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Toxic Epidermal Necrolysis: Case Report and Review

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Abstract

BACKGROUND: Stevens–Johnson syndrome and toxic epidermal necrolysis (TEN) are severe mucocutaneous adverse drug reactions primarily caused by drugs. Characterized by fever, prodromal symptoms, and extensive epidermal sloughing with mucous membrane involvement (>90%), they are collectively termed epidermal necrolysis and are considered a disease continuum.

CASE PRESENTATION: A 65-year-old man presented with widespread erythema and distinctive target-like lesions, accompanied by ruptured flaccid vesicles on the extremities. Following a 4-week carbamazepine treatment for a previous cerebrovascular insult, hematological analysis revealed abnormalities. A multidisciplinary team, including a neurologist, endocrinologist, and ophthalmologist, prescribed a 3-day course of intravenous immunoglobulin at 0.5 g/kg and an initial dose of 300 mg prednisolone for 3 days, supported by additional therapy. Discharged after 3 weeks, the rash completely resolved within 2 months.

CONCLUSION: TEN, a severe mucocutaneous condition with a 30% mortality rate, often results from drug exposure. Swift identification of the causative drug is crucial for optimal outcomes. Treatment primarily includes discontinuing the offending drug and offering supportive care for mucocutaneous lesions. A multidisciplinary approach is vital based on organ system involvement. The effectiveness of pharmacological treatments, such as intravenous immunoglobulin and corticosteroids, is continually under evaluation.

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe mucocutaneous reactions, often triggered by medications. Symptoms include fever, prodromal signs, extensive mucous membrane involvement (>90%), and significant skin detachment. These conditions form a disease continuum known as epidermal necrolysis [1]. Classification is based on the extent of total body surface area (BSA) affected by skin detachment: SJS (<10% BSA), TEN (>30% BSA), and SJS/TEN overlap (10–30% BSA). This classification system helps in understanding and categorizing the severity of these potentially life-threatening reactions [2]. Incidence is rare (5–6 cases per million per year), with increased risk in older age, particularly after the fourth decade, and a higher occurrence in females (sex ratio of 0.6) [3]. Some reports suggest a higher incidence of epidermal necrolysis [4]. Mortality rates range from 12% to 49%, with a specific rate of 16% in the pediatric population [5].

TEN is predominantly triggered by medications, although there are reports linking infections or vaccines to SJS and TEN. High-risk medications include allopurinol, lamotrigine, sulfamethoxazole, carbamazepine, phenytoin, nevirapine, sulfasalazine, other sulfonamides, oxicam nonsteroidal anti-inflammatory drugs (NSAIDs) (such as piroxicam and tenoxicam), and phenobarbital [6], [7]. Symptoms typically arise within the first 4 weeks of treatment, with a clinical presentation involving a morbilliform rash or atypical targetoid macules. Almost all TEN patients develop flaccid bullae and skin erosions and endure painful inflammation and oral ulceration lasting 1–2 weeks. TEN is associated with erosion, necrosis, and severe dysfunction in the ocular, pulmonary, cardiovascular, gastrointestinal, renal systems, and hematopoietic abnormalities [8]. Prodromal symptoms, such as malaise, fever, myalgia, sore throat, and conjunctivitis, are characteristic. Diagnosis relies on clinical signs, history, and recent drug exposure, with confirmation usually through laboratory and imaging findings. The algorithm of drug causality for epidermal necrolysis (ALDEN) is specifically designed to assess

drug causality in such cases [9], [10]. Essential treatment involves promptly discontinuing the causative drug. Crucial supportive care encompasses wound care, fluid management, nutrition, pain relief, infection prevention, ocular treatment, and organ support, emphasizing the importance of multidisciplinary care. Systemic immunosuppressive agents such as cyclosporine, corticosteroids, intravenous immunoglobulin (IVIG) combined with corticosteroids, etanercept, and anti-TNF agents are utilized in treatment [11].

Case Report

A 65-year-old man was admitted to the University Clinic of Dermatology, Ss Cyril and Methodius University in Skopje, Republic of North Macedonia. He presented with widespread erythema, atypical target lesions with dusky red centers on both upper and lower extremities, and flaccid blisters on the upper extremities, axillae, and thighs – some of which had ruptured, leading to painful exposed skin. Pityriasiform scaling was observed on the face, neck, and scalp. Skin tenderness, hyperemic conjunctivae, and a positive Nikolsky sign were evident. The affected BSA exceeded 90%. The patient provided informed consent for photograph documentation (Figure 1).

Five days before the current assessment, the patient manifested an exanthematous rash that originated on the face and upper extremities, subsequently extending to other regions of the body. The patient received treatment for a rash with corticosteroids and antihistamines. Three months back, the patient had a stroke and was treated with carbamazepine for 4 weeks. His medical background involves diabetes mellitus, hyperlipidemia, and hypertension, for which he is currently on a regimen of metformin, anticoagulants, anti-lipemic medications, and antihypertensive therapies. In response to a reaction, carbamazepine was promptly discontinued.

The blood analysis revealed hematologic abnormalities, including leukocytosis, elevated C-reactive protein, reduced protein levels, and elevated glucose levels. The coagulation profile showed increased D-dimer levels, suggesting pronounced secondary fibrinolysis. Detailed results can be found in Table 1.

Various diagnostic examinations were conducted, encompassing a microbiological analysis of wound swabs that identified *Klebsiella pneumoniae* v. aerogenes with extended-spectrum beta-lactamase (ESBL) positivity. In addition, hemoculture confirmed the isolation of *Klebsiella pneumoniae* v. aerogenes (ESBL positive). To evaluate bacterial sepsis, an immunofluorescence test was conducted utilizing the Cobas 411 analyzer. This assessment employed the Eclia method, harnessing ElectroChemiLuminescence technology for precise immunoassay analysis. Procalcitonin levels were measured on two occasions, yielding the results shown in Table 2.

These findings provide valuable insights into the microbial composition and the patient's immune response. Notably, the procalcitonin levels, initially elevated, demonstrated a subsequent decrease.

A collaborative effort from a multidisciplinary team, including a neurologist, endocrinologist, and ophthalmologist, contributed to the patient's care. The treatment regimen involved the administration of IVIG at a dosage of 0.5 g/kg over a 3-day period. In addition, the patient was prescribed an initial dose of 300 mg of prednisolone for 3 days, with a gradual tapering over one month. To address potential complications, a combination of anticoagulant therapy and antibiotics was administered. Topical measures encompassed the application of low-potency steroid emulsions and antiseptics on the oral mucosa, along with the use of antibiotic solutions for ocular care. Following a 3-week hospitalization, the patient was discharged. Subsequent follow-up confirmed the complete resolution of the rash after two months (Figure 2), underscoring a favorable response to the comprehensive treatment strategy.

Discussion

The pathogenesis of SJS and TEN is often linked to cytotoxic T-cell-mediated drug hypersensitivity,

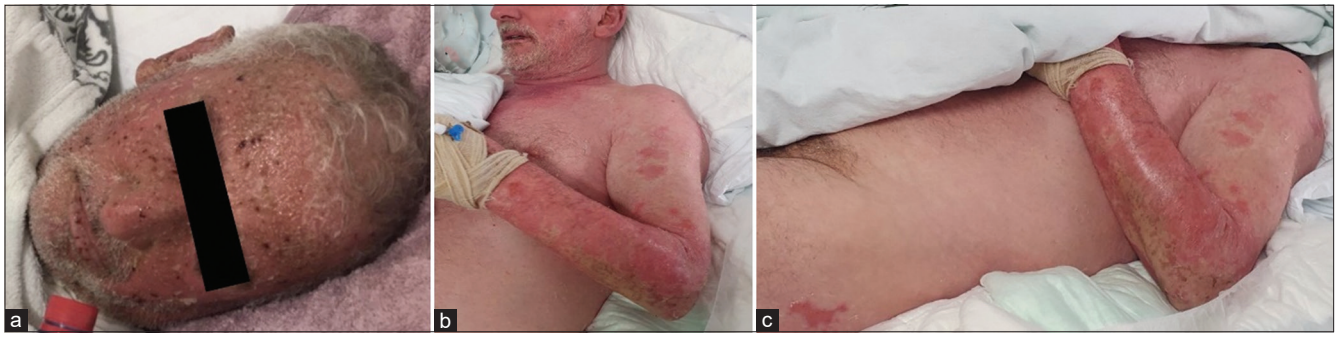

Figure 1: Erythema with pityriasiform scaling on the face and neck (a) and disseminated erythema with erosions and denuded skin on the trunk and limbs (b and c)

Table 1: A comprehensive overview of hematologic and enzyme status based on multiple blood test results conducted on different dates

Test	Results (September 11, 2022)	Results (September 13, 2022)	Results (September 17, 2023)	Results (September 20, 2023)	Reference range
			Hematologic status		
ESR	12	30	30	33	Female <50 year: 4–20, >50 year: 4–30; Male <50 year: 4–15, >50 year: 4–20
RBC	4.35	4.24	3.86	4.22	4.20–5.50×10^{12}/L
HGB	126	130	116	133	120–180 g/L
HCT	0.364	0.358	0.333	0.381	0.37–0.54 rv
MCV	83.7	84.4	86.3	90.1	82.0–98.0 fL
MCH	29	30.7	30.1	31.6	27.0–33.0 pg
MCHC	34.6	36.6	34.8	35.1	32.0–36.0 g/dL
RDW–SD	46.5	46.3	48.8	/	37.0–54.0 fL
RDW–CV	15.2	15.2	15.3	15.6	11.0–16.0%
WBC	10.8	10.11	7.9	8.2	4.00–9.00×10^{9}/L
LYMH	11.5	21.4	22.3	16.9	15–50%
MXD	4.4		10	6.4	2–15%
NEUT	84.1	69.3	67.7	76.7	35–80%
LYMPH_N	1.2	2.16	1.8	1.4	0.5–5.0×10^{9}/L
MXD_N	0.5		0.8	0.5	0.1–1.5×10^{9}/L
NEUT_N	9.1	7.01	5.3	6.3	1.2–8.0×10^{9}/L
PLT	151	197	255	250	150–450×10^{9}/L
PDW	13.9	15.9	13.6	/	9.0–17.0 fL
MPV	10.5	11.6	10.1	8.8	9.0–13.0 fL
P–LCR	30.0	38.3	27.3	/	13.0–43.0%
MONO	/	7.7	/	/	0.0–14.0%
BASO	/	0.4	/	/	0.0–1.0%
EO	/	1.2	/	/	0.0–6.0%
CRP	78	164.20	59.3	20.82	<6 mg/L
			Enzyme status (serum)		
ALT	39	37	58	36	10–45 U/L
AST	24	22	34	25	10–34 U/L
			Proteins		
Albumin	27	/	/	28	35–50 g/L
Total proteins	46	/	/	66	63–83 g/L
			Electrolytes		
Kalium	4.1	/	3.8	/	3.8–5.5 mmol/L
Sodium	131	/	133	/	131 mmol/L
Creatinin	/	57	55.9	55	45–109 mmol/L
Urea	/	8.3	8.2	4.7	2.7–7.8 mmol/L

dependent on the human leukocyte antigen (HLA). When drug metabolites bind to HLA proteins, it triggers cell toxicity and autogenous cell death. Despite indications of a genetic connection in various studies, the precise mechanism remains uncertain. The reaction is primarily driven by drug-specific T cells, where HLA-drug-T cell receptor engagement activates CD8+T cells, releasing cytotoxic proteins, and causing epidermal necrolysis [12]. Numerous cytotoxic proteins and cytokines serve as mediators, including soluble granulysin, Fas ligand, perforin/granzyme, tumor necrosis factor (TNF)-alpha, and TNF-related apoptosis-inducing ligand. Significantly, granulysin, a cytolytic protein found in cytotoxic T cells, NK/T cells, and NK cells, is now recognized as the key mediator driving keratinocyte death in SJS and TEN [13]. Moreover, the association between specific HLA haplotypes and elevated susceptibility to SJS and/or TEN is limited to particular ethnicities and specific medications. Notably, a significant correlation was identified among Han Chinese individuals in Taiwan with the HLA-B*15:02 allele, particularly in cases of SJS triggered by carbamazepine [14].

Table 2: Procalcitonin levels measured on two different dates

Test	Results (September 17, 2022)	Results (September 20, 2022)	Reference range
Procalcitonin	0.636	0.117	<0.5 ng/mL

TEN involves the necrosis and widespread detachment of the epidermis, primarily stemming from keratinocyte apoptosis induced by an immune mechanism. The onset of TEN is often associated with a cumulative impact of various factors related to the drug's structure, drug metabolism, and T-cell clonotypes [15].

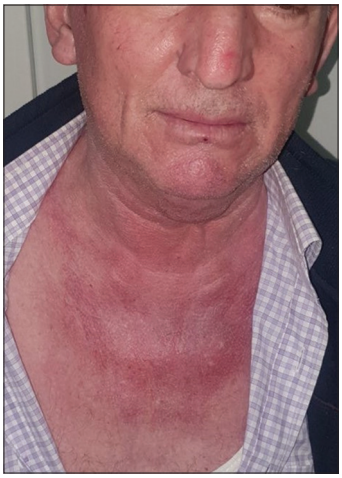

Figure 2: Dermatological improvement, emphasizing the face and neck. Image captured 8 weeks post-admission

In most cases, SJS and TEN manifest as severe cutaneous reactions triggered by medications. While various drugs have the potential to induce these conditions, epidemiological studies have pinpointed a specific group of high-risk medications responsible for the majority of cases. A comprehensive multinational case-control study, incorporating 379 cases of SJS/TEN and 1505 controls, identified key high-risk drugs, including allopurinol, aromatic antiseizure medications (such as lamotrigine), sulfonamides (such as sulfasalazine and nevirapine), oxicam NSAIDs, and carbamazepine [7]. The patient in this case report was

also diagnosed with TEN attributed to the administration of carbamazepine. Furthermore, a retrospective study spanning 7 years, focusing on inpatients diagnosed with TEN or SJS, revealed that anticonvulsants constituted the most commonly implicated group of drugs (53%). Among anticonvulsants, the majority of cases (81%) were attributed to carbamazepine [16].

During the acute phase, the management strategy focuses on providing supportive care and the prevention of both short and long-term complications. A critical aspect of improving prognosis involves the prompt identification and withdrawal of the causative agent. In a decade-long observational study involving 113 patients diagnosed with TEN or SJS, it was observed that the early cessation of causative drugs with short half-lives led to a significant reduction in the risk of death. Specifically, for each day preceding the development of blisters and erosions, there was a 30% decrease in the risk of mortality [11].

The absence of a standardized pharmacological treatment for SJS and TEN presents a significant challenge in clinical management. Ongoing evaluations of current therapeutic strategies, including IVIG and corticosteroids, underscore the need for effective interventions. Meta-analyses suggest potential benefits associated with alternative treatments such as cyclosporine, systemic corticosteroids, a combination of IVIG and systemic corticosteroids, and anti-TNF agents. In our case report, the patient's treatment approach incorporated a comprehensive strategy. IVIG administration at 0.5 g/kg over 3 days, along with an initial dose of 300 mg of prednisolone for 3 days, gradually tapered over 1 month, formed a central part of the therapeutic plan. To address potential complications, a combination of anticoagulant therapy and antibiotics was administered. Topical measures, including low-potency steroid emulsions and antiseptics on the oral mucosa, along with antibiotic solutions for ocular care, were implemented. Khalili and Bahna's study explored the pathophysiological mechanisms and emerging therapeutic trends in SJS and TEN [17]. Drawing insights from original research articles and reviews in peer-reviewed journals, their analysis focused on epidermal cell apoptosis mediated through Fas-FasL interaction or cytotoxic T-cell release of perforin and granzyme B. While systemic corticosteroid therapy showed inconsistent results, IVIG and cyclosporine exhibited promising outcomes. IVIG, featuring anti-Fas antibodies, demonstrated improvements in disease progression and skin healing time across various studies, with varying mortality rates. Cyclosporine, inhibiting CD8 activation, significantly improved disease arrest and complete reepithelization, without reported fatalities. The study emphasizes the need for rigorous validation through multicenter, randomized, placebo-controlled trials with a standardized design, emphasizing the urgent requirement for robust evidence in guiding the treatment landscape for SJS and TEN.

In a 2021 meta-analysis encompassing data from 38 trials published between 2000 and 2019, which evaluated the efficacy of systemic corticosteroids, supportive care, IVIG plus systemic corticosteroids, and cyclosporine in reducing mortality, the findings indicated that only cyclosporine and the combination of IVIG plus corticosteroids demonstrated a significant survival benefit [18]. Similarly, in another 2021 network meta-analysis involving 67 studies and 2079 patients, no treatment surpassed the effectiveness of supportive care in reducing the mortality rate. Notably, combination therapy with IVIG and corticosteroids emerged as the sole treatment associated with a survival benefit [19].

The importance of presenting case reports of TEN in the scientific literature cannot be overstated. Given the rarity and severity of TEN, each case report contributes significantly to its recognition, documentation, and understanding, assisting clinicians, researchers, and educators alike. These reports offer valuable insights into diverse clinical presentations, diagnostic challenges, and treatment outcomes, guiding medical professionals in managing similar cases. The aggregated data from case reports contribute to research, epidemiological studies, and the development of evidence-based guidelines. Moreover, case reports serve as educational tools, fostering a deeper understanding of TEN for medical students and practitioners, and by sharing experiences, they contribute to early detection, improved treatment strategies, and preventive measures, ultimately enhancing patient care and advancing the understanding of this challenging condition in dermatology and adverse drug reactions.

Conclusion

SJS and TEN constitute rare and severe mucocutaneous adverse reactions, typically triggered by drugs. Swift identification of the causative drug is imperative for initiating appropriate treatment and achieving the most favorable outcome. The primary therapeutic approach involves withdrawing the offending drug and providing supportive care for mucocutaneous lesions. Depending on the affected organ systems, a multidisciplinary approach may be necessary. In severe cases, prompt transfer to a specialized burn unit is crucial to reduce morbidity and mortality. The effectiveness of pharmacological interventions, including intravenous immunoglobulin and corticosteroids, warrants further evaluation. In addition, survivors of SJS and TEN should receive education on avoiding the implicated drug in the future.

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