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The rash that presents as target lesions

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Abstract We have explored the rash that appears as target lesions, with the central and dominant diseases belonging to the Stevens-Johnson syndrome/toxic epidermal necrolysis group. After presenting the clinical patterns of an individual target lesion and classifying them into different types of lesions, the contribution has been organized with groups characterized by such specific findings according to the type of lesion: flat or raised, typical or atypical, presence or absence of fever, presence or absence of mucosal ulcerations, presence or absence of arthralgias, and/or internal organ involvement. Other specific features, such as histologic appearance, immunofluorescence findings, and laboratory changes, are considered. We provide clinicians with an algorithmic, systematic, and logical approach to diagnose the condition of the patients who present with targetoid lesions, and enable them to differentiate between those with serious systemic and life-threatening diseases from others with ordinary skin ailments.

Introduction

Our approach is directed toward helping clinicians to arrive at an initial diagnosis, identify critical situations, recognize red flags that signal real emergencies, and differentiate ordinary skin ailments from conditions that are genuinely serious to the point of being life-threatening. The focus is on the morphology of the eruptions, their reaction patterns, and the cutaneous manifestations of serious systemic diseases.

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Historical background

The prototypes of diseases with target lesions are erythema multiforme (EM) and Stevens-Johnson syndrome (SJS). What is probably the first description of a targetoid or iris lesions, as they appear in EM, can be found in Thomas Bateman's (1778-1821) textbook *Practical Synopsis of Cutaneous Diseases According to the Arrangement of Dr. Willan.*[1]

In his classic 1866 treatise, "On Disease of the Skin," Ferdinand von Hebra (1816-1880) precisely described EM as *erythema exudativum multiforme.*[2] In 1922, two American physicians, Albert Stevens (1884-1934) and Frank Johnson (1894-1934), described the cases of two boys, aged 7 and 8 years, who had "an extraordinary, generalized eruption with continued fever, inflamed buccal mucosa, and severe purulent

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conjunctivitis,"[3] which was later given the name "Stevens-Johnson syndrome". In 1950, Bernard Thomas divided EM into 2 categories, EM minor (von Hebra) and EM major, also known as SJS.[4] In 1956, Alan Lyell (1917-2007) wrote the most highly cited contribution ever to appear in the *British Journal of Dermatology,* in which he described the cases of four patients with a scalding disease, which was later given the name "toxic epidermal necrolysis" (TEN), also known as Lyell syndrome or Lyell's disease.[5,6] These severe, acute, life-threatening adverse drug reactions were not classified and defined according to their clinical appearance and linked to their etiology and prognosis until around 1993.[7]

Definition and classification

EM was initially described as an acute self-limited skin disease, symmetrically distributed on the extremities with typical concentric "target" lesions and often being recurrent.[2] The terminology "EM minor" was later proposed to separate the mild cutaneous syndrome from the more severe forms that involved mucous membranes, "EM major." SJS had for years been considered an extreme variant of EM, and TEN as being a different entity. In 1993,[7] a group of contemporary experts proposed a new classification in which they separated SJS from the EM spectrum and added it to TEN, thereby creating a new spectrum of drug-related severe diseases (eg, SJS/TEN). Two disease spectra were created:

1. EM consisting of EM minor and EM major
2. SJS/TEN. (The former is often a recurrent, postinfectious disorder [especially due to herpetic and mycoplasma infections] with low morbidity and almost no mortality. The latter is usually a severe drug-induced reaction with high morbidity and poor prognosis.)

According to the new "consensus definition and classification,"[7] these diseases are categorized essentially by the percentage of skin detachment and by the characteristic appearance of the typical individual "EM-like" or "target" lesions. Accordingly, the clinical pattern of an individual skin lesion was classified into four different types:

1. *Typical targets*—individual lesions less than 3 cm in diameter with a regular round shape, well-defined border, and at least three different zones (ie, two concentric rings around a central disk). One ring consists of palpable edema, paler than the center disk.
2. *Raised atypical targets*—round, edematous, palpable lesions, similar to EM but with only two zones and/or a poorly defined border.
3. *Flat atypical targets*—round lesions characteristic of EM but with only two zones and/or a poorly defined border and nonpalpable with the exception of a potential central blister.
4. *Macules with or without blisters*—nonpalpable, erythematous or purpuric macules with an irregular shape and size and often confluent. Blisters often occur on all or part of the macule.

The involved body surface area (BSA) should measure the extent of detached and detachable epidermis (which is often much less than the area of erythema) at the worst stage of the disease.

Accordingly, the following consensus classification was created:

1. *EM*—detachment <10% of BSA, localized typical targets, or raised atypical targets.
2. *SJS*—detachment <10% of BSA, widespread erythematous or purpuric macules, or flat atypical targets.
3. *Overlap SJS/TEN*—detachment between 10% and 30% of BSA, widespread purpuric macules, or flat atypical targets.
4. *TEN with spots*—detachment >30% of BSA, widespread purpuric macules, or flat atypical targets.
5. *TEN without spots*—detachment >10% of BSA, large epidermal sheets, and no purpuric macules.

The group suggested a practical algorithm, according to the definition and categorization of these diseases based on their classification.

1. The first question the clinician needs to ask is: "What is the percent of detachment?"
2. The second question is: "What is the nature of the discrete lesions?"

They also suggested that their purely descriptive clinical classification might indicate a causative agent, namely, that SJS, TEN, and overlap are drug induced, whereas the diseases in the EM group are due to infectious agents.

Because the involved area of detachment is defined as such at the worst stage of the disease, it cannot always be delineated, when the clinician first sees the patient. Consequently, the most —and often the only—reliable means of classifying the cases is through observing the pattern of the individual lesions.

One of us[8] proposed a small modification of the current classification to enable the clinician to quickly and precisely pinpoint the type of lesion to implement the appropriate treatment without delay. We have observed that patients in the SJS/TEN group occasionally also have *typical* targets that are flat with a flat ring around the center instead of a palpable one. We, therefore, suggested adding another type of lesion to the

Table 1 Original classification

EM	SJS/overlap/TEN
Typical targets	Flat atypical targets
Raised atypical targets	Macules with/without blisters

EM, erythema multiforme; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Table 2 Proposed new classification

EM	SJS/overlap/TEN
Raised typical targets	Flat typical targets
Raised atypical targets	Flat atypical targets
	Macules with/without blisters

EM, erythema multiforme; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

nomenclature, namely, "flat typical target," and to refer to the original typical target as "raised typical target." The new classification will thus contain five types of lesions instead of four (see Tables 1 and 2). (See Tables 3 and 4.)

Our proposed modification gives the classification greater leeway for incorporating all the variations characteristic of these lesions. The new addition makes the classification easier to understand and, not less importantly, easier to remember. How? Just by adding the words "raised" and "flat" to all the lesions. If a patient is found to have raised lesions (raised typical or raised atypical targets), the clinician is directed toward a diagnosis of postinfectious EM (Figure 1). Should the patient have flat lesions (flat typical targets, flat atypical targets, or macules with or without blisters), the diagnosis of drug-induced SJS/TEN (Figures 2 to 4) should be considered.

Other diseases with targetoid lesions

Diseases presenting with flat targetoid lesions

Paraneoplastic pemphigus

Paraneoplastic pemphigus (PNP) is a distinct autoimmune blistering skin disease that, by definition, is always associated with a neoplasm.

Table 3 Diseases presenting with flat targetoid lesions

Disease	Target lesion	Mucosa	Detachment	Fever	Associated condition	Immunologic
Paraneoplastic pemphigus	Flat	Yes, early severe	Yes	No	Malignancy	Yes, specific
Generalized bullous fixed drug eruption	Flat 2 zones	Occasionally	Yes	No	Drug ingested hours before	No
Linear IgA bullous dermatosis LABD	Flat targetoid	Rare	Yes	No		Yes, specific
Drug-induced LABD	Flat targetoid	~50%	Yes	No	Vancomycin	Yes, specific

LABD, linear immunoglobulin A bullous disease.

Table 4 Diseases presenting with raised targetoid lesions

Disease	Target lesion	Mucosa	Detachment	Fever	Associated condition	Immunologic
Mycoplasma-induced dermatitis & mucositis	Sparse raised targets	Prominent, ≥2 sites	Vesiculobullous	Yes	Pneumonia	No
Acute hemorrhagic edema of infancy	Raised typical & atypical	Rare	Never	Yes, prodromal	After viral infection	No
Bullous lupus erythematosus	Raised urticarial	Yes	Bullae	Occasional	Systemic lupus erythematosus	Yes
Rowell's syndrome	Raised, 2 zones	Occasional	Vesicular borders	No		
Polymorphic eruption of pregnancy	Raised	Never	Vesicles	No	Pregnancy	No
Pemphigus gestationis	Raised	Never	Vesicles	No	Pregnancy	Yes
Bullous pemphigoid	Raised	Rare	Bullae	No		Yes
Kawasaki syndrome	Raised atypical & typical	Yes (nonerosive)	No	Always		No
Toxic shock syndrome	Raised & flat atypical	Yes (nonerosive)	Yes	Always	Sepsis	No
Serum sickness–like reaction	Raised, urticarial	Yes (nonerosive)	No	Always	Drugs	No
Annular urticaria = Urticaria multiforme	Raised, urticarial	Yes (nonerosive)	No	Never		No
Sweet syndrome	Raised	Very rare	No pseudovesicles	Almost always	Malignancy, drugs, IBD	No
Syphilis (congenital and secondary)	Raised	Yes	Bulla	Always		No
Annular leukocytoclastic vasculitis	Raised purpuric	No	No	Never	Systemic diseases, drugs	No

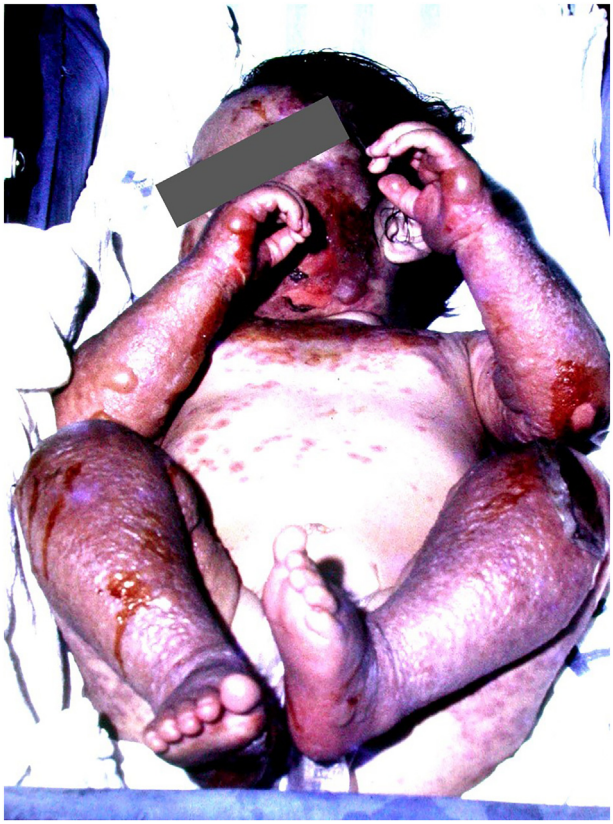

Fig. 1 Erythema multiforme major in a 6-month-old febrile child.

The most consistent and, in most of the cases, also the earliest clinical feature of PNP is the development of a painful stomatitis and severe painful oral erosions.[9–12] The nasopharynx, anogenital region, and esophagus could also be affected by large and painful mucosal lesions. Ocular involvement occurs in 70% of PNP cases, thus resembling SJS. The cutaneous lesions of PNP are much more variable than those of SJS, however, and different morphologies may also be observed in an individual patient at various times. Confluent erosive lesions can develop

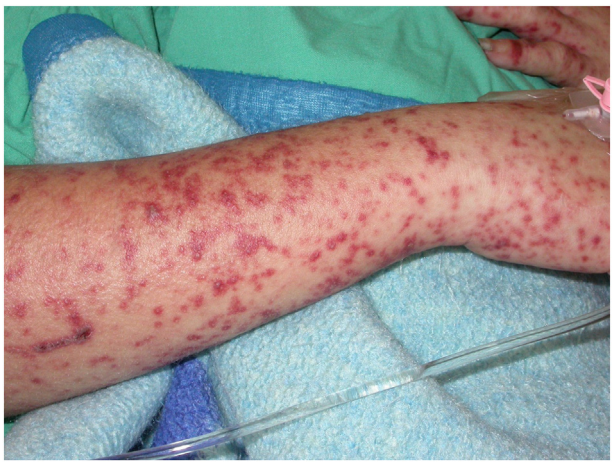

Fig. 2 Macules without blisters in a patient with toxic epidermal necrolysis.

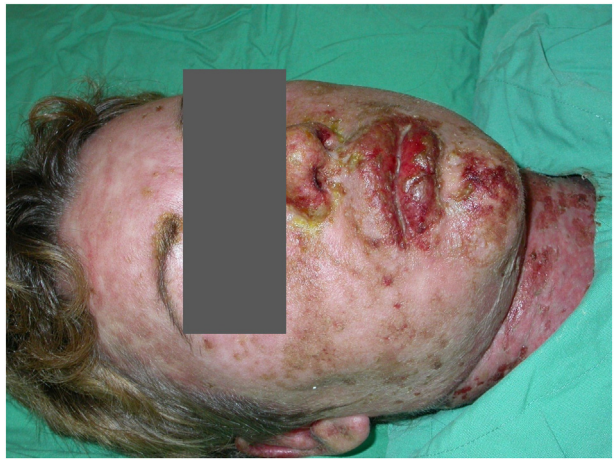

Fig. 3 Face of the patient.

on the upper areas of the chest and back, producing a picture resembling TEN. The similarity of the mucocutaneous features to SJS/TEN and the rapid onset of both conditions explain why SJS/TEN is the most common differential diagnosis for PNP.[10]

An associated neoplasia, most frequently a hematologic one (84%), might help in the diagnosis; however, PNP precedes the detection of the tumor in about 30% of the patients.[11] Notably, TEN also occurs in patients with neoplasia who are undergoing chemotherapy or other treatments.

The five criteria defined in 1990[9] are still valid today, but with minor modifications, and help to differentiate PNP from other blistering diseases.

1. Clinical features: Painful mucosal erosions with or without polymorphous skin eruption producing blisters and erosions and occurring in association with an occult or discernible neoplasm.
2. Histopathology: Suprabasal intraepithelial acantholysis, vacuolar interface changes, and necrosis of individual keratinocytes.

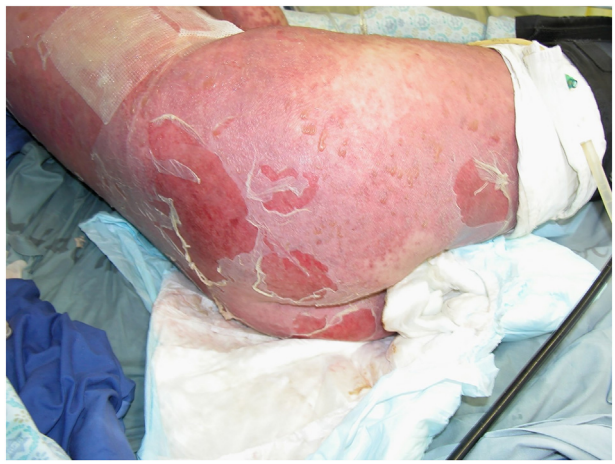

Fig. 4 Same patient 1 week later. She had a detachment area of nearly 90%.

3. Direct immunofluorescence: Deposition of IgG and complement in the epidermal intercellular spaces, as well as granular-linear complement deposition along the epidermal basement membrane zone.
4. Indirect immunofluorescence: Serum autoantibodies that bind to the cell surface of skin and mucosa in a pattern typical of pemphigus, but additionally bind to simple, columnar, and transitional epithelia.
5. Immunoprecipitation: A complex of four proteins (250, 230, 210, and 190 kD) immunoprecipitated from keratinocytes by these autoantibodies. The 250-kD antigen apparently comigrates with desmoplakin I, and the 230-kD antigen comigrates with the 230-kD antigen of bullous pemphigoid (BP). The 210-kD desmoplakin II and the 190-kD periplakin are the most consistently and heavily labeled proteins.

Generalized bullous fixed drug eruption

Fixed drug eruption is a distinct cutaneous drug eruption characterized by well-demarcated dusky red or heavily pigmented patches involving the skin and mucosa. The lesions tend to recur at the same sites after repeated exposure to the same drug.

Generalized bullous fixed drug eruption (GBFDE) is a distinct subtype of fixed drug eruption characterized by widespread blisters and erosions involving the skin of the whole body, as well as oral and genital mucous membranes. The target lesions of GBFDE often have two zones, are flat, and usually have a darker, dusky hue in the center. GBFDE has many features in common with SJS/TEN. Differentiating between these two diseases can be difficult and even impossible, making the cause a real challenge to the intensive care physician.

There are some differences that can help distinguish between these two diseases, and most of them are quantitative, suggesting that they appear more often in one of these diseases but can appear in both.

- GBFDE usually has a more abrupt onset than SJS/TEN, with the full-blown disease appearing within hours of ingestion of the offending drug, as opposed to SJS/TEN, which develops within several days.
- GBFDE does not have a prodromal phase, whereas SJS/TEN usually has a "fluelike" prodromal phase of 1 to 3 days' duration.

Constitutional clinical manifestations (fever, chills, or malaise) are seen in more than 50% of patients with SJS/TEN, whereas patients with GBFDE usually appear healthy and very rarely have fever or other constitutional clinical manifestations.

Painful inflammation and erosions of mucosal surfaces occur in 87% to 100% of cases of TEN, most of them with involvement of at least two sites.[13] GBFDE patients can occasionally show mucosal membrane involvement, in 43% of cases according to one study,[14] and there are no conjunctival lesions.

Some lesions characteristic of FDE can often be found among other lesions of GBFDE.

A history of recurrent lesions at the same sites has been reported by almost 70% of patients with GBFDE,[15] providing a definite clue to the diagnosis.

In a retrospective study[14] that analyzed patients for 10 years, specific features of patients with GBFDE were compared with patients with SJS/TEN. The GBFDE patients showed more eosinophil infiltration and dermal macrophages histologically. Lesional infiltrates in GBFDE had more dermal $CD4^+$ cells, including $Foxp3^+$ regulatory cells, fewer intraepidermal $CD56^+$ cells, and fewer intraepidermal $granulysin^+$ cells. The serum level of granulysin in GBFDE was also significantly lower than that in SJS/TEN. The authors concluded that "the expression of granulysin both in lesional skin and in serum is the most important discriminator to differentiate GBFDE from SJS/TEN." We believe that clinical features and history are more important.

As for the prognosis of these two diseases, there is a generally accepted concept that GBFDE has a better prognosis than SJS/TEN. The prognosis of 58 patients with GBFDE, matched by age and extent of skin detachment to 170 control patients with a validated diagnosis of SJS or SJS/TEN overlap, was compared in a study[16] that used data extracted from the EuroSCAR (SCAR = severe cutaneous adverse drug reaction) and RegiSCAR databases. The investigators concluded that GBFDE did not show a better prognosis than SJS or SJS/TEN of similar disease extent. Accordingly, severe cases of GBFDE should be regarded with the same level of urgency, seriousness, gravity, and attention as cases of SJS/TEN.

Linear immunoglobulin A (IgA) bullous disease

Linear immunoglobulin A (IgA) bullous disease (LABD) encompasses a heterogenous group of subepidermal autoimmune blistering diseases, characterized by linear deposition of IgA along the basement membrane zone on direct immunofluorescence. LABD may be subclassified: as spontaneous or as drug-induced LABD associated with various drugs, vancomycin being the most common.

In children, annular or polycyclic plaques and papules with blistering around the edges (string of pearls sign) is the classic presentation of LABD. In adults, there is a variety of presentations, mimicking many other bullous diseases (eg, dermatitis herpetiformis, BP, cicatricial pemphigoid, pemphigus, and SJS/TEN; the latter is very rare, with 16 cases having been reported until 2013[17]).

The individual lesion presents as a flat target lesion with a tense bulla at the center. Lesions tend to coalesce. They appear on the trunk and extremities, and many patients also show palmoplantar involvement. Nikolsky's sign is positive. There is no fever. Mucosal involvement is highly variable (~50% of reported cases). The majority of cases are drug-induced, mostly by vancomycin, followed by phenytoin.[17] The clue to diagnosis is the histology of subepidermal blister and linear deposition of IgA along the basement membrane zone on direct immunofluorescence.

Diseases presenting with raised targetoid lesions

Mycoplasma-induced dermatitis and mucositis

Mycoplasma-associated mucocutaneous disease has for decades and until very recently been classified into the framework of EM-spectrum or SJS/TEN. In 2015,[18] based on a systematic literature review comprising 202 reported cases, it was suggested that the disease be designated as a distinct clinical entity, named "*Mycoplasma*-induced dermatitis and mucositis" (MIRM). Five criteria were proposed for the diagnosis of the classic cases of MIRM:

1. Detachment of <10% BSA
2. Involvement of ≥2 mucosal membranes
3. Few vesiculobullous lesions or scattered atypical targets
4. Targetoid lesions (not mandatory)
5. Clinical evidence of atypical pneumonia (fever, cough, positive auscultatory findings) and laboratory findings (increase in mycoplasma IgM antibodies, mycoplasma in oropharyngeal or bullae cultures or PCR and/or serial cold agglutinins)

It was later suggested to add an age range as an additional criterion, for example, 5 to 15 years, because anyone younger than 2 years of age or older than 20 years is less likely to have MIRM.[19]

An excellent systematic review[18] synthesized the following clinical presentations of the reported cases of MIRM.

- The patients were young, with a mean age of 11.9 ± 8.8 years.
- Prodromal clinical manifestations were nearly universal and included cough, malaise, and fever that preceded the eruption by approximately 1 week.
- The skin eruption was vesiculobullous in 77% of patients, targetoid in 48%, papular in 14%, macular in 12%, and morbilliform in 9%.
- The extent of skin involvement was usually sparse and characterized by single or few scattered lesions in 47% of the patients, severe mucositis alone with no skin lesions in 34%, and moderate cutaneous involvement in 19%, the latter including 2 cases of TEN-like presentation.
- Predominant acral distribution was most common (46%), followed by generalized (31%), and truncal (23%) distribution.
- The hallmark of the disease is severe mucosal involvement, with oral lesions in 94% of cases, ocular in 82%, and urogenital in 63%.

MIRM has a milder disease course than SJS/TEN, with the exception of more frequent pulmonary disease, which probably stems from the *M pneumoniae* infection itself. Patients with MIRM usually recover fully with infrequent recurrence (8%). The mortality of the reported cases in the review was very low (3%), and the reported deaths occurred in the preantibiotic 1940s.

Acute hemorrhagic edema of infancy

Acute hemorrhagic edema of infancy (AHEI) is an acute, benign, self-limiting leukocytoclastic vasculitis affecting infants and young children.[20,21]

In 1996, a group of Israeli dermatologists and pediatrician defined AHEI as a separate entity and proposed the following clinical criteria for its diagnosis[21]:

1. Patients younger than 2 years
2. Purpuric or ecchymotic target–like skin lesions with edema on the face, auricles, and extremities, with or without mucosal involvement.
3. Absence of systemic disease or visceral involvement.
4. Spontaneous recovery within a few days or weeks

AHEI has a sudden appearance and is characterized by the triad of fever, purpuric eruption, and edema. The patient is usually not toxic and is in good general condition. The skin eruption generally starts with erythematous macules or urticarial plaques that rapidly progress into annular, rounded, medallionlike, or targetoid purpuric lesions. The targets are a mixture of typical three-zone and raised atypical two-zone targets that are symmetric and occur on the face (mainly cheeks), auricles, and extremities. Other locations may be involved. Nonpitting edema of the face and extremities is common and is often the presenting sign. Mucous membranes are only rarely involved.[20,21] The histopathology of AHEI classically shows features of dermal leukocytoclastic vasculitis with or without fibrinoid necrosis.

AHEI looks more alarming than it really is, but it should be differentiated from SJS/TEN and other severe diseases, having a similar appearance.

Rowell's syndrome (Figure 5)

In 1963, Neville Rowell (1926-) and his group[22] reported a new syndrome, characterized by lupus erythematosus, EM-

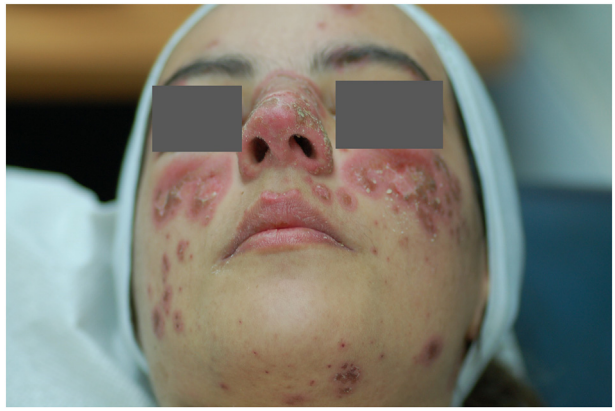

Fig. 5 Histologically and immunologically proven Rowell's syndrome in a 20-year-old woman of Arabic origin.

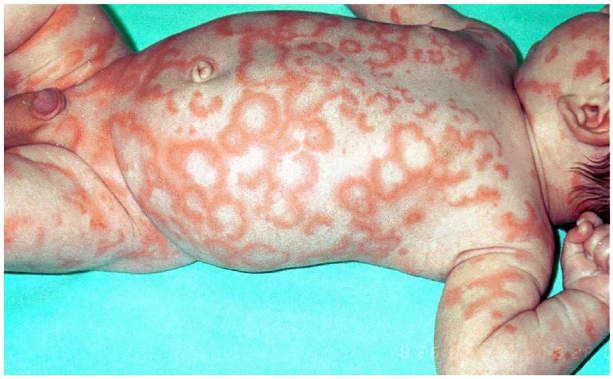

Fig. 6 Urticaria multiforme. Courtesy Prof. Alex Zvulunov.

like lesions, speckled pattern of antinuclear antibody, anti-La, and positive rheumatoid factor. In 2000 major and minor criteria for the diagnosis were proposed.[23]

- The major criteria:
  1. Systemic LE, discoid LE, or subacute cutaneous LE
  2. Erythema multiforme–like lesion (with or without involvement of the mucous membranes)
  3. Speckled pattern of antinuclear antibody
- The minor criteria:
  1. Chilblains
  2. Anti-Ro antibody or anti-La antibody
  3. Positive rheumatoid factor
- All three major and at least one minor criteria are required to establish the diagnosis.

The targetoid EM-like lesions are usually two zones raised erythematous lesions with vesicular borders. (See Figs. 6 and 7.)

In a review of 71 cases reported until 2012,[24] an Italian group of researchers raised doubts whether Rowell's syndrome is indeed a distinct entity. According to them, and in agreement with several other cited authors, LE with EM-like dermatitis represents a subset of subacute cutaneous LE with targetoid lesions. Although we are not convinced that the dramatic title of their paper "The last word on the so-called 'Rowell's syndrome'?" really reflects the last word, the present presentation is not an appropriate arena for conflict. The acute appearance of targetoid lesions can occur in several forms of LE and can easily be differentiated from EM by their characteristic immunologic features.

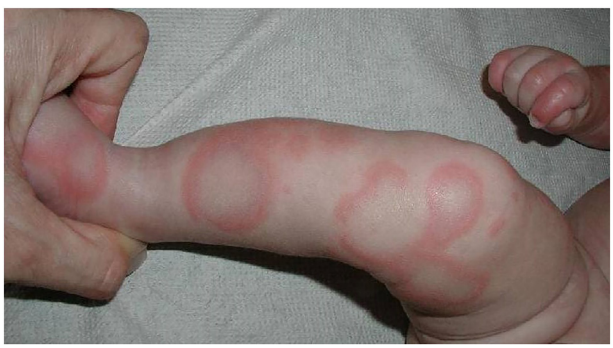

Fig. 7 Urticaria multiforme. Courtesy Prof. Alex Zvulunov.

Polymorphous eruption of pregnancy

Polymorphous eruption of pregnancy (PEP) is the most common specific skin eruption in pregnancy, affecting 1 of 160 deliveries.[25] The classic clinical presentation of PEP includes intensely pruritic urticarial papules and plaques (PUPP) starting within and/or adjacent to striae and sparing the periumbilical area. The lesions can later spread to nonabdominal sites. Approximately one-half of the patients develop polymorphic skin lesions. According to a large case series,[25] 49% of the 181 reported patients with PUPP remained with PUPP-like lesions. All the others (51%) developed additional features, including eczematous lesions (22%), vesicles (17%), nonurticarial, at times polycyclic erythema (6%), and/or targetoid or EM-like lesions (6%). An earlier report on 57 patients showed similar results, with 5.3% of the patients presenting targetoid lesions.[26]

PEP should be considered in the differential diagnosis of EM in pregnant women presenting with PUP, even though only ~6% of patients with PEP will have this type of lesion. The target lesions are raised erythematous pruritic plaques with a central dusky red area and vesicle. There will not be any mucosal involvement, immunofluorescence studies are generally negative, and the histologic examination can be expected to be nonspecific.

Bullous pemphigoid

BP is the most common chronic autoimmune bullous dermatosis; nonetheless, erythema multiforme–like BP has rarely been reported, with only 9 cases found in the literature.[27] The clinical findings include manifestations of EM and BP.[27] The lesions are mostly raised and edematous, with essentially no mucosal involvement (one out of the nine patients had mucosal membrane involvement).

Kawasaki disease

Kawasaki disease (KD) is an acute, self-limited multisystem medium-vessel vasculitis of unknown etiology. It predominantly affects infants and young children with a predilection for the involvement of coronary arteries. Because mucocutaneous signs make up four of the five clinical criteria for the diagnosis of KD, dermatologists have an important role in the early diagnosis of this disease, which has potential morbidity and mortality.

The diagnosis of KD is based on the presence of fever of ≥5 days as an obligatory criterion and the presence of at least 4 of the following 5 criteria:

1. Bilateral conjunctival injection without exudate
2. Changes in the lips and oral cavity (erythema, fissured lips, strawberry tongue, injected pharynx)
3. Polymorphous exanthem

4. Changes in the extremities (acute: erythema or edema of hands and feet; subacute: periungual desquamation of fingers and toes from week 2)
5. Cervical lymphadenopathy

The clinical signs do not present simultaneously and the typical acral desquamation is often a late sign.[28] The skin eruption is nonspecific and has been described as scarlatiniform, morbilliform, maculopapular, or urticarial exanthema.

Annular EM-like lesions, as a manifestation of KD, are extremely rare, having been reported in fewer than 10 cases.[29,30] The EM-like lesions are raised atypical or typical classic targets. The mucosal membrane involvement is not ulcerative; however, the crusted lips together with conjunctivitis or conjunctival injection in febrile children can easily lead to an erroneous diagnosis of SJS.

Toxic shock syndrome

Toxic shock syndrome is a condition caused by either localized superficial (*Staphylococcus aureus*) or invasive (*Streptococcus pyogenes*) bacterial superantigens. Staphylococcal toxic shock syndrome is characterized by high fever, hypotension, dermatitis, skin desquamation (later), and multiorgan dysfunction.[31] Target lesions have been described in fewer than five patients,[32] and it is included here for the sake of completeness.

Serum sickness–like syndrome

Serum sickness was first described in 1905 by Clemens von Pirquet (1974-1929) and Bela Schick (1877-1967)[33] after the use of horse serum containing diphtheria antitoxin.

A serum sickness–like reaction (SSLR) is a nonprotein drug reaction that demonstrates several of the clinical findings of serum sickness disease but usually lacks the immune complex formation characteristic of the latter. SSLR is caused by various drugs, such as beta-lactam antibiotics, penicillins, sulfonamides (among the most frequent), minocycline, ciprofloxacin, nonsteroidal anti-inflammatory drugs, anticonvulsants, and antidepressants. More recently, immune modulators, commonly referred to as "biologicals," have attracted some attention.[34] The interval from the introduction of the medication to the onset of SSLR is usually 8 to 14 days, but it can sometimes take up to 3 weeks.

An SSLR consists of a triad of dermatitis, fever, and arthralgia, without any evidence of cutaneous or systemic vasculitis. Cutaneous eruptions can be seen in up to 95% of cases. The most common skin findings include macular exanthem, urticarial dermatitis, morbilliform dermatitis, and an eruption mimicking EM.[35] Urticarial lesions that have a dusky-to-purple center may well resemble the target lesions of EM.[36] Unlike urticaria, SSLR lesions tend to persist for more than 24 to 36 hours, and are generally ecchymotic. Periocular edema is common,[35] and the hands and feet are often erythematous and edematous. Another primary clinical feature is joint involvement manifested by arthralgia and joint swelling. Elbows, knees, and ankles are the most commonly affected joints.[35]

Laboratory findings of SSLR include leukocytosis, a high erythrocyte sedimentation rate, and mild proteinuria or hematuria.[35] SSLR has a benign course and favorable prognosis.

Urticaria multiforme

In 2007, the term "urticaria multiforme" (UM) was introduced to replace acute annular urticaria to highlight the distinct clinical features of the disease.[37]

UM is a common and benign cutaneous hypersensitivity reaction seen in children and characterized by typical annular, arcuate, and polycyclic urticarial lesions in association with acral edema. It is most commonly misdiagnosed as EM, SSLR, or urticarial vasculitis.[37]

The individual lesion is a blanchable annular, arcuate, and polycyclic erythematous wheal. The lesions may display either central clearing or a dusky, ecchymotic center, which may be mistaken as a target lesion of EM. The most important clinical feature of a UM lesion is that the duration of an individual lesion is less than 24 hours. There is often an associated angioedema of the face, hands, and feet, and dermographism is common.

UM is confirmed by applying the diagnostic criteria.[37]

1. Typical annular and polycyclic morphology and the configuration of urticarial lesions; absence of true target lesions and/or skin necrosis or blistering; absence of mucous membrane involvement with blisters or erosions
2. Duration of individual lesions <24 hours
3. Dermographism
4. Angioedema but not arthralgia or arthritis. Angioedema typically involves the hands and/or feet but may also involve the periocular or oral mucosa. Children with significant edema of the feet may find walking difficult, which should not be confused with arthritis or arthralgia.
5. Favorable response to antihistamines.
6. Modest but nonsignificant elevations in acute-phase reactants, but not the elevations typically seen in patients with rheumatologic disorders, serious systemic infections, or KD.

UM mostly affects children between 4 months and 4 years of age. Pruritus is an almost universal finding associated with UM, and fever occurs in ~40% of the patients.[37]

In the 2007 report,[37] the authors provided a table describing distinguishing features of UM, EM, and SSLR, a table that has been adapted by many forthcoming reports on this disease. The main features include:

- The duration of the individual lesion in UM is <24 hours and in UM and EM days to weeks.
- The total duration of the dermatitis in UM is 2 to 12 days, compared with 2 to 3 weeks in EM and 1 to 6 weeks in SSLR.

- Erosions are present in EM and absent in UM and SSLR, the latter two featuring oral edema. Facial and acral edema are present in UM and SSLR and absent in EM, and dermographism is seen only in UM.

The comparison of UM is to EM, not so much to SJS/TEN.

Sweet's syndrome

Febrile neutrophilic dermatosis was first described by Robert Sweet (1918-2001) in 1964 and hence called Sweet's syndrome. Although abrupt onset of painful erythematous plaques or nodules is an obligatory major criterion of Sweet's syndrome (SS),[38,39] coexisting atypical targetoid lesions have also been reported.

A large retrospective study of 90 cases from a tertiary care center in Tunisia[40] reported atypical targetoid lesions in 11 out of the 90 studied patients, and 9 of those 11 had the classic idiopathic form. In a Brazilian study of 73 SS cases,[41] targetoid lesions were found in 12 (18.5%) of the patients. Sixty-eight percent of the patients had a second diagnosis of EM. Those authors mentioned that 13 of 21 cases of SS (62%) had a second diagnosis of EM in another study from the same hospital.

SS can easily be distinguished from EM, particularly in view of the fact that the targetoid lesions— if there are any —almost always appear along with classic lesions, which are the major and obligatory criterion of SS.

Congenital and secondary syphilis

Syphilis was referred to "the great imitator" by Sir William Osler (1849-1919) due to its manifold presentations, which make the diagnosis in the emergency room difficult.

There are very few cases of syphilis presenting with targetoid lesions and mimicking EM. Six cases of EM-like secondary or congenital syphilis were described in a case series that appeared in 2013,[42] and two additional cases were reported later on.[43,44] It is not yet known whether the form of an EM-like presentation of syphilis is a true EM triggered by some type of immune response against *T pallidum* (*T pallidum*–induced EM) or a presentation of the disease itself.

Annular leukocytoclastic vasculitis

Annular leukocytoclastic vasculitis (ALV) is a rarely reported clinical variant of leukocytoclastic vasculitis. ALV has been linked to various systemic diseases and drugs.

A 1996 report revealed that some patients with ALV constitute a distinct subtype, which satisfies the following 6 criteria[45]:

1. Multiple attacks for years with a sudden onset and spontaneous regression after 7 to 10 days
2. Annular purpuric patches that show a centrifugal extension
3. Extension over the limbs and trunk creating polycyclic lesions that clear with mild hemosiderin deposition
4. No extracutaneous clinical manifestations and good general health during the attacks
5. Histologic changes of leukocytoclastic vasculitis with mild vascular changes and intense polymorphonuclear cell infiltration
6. Complete clearance of all lesions with dapsone therapy

Many of the following cases showed only several of the 6 criteria.[46] Also not all[47] of the reported cases showed target-like appearance and had a resemblance to EM, like the initial cases.

TEN-like diseases without target lesions

In 2004, a group of dermatologists[48] described a case of TEN-like acute cutaneous lupus erythematosus and drew attention to the fact that TEN-like skin manifestations can occur in LE and in some other diseases not associated with drug-induced TEN. They proposed the term "acute syndrome of apoptotic pan-epidermolysis (ASAP)" for this syndrome, which is characterized by acute and massive cleavage of the epidermis resulting from hyperacute epidermal basal cell apoptotic injury. The three diseases included in this syndrome were LE, acute graft versus host disease (GVHD), and pseudoporphyria.

These authors also proposed an alternative definition of the acronym ASAP, one that is often used ("as soon as possible") to reinforce the sense of urgency that is required in clinically managing patients in this setting. The importance of this paper is not so much the proposed name of the syndrome, although it is appropriate, but in drawing attention to the idea that a differential diagnosis of other diseases should be considered in cases of drug-induced TEN.

TEN-like systemic lupus erythematosus

The first report on the association of systemic lupus erythematosus (SLE) and TEN appeared in Spanish in 1977,[49] and the first report in the English literature appeared in 1984.[50] In the latter publication, LE was considered as a cofactor in the causation of drug-induced TEN. Two out of 17 described cases of drug-induced TEN also suffered from SLE, and the causative drug was penicillamine in one patient and metronidazole in the other. Very few cases have appeared in the subsequent 20 years.[51–55]

In 2004,[48] a new designation of ASAP was applied to cases of TEN-like appearance. These authors proposed new classification for vesiculobullous skin disorders that can be encountered in LE patients. Relevant for the current paper are the findings that TEN-like lesions can appear in acute and subacute cutaneous LE and in SLE with no LE-specific skin lesions.

In 2013, a Turkish group reviewed all of the 21 published cases of TEN-like SLE and an additional one of their own.[56] The patients had progressive epidermal necrosis and sloughing. Mucosal involvement was seen in ~30% of patients. All 22 patients had TEN-like histopathology. They had various degrees of systemic involvement resulting from SLE, such as hematological anomalies (36%) and lupus nephritis (27%).

Few cases have been reported since then. TEN-like SLE and drug-induced TEN share clinical and histopathologic similarities. The main differences are as follows:

1. Presence of photodistribution
2. Discrete or absence of mucosal membrane involvement
3. Positive antinuclear antibody, and/or anti–double-stranded DNA, and/or anti-Ro or anti-La antibodies
4. Positive lupus band test in direct immunofluorescence in TEN-like SLE but not in drug-induced TEN

Acute graft-versus-host disease

Acute severe stage 4 GVHD can bear a striking clinical resemblance to TEN and is potentially indistinguishable from it. Both diseases show extensive erythema with epidermal detachment and skin sloughing of >10% BSA. Both diseases are characterized by mucous membrane involvement, fever, bone marrow depression, and internal organ involvement (eg, gastrointestinal mucosa and abnormal liver function tests), and both show a rapid progression to death.[57–60]

There is an overlap of histologic appearance as well. Both diseases show keratinocyte apoptosis, subepidermal blister formation, and satellite cell necrosis. There is almost no inflammatory lymphocytic infiltrate in the papillary and reticular dermis in either of them. Unfortunately, there is currently no reliable way to distinguish between TEN and severe acute GVHD. At the same time, it is of paramount importance to do so early in the disease course, because the therapy is different for the two conditions. Whereas the mainstay therapy for GVHD is immunosuppression, including corticosteroids, such treatments—particularly if continued over time—might worsen the prognosis of TEN.

Some methods have been proposed for differentiating these two conditions:

- The demonstration of a chimerism (significant number of donor lymphocytes) in circulating lymphocytes has been suggested to favor GVHD over TEN.[58,61]
- A high dermal $CD8^+/CD4^+$ T-lymphocyte ratio (≥ 4) has been proposed as a guide for the diagnosis of TEN over GVHD.[57]

These and other findings can be suggestive at best but not confirmatory of either one of the two diseases. As the authors write, they are contributory if they appear "in the appropriate clinical setting."[57] Several authors have also suggested that TEN can be a manifestation of GVHD.[60]

Conclusions

Our purpose has been to assist clinicians to quickly and correctly identify critical situations, recognize life-threatening conditions, and interpret red flags that signal real emergencies so that they can differentiate them from dermatitis that do not pose immediate danger. To best treat sick patients who present with a dermatitis, it is appropriate to focus on the morphology of the eruptions and their reaction pattern after having taken the vital comprehensive history.

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