Oral erythema multiforme: trends and clinical findings of a large retrospective European case series

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Objective. Erythema multiforme (EM) continues to be an underestimated disease with a lack of strict classification and diagnostic criteria. We present the analysis of a case series of 60 oral EM patients from 2 centers and illustrate the range of oral clinical presentations.

Study Design. Clinical data from 60 EM patients with oral involvement, diagnosed and treated between 1982 and 2014, were retrospectively collected from the archives of 2 independent hospitals. Statistical analyses of the data were performed using the Pearson χ-squared test and the Mann-Whitney U test.

Result. Thirty-one patients (51.7%) were male and 29 (48.3%) were female, with a mean (±SD) age of 37.9 years (±18.1). The frequency of previous occurrences ranged from 0 to 10 (mean ± SD: 1.4 ± 2.0). Twenty-nine patients (48%) had no previous occurrence. Medications (particularly antipyretics, food additives, and antibiotics) were the suspected precipitants in 28 patients (46.7%), whereas herpes simplex virus infection was suspected in 18 (30.0%). All but 1 patient had involvement of multiple oral sites, with the buccal mucosa being the most commonly involved oral site (75%), followed by the vermillion border (71.7%).

Conclusions. Patients with EM may present initially to oral health care workers. Medications and herpes simplex virus continue to be the most typically involved precipitating factors. Our data highlight the additional role of food-derived antigens. Although laboratory tests can provide support diagnostically, EM diagnosis continues to be based on clinical features. A medication and food diary should be encouraged particularly in patients with recurrent forms. (Oral Surg Oral Med Oral Pathol Oral Radiol 2015;120:707-716)

Erythema multiforme (EM) is a group of acute immune-mediated disorders that can affect the skin and mucous membranes. It has previously been classified into 4 major variants: erythema multiforme minor (EMm), erythema multiforme major (EMM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN, also known as Lyell disease).[1-3]

Many authors still consider EMm, EMM, SJS, and TEN to be a single disease continuum, varying on a spectrum of clinical severity. Others consider EM a separate entity to SJS and TEN, particularly due to its strong association with infections, such as herpes simplex virus (HSV).[3] This is in contrast to the majority of cases of SJS and TEN, which are commonly medication induced. Additionally, cutaneous findings may be distinct, although clinical overlap does exist.[3-9]

The development of EM has been linked to a type 4 cytotoxic reaction, mediated by T lymphocytes and triggered by numerous factors. These include infections (particularly HSV-1 and HSV-2), medication use, malignancy, autoimmune diseases, radiation therapy, and immunizations.[10]

Many pathogens have been associated with EM, including *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, hepatitis viruses, Epstein-Barr virus, Orf virus, human immunodeficiency virus, cytomegalovirus, *Mycobaterium leprae*, and varicella zoster virus, as well as several vaccination agents (small pox, rabies, and human papillomavirus).[11-31] Additionally, endocrine triggers have been implicated in the occurrence of EM.[32,33]

The differential diagnosis of EM encompasses a wide range of diseases, including urticaria, fixed drug

Statement of Clinical Relevance

Prompt recognition of erythema multiforme by all oral health clinicians is important to prevent diagnostic delay as oral mucosal involvement may precede extension of the disease. Identification of trigger factors and diagnostic features is pertinent as illustrated by this case series.

The study was approved by the Ethics Committee of the University "Federico II" of Naples in June 2014.

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eruption, bullous pemphigoid, paraneoplastic pemphigus, Sweet syndrome, Rowell syndrome, polymorphous light eruption, and cutaneous small vessel vasculitis. To improve the diagnostic accuracy, histopathologic analyses and others laboratory tests can be used.[14] Cutaneous involvement is variable, ranging from isolated symmetric targetoid lesions, which are commonly distributed on the extensor surfaces of the extremities; on the hands; around the elbows and knees with extensive involvement of the arms, legs, and trunk; and with or without oral or other mucous membrane involvement.[1,14] Both SJS and TEN can be fatal, with a reported mortality rate of 1% to 5% and 25% to 35%, respectively.[34]

EM is usually a self-limiting disease, resolving within weeks without significant sequelae. However, in a minority of cases, the disease may recur frequently, establishing a well-defined variant known as "recurrent EM."[35,36]

Most patients with EM can be managed with symptomatic therapy along with identification and modification of all the suspected initiating factors. However, patients with severe EM may require hospitalization for hydration, analgesia, antiviral therapy, and systemic therapy with corticosteroids, immunosuppressants, and/or antiviral suppressive therapy.[14,35] Daily antiviral therapy has been used successfully to control the disease in patients with recurrent EM.[37]

Knowledge about EM is full of conflict. Diagnostic criteria are not universally accepted, and the diagnosis continues to be one of exclusion, based on clinical history. Epidemiologic data and case series in the literature are dated. Additionally, there is a lack of extensive EM case series demonstrating the range of oral presentations. Here, we present the analysis of a series of 60 patients affected by EM with oral involvement. The range of clinical presentation is illustrated.

MATERIAL AND METHODS

Data were collected from clinical records of 60 EM patients, diagnosed and treated between 1982 and 2014 in 2 centers: the Oral Medicine Unit, Federico II University of Naples in Naples, Italy (Center 1), and the Oral Medicine-Oral Pathology Department, University of Medicine and Pharmacy in Bucharest, Romania (Center 2).

The study was approved by the Ethics Committee of the University "Federico II" of Naples in June 2014. Data were collected by 2 blinded researchers and confirmed by 1 supervisor, the heads of the respective Oral Medicine departments. A digital template, developed at Center 1, was utilized at both centers. Data collected included age, gender, habits, number and duration of outbreaks, previous or concomitant infections, antecedent drugs or other precipitants, presence of mucosal and cutaneous lesions, oral sites involved, histopathologic findings, and details of hospitalization.

Inclusion criteria of the first phase of the study required a definitive diagnosis of EM and/or SJS in the clinical discharge summary. Acknowledging the absence of unique validated diagnostic methods for EM,[3,7] this study included only those cases in which other diseases were clearly excluded from the differential diagnosis. Cases were only included in the study if the following data were clearly recorded: patient medical history, medication history, outbreaks details, course of the illness (self-limiting and well-responder to symptomatic therapy), evidence of mucocutaneous lesions (fixed targetoid lesions, raised atypical papules, mucosal involvement, or a combination of these) with clinical and/or photographic morphology descriptions and/or information on the extent of mucocutaneous involvement, signs, and symptoms. The clinical-based approach described by Al-Johani et al (2007) was used to classify the clinical forms of our cases.[3] The analysis of site distribution was performed with the Pearson χ-squared test. The dependence analysis between lesion site and age and significant difference between medians was determined using a Mann-Whitney U test.

RESULTS

Initially, 67 EM medical records were included; however, 7 cases were inadequate in description or did not satisfy the diagnostic criteria and were excluded from the study, thus leaving 60 patients. Fifteen EM patients were obtained from Center 1 and 45 patients from Center 2.

Thirty-one patients (51.7%) were male, and 29 (48.3%) were female, with a mean ($\pm$SD) age of 37.9 years ($\pm$18.1) at the time of diagnosis. Seventeen patients were smokers, and 1 case of alcohol abuse was reported.

Fifty-one (85.0%) patients were classified as EMm, and 9 (15%) were classified as EMM.

The mean duration of the EM outbreaks was 7 ± 6 days (ranging from 2 to 42 days). The number of previous outbreaks ranged from 0 to 10 (mean $\pm$ SD $= 1.4 \pm 2.0$). Twenty-nine patients (48%) had not experienced a previous outbreak, 9 patients (15%) had a single previous outbreak, and 22 patients (37%) had 2 or more outbreaks. Sixteen cases had accompanying histopathology with predominant findings of necrosis, intraepithelial exocytosis, necrotic keratinocytes, Civatte bodies, edematous corium hyperemic vessels, lymphohistiocytic inflammatory infiltrate with rare eosinophils, and subepidermal clefts. No deeper extension of the infiltrate or prominent melanin incontinence was observed, which allowed us to exclude cases of fixed drug eruptions. Drugs were suspected as

Table I. Data of 60 patients: epidemiology, predisposing factors and clinical features

						Involved oral sites								
No.	*HSV infection*	*Other infections*	*Drug antecedents/other precipitants*	*Other affected mucosae*	*Skin lesions*	*B*	*L*	*V*	*T*	*A*	*F*	*P*	*TP*	*Classification*
1	No	No	Sulfonamide	No	Yes: Arms symmetrically	X	X	X	X	X				EMm
2	No	No	Sulfonamide (Sumetrolim)	No	No	X	X							EMm
3	No	No	No	No	Yes: Lips symmetrically		X	X						EMm
4	No	No	Sulfonamide (Sumetrolim)	No	No	X			X					EMm
5	Yes	No	No	No	No					X		X		EMm
6	No	No	Food allergen	No	Yes: Lips	X	X	X	X					EMm
7	No	Respiratory virosis	No	No	No	X	X					X		EMm
8	No	Tonsilar infection	No	No	Yes: Perioral			X		X		X		EMm
9	No	No	Phenazone	No	Yes: Perioral	X	X	X			X	X		EMm
10	Yes	No	Phenazone	No	Yes: Perioral	X			X			X		EMm
11	Yes	Flu	Phenazone	No	Yes: Perioral	X	X	X						EMm
12	No	No	Food allergen	No	No	X	X	X	X					EMm
13	Yes	No	No	No	Yes: Perioral	X	X	X	X	X	X	X		EMm
14	No	No	Paracetamol	No	No			X	X			X		EMm
15	No	No	Phenazone	Yes: ocular	No	X		X			X	X		EMM
16	No	No	Fluanxol, haloperidol	No	No	X		X	X					EMm
17	No	No	Phenazone	No	Yes: Arms, palms			X		X				EMm
18	No	No	No	No	Yes: Knees, elbows, feet,	X		X	X					EMm
19	No	No	No	No	No	X								EMm
20	No	No	Amoxicillin, paracetamol	Yes: ocular	No	X	X	X	X			X		EMM
21	No	HCV	No	No	No			X						EMm
22	No	No	Food conservants	No	No	X	X				X	X	X	EMm
23	No	Pericoronarytis of 48	No	No	Yes: Perioral		X	X	X					EMm
24	Yes	No	No	No	No	X		X						EMm
25	No	Urinary Infection (2005)	Augumentin, ciprofloxacin, fluoconazol	No	No			X						EMm
26	No	No	Food antigens	No	No		X							EMm
27	No	Urinary infection	Nystatin, bioparox, local antiseptics, local propolis	No	Yes: Palms	X	X	X			X			EMm
28	No	Pneumonia	No	No	No		X	X						EMm
29	No	No	Doxicyclin	No	Yes: Fingers symmetrically	X	X	X				X		EMm
30	No	Tubes infection (genital)	Triregol, ciprofloxacin, sumetrolin, ampicillin, birth control pills	No	No	X	X	X				X		EMm
31	Yes	No	No	No	No	X		X					X	EMm
32	Yes	No	No	No	No	X			X					EMm
33	No	No	Diclofenac, diflucan	No	No	X	X	X	X	X	X	X		EMm
34	No	No	Amoxicillin, metronidazol, food allergens	No	No	X			X	X		X		EMm
35	Yes	No	Acyclovir	No	Yes: Arms, perioral	X		X				X		EMm
36	No	No	Paracetamol	No	Yes: Arms	X	X		X				X	EMm

(*continued on next page*)

Table I. Continued

No.	HSV infection	Other infections	Drug antecedents/other precipitants	Other affected mucosae	Skin lesions	Involved oral sites								Classification
						B	L	V	T	A	F	P	TP	
37	Yes	No	Acyclovir	No	Yes: Arms, palpebral	X	X	X	X					EMm
38	Yes	No	No	Yes: genital	No	X	X	X	X	X	X	X		EMM
39	No	HBV (2009)	No	No	No	X	X	X	X					EMm
40	No	No	Food antigens	No	No	X	X							EMm
41	Yes	No	No	No	Yes	X	X							EMm
42	Yes	No	No	No	No		X							EMm
43	No	No	Phenazone	No	No	X		X					X	EMm
44	No	Pneumonia	Phenazone	No	No		X	X	X				X	EMm
45	No	HCV	No	No	No	X	X	X	X			X		EMm
46	No	No	Food antigens	No	No			X	X					EMm
47	Yes	No	No	Yes: Genital	Yes: Elbows, palms	X	X	X						EMM
48	No	No	Phenazone	Yes: Ocular, Genital	Yes: Acral	X	X		X					EMM
49	No	Mycoplasma	No	No	Yes: Widespread				X		X			EMM/mild SJS
50	Yes	No	No	No	Yes: Acral	X	X	X	X	X	X	X		EMm
51	No	No	Salycilate	No	Yes:Acral	X		X	X	X				EMm
52	No	No	K sigma 1 year before	Yes: Genital	No	X	X	X	X		X		X	EMM/mild SJS
53	Yes	No	No	No	Yes: Perioral	X	X	X	X	X	X			EMm
54	Yes	No	No	No	No	X	X	X	X			X		EMm
55	No	No	Ketoprofen	No	Yes: Acral	X			X	X		X		EMm
56	No	No	Ampicillin	No	No	X	X	X	X					EMm
57	No	Adenovirus (pharynx)	No	No	No	X	X	X	X	X				EMm
58	Yes	No	Paracetamol	No	No	X		X	X	X		X		EMm
59	Yes	No	No	Yes: Nasal	No	X	X	X	X	X	X	X	X	EMM/mild SJS
60	No	No	Mefloquine	Yes: Genital	Yes: Acral	X	X	X	X	X	X			EMM

Involved oral sites: B, buccal mucosa; L, labial mucosa; V = vermilion border; T, tongue; A, alveolar mucosa; F, floor of the mouth; P, palate; TP, tonsillar pillar.
EMm, erythema multiforme minor; EMM, erythema multiforme major; SJS, Stevens-Johnson syndrome; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus.

Table II. Distribution of site of lesions by gender

Site	Gender		Total	P value*
	Female	Male		
B	Yes 79.3%	Yes 71.0%	Yes 75.0%	.556
	No 20.7%	No 29.0%	No 25.0%	
L	Yes 72.4%	Yes 51.6%	Yes 61.7%	.098
	No 27.6%	No 48.4%	No 38.3%	
V	Yes 79.3%	Yes 64.5%	Yes 71.7%	.204
	No 20.7%	No 35.5%	No 28.3%	
T	Yes 62.1%	Yes 51.6%	Yes 56.7%	.414
	No 37.9%	No 48.4%	No 43.3%	
A	Yes 27.6%	Yes 25.8%	Yes 26.7%	.876
	No 72.4%	No 74.2%	No 73.3%	
F	Yes 37.9%	Yes 6.5%	Yes 21.7%	.003†
	No 62.1%	No 93.5%	No 78.3%	
P	Yes 34.5%	Yes 38.7%	Yes 36.7%	.734
	No 65.5%	No 61.3%	No 63.3%	
TP	Yes 13.8%	Yes 9.7%	Yes 11.7%	.620
	No 86.2%	No 90.3%	No 88.3%	
Number of sites with lesions	Median−IQR 4.03.0	Median−IQR 3.0 2.0	Median−IQR 3.5−3.0	.095

IQR, Interquartile range. The significance difference between conditional distributions was measured by the Pearson χ-squared test. The significance difference between medians was measured by the Mann-Whitney U test.
*Significant $P < .01$ to $\leq .05$.
†Significant $P \leq .01$.

Table III. Dependence analysis between drug antecedents and precipitators

	Precipitators	Median−IQR	P value*
No. of drug antecedents	Herpes		.002†
	Yes	0.0−1.0	
	No	1.0−1.0	
	Infection		.418
	Yes	0.0−2.0	
	No	1.0−1.0	
	Classification		.929
	EM minor	1.0−2.0	
	EM major	1.0−1.0	

IQR is the interquartile range. The significance difference between medians was measured by Mann-Whitney U test.
*Significant $.01 < P \leq .05$.
†Significant $P \leq .01$.

Table IV. Dependence analysis between demographic characteristics and precipitators

Precipitators	Gender		P value*
	Female	Male	
Herpes simplex virus	Yes 34.52%	Yes 25.8%	0.464
	No 65.5%	No 74.2%	
Other Infections	Yes 17.2%	Yes 29.0%	0.281
	No 82.8%	No 71.0%	
Classification	EM major 24.1%	EM major 6.5%	.045†
	EM minor 75.9%	EM minor 93.5%	
	Age Median−IQR		
HSV	Yes 29−17		.628
	No 30−33		
Other Infections	Yes 29−34		.993
	No 29−27		
Classification	EM major 39−40		.045†
	EM minor 29−27		

IQR is the inter-quartile range. The significance difference between conditional distributions was measured by the Pearson χ-squared test. The significance difference between medians was measured by the Mann-Whitney U test.
*Significant $P < .01$ to $\leq .05$.
†Significant $P \leq .01$.

precipitants in 28 patients (46.7%), the most implicated being antipyretics, food allergens, and antibiotics.

HSV infection was suggested to be a triggering factor in 18 patients (30.0%), 10 of whom had supportive serologic HSV testing (8 enzyme-linked immunosorbent assay test and 2 polymerase chain reaction [PCR]). In 13 patients (21.6%), a medical history of previous infections was reported, 11 of which were concomitant to the EM outbreak. These infections included pneumonia (3 cases), urinary infection (2 cases), and *M. pneumoniae* (1 case). Two patients were found to be positive for hepatitis C. A concomitant history of candidiasis was reported in 3 cases (2 oral and 1 genital). Hospitalization of the patient was required in 7 cases (11.6%). Table I presents the summary of clinical data from case series. All infections reported in the clinical record within 30 days from the diagnosis of EM were recorded under consideration as "concomitant" infections. The infections described in Table I thus occurred within 30 days before the EM presentations, unless otherwise specified.

Exclusive oral involvement was observed in 29 patients (46.66%). All but 1 patient had involvement of

multiple oral sites. The buccal mucosa was the most commonly involved oral site (75%) followed by the vermillion border (71.7%) and labial mucosa (61.7%). Twenty-four of 60 patients (40.0%) had concomitant involvement of all of these sites, and 44 (73.3%) patients had involvement of at least 2 of 3 sites. Details of sites involved for each case are described in Table I.

The floor of mouth was significantly more commonly involved in females (37.9%) than in males (6.5%) ($P = .003$) (Table II). Involvement of the tongue was significantly related to age (median interquartile range: Yes = 32-33 years; no = 25-21 years; $P = .013$). Clinical forms were significantly associated with gender (female: EMM = 24.1%; EMm = 75.9%; male: EMM = 6.5%; EMm = 93.5%; $P = .045$). Other significant results of the dependence analysis are shown in Tables III and IV.

DISCUSSION

Current literature regarding the epidemiology of EM remains scarce and controversial. This is reflective of the lack of universally accepted classification criteria. Additionally, there may be a component of underreporting, particularly of cases of short duration when hospitalization is not required. This study presents the largest oral EM case series in last 2 decades,[38,39] describing the multiple clinical features that characterize this group of diseases, and the dependence analysis of associated variables.

The consensus is that EM and related disorders occur predominantly in young adults, with majority of cases occurring between the second and fifth decades of life.[3,39] There is no a clear predilection for gender or race. However, variation in age at presentation should not be underestimated, as several cases of pediatric patients have been reported, including neonates.[20,40-45] In our case series, the mean age was 37.9 years (range 7-78 years), with no significant difference between males and females. Interestingly, there was a significant gender predilection for the clinical forms with EMM being more frequent in the females and EMm being more frequent in males. Clinical forms were additionally significantly related to age (see Table IV).

The most commonly reported triggers are infections agents and medications, with HSV-1 and HSV-2 being the most commonly reported precipitators of EMm and EMM. Medications and HSV, taken together, were implicated in approximately 67% of cases in our series.

Typically, the onset of EMm and EMM lesions begins 10 to 14 days after the clinical manifestation of an HSV infection.[3] Unfortunately, the number of studies using confirmatory PCR to assess for the presence of HSV-DNA is low, with conclusion of infection based predominantly on clinical history. The reported association of HSV with the recurrent variant of EM is between 61% and 100%.[14] The percentage of patients affected solely by HSV without a history of medication use in our series was 21.6% (13 cases), which is similar to the 23% reported by Wetter and Davis in 2010, but dissimilar from the 70% to 100% values reported by Schofield in 1993 and Huff in 1983.[2,35,46]

Five more cases were also potentially associated with HSV, but the patients were using medications simultaneously. It is not uncommon for patients affected by EM, in association with a concomitant or previous infection, to have started drug therapies (e.g., antibiotics, antivirals, or anti-inflammatory drugs). Of the total of 18 patients (30.0%), 10 patients (16.7%) were screened for HSV exposure by using serologic tests. Some authors have suggested the use of a Tzanck smear test, which is an easy and inexpensive test to identify viral balloon cells.[47] However, PCR assays are much more sensitive and target a wide range of infectious agents. Thus, PCR should form part of the mandatory criteria to clearly identify the trigger and to support the use of antivirals in particular patients.

Currently, the literature consistently supports medications as precipitants in more than 50% of EM episodes.[1-3,48] Some authors have reported figures as low as 10% of cases, although this has not been our experience.[49,50] Moreover, the list of the medications associated with the induction of EM continues to expand and include new categories of drugs, such as tyrosine-kinase inhibitors; biologic agents, such as tumor necrosis factor-α inhibitors, phosphoinositide 3-kinase inhibitor, retinoids.[51-59] In our experience, medication use has a marked role as a triggering factor in 28 patients (46.7%). The most commonly implicated medications were nonsteroidal anti-inflammatory drugs, antibiotics, antifungals, and antivirals. In 1 case, the oral contraceptive pill was also considered to be associated. Alcohol consumption has been reported as a risk factor in drug-induced EM, particularly if it is associated with antiepileptic therapies.[60,61] Our case series included 1 case of alcohol abuse with unknown significance.

Food-borne antigens, triggers first suggested by Lozada in 1978, were supported by evidence as playing an important role in 7 cases of our series.[62] Another suggested trigger is radiotherapy, although concomitant medication use is an expectant common confounder.[63-65] There was no history of radiotherapy present in our case series.

In a previous case series, *M. pneumoniae* infection was reported to be responsible for almost two-thirds of SJS cases, particularly in childhood cases, although it was never associated with a typical EM eruption.[66] In contrast, the role of this infection in EM has recently been challenged and re-evaluated, suggesting that the *M. pneumoniae*-induced rash and mucositis may

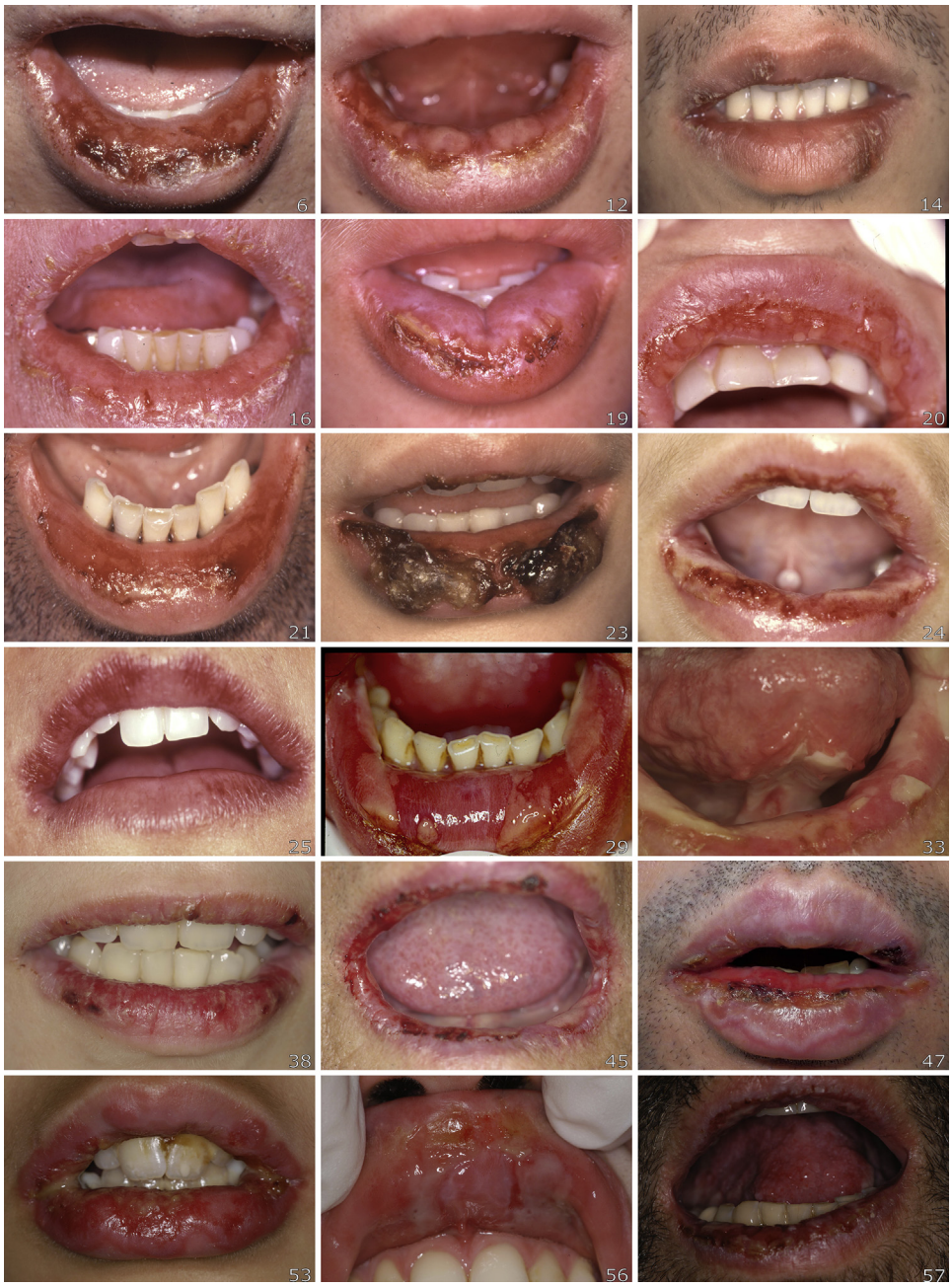

Fig. 1. The presenting labial clinical features were dominated by an erosive/bullous pattern and crusting. The number found in the lower right corner corresponds to the patient number as reported in Table I.

represent a distinct syndrome from EM and SJS.[67] An established association with *M. pneumoniae* was clearly reported in only 1 of our 3 pneumonia case, a 73-year-old female. Positive culture tests for *Candida* were only found in only 3 (5%) of our cases (2 oral and 1 genital), a lower rate than the 20% reported by Lozada-Nur in 1989.[38] Cases of "persistent EM," a rare variant of the disease characterized by uninterrupted lesion eruptions often linked with Epstein-Barr virus infection, were not present in our series.[14,15]

The character of presenting clinical features of EM potentially can change during the course of the disease, leading to an overlap of the variants. Oral involvement in EM is reported in 60% to 70% of cases.[1,2] In our series, exclusive oral involvement was observed in 29 patients (46.6%). Lesions were predominantly erosive or bullous with the buccal mucosa, vermilion border, and labial mucosa being the most commonly affected sites. Figure 1 presents typical crusting of the vermilion border seen in exclusively oral EM. This site may

predisposed to by its particular epithelial and connective tissue structures and the immunologic composition. In these cases of exclusive oral involvement, clinicians should consider the differential diagnosis with focus on the timing of the outbreak, history of drug consumption, the course of the illness, atypical sites involved, and symmetric distribution of the lesions. Eight cases (13.3%) of our series presented with at least 1 additional site of mucosal involvement, genital in 4 cases (6.7%), ocular in 2 cases (3.3%), nasal in 1 case (1.7%) and genital and ocular in 1 case (1.7%). Cutaneous involvement was found in 25 cases (41.7%), particularly perioral lesions in 10 cases (16.7%), followed by acral in 5 cases (8.4%) and arm lesions.

According to the current classification criteria, different clinical forms are broadly categorized on the basis of the presence, morphology, and extension of the mucocutaneous disease. Some authors accept a diagnosis of EM in patients with less than 10% of body surface area (BSA) involvement, defining the disease beyond this as SJS/TEN.[3] All the cases described in our case series had no more than 10% of BSA involvement. EM is further subdivided into EMm and EMM and variably defined by either the presence or absence of mucous membrane involvement or the extent or number of mucosal sites involved.[3,14,46,68] In our study, we utilized the classification system described by Al-Johani et al (2007), which distinguishes EMm and EMM as involvement of 1 or more than 1 mucosal sites, respectively.[3] Fifty-one (85.0%) of our patients were classified as EMm, and 9 (15%) were classified as EMM.

The most accepted criteria to differentiate the diagnoses of EMM and SJS, regardless of BSA involvement, are centered on the basis of the presence of systemic symptoms and a positive Nikolsky sign.[3] Utilizing such criteria, 3 of our EMM cases that required hospitalization could be reclassified as mild forms of SJS.

More than half of the patients had experienced at least 1 previous outbreak, which supports the commonality of recurrence. Seven of our cases (11.6%) could be considered the recurrent variant of EM, which is lower than the rate reported by Cretu et al (20%).[69]

The limitations of this retrospective study include acceptance of the variations in the use of clinical tests and the limited use of HSV PCR and dietary records across the 30 years during which these patients were observed. Furthermore, the difficulty in collecting recent data on the same patients through recall affected our ability to better define the clinical behavior of the disease and patient responses to previous exposures to triggers, and therefore the outcome of our cohort.

CONCLUSIONS

EM may present initially with oral mucosal involvement before an increase in disease severity. Prompt recognition, particularly of bilateral bullous and ulcerative involvement of the buccal mucosa, the labial mucosa, or the vermilion border, is important to avoid any delay in diagnosis. Although approximately half of those presenting with EM report no previous episodes, it remains unclear which of these patients will progress to recurrence, so all patients should be informed and encouraged to have an awareness of their exposures to drug and food antigens. With the lack of universally accepted classification criteria and the absence of specific diagnostic tests, EM, especially in its mild forms, continues to be an underestimated disease.

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