Toxic epidermal necrolysis: an update

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1. Introduction

Stevens-Johnson syndrome (SJS), was first described in 1922, as an acute mucocutaneous syndrome in two young boys. The condition was characterized by severe purulent conjunctivitis, severe stomatitis with extensive mucosal necrosis, and purpuric macules. It became known as SJS and was recognized as a severe mucocutaneous disease with a prolonged course and potentially lethal outcome that is in most cases drug-induced, and should be distinguished from erythema multiforme (EM). There is broad agreement in medical literature that SJS can be considered a more severe form of Stevens Johnson syndrome, and debate whether it falls on a spectrum of disease that includes erythema multiforme. Some authors consider that there is an overlap between the two syndromes (usually between 10% and 30% of skin detachment). This article deals with history, epidemiology, diagnosis, pathophysiology treatment and management of SJS.T]

PEER REVIEW

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Comments
The article is good and has focused on all related matters of the disease. Authors have sincerely reviewed and studied the topic with marvelous efforts and showed the qualitative capacity in composing this article. The paper is satisfactory as per standards of the journal. Scientific works has been honestly represented.

ABSTRACT

Toxic epidermal necrolysis (TEN), also known as Lyell’s syndrome, is a rare, life-threatening dermatological condition that is usually induced by reaction to medications. It is characterized by the detachment of the top layer of skin (the epidermis) from the lower layers of the skin (the dermis) all over the body. There is broad agreement in medical literature that TEN can be considered a more severe form of Stevens Johnson syndrome, and debate whether it falls on a spectrum of disease that includes erythema multiforme. Some authors consider that there is an overlap between the two syndromes (usually between 10% and 30% of skin detachment). This article deals with history, epidemiology, diagnosis, pathophysiology treatment and management of TEN.

KEYWORDS
Toxic epidermal necrolysis, Stevens Johnson syndrome

human immunodeficiency virus (HIV) infection. TEN is a potentially life-threatening disorder characterized by widespread erythema, necrosis, and bullous detachment of the epidermis and mucous membranes. Without proper management, TEN can cause sepsis leading to death of the patient. Though TEN is commonly drug induced, isoniazid (INH) has been uncommonly associated with TEN. TEN is a rare, severe cutaneous adverse drug reaction with average mortality of 25%–35%, especially among elderly multimorbid patients. Established therapeutic guidelines do not exist, and controversies underlie on many of the presently suggested treatment regimens. TEN is a unique rapid developing mucocutaneous reaction pattern which is characterized by sheets of erythema, necrosis and bullous detachment of the epidermis having a close resemblance to that of scalding of the skin. It is a rapid fatal disease. It

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was first described by Lyell and now is recognized as TEN Lyell’s syndrome. It had become clear that TEN was drug-induced, and the drugs such as sulfonamides, pyrazolones, barbiturates, and antiepileptics were the most frequent triggers of TEN.

SJS and TEN are considered to be two ends of a spectrum of severe epidermolytic adverse cutaneous drug reactions, differing only by their extent of skin detachment.

2. Background and disease name

Pemetrexed is an antifolate drug approved for maintenance and second-line therapy, and in combination with cisplatin, for first-line treatment of advanced nonsquamous non–small cell lung cancer (NSCLC). The same combination is nowadays approved in the first-line setting for locally advanced or metastatic nonsquamous NSCLC. The side-effect profile includes fatigue, hematological and gastrointestinal toxicity, increasing in hepatic enzymes, sensory neuropathy and pulmonary and cutaneous toxicity in various degrees. TEN–like presentations have been described in non–drug-induced settings.

TEN is a rare, mostly drug–induced, severe mucocutaneous reaction to a causative drug with mild side effects. TEN caused by fluconazole is rare, and till now only few cases have been reported in the literature.

There are evidences showing that drug-specific T cells are involved in inducing keratinocyte apoptosis in acute stage of SJS and TEN. However, there were few studies that had attempted to examine T cell memory responses over time. Duration of IFN-γ and sFasL memory response to causal drugs in patients with SJS and TEN after remission and findings confirmed that drug-specific IFN-γ and sFasL memory response against causal drugs could be sustained over several years and further suggest that patients should avoid causal drug re-exposure after the recovery of TEN and SJS. Severe cutaneous adverse reactions to drugs (SCARs) include acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) and epidermal necrolysis (Stevens–Johnson syndrome–toxic epidermal necrolysis [SJS–TEN]). Due to the varied initial presentation of such adverse drug reactions, diagnosis may be difficult and suggests overlap among SCARs. Overlapping SCARs are defined as cases fulfilling the criteria for definite or probable diagnosis of at least 2 ADRs according to scoring systems for AGEP, DRESS and SJS–TEN.

TEN is an unpredictable, life-threatening drug reaction associated with a 30% mortality. Massive keratinocyte apoptosis is the hallmark of TEN. Cytotoxic T lymphocytes appear to be the main effector cells and there is experimental evidence for involvement of both the Fas–Fas ligand and perforin/granzyme pathways. Optimal treatment for these patients remains to be clarified. Discontinuation of the offending drug and prompt referral to a burn unit are generally agreed upon steps. Beyond that, however, considerable controversy exists. Evidence both pro and con exists for the use of IVIG, systemic corticosteroid, and other measures. There is also an evidence suggesting that combination therapies may be of value. All the clinical data, however, is anecdotal or based on observational or retrospective studies. Definitive answers are not yet available. Given the rarity of TEN and the large number of patients required for a study to be statistically meaningful, placebo controlled trials are logistically difficult to accomplish. The absence of an animal model further hampers research into this condition and comprehensive knowledge of our current understanding of the classification, clinical presentation, etiology, pathophysiology, prognosis, and treatment of TEN

3. Signs and symptoms

TEN affects many parts of the body, but the mucous membranes is the most severely affected, such as the mouth, eyes, and vagina. The severe findings of TEN are often preceded by 1 to 2 weeks of fever. These symptoms may mimic those of a common upper respiratory tract infection. When the rash appears, it may be over large and varied parts of the body, and it is usually warm and appears red. The dermal layer fills with fluid being deposited there by the body’s immune system, usually as a result of a negative reaction to an antibiotic. The skin then begins to sag from the body and can be peeled off in great swaths. The mouth becomes blistered and eroded, making eating difficult and sometimes necessitating feeding through a nasogastric tube through the nose or a gastric tube directly into the stomach. The eyes are affected, becoming swollen, crusted, and ulcerated and blindness may occur. The characteristic features of TEN are shown in Figure 1.
4. Pathology

TEN, like SJS and EM, are characterized by confluent epidermal necrosis with minimal associated inflammation. The acuity is apparent from the (normal) basket weave-like pattern of the stratum corneum.

5. Cause

Drug allergy describes clinical adverse reactions that are proved or presumed to be immunologically based. Allergic drug reactions do not resemble pharmacologic actions of the incriminated drug and may occur at fractions of what would be the therapeutic dosage. Allergic drug reactions are unpredictable; nevertheless, there are increased risks of drug hypersensitivity in:

1. Patients with cystic fibrosis who receive antibiotics;
2. Patients with HIV/AIDS who receive trimethoprim/sulfamethoxazole and receive the antiretroviral agent, abacavir;
3. Other genetically susceptible populations such as Han-Chinese who have HLA-B*1502(+) gene develops SJS and TEN from carbamazepine. Subjects having HLA-B*5801(+) are at increased risk for such reactions from allopurinol;
4. Patients with a history of previous compatible allergic reaction to the same medication, similar class, or potentially unrelated medication[13].

TEN is a rare and usually severe adverse reaction to certain drugs. History of medication use exists in over 95% of patients with TEN. The drugs most implicated in TEN are antibiotics such as sulfonamides, nonsteroidal anti-inflammatory drugs, allopurinol, antimetabolites (methotrexate), antiretroviral drugs, corticosteroids, chloroquine, and anticongestants such as phenobarbital, phenytoin, carbamazepine, and valproic acid. The condition might also result from infection with agents such as Mycoplasma pneumoniae (M. pneumoniae) or the herpes virus; and transplants of bone marrow or organs.

6. Pathogenesis

Microscopically, TEN causes cell death throughout the epidermis. Keratinocytes, which are the cells found lower in the epidermis, specializing in holding the skin cells together, undergo necrosis (cell death). TEN is a severe cutaneous drug reaction with a mortality rate of approximately 30%. The hallmark of TEN is widespread epidermal sloughing due to keratinocyte apoptosis. Multiple genetic associations between TEN and species-specific ethnic populations have been determined. The pathophysiology of TEN has yet to be fully elucidated; however, current pathogenetic models implicate Fas ligand, granulysin, and reactive oxygen species. The value of current therapies, such as intravenous immunoglobulin (IVIG) and corticosteroids, remains under evaluation[14].

7. Epidemiology

Drug hypersensitivity syndrome (DHS) is believed to be an adverse idiosyncratic drug reaction associated mainly with administration of aromatic antiepileptic drugs, such as phenytoin, carbamazepine, phenobarbital, lamotrigine[15]. La Grenade et al. reported similar results, with 1.9 cases of TEN per million inhabitants per year based on all cases reported to the FDA AERS database in the USA[16]. Scorten provides severity-of-illness scores for TEN, to compare predicted and actual mortality rates, and to evaluate the efficacy of treatment modalities[17]. SJS/TEN may be initiated by certain types of medication coupled with possible infection; however, few susceptibility genes have been identified as indicators for risk prediction, except for certain human leukocyte antigen allele, although several candidate susceptibility genes were identified by candidate gene and genome-wide approaches[18]. Immunologically mediated drug reactions have been traditionally classified as unpredictable based on the fact that they can not be predicted strictly on the pharmacological action of the drug. Such adverse drug reactions are associated with considerable morbidity and include severe cutaneous adverse reactions such as SJS/TEN and the drug hypersensitivity syndromes (drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome)[19]. Drug hypersensitivity reaction is an immune-mediated reaction to otherwise innocuous antigens derived from drugs. These reactions can affect many different organs, with the skin being the commonest and regional differences in drug prescription, the genetic background of patients (HLA, metabolizing enzymes), the coexistence of cancer, or concomitant radiotherapy, can have an impact on the incidence of SJS and TEN[20-22].

EM, SJS and TEN are all parts of a single spectrum illness. M. pneumoniae infections are widely documented to cause SJS and case of SJS/TEN of acute clinical course with massive occupation of the mucus membranes of the respiratory system, oral cavity, genitals and conjunctiva in a patient with pneumonia[23-25]. Furthermore, TEN are clinical conditions manifesting as adverse cutaneous reaction to drugs in majority of cases, constituting the same clinical spectrum, differing only in severity of epidermolysis; both conditions are distinguished by their severity and extentiveness of skin lesions; it can also involves mucous membranes of eyes, respiratory, digestive and urogenital tracts[26]. TEN is an acute, rapidly evolving mucocutaneous reaction with a high mortality rate characterized by extensive painful cutaneous and mucosal exfoliation and systemic involvement that is frequentely associated with medication use or reactivation of herpes simplex under treatment with azithromycin as potential causes of SJS[27,28]. AGEP is a clinical reaction pattern characterized by the rapid appearance of widespread sterile, nonfollicular pustules arising within edematous erythematous skin. This aseptic pustular eruption is commonly accompanied by leukocytosis and fever and usually follows recent administration of oral or parenteral drugs[29]. However, there are still cases of SJS/TEN...
without any obvious identifiable cause.

8. Genetic susceptibility

Genetic factors associated with drug hypersensitivity are a complex issue that has been studied in different populations and a variety of ethnic backgrounds. A unique and strong association between HLA, drug hypersensitivity and ethnic background was discovered by Chung et al. who showed a strong association in Han Chinese between the HLA-B*1502, SJS and carbamazepine[30]. This high association with an odds ratio of 2504 led to further studies in a similar ethnic group of Hong Kong Han Chinese with severe adverse reactions to antiepileptic drugs[31]. Another study confirmed the susceptibility of individuals with HLA-B*1502 to carbamazepine in a Thai population[32]. A smaller Indian based study, however, showed only a weak correlation between HLA-B*1502 and carbamazepine induced severe drug allergy. A genetic correlation, however, could not be shown in Japanese or European[33-35]. Indeed, in a large European study (RegiSCAR), HLA-B genotyping was performed in patients with severe cutaneous adverse reactions caused by the two previously mentioned drugs (carbamazepine, allopurinol) and another three high risk drugs (sulfamethoxazole, lamotrigine, NSAID’s of oxicam-type). This RegiSCAR study revealed that HLA-B*1502 is neither a marker for carbamazepine, sulfamethoxazole, lamotrigine, or NSAID’s of oxicam-type induced SJS/TEN nor a sufficient explanation for the cause of the disease in Europeans[35,36]. This leads to the conclusion that this genetic constellation (HLA-B*1502) is not a population independent marker for SJS/TEN in carbamazepine exposed individuals. Severe cutaneous reactions in HLA-B*1502 subjects were not only associated with the drug carbamazepine, but also, to a lesser extent (lower odds ratio), with phenytoin and lamotrigine[31].

A second strong association between HLA genotype and SJS/TEN has been reported for allopurinol. Indeed, 100% of Han Chinese patients with a severe adverse drug reaction to allopurinol were HLA-B*5801 positive[37]. Subsequently, a strong association between SJS/TEN and HLA-B*5801 was found in Japanese patients[34], Thai patients[32], and also, to a lesser extent (55% of cases), in patients of European origin[38].

9. Diagnosis

Generally, if the clinical history is consistent with SJS, and the skin lesion covers greater than 30% of the body surface area, the diagnosis of TEN is appropriate. Sometimes, however, examination of affected tissue under the microscope may be needed to distinguish it between other entities such as staphylococcal scalded skin syndrome. Typical histological criteria of TEN include mild infiltrate of lymphocytes which may obscure the dermoepidermal junction and prominent cell death with basal vacuolar change and individual cell necrosis[39]. Nikolsky’s sign is almost always present in toxic epidermal necrolysis (Figure 2)[40].

10. Diagnosis and diagnostic methods

The diagnosis on the one hand relies on clinical symptoms and on the other hand on histological features. Typical clinical signs initially include areas of erythematous and livid macules on the skin, on which a positive Nikolsky sign can be induced by mechanical pressure on the skin, followed within minutes to hours by the onset of epidermal detachment characterized by the development of blisters. It should be noted, however, that the Nikolsky sign is not specific for SJS/TEN. Mucosal, including ocular, involvement develops shortly before or simultaneously with skin signs in almost all cases. To distinguish SJS, SJS-TEN and TEN the surface area of the detachment is the main discriminating factor. Histological work up of immediate cryosections or conventional formalin-fixed sections of the skin revealing wide spread necrotic epidermis involving all layers confirms the diagnosis. In order to rule out autoimmune blistering diseases, direct immune fluorescence staining should be additionally performed and no immunoglobulin and/or complement deposition in the epidermis and/or the epidermal–dermal zone should be detected. Major differential diagnosis of SJS/TEN are autoimmune blistering diseases, including linear IgA dermatosis and paraneoplastic pemphigus but also pemphigus vulgaris and bullous pemphigoid, AGEP, disseminated fixed bullous drug eruption and staphylococcal scalded skin syndrome (SSSS). SSSS was one of the most important differential diagnoses in the past, but the incidence is currently very low with 0.09 and 0.13 cases per one million inhabitants per year[38].

11. Drug therapy

Several treatment modalities given in addition to supportive care are reported in the literature.
Systemic steroids were the standard treatment until the early 1990’s, although no benefit has been proven in controlled trials. In the absence of strong evidence of efficacy, and due to the conclusion resulting from the numerous steroid treatment regimens reported (treatment of short versus long duration, various dose regimens), their use has become increasingly disputed. A recent retrospective monocenter study suggests that a short course “pulse” of high dose corticosteroids (dexamethasone) may be of benefit[41]. On the other hand, a recent retrospective case–control study conducted by Schneck et al. in France and Germany concluded that corticosteroids did not show a significant effect on mortality in comparison with supportive care only[42].

The majority of cases appear to be related to idiosyncratic drug reactions. The drugs most commonly involved are antibiotics (e.g. sulfonamides, beta-lactam, tetracyclines and quinolones; anticonvulsants (e.g. phenytoin, phenobarbital and carbamazapine); antiretroviral drugs; nonsteroidal anti-inflammatory drugs, and allopurinol. There is a common agreement to consider TEN as the manifestation of a disregulated immune reaction against epithelial cells and anti-angiogenetic has been evaluated for the treatment of TEN[43,44]. Unfortunately, in a double-blind, randomised, placebo-controlled study, higher mortality was observed in the thalidomide–treated group suggesting that thalidomide is detrimental in TEN.

Proposed pathogenic mechanisms are conflicting, and the evidence for the benefits of individual treatments is inadequate, and in some cases contradictory. The mortality rate remains high, and the literature pertains to the pathogenesis of TEN and drug reactions in general. The rationale for therapeutic interventions, together with reported evidence of efficacy, are considered[45]. Infections particularly in M. pneumoniae and HSV have been reported to be the commonest precipitating cause for SJS in children in developed countries, and drugs are the commonest triggers reported in the Indian context. IVIG is emerging as a therapeutic option instead of glucocorticoids. Although, case of SJS in association with M. pneumoniae in a 5-year-old girl who recovered with IVIG therapy[46], confirms the known excellent tolerability and a low toxic potential of IVIG when used with appropriate precaution in patients with potential risk factors (renal insufficiency, cardiac insufficiency, IgA deficiency, thrombo-embolic risk)[47].

A new therapeutic approach targeting the proinflammatory cytokine TNFα has been proposed by Hunger et al.[48]. They treated one patient with a single dose of the chimeric anti–TNFα antibody (infliximab 5 mg/kg) and reported that disease progression stopped within 24 h followed by a complete re-epithelialisation within 5 d[48]. Meiss et al. reported three cases with an overlap of acute generalized exanthematous pustulosis and TEN and treatment response to infliximab[49]. Administration of the soluble TNFα receptor etanercept 25 mg on Days 4 and 8 after onset of TEN in a single case resulted in cessation of epidermal detachment within 24 h but subsequent death of the patient. The published data is currently insufficient to draw a conclusion on the therapeutic potential of TNF antagonists in TEN.

Although there is no standard therapeutic intervention in TEN, plasmapheresis (PP) is being used increasingly to treat extremely ill TEN patients. In addition to conventional PP, double–filtration PP (DFPP) has been recently used for severe and refractory TEN. Study describes the efficacy of plasmapheresis for the treatment of toxic epidermal necrolysis (TEN), as reported in Japan. TEN patients treated with plasmapheresis were collected from Japanese literature. The type of plasmapheresis, number of sessions, efficacy of plasmapheresis, and present outcome were examined., but the current data does not allow a conclusion as to the potential of this approach to be drawn due to the small number of patients treated, the frequent confounding factors including different or combined treatments, and other potential biases[50], [51], [52]. Furthermore, treatment is not established due to the unknown pathogenesis and lack of randomized clinical trials. It is mostly based on withdrawal of the culprit drug and symptom–related approach. The role of corticosteroids and plasmapheresis in the disease treatment remains controversial[53].

Stevens Johnson (SJS) and Toxic Epidermal Necrolysis (TEN) are two uncommon mucocutaneous diseases usually considered as severe drug reactions and are characterized by different grades of epidermal necrosis. Several treatment modalities have been proposed with variable results but the lack of controlled studies makes difficult to analyze them objectively especially in children[54]. While the clinical manifestations of SJS and TEN are well–defined, the optimal treatment for these disorders is not. Case reports have shown benefit with the use of a variety of agents including tumor necrosis factor–α inhibitors and cyclophosphamide, whereas thalidomide was associated with an increased mortality. Plasmapheresis and cyclosporine have also demonstrated efficacy anecdotally, albeit with an even smaller number of cases in the literature. Most of the reportings have focused on the use of systemic corticosteroids and IVIG for these severe reactions[55].

TEN traditionally has been treated with immunomodulators such as glucocorticoids, intravenous gammaglobulin, cyclophosphamide, thalidomide or plasmapheresis. A variable, and sometimes contradictory response, has been obtained in some series. Cyclosporin A has been tested as a single immunomodulator in patients with TEN[56]. Although a beneficial effect of CPP is suggested by the authors of these small trials, larger studies are needed to clarify these preliminary results with a special attention to potential side effects.

12. Treatment

The first line of treatment is early withdrawal of culprit drugs, early referral and management in burn units or
intensive care units, supportive management, and nutritional support. The second line is IVIG. However some trials showed promising effect of IVIG on treatment of TEN[57]; a randomized control trial is needed in the future to determine the efficacy of IVIG in TEN. The third line is cyclosporin, cyclophosphamide, plasmapheresis, pentoxifylline, N-acetylcysteine, ulinastatin, infliximab, and/or Granulocyte colony-stimulating factors (if TEN associated--leukopenia exists).

13. Prognosis

The mortality for TEN is 30–40 percent. Loss of the skin leaves patients are vulnerable to infections from fungi and bacteria, and can result in sepsis, the leading cause of death in the disease. Death is caused either by infection or by respiratory distress which is either due to pneumonia or damage to the linings of the airway. Microscopic analysis of tissue (especially the degree of dermal mononuclear inflammation and the degree of inflammation in general) can play a role in determining the prognosis of individual cases[58].

Cutaneous drug reactions are among the most commonly reported adverse drug reactions. Drugs prescribed by orthopedic surgeons, such as antibiotics, opiates, and nonsteroidal anti-inflammatory drugs, are common offenders. Cutaneous drug reactions can range from those that are common, mild nuisances to those that are rare, severe, and life-threatening. Medications should be considered part of a differential diagnosis for any dermatologic condition. It is important to recognize the different clinical features and common drugs that are related to each type of reaction[59]. A Swiss medical study recorded the day to day evolution of the epidermis in a TEN patient. Pictures showed the initial bullous stage as well as the skin healing[60]. SJS and TEN are severe and life-threatening. The average reported mortality rate of SJS is 1%–5%, and of TEN is 25%–35%; it can be even higher in elderly patients and those with a large surface area of epidermal detachment.

14. Conclusion

TEN is a disease about to provide a lot of scopes for the researchers to work in the field. For example, no animal model is present for TEN, so if any model could develop, various dimensions for the treatment could be done. More emphasis should be also laid on clinical trials of this disease so that more efficient treatments of the disease could be done. The presented review would be beneficial for the researchers working in the field of development of new drugs for the treatment of epidermal necrosis disorder and to look forward for more effective strategies so as to eradicate this difficulty completely.

Conflict of interest statement

We declare that we have no conflict of interest.

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Related reports

TEN induced by drug sever toxic dermatologic disorders. There are evidences showing that drug–specific T cells are involved in inducing keratinocyte apoptosis in acute stage. TEN affects many parts of the body, but it most severely affects the mucous membranes, such as the mouth, eyes, and vagina.

Innovations & breakthroughs

More emphasis laid on diagnosis, recent clinical trials, and drug therapy of this disease so that more efficient treatment of the disease could be done.

Applications

The article is a resource for scientists and researchers working on various aspects of TEN, its treatment, drug therapy, diagnosis, and diagnostic methods, genetic susceptibility, epidemiology, pathogenesis, cause and pathology sign and symptoms.

Peer review

The article is good and has focused on all related matters of the disease. Authors have sincerely reviewed and studied the topic with marvelous efforts and showed his qualitative capacity in composing this article. The paper is satisfactory as per standards of the journal. Scientific works has been honestly represented.


