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Kardaun, Sylvia H.

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21 Stevens Johnson Syndrome/Toxic Epidermal Necrolysis and Erythema Exsudativum Multiforme

Sylvia H. Kardaun

Introduction and Aims

Short Introduction in Layman Terms

Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are the most severe, mainly drug induced reactions with widespread skin and mucous membrane involvement, characterised by massive epidermal necrosis, and associated with significant morbidity, mortality, and long-lasting sequelae. Erythema exsudativum multiforme (EEM) presents an acute, most often acrofacial eruption characterised by target lesions. Although generally relatively mild and self-limiting, EEM can be recurrent and is generally triggered by infections.

Learning Objectives

After reading this chapter you are able to distinguish SJS/TEN from EEM and other (autoimmune) blistering diseases. You understand that SJS/TEN presents a spectrum that can be divided in three subtypes, predominantly based on the percentage of the detached and detachable body surface area (BSA), and is most often caused by drugs. Besides, you are able to identify the associated medication. Moreover, you will know that EEM, although not an infection by itself, is most often caused by various infections, with herpes simplex virus (HSV) as the most important, while drugs are rarely the cause.

Didactical Questions; Cross Sections to Prime the Readers Interest

What are typical and atypical targets and what is their importance? Can EEM evolve to SJS or TEN? Which drugs are notorious for inducing SJS/TEN and should patients avoid all of these after having experienced SJS/TEN? What are long-lasting sequelae of SJS/TEN? What special care should be taken for patients, suffering from eye involvement?

S. H. Kardaun (✉)
Center for Blistering Diseases, Department of Dermatology, University Medical Center Groningen, University of Groningen,
Groningen, The Netherlands
e-mail: s.h.kardaun@gmail.com

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Case Study: Part 1
A 46-year old man complained of a painful throat and subfebrile temperature starting 2 weeks after neurosurgery. Because 2 days later a skin rash and stinging eyes develop, he decides to consult his GP. What is your differential diagnosis? What further info do you need to come to a diagnosis?

Definitions and Classification

SJS/TEN are severe, potentially fatal, mucocutaneous adverse drug reactions, characterised by massive epidermal necrolysis. EEM has been reported under a variety of labels and eponyms, and up to now is still surrounded by some confusion. It can be divided in two main types: EEM minus, characterised by the sudden onset of red papules or plaques, some of which develop to "target" or "iris" lesions, and EEM majus, showing in addition haemorrhagic mucosal involvement as can be seen in SJS/TEN. In particular EEM majus and SJS are still often erroneously used as synonyms. However, EEM is an entity different from SJS/TEN with a different course, prognosis, and aetiology. In 1993, consensus was reached on case definition, classification and nosology, recognising four main categories varying from EEM majus to TEN (Table 21.1) [1]. Within this classification, SJS and TEN are considered to represent two ends of a spectrum of a single disease in which TEN is the maximal variant, mainly differing by the extent of skin detachment, but based on similar pathogenesis, risk factors and causality, whereas EEM majus is regarded a distinct entity. In contrast to SJS/TEN, there is no risk for skin failure or visceral involvement in EEM.

The classification is based on three clinical criteria: the morphology of the individual lesions, their distribution, and the maximal extent of epidermal detachment. Typical target lesions have regular round and well-defined borders with at least three different concentric zones: a purpuric central disk with or without a blister, a raised oedematous, pale intermediate ring, and an erythematous outer ring (bull's eye or iris lesion) (Fig. 21.1). By contrast, atypical target lesions, which can be raised or flat, have an appearance reminiscent of targets, but present with only 2 zones and/or poorly defined borders, while the centre can also be vesicular or bullous (Fig. 21.2). Detachment of skin and mucosae can present as blistering or erosions.

EEM majus is characterised by mainly acrofacial raised typical or atypical targets and epidermal detachment <10% of the BSA. In the spectrum of SJS/TEN on the other hand, skin

Table 21.1 Differences between erythema exsudativum multiforme majus (EEM majus), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and SJS/TEN overlap syndrome

Clinical entity	EEM majus	SJS	SJS/TEN overlap	[a]TEN
Primary lesions	Raised typical or atypical target lesions	Flat atypical target lesions, erythematous/ purpuric maculae	Flat atypical target lesions, ill-defined erythematous/ purpuric maculae	Ill-defined (dusky) erythema and maculae, flat atypical target lesions
Distribution	Mainly acrofacial	Isolated lesions, partly confluent on the face and trunk	Isolated lesions, partly confluent on the face and trunk	Isolated lesions, partly confluent on the face, trunk, and elsewhere
Intensity	+	+	++	+++
Mucosae	Involved	Involved	Involved	Involved
Systemic symptoms	Minimal/absent	Usual	Always	Always
Detached body surface area (BSA)	<10%	<10%	10–30%	>30%[a]

+ mild, ++ moderate, +++ severe
[a]NB: including TEN with large confluent erythema without discrete lesions with a detached BSA ≥10%

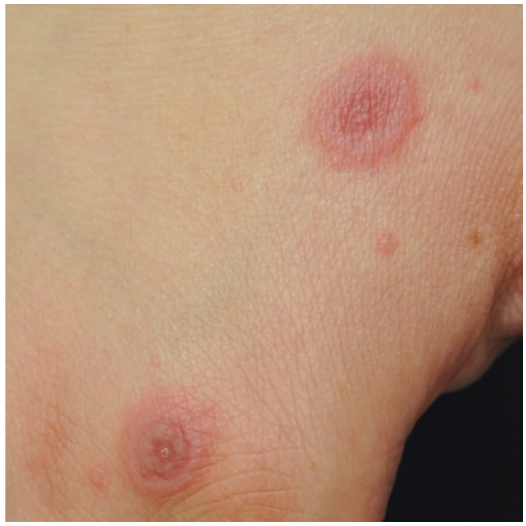

Fig. 21.1 Typical target lesions in EEM minor showing three well-defined color zones and borders

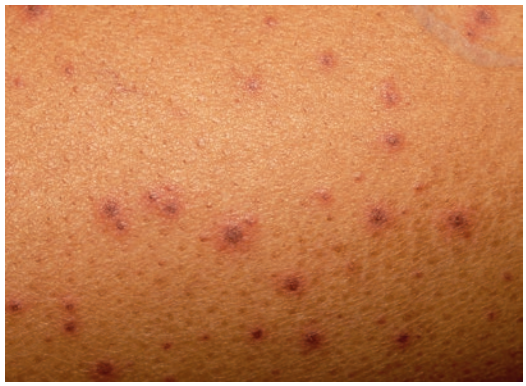

Fig. 21.2 Flat atypical target lesions in SJS with poorly defined borders and two color zones

lesions are widespread with blisters arising on erythematous or purpuric macules and/or flat atypical targets. In EEM, lesions usually appear symmetrically on the distal extremities and may progress proximally, while in SJS/TEN the reaction often starts on the upper trunk and face and evolves distally. Mucous membrane involvement, present in both SJS/TEN and EEM majus, tends to be more severe in SJS/TEN. EEM majus differs from SJS/TEN by occurrence in younger males, frequent recurrences, less fever, milder mucosal lesions and lack of risk factors associated with SJS/TEN [2]. Where EEM is mainly associated with infections, SJS/TEN is most often drug induced. However, especially at their early stages, differential diagnosis can be challenging. Moreover, SJS can progress into TEN.

Stevens Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)

Facts and Figures

The onset of SJS/TEN is abrupt. It can be preceded by prodromes, usually starting as flu-like symptoms such as fever, sore throat, anorexia and malaise, often followed by erosive stomatitis and eye involvement. Next, burning, painful, and often ill-defined erythematous and/or purpuric maculae (spots), flat atypical target lesions, and photophobia occur. Maculae most often start in a symmetrical distribution on the face, neck, and upper trunk, extending distally with a tendency to rapid coalescence. Generally, within hours extensive mucocutaneous blistering and detachment on an erythematous base develop within 1 week up to 10 days. Blisters are flaccid and can become confluent, while large sheets of epidermis slough off, leaving an exposed, weeping dermis and large areas of detachment. At gentle pressure, blisters can often be moved laterally due to detachment (positive Asboe Hansen sign, Fig. 2.3). Also pressure on erythematous skin may cause detachment (pseudo-Nikolsky‘s sign, Fig. 2.2). Target lesions in SJS/TEN reminiscent of the target lesions in EEM, however, are flat and atypical.

In SJS, maculae, atypical target lesions, blisters and areas of detachment are most often prominent on the upper chest and face. Although boundaries are rather artificial, total detached and detachable skin at the maximum stage in SJS is <10% of the BSA, between 10 and 30% in SJS/TEN overlap, and over 30% in TEN (Figs. 21.3, 21.4, and 21.5).

Generally, multiple mucosal membranes, including oral, ocular, nasal, urethral, vaginal, anal, tracheobronchial, and gastrointestinal mucosae can be affected in SJS/TEN, with haemorrhagic blistering and erosions. Visceral involvement (liver) may occur; anaemia and lym-

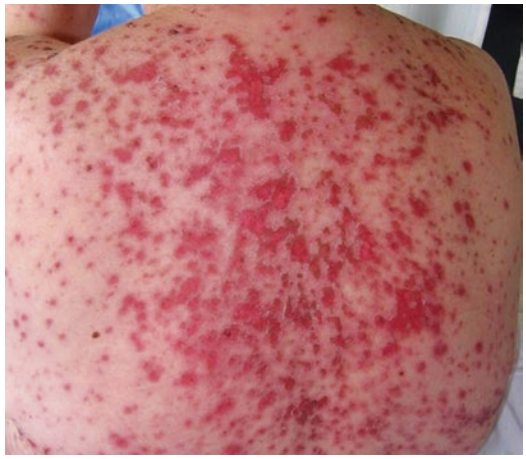

Fig. 21.3 SJS showing wide-spread small erythematous macules. Mainly on the central part of the thorax the lesions are partly confluent with small areas of detachment

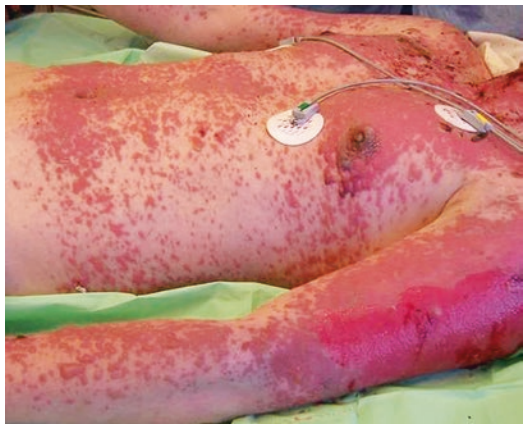

Fig. 21.4 SJS/TEN-overlap with widespread maculopapular lesions on the face, neck, arms and thorax and hemorrhagic mucosal involvement. Lesions are confluent on the neck, arms and central thorax and in addition show bullae and extensive erosive areas

phopenia are frequent, while neutropenia often predicts bad prognosis. Pneumonitis or even acute respiratory distress syndrome may occur. Complete healing, especially in TEN, can last 3–6 weeks, while especially erosions on the back, buttocks and mucosae may take longer.

SJS/TEN presents a severe, life-threatening disease. The overall mortality rate, mainly caused by sepsis or multiorgan failure, is on average about 25%, ranging from 12% in SJS to

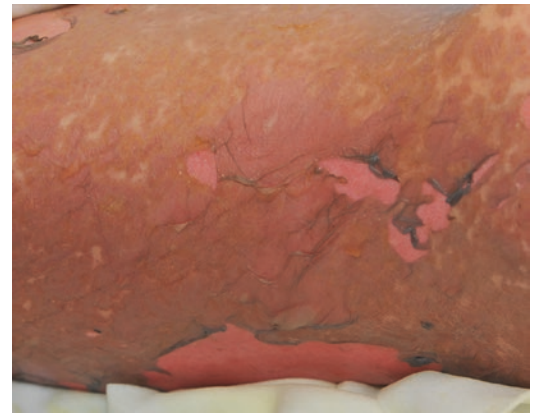

Fig. 21.5 TEN with large areas of necrotic epidermis and large sheets of sloughed-off moist, erosive erythematous skin

46% in TEN [3]. Over 90% of survivors suffer from variable long-term sequelae, and/or long-lasting, often underrecognized psychosocial problems, strongly affecting the quality of life. Frequent, often ongoing ocular complications, not rarely leading to impaired vision and even blindness, are most feared. Over 50% of survivors are afraid of taking drugs or avoid taking them. Other sequelae include lung function impairment, symblepharon, conjunctival synechiae, dry eyes, entropion, ingrowing eyelashes, cutaneous scarring, altered pigmentation, eruptive nevi, dental problems, persistent erosions/strictures of the mucous membranes (especially genital), nail changes and post-traumatic stress disorders [4].

Epidemiology

In Europeans, the incidence of SJS is estimated at 1.2–6.0 and that of TEN at 0.4–1.2 per million per year. The mean age for SJS/TEN ranks between 48.2 and 53.4 years (range 1–98 years), with a slight female preponderance in TEN [2]. In HIV the incidence was approximately 1000-fold higher than in the general population.

Pathogenesis

Although pathogenesis is not yet fully elucidated, several mechanisms have been postulated. Nowadays it is believed that SJS/TEN is a process in which an inappropriate immune activation

is triggered in response to certain drugs or their (toxic) metabolites. Massive keratinocyte apoptosis is the main feature and drug-specific cytotoxic CD8+ T cells (CTLs) and NK-cells are the main effector cells. CTLs can activate the caspase cascade, including apoptosis either through Fas-Fas ligand binding or the perforin/granzyme B pathway, TNF-α and annexin A1 release, responsible for keratinocyte death in SJS/TEN [5]. Blister T cells from patients exert drug specific cytotoxic activity against both autologous B-lymphocyte cell lines and keratinocytes, and is mediated by granzyme B. The discrepancy between the paucity of the infiltration of immune cells in the skin of patients with SJS/TEN and the overwhelming keratinocyte apoptosis has led to the search for cytotoxic proteins and/or cytokines that may "amplify" the extent of keratinocyte apoptosis that CTLs alone could induce upon cell-cell contact. Recent findings suggest that especially granulysin, a powerful pro-inflammatory cytotoxic cationic protein released from CTLs and NK-cells, turns on extensive keratinocyte apoptosis [5]. Serum levels of granulysin and IL-15 are associated with severity and mortality in SJS/TEN.

Risk factors include immune dysregulation (HIV, SLE), active malignancy and genetic predisposition. A strong association has been found between SJS/TEN and specific drugs in ethnicity specific populations with some genes coding for specific HLA or drug metabolizing enzymes: HLA-B*1502 for instance, is strongly associated with the use of carbamazepine in SJS/TEN patients of Southeast Asian ancestry, especially in Han Chinese [5]. Genetic pretesting has since then significantly reduced the prevalence in at-risk populations for carbamazepine.

Aetiology

SJS/TEN nearly always represents an idiosyncratic reaction to medication. Although about 200 drugs have been reported to cause SJS/TEN, only a limited number of drugs is responsible for the majority of the reactions. In absolute case numbers, allopurinol is the most common cause of SJS/TEN in Europe. The highest risk occurs during the first 2 months of first treatment with a sharp drop of incidence thereafter. However, although some drugs have a high relative risk compared to other drugs, the actual risk remains low. Drugs with a significantly raised risk are allopurinol, carbamazepine, phenytoin, phenobarbital, lamotrigine, sulfamethoxazole-trimethoprim and other sulphonamide antibiotics such as sulfasalazine, NSAID's of the oxicam-type, and nevirapine [6].

Targeted drugs and immunotherapy that have revolutionized cancer therapy and are increasingly used, have also been implicated. Amongst them are PD-1 (e.g. nivolumab and pembrolizumab), PD-L1, and CTLA-4 (e.g. ipilimumab) checkpoint inhibitors, but also EGFR-inhibitors, and combinations of BRAF (e.g. vemurafenib) and MEK inhibitors. However, these reports, especially those implicating checkpoint inhibitors, often relate to atypical, SJS/TEN-like bullous lichenoid reactions, regularly in patients on polypharmacy (including high-risk drugs for SJS/TEN) and/or (pre)treated with another immunomodulating agent. Of note, these reactions regularly only occur after prolonged drug use and show a mild initial presentation and slowly evolving course, followed by a rapid progression.

The ALDEN score, an SJS/TEN-specific drug-causality score, can be helpful to identify the culprit drug, especially in cases with polypharmacy. It is based on the time latency between start of drug use and onset of the adverse reaction, drug presence in the body at onset (drug's half-life and liver- and kidney function), drug notoriety, prechallenge, rechallenge and dechallenge, and exclusion of alternative causes.

However, some cases are of infectious origin (e.g. Mycoplasma pneumonia in SJS) or are without any plausible identifiable cause (especially in the under-18-year-olds). Confounding non-drug risk factors are HIV, other infections, recent cancer, recent radiotherapy, and collagen vascular disease [6].

Diagnosis Paths

History and Physical Examination

Most important is the acute onset of extensive painful mucocutaneous blistering with the typical

clinical presentation and systemic symptoms, often preceded by a prodromal stage. At suspicion of SJS/TEN, an early accurate medication history is essential to detect a possible association, with special attention to drugs, introduced 4–28 days before onset of the reaction.

General Diagnostics

Diagnosis mainly relies on the clinical picture, confirmed by histopathology (clinicopathological correlation) and negative immunofluorescence investigations. Typical clinical signs initially include painful erythematous and violaceous purpuric macules on the skin with progressive coalescence on which a positive pseudo-Nikolsky's sign (Fig. 2.2) can be induced. This is often followed by blistering and epidermal detachment within hours. Involvement of two or more mucosae develops shortly before or simultaneously with skin signs in almost all cases.

Work up of immediate cryosections or conventional formalin-fixed sections of the skin, preferentially taken from a blister edge, should confirm diagnosis. Histopathology of SJS, SJS/TEN overlap and TEN essentially shows the same picture, featuring widespread keratinocyte apoptosis scattered throughout the epidermis with subepidermal blistering secondary to extensive presence of necrotic keratinocytes, resulting in (almost) full-thickness epidermal necrosis. The dermis may show slight perivascular lymphocytic infiltrates (Fig. 21.6).

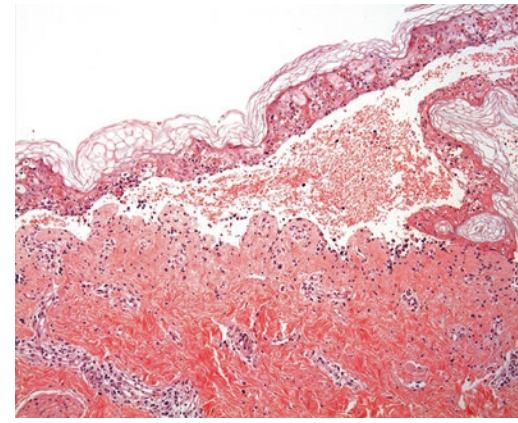

Fig. 21.6 Histopathology of SJS/TEN showing many apoptotic cells resulting in almost total necrotic epidermis and subepidermal splitting. The dermis shows very sparse lymphocytic infiltrates

Table 21.2 SCORTEN criteria and mortality

Independent prognosis factors	Weight
Age ≥ 40 years	1 point
Malignancy present	1 point
Detached body surface area ≥ 10%	1 point
Heart rate ≥ 120/min	1 point
Serum urea >10 mmol/l	1 point
Serum glucose >14 mmol/l	1 point
Serum bicarbonate <20 mmol/l	1 point
Total score	**Mortality (%)**
0–1 points	3.2
2 points	12.1
3 points	35.3
4 points	58.3
≥5 points	90.0

Specific Diagnostics

To distinguish SJS from SJS/TEN-overlap or TEN the total maximum detached BSA is the predominant discriminating factor (Figs. 21.3, 21.4, and 21.5).

The main differential diagnoses of SJS/TEN are acute generalized exanthematous pustulosis (AGEP), generalized bullous fixed drug eruption (GBFDE), staphylococcal scalded skin syndrome (SSSS), graft versus host disease (GvHD) and autoimmune blistering diseases, including linear IgA bullous dermatosis and paraneoplastic pemphigus, but also pemphigus vulgaris, bullous pemphigoid, and (sub)acute lupus erythematodes. Differentiation of AGEP and SSSS can be made by histopathology, while autoimmune blistering diseases can be ruled out by (in)direct immunofluorescence investigations. Differentiation of GBFDE is difficult and can be made on subtle differences in the clinical presentation and on history.

Within the first 3 days of admission SCORTEN, a severity-of-illness score for TEN predicting prognosis, should be performed (Table 21.2). Although in vivo or in vitro testing (patch test or lymphocyte transformation test) may confirm the suspected culprit drug, the sensitivity of these tests is rather limited in SJS/TEN.

Case Study: Part 2

History reveals that carbamazepine was taken since 2 weeks. Two days later body temperature is 38.9 C. The skin eruption has meanwhile extended and is very painful, with many erythematopapular lesions mainly on the upper torso, face, arms and legs, some with blistering. Severe conjunctivitis is observed, while lips, mouth and genital area show extensive blistering and erosions. Pseudo-Nikolsky's sign is positive (Fig. 21.7). What is your differential diagnosis now?

Treatment Tricks

Initial Treatment and Therapeutic Ladder

Treatment requires specific expertise and facilities: early admission to a referral centre reduces the risk of infection, mortality and length of hospitalisation. Management in the acute stage should be multidisciplinary and includes supportive care and evaluation of the severity and prognosis by means of SCORTEN. With a score of ≥3 or when ≥20% of the BSA is detached or detachable, transfer to an intensive care unit should be considered. Restoring the barrier function of skin and mucosae as quickly as possible and in the meantime preventing the negative effects of its loss is of eminent importance [7]. Because of massive loss of body temperature and fluid, the patient is preferentially treated on an "air-fluidized" bed in a temperature and moisture regulated room with, for aseptic reasons, a laminar down flow stream. To protect patients from infection, nursing has to be barrier protected.

First line of treatment is cessation of the suspected culprit. For drugs with short half-lives, prompt withdrawal on the first day of blistering/erosions has a positive effect on the outcome and lowers mortality.

Apart from withdrawal of the culprit and intensive, multidisciplinary, supportive care, various options for immunomodulating treatment have been suggested. However, results are variable and generally accepted guidelines are still lacking. Corticosteroids, especially a short course of high dosed pulse therapy, e.g. 1.5 mg/kg bodyweight dexamethasone on 3 consecutive days, early in the process, might positively influence the immune mediated cascade leading to apoptosis [7]. The supposed rationale that intravenous immunoglobulins (IVIG) inhibit activation of the death receptor by Fas-inhibiting antibodies is questioned and the reported results are inconsistent. More recently, also TNF-α blockers, espe-

Fig. 21.7 Describe what you observe. What is your diagnosis?

cially etanercept have been suggested and a favourable outcome has been reported for treatment with ciclosporin [8, 9].

Follow-Up and Tapering

Intensive monitoring includes vital parameters, laboratory investigations (blood count, electrolytes, renal-, liver function, blood gases, bicarbonate, glucose, blood culture, urine analysis, etc.) mucocutaneous cultures, and BSA involvement.

The hypercatabolic state and mucosal involvement induced by SJS/TEN often demands nutritional correction by nasogastric feeding. A critical element of supportive care is the management of fluid and electrolyte requirements. Hyponatremia, hypokalaemia or hypophosphatemia, which quite frequently do occur, necessitate appropriate early and aggressive replacement therapy.

Blisters should be treated conservatively because blistered skin acts as a natural biological dressing, likely favouring re-epithelialization. Removing only epidermis that is curled up is preferred over debridement, which is still regularly performed in burn units. Extensive wound care includes emollients (petrolatum gauzes), local antiseptics, and non-adhesive dressings. Central lines should be avoided while antibiotics are only given if needed. Pain and anxiety control are essential; systemic corticosteroids should be avoided late in the process [7, 9].

Because of the combined involvement of skin, eyes and other mucous membranes, interdisciplinary follow up and treatment of sequelae is recommended. Special attention should be given to the prevention of genital and ocular complications. Daily examination by an ophthalmologist can help to diminish the risk for permanent visual loss due to corneal scarring or neovascularisation. Preservative-free eye drops including saline, topical steroids or antibiotics should be installed every two hours; developing synechiae should be disrupted. In the early phase of corneal defects, amniotic membranes covering the ocular surface decrease pain, preserve visual acuity, and protect against scarring [9]. Scleral contact lenses may promote corneal healing. Prolonged ophthalmologic follow up is recommended because corneal involvement may progress for months to years.

Survivors should be educated on the cause of the reaction and future drug use, and not be re-exposed to the suspected or chemically related drugs.

Case Study: Part 3

Histology of the edge of a blister reveals nearly full thickness epidermal necrosis, subepidermal splitting and sparse dermal lymphocytic infiltrates. Together with the clinical picture the diagnosis fits within the spectrum of SJS/TEN. The total detached BSA that will ultimately be reached, determines the final diagnosis. Carbamazepine is immediately stopped and treatment is started with dexamethason pulse therapy 1.5 mg/kg for 3 days intravenously. Patient is nursed barrier protected in a laminar down flow room on an "air-fluidized" bed and intensively monitored e.g. including SCORTEN and vital parameters and received extensive wound care.

Erythema Exsudativum Multiforme (EEM)

Facts and Figures

Definitions and Classification

EEM is an acute, often symmetrical, mucocutaneous, polymorphous eruption, with a diversity of lesions: erythema, papules or plaques, vesiculo-bullae, and purpura. It may present with only few lesions, but can also be rather extensive. Characteristic is the acrofacial distribution, which may spread centripetal. Most lesions develop within 24–72 hrs as small wheal-like erythematous lesions, which may become papular and individual lesions may persist for over a week; lesions however, may also appear in serial crops. Some are highly regular and circular, measuring a few millimetres to three centimetres and may become livid. Bullae or purpura may develop in the center, creating the so-called target or iris lesions. Target lesions in EEM are raised and can be typical (Fig. 21.1) and/or atypical (Fig. 21.2).

EEM varies from mild (EEM minus, the most common form with symmetrical distributed, most often mildly itching or burning classical "target lesions" on the extensor sides of the extremities, face, and neck), to a more severe form (EEM majus). The difference is based on the presence and severity of systemic symptoms (e.g. fever and malaise) and involvement of mucosae, which is absent or minor and often restricted to the lips in the minus, and more pronounced in the majus form.

EEM majus may be preceded by influenza-like prodromes with a classic time course, usually starting 1–14 days before lesions appear, while prodromal symptoms are mostly absent or mild in EEM minus. Lesions evolve over 1–2 weeks. Mucosal involvement often presents with clearly haemorrhagic crustae and erosions including on lips, mouth, eyes, nose, genitals, urethra and/or anus. In children and adolescents, the mucosae can be severely affected in cases caused by Mycoplasma pneumoniae (M. pneumoniae) or respiratory infections, sometimes even extending into the throat, larynx and bronchi [10]. Whatever the clinical relevance, further subtypes have been identified, e.g. atypical EEM majus (with giant targets located on the trunk) and the recently introduced qualification "M. pneumoniae-induced rash and mucositis" (MIRM). In all subtypes, infections have been found the most common aetiology.

Resolution normally results within 2–3 weeks; EEM majus may have a more protracted course: mucosal lesions generally heal without sequelae within 3–6 weeks, except in severe eye involvement. Skin lesions may heal with hyper- and/or hypopigmentation, scarring is usually absent. Most patients have an uncomplicated course, with exception of the immunocompromised and those with secondary bacterial infections. Although generally self-limiting, recurrences are common and are most often preceded by or occur with an overt or subclinical HSV infection.

Mortality in EEM minus is virtually absent and approximately 1% in EEM majus, mainly concerning patients of older age and with underlying conditions; sepsis secondary to loss of the cutaneous barrier is the principle cause [2].

Epidemiology

The exact incidence of EEM is not known, but is estimated at somewhere between 0.01% and 1% of the population, with the minus variant as the most prevalent. EEM occurs in patients of all ages, but is predominantly observed in adolescents and young adults with a peak incidence in the second and third decades of life. It is rare during early childhood and in adults older than 50 years, EEM majus has a slight male preponderance, but no racial bias. Recurrences occur in 30% of EEM minus and of 10% of EEM majus [10].

Pathogenesis

Pathophysiology of EEM is still not fully understood. Most likely it is a distinct hyperergic mucocutaneous immune reaction, triggered by a variety of stimuli, in particular various infections (about 90%) or chemical products in certain "predisposed" individuals. Although, predisposing genes have been associated (HLA-DQB1*0301), its predictive value is too low to have clinical relevance. Otherwise, a clear genetic predisposition for EEM is still to be defined. Of note, several physical agents such as trauma, cold, and ultraviolet radiation have been described as triggers for outbreaks of EEM related to infectious agents, drugs or systemic disease.

HSV is clearly most commonly associated with EEM minus and in the majority of adults with EEM majus. M. pneumoniae is the second cause of EEM overall and the first in children. In cases related to mycoplasma, the target lesions are usually atypical and appear predominantly on the trunk [10]. Rarely, EEM has been associated with drugs or systemic disease. The majority of children and adults where the disease is precipitated by HSV types 1 and 2 have a normal immunity to HSV, but they possibly have difficulty in clearing the virus. HSV suppression and prophylaxis with antiviral therapy (e.g. valacyclovir) has been shown to prevent recurrent EEM.

Diagnosis Paths

History and Physical Examination

The most important differential diagnosis is SJS, because of its possible life-threatening complica-

tions and the need of timely withdrawal of a suspected drug. Diagnosis relies on the clinical picture: typically, it presents as an acute mucocutaneous eruption in an adolescent or young adult, suffering or recovering from herpes, or having a history of recurrent, similar attacks. Characteristic is the presence of typical target lesions and the acral predilection on the back of the hands and feet (sometimes palmoplantar), and extensor sites of the elbows, knees, neck, face, mouth, eyes and genitals. History should document recent constitutional symptoms, previous or current HSV, M. pneumoniae or other infections, and all use of medication, in particular started in the previous 2 months.

General Diagnostics

Besides SJS/TEN, several other diseases may be considered including urticaria, (urticarial)vasculitis, toxic/viral exanthema, serum sickness-like eruption, annular/gyrated erythemas, and M. Sweet; while e.g. herpes stomatitis, aphtosis, auto-immune bullous diseases, including (sub) acute cutaneous lupus erythematodes, and SJS should be considered in cases with mucosal involvement. The possibility of SJS, GBFDE, polymorphous maculopapular eruption or urticaria should be strongly considered if the presumed aetiology is drug-induced. The most important differential diagnosis however is urticaria, especially in its early acute stage. The main difference is that in EEM the centre of the lesions may show a darker, dull, purple aspect, blisters, erosions or crusts, versus normal skin in urticaria. Moreover, in EEM lesions are not transient, but will remain during a period of several days, while oedema is not a prominent feature.

Specific Diagnostics

Histopathology typically reveals an acute interface dermatitis with apoptotic epidermal keratinocytes, especially at the interface, sometimes resulting in more widespread epidermal necrosis, and in addition a moderate lymphocytic, sometimes mixed superficial perivascular infiltrate. Differentiation from SJS/TEN just on histopathology can be problematic and should be based on the clinicopathological correlation. Most important clues for SJS/TEN are a severely painful skin, rapid progression with dark violaceous, often confluent macules and blisters, constitutional symptoms, and recent drug use. In urticaria, histopathology shows some perivascular mixed infiltrates, while an interface dermatitis or apoptotic epidermal cells, characteristic for EEM, are lacking. Immunofluorescence findings can help to exclude autoimmune bullous disorders. HSV can be confirmed by PCR. Chest radiography, PCR-assay and/or serology, especially in cases with respiratory symptoms, may help to detect M. pneumonia,

Treatment Tricks

Most often, EEM is self-limiting. However, it is essential to potentially identify and treat the eliciting factor. Admission should be considered for patients with severe oral involvement, impairing feeding and drinking, or presenting with severe constitutional symptoms.

Otherwise, treatment is usually symptomatic, including oral antihistamines, analgesics, local skin and mucosal care. Liquid antiseptics, such as 0.05% chlorhexidine, help to prevent superinfection. Patients feeling ill and having extensive lesions can be treated with corticosteroid creams against pruritus and anti-inflammatory drugs and/or xylocaine for pain management. For oral lesions antiseptics can be useful, as are local corticosteroids and/or painkilling preparations. For eye involvement an ophthalmologist should be consulted, especially in the acute phase to prevent infection and scarring. Topical treatment, including for genital lesions, can be performed with gauze dressings or a hydrocolloid. In more severe cases, meticulous wound care is needed. Infections should be appropriately treated after cultures/PCR and/or serologic tests have been performed. Suppression of HSV can prevent HSV-associated recurrent EEM, but antiviral treatment after the eruption of EEM has started, is without effect on the course of EEM. Treatment of M. pneumonia can be useful in case of respiratory symptoms, but does not result in a more rapid healing of the associated EEM. Although systemic corticosteroids are often given in severe cases, their beneficial use

has not been evidenced; they should be restricted to the very early stage of the disease. Azathioprine, thalidomide, and mycophenolate mofetil have been suggested for recurrent or therapy resistant cases [10].

Review Questions

1. Which drug is most often associated with SJS/TEN?
   a. Allopurinol
   b. Penicillin and its derivates
   c. NSAIDs
   d. Quinolones
2. The following clinical symptoms differentiate SJS from EEM majus:
   a. Typical target lesions
   b. Detached and detachable BSA > 10%
   c. Fever
   d. All of mentioned above
3. Regular observed long-lasting sequelae in SJS/TEN are:
   a. Impaired vision
   b. Disturbed liver function
   c. Disturbed kidney function
   d. Cutaneous scarring
4. SCORTEN indicates:
   a. The severity of SJS/TEN
   b. The total detached and detachable BSA
   c. The prognosis in TEN
   d. The severity and prognosis in EEM/SJS/TEN
5. Regarding medication in SJS/TEN:
   a. SJS and TEN can be elicited by identical medication
   b. In SJS/TEN the half-life of a culprit medication that has been withdrawn is decisive for its course
   c. In SJS/TEN all medication should be stopped
   d. A relatively limited number of drugs has been associated with SJS/TEN

Answers

1. a.
2. a.
3. a.
4. c.
5. a.

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