GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(CASE REPORT)

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Early high-dose corticosteroid treatment on carbamazepine-induced toxic epidermal necrolysis: A case report

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GSC Biological and Pharmaceutical Sciences, 2024, 28(02), 270–277

Publication history: Received on 14 July 2024; revised on 21 August 2024; accepted on 24 August 2024

Article DOI: https://doi.org/10.30574/gscbps.2024.28.2.0309

Abstract

Introduction: Toxic Epidermal Necrolysis (TEN) is a severe and life-threatening allergic reaction. Although there is ongoing debate, some guidelines suggest that early administration of high-dose systemic corticosteroids may be beneficial.

Case Illustration: A 42-year-old man was hospitalized with painful, multiple erythematous patches that initially appeared in the chest area and then spread to the entire head, hands, and legs. On the third day, the lesions had spread and developed into blisters in multiple areas. The patient had a known history of food allergies to eggs and chicken, as well as a history of stroke, with ongoing therapy for the past eight years. However, about a week ago, the patient was introduced to a new medication, Carbamazepine. Before the skin lesions appeared, the patient had been consuming the drug for 5 days. After diagnosing with TEN, treatment plan included intravenous methylprednisolone 500 mg/24 hours for 3 days, followed by tapering off, diltiazem 100 mg b.i.d., calcitriol 0.5 mg o.d., and a combination of topical therapy, including dexamethasone 0.25%, vaseline album, mupirocin 2%, triamcinolone acetate, and momethasone furoate. After the thirteenth day of treatment, the patient's entire skin had peeled off, and only hypopigmented patches remained. The patient was discharged and sent home, and a follow-up was carried out a month later and was able to carry out his normal daily activities.

Conclusion: Comprehensive management, starting with drug withdrawal, supportive therapy, adequate wound medication, and early administration of high-dose systemic steroids, can be a life-saving and low-cost therapy in resource-constrained settings.

Keywords: Anticonvulsants; Carbamazepine; Corticosteroid; Toxic Epidermal Necrolysis

1. Introduction

Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are serious and potentially life-threatening conditions that affect the skin and mucous membranes. These conditions are characterized by blister formation and skin separation [1]. Numerous studies have shown individuals often experience non-specific symptoms for one to seven days before the onset of TEN and SJS. Discomfort, trouble swallowing (dysphagia), and eye irritation (ocular pruritus) are possible symptoms. After experiencing these initial symptoms, individuals may experience a high temperature, respiratory problems, and rashes that include blisters or lesions causing the mucous membranes to become inflamed. Skin lesions are frequently preceded by a few days of oral and vaginal dryness and inflammation. The mucous membranes of the mouth, eyes, and genitalia gradually deteriorate and exhibit erythema, erosion, and

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pseudomembrane development. In patients with SJS/TEN, bullous lesions on the skin and mucous membranes can develop rapidly, often within 12 hours, and these patients are typically critically ill [2].

SJS, TEN, and SJS-TEN overlap syndrome are all included in SJS/TEN. The polymorphic lesions that cover less than 10%, 10% to 30%, or more than 30% of the body's surface area (BSA) characterize each of the three distinct forms of the same disease. SJS and TEN have different incidence rates such as 1.2 to 6/million patient-years for SJS and 0.4–1.2/million patient-years for TEN, respectively, and the death rate for TEN is three times higher than that of SJS. High morbidity and mortality are characteristics of the SJS/TEN illness spectrum. According to earlier investigations, the mortality rates for SJS and TEN include 19.4% to 29% and 14.8% to 48% respectively. Age over 40, cancer, BSA involvement greater than 10%, heart rate greater than 120 beats per minute, serum bicarbonate levels less than 20 mmol/L, serum urea nitrogen levels more than 10 mmol/L, serum glucose levels more than 14 mmol/L, and chronic kidney disease are known risk factors [3,4].

Comprehensive symptomatic and supportive care is crucial in all cases, ideally provided in a burn unit. The use of specific treatments, such as intravenous immunoglobulin (IVIG) or systemic corticosteroids, remains a subject of debate. While some studies have showed that corticosteroids lengthen hospital stays and increase mortality, others have showed that they can be a life-saving treatment if administered early in the course of the disease and in high dosages. While some investigations found worse outcomes, several studies report better outcomes after IVIG treatment, although one significant barrier is the expense of IVIG [5].

2. Case Presentation

A 42-year-old man was referred to the emergency department after many erythematous rashes gradually appeared on the chest over the past two days. The examination showed that the head, arms, and legs were covered in rashes, itchy, uncomfortable, and visible rashes were present. While some of the rashes in the oral area turned into crusts, others became blisters. Subsequently, the rashes and the fever started at the same time, and despite acknowledging a history of allergies to chicken and eggs, this was the first time the patient had ever experienced these symptoms. In addition, the patient had a history of hypertension and recurrent stroke, both of which had been treated with medication. Prior to admission, the patient had recently started carbamazepine treatment.

Vital signs include temperature of 36 °C, heart rate of 98 beats per minute, respiration rate of 20 beats per minute, and blood pressure of 146/89 mmHg. Examinations of liver and kidney function, and hematopoietic yielded normal results. Following the establishment of the diagnosis of TEN based on clinical criteria, the patient was given the following medication as intravenous methylprednisolone 500 mg/day for three days, then the dose was reduced by 10% to 20% every 3–5 days until the drug treatment was discontinued, diltiazem 100 mg/day, Paracetamol 1 gram t.i.d., cetirizine 10 mg b.i.d., calcitriol 0.5 mg/day, and a combination of topical therapy consisting of Desoxymethasone 0.25%, Vaseline album, Mupirocin 2%, Triamcinolone Acetate, and Mometasone Furoate.

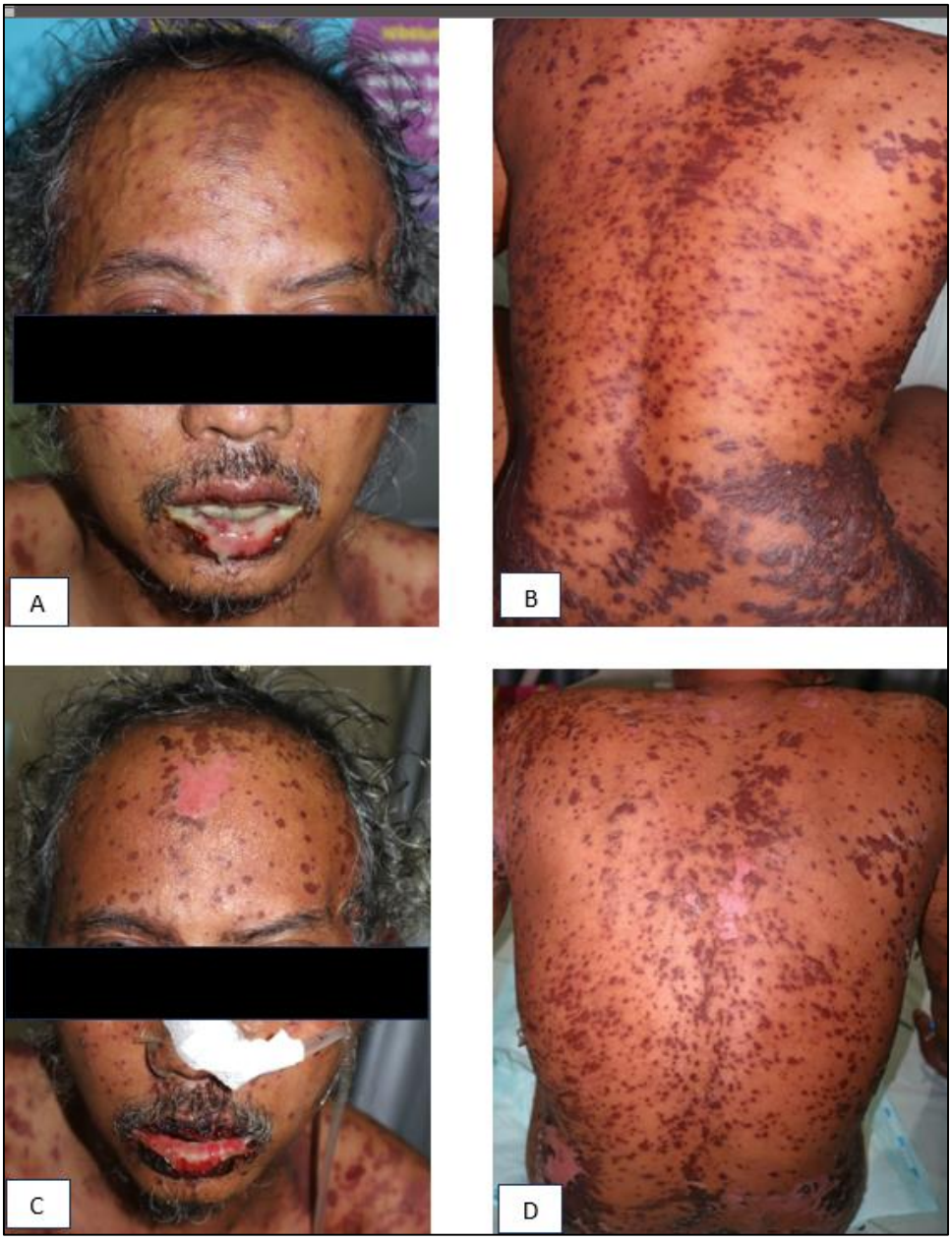
After thirteen days of treatment, the condition improved, and the patient's skin fully peeled off, leaving behind non-palpable patches of hypopigmented skin. The dose of methylprednisolone was then reduced to 8 mg b.i.d., and a combination of desoximetasone 0.25%, vaseline album, and mometasone furoate 0.1% was prescribed by the dermatologist for topical application. The patient was then discharged and scheduled for monthly monitoring. A month after hospitalization, the rash completely resolved, and the hypopigmented patches diminished. Once the patient resumed normal activities, the rate of methylprednisolone was reduced to 4 mg b.i.d. and then stopped.

Table 1 Results of laboratory and immunology investigations in the patient at presentation

Parameter	**Value**				
	1st day	**5th day**	**10th day**	**13th day**	**43rd day**
Hemoglobin (g/dL)	14.1	13.7	11.9	14.7	13.1
Haematocryte (%)	41	39	34	44	38
Platelets ($10^3/\mu L$)	203	382	338	327	344
WBC ($10^3/\mu L$)	8.0	5.1	10.9	9.8	7.2
Erythrocyte ($10^6/\mu L$)	4.53	4.57	3.90	4.97	4.53

MCV (/µm)	89.5	86.1	86.9	88.3	84.5
MCH (pg)	31.0	30.1	30.6	29.6	28.9
MCHC (g/dl)	34.7	34.9	35.2	33.5	34.2
RDW (%)	13.6	13.4	13.5	13.9	13.1
MPV (fl)	8.1	9.5	8.9	9.3	8.4
PDW (%)	15				8
Eosinophils (%)	0.70	0.00	0.05	0.51	1.50
Basophils (%)	0.10	0.00	0.13	0.36	0.40
Neutrophils (%)	84.00	58.00	80.40	75.80	61.70
Lymphocytes (%)	10.60	30.00	11.10	16.80	27.70
Monocytes (%)	4.60	12.00	6.10	5.81	8.70
PT (second)	12.8				
aPTT (second)	28.9				
INR	0.920				
Creatinin (mg/dL)	1.3	0.9		1.0	
Ureum (mg/dl)	36	59		41	
Glucose (mg/dL)	120				
Albumin (mg/dL)	4.1				
ALT (u/L)	26				
AST (u/L)	31				
Bilirubin (mg/dl)	0.68				
Urinalysis					
Color	Light yellow				
Appearance	Clear				
pH	6.5				
Specific gravity	1.017				
Leukocyte esterase	–				
Nitrit	–				
Albumin	–				
Glucose	–				
Keaton	–				
Urobilinogen	–				
Bilirubin	–				
Blood	–				
Casts	–				
Cell/epithelium	–				
Bacteria	–				
HCO3 (mmol/L)	24				

Sodium (mmol/L)	126	130	130	135	
Potassium (mmol/L)	4.4	4.7	3.8	4.0	
Calcium (mmol/L)	1.17	1.21	1.14	1.20	
HBsAg	Non-reactive				
Anti-HCV	Non-reactive				



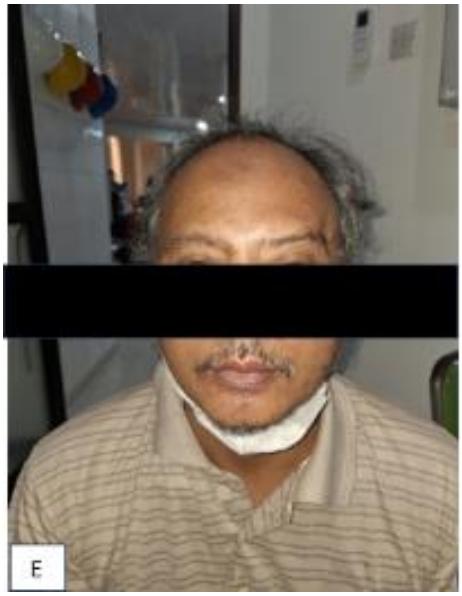


Figure 1 (A) & (B) 1st day of treatment; (C) & (D) 5rd day of treatment; (E) 30th day of treatment

3. Discussion

A 42-year-old male with a history of stroke and hypertension was brought to the emergency room five days after starting carbamazepine, presenting with extensive erythematous rashes covering nearly the entire body. The diagnosis of TEN was subsequently carried out.

Vaccines, medications, infections, and even idiopathic illnesses can cause TEN, although the most frequent reason is by far medication reactions. TEN has been linked to several drugs, including antiepileptics (barbiturate, carbamazepine, phenytoin, valproate, and lamotrigine), antibiotics (sulfonamides, chloramphenicol, penicillins, and quinolones). Additionally, non-steroidal anti-inflammatory drugs (NSAID), specifically oxybutazone and piroxicam, antiviral drugs (oseltamivir and abacavir), and allopurinol. Lamotrigine, carbamazepine, phenytoin, nevirapine, phenobarbital, sulfonamide, sulfasalazine, allopurinol, and oxicam-NSAIDs are the medications most likely to cause TEN, according to the 2008 Euro-SCAR study. The majority of instances manifest within the first four weeks of starting medication [6].

Carbamazepine is known to induce TEN and SJS, particularly in individuals who are immunologically and genetically susceptible. Symptoms typically manifest 4 to 21 days after exposure. Individuals who possess the HLA-B*15:02 allele, which is a variation of HLA-B, are regarded as genetically vulnerable. It is more common in Asian populations (Indians, Han Chinese, Thais, and Malays), and its association with carbamazepine-induced SJS/TEN is well known [7].

Dysregulation of cellular immunity results in the development of drug-induced SJS/TEN. Natural killer (NK) cells and cytotoxic T lymphocytes (CTLs) are involved in this process. These immune cells may identify medications that have not been altered, substances that are illicit, or metabolites. They accomplish this through interacting with keratinocytes' human leukocyte antigen (HLA) class I molecules. The release of many cytotoxic signals, such as Fas/Fas ligand, perforin/granzyme B, and granulysin, is triggered by the activation of immune cells. These signals aid in the keratinocytes' death and the skin's and mucous membranes' subsequent separation [8-10].

Patients' lives are in danger not just from SJS and TEN, which impact numerous systems and necessitate a multidisciplinary response, but also from their consequences. Early diagnosis and intervention are essential, and providing patients with appropriate counseling always helps to prevent life-threatening situations [7].

The patient was then diagnosed with TEN and treated with a combination of topical therapy consisting of desoximetasone 0.25%, vaseline album, mupirocin 2%, triamcinolone acetate, and momethasone furoate. Additionally, the patient received intravenous methylprednisolone 500 mg/24 hours for three days, followed by tapering off; the dose was reduced by 10% to 20% every three to five days until the drug treatment was discontinued, diltiazem 100 mg b.i.d. and calcitriol 0.5 mg o.d.

The first step in the complex management of SJS/TEN is identifying and eliminating the causal cause. Since most instances arise between 4 days and 4 weeks of taking a medication, a complete history is important in determining the causal agent. Symptoms usually appear within 8 weeks of commencing therapy. A study by Garcia-Doval et al. showed that a better prognosis is linked to an earlier drug cessation. Moreover, studies have shown that patients who take medications with extended half-lives and develop TEN have a higher chance of dying. It is essential to maintain a tight aseptic environment, appropriate fluid-electrolyte balance, and an ambient body temperature of 31°–32°C. Debridement and dressing changes might be considered [3,11]. Given that carbamazepine was identified as the likely cause in this case, its use was discontinued.

As prognostication can direct management and placement in an intensive care or burn unit, it is also a crucial step in the management of SJS/TEN. The most popular method for assessing prognosis in SJS/TEN patients is the severity-of-illness score for Toxic Epidermal Necrolysis (SCORTEN) scale. The usefulness of this tool has been validated by numerous investigations [11]. With a body surface area (BSA) detachment of more than 10% and an age under 40, the patient's SCORTEN score of 2 showed an expected mortality rate of 12.1%. Patients with these factors are managed in conventional wards with close monitoring.

Certain therapies that involve the immune system and cytotoxic processes are still debatable. A recent systematic study found that corticosteroids are effective for SJS-NET. The theory behind the administration of high dosages of IVIG is that an anti-Fas action stops Fas-L from attaching to the Fas receptor, which stops apoptosis. However, other studies advise against using IVIG because of potential difficulties, and new investigation shows that Fas may not be the only factor contributing to the SSJ-NET pathway [12].

The 2016 UK guidelines for the management of SJS/TEN determined that multimodal supportive care and drug withdrawal should take precedence over systemic treatment due to the lack of evidence supporting the benefits of systemic treatment. Despite this, systemic corticosteroid therapy was recommended as the first-line treatment for SJS/TEN in the 2016 Japanese regulations. Clinicians supplement the standard corticosteroid treatment with IVIG or PP if the patient is refractory to systemic corticosteroid alone or if the clinical adverse effects are severe [1,13].

For many years, Indians have been using systemic steroids to treat the illness. The majority of cases are ascribed to corticosteroid-sensitive hypersensitivity phenomena known as antibody-dependent cell-mediated cytotoxicity. Earlier steroid treatment was linked to better results. Optimal outcomes are achieved by starting oral steroids 24–48 hours after the disease onset and tapering them over the next 7–10 days. It is recommended to administer 8–16 mg of dexamethasone daily, though higher doses may be necessary. If recovery is inadequate, the dose can be increased by 4 mg of dexamethasone the following day, with a reassessment of treatment plan. However, no randomized controlled studies have proven the effectiveness of steroids. It has been discovered that methylprednisolone pulse treatment (MPT) lowers pro-inflammatory cytokine levels, including interferon-gamma, tumor necrosis factor (TNF)-α, and interleukin-6 (IL-6), and increases the survival rate in TEN patients. In order to comprehend MPT's involvement in TEN, blinded experiments had to be conducted. Conversely, several studies have shown a link between the usage of steroids and longer hospital stays, and this caused the rate of SJS-TEN-related infectious complications to rise. Accordingly, there is debate concerning the efficacy of systemic corticosteroids in treatment of TEN [3]. However, early systemic corticosteroids, either by themselves or in conjunction with cyclosporin, are advised as the first-line treatment for SJS/TEN according to Japanese recommendations [14]. Subsequently, administering methylprednisolone intravenously as a steroid produced positive outcomes for this patient.

The following are potential advantages of using systemic steroids in treatment of SJS/TEN: In order to stimulate transcription of the corresponding genes, steroids attach to glucocorticoid receptors in the cytoplasm and operate on the promoter regions of target genes. Furthermore, steroids decrease the transcription of inflammatory cytokines by binding to transcription factors such as AP-1 and NF-κB [15]. Contradictory information is now available on the benefits of corticosteroids for people with SJS/TEN. High-dose steroid benefits must be weighed against possible risks, which include gastrointestinal (GI) bleeding, prolonged wound healing that increases the risk of infection, and higher mortality [16]. Early systemic glucocorticoid administration at medium and high doses reduces mortality, successfully treats SJS/TEN, and has minimal impact on underlying illnesses. Hormone therapy carries a small risk of associated complications, but it is safe because patients recover quickly [17].

Japanese treatment guidelines state that, as long as infections are adequately controlled, pulse corticosteroid therapy should be one of the first treatments for SJS/TEN, although the majority of the evidence supporting the beneficial effects of systemic corticosteroids was obtained from outdated or single-arm studies that did not compare treatments [14].

4. **Conclusion**

In conclusion, the most important components of managing SJS/TEN are supportive care, multidisciplinary management, early diagnosis, and stopping the offending medication. There is currently no established gold standard for the management of SJS/TEN. Systemic corticosteroids may be a cheap, life-saving treatment in environments with limited resources. In this patient, early systemic corticosteroid administration produced positive results.

Compliance with ethical standards

Acknowledgments

The authors are grateful to Fata Prihatsari for her indispensable assistance in manuscript preparation.

Disclosure of conflict of interest

The authors report no conflicts of interest in this work.

Statement of ethical approval

The present research work does not contain any studies performed on animals/human subjects by any of the authors.

Statement of informed consent

Informed consent was obtained from the patient.

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