration of attacks, recurrence time, and pain occurred within individuals. Age and sex did not appear to be influential factors relative to occurrence or any other features of the disease. In addition, there were no positive family histories to suggest a genetic predisposition.

Systemic corticosteroid treatment was administered in forty-nine of the fifty patients. It was required in thirty-eight of the patients because of painful symptoms and no immediate evidence that the disease was self-limiting. Although all patients would respond
to corticoid therapy, time-dosage schedules were quite variable. Some persons would respond dramatically to 20 mg. of prednisone daily within 72 hours, while others would require dosages exceeding 50 mg. per day. Several of these patients had endured persistent manifestations for many years until the present diagnosis was established and treatment implemented.

In ten of the patients with observed self-limiting disease, corticosteroid treatment was initiated because of the disabling pain that accompanied some flare-ups. In these patients, not every attack required definitive therapy, since occasionally the pain was moderate. The duration of attacks in the patients with cyclical disease when corticoids were not used varied from 2 weeks to 6 months. In general, the sites of mucosal or cutaneous manifestations during active attacks were quite constant and predictable.

**Causative factors**

In 52 percent of the patients an initiating factor could never be identified. In the remaining cases, although there were no consistently identifiable factors, the patients reported events that they were certain led to the signs and symptoms on occasion (Table II). Stress or emotional upset was identified by 20 percent of the patients. Food products were mentioned in only 16 percent; in two of these patients, nuts were specifically identified.

Herpes labialis was thought to precede some attacks in 14 percent. Drugs were identified by only two patients as a cause; however, in both of these patients attacks would also occur when the drug was not being used. In no instance was a definitive trigger mechanism responsible for every flare-up in a patient.

**Laboratory examinations**

The laboratory tests performed did not yield any specific interpretive information regarding causation, predisposition, or progress of the disease. All complete blood counts were within normal limits before, during, and after attacks. Cultures for HSV obtained from thirteen patients during active flare-ups were all negative for viruses.

Biopsy specimens prepared for routine microscopic study showed a nonspecific inflammatory infiltrate and acanthosis in most instances. In some patients, however, an
irregular epithelial hyperplasia with a tendency toward acantholysis and discrete perivascular lymphocyte infiltrates appeared suggestive diagnostically. Ten of the specimens from active disease sites were prepared for direct immunofluorescence. Seven specimens showed no activity; three revealed activities that were nonspecific for any disease and inconsistent with each other.

**DISCUSSION**

This study of fifty patients with erythema multiforme (EM) confirmed the idiopathic nature and extremely variable features of this disease. Fifty-two percent of the patients could never correlate the onset of signs and symptoms with any specific event or agent. In addition, not one of the remaining patients could identify contributory factors in all, or even most, of their attacks.

The lesions occurred on the mucous membranes, the vermilion border of the lips, and the skin independently or simultaneously. Close examination of the lesions with respect to location, frequency, duration, and severity of attacks has not yielded any clues as to trigger mechanisms, persons who might be predisposed to such attacks, treatment responses, or prognosis. In those patients who have had persistent lesions (not self-limiting for periods exceeding a minimum of one month), there were no evident explanations as to onset or persistence.
Fig. 8. Tongue erosions of erythema multiforme that were not self-limiting and always recurred almost immediately when prednisone was withdrawn.

Fig. 9. Buccal mucosa involvement that would respond rapidly to corticoids and remain in remission for varying periods of time. Note ulceration \( U \) and keratotic component \( K \).

Fig. 10. Gingival manifestation chiefly of erythema that had been present and painful for 4 months \( (arrows) \). There was an immediate response to prednisone; recurrent flares occurred irregularly. There was no associated periodontal disease.

Fig. 11. Typical palatal lesion showing irregular ulcerations with pseudomembrane formation, erythema, and keratosis.

Many authors quoted in the review of the literature have indicated that the herpes simplex virus (HSV) may be an etiologic factor of EM. Specifically, Soltz-Szots\(^20\) reproduced EM in human subjects following local intradermal injections of inactivated HSV. In our group, seven patients reported that cold sores (herpes labialis) sometimes preceded attacks involving either mucous membranes and/or skin. This supports the possibility that in some patients HSV may serve as a co-antigenic factor in this debilitating inflammatory process. Negative viral cultures do not necessarily rule out a viral relationship, since at the time of sampling the virus could be in the nonviral form (core protein that must be identified by special complement-fixation procedures). Also, in recurrent viral attacks (herpes labialis and herpes genitalis), the viral disease can be manifested even in the presence of circulating antibodies.

This series also confirmed that the symptoms of erythema multiforme could be so severe that some patients were incapacitated to the extent of not being able to speak, eat, or work. Therefore, recognition and correct management of the condition are extremely important. Because the disease has such variable signs and symptoms, diagnosis is often difficult; thus, many patients are misclassified and mistreated. This may be the principal
Table II. Causative factors in fifty patients with erythema multiforme

<table>
<thead>
<tr>
<th>Alleged trigger mechanism</th>
<th>Oral</th>
<th>Oral, lip</th>
<th>Oral, lip, skin</th>
<th>Frequency (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always unknown</td>
<td>10</td>
<td>12</td>
<td>4</td>
<td>52</td>
</tr>
<tr>
<td>Occasionally associated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>Food(s)</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Herpes</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Sunlight</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Trauma</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Flu</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Drugs</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Menstruation</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

reason why there is such relatively scant literature on EM. Our group constitutes the largest prospective study of EM patients that could be identified by a review of the literature.

The patients in this study used a variety of topical agents and systemic drugs to palliate their symptoms. The only reproducibly effective means of control was with the systemic use of corticosteroids (prednisone). Drug dosage, duration of treatment, side effects, and subsequent flare-ups varied widely between patients. The side effects in some cases were so objectionable to the patients that the course of treatment often had to be modified. A critical assessment of prednisone efficacy and side effects in a double-blind study is currently being carried out. Since some treatment requires long-term use of corticosteroids, the side effects on blood sugar, weight, blood pressure, and circulating cortisol levels will be included with the analysis of side effects. While prednisone, when used, diminished the duration of each flare-up, it did not seem to influence the frequency of attacks.

According to clinical and historical findings, the patients appeared to be immunocompetent in that they had no particular problems with allergies or other chronic illnesses. Thirteen of the patients at random were evaluated by skin testing with four recall antigens and by in vitro immunologic tests. They were also entered in a therapeutic trial using levmisole. The findings will be reported in subsequent papers.

Since these patients were selectively referred patients, extrapolations of EM as it occurs in a more general population cannot be assumed. However, this study at least confirms that a segment of the EM population forms a group presenting difficulties in diagnosis and management.

Appreciation is expressed to Dr. Denis Lynch for his assistance in the review of the literature.

REFERENCES


Reprint requests to:
Dr. Francina Lozada
Room 657-S
Department of Oral Medicine and Hospital Dentistry
School of Dentistry
University of California
San Francisco, Calif. 94143