Chapter

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Thi Huyen Tran

Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse drug reactions (SCARs). The most common causative drugs of SJS/TEN are allopurinol, carbamazepine, abacavir, phenytoin, and lamotrigine. SJS/TEN are categorized based on the percentage of epidermal detachment area: (i) SJS: less than 10%, (ii) TEN: greater than 30%, (iii) and overlapping SJS/TEN: 10–30%. The pathogenesis of SJS/TEN is not fully understood, but some immunological and genetic factors are believed to be involved. There is a strong association between some specific HLA haplotypes and drug-induced SJS/TEN, for example, HLA-B*15:02 and carbamazepine-, HLA-B*58:01 and allopurinol. CD8+ cytotoxic T cells and natural killer (NK) cells play an important role in the pathogenesis of SJS/TEN, and upon the activation, they produce cytokines, chemokines, and cytotoxic proteins, that cause extensive keratinocytes apoptosis. Systemic corticosteroid and cyclosporine are still used as the first line in the treatment of SJS/TEN, in combination with care support.

Keywords: Stevens-Johnson syndrome, toxic epidermal necrolysis, severe cutaneous adverse drug reactions, HLA-B*15:02, HLA-B*58:01, granulysin

1. Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) belong to severe cutaneous adverse drug reactions (SCARs). Although their incidence is rare, around 2–3 per million per year, their mortality rate can be up to 5–30%. These reactions are life-threatening due to internal organ failures, disseminated skin detachment, and necrolysis. The most common causative medicines inducing SJS/TEN are allopurinol, carbamazepine, sulfamethoxazole, and other antibiotics, even traditional medicine. The pathogenesis of SJS/TEN is not fully understood, but some immunological and genetic factors are believed to be involved. The treatment of SJS/TEN is still controversial in which several studies showed variable results, including systemic corticosteroid, cyclosporine, intravenous immunoglobulin (IVIG), etanercept, thalidomide, and plasmapheresis.

2. Concepts, terms, and classification

In the SCARs group, in addition to SJS/TEN, there are other forms of drug allergy such as drug reaction with eosinophilia and systemic symptoms (DRESS syndrome),

acute generalized exanthematous pustulosis (AGEP), drug-induced hypersensitivity syndrome (DIHS), maculopapular exanthema (MPE).

Previously, the classification between erythema multiforme (EM), SJS, and TEN was still inconsistent due to unclear pathogenesis. There are different opinions on the differential diagnosis of severe EM from SJS/TEN. Since 1983, SJS has been considered synonymous with severe EM, both with the involvement of more than one mucosa with skin involvement [1]. In 1993–1994, Bastuji-Garin and Roujeau proposed the distinction of the two diseases based on clinical and etiological factors. In severe EM, there are mucosal lesions, bullae, skin lesions less than 10% of body surface area [2]. But unlike SJS, the skin lesions in severe EM are typical and/or atypical target lesions that are prominent compared to normal skin, distributed mainly in the extremities. Stevens-Johnson syndrome is characterized by widespread blisters due to drug reactions, which appear on the background of erythema, necrosis, and pruritus, concentrated mainly on the face and trunk. Etiologically, EM is often associated with herpes simplex virus reactivation, rarely drug-induced, SJS/TEN mainly drug-induced, rarely infection [3, 4]. There are few reports of stomatitis caused by *Mycoplasma pneumonia*, mostly in young people, characterized by primary mucosal lesions, with little or no skin lesions. This form is called *Mycoplasma pneumonia*-related mucositis [5]. Today, EM is considered as a separate disease, separate from the SJS/TEN group, with specific clinical, epidemiological, and pathophysiological features. Due to the similarity in clinical and histopathological characteristics and epidermal detachment and necrosis, SJS and TEN are classified into a spectrum of diseases, abbreviated as SJS/TEN [1, 6, 7].

Based on the area of epidermal detachment (blister, erosion), Bastuji-Garin classified the spectrum of SJS/TEN into SJS, overlapping SJS/TEN and TEN. According to this classification, there are four subgroups as follows: (1) SJS with an epidermal detachment of less than 10% of the body area, red, pruritic, atypical target macules that are flat with normal skin; (2) overlap SJS/TEN with 10–30% epidermal detachment; (3) TEN with spots (spots) when the lesions are epidermal detachment over 30% of the body area, with red, widespread pruritus, atypical target macules; (4) TEN without spot with epidermal detachment lesions of more than 30% of the body area, no individual macules, no atypical target lesions [1, 2].

3. Etiology and pathogenesis of SJS/TEN

3.1 Etiology

Several microorganisms are considered to be the cause of SJS/TEN. For example, SJS/TEN can occur after vaccination with chickenpox, measles [8], *Mycoplasma pneumonia* [9], dengue virus [10], it is also associated with cytomegalovirus reactivation [11], currently, SJS may be related with Covid 19 [12] or Covid 19 vaccination [13, 14]. Other causes include serum injection, host graft rejection [15]. Chung's study showed that a novel variant of *Coxsackievirus A6* can induce severe mucosal bullous reactions, mainly mediated by granulysin-expressing T lymphocytes and NK cells. The clinical symptoms in that group of patients resembled severe EM or SJS [16]. A classic example of the role of viruses in drug response: in DIHS, human herpesvirus 6 (HHV6) plays an important role. HHV6 reactivation in DIHS patients may increase T-cell activity after the onset of drug response, induce the synthesis of

proinflammatory cytokines including TNF-α and IL-6 that are capable of regulating T cell-mediated responses [17].

The majority of cases of SJS/TEN were related to drug hypersensitivity. Some studies show that in people infected with HIV, the prevalence of the disease is about 1 in 1000, which is a thousand times higher than in the population without HIV [6]. In sub-Saharan Africa, where HIV prevalence is high, there is an association between SJS/TEN and HIV due to the use of antiretroviral and anti-tuberculosis drugs [18]. The drugs most commonly causing SJS/TEN are nevirapine, lamotrigine, carbamazepine, phenytoin, phenobarbital, cotrimoxazole, sulfonamides, sulfasalazine, allopurinol, and non-steroidal anti-inflammatory drugs (oxicam group) [6, 19]. Other less common drugs are aminopenicillin, cephalosporin, quinolone. In Asian countries, traditional medicine can also be a causative drug of SJS/TEN [20]. Currently, SJS/TEN is reported to be associated with pembrolizumab [21], and itraconazole [22]. Patch test, lymphocyte transformation test, and enzyme-linked immunospot can be used to detect culprit drugs in SJS/TEN but none of them is considered as standard [1, 23].

Sassolas et al. developed an algorithm for drug causality for epidermal necrolysis (ALDEN). This algorithm rates each drug with a score of −12 to 10 based on six criteria: (1) delay from initial drug component intake to the onset of reaction (index day); (2) drug present in the body on the index day; (3) pre-challenge/rechallenge; (4)dechallenge; (5) type of drug (notoriety); (6) other cause. Allergenic possibilities are given based on the following total score: ≥ 6: very probable; 4–5: probable; 2–3: possible; 0–1: unlikely; < 0: very unlikely [19].

Stevens-Johnson syndrome and TEN are equally common in men and women. The frequency of the disease increases with age, peaking in people over 50 years of age [24, 25]. In the population of people living with HIV/AIDS, the prevalence of SJS/TEN is higher than in the general population [6].

3.2 Pathogenesis

In SJS/TEN, keratinocytes are necrotic to varying degrees. The pathogenesis of SJS/TEN is related to the mechanism of death of keratinocytes [26–28]. These cells undergo apoptosis or necroptosis, causing the entire epidermal structure to necrosis, detachment, form blisters [26, 28].

3.2.1 Immune mechanisms in SJS/TEN

Toxic epidermal necrolysis is a T-cell-mediated disease, TCD8+ lymphocytes are found in bullous fluid [29–31], perivascular in the superficial dermis [6, 32]. TCD8+ lymphocytes together with NK cells are considered to be the main agents of apoptosis of keratinocytes [29–31]. TCD4+ lymphocytes and other immune cells such as dendritic cells and mast cells also play an important role in TEN [6]. Caproni's study of cell infiltration in the skin of TEN patients showed a high density of CD40 ligand (CD40L) staining cells in the dermis, some infiltrating the epidermis [32]. CD40L is a molecule expressed on the surface of activated CD4+ T cells, and is a co-stimulator of macrophages, dendritic cells, B lymphocytes, and endothelial cells, leading to the release of tumor necrotic factor-alpha (TNF-α), nitric oxide (NO), interleukin (IL)-8, and cell adhesion molecules. Soluble CD40L is elevated in the serum of TEN patients. The TCD4+ lineage in the epidermis and

dermis of TEN patients has a balance between T helper (Th) 1 and Th2 as well as cytokine levels from these two cell types [33].

Macrophages, neutrophils, and NK cells are also involved in the pathogenesis of TEN, and studies have shown that macrophages infiltrate in predominant numbers in skin samples [32, 33]. Tohyama noted the presence of CD14+ CD16+ monocytes in the epidermis and the dermal-epidermal junction in skin lesions of SJS/TEN patients. This reinforces the proliferation and cytotoxicity of TCD8+ lymphocytes through the CD137/CD137L system. Monocytes and macrophages contribute to apoptosis through the production of TNF-α, TNF-related apoptosis ligands [34]. Neutrophils and dendritic cell factor XIIIa+ were also found in these skin samples, but their role in TEN has not been elucidated [32, 33, 35]. NK cells are present in the bullous fluid along with highly cytotoxic T cells that express the NK cell CD56 receptor. Both of these cell types are considered to be major contributors to keratinocyte apoptosis [30]. The important role of TCD8+ lymphocytes in the pathogenesis of TEN has been recently demonstrated with the murine model of TEN, which tends to resemble that of humans [36].

T cells are hyperactive due to decreased T regulatory (Treg) cell function and upregulation by monocytes. CD8+ T cells themselves are not specific for TEN; they are also present in other drug-induced reactions. Treg's function in increasing TCD8+ activity is an important factor in TEN, which causes epidermal injury. The mechanism by which Treg cells degrades function is unknown, but the loss of TCD8+ inhibition has been documented. Treg cells from the peripheral blood of TEN patients do not inhibit T cells. Treg cell counts in TEN patients do not differ from that in normal subjects, but their function is impaired during the acute phase of TEN [37].

Th17 cells, which are subtypes of TCD4+ cells, are present in SJS/TEN at a higher rate than other ordinary drug skin reactions (ODSRs), producing IL-17 and IL-22. In SJS/TEN patients, there are more IL-17-producing CD4+ T cells than in EM patients and healthy subjects. As the disease improves, the Th17 cell count decreases. They can regulate the mobilization of neutrophils and other inflammatory leukocytes, causing inflammation and skin damage. Furthermore, neutropenia, a cause of death in TEN, may be due to the action of Th17 [37].

3.2.2 Role of human leukocyte antigen (HLA) class I in SJS/TEN and SCARs

Many studies show an association between HLA class I and SCARs. In Han Chinese patients with SJS/TEN, there is a strong association between antiepileptic aromatics such as carbamazepine, phenytoin, oxcarbazepine, and lamotrigine with HLA-B*15:02 [38], and between allopurinol and HLA-B* 58:01 [39, 40]. An association between HLA-B*15:02 and carbamazepine was also seen in Thai, Vietnamese, Malaysian, and South Indian SJS/TEN patients, but not in Japanese, Korean, or European populations [41]. In patients of European descent, there was an association between HLA-B*57:01 and abacavir-induced SJS/TEN [42], and between HLA-A*31:01 and carbamazepine-induced SJS/TEN [43]. A study in Japan showed that the HLA-B*15:11 allele is a risk factor for carbamazepine-induced SJS/TEN, with an association between HLA-A*02:06 and acetaminophen-induced SJS/TEN [44]. The significant association between SJS/TEN and certain HLA haplotypes has led to speculation that these haplotypes play a role in the pathogenesis of TEN [45]. This concept was proposed when investigating the role of HLA-B*57:01 in the pathogenesis of abacavir-induced DIHS [46]. From the above studies, it is recommended to screen for some HLA alleles before prescribing some drugs that cause allergies,

related to HLA. For example, HLA-B*58:01 allele carriers should not take allopurinol, and HLA-B*15:02 allele carriers should not take carbamazepine [41, 43].

3.2.3 Mechanism of death of keratinocytes in SJS/TEN

3.2.3.1 Mechanism of apoptosis of keratinocytes

In SJS/TEN, keratinocytes undergo massive, widespread necrosis. The main reason is due to the apoptosis mechanism. There are many cytotoxic proteins and molecules involved in apoptosis initiation in SJS/TEN, of which granulysin has been shown to play a major role. Other factors including FasL, TNF-α, perforin, granzyme B, and NO also play a certain role [6, 26, 47].

3.2.3.1.1 Granulysin

Granulysin is a molecule found in the granules of cytotoxic cells (along with granzyme B and perforin) such as TCD8+, NK, and natural killer T cells, that act as a tumor killer and kills bacteria. When there is an interaction between the drug and the specific HLA and T cell receptor of TCD8+, granulysin is released from the granules of TCD8+, causing apoptosis of keratinocytes. Granulysin can cut through the target cell membrane, causing ion imbalance, damage to mitochondria, releasing oxidants and caspase cascade, causing apoptosis [48].

To investigate the role of granulysin in TEN, Chung et al. compared the gene expression of bullous fluid cells. The results showed that the expression of the granulysin gene of bullous cells increased 10–20 times, granzyme B increased 8 times, perforin increased 3 times, serum FasL increased 2 times [26]. When measuring granulysin concentrations in bullous fluid following a similar pattern, granulysin levels were 2–4 times higher than perforin, granzyme B, and soluble FasL, which correlated with disease severity. On immunohistochemical staining, the skin tissues of patients with TEN were strongly stained with granulysin, while the skin tissues of patients with ODSRs were weakly stained [26]. Abe showed that serum granulysin levels were elevated in 4 out of 5 patients with SJS/TEN before epidermal detachment or mucosal lesion. Meanwhile, this concentration increased only in 1 in 24 patients with ODSRs [49].

The above studies demonstrate that granulysin is an important cause of apoptosis in TEN, it is also a marker for early diagnosis and prognosis of disease severity [24, 26].

3.2.3.1.2 Fas-FasL

Fas ligand (FasL) is a transmembrane protein of the TNF family, found on the surface of cytotoxic T cells, NK cells. When these cells are activated, FasL is expressed, binds to its receptor on the target cell, and activates the intracellular caspase, leading to uncontrolled destruction of the target cell. In addition, Fas can be separated from the cell membrane by metalloproteinase enzymes, producing soluble Fas from FasL, still maintaining the ability to bind to Fas receptors, causing apoptosis [6, 50].

The Fas receptor has a region of repeat cysteines and an intracellular region of 80 amino acids, identical to the region in TNF-R1, named the death domain. This region is required for Fas to induce apoptosis. Mutations in this region destroy apoptosis induction. The only known physical Fas ligand is FasL (CD95L), which belongs to the

family of TNF-related cytokines. Like its relatives, FasL is synthesized as transmembrane and trimer-soluble forms, by the enzyme metalloprotease. Fas signaling plays a decisive role in lymphocyte homeostasis. Repeated activation of antigen receptors on T cells induces FasL expression, leading to apoptosis via Fas signaling. When this process fails, due to mutations in Fas or FasL, lymphomas and autoimmune diseases occur [51]. FasL induces apoptosis by binding to the Fas receptor, causing activation of caspases [52]. Fas is expressed mainly on activated T lymphocytes and NK cells. Viard showed that FasL is also expressed in keratinocytes in TEN lesions [27]. Serum soluble FasL levels are elevated in patients with SJS/TEN before skin detachment, mucosal lesion, or both [53].

3.2.3.1.3 Granzyme B and perforin

Granzyme B and perforin have roles in the apoptosis of keratinocytes and endothelial cells [52]. Cytotoxic T cells, once activated, secrete perforin and granzyme B, create channels on target cell membranes, and activate apoptosis-inducing caspase [6]. In TEN, monocytes from bullous fluid induce apoptosis in the presence of anti-Fas antibodies, but not apoptosis in the presence of perforin/granzyme B inhibitors, indicating perforin/granzyme B is the causative agent of apoptosis [30, 31, 50]. The concentrations of these molecules correlate with the severity of the drug reactions. Therefore, testing for perforin and granzyme B may help differentiate TEN from other drug reactions [47]. Recent studies on skin biopsies of TEN patients showed that endothelial cells were apoptosis, and immunohistochemical staining showed granzyme B and TNF-α around the dermis vessels. Although not found on biopsies, the possibility that soluble FasL is the cause of apoptosis of endothelial cells cannot be excluded. The reason is that the biopsy samples were taken 2–4 days after the onset of the disease when the soluble FasL concentration was greatly reduced [54, 55].

3.2.3.1.4 Other factors

Other molecules, cytokines such as TNF-α and NO have certain roles in apoptosis. TNF-α acts on the "death receptor" TNF-R1, causing activation of caspases, causing cell death. TNF-α is elevated in the bullous fluid, skin, and serum of patients with TEN. Its role, though, is unclear. In addition to its ability to induce apoptosis, TNF-α also has a protective role by activating the anti-apoptosis pathway with nuclear factor-kappaB (NF-κB). This may explain why the mortality of TEN is increased with treatment with anti-TNF-α (thalidomide) [56]. NO induces apoptosis through its effect on the *p53* gene. Skin samples before blistering of patients with SJS/TEN had increased NO synthase (inducible NO synthase, iNOS) enzyme. IFN-α and TNF-α secreted from activated T cells can induce iNOS expression, which downregulates NO-dependent FasL, especially apoptosis in keratinocytes. Thus, IFN-α, TNF-α, and iNOS are potential molecular bridges between the immune response to drugs and the expression of proapoptotic molecules. The combination of IFN-α, NO, and an increase in reactive oxygen species causes oxidative stress, disrupts the intracellular machinery and cell membranes, leading to apoptosis [6].

3.2.3.2 Mechanism of necroptosis of keratinocytes

Cell death resembles necrosis but is regulated by a specific intracellular program known as necroptosis [57]. Experimental studies by Saito et al. showed that apoptosis is

not the only mechanism of keratinocyte death in SJS/TEN. When pan-caspase inhibitors were added to the supernatant cultures of peripheral blood monocytes (PBMCs) of patients with SJS/TEN, incubated with keratinocytes, cell death still occurs. Thus, the PBMCs cultures of patients with SJS/TEN contain a specific molecule that causes the death of keratinocytes, which is independent of the apoptosis mechanism. The authors found that the concentration of annexin A1 protein in PBMCs cultures was significantly higher in SJS/TEN patients than in ODSR patients. Anti-annexin A1 antibody inhibits the death of keratinocytes [28]. Annexin A1 is a member of the family of 13 annexin proteins, which bind to acidic phospholipids with high affinity in the presence of Ca^{2+} ions [58]. When annexin A1 binds to the formyl peptide receptor 1 (FPR1) receptor on the cells, it causes necroptosis. The level of FPR1 expression was significantly different between the SJS/TEN group and the ODSR group. Therefore, it can determine the probability of SJS/TEN or ODSRs. Although there is no gene difference in the FPR1 promoter region between SJS/TEN, ODSRs, and healthy subjects, the annexin A1-FPR1 interaction may predict the occurrence of SJS/TEN and hold promise for targeted therapy in which necrosulfonamide inhibits the necroptosis pathway related to the annexin A1-FPR1 complex [28, 52].

4. Clinical and paraclinical characteristics of SJS/TEN

4.1 Clinical characteristics

Stevens-Johnson syndrome and TEN develop acutely, with epidermal necrosis, mucositis at multiple sites, accompanied by systemic and other organ changes [1, 2]. In general, the first symptoms are fever, fatigue, discomfort in the upper respiratory tract, appearing a few days before skin and mucosal lesions [1, 6]. Often, it is difficult to diagnose ODSRs and predict the likelihood of progression to SJS/TEN at this stage. Many patients have EM-like lesions with atypical target lesions. However, according to Abe's study, serum granulysin levels were elevated during this time, based on which could predict the possibility of SJS/TEN [49], helping to treat early avoid complications, and reduce the risk of death.

The time from taking a suspected drug to the onset of symptoms varies widely, ranging from a few days to two months. Therefore, it is necessary to carefully review all drugs used by the patient within the previous two months, including over-the-counter drugs and dietary supplements [1].

Lesions of the ocular mucosa may precede skin lesions. Manifestations include eye discomfort, conjunctivitis, and scleritis. After a few days, the conjunctiva becomes ulcerated, oozing. Lesions on the ocular mucosa may occur concurrently with lesions of the oral mucosa and genital mucosa [1]. According to Revuz's research, 97% of SJS/TEN patients had mucosal lesions, of which, oral mucosal lesions were found in 93% of patients, ocular mucosa 78%, genital mucosa 63%, and other mucous membranes 66% [59].

Skin pain is an early symptom in SJS/TEN, the presence of which signals an epidermal necrolysis event [1]. There are many types of skin lesions with varying degrees of severity. The earliest lesions are atypical target lesions and/or itchy erythematous macules. The first sites where lesions appear are usually the upper half of the body, the head near the extremities, and the face. After that, the skin lesions spread to the rest of the body and distal extremities. Lesions on the palms and soles of the feet are quite prominent. In many patients, the first symptom is an intensely red, erythematous rash on the palms of the hands. In severe cases, the erythema may coalesce into

large macules. The skin becomes tender, vulnerable, and mild pressure can cause epidermal detachment (positive Nikolsky test). The maximum extent of skin lesions after onset is 5–7 days. Necrotic blisters appear when the necrotic epidermal detachment separates from the underlying skin [1, 59]. Extensive necrosis epidermal detachment leaves open dermis, serous exudates, susceptible to infection and bleeding (see **Figures 1**–**4**) [60].

Multiple organs are affected in SJS/TEN, with necrosis and erosion occurring in the conjunctiva, trachea, bronchi, kidneys, and intestines [52]. There have been reports of acute renal failure with increased microalbuminuria, renal tubular enzymes in the urine, demonstrating glomerular and proximal tubular damage. Lung and respiratory

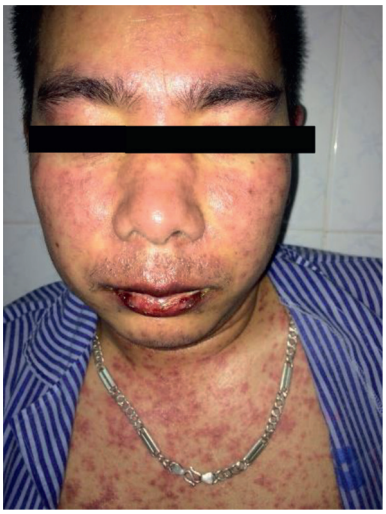

Figure 1.
A male patient with carbamazepine-induced SJS. He had erosions and dark crust on the lips, pruritic erythematous lesions on the face and the upper trunk. (photo: Tran Thi Huyen).

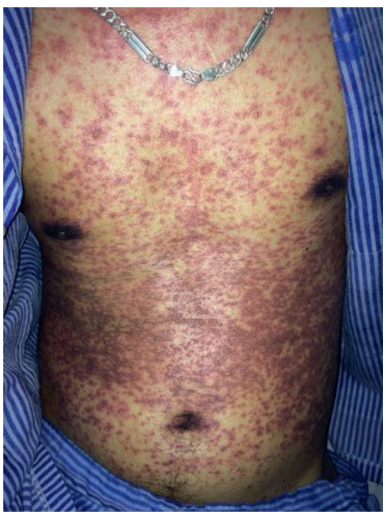

Figure 2.
A lot of blisters were formed on the dark erythematous rashes on the trunk of the patient with carbamazepine-induced SJS. (photo: Tran Thi Huyen).

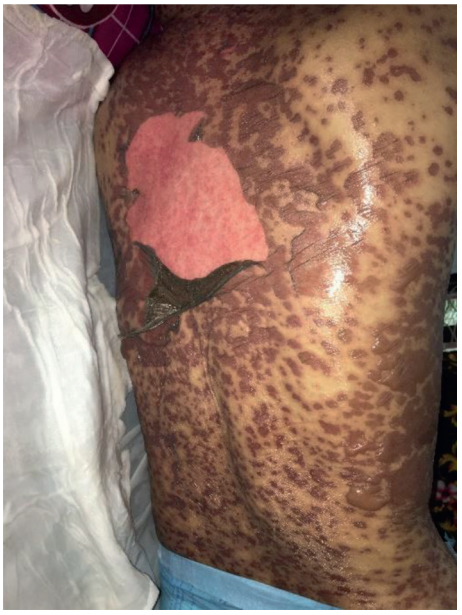

Figure 3.
Epidermal detachments, blisters, and necrotic rashes on the trunk of a patient with allopurinol-induced TEN (photo: Tran Thi Huyen).

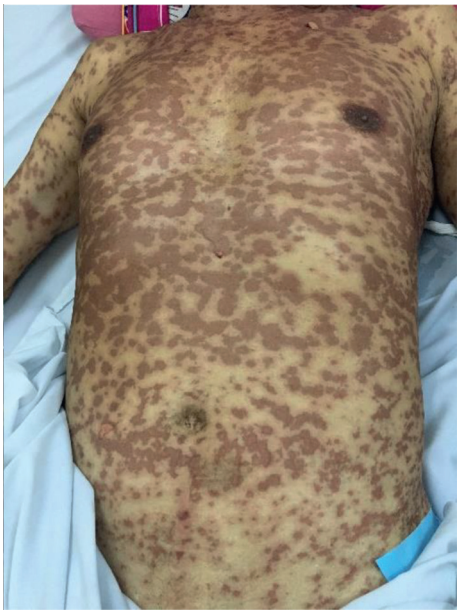

Figure 4.
The extensive epidermal necrosis in a patient with allopurinol-induced TEN (photo: Tran Thi Huyen).

lesions include tracheobronchitis, subcutaneous emphysema, dyspnea, and respiratory failure. Other systemic manifestations may include anemia, leukopenia, hepatitis, abdominal pain, diarrhea, transient elevation of liver enzymes, hypoalbuminemia, hyponatremia, and myocarditis [1].

4.2 Paraclinical characteristics

4.2.1 Histopathology

The diagnosis of SJS/TEN is mainly clinical. However, skin biopsy for histopathology is necessary to further confirm the diagnosis and rule out other bullous skin diseases [1]. On histopathology, there are different degrees of epidermal lesions, the keratinocytes are necrotic individually or in plaques, forming blisters. Appendical structures such as sweat ducts and hair follicles may be affected. The dermis has an inflammatory infiltrate (mainly perivascular) of lymphocytes, histocytes, and a few eosinophils [61]. In addition, there may be liquid degeneration of the basal layer, squamous separation, and spongiosis [62]. Depending on the stage of the disease, the histopathological picture can be different. In the early stages, a histopathological picture is a group of necrotic keratinocytes with some inflammatory cells (monocytes and neutrophils). In the late and severe stages, the keratinocytes are more necrotic, the basal epithelial cells degenerate, leading to the separation of the epidermis from the dermis, the entire layers of keratinocytes of the epidermis are necrotic, only intact horny layer. In some cases, the superficial layer of the epidermis is more necrotic than the deeper layers, forming slits between the two layers of the epidermis [29]. Monocytes and neutrophils can infiltrate areas of necrosis [29, 62].

In the early stages of SJS/TEN, necrotic keratinocytes are scattered in the lower epidermis, similar to those seen in severe EM: extensive necrotic keratinocytes with vacuoles at the dermal-epidermal junction [6, 61]. When SJS/TEN is evident, the entire epidermis is necrotic, forming subepidermal bullae. Meanwhile, in severe EM, the epidermis is less necrotic, the change occurs mainly in the basal layer. The Japanese diagnostic criteria suggested that in SJS/TEN at least 10 necrotic keratinocytes were seen at 200x magnification [63]. In the superficial dermis, perivascular inflammatory infiltration and exocytosis are usually absent. In SJS/TEN, inflammation in the dermis occurs less frequently than in severe EM [61]. The degree of inflammation correlates with the disease severity, the number of infiltrating mononuclear cells in the dermis has the same prognostic value as the SCORe for TEN (SCORTEN) index to assess the severity of TEN [35].

4.2.2 Microbiological tests

Serology for diagnosis of *Mycoplasma pneumonia* [64], herpes simplex virus, Epstein-Barr virus, cytomegalovirus, ... to rule out microbial causes of mouth ulcers and skin lesions [1, 6].

4.2.3 Biochemistry and hematology tests

In SJS/TEN, the blood count may be normal or there may be disorders such as leukocytosis, leukopenia, and anemia. Many patients have a transient elevation of liver enzymes, increased urea, creatinine, blood bicarbonate, blood glucose, C-reactive protein, procalcitonin.

4.3 Prognosis and complications

4.3.1 Prognostic factors

In severe cases of SJS/TEN, acute systemic disorders can lead to multi-organ failure and death. In 2000, Bastuji-Garin et al. published a valuable prognostic score for

Risk factors	0 point	1 point
1. Age	<40	≥ 0
2. Have a malignancy	No	Yes
3. Heart rate (beats/minute)	<120	≥120
4. Area of skin detachment	<10%	≥10%
5. Blood urea (mmol/l)	≤10	>10
6. Blood glucose (mmol/l)	≤14	>14
7. Blood bicarbonate (mmol/l)	≥20	<20

Risk of death by score: 0–1 point: 3.2%; 2 points 12.1%; 3 points 35.3%; 4 points 58.3%, 5–7 points: 90%.

Table 1.
SCORTEN score for Stevens-Johnson syndrome/toxic epidermal necrolysis and risk of in-hospital mortality based on the SCORTEN [1, 65].

SJS/TEN, called SCORTEN, which used seven clinical factors to predict in-hospital mortality. Each factor is worth one point, the higher the total score, the higher the risk of death [65]. Several studies have shown a gradual increase in SCORTEN scores during patient hospitalization, with a significant change observed on day 1 and day 4 (see **Table 1**) [66].

4.3.2 Complications

It is a disease with a high risk of death, but with time management and treatment, SJS/TEN can be cured. However, it is necessary to note visceral complications (liver, kidney) [52], eye complications, nail disorders [67], skin pigmentation changes after the disease as well as the psychological trauma of the patient. Among them, eye complications are noted the most, with different degrees [68]. Mild degree with eyelid edema, conjunctivitis; a moderate degree of membranous conjunctivitis, corneal epithelial loss, corneal ulceration, corneal infiltrates; in severe cases, there is the irreversible loss of corneal epithelium, loss of vision [1, 68, 69].

5. Differential diagnosis

Erythema multiforme.
Generalized fixed drug eruption.
Staphylococcal scalded skin syndrome.
Graft versus host disease.
Mycoplasma pneumonia-related mucositis.
Pemphigus Vulgaris.
Other bullous autoimmune diseases.

6. Treatment

6.1 General principles

Experts recommend that patients with more than 10% of their body area peeled off should be treated in an emergency care unit with doctors and nurses in a variety

of specialties. Some patients are treated and cared for as burn patients. Many studies have shown that prompt admission to burn centers improves survival, while delay increases mortality [70, 71]. In the ward, room temperature should be maintained to reduce the patient's energy consumption. Energy consumption is increased to 40% of basal metabolic rate when the area of skin loss is 10%, increasing to 120% when the area of skin loss is 80% [72]. The patient's drug history should be taken, and possible tests performed to identify and discontinue the allergen. Limit the use of drugs during the treatment of SJS/TEN.

6.2 Care support

Medical staff should use protective equipment when in contact with patients to avoid oral and respiratory infections. It is important to avoid holding or pulling the patient strongly and to limit injury to the epidermis (blood pressure measuring tape, electrocardiogram) [73]. Bacteria, viruses, and Candida fungi from three skin lesions should be cultured. Herpes infection should be excluded, especially in the case of severe mucous membrane lesions. Systemic antibiotics should be used if there is evidence of infection. In patients who have diarrhea or are unable to move, avoid getting dirty stools into skin lesions. Pay attention to using pain relievers if the pain is severe [1, 74].

Skin lesions should be washed with sterile warm water or physiological saline or with an antiseptic solution such as chlorhexidine (1/5000). A moisturizer with fatty properties such as vaseline, paraffin all over the skin, including the area that is growing granules should be applied. Scaly skin could be improved with topical antimicrobial drugs. Peeled epidermal fragments should be kept as a bio-bandage. The blisters should be aspirated and drained. Areas of skin that have lost the epidermis should be covered with non-stick gauze. Necrotic and infected epidermal fragments should be removed.

Eye mucosa is often damaged in SJS/TEN, if not detected, timely treatment can leave complications such as corneal ulceration, eye corner adhesions, pterygium adhesions, blindness [68]. Patients with SJS/TEN should be examined, treated, and monitored by an ophthalmologist from the acute stage of the disease until the disease has recovered. The mucous membrane of the vulva, vagina needs to be regular check-ups and cleaning with antiseptic solutions, moist gauze. Topical corticosteroids can reduce inflammation [75]. Oral mucosa needs to be cleaned with antiseptic solutions such as chlorhexidine. Lips and mouth should be covered with moist gauze, corticosteroid solution can be applied to rinse the mouth, oral hemorrhages need to be controlled [76].

Peripheral and central lines should be placed in preserved areas. The fluid balance will be monitored by a catheter. The amount of fluid to compensate could be calculated by referring to the formula of Shiga and Cartotto [77]:2 ml kg^{-1} body weight/% of epidermal area detachment, necrotic.

If the patient can drink, oral rehydration should be maintained. Patients with SJS/TEN need more nutrition than usual. If the mouth is severely damaged, eating is difficult, a nasogastric tube should be placed or parenteral nutrition. In the acute phase, the required calorie intake is 20–25 kcal kg^{-1} per day. During the recovery phase, the calorie requirement is 25–30 kcal kg^{-1} per day [1].

Patients with SJS/TEN have pain in the skin, especially at epidermal detachment sites. There are no studies on analgesic regimens in SJS/TEN. Therefore, analgesics according to the World Health Organization tiers can be used. Paracetamol or

synthetic opiate pain relievers (tramadol) should be used, but not non-steroidal anti-inflammatory analgesics because of the risk of kidney and stomach damage. Some care procedures such as bathing and changing clothes require the use of analgesics.

Other treatments including proton pump inhibitors, anticoagulants, and drugs to treat leukopenia, anemia (granulocyte colony-stimulating factor, G-CSF) should be used appropriately.

6.3 Specific medicines

6.3.1 Intravenous immunoglobulin

The basis for the use of IVIG in SJS/TEN are studies that show the role of Fas-FasL interaction in the mechanism of apoptosis of squamous cells [78]. FasL is a transmembrane protein of the TNF family that is expressed on the surface of cytotoxic T cells and natural killer cells. When cytotoxic T cells are activated, FasL is expressed, binds to its receptor on the target cell, activates the intracellular caspase, leading to uncontrolled destruction of the target cell. In addition, Fas can be separated from the cell membrane by metalloproteinase enzymes, producing soluble Fas from FasL, still maintaining the ability to bind to Fas receptors, causing apoptosis [6, 79]. High concentrations of normal immunoglobulin inhibit Fas-Fas ligand and apoptosis interactions through activation of anti-Fas antibodies.

In a systematic review and meta-analysis published by Huang in 2012 (all studies included at least 8 IVIG-treated SJS/TEN patients), cumulative estimates of risk mortality were determined, comparing IVIG and supportive care alone in patients with TEN and overlapping SJS/TEN. Statistical analysis was performed on the raw data to compare the clinical differences between high- and low-dose treatment in adult patients, and between pediatric and adult patients receiving IVIG. The mortality rate in the group of TEN and overlapping SJS/TEN patients treated with IVIG was 19.9%. Pediatric patients treated with IVIG had a lower mortality rate than adults (0% vs. 21.6%, $p = 0.01$). Adult patients treated with high dose IVIG had a lower mortality rate than those treated with low dose (18.9% vs. 50%, $p = 0.02$). However, the multivariable logistic regression model showed that IVIG dose was not correlated with mortality. But these results should be interpreted with caution due to limitations in the study design [79]. Following Huang's publication, a further study performed by Firoz et al. including 23 TEN patients treated with IVIG, demonstrated that IVIG did not improve survival compared with supportive care simply [80]. In 2013, Lee et al. published a retrospective analysis of 64 patients with overlapping SJS/TEN and TEN receiving IVIG. Based on the actual mortality compared with the SCORTEN estimated mortality, IVIG therapy showed no benefit. In addition, there was no difference between the high dose (>3 g/kg) and the low dose (<3 g/kg) [81].

6.3.2 Systemic corticosteroid therapy

Corticosteroids have been used to treat SJS/TEN for many years. Advocates emphasize the anti-inflammatory role of high doses of corticosteroids in the early stages of the disease. Opponents argue that systemic corticosteroids increase the risk of infection. Retrospective analysis of EuroSCAR data showed a lower mortality rate in the German group of patients receiving corticosteroids than in the supportive care group alone. To limit the side effects of long-term corticosteroid use, some authors use very high doses for a short time (pulse therapy) [82]. In the study by Kardaun and

Jonkman, 12 patients treated with intravenous dexamethasone 100 mg or 1.5 mg/kg for 3 days had a lower mortality rate compared with the estimated mortality according to the SCORTEN [83]. Hirahara et al. had 8 patients with SJS/TEN treated with intravenous methylprednisolone 1000 mg for three consecutive days, followed by dose reduction with oral prednisolone or 2 days of methylprednisolone at half the initial dose. No patient died although the SCORTEN estimated mortality was 1.6. Serum biomarkers IFN-γ, TNF-α, IL-6, and IL-10 were measured in 5/8 patients. On the fourth day post-treatment, the mean concentrations of these cytokines decreased compared with pre-treatment, but only significantly changed for interferon-gamma (IFN-γ) and IL-6. On day 19, there was a significant reduction in both IFN-γ, TNF-α, and IL-6, whereas IL-10 levels were higher than before treatment [84].

6.3.3 Cyclosporine

Cyclosporine is an immunosuppressive drug, indicated in many diseases such as rheumatoid arthritis, psoriasis, Crohn's disease, nephrotic syndrome, anti-rejection in organ transplantation. The mechanism of action of the drug is to reduce the function of lymphocytes by forming a complex with cyclophilin to inhibit the activation of calcium channel phosphatase, thereby reducing the production of cytokines by T lymphocytes.

Its inhibitory effect on lymphocytes defines cyclosporine as the theoretical standard drug of action in SJS/TEN [1]. A study by Valeyrie-Allanore showed that in 29 SJS/TEN patients treated with cyclosporine (1.5 mg/kg/day in 2 divided doses for the first 10 days, then reduced to 1 mg/kg/day days for the next 10 days, the last 10 days is 0.5 mg/kg/day) is effective. No patient died, although the SCORTEN estimated number of deaths was 2.75/29 [85]. Singh reported 11 patients with SJS/TEN who were treated with cyclosporine 3 mg/kg/day for 7 days, followed by dose reduction. This group was compared with 6 corticosteroid-treated SJS/TEN patients. In the cyclosporine group with a shorter hospital stay, the epithelialization rate was faster. Cyclosporine was more effective than corticosteroids when comparing SCORTEN estimated mortality. Kirchhof retrospectively studied 64 SJS/TEN patients treated with cyclosporine or IVIG (dose varied from patient to patient). Comparison of SCORTEN estimated mortality with actual mortality suggests a benefit of cyclosporine over IVIG [86]. Cyclosporine is well-tolerated, despite treatment in patients prone to hemodynamic instability and prerenal hypovolemia. It contributed to improved patient survival. Disease progression was slow and halting in the majority of patients [85, 87].

6.3.4 Other methods of treatment

Other therapies were used in SJS/TEN but in small sample sizes, no comparisons were made. Plasmapheresis is used in difficult-to-treat cases, and some reports have shown it to be effective [88, 89]. The immunoregulatory and regenerative role of G-CSF is used in the treatment of SJS/TEN (helps to stop hypersensitivity, stimulate epithelialization, control neutropenia) [90]. Biologics such as TNF-alpha antagonists have been conducted to improve the prognosis of SJS/TEN [23, 52]. Paradisi reported 10 patients with SJS/TEN treated with etanercept with a single dose of 50 mg subcutaneously. The study did not have a control group. All patients responded with a mean time of epithelialization of 8.5 days. Although the SCORTEN estimated mortality rate was 50%, no patient died [91].

6.3.5 Follow-up after patient discharge

Notes on suspected culprit drugs. Advise patients to avoid over-the-counter medications if the cause of SJS/TEN is unknown. If the patient has damage to the ocular mucosa, an ophthalmologist should be examined a few weeks after discharge from the hospital. Monitor for complications after discharge such as skin, oral, urogenital, respiratory, digestive, and psychological problems.

7. Conclusion

Stevens-Johnson syndrome and TEN have aggressive, acute, severe clinical manifestations, diagnosis is mainly based on clinical characteristics. Tests are mainly used to find probable etiology, assess severity, and differentiate from other bullous skin diseases. Treatment includes discontinuation of the suspected allergen/drug, supportive care, and/or a combination of specific drugs such as corticosteroids, cyclosporine, IVIG, and others.

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Conflict of interest

The author declares no conflict of interest.

Abbreviations

ALDEN	algorithm for drug causality for epidermal necrolysis
CD	cluster of differentiation
DIHS	drug-induced hypersensitivity syndrome
EM	erythema multiforme
FasL	Fas ligand
FPR1	formyl peptide receptor 1
G-CSF	granulocyte colony-stimulating factor
HHV 6	human herpesvirus 6
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IFN-γ	interferon-gamma
IL	interleukin
iNOS	inducible nitric oxide synthase
IVIG	intravenous immunoglobulin
MPE	maculopapular exanthema
NK	natural killer
NO	nitric oxide

ODSRs	ordinary drug skin reactions
OR	odd ratio
PBMCs	peripheral blood monocytes
SCARs	severe cutaneous adverse drug reactions
SCORTEN	SCORe for TEN
SJS	Stevens-Johnson syndrome
TEN	toxic epidermal necrolysis
Th	T helper
TNF-α	tumor necrosis factor-alpha
Treg	T regulatory

Author details

Thi Huyen Tran
National Hospital of Dermatology and Venereology, Hanoi Medical University, Hanoi, Vietnam

*Address all correspondence to: drhuyentran@gmail.com

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