

Toxic epidermal necrolysis: lessons from three fatal cases

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Abstract

Introduction: Toxic epidermal necrolysis (TEN) is a severe cutaneous adverse reaction triggered by various classes of drugs. Clinical manifestations include prodromal symptoms resembling a febrile illness, followed by skin and mucosal lesions. This study presents a series of fatal TEN cases, with a focus on factors that may have influenced mortality, including differential diagnoses, associated comorbidities, treatment choices, and complications of TEN.

Methods: Data were collected from electronic medical records of patients hospitalized at a dermatology clinic.

Results: Case 1 involved TEN in a 42-year-old female, initially misdiagnosed as mycoplasma-induced rash and mucositis (MIRM), who succumbed to sepsis. Case 2, a 50-year-old female with 80% of her body surface area affected, saw low-dose IVIg treatment prove ineffective, leading to multiorgan failure. Case 3 involved allopurinol-induced TEN in a 53-year-old with Balkan endemic nephropathy, resulting in fatal renal failure.

Conclusions: The cases presented highlight potential challenges in differentiating TEN from MIRM in the early stages of TEN. High-dose IVIg is generally recommended, whereas the effectiveness of low-dose IVIg is inconsistent, and it proved insufficient in the case presented, potentially due to the presence of multiple comorbidities. Preexisting conditions such as renal disease significantly influence fatal outcomes in TEN patients.

Keywords: Balkan endemic nephropathy, cutaneous adverse reactions, low-dose IVIg, mycoplasma-induced rash and mucositis, toxic epidermal necrolysis

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Introduction

Toxic epidermal necrolysis (TEN) represents the most severe form of adverse cutaneous reaction within the spectrum that includes Stevens–Johnson syndrome (SJS), SJS/TEN overlap, and TEN. These conditions are distinguished by the percentage of skin detachment: less than 10% for SJS, between 10% and 30% for SJS/TEN overlap, and more than 30% for TEN (1). The most common triggers of TEN are various medications, particularly anticonvulsants, non-steroidal anti-inflammatory drugs (NSAIDs), and antibiotics (2).

TEN typically starts with prodromal symptoms resembling a febrile illness, occurring 1 to 21 days prior to the appearance of skin and mucosal lesions (1). The evaluation of patients diagnosed with TEN includes the use of the Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN) scale, assessing clinical and laboratory risk factors to predict mortality. The mortality rate varies from 3.2% with one risk factor to over 90% with five or more risk factors (1).

We present a series of patients diagnosed with or treated for TEN at our center, all of whom had fatal outcomes. We discuss differential diagnoses, associated comorbidities, and complications that may have contributed to poor outcomes, supported by data from current research.

Methods

Data were collected from the electronic medical records of patients hospitalized at the women's department of the Belgrade Dermatology Clinic from 2016 to 2021. Information was collected on the clinical presentation, comorbidities, medical treatment,

laboratory findings, and histopathological results. Three patients with unique clinical features were identified.

Results

Case 1

A 42-year-old and otherwise healthy female patient presented with high fever and cough that began 3 days prior, along with erythema and erosions on the conjunctiva, genitalia, and minor intraoral lesions, with sparse atypical targetoid lesions on her hands involving 5% of the body surface area (BSA), raising suspicion of mycoplasma-induced rash and mucositis (MIRM; Figs. 1a, 1b). Empirical treatment with azithromycin and low-dose corticosteroids was initiated; however, 1 day later, the lesions spread to the oral mucosa, and skin lesions covered 60% of her BSA (Figs. 1c, 1d). Conjointly, a negative serology test for *Mycoplasma pneumoniae* and the history of ibuprofen use prompted a diagnosis of TEN with a SCORTEN 2. Intravenous immunoglobulin (IVIg) treatment was started, but the patient soon developed decreased oxygen saturation, requiring respiratory support. She was transferred to urgent care and developed sepsis, ultimately succumbing to septic shock 1 week after admission.

Case 2

A 50-year-old patient was transferred from a secondary medical center due to TEN, affecting 80% of her BSA, with confluent erythema and 40% denuded skin, as well as oral and genital erosions (Figs. 2a, 2b). She was on ventilatory support and unresponsive. The condition began 9 days prior with a high fever, and she had

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been taking over-the-counter NSAIDs while her skin lesions developed. Four days after symptom onset, she was diagnosed with TEN and treated with high-dose corticosteroids and low-dose IVIg (0.07 g/kg/day for 5 days), without improvement. Upon admission to our center, we started treatment with high-dose corticosteroids and IVIg (1 g/kg/day). Despite this, her condition deteriorated, and she was transferred to the urgent care unit for multiorgan failure, where the fatal outcome ensued.

Case 3

A 53-year-old patient presented with severe erythema, bullae, and erosions covering 50% of her BSA and a SCORTEN 5. Her history included Balkan endemic nephropathy (BEN) and stage IV chronic renal insufficiency. Two weeks before developing TEN, she was prescribed allopurinol. A fever emerged 10 days after starting allopurinol, followed by mucosal and skin lesions. Initially treated with low-dose corticosteroids at a regional medical center, her condition worsened. At our center, she received high-dose corticosteroids and IVIg therapy (1 g/kg/day for 3 days), which initiated epithelization (Figs. 2c, 2d). However, 4 days after admission

to our center, her renal function deteriorated, requiring hemodialysis. Severe renal damage led to transfer to the nephrology clinic, where she ultimately succumbed to renal failure. Key characteristics of the three cases are summarized in Table 1.

Discussion

The differential diagnoses of TEN are extensive, encompassing a variety of conditions including infections (staphylococcal scalded skin syndrome, toxic shock syndrome, purpura fulminans, coxsackievirus-induced severe mucocutaneous disease, chikungunya fever), immune-mediated conditions (lupus erythematosus, pemphigus vulgaris, paraneoplastic pemphigus, lichen planus pemphigoides, graft-versus-host disease, inflammatory epidermolysis bullosa acquisita), other drug-induced skin reactions (acute generalized exanthematous pustulosis, generalized bullous fixed drug eruption, drug reaction with eosinophilia and systemic symptoms, toxic erythema of chemotherapy), metabolic conditions such as pseudoporphyria, and (thermal/chemical) burns (3–14). A potential challenge in diagnosis lies in differentiating the SJS/TEN spectrum from MIRM, especially during the



Figure 1 | (a, b) Patient 1 on the day of admission, displaying involvement of the lips, conjunctiva, and acral sites; (c) 1 day after admission, progression of skin lesions with involvement of trunk is seen; (d) 2 days after admission, extensive skin involvement with multiple targetoid and confluent lesions as well as bullae is seen.

early phases of the disease, when they may exhibit overlapping clinical features. As established by Canavan et al. in 2015, MIRM and SJS are distinct entities with different etiologies, presentations, and outcomes (15). However, both MIRM and SJS/TEN are



Figure 2 | (a, b) Patient 2, previously treated with very low-dose intravenous immunoglobulins for 5 days, presenting with extensive skin erythema, bullae, and areas of skin detachment, unresponsive and on ventilatory support at admission to our center; (c, d) patient 3, with significant re-epithelization of skin lesions, but worsening renal disease unresponsive to the therapy provided.

Table 1 | Primary demographic, clinical, and laboratory data for toxic epidermal necrolysis (TEN) patients.

	Patient 1	Patient 2	Patient 3
Age (years)	42	50	53
Sex	Female	Female	Female
Comorbidities	None	Hypertension, chronic renal insufficiency, chronic obstructive pulmonary disease	Balkan endemic nephropathy, chronic renal insufficiency grade 4, hypertension
Symptom onset before admission	3 days	9 days	6 days
Probable culprit drug	Ibuprofen	Penicillin and ibuprofen	Allopurinol
Skin lesion localization at admission	Oral, conjunctival, genital mucosa, upper extremities	Oral, conjunctival, genital mucosa, diffuse skin involvement	Oral and conjunctival mucosa, trunk, extremities
BSA at admission	5%	80%	50%
SCORTEN at admission	2/7	6/7	5/7
Histologically proven disease	Yes	Yes	Yes
Treatment received	IVIg (2 g/kg over 5 days), methylprednisolone pulse therapy (1,000 mg over 3 days)	IVIg (0.07 g/kg/day over 5 days), methylprednisolone pulse therapy (500 mg over 3 days)	IVIg (2 g/kg over 5 days), dexamethasone pulse therapy (100 mg over 3 days*)
Complications leading to fatal outcome	Respiratory failure, acute renal insufficiency, sepsis	Hypotensive shock	Sepsis

*Prior to admission to our center, the patient received 25 mg of dexamethasone over 2 days, followed by 100 mg of dexamethasone over 3 days at our center. SCORTEN = Severity-of-Illness Score for Toxic Epidermal Necrolysis, BSA = body surface area, IVIg = intravenous immunoglobulins.

mucocutaneous eruptions characterized by prominent mucosal involvement. In their early stages, both can present with fever and painful mucositis, and the cutaneous lesions in MIRM can resemble those seen in SJS/TEN. This similarity led early classifications to often label *M. pneumoniae*-associated eruptions under designations such as SJS or erythema multiforme (15, 16). Case 1 in our series initially raised suspicion of MIRM given the involvement of three different mucosal sites, sparse atypical target lesions on the skin, absence of widespread detachment, and prodromal symptoms of fever and cough. Our case parallels a case report of a 3-year-old patient initially diagnosed with atypical SJS that was later confirmed to have MIRM due to positive *M. pneumoniae* serology, and a 36-year-old woman, whose condition was initially considered SJS before being diagnosed as MIRM (17, 18). Key distinctions between MIRM and TEN are shown in Table 2.

Regarding TEN treatment, high-level evidence suggests that cyclosporine, corticosteroids, and IVIg combination therapy, as well as etanercept, are efficacious. However, conclusions are mixed for corticosteroid monotherapy, and thalidomide use is associated with high mortality (19–30). A significant area of debate concerns the optimal dosage of IVIg. European guidelines for treating TEN indicated that high-dose IVIg (≥ 2 g/kg) was associated with significantly lower mortality than low-dose IVIg (< 2 g/kg, $p = 0.022$), with a strong inverse correlation between IVIg dosage and standardized mortality rate, suggesting that dosages of ≥ 2 g/kg significantly decreased mortality (31). However, evidence regarding optimal IVIg dosage is inconsistent. A recent meta-analysis found a significantly lower mortality rate in adult patients treated with high-dose IVIg (18.9%) compared to low-dose (50%), but this was not significant when adjusted for confounding factors such as age, total BSA, and time to treatment. Furthermore, another systematic review and network meta-analysis found no differences in efficacy based on IVIg treatment dose (≥ 3 g/kg or < 3 g/kg) (23, 29). Our Case 2 provides additional information on the therapeutic effect of low-dose IVIg. The patient received a cumulative low dose of IVIg (0.35 g/kg over 5 consecutive days, or 0.07 g/kg/day) in conjunction with high doses of corticosteroids. It is important to note that this low-dose IVIg therapy was administered at a referring secondary medical center prior to transfer to our facility. This treatment occurred in early 2016, which predates the 2016 European guidelines recommending high-dose IVIg for TEN, reflecting the local protocols and prevailing clinical evidence. Unfortunately, this treatment was ineffective because the patient’s skin detachment progressed from an initial 30% to 80% of BSA. This patient represents one of the rare cases in the literature for whom such low doses of IVIg were utilized. The hypoth-

esis for low-dose IVIg efficacy centers on its ability to block the Fas-FasL pathway (implicated in TEN pathogenesis and thought to be dosage independent), but this intervention did not yield an adequate response in our patient. This lack of response was presumably due to the presence of multiple comorbidities, including uncontrolled hypertension, stage II chronic renal insufficiency, and chronic obstructive pulmonary disease, a profile similar to that of a patient with a fatal outcome in another study (32). Despite the outcome in Case 2, evidence for the effectiveness of low-dose IVIg in certain TEN cases exists, relying on prospective cohort studies and case reports. A prospective comparative study involving 36 (adult and pediatric) patients demonstrated that low-dose IVIg (0.2–0.5 g/kg, divided over 3 days) combined with systemic steroids effectively halted disease progression compared to steroid therapy alone (32). Similarly, an open uncontrolled study in 10 pediatric patients found that low doses of IVIg (0.05–0.1 g/kg per day for 5 days) halted disease progression and facilitated rapid re-epithelialization (33). A case report also described an excellent outcome in a patient with TEN treated with a combination of systemic steroids and low-dose IVIg (1.2 g/kg) over 3 days (34).

Factors affecting outcome in SJS and TEN are traditionally incorporated into validated scores that predict mortality. The SCORTEN scale is the most widely recognized, proving beneficial in predicting mortality when the score exceeds 2 within the first 24 hours (35). In addition, the new Clinical Risk Score for TEN (CRISTEN) score has been developed, focusing exclusively on clinical aspects for prognosis determination (36). The specific clinical risk factors that constitute this score are presented in Table 3. Beyond these scores, a recent meta-analysis highlights other factors highly relevant to adverse outcomes, including the general presence of comorbidities, longer time to hospitalization, preexisting renal disease, diabetes mellitus, involvement of the respiratory tract, and

Table 3 | Clinical Risk Score for TEN (CRISTEN) to predict mortality in patients with Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in early stages based on clinical information (36).

Risk factors	Points assigned
Patient age ≥ 65 years	1
$\geq 10\%$ of body surface area (BSA) involved	1
Use of antibiotics as culprit drugs	1
Prior systemic corticosteroid therapy before onset	1
Damage affecting ocular, buccal, and genital mucosa	1
Underlying condition: renal impairment	1
Underlying condition: diabetes (under treatment)	1
Underlying condition: cardiovascular disease	1
Underlying condition: malignant neoplasm	1
Underlying condition: bacterial infection	1

Each of the 10 clinical risk factors identified contributes one point to the total score, which then correlates to a predicted probability of mortality ranging from 0% (0 points) to 100% (8 or more points).

Table 2 | Key differences between mycoplasma-induced rash and mucositis (MIRM) and toxic epidermal necrolysis (TEN).

	MIRM	TEN
Primary cause	<i>Mycoplasma pneumoniae</i> infection	Drug-triggered disease
Age	Primarily young patients	Most frequently in adults
Cutaneous involvement	Sparse or absent; detachment typically $< 10\%$ of BSA; extensive detachment extremely rare	Widespread epidermal necrosis and sloughing; $> 30\%$ of body surface area
Mucosal involvement	Prominent and nearly universal (oral 94%, ocular 82%, urogenital 63%); major cause of morbidity	Universal; two or more mucosal surfaces involved in up to 80% of cases
Lesion morphology	Vesiculobullous (77%), targetoid (48%), atypical targets, or macules; true targets are rare; lesions often in acral distribution or on extremities	Erythematous macules or atypical target lesions on the trunk that progress to confluent areas of erythema with dusky centers, flaccid blisters with a positive Nikolsky sign, and sheets of denuded epidermis
Disease course	Generally milder with excellent prognosis; infrequent long-term sequelae	More severe than MIRM; associated with significant morbidity
Mortality rate	Very low; fatalities likely due to pulmonary complications in pre-antibiotic era	Associated with significant mortality

BSA = body surface area.

the development of sepsis (37). Further cohort studies have identified additional potential risk factors for mortality, such as fever, hypertension, presentation with vesicles and bullae, utilization of plasmapheresis, urinary microscopic abnormalities, visceral organ involvement, HIV infection, a high neutrophil-to-lymphocyte ratio, cutaneous lesions preceding mucosal lesions, female sex, inborn errors of urea cycle metabolism, chronic obstructive pulmonary disease, lower hemoglobin, and higher platelet count (2, 35, 38–48). The identification of preexisting renal disease as a significant risk factor is particularly pertinent for Case 3, which involved the rare occurrence of TEN in a patient with BEN. BEN is a chronic tubulointerstitial disease primarily found in the Balkan Peninsula, which over time leads to end-stage renal disease in nearly all individuals affected (48). This case represents a unique intersection of TEN with BEN, which is especially important given that approximately 100,000 individuals are at risk for BEN, with about 25,000 already affected by the disease (49).

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Conclusions

In summary, the cases presented highlight several key points: there are possible difficulties in differentiating the SJS/TEN spectrum and MIRM due to overlapping clinical features in early disease phases, the cases provide additional information on the therapeutic effect of low-dose IVIg in combination with systemic corticosteroids for TEN treatment, and they underscore the potential for severe kidney complications among individuals with BEN that develop TEN.

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