STUDY

Correlations Between Clinical Patterns and Causes of Erythema Multiforme Majus, Stevens-Johnson Syndrome, and Toxic Epidermal Necrolysis

Results of an International Prospective Study

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Background: It was proposed that Stevens-Johnson syndrome and toxic epidermal necrolysis differed from erythema multiforme majus by the pattern and localization of skin lesions.

Objective: To evaluate the validity of this clinical separation.

Design: Case-control study.

Settings: Active survey from 1989 to 1995 of 1800 hospital departments in Europe.

Patients: A total of 552 patients and 1720 control subjects.

Methods: Cases were sorted into 5 groups (erythema multiforme majus, Stevens-Johnson syndrome, Stevens-Johnson syndrome–toxic epidermal necrolysis overlap, toxic epidermal necrolysis, and unclassified erythema multiforme majus or Stevens-Johnson syndrome) by experts blinded as to exposure to drugs and other factors. Etiologic fractions for herpes and drugs obtained from case-control analyses were compared between these groups.

Results: Erythema multiforme majus significantly differed from Stevens-Johnson syndrome, overlap, and toxic epidermal necrolysis by occurrence in younger males, frequent recurrences, less fever, milder mucosal lesions, and lack of association with collagen vascular diseases, human immunodeficiency virus infection, or cancer. Recent or recurrent herpes was the principal risk factor for erythema multiforme majus (etiologic fractions of 29% and 17%, respectively) and had a role in Stevens-Johnson syndrome (etiologic fractions of 6% and 10%) but not in overlap cases or toxic epidermal necrolysis. Drugs had higher etiologic fractions for Stevens-Johnson syndrome, overlap, or toxic epidermal necrolysis (64%-66%) than for erythema multiforme majus (18%). Unclassified cases mostly behaved clinically like erythema multiforme.

Conclusions: This large prospective study confirmed that erythema multiforme majus differs from Stevens-Johnson syndrome and toxic epidermal necrolysis not only in severity but also in several demographic characteristics and causes.

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UNTIL RECENTLY, most textbooks of medicine considered erythema multiforme to be a spectrum of disorders that included erythema multiforme majus (EMM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). A few years ago, an international group of investigators began a large case-control study, the Severe Cutaneous Adverse Reactions (SCAR) study, to determine the risk factors for EMM, SJS, and TEN. As a preliminary step, participants had to agree on definition and classification criteria. After reviewing several hundred photographs of historic cases, they agreed that it was usually possible to distinguish 2 different clinical groups within cases that had been labeled EMM or SJS.[1] In both groups mucous membrane erosions were present, but the individual pattern and distribution of the skin lesions differed. The first group was characterized by acrally distributed targets typical enough to fit the original description of erythema multiforme.[2] In the second group, including patients with SJS and TEN, the skin lesions were widespread and consisted of blisters arising on erythematous or purpuric macules, closely resembling the original description of SJS.[3] Implicit to this new classification were the hypotheses that (1) EMM is different from SJS and (2) SJS and TEN are only severity variants of a single entity.

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PATIENTS AND METHODS

The SCAR study[4,5] was a multinational case-control study conducted through extensive surveillance networks of about 1800 hospital departments and 120 million inhabitants of France, Germany, Italy, and Portugal from February 1, 1989, to July 31, 1995.

Potential case patients with skin vesicles, blisters, or erosions and a diagnosis of TEN, SJS, or EMM were identified through regular and frequent contacts with hospital departments. After obtaining informed consent, trained physicians interviewed these patients and 3 control subjects matched for age and sex.

Control subjects were patients admitted to the same hospitals as cases for acute conditions or elective procedures not suspected of being related to medication use (eg, traumatic injuries, acute infections, and abdominal emergencies). A total of 1720 control subjects were included.

In cases and controls, a structured questionnaire was used to gather information on medical history, demographic characteristics, and exposures to drugs and other factors. Information on drug use was collected for the 4 weeks preceding hospitalization.

CLASSIFICATION OF CASES

Cases were validated by a review committee by means of a predefined algorithm to score standardized clinical information, photographs (available in 79% of cases), and pathological slides (available in 48%). The review committee was not aware of exposure to risk factors. On the basis of these scores, potential case patients were either excluded or accepted as having possible, probable, or definite disease. Only patients with biopsy data, photographs, or both were accepted as having definite disease.

Nonexcluded cases were then classified according to clinical patterns based only on predefined classification rules (**Figure**, **Table 1**).[1] In addition to these 5 initial categories, another group, "unclassified EMM or SJS," was created for patients with detachment of less than 10% of body surface area who did not satisfy the criteria for either EMM or SJS. For the analysis, the 13 cases of TEN without spots were pooled with the other TEN cases.

Another group of investigators used a set of predefined rules to determine an "index date" as the most probable date of onset of the disease.

DEFINITION OF VARIABLES

Recent herpes was defined as any occurrence of "herpes," "cold sores," or "fever blisters" within the 4 weeks preceding the index date. An *other herpes* label was used for recurrent herpes, cold sores, or fever blisters in the past, but without clinical lesions within the 4 weeks before the index date. No attempt was made to confirm the clinical diagnosis of herpes among either cases or controls.

Mycoplasma pneumoniae infection was considered possible when it had been mentioned in the discharge sheet (available only for cases). Other recent infections were defined as any occurrence of signs or symptoms suggesting an infection within the 4 weeks preceding the index date. Because information was obtained by interview, without laboratory documentation, we considered the infection "probably bacterial" or "probably viral" according to the site of involvement. Pneumonia, pharyngitis, sinusitis, pyelonephritis, urinary tract infection, and wound infections were labeled probably bacterial. Common cold, rhinitis, otitis, tracheitis, and bronchitis were considered probably viral.

On the hypothesis that a drug does not induce a reaction when no longer present in the body, we restricted the window for relevant exposure to 1 week before the index date (whether the treatment had been initiated during that week or earlier), except for drugs with long elimination half-life, for which 2 or 3 weeks was used.

Associated drugs were drugs that have been shown to be significantly associated with SJS, SJS-TEN overlap, or TEN in the published case-control analysis of the first 245 cases and 1147 controls of this SCAR study.[5] They were antibacterial sulfonamides, anticonvulsants (phenobarbital, phenytoin, carbamazepine, valproic acid), oxicam nonsteroidal anti-inflammatory drugs, chlormezanone, allopurinol, acetaminophen in countries other than France (see Roujeau et al[5] for clarification), imidazole antifungal agents, corticosteroids for systemic use, aminopenicillins, cephalosporins, quinolones, and tetracyclines.

Highly suspected drugs were the subset of associated drugs with relative risks above 20 in the same analysis, ie, antibacterial sulfonamides, anticonvulsants, oxicam nonsteroidal anti-inflammatory drugs, chlormezanone (a drug used in Europe at that time as a myorelaxant), and allopurinol.

STATISTICAL ANALYSIS

Differences between classes of cases were evaluated by the χ^2 test for categorical variables and the Wilcoxon test for continuous variables.

The etiologic fraction (the proportion of cases that can be attributed to the exposure under consideration) was calculated as $[Pe(RR-1)]/RR$, where Pe is the proportion of exposed cases and RR is the relative risk estimate.[6] This measure is meaningful only for exposures with strong assumptions of causality, which is the case for herpes and drugs in the context of EMM, SJS, or TEN.

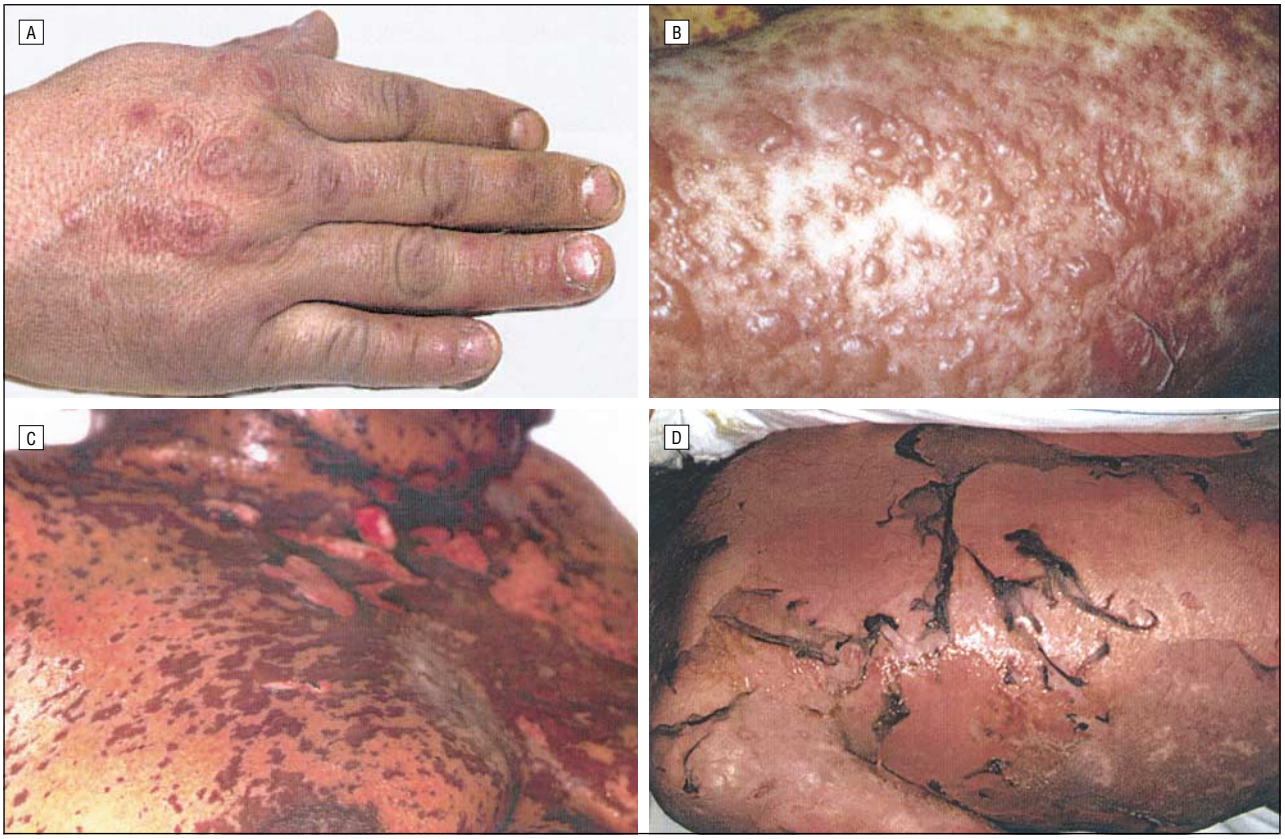
The relative risks were estimated by multivariate logistic regression as in the previously published results.[5] The model included sex, age, country, associated drugs, recent radiotherapy, human immunodeficiency virus (HIV) infection, and collagen vascular disease.

Analyses presented herein were based on comparison of cases in each category with the whole group of control subjects. When comparisons were done between cases in each category and their matched controls, the results were basically unchanged (data not shown).

The aim of this study was to determine whether the results of the SCAR study supported the above hypothesis that SJS and TEN are severity variants of the same disease and differ from EMM in terms of clinical characteristics and risk factors.

RESULTS

Results are based on the analysis of all 552 cases that occurred in the community, were accepted by the review committee as having a probable or definite diagnosis, and



Clinical patterns and classification of the diseases included in the study. A, Erythema multiforme: typical targets, with regular round shape, well-defined borders, 3 different zones, predominant on the extremities. B, Stevens-Johnson syndrome: erythematous or purpuric macules with irregular shape and size. Blisters often occur on all or part of the macule. Lesions are widespread. Confluence of individual lesions remains limited, involving less than 10% of the body surface area. C, Overlap Stevens-Johnson syndrome–toxic epidermal necrolysis: confluent blisters result in detachment of the epidermis and erosions on 10% to 29% of the body surface area. D, Toxic epidermal necrolysis: widespread detachment of epidermis on more than 30% of the body surface area. All photographs were printed from digital records of the original color photographs with no other change than magnification.

Table 1. Classification Used in the Study*

	Pattern of Lesions	Distribution	Extent of Blisters/Detachment, %
Erythema multiforme majus (EMM)	Typical targets, raised atypical targets	Localized (acral)	<10
Stevens-Johnson syndrome (SJS)	Blisters on macules, flat atypical targets	Widespread	<10
Overlap SJS-TEN	Blisters on macules, flat atypical targets	Widespread	10-29
Toxic epidermal necrolysis (TEN) with "spots"	Blisters on macules, flat atypical targets	Widespread	≥30
TEN without "spots"	No discrete lesion, large erythematous areas	Widespread	≥10

*An "unclassified EMM-SJS" category applied when mixed criteria for EMM and SJS were present (eg, widespread typical targets or acral flat atypical lesions).

had accurate determination of an index date and information on drug exposure for at least 1 week before that index date. Among these 552 cases, 88 were classified as EMM, 150 as SJS, 108 as SJS-TEN overlap, and 114 as TEN, and 92 remained in the group of unclassified EMM or SJS.

As shown in **Table 2**, patients with SJS, SJS-TEN overlap, and TEN did not differ with respect to any of the studied factors, with the exception of extent of detachment and mortality.

The patients classified as having EMM differed significantly from patients classified as having SJS, SJS-TEN overlap, or TEN for all characteristics analyzed. They were younger (median, 24 vs 45 years; $P<.001$), were more often male (64% vs 43%; $P<.001$), had a 10-fold higher rate of recurrence (30% vs 3%; $P<.001$), less often had temperature at or above 38.5°C (32% vs 54%; $P=.002$), and less frequently had involvement of 2 or more mucous membranes (71% vs 85%; $P=.01$). The EMM cases, in contrast to the pooled 3 groups of SJS, SJS-TEN overlap, and TEN, were never or rarely associated with collagen vascular diseases (none vs 5%, $P=.03$), HIV infection (none vs 8%; $P=.004$), and cancer (2% vs 11%; $P=.01$).

When the above comparisons were restricted to EMM vs SJS cases only, they all remained significant at the 5% level except for collagen vascular diseases ($P=.3$) and cancer ($P=.09$). The median extent of detachment (interquartile range) was also significantly lower in EMM than in SJS cases (1% [1%-2%] vs 4.5% [1%-8%]; $P<.001$). Among patients with EMM or SJS for whom the exact percentage of detachment had been determined, the detachment was more than 1% of the body surface area for

Table 2. Clinical Characteristics of Patients in Each Group*

	EMM (n = 88)	EMM-SJS (n = 92)	SJS (n = 150)	SJS-TEN (n = 108)	TEN (n = 114)
Median age, y	24†	23†	44	44	48
Male sex, No. (%)	56 (64)†	55 (60)†	71 (47)	41 (38)	49 (43)
Recurrent case, No. (%)	26 (30)†	13 (14)†	5 (3)	4 (4)	3 (3)
Temperature ≥38.5°C, No. (%)‡	24 (32)†	42 (59)	68 (54)	43 (48)	52 (59)
≥2 Mucous membranes involved, No. (%)‡	40 (71)†	41 (84)	125 (84)	93 (88)	93 (85)
Collagen vascular disease, No. (%)	0§	0§	4 (3)	6 (6)	8 (7)
HIV infected, No. (%)	0†	1 (1)†	12 (8)	11 (10)	5 (4)
Cancer, No. (%)	2 (2)§	1 (1)§	12 (8)	15 (14)	13 (11)
Median detachment, % of BSA	1†	1†	4.5	19	40
Deaths, No. (%)	1 (1)§	1 (1)§	4 (3)	7 (6)	45 (39)

*EMM indicates erythema multiforme majus; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; HIV, human immunodeficiency virus; and BSA, body surface area.
†$P<.05$ vs each of the 3 categories of SJS, overlap, and TEN (see "Results" section for individual values).
‡Percentages were calculated on numbers of patients with available information for each variable.
§$P<.05$ vs categories of SJS, overlap, and TEN taken all together.

Table 3. Etiologic Fractions for Herpes and Drugs*

	Etiologic Fraction, %				
	EMM (n = 88)	EMM-SJS (n = 92)	SJS (n = 150)	SJS-TEN (n = 108)	TEN (n = 114)
Herpes					
Recent	29	14	6	. . .	. . .
Other	17	11	10	. . .	. . .
Associated drugs	18	34	64	66	65
Highly suspected drugs†	5	14	48	47	43

*The etiologic fraction is an estimate of the proportion of cases that are due to the exposure under consideration. It was calculated from the proportion of exposed cases and the relative risk estimates obtained by comparing rates of exposure among cases and controls (see "Patients and Methods" section). EMM indicates erythema multiforme majus; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; and ellipses, no association.
†Oxicam nonsteroidal anti-inflammatory drugs, allopurinol, anticonvulsants (phenobarbital, phenytoin), antibacterial sulfonamides, and chlormezanone.

35% (31/88) of patients with EMM, vs 66% (88/133) of patients with SJS ($P<.001$).

The unclassified cases of EMM or SJS were similar to EMM for 6 criteria: age, sex, extension of detachment (only 40% [36/91] had more than 1% detachment), and absence of association with collagen vascular diseases, HIV infection, or cancer. They were similar to SJS and differed from EMM for 2 criteria: frequent fever ($P<.001$) and number of mucosal sites involved ($P=.16$). In their intermediate rate of recurrences, they differed from both EMM ($P=.02$) and SJS ($P=.004$).

Risk factors for each category were evaluated by calculation of the etiologic fractions for herpes and suspected drugs. As shown in **Table 3**, associated drugs had a high etiologic fraction in 3 groups (SJS, SJS-TEN overlap, and TEN), with very similar figures (64%, 66%, and 65%, respectively). Herpes played no role in the SJS-TEN overlap and TEN groups, but was still significantly associated with SJS, with etiologic fractions of 6% for recent herpes ($P=.01$; relative risk, 3.4; 95% confidence interval, 1.5-7.5) and 10% for other herpes ($P<.03$; relative risk, 1.9; 95% confidence interval, 1.1-3.1). In contrast, EMM cases were principally associated with herpes, with etiologic fractions of 29% for recent herpes and 17% for other herpes. Exposure to any of the associated drugs accounted for 18% of the cases of EMM. The unclassified EMM or SJS category had etiologic fractions for herpes and drugs that were intermediate between those found for EMM and SJS. They were 34% for associated drugs, 14% for recent herpes, and 11% for other herpes.

When we repeated the calculation for the few highly suspected drugs, the etiologic fraction decreased to 5% for EMM, while it remained between 43% and 48% for SJS, SJS-TEN overlap, and TEN. No drug (or drug class) other than those categorized as associated or highly suspected drugs was detected in the EMM group more frequently than in control subjects.

Recent infection with *M pneumoniae* had been reported in 3 cases of EMM, 4 cases of unclassified EMM-SJS, 5 cases of SJS, 1 case of SJS-TEN overlap, and 1 case of TEN. An evaluation of the risk linked to this infection was not possible because of absence of information among control subjects. Other recent infections of probable viral origin had a borderline significant association with EMM and unclassified EMM or SJS (etiologic fractions of 9% and 11%, respectively) but not with SJS, SJS-TEN, or TEN. Recent infections of probable bacterial origin were significantly associated with all groups but TEN (etiologic fractions of 8%, 9%, 13%, and 10% for EMM, unclassified EMM or SJS, SJS, and SJS-TEN overlap, respectively). When we restricted the analysis to definite cases, the results did not change substantially (data not shown).

Among the 552 cases, 51 (9%) were recurrent. Recurrence rates were higher in the EMM (26/88 [30%]) and unclassified EMM or SJS (13/92 [14%]) groups than in the SJS (5/150 [3%]), SJS-TEN overlap (4/108 [4%]), and TEN (3/114 [3%]) groups. In each clinical category, recurrent cases did not differ substantially from other cases in terms of demographic characteristics or exposure to risk factors (data not shown).

COMMENT

The SCAR study had been originally designed for quantifying the risks of drugs and other risk factors in severe

cutaneous adverse reactions, mainly SJS and TEN. Because there was considerable confusion about case definition at the beginning of this study (1989), EMM cases were enrolled as well and rules were established for sorting out cases in diagnosis classes.

The present work assessed all 552 cases enrolled in this study for homogeneity or heterogeneity of the different diagnosis classes with respect to clinical characteristics and risk factors.

Classification rules based on 3 clinical criteria (pattern of individual skin lesions, distribution of lesions, and maximum extent of detachment of the epidermis during the course of the disease) resulted in 5 groups of patients. The SJS, SJS-TEN overlap, and TEN groups were similar in terms of demographic characteristics, recent exposure to drugs, and association with risk factors other than drugs, such as HIV infection, collagen vascular diseases, and cancer. There were only 2 differences between these 3 groups. First, in patients classified as having TEN because of larger detachment of the epidermis (≥30%) the mortality was much higher, a finding that was not unexpected. Second, herpes played a small but still significant role in SJS but not in the other 2 categories. Others had already suggested that SJS and TEN were only severity variants of a single drug-induced disease. They proposed unifying denominations: *exanthematic necrolysis*[7] and *acute disseminated epidermal necrosis types 1 to 3*.[8] There is some concordance in these different attempts at reclassification and our consensus definition, which has been successfully used in another large epidemiologic study (the German registry on severe skin reactions[9]).

The EMM group was different from the SJS, SJS-TEN overlap, and TEN groups for all the criteria evaluated concerning demographic characteristics and risk factors. The presence of EMM was not associated with HIV infection, cancer, or collagen vascular diseases. From case-control analyses, herpes appeared as the principal factor associated with EMM. Exposure to drugs in this class was also a significant risk factor, but the etiologic fraction decreased to 5% when the analysis was restricted to drugs with the highest level of suspicion, in contrast to 48%, 47%, and 43% in the SJS, SJS-TEN overlap, and TEN groups, respectively.

The last group of cases, unclassified EMM or SJS, did not fit our classification rules. This was not related to insufficient information. With 92 cases, this group was rather large, in part because it included all borderline cases that did not fit strictly our definitions of EMM or SJS. For most demographic criteria and risk factors, this group turned out to be similar to EMM. For a few other criteria it was closer to SJS or intermediate. Misclassification within our set of rules probably did not have a major impact, since the strength of associations with all risk factors did not change when the analyses were restricted to cases labeled "definite." We rather interpret the findings of intermediate risks in this "unclassified" category, as well as the persistent association with herpes in the SJS category, as a need to improve our classification. We are also aware of the limitation of judging by photographs and reported clinical features rather than by direct examination. This may be one of the reasons for the persistence of a degree of inaccuracy and overlapping among clinical categories. An assessment of our criteria in real-life clinical examinations should be considered.

An important point is that most cases in the unclassified EMM or SJS group were similar to EMM cases in terms of very limited extension of blisters and detachment (no more than 1% of the body surface area for 60% and 65% of cases, respectively).

This study had several strengths. The first was the prospective enrollment of a large number of cases on the basis of active detection. The second was the use of a few trained investigators for standardized collection of information. The third was the classification of cases by an international group of dermatologists who were partly blinded to clinical characteristics of the patients and totally blinded to possible causes. Finally, the enrollment of a large control group allowed us to quantify the risks associated with a variety of factors.

The study had also some areas of weakness: only 79% of patients had clinical photographs, and the remaining 21% may have been more easily misclassified. Nevertheless, when we restricted the analysis to definite cases (all with clinical pictures), the results did not change.

A diagnosis of herpes was accepted as reported by the patient, with some risk of confusion with the first mucosal symptoms of the disease. Such confusion should have resulted in overestimating the role of herpes in all categories in a similar way. The absence of association with herpes in some categories suggests that the impact of this confusion was minimal.

Documentation of a recent infection with *M pneumoniae* was poor, and our study cannot bring any firm answer on this topic. It seems that *M pneumoniae* can be found more often in less severe reactions (EMM, SJS, and EMM-SJS) than in SJS-TEN overlap and TEN. The results for other infections should be interpreted carefully. The diagnosis of infection was recorded as provided by the patient on interview, without bacteriologic sampling and with no attempt at systematic collection of signs and symptoms. Misclassification probably occurred, and we suggest considering this part of our results as exploratory.

Finally, the milder forms (mainly EMM) were certainly underrepresented in this study. Only hospitalized cases were enrolled, and milder forms may be found in a larger variety of hospital departments than the more severe forms for which our detection network had been primarily designed. For the milder forms, the generalization of our results is therefore more questionable than for the severe ones.

Previous studies had already suggested that the classification used in the present study allowed separation of groups of cases with different lesions on histologic examination and distinct causes.[10-13] These studies had the limitations of being retrospective and based on small numbers of patients. The results of the present prospective study on a large number of patients confirm that EMM on one hand and SJS and TEN on the other behave as different disorders, occurring in patients with different demographic characteristics, presenting with different clinical patterns, and having different risk factors. A recent

in vitro investigation suggested that different mechanisms were involved in herpes-related erythema multiforme and "drug-induced erythema multiforme."[14] In that study, herpes-related erythema multiforme has been defined by means of the same criteria we used (acrally distributed targets), but "drug-induced erythema multiforme" was not described, and we can only postulate that it may correspond to what we called SJS.

In conclusion, we believe our results strongly support the initial hypothesis that SJS and TEN can be easily separated from EMM on the basis of simple clinical criteria (pattern and distribution of individual cutaneous lesions) that can be used in individual patients. In addition, it would be easier to compare case reports, case series, and other publications on severe skin reactions when the same clinical classification is used.

Our results have other practical implications. Herpes is the main identified risk factor in milder forms, whether they are easily classified as EMM or remain unclassified. Further efforts may be needed for subclassification[15] and search for other risk factors in these categories. Nevertheless, these forms are characterized by a very restricted extent of lesions and a favorable prognosis. The principal clinical problem is a high risk of recurrences (14% to 30%). Prevention of recurrences by oral antiviral drugs should be considered.[16]

Stevens-Johnson syndrome and TEN, defined by widespread blisters arising on macules and/or flat atypical targets, are diseases with homogeneous clinical characteristics, a potentially lethal outcome, and an elevated probability of being drug induced. When this diagnosis is suspected, patients should be referred immediately to specialized intensive care or burn units.[17]

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