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CASE REPORT

Phenytoin-induced toxic epidermal necrolysis (TEN). Combined treatment with steroids and human intravenous immunoglobulin: Case report

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ABSTRACT

Background. Toxic epidermal necrolysis (TEN) is a severe systemic disease that affects the skin and mucosa, with a mortality rate above 30%. Pharmaceutical drugs are the main causal agents of this reaction, with most cases being largely associated with phenytoin. There is no generally accepted treatment for TEN. The administration of systemic corticosteroids combined with human intravenous immunoglobulin (IVIG) may be a possible adjuvant therapy.

Case presentation. A 72-year-old patient who received phenytoin for four weeks as a prophylactic treatment after undergoing surgery to drain a chronic subdural hematoma developed TEN-compatible symptoms, which prompted treatment with methylprednisolone (1 g/day for 3 days) combined with IVIG (0.5 gr/kg/day for 5 days), with favorable response.

Conclusion. Our patient's response to the combination of corticosteroids and IVIG was favorable. However, due to the nature of this report, the function this combination of drugs has must be further researched.

Key words: *Toxic epidermal necrolysis; TEN; Toxicodermy; Phenytoin; Immunoglobulin.*

Toxic epidermal necrolysis (TEN) is a severe systemic disease that affects the skin and mucosa, with a mortality rate above 30%.[1] Its main symptoms are extended necrosis and epidermal detachment. Together with Stevens-Johnson syndrome (SJS) it forms a spectrum of disease, on which each case is classified according to the percentage of detached skin: <10% SJS, 10-30% SJS/TEN concurrence, and >30% TEN.

The exact mechanism of toxic epidermal necrolysis is unknown; however, one theory suggests that abnormalities in some patients' drug metabolism (e.g.: the lack of elimination of reactive metabolites) causes a T-cell-mediated cytotoxic reaction against keratinocyte-presented drug antigens. CD8+ T cells have been identified as a key agent in the formation of blisters.[2]

Pharmaceutical drugs are the main causal agents of this reaction,[2-5] with TEN being largely associated with phenytoin.[6] There is no generally accepted adjuvant pharmaceutical treatment for this disease, but various immunosuppressive or immunomodulating agents have been used to treat TEN based on varying levels of empirical evidence, such as systemic corticosteroids, intravenous immunoglobulin (IVIG),[7] ciclosporin,[8] plasmapheresis,[9] and anti-tumor necrosis factor (TNF).[10]

The case of a patient suffering from secondary TEN after being treated with phenytoin is presented. Her response was favorable after treatment with systemic corticosteroids and IVIG.

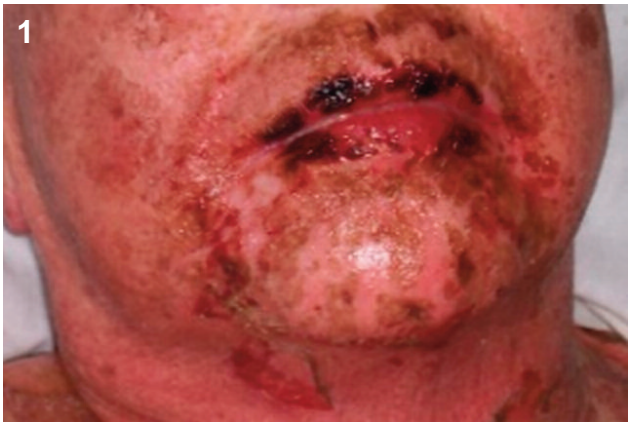
CLINICAL CASE

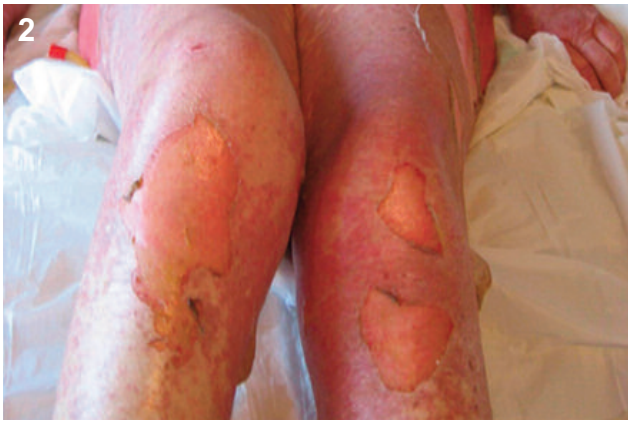
A 72-year-old female patient with a history of hypothyroidism, hypertension, myocardial ischemia and myelodysplasia was on phenytoin (100 mg every 6 hours) as

a prophylactic outpatient treatment after undergoing surgery to drain a chronic subdural hematoma one month prior. She came to the emergency ward after developing a pruritic maculopapular rash in her upper and lower limbs, which progressively spread, along with facial and mucosal edema accompanied by dysphonia and odynophagia in the previous 48 hours, which prompted her admission. During the physical examination, confluent lesions and blisters were observed, which caused erosions in her face, chest and limbs. Her mucosa was also affected, presenting blood-serum slough. She was also positive for Nikolsky's sign, with 30% of her superficial epidermal tissue being compromised (Fig. 1 and 2).

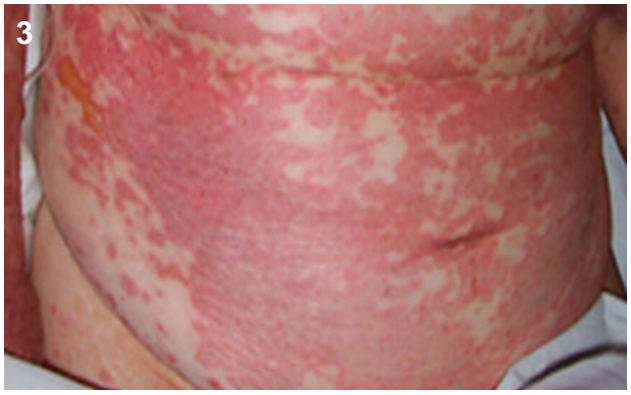
The case was initially diagnosed as phenytoin-induced angioedema, and the prescribed treatment was intravenous (IV) hydrocortisone (200 mg every 6 hours), diphenhydramine (50 mg every 8 hours) and parenteral hydration. Since the patient's condition did not improve, 1 mg/ml intradermal bolus adrenaline was administered. The ophthalmic exam was normal. The patient developed persistent fever; therefore, blood and urine samples were taken (no posterior bacterial growth), and vancomycin and cefepime were administered as an antibiotic empiric treatment. The skin biopsy showed evidence of keratinocyte necrosis, vacuolar degeneration of the basal layer and subepidermal blistering, which were compatible with TEN. Both the Naranjo algorithm and the TEN-specific drug causality algorithm (ALDEN) showed probable causality for phenytoin (7 "probable" and 6 "highly probable", respectively).

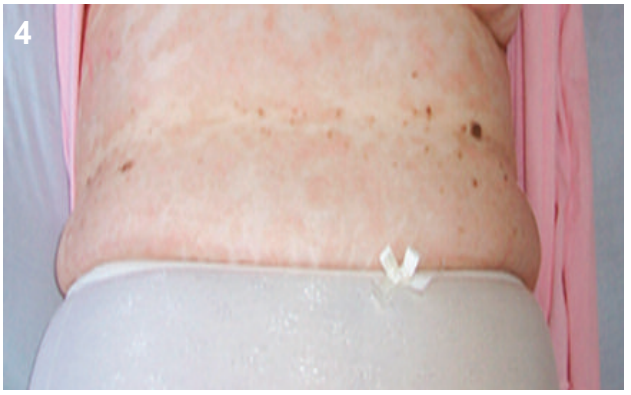
In view of the seriousness of the case, on the fourth day of hospitalization it was decided to administer IVIG (0.5 gr/kg/day for five consecutive days), and methylprednisolone (1 g/day IV for three days). The patient responded favorably, with lesion regression, no new tissue being compromised, and full mucosa recovery (Fig. 3 and 4). The National Administration of Drugs, Food and Medical Devices (ANMAT, as per the Spanish acronym) was informed of the adverse drug reaction and the patient was discharged after 30 days.





Figures 1 and 2. Day 1. Confluent erythema and blister sores combined with erosions and necrosis can be seen on face, torso, and limbs.





Figures 3 and 4. There is a noticeable improvement on the erythema and denudation.

DISCUSSION

While the case reported is an isolated one, it is a useful observational account regarding TEN treatment with systemic corticosteroids combined with IVIG. Despite that the route of administration (oral vs. IV), dosage, time, and duration of the treatment are not clear, and that immunoglobulin is not recommended as a monotherapy, the combination of IVIG and corticosteroids should be further studied.

TEN-suspected patients must be immediately examined in a medical facility in order to reach a definitive diagnosis, evaluate the seriousness of the case and its prognosis, determine a causal agent and implement the appropriate treatment. The prognosis can be improved by rapidly identifying and removing the causal agent. In a 10-year observational study of 113 TEN or SJS patients, the early discontinuation of the causal drugs with short half-lives reduced the risk of death by 30% for each day before the development of blisters and erosions (odds ratio [OR] 0.69; 95% CI: 0.53-0.89).[11] However, drugs with longer half-lives were linked to higher death risk, regardless of early or late discontinuation (OR 4.9; 95% CI: 1.3-18.9). This difference between drugs with short and long half-lives may be a result of the drug or the substrate that caused the reaction still being active, despite the discontinuation.

In our case at hand, the suspected causal drug was discontinued immediately while trying to determine the causal agent. As for the determination of causality, the timeline and suspected agent must be taken into account. Most treatments with TEN-inducing drugs are started 5 to 28 days (sometimes up to two months) before any symptoms develop.[2] This is consistent with our patient, who started her treatment 4 weeks prior. Furthermore, most TEN cases are triggered by a handful of high-risk medications,[3-5] phenytoin being one of them. A number of algorithms to determine drug causality have been created. The Naranjo algorithm is widely known in the field of pharmacovigilance, but to determine the causal drug of this adverse reaction, the ALDEN score has been specifically applied. In this case, both algorithms (Naranjo and ALDEN) have determined phenytoin as a probable or highly probable cause of TEN.

Regarding TEN-specific treatment, there is limited evidence that adjuvant treatments are beneficial, and none can be conclusively recommended. Nevertheless, the results of different meta-analysis suggest that treatment with ciclosporin, etanercept, systemic corticosteroids, and a combination of IVIG and systemic corticosteroids may be potentially beneficial. In our patient's case, due to a lack of availability of ciclosporin and etanercept, IVIG and systemic corticosteroids was the treatment of choice. This combination has been investigated in only a handful of studies, which are summarized in Table 1.

In Micheletti et al.'s research (2018) on SJS/TEN hospitalized patients, the standardized mortality ratio (SMR) of patients that were administered systemic corticosteroids (average daily dose of 148 mg of prednisone) and IVIG (average dosage of 1 g/kg/day for three days) was lower than the SMR of the populations who received corticosteroids alone, IVIG alone, or supportive care alone.[12]

In the propensity-matched study of Yang et al. (2022), there was no difference in the SMR of the two groups. Nevertheless, in contrast with corticosteroid monotherapy, the combined therapy was linked to shorter hospitalization times (-3.37 days) and a lower rate of skin infection.[13]

In Jagadeesan et al.'s non-randomized study (2013), all 36 TEN patients were administered small doses of IVIG (0.2 to 0.5 g/kg) and intravenous dexamethasone (0.1 to 0.3 mg/kg/day, gradually reduced within one or two weeks), or dexa-methasone alone. Differences in SMR were significant.[14]

In Schneck et al. (2008), 35 patients were treated with IVIG alone and 40 with IVIG combined with systemic corticosteroids.[15] The IVIG dose ranged between 0.7 and 2.3 g/kg and was administered during one to seven days. Gross mortality rate was 18% in the group treated with corticosteroids alone and 18% as well in the group treated with IVIG and corticosteroids.

In Zhu et al.'s research on TEN patients (2012), 39 patients were treated with 0.4 g/kg of IVIG for five days combined with 1.5 mg/kg methylprednisolone for three to five days, and 22 were administered methylprednisolone alone. Differences in SMR were not significant.[16]

Yang et al. (2009) compared 65 patients over a period of 14 years. 45 patients were treated with corticosteroids (1 to 1.5 mg/kg/day of methylprednisolone), and 20 were treated with IVIG (2 g/kg for five days) and corticosteroids (1 to 1.5 mg/kg/day of methylprednisolone). There was no statistical difference in mortality between the two groups.[17]

Chen et al. (2010) conducted a similar study, comparing patients treated with corticosteroids (n = 58) and patients treated with IVIG and corticosteroids (n = 24) and did not find any significant difference between the SMR of the two groups.[18]

By analyzing these studies, it is possible to conclude that a combination of corticosteroids and IVIG can be more effective than those two administered separately. However, given the nature of said studies, the small number of patients, their single-centered and retrospective nature, as well as the

TABLE 1. Summary of the main studies on TEN adjuvant treatment with corticosteroids alone versus treatment with corticosteroids + IVIG.

Study	Study type	Year	Total N	SMR	
				Corticosteroids	Corticosteroids + IVIG
Micheletti et al. (USA)	Multicenter retrospective observational	2018	377	0.72 [95% CI: 0.48-0.89]	0.52 [95% CI: 0.21-0.79]
Yang et al. (China)	Single-center retrospective observational	2022	145	0.75 [95% CI: 0.00-1.76]	0.38 [95% CI: 0.00-0.91]
Jagadeesan et al. (India)	Single-center prospective observational	2013	36	0.63 [95% CI: 0.00-1.34]	0.18 [95% CI: 0.00-0.54]
Schneck et al. (Germany and France)	Multicenter retrospective observational	2008	35	Authors report 18% gross mortality rate	Authors report 18% gross mortality rate
Zhu et al. (China)	Single-center retrospective observational	2012	55	0.93 [95% CI: 0.11-1.75]	0.54 [95% CI: 0.07-1.01]
Yang et al. (China)	Single-center retrospective observational	2009	65	1.16 [95% CI: 0.56-2.13]	0.85 [95% CI: 0.18-2.5]
Chen et al. (China)	Single-center retrospective observational	2010	82	0.48 [95% CI: 0.08-1.92]	0.57 [95% CI: 0.32-1.91]

diverse characteristics of the patients, the different corticoids used, and systemic dosages and duration of the treatments it is only possible to assign their findings a hypothetical status that needs to be confirmed by further randomized and controlled research.

Our patient's case is compliant with the treatment guidelines and serves as additional experience describing that the treatment combining corticosteroids + IVIG caused a favorable response and the patient's discharge.

CONCLUSION

Our patient's response to the combination of corticosteroids and IVIG was favorable. However, since this is a case report, the function this combination of drugs has must be further researched.

Conflicts of interest

The authors declare no conflicts of interest.

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