International Journal of Contemporary Pediatrics
Beg S et al. Int J Contemp Pediatr. 2024 Sep;11(9):1320-1323
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20242351

Case Report

Toxic epidermal necrolysis associated with phenytoin in a 6-year-old child: a case report

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Received: 05 July 2024
Revised: 03 August 2024
Accepted: 07 August 2024

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ABSTRACT

Toxic epidermal necrolysis (TEN) is a severe mucocutaneous syndrome often triggered by adverse drug reactions, characterized by extensive skin detachment**.** We present a rare case of a 6-year-old boy developing TEN associated with phenytoin use for post-bacterial meningitis seizures. The patient initially presented with fever, epigastric pain, oral ulcers, and skin rashes, later progressing to extensive skin peeling. Phenytoin was promptly discontinued. The SCORTEN score indicated a mortality rate of 35.3%. Informed consent was taken by parents. The patient received supportive care, including IV fluids, antibiotics, and topical treatments. The patient exhibited a positive response to early initiation of systemic steroids (Dexamethasone) and cyclosporine, leading to a successful recovery within 15 days. This case underscores the importance of recognizing and managing drug induced TEN promptly, especially in pediatric populations, and highlights potential immunopathologic pathways and genetic predispositions to the condition.

Keywords: TEN, Phenytoin, Cyclosporine

INTRODUCTION

Toxic epidermal necrolysis (TEN) is a potentially life-threatening acute mucocutaneous syndrome characterized by blistering and peeling of the skin. It typically occurs due to inappropriate immune reactions to certain drugs, leading to keratinocyte necrosis with the separation of the epidermis from the underlying dermis. Prompt recognition of cases and discontinuation of the offending drug constitute the mainstay of treatment. Steven-Johnson syndrome (SJS) exhibits the same disease process and is considered part of the same spectrum of drug-induced epidermolysis. The primary distinction lies in the extent of skin detachment, with TEN involving more than 30% of the total body surface area (BSA), while SJS affects less than 10%.[1] Detachments covering 10-30% of the BSA fall within the overlap of SJS/TEN. The mortality rate for SJS-TEN ranges from 10% to 34%. The mean adjusted mortality rates are 4.8% for SJS,19.4% for SJS/TEN, and 14.8% for TEN.[2]

The incidence of SJS is 1.2 to 6 per million patient-years, and for TEN, it is 0.4 to 1.2 per million patient-years. There is a female sex predilection, with a female-to-male ratio of 1.5 to 1, and an approximately equal incidence in children.[3,4] TEN is triggered by medications or upper respiratory infections in 74% to 94% of cases. In children, medications are the most common precipitants of SJS/TEN. Common culprit medications include sulfa antibiotics, phenobarbital, lamotrigine, carbamazepine, and NSAIDs. Adverse effects typically present within the first 8 weeks after initiation, with a higher risk at higher doses and with rapid introduction. In certain study populations, there is a genetic association with HLA-B alleles for lamotrigine, phenytoin, carbamazepine, and cold medicine-induced SJS. The second most frequent precipitant is infection, with the main offenders including

Mycoplasma pneumoniae, cytomegalovirus, herpes virus, and hepatitis A. Other predisposing conditions include HIV, malignancy, SLE, radiotherapy, collagen vascular disease, UV light, genetics, and underlying immunologic disease.[4]

CASE REPORT

A 6-year-old boy, a follow-up case of bacterial meningitis with seizures on anti-epileptic drug (phenytoin), presented to our emergency department with complaints of fever and epigastric pain for 3 days. He also reported oral ulcers and itchy rashes over the face and hands for 2 days. The fever was high-grade with chills and continuous in nature. Lesions initially appeared on the face and bilateral upper limbs, coupled with oral ulcers and facial puffiness. He had no known history of drug and food allergies. The patient had achieved all developmental milestones according to his age and was fully immunized.

Upon physical examination, the patient was conscious, irritable, and hemodynamically stable, with good nutritional status. Growth was between 0 to-1SD for both weight for age and height for age. Vitals were as follows: HR-126 bpm, RR-26/min, temp-101.6°F, BP-100/72 mmHg, RBS-83 mg/dl, and oxygen saturation was 98% on room air. No signs of dehydration were observed, and pallor, clubbing, lymphadenopathy, and edema were absent. Skin and mucous membrane examination revealed multiple oral ulcerations with lower lip swelling, widespread hyperpigmented maculopapular eruptions with an erythematous base on the upper half of the body. The lesions showed crusting and skin peeling with sparing of the scalp. Initially, lesions involved less than 10% of BSA, and a clinical diagnosis of SJS was made. Phenytoin was identified as the culprit and discontinued immediately. Examinations of the rest of the systems were within normal limits.

Management and outcome

All relevant routine investigations were initiated, and conservative management, along with IV fluids and IV antibiotics (Ceftriaxone and Amoxiclav), was started. The patient was kept in isolation. Blood reports revealed elevated SGOT (57.9 U/L) and SGPT (106 U/L), in addition to hyponatremia (127 mmol/L); the remaining hematological values were within normal ranges. Sloughed skin was cleaned with regular saline-soaked gauges with full aseptic precautions and treated with mupirocin and paraffin gauze. Frequent mouthwashes with antibiotic solution were advised to treat oral lesions. Topical eye drops and ocular lubricant gel were advised prophylactically.

Over the next 48 hours of hospitalization, skin lesions further evolved over the rest of the body with eruptions and bullous lesions followed by sloughing out of the skin. Nikolsky's sign was positive. The patient then developed diffuse skin peeling and epidermal detachment encompassing more than 80% of the BSA, and the diagnosis was revised to TEN. An opinion from the dermatology department was sought, and they clinically confirmed the diagnosis of TEN. Skin biopsy could not be done due to caregiver refusal.

The SCORTEN score of the patient was 3, suggesting a mortality rate of 35.3%. There was a continuous fever along with sloughing, crusting, and erosion of the skin. Due to persistent high-grade fever, repeat blood investigations were sent, revealing thrombocytopenia. Urine culture was positive for *E. coli* (sensitive to levofloxacin, gentamycin, ceftriaxone), and blood culture was sterile. On day 3, dexamethasone (@ dose 0.5 mg/kg/day), cyclosporine (@ dose 5 mg/kg/day), azithromycin, and clindamycin were added. Initially, feeding was started via Ryle's tube, which was later converted to oral feeds.

Recovery was sluggish initially, but the patient made significant improvement over the next 72 hours. Dexamethasone was gradually reduced and then discontinued after 5 days, but cyclosporine continued for 10 days and then stopped. The patient was successfully discharged on day 15 with full recovery (Figure 1).

Figure 1 (A and B): Involvement of BSA with erosion and ulcer on day 7 and on day 15.

DISCUSSION

The pathophysiology of TEN has not been fully elucidated; however, various theories have received wide acceptance. The widespread epidermolysis and blistering of TEN results from keratinocyte apoptosis.[5] However, the number of inflammatory T cells in the skin of patients with TEN is variable and perhaps too low to explain the widespread destruction.[6]

There is evidence supporting several immunopathologic pathways leading to keratinocyte apoptosis in TEN, including the following: Fas ligand activation on keratinocyte membranes leading to death receptor-mediated apoptosis.[7] Release of destructive proteins (perforin and granzyme B) from cytotoxic T lymphocytes

generated from an interaction with cells expressing MHC class I.[8] Overproduction of T cell-and/or macrophage-derived cytokines (interferon-γ, tumor necrosis factor-α, and various interleukins).[9,10] Drug-induced secretion of granulysin from CTLs, natural killer cells, and natural killer T cells.[11]

Among antiepileptics, phenytoin and carbamazepine are reported as the most common culprits.[12] The food and drug administration (FDA) is currently investigating the potential link between the HLA-B 1502 allele and phenytoin-induced SJS in Asian patients.[13] This suggests a potential genetic predisposition to SJS/TEN in specific populations, emphasizing the importance of further research to understand the role of genetic factors in susceptibility to this condition.[14]

TEN is a clinical diagnosis that is confirmed by early histological analysis of the affected skin. There are no specific blood tests to diagnose TEN. However, a basic screen including (CBC, ESR, coagulation studies, urea and electrolytes, and LFT) is essential to plan supportive treatment, detect organ failure, and assess the overall prognosis. Anemia and lymphopenia are common. However, the presence of neutropenia is an unfavorable prognostic factor.[15]

The score of TEN (SCORTEN scale) is a tool to assess the severity of illness and to predict the mortality rate. It contains 7 independent variables assessed in the first 24 hours of presentation to the hospital, and it gives an indication of the mortality rate (Table 1).

Table 1: SCORTEN risk factors, scoring and mortality rates

Risk factors	Score 0	Score 1
Age (in years)	<40	>40
Associated malignancy	No	Yes
Heart rate (beats/min)	<120	>120
Serum BUN (mg/dl)	<27	>27
Detached or compromised body surface	<10%	>10%
Serum bicarbonate (mEq/l)	>20	<20
Serum glucose (mg/dl)	<250	>250
Number of risk factors	**Mortality rate**	
0-1	3.2%	
2	12.1%	
3	35.3%	
4	58.3%	
≥5	>90%	

The SCORTEN score of our patient was 3 (Age-6 years, no associated malignancy, HR-126, serum BUN-18.95 mg/dl, compromised body surface >10%, serum bicarbonate 14.9 mEql/L, and serum glucose-83 mg/dl).

Covering any exposed skin with sterile cloths embedded with paraffin or saline is advised. According to past research, systemic steroids, antibiotics, and adjunct therapies were used to treat the majority of TEN patients.[16] Etanercept and cyclosporine have been shown to be effective, as suggested by some studies.[17,18] Careful handling, nutritional support, aggressive fluid and electrolyte control, and pain management are all required. Our patient underwent all the aforementioned precautions and medications. Dexamethasone and cyclosporine were given, helping to reduce the healing time as the treatment was initiated early in the course of the disease. The patient's full recovery was probably attributed to the prompt and successful management of inflammation with systemic steroid therapy and the appropriate topical care along with cyclosporine and fluid and sepsis management.

In a retrospective study of 55 cases, 10 children had a recurrence between 2 months and 7 years after the first episode, 3 had multiple recurrences, and 1 died. These findings may suggest a long-lasting vulnerability and genetic predisposition for SJS/TEN.[4] Hence, we will keep a close follow-up on the patient for future complications.

CONCLUSION

This case highlights the rare occurrence of TEN associated with phenytoin use in a 6-year-old boy. Our patient developed TEN approximately 3 weeks after initiating phenytoin therapy. We present this case due to its uncommon nature, extensive skin involvement, and the positive response to cyclosporin and supportive therapy. Early recognition, prompt discontinuation of the offending drug, and aggressive management, including systemic steroids and cyclosporine, played a crucial role in the patient's successful recovery. The case underscores the importance of vigilance in monitoring adverse drug reactions, particularly in pediatric populations. The study also provides insights into the immunopathologic pathways leading to TEN and emphasizes the need for further research on genetic predispositions to this condition.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Beg S, Qureshi J, Abbas J, Rahman K. Toxic epidermal necrolysis associated with phenytoin in a 6-year-old child: a case report. Int J Contemp Pediatr 2024;11:1320-3.