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WHEN SKIN TURNS AGAINST THE BODY: A CLOSER LOOK AT SJS AND TEN

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ABSTRACT

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis are very rare, severe, life-threatening dermatological conditions characterized by severe skin and mucosal changes. The most common triggers are drugs, including β-lactam antibiotics, allopurinol, nonsteroidal anti-inflammatory drugs, nevirapine, and febuxostat. This article reviews the literature from 2000-2025 on the clinical manifestations that characterize SJS/TEN, pathogenesis, diagnosis necessary for proper treatment, prognostic scales such as SCORTEN, ABCD-10 and CRISTEN useful for predicting patient mortality, and treatment. Due to the rarity and high mortality rate of people with SJS/TEN, there is still a lack of high-quality studies on the pathogenesis of the disease and evaluating the efficacy of immunomodulatory drugs in inhibiting epidermal necrolysis and reducing mortality.

KEYWORDS

Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Severe Cutaneous Adverse Reactions (SCARs), Clinical Presentation, Diagnostic Criteria, Prognostic Scoring Systems (SCORTEN, ABCD-10, CRISTEN), Therapeutic Strategies

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Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), or Lyell's syndrome [1], are rare, life-threatening dermatological conditions characterized by severe involvement of the skin and mucous membranes [2]. Severe skin reactions are mainly caused by drugs, leading to prolonged hospital stays, as well as long-term physical and psychological sequelae [3].

The incidence ranges from 2 to 13 cases per million patients per year [4].

The incidence of drug-related SJS/TEN in people over 64., is twice as high compared to those aged 20-64 [5].

The key feature to distinguish whether one is dealing with SJS, TEN or SJS-TEN overlap is the degree of skin surface involvement. In SJS, < 10% of the body surface area (BSA) is covered, in SJS-TEN 10-30% of the BSA, and in TEN > 30% of the BSA. The degree of skin involvement is a prognostic factor. In SJS syndrome, lesions are usually limited, while in TEN they are extensive. In SJS, general symptoms may not be present [6].

The mortality rate for SJS ranges from 1 to 5%, while the mortality rate in TEN is significantly higher and reaches 20-30% [7]. In elderly and immunocompromised patients, it can exceed 50% [5]. Early admission to referral centers and initiation of treatment is associated with better outcomes [8].

Clinical Presentation

The disease usually begins with flu-like symptoms - fever, sore throat, conjunctivitis. An important diagnostic feature is a positive Nikolsky's sign, consisting of a slight mechanical pressure, causing epidermal detachment [6, 10]. However, this sign is not pathognomonic for SJS/TEN, as it can also be positive in autoimmune blistering skin diseases [6].

There are two phases of the disease: the acute phase and the chronic phase [9].

The acute phase is sudden and can be life-threatening, the prognosis depends on respiratory and septic complications, and the basis of treatment is supportive care in a specialized center.

In the chronic phase, there are many disease complications that translate into patients' quality of life. Complications usually involve the skin (dryness, abnormal pigmentation, cutaneous pain), eyes (dry eye, chronic conjunctivitis, symblepharons, corneal abnormalities, with potential visual impairment leading

sometimes to blindness), mouth (dryness and dental alterations), and genital organs (preputial and vaginal adhesions) [9].

In the study conducted by Yamane Y et al. patients also had complications such as hepatitis, renal dysfunction, gastrointestinal disorders (diarrhea, intestinal bleeding, severe appetite loss, intestinal perforation), tracheal/laryngeal edema, respiratory failure, and pneumonia [11].

Wibowo E et al. described the case of a 10-year-old boy who developed symblepharon mentioned earlier as an ocular complication of Stevens-Johnson syndrome. Symblepharon is the cicatricial adhesion between the eyelid and eyeball conjunctiva [12, 13]. The patient complained of narrowing the eyes, decreased vision in the left eye, and he was unable to produce tears. There was a history of SJS, manifested by a severe skin rash all over the body and ocular complications. After attempting treatment with antibiotic drops, the condition worsened. Treatment in the form of a symblepharectomy was applied, which resulted in an improvement in vision, but less than a year later the symptoms recurred. Early detection of complications can prevent worsening of symptoms [13].

Pathogenesis

The pathogenesis of these dermatological conditions is not fully understood.

SJS/TEN is believed to be a severe type IV (delayed, cytotoxic) hypersensitivity reaction dependent on HLA and T lymphocytes [14, 15]. Drug metabolites bind with HLA protein in the body, leading to cell toxicity by killing autologous cells. The mechanism of the disease is described as the complex interaction among multiple gene variants and environmental factors. Biochemical and immunological reactions with drug metabolites are also possible [15].

Elevated concentrations of granulysin, a cytolytic protein, tumor necrosis factor (TNF-α), and inflammatory cytokines such as IL-6, IL-8, IL-15 can be detected in the plasma and blister fluids of people with epidermal necrolysis [16, 17].

Evidence suggests a key contribution of the cytotoxic molecules granulysin and FasL as the molecules responsible for diffuse apoptosis of keratinocytes [6].

Chung WK et al. showed that SJS/TEN blister cells were mainly composed of CD8+ CTLs (cytotoxic lymphocytes) and CD56+ NK and NKT cells (natural killer), and these effector cells exhibited cytotoxicity against target cells. Their main achievement was the demonstration of high levels of granulysin in the blister fluid, which may suggest that this is the key molecule responsible for the disseminated keratinocyte apoptosis in SJS/TEN [18,19].

Other sources report that the Fas-Fas ligand (FasL) pathway is a key initiator of apoptotic cell death of epidermal cells. Fas is present in various cell types, including keratinocytes, and FasL is primarily present in activated T-cells and NK cells [19]. Abe R et al. showed that peripheral blood mononuclear cells (PBMC) of patients secrete soluble FasL (sFasL), which mediate keratinocyte apoptosis, and detected high levels of serum sFasL, especially in the early stages, suggesting the possibility of using this as a marker for early diagnosis of TEN and SJS [20].

A study by Sooranahalli Ch et al. investigated the potential roles of IL-1B, IL-6 and RIPK3 in the pathogenesis of Stevens-Johnson syndrome/toxic epidermal necrolysis. IL-1B, IL-6 and RIPK3 are biomarkers that play key roles in various inflammatory diseases. In this study, skin biopsy slides of SJS/TEN, lichen planus patients and healthy people without dermatological conditions were compared. It was shown that the expression levels of IL-1B, IL-6 and RIPK3 were significantly elevated in the skin of SJS/TEN patients compared to those with lichen planus (LP) and normal controls. One limitation of the study was the small sample size [7].

Etiology

SJS/TEN are most often caused by drugs. Most medication-associated cases occur within the first four weeks after starting the treatment [19]. In a retrospective study of 377 adult patients, medications were the cause of the disease in nearly 90% of the study participants, most commonly trimethoprim/sulfamethoxazole, β-lactam antibiotics, phenytoin, lamotrigine, allopurinol and nonsteroidal anti-inflammatory drugs. Mycoplasma pneumoniae, and herpes simplex virus, as well as idiopathic factors, have also contributed to the disease among the few studied [4]. In addition, other drugs, such as carbamazepine, nevirapine, febuxostat, itraconazole, fentanyl, as well as cytomegalovirus and COVID-19 infection, can also cause the disease [13, 21, 22, 23].

Stevens Johnson syndrome was diagnosed in an HIV-infected man who was on antiretroviral therapy consisting of three drugs - nevirapine (a non-nucleoside reverse transcriptase inhibitor - NNRTI), tenofovir and lamivudine. Disease symptoms in the form of a generalized erythematous maculopapular rash

accompanied by pruritus appeared after just 48 hours of nevirapine initiation. The lesions progressed rapidly, and the mucous membranes of the oral cavity and ocular conjunctiva were also involved. The first step in treating the patient was to discontinue the drug that could cause Stevens Johnson syndrome, in this case nevirapine [24].

Cases of SJS syndrome have also been described in HIV-1-positive pregnant women treated with antiretroviral drugs containing nevirapine in their regimen, and in infants whose hypersensitivity reactions resolved after replacing nevirapine with lamivudine [25, 26].

Another case described was a woman with a diagnosis of gout, treated with paracetamol, prednisolone, cetirizine, omeprazole, and febuxostat (a non-purine selective xanthine oxidase inhibitor) the day before admission to the hospital, and nonsteroidal anti-inflammatory drugs before febuxostat. The patient's rash involved the whole body, face, and lesions appeared around the mouth and eyes. Medications that could have contributed to the appearance of SJS, including febuxostat, were also discontinued first [27].

Tana T et al. described another case of SJS also caused by febuxostat. A 30-year-old man with recurrent gout attacks had been taking allopurinol, well tolerated by him for several years. When buproprion was added to his treatment regimen, within 5 days, he developed generalized exfoliative dermatitis requiring hospitalization. It was determined that his presentation of SJS was caused by the allopurinol through a drug-drug interaction with buproprion or was induced by buproprion alone, so he was prescribed febuxostat. However, he developed a raised pruritic erythematous maculopapular rash on his trunk within 24 hours of administration, which resolved after several days of discontinuing the drug. When the man was given febuxostat again 4 years later, he once again developed the same raised pruritic erythematous maculopapular eruption, also resolving after discontinuing the drug [28].

Kumar P et al. described the case of a 55-year-old woman taking aspirin, statins, ramipril, metoprolol, thyroxine and torasemide on a regular basis for hypertension, ischemic heart disease and hypothyroidism. A week before reporting to the hospital, her cardiologist prescribed metolazone (a thiazide diuretic used to treat congestive heart failure and chronic kidney disease) for refractory pedal oedema. After several days on the drug, the patient's skin developed irregular erythematous maculo-papular rashes with blister formation and skin excoriation with ulcerations, covering 10-30% of body surface area, accompanied by pain and low-grade fever. Nikolsky's sign was positive. Immediately discontinued the administration of metolazone, which most likely caused the onset of SJS/TEN, intravenous fluids, empirical antibiotics were administered, unfortunately, the patient died of complications, which were sepsis and septic shock [22].

Diagnosis

The first healthcare professional to come into contact with the patient may be a primary care physician, but the patient's condition can deteriorate rapidly and intervention by emergency physicians, intensive care physicians and dermatologists may be needed. The key is to diagnose as early as possible and implement treatment measures quickly enough. It is very important to transport the patient to a center that specializes in treating severe skin reactions to drugs and has an intensive care unit (ICU) [9].

Diagnosis of SJS/TEN is based mainly on clinical symptoms, as described above. The examination should also include an interview with the patient and his family regarding his medical history, including comorbidities, active cancer, drug allergies, and baseline vital signs (temperature, blood pressure, heart rate, respiratory rate, oxygen saturation), non-invasive investigations for pharyngeal, laryngeal, tracheal and bronchial involvement. Skin biopsies are taken, which usually show full-thickness epidermal necrosis with negative direct immunofluorescence results. This confirms the diagnosis and rules out autoimmune bullous dermatosis [9, 29].

Emergency laboratory tests should include: complete blood count, serum electrolytes, bicarbonate, urea, creatinine including its clearance, liver function tests, blood glucose, C-reactive protein (CRP), calcium and phosphorus concentrations, creatine phosphokinase (CPK), lactate dehydrogenase (LDH), albumin concentrations, prothrombin time (PT), blood arterial lactate and arterial blood gases [9, 29].

Tests for human immunodeficiency virus (HIV), hepatitis B, hepatitis C, beta-human chorionic gonadotropin (hCG) levels in women of childbearing age, and specific HLA screening if the epidermal necrosis was caused by a drug with known genetic susceptibility are also performed to assess the general condition [9].

Differential diagnoses that mimic SJS/TEN include diseases such as generalized bullous

fixed-drug eruptions, drug-induced linear IgA bullous dermatosis, staphylococcal scalded skin syndrome, erythema multiforme major, autoimmune bullous diseases such as bullous pemphigoid. A detailed patient history and clinical examination, along with histopathologic specimen collection, are necessary for differential diagnosis [19, 29].

Prognostic Scales

Research on SJS/TEN is mainly based on 2 goals. The first goal is to reduce patient mortality by accelerating skin and mucosal healing, while the second goal is to limit the sequelae of the disease [30]. The severity and risk of patient death can be estimated using several useful scales.

The SCORTEN scale is a useful prognostic scale for predicting in-hospital mortality in SJS/TEN patients. It should be assessed within the first 24 h of hospital admission and re-evaluated on day 3 of hospitalization [31].

Risk factors included in this scale are:

- age above 40 years,
- malignancy,
- heart rate above 120 per min
- BSA involved above 10%,
- serum urea level above 10 mmol per liter
- serum glucose level above 14 mmol per liter
- serum bicarbonate level below 20 mmol per liter [19, 32].

Another scale that predicts the risk of death is the ABCD-10 scale, which takes into account:

- age greater than or equal to 50 years
- epidermal detachment greater than 10% of BSA,
- serum bicarbonate level below 20 mmol per liter,
- active or ongoing cancer,
- the need for dialysis [19, 33].

The CRISTEN scale is the latest scale for predicting the severity and mortality of SJS/TEN, using ten clinical parameters and not requiring laboratory results:

- age above 65 years,
- epidermal dehiscence above 10% of BSA,
- active cancer,
- diabetes mellitus on treatment with medication,
- chronic kidney disease,
- bacterial infection (including pneumonia, sepsis, urinary tract infection),
- cardiac disease (including hypertension under treatment),
- antibiotics in the list of culprit drugs,
- mucosal damage involving ocular, buccal, and genital mucosa,
- recent systemic corticosteroid therapy before the onset of SJS/TEN [14].

Treatment

The key to treating SJS/TEN is prompt diagnosis and discontinuation of the drug that is responsible for causing the disease, as well as intensive supportive care from specialists in many fields, including an intensive care specialist, an ophthalmologist, a dermatologist and a psychiatrist [29]. If one is not sure which drug is the culprit of the disease, or if several drugs taken by the patient are suspicious, all medications should be discontinued [5]. The earlier the exposure to the drug causing the disease is stopped, the better the patient's prognosis will be, while the prognosis is worse for medications with a long half-life [19].

Supportive treatment includes fluid therapy with Ringer's lactate or saline solutions [19]. For intravenous irrigation, a peripheral catheter placed on a nonlesional skin area and replaced regularly is preferred, but a central catheter may be necessary in patients with extensive skin lesions. The amount of fluid therapy transfused in the first 24 hours can be calculated using the modified Brooke formula (1.5 ml x % of detached skin surface x kg body weight/day), and then the fluid volume should be adapted to the urine output volume and the biological markers. Patients have a high risk of respiratory complications, so monitoring of respiratory parameters is essential. Feeding is often by the enteral route or, in the case of esophageal damage, by the parenteral route. Blood glucose level is monitored and if levels ≥ 10 mmol/L insulin therapy is initiated [29].

It is also important to prevent nosocomial infections through the use of antiseptic rules and hygiene precautions, especially regarding hand hygiene. Repeated microbiological tests are useful to monitor the risk of infections. Prophylactic antibiotics are not recommended unless there are indications for their use, such as suspected sepsis [29].

In the treatment of skin lesions, sterile non-adherent dressings or petroleum jelly are used, while mechanical removal of the epidermis is contraindicated. Morphine is often administered for skin pain relief [29].

Pharmacological therapy includes the use of systemic steroids, plasmapheresis, cyclosporine, anti-TNF-α therapies and intravenous immunoglobulin (IVIG), however all guidelines acknowledge the lack of sufficient scientific evidence to support the preference for one systemic treatment over another, or the use of such treatments over supportive skin care alone [19, 34].

Corticosteroids effectively suppress an excessive immune response. Their use is controversial, but some studies suggest that they can reduce mortality, but they also point to the risk of secondary infections [11, 35, 36].

Cyclosporine is an inhibitor of calcineurin activity that suppresses the antigen-specific T-cell activation. The drug shows promising survival results, but a recent retrospective study did not show that cyclosporine improved the progression of skin detachment, duration of progression or mortality compared with supportive care only. [37, 38].

A retrospective study by Thakur V. et al. observed slightly better efficacy of cyclosporine (patients were given 3-5 mg/kg/day) compared to corticosteroids (patients were given prednisolone at 0.5 mg/kg/day). Patients receiving prednisolone had a higher mortality rate and complication rate. Both drugs should be started early in the course of the disease to stop the progression of epidermal necrosis [21].

A meta-analysis by Ng QX also observed an improvement in mortality in patients receiving cyclosporine therapy compared to supportive care. However, the drug is contraindicated in patients with severe kidney disease, severe infections and internal malignancy. Cyclosporine may be a potential treatment option for SJS/TEN, but a rigorous double-blind, randomized trial is needed [39].

TNF-α inhibitors, such as etanercept, block tumor necrosis factor alpha (TNF-α). TNF-α expression is high in plasma and blister fluids in SJS/TEN patients. Secretion of TNF-alpha and granulysin (the key mediator for keratinocyte detachment of epidermidis in SJS/TEN) in plasma and blister fluids of SJS/TEN patients clearly decreased after treatment with etanercept or corticosteroids. In a randomized controlled trial by Wang CW et al., etanercept showed potential immunosuppressive and immunomodulatory effects in patients with severe cutaneous adverse reactions like SJS/TEN. Compared to systemic corticosteroids, etanercept showed a shorter skin-healing time for patients with moderate to severe skin reactions, with a lower incidence of gastrointestinal side effects [40].

Intravenous immunoglobulin most likely acts by blocking the Fas receptor, responsible for keratinocyte apoptosis, which may inhibit the progression of epidermal necrolysis [41]. Studies using IVIG have yielded conflicting results. A meta-analysis by Tsai TY et al. showed that the use of IVIG in combination with corticosteroids may reduce the risk of mortality compared to the control group. [42] A multicenter retrospective analysis by Prins C et al. showed inhibition of epidermal necrolysis and improved survival [43]. However, other studies suggest limited benefit to IVIG, and it may even be detrimental in those with renal impairment, suggesting strong nephrotoxic effects [14, 41, 44].

Plasmapheresis or therapeutic plasma exchange (TPE), can be used to clear drug metabolites and cytotoxic mediators in cases refractory to standard treatment [23, 45]. Varol F et al. described two cases of toxic epidermal necrolysis in children associated with COVID-19. In the first child, TPE was performed on the fifth day of disease, 48 hours after the IVIG and steroid therapies, due to a worsening condition. Pulse steroids and IVIG treatment were also given after each of three TPE sessions. In the second child, as a result of worsening lesions, TPE was performed on the seventh day of disease, 96 hours after the IVIG and methylprednisolone treatments. Also, three sessions of TPE treatment were performed, and after each session pulse steroid and IVIG treatment were given. In both cases, successful outcomes and improvement in health status were obtained, suggesting that plasmapheresis may be effective when other methods fail [23]. A study by Miyamoto Y evaluated plasmapheresis treatment compared with IVIG treatment in patients after ineffective corticosteroid therapy. There were no significant differences in mortality rates between the two groups, but patients treated with TPE first had longer hospitalization stays and higher treatment costs [45].

The lack of an evidence-based hierarchy in pharmacological treatment, combined with the acute progression of the disease, underscores the necessity for collaboration between physicians of different specialties. This collaboration is key to providing comprehensive, consistent, quality and safe health care [34].

Mental Health

In patients with SJS/TEN, the disease can have a persisting impact on life, both physically and psychologically. Such individuals often suffer from anxiety, depression or post-traumatic stress disorder (PTSD). The first years of recovery are particularly hard. Such symptoms may also affect those close to the patient, so psychological support should already be offered during hospitalization, as well as contact with a psychologist after the patient is discharged home [5].

In a survey study by Coromilas AJ et al. of 54 patients, as many as 88.2% and 94.1% of participants indicated that their diagnosis of SJS/TEN affected their physical and mental health respectively, with more than 70% follow regularly with a primary care physician. The majority of respondents do not feel that their doctors adequately address the long-term health impacts of SJS/TEN, which is cause for concern. More than half of the patients were unsure what medications to avoid in the future and more than 70% of participants had other unanswered questions about their SJS/TEN. The survey results highlight significant long-term care needs and insufficient education and support services for patients with SJS/TEN [46].

In addition to psychological support, psychotropic medications prescribed by a psychiatrist may be needed. Alternative methods such as hypnosis, sophrology or relaxation may also be considered for some patients [29].

Conclusions

Stevens-Johnson syndrome and toxic epidermal necrolysis are very rare, severe, life-threatening dermatological conditions characterized by severe skin and mucosal changes. They are most often drug-induced, with mortality rates of up to 50% in the elderly. The exact mechanisms involved in the pathogenesis of these diseases are still not fully understood. Diagnosis is based on a thorough interview and clinical examination, as well as a skin biopsy to exclude other dermatological diseases. Treatment is divided into supportive treatment and pharmacological treatment, and the key step is to stop the drug causing epidermal necrolysis as soon as possible and the cooperation of specialists in many fields. Pharmacological treatment includes systemic steroids, plasmapheresis, cyclosporine, anti-TNF-α and intravenous immunoglobulin, but there is insufficient scientific evidence to identify the "gold standard" in treatment. Most patients struggle with psychological distress after recovery, so it is essential to provide them with adequate psychological support, as well as education about the disease that is SJS/TEN. More randomized controlled trials are needed to improve treatment outcomes, but this is hampered by the rarity and life-threatening nature of SJS/TEN.

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