

Disease in a Nutshell

Stevens–Johnson syndrome and toxic epidermal necrolysis

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ARTICLE INFO

Article history:

Received for publication October 16, 2016.

Received in revised form November 21, 2016.

Accepted for publication November 26, 2016.

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN or Lyell disease) are rare diseases that cause acute destruction of the epithelium of the skin and mucous membrane by a violent immune response. SJS, TEN, and SJS–TEN overlap are considered variants in a spectrum of disease severity. SJS involves epidermal detachment of less than 10% of total body surface area, TEN involves epidermal detachment of more than 30% of total body surface area, and SJS–TEN overlap involves epidermal detachment of 10% to 29% of total body surface area. The high rate of morbidity and mortality associated with TEN makes early diagnosis and treatment essential.¹

Medications are the most commonly reported cause of SJS and TEN. The most common culprits include sulfonamides, carbamazepine, nonsteroidal anti-inflammatory drugs, allopurinol, phenytoin, phenobarbital, valproic acid, cephalosporins, quinolones, aminopenicillins, and tetracyclines.^{2–4} In particular, trimethoprim-sulfamethoxazole has been implicated most commonly and accounted for 69% of the cases in one review.^{2,3} Less commonly, cases of SJS and TEN are caused by *Mycoplasma pneumoniae*, herpes simplex virus (HSV), and cytomegalovirus (CMV) infections or have to be considered idiopathic.⁵ Penicillin and cephalosporins can cross-react in certain patients, as can the anti-epileptics.⁴ However, cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotic drugs is less likely.⁴

Pathophysiology

Genetic factors and offending medications can result in activation of an inflammatory cascade, leading to keratinocyte apoptosis,

blistering, and systemic inflammation (Fig 1). The precise molecular and cellular pathogenic mechanism of SJS and TEN can only be partially explained. It is thought to be initiated by an immune response to an antigenic drug–host tissue complex. Three different hypotheses have been proposed⁶: (1) the hapten/prohapten concept in which covalent binding of the drug to a cellular surface peptide induces an immune-inflammatory response; (2) the pharmacologic interactions of drugs with immune receptors concept in which noncovalent, direct interaction of the drug with a specific major histocompatibility complex class I allotype results in T-cell activation and cytokine secretion; and (3) the altered peptide concept in which presentation of an altered self-repertoire by direct drug–major histocompatibility complex I interaction occurs, leading to immune activation and systemic inflammation.

It has also been suggested that SJS and TEN may be induced via direct interaction between a medication and an immune system component, as described with a carbamazepine and HLA-B*1502 interaction. This finding is clinically relevant because screening for the HLA-B*1502 allele in Asian patients before drug intake may identify persons at risk of developing severe cutaneous drug reactions.⁷

Several other factors have been identified that might contribute to the induction of excessive apoptosis of keratinocytes.^{3,8} Immune activation by the drug–host tissue complex induces an interaction between Fas ligand (FasL) and Fas (CD95), leading to keratinocyte apoptosis. Fas is a receptor that is expressed on keratinocytes, and when it interacts with soluble FasL, it leads to keratinocyte apoptosis with subsequent epidermal necrosis and detachment. Levels of FasL are very elevated in patients with SJS and TEN in contrast to patients with typical morbilliform drug eruptions.⁹ There is also an induction of granulysin and annexin A1 secretion by cytotoxic T cells, natural killer cells, natural killer T cells, and monocytes, causing granulysin-mediated apoptosis and/or annexin-dependent necroptosis of keratinocytes.⁸

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<http://dx.doi.org/10.1016/j.anai.2016.11.019>

1081-1206/Published by Elsevier Inc. on behalf of the American College of Allergy, Asthma & Immunology.

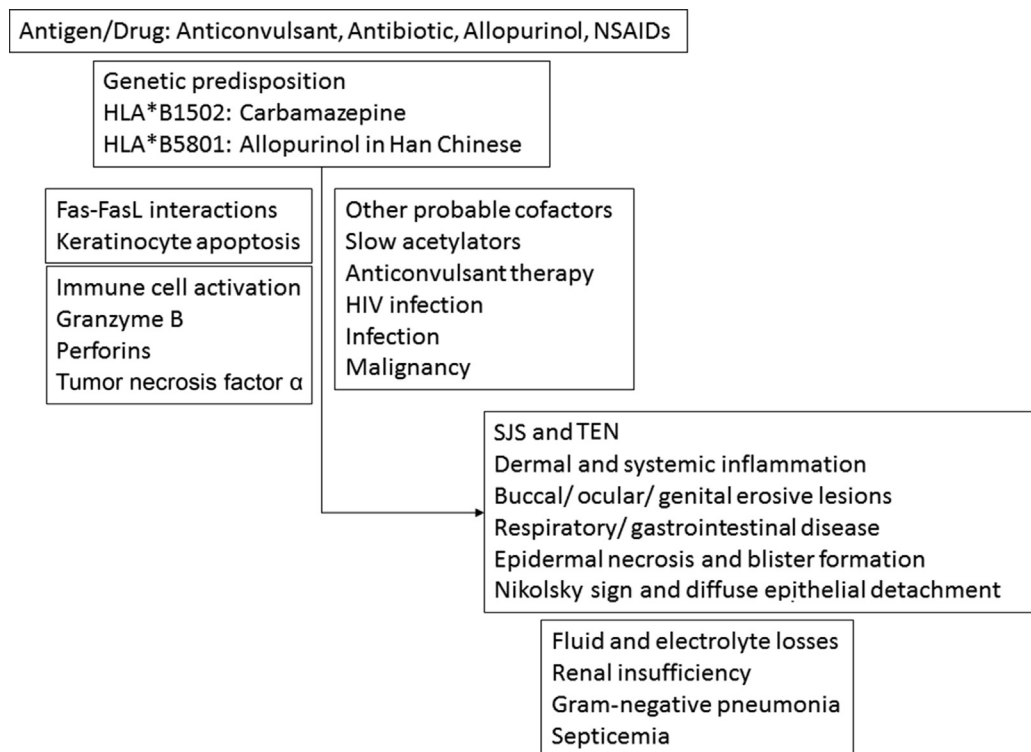


Figure 1. Genetic factors and offending medications or drugs can result in activation of an inflammatory cascade, leading to keratinocyte apoptosis, blistering, and systemic inflammation. Cofactors (eg, human immunodeficiency virus [HIV], infections, malignant tumors, and medication use or acetylation rate) and immune-inflammatory factors and mediators (eg, perforin, granzyme B, or inflammatory cytokines, such as tumor necrosis factor α) can lead to mucocutaneous inflammation, systemic complications, and multiorgan disease. Fluid and electrolyte losses, renal failure, gram-negative pneumonia, and sepsis can all contribute to the disease severity and mortality. The extent of skin surface involvement differentiates Stevens-Johnson syndrome (SJS) from toxic epidermal necrolysis (TEN), with the latter having a more complicated course and associated with a poorer prognosis. FasL indicates Fas ligand; NSAIDs, nonsteroidal anti-inflammatory drugs.

Clinical Presentation

SJS and TEN typically occur 4 to 21 days after starting use of the offending drug. A prodrome of fever, influenza-like symptoms, lymphadenopathy, and discomfort while swallowing presents 1 to 3 days before the development of mucocutaneous lesions. Cutaneous lesions typically first appear on the thorax and face before spreading to other areas in a symmetrical distribution.² The cutaneous lesions present as ill-defined, coalescing, dusky red macules with purpuric centers that progress into vesicles and bullae and eventually lead to skin sloughing (Fig 2A, C, and D). The Nikolsky sign (the separation of intact superficial epidermis by a shearing force) is positive. Mucosal involvement occurs in nearly all cases, most commonly presenting as stomatitis and conjunctivitis (Fig 2D).¹⁰

In addition, systemic manifestations can occur, affecting the kidneys (acute renal failure), lungs (pneumonitis, adult respiratory distress syndrome, bronchiolitis obliterans, and subcutaneous emphysema), and liver (hepatitis).⁵ Erosions can affect any mucous membrane, resulting in significant morbidity. Erosions and sloughing may extend into the esophagus and upper airway, leading to serious complications. Ocular involvement is not uncommon and usually presents with conjunctival injection and can be complicated by pseudomembranes and synechiae formation. Synechiae are adherent connections between the iris and the cornea that must be broken urgently by an ophthalmologist to prevent permanent corneal scarring. Dyscoria, or an irregular, noncircular shaped pupil on dilation, may indicate synechiae formation. Adhesions between the palpebral and bulbar conjunctivae (symblepharon) are a well-recognized complication.^{11,12} Urethral involvement often presents as dysuria, and scarring can occur. Vaginal involvement can result in scarring of the introitus. Any

early adhesions should be cleaved to prevent future dyspareunia.⁹ A summary of the clinical characteristics is given in Table 1.

Diagnosis

Clinical Findings

SJS and TEN are typically diagnosed clinically based on recent exposure to a high-risk medication or mycoplasma, HSV, or CMV infection, along with targetoid skin lesions with central necrosis and mucosal involvement.⁹ Systemic symptoms with fever preceded by characteristic skin lesions should alert the clinician to have a high suspicion for SJS and TEN. An important clue to the diagnosis of SJS and TEN is the nonblanchable, nontransient, and often painful nature of the skin lesions.⁹ Sloughing with hemorrhagic crusting of the lips is often present early in the disease.⁹ Erythema multiforme (EM) can also present with mucocutaneous disease, but the presence of typical target lesions suggests the diagnosis (Fig 2B). Specifically, erythema multiforme major, which describes EM with mucosal membrane involvement, is a distinct disease entity and should not be used to describe SJS.

Allergy Testing

Allergic workup to identify the causative agents includes skin tests (epicutaneous testing), in vitro assays (lymphocyte transformation tests), and drug-induced cytokine production assays (eg, enzyme-linked immunospot). Skin tests are safe in patients with TEN, but their specificity and sensitivity are rather low. Positive patch test reactions were observed in only 24% of those patients in one study.¹³ Lymphocyte transformation tests also have a low sensitivity in patients with SJS and TEN.⁸



Figure 2. Clinical manifestations of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TENS). A, Foot involvement and Nikolsky sign demonstration. B, Typical target lesions in a patient with erythema multiforme. SJS and TENS may cause target-like lesions. C, Extensive hand peeling in a patient with TENS. D, Typical skin lesions of SJS and TENS with blistering, hemorrhagic stomatitis, and lip blistering and peeling.

Skin Biopsy

Autoimmune blistering diseases, generalized fixed drug eruption, acute generalized exanthematous pustulosis, drug-induced linear IgA bullous dermatosis, paraneoplastic pemphigus, and staphylococcal scalded skin syndrome should be considered in the differential diagnosis. Rapid histologic examination of lesional skin is paramount in the diagnostic workup of SJS and TEN and will

reveal necrotic keratinocytes, as in EM, but with full-thickness epidermal necrosis, an intact (acute) stratum corneum, and a sparse dermal inflammatory infiltrate. Apoptosis of the stratum malpighii is more typical of EM. Direct immunofluorescence of perilesional skin is indicated to rule out diagnoses that can imitate TEN clinically, such as linear IgA bullous dermatosis and paraneoplastic pemphigus, which test positive on direct immunofluorescence, whereas SJS and TEN always test negative.⁸

Table 1
Differentiation Between Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

Feature	SJS	TEN
Skin involvement	<10% of total skin surface	>30% of total skin surface
Mucosal and cutaneous findings	Erythema, pseudotarget lesions, mucosal erosion, ulcerative hemorrhagic stomatitis is typical	Diffuse erythema, painful skin lesions, bullae, epidermal detachment, severe mucosal disease Nikolsky sign positive
Constitutional	Fever, malaise, arthralgia	Fever, malaise, arthralgia
Respiratory disease	Pharyngitis, laryngitis, tracheobronchitis	>25% Respiratory disease, hypoxemic respiratory failure with normal chest radiologic findings or ARDS, subcutaneous emphysema, bronchopneumonitis, tracheobronchial sloughing
Infection	Herpes simplex and mycoplasma infection may trigger disease	Complicated by gram-negative bronchopneumonia and sepsis, urosepsis
Fluid and electrolyte losses	Minimal	Significant losses but not as severe as with thermal injury, hypoproteinemia, hypoalbuminemia
Hematologic	Leukocytosis, anemia	Pancytopenia may be ominous sign
Ocular disease	Corneal ulcers, ocular cicatricial pemphigoid	Keratoconjunctivitis, corneal ulceration, ectropion/entropion, symblepharon formation, neovascularization, blindness
Gastrointestinal disease	Proctitis, oral ulcerations	Oral ulceration, esophagitis, stricture formation
Genital disease	Vulvovaginal erosions, urethritis	Vaginal blistering and erosion

Abbreviation: ARDS, acute respiratory distress syndrome.

Table 2
SCORTEN^{19,20} (SCORE of Toxic Epidermal Necrosis) Severity of Illness Scale^a

Risk factors		No. of risk factors	Mortality rate, %
0 points	1 point		
Age <40 years	Age >40 years	0–1	3.2
No malignant tumor	Malignant tumor present	2	12.1
Heart rate <120/min	Heart rate >120/min	3	35.3
Serum BUN <28 mg/dL	Serum BUN >28mg/dL	4	58.3
BSA epidermal detachment <10%	BSA epidermal detachment >10%	>5	>90
Serum bicarbonate >20 mEq/L	Serum bicarbonate <20 mEq/L		
Serum glucose <252 mg/dL	Serum glucose >252 mg/dL		

Abbreviations: BSA, body surface area; BUN, blood urea nitrogen.

^aAdapted from https://en.wikipedia.org/wiki/SCORTEN_scale.

Treatment

Management of SJS and TEN involves identifying the cause and immediate discontinued use of the offending drug, halting the reaction if possible, and intensive supportive care.⁹ Unfortunately, there is no clear consensus on best treatment for TEN. The rarity of TEN makes it difficult to have large enough numbers to complete a randomized clinical trial, and the high mortality rate of this disease may make it difficult to justify withholding treatment that could potentially benefit such patients. It is vital that therapy is started as soon as possible because cell death cannot be reversed and any areas of full-thickness necrosis will progress to blistering and sloughing.⁹

Immunomodulation

Several agents have been described in the literature for treatment of TEN, including cyclosporine, cyclophosphamide, *N*-acetylcysteine, tumor necrosis factor α antagonists (eg, etanercept and infliximab), systemic corticosteroids (favoring pulsed corticosteroid treatment), thalidomide, plasmapheresis, and intravenous immunoglobulin (IVIG) (≤ 2 g/kg).⁸ IVIG blocks the binding of Fas to FasL, thus inhibiting keratinocyte apoptosis.⁹ More recently, the role of cyclosporine has been described to slow disease progression, promote rapid reepithelialization, and increase the chance of survival.¹⁴

The use of systemic steroids to decrease mortality of SJS and TEN is often debated and generally not supported by studies. Some studies have found that combining systemic corticosteroids with IVIG yields better treatment results than corticosteroids or IVIG alone.¹⁵ A recent retrospective study from China reviewed the records of 70 patients with SJS or TEN treated with corticosteroids and found a lower than expected mortality in the treated patients.¹⁶ The authors recommended early and cautious use of steroids, factoring in additional systemic disease, antimicrobial use, and nutritional status as measured by serum albumin levels. One other study revealed the efficacy of IVIG (400 mg/kg daily for 5 days) combined with systemic glucocorticoids in SJS and TEN.¹⁷ Plasmapheresis may be a safe and effective tool in this disease, and the outcomes of 2 small trials suggest that this procedure may result in complete remission.¹⁸

Supportive Care

Supportive care is essential in the management of patient with TEN. Exudative necrotic epithelium may compromise the airway; therefore, attempts to insert a nasogastric tube or endotracheal tube should be done carefully.⁹ Proper wound care is vital to prevent fluid loss, monitor and prevent secondary skin infections, and promote healing. If available, widespread

desquamation may be best managed in a burn center setting. Bland emollients, such as petrolatum gauze, provide a barrier and moisturizing layer to help with reepithelialization. Use of silver sulfadiazine cream and silver-impregnated clothing may also be helpful. Topical antibiotics may be useful in areas that have high risk of superinfection, such as periorificial and intertriginous areas. Oral care is important for pain control and to prevent infection. Mouthwash preparations that contain various formulations of diphenhydramine and antacids with aluminum and magnesium help to debride the dead skin and to control pain.⁹ Prophylactic antibiotics are rarely indicated because they generally put patients at risk for resistant or atypical infections, such as candidemia. Antibiotics should be guided by cultures and targeted to the most common pathogens, which include *Staphylococcus aureus*, Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Candida* species.¹⁹ Prophylactic antiviral therapy should also be added if viral pathogens, such as HSV or CMV, are suspected as likely cause of SJS and TEN.

Prognosis

Mortality rates reported with TEN range from 25% to 45% and depend on a number of factors. SCORTEN (Score of Toxic Epidermal Necrosis; https://en.wikipedia.org/wiki/SCORTEN_scale) is an illness severity score used to predict mortality in SJS and TEN (Table 2).^{5,20} It is assessed on days 1 and 3 of hospitalization for SJS and TEN. SCORTEN is useful in triaging patients into their appropriate clinical setting (ie, intensive care/burn unit vs nonspecific hospital ward), guiding treatment decisions, and discussing prognostic factors with patients and their families.^{5,20} An online version of the form is available and provides a rapid calculation of the mortality rate (SCORTEN online calculator: <http://www.pmidcalc.org/?sid=10951229&newtest=Y>).

Conclusion

SJS and TEN are life-threatening mucocutaneous diseases characterized by acute, extensive epidermal detachment. SJS and TEN are most commonly caused by drugs and are therefore typically classified as severe adverse drug reactions. SJS and TEN exist as different points on the same spectrum, differing only in the extent of mucocutaneous involvement. Early recognition of SJS and TEN and prompt withdrawal of the causative agent are imperative for increasing patient survival.

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