Case Report

Levetiracetam-induced Stevens–Johnson syndrome/toxic epidermal necrolysis overlap: A fatal case report

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ABSTRACT

Levetiracetam is a second-generation antiepileptic drug (AED) that is generally regarded as having a favorable safety profile and a lower propensity for severe cutaneous adverse reactions (SCARs) than the aromatic AEDs such as carbamazepine, phenytoin, and lamotrigine. Nevertheless, rare and occasionally fatal SCARs, including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with its use. We describe a 29-year-old female with hypertension, hypothyroidism in the past 3 years, and a 1-year history of a seizure disorder who developed painful oral mucosal ulceration followed by generalized erythematous and dusky macules with epidermal detachment 10 days after the initiation of levetiracetam. The extent of epidermal detachment was estimated at approximately 18% of the body surface area, placing the eruption within the SJS/TEN overlap spectrum. Causality assessment using the Naranjo Adverse Drug Reaction Probability Scale and the World Health Organization–Uppsala Monitoring Centre criteria categorized the reaction as probable. Despite immediate withdrawal of the offending drug, fluid and electrolyte resuscitation, meticulous wound care, and supportive intensive management, the patient developed secondary sepsis with multiorgan dysfunction and died. Although levetiracetam is considered comparatively safe, clinicians must remain vigilant for life-threatening cutaneous reactions. Early recognition, immediate withdrawal of the suspected agent, and prompt referral to a specialized burn or intensive care unit are critical determinants of outcome.

Key words: Adverse drug reaction, Antiepileptic drug, Levetiracetam, Severe cutaneous adverse reaction, Stevens–Johnson syndrome, Toxic epidermal necrolysis

Levetiracetam is a second-generation antiepileptic drug (AED) that is widely prescribed for both focal and generalized seizures because of its broad spectrum of activity, predictable pharmacokinetics, minimal hepatic metabolism, and a comparatively favorable adverse-effect profile. Unlike the older aromatic anticonvulsants, levetiracetam is not metabolized through the cytochrome P450 system and lacks the reactive arene-oxide intermediates that are classically implicated in anticonvulsant hypersensitivity. For this reason, it is often selected as a safer alternative in patients considered to be at higher risk of cutaneous drug reactions. Despite this reputation, a growing number of reports have documented severe cutaneous adverse reactions (SCARs) associated with its use, including Stevens–Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) [1]. Systematic appraisal of the published literature confirms that levetiracetam-associated cutaneous reactions, although uncommon, span the full clinical spectrum from benign maculopapular exanthems to fatal epidermal necrolysis [2]. Comparative analyses of AEDs have consistently ranked levetiracetam as carrying a lower, but not negligible, risk of SJS/TEN relative to carbamazepine, phenytoin, lamotrigine, and phenobarbital [3,4]. More recent real-world pharmacovigilance reviews have emphasized that the reporting of these events has increased as levetiracetam prescribing has expanded, underscoring the need for continued clinician awareness [5]. The propensity of AEDs as a class to provoke immune-mediated hypersensitivity has long been recognized within the framework of the anticonvulsant hypersensitivity syndrome [6].

SJS and TEN form a continuum of the same disease process, distinguished principally by the extent of epidermal detachment: <10% of the body surface area in SJS, more than 30% in TEN, and 10–30% in the SJS/TEN overlap form. The estimated annual incidence of SJS/TEN is approximately one to two cases per million population, and the conditions carry substantial

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mortality, ranging from around 10% in SJS to more than 30% in TEN [7,8]. Acute systemic complications, including acute kidney injury, are well documented and contribute to the high case fatality rate [9].

We report a fatal case of levetiracetam-induced SJS/TEN overlap syndrome in a young woman, intending to reinforce the importance of early recognition and prompt management of this rare but devastating reaction.

CASE REPORT

A 29-year-old female presented to the emergency department with a 4-day history of painful oral ulceration and a rapidly progressive skin eruption. She was a known case of hypertension and hypothyroidism, both diagnosed 3 years before the current presentation, and had been diagnosed with a seizure disorder 1 year before presentation. Her regular medications included an antihypertensive agent and levothyroxine, both of which she had tolerated without difficulty for several years. Approximately 3 weeks before presentation, owing to inadequate seizure control on her previous regimen, levetiracetam was introduced and titrated to a maintenance dose. No other new medication, herbal preparation, or over-the-counter product had been started during this period. Ten days after the initiation of levetiracetam, the patient developed a prodrome of low-grade fever, malaise, sore throat, and a burning sensation of the eyes. This was followed within 48 h by painful erosions of the lips and oral mucosa that interfered with eating and drinking. Over the next 2–3 days, erythematous, dusky, and targetoid macules appeared over the face and trunk. They rapidly became confluent, with subsequent flaccid blistering and sheet-like detachment of the epidermis. The patient also reported ocular grittiness and photophobia, as well as genital mucosal soreness.

On examination, she was febrile (38.9°C), tachycardic (heart rate 118 beats/min), and hypotensive (blood pressure 96/60 mmHg). Cutaneous examination revealed widespread erythematous and purpuric macules with areas of confluent epidermal detachment and a positive Nikolsky sign. The total area of epidermal involvement was estimated at approximately 18% of the body surface area, consistent with SJS/TEN overlap. Hemorrhagic crusting of the lips, extensive oral erosions, bilateral purulent conjunctivitis, and erosive genital mucosal lesions were present, confirming involvement of three mucosal sites (Fig. 1).

Laboratory investigations demonstrated leukocytosis with relative neutrophilia, mild anemia, hypoalbuminemia, and electrolyte derangement with hyponatremia. Renal function was deranged, with a rising serum creatinine and reduced urine output consistent with acute kidney injury, while liver enzymes were mildly elevated and C-reactive protein was markedly raised. Blood and skin-swab cultures were obtained. Based on the patient's age, heart rate, body surface area involvement, serum urea, bicarbonate, and glucose, the estimated SCORTEN

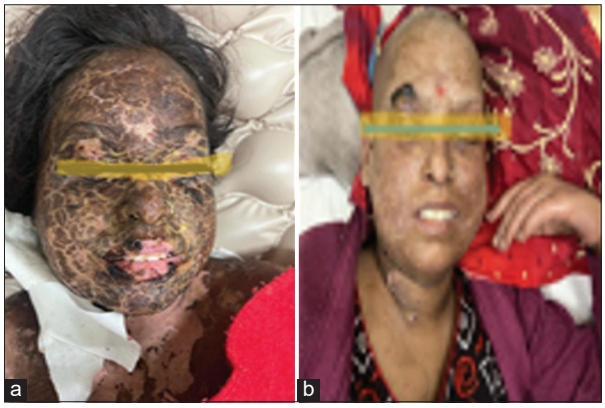

Figure 1: (a) Cutaneous involvement at presentation showing confluent erythematous and dusky macules with early flaccid blistering and a positive Nikolsky sign, together with hemorrhagic crusting of the lips; (b) Progression of the eruption with widespread sheet-like epidermal detachment involving approximately 18% of the body surface area, consistent with Stevens–Johnson Syndrome/toxic epidermal necrolysis overlap

severity-of-illness score predicted a high risk of mortality. A skin biopsy, where feasible, showed full-thickness epidermal necrosis with subepidermal separation and a sparse dermal lymphocytic infiltrate, supporting the clinical diagnosis.

Levetiracetam was identified as the most probable culprit on the basis of the temporal relationship and the absence of any other recently introduced agent. The temporal association between drug initiation and onset of the reaction, the recognized potential of levetiracetam to cause SCARs, the expected response to withdrawal, and the lack of an alternative explanation were systematically evaluated. Causality assessment using the Naranjo Adverse Drug Reaction Probability Scale [10] yielded a score in the "probable" range, and assessment using the World Health Organization–Uppsala Monitoring Centre (WHO-UMC) criteria [11] similarly categorized the reaction as probable.

Levetiracetam was discontinued immediately. The patient was managed in a high-dependency setting with an approach analogous to that used for major burns: Aggressive intravenous fluid and electrolyte replacement, strict temperature control, nutritional support, meticulous non-adherent wound dressings, scrupulous aseptic technique, ophthalmological review with lubricant and topical therapy, and oral and genital mucosal care. Adjuvant immunomodulatory therapy was instituted in accordance with prevailing practice. Despite these measures, the cutaneous detachment continued to progress over the ensuing days, and the patient developed secondary bacterial sepsis with worsening acute kidney injury and progressive multiorgan dysfunction. She succumbed to her illness despite maximal supportive care.

DISCUSSION

This case illustrates that levetiracetam, despite its reputation as a relatively safe antiepileptic agent, can

precipitate fatal SJS/TEN overlap syndrome. AEDs are among the most frequently implicated causes of SCARs worldwide, and although the aromatic anticonvulsants carry the highest risk, levetiracetam is not exempt. The two cases described by Duong *et al*. [1] and the case reported by Gupta *et al*. [9] have documented levetiracetam-associated SJS/TEN, including a case complicated by acute kidney injury that mirrors the renal involvement observed in our patient. In a hospital-based case series, Trivedi *et al*. likewise documented several instances of AED-induced SJS, predominantly attributable to the aromatic anticonvulsants [12]. Large adverse-event database analyses further confirm that, although uncommon, these reactions occur in new users of levetiracetam and other AEDs [4,5].

The pathogenesis of SJS/TEN is understood to be a delayed, T-cell-mediated cytotoxic immune response directed against keratinocytes. Drug-specific cytotoxic T lymphocytes and natural killer cells release soluble mediators, most notably granulysin, together with perforin, granzyme B, and the Fas–Fas ligand interaction that drives the widespread keratinocyte apoptosis responsible for epidermal detachment. The latency between drug exposure and onset, typically 4 days–4 weeks, is consistent with such an immunologically primed mechanism and corresponds closely with the 10-day interval observed in our patient. This class-wide tendency of anticonvulsants to provoke immune hypersensitivity has historically been described as the anticonvulsant hypersensitivity syndrome [6].

The diagnosis of SJS/TEN is primarily clinical, supported where possible by histopathology demonstrating full-thickness epidermal necrosis. Several conditions were considered in the differential diagnosis. Drug reaction with eosinophilia and systemic symptoms was considered but was thought less likely given the predominance of mucocutaneous detachment over facial edema and the absence of marked eosinophilia. Erythema multiforme major was distinguished by the typical absence of widespread epidermal detachment and its characteristic acral, target-lesion distribution. Pemphigus vulgaris and other autoimmune blistering disorders were considered unlikely on clinical grounds and could be excluded by the histological pattern and, where available, immunofluorescence. Staphylococcal scalded skin syndrome was excluded because the plane of cleavage in that condition is subcorneal, and mucosal involvement is characteristically absent, whereas our patient had extensive mucosal disease and a subepidermal split.

Comparative analyses of the relative risk of SJS/TEN among AEDs are valuable in guiding rational prescribing, and they reaffirm that no anticonvulsant can be regarded as entirely free of this risk [3]. Contemporary real-world reviews advocate maintaining a high index of suspicion even for agents traditionally viewed as low-risk, and they highlight the increasing recognition of levetiracetam-associated SCARs as its clinical use widens [5]. Structured causality assessment instruments, such as the Naranjo scale [10] and the WHO-UMC system [11], provide a standardized and reproducible means of attributing the reaction to a specific drug, which is particularly important in patients receiving multiple medications.

The cornerstone of management is the prompt identification and immediate withdrawal of the offending drug, since each day of delay in discontinuation is associated with increased mortality [2]. Beyond drug cessation, supportive care delivered in a specialized burn or intensive care unit, comprising fluid and electrolyte management, temperature regulation, nutritional support, infection control, and multidisciplinary wound, ocular, and mucosal care, remains the most important determinant of survival [7,8]. The role of adjuvant pharmacological therapy, including systemic corticosteroids, intravenous immunoglobulin, cyclosporine, and tumor necrosis factor inhibitors, continues to be debated, and current evidence does not establish a single, universally accepted regimen. Prognosis is best estimated using the SCORTEN score, and in our patient, the constellation of extensive body surface area involvement, tachycardia, acute kidney injury, and metabolic derangement predicted a high probability of death, which unfortunately ensued.

CONCLUSION

Although levetiracetam is widely regarded as one of the safer AEDs, this case is a sobering reminder that it can provoke rare, severe, and even fatal cutaneous adverse reactions such as SJS/TEN overlap syndrome. Clinicians prescribing any antiepileptic agent should counsel patients about the early warning symptoms of SCARs – fever, mucosal soreness, and a painful or blistering rash – and should encourage immediate medical review should they occur. Early diagnosis, prompt withdrawal of the suspected drug, structured causality assessment, and timely transfer to a specialized unit for intensive supportive care offer the best opportunity to reduce morbidity and mortality from this potentially lethal condition.

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