

CLINICAL EXPERIENCE

Successful treatment of a female pediatric patient with carbamazepine-induced toxic epidermal necrolysis: Active wound care and systemic therapy

Yuan Liang | Yan Chu | Zigang Xu | Lin Ma

Department of Dermatology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

Correspondence

Lin Ma, Department of Dermatology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China.
Email: bch_maleen@aliyun.com

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ABSTRACT

We describe a 6-year-old female patient who developed carbamazepine-associated toxic epidermal necrolysis. With active wound care, systemic methylprednisolone and intravenous immunoglobulin pulse therapies and multidisciplinary supportive care, the patient improved significantly. This case indicates that improving the management of Stevens-Johnson syndrome/Toxic epidermal necrolysis patients requires attention not only to the process of wound management but also to individual supportive care and active therapeutic intervention. Only through this can standardized care, including muco-cutaneous and visceral wound care, be delivered to provide high-quality care with improved clinical prognosis and quality of life.

KEYWORDS

Drug reaction, Wound care, Toxic epidermal necrolysis

METHODS AND RESULTS

A 6-year-old female was transferred to the dermatology department of Beijing Children's Hospital with a 6-day history of a progressive rash, fever, malaise, and conjunctivitis. The patient had been healthy until 2 weeks before admission, when carbamazepine was prescribed to treat a headache. Six days before admission, a rash appeared on the patient's neck and trunk, the body temperature rising to 39°C. The rash rapidly progressed, forming extensive confluent dusky macules, patches, and necrosis eruption with blistering, and body temperature

increased to 41°C. A diagnosis of drug eruption was made. Carbamazepine treatment was discontinued and methylprednisolone administered intravenously (1.5mg/kg body weight). After 3 days, the rash spread to involve most of the body, with increased vesicles and bullae and the appearance of oral, vulvar, and ocular lesions. The patient was admitted to the dermatology unit for suspected carbamazepine-induced toxic epidermal necrolysis (TEN).

On examination, the patient displayed fever (38.9°C) and coalescing violaceous macules with multiple flaccid vesicles and bullae involving the face, trunk, back,

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extremities, feet, and hands. Nikolsky's sign (ready removal of the epidermis with slight tangential pressure) was positive, involving approximately 70% of the total body surface, while epidermal detachment was >45%. Erosions with hemorrhagic crusts developed on the lips. Oral, anal, and vulvar ulcerations and bilateral pseudo-membranous conjunctivitis were present. The physical examination was normal. The patient was clinically diagnosed as having TEN, which was identified from the pathology of a skin biopsy.

Over the following 48 hours, the patient developed increased pain in the mouth with dysphagia, pain on urination, and additional blistering skin lesions, sloughing of the skin and oral mucosa occurred (Figure 1), full-thickness epidermis peeled off the hands in sheets (Figure 2), and megalgia made the patient agitated. On the third day after hospitalization, the condition continued to deteriorate, the patient displaying high fever, tachypnea, tachycardia, oliguria, and mild hypotension, the extent of epidermal skin detachment increased, involving the trunk, back, arms, and hands, and sloughing of oral and respiratory mucosa worsened. The patient complained of severe pain in the skin, had dyspnea, and became increasingly dysphoric. Later that day, the patient was transferred to the intensive care unit (ICU). On admission to the ICU, body temperature was 40°C, the pulse 211 beats/minute, the respiratory rate 35 breaths/minute, and the blood pressure 146/67mm Hg. Multiple mucosa erosions, ulcerations, severe hemorrhagic crusting involving oral, nasal, vulvar, and anal mucosa, and pseudo-membranous conjunctivitis occurred. Breathing was rough and wheezy, while heart sounds were low and muffled. Bowel sounds were absent. The patient had extensive sloughing from the face, trunk, hands, and feet, with a denuded, second-degree burn appearance, and intact bullae covered much of the skin of the arms and legs. In total, 93% of the epidermis was involved, only the scalp being spared. Because multiple-organ dysfunction was present, involving the lungs, heart, liver, and gastrointestinal tract, nasal continuous positive airway pressure (NCPAP) treatment was initiated, whereby a double-cavity central venous catheter was inserted and a normal saline infusion started to maintain fluid and achieve electrolyte repletion. Methylprednisolone (20 mg/kg body weight), midazolam, morphine, azithromycin, vancomycin, cedilanid, and dopamine were administered intravenously. To the intravenous therapy were added 5% albumin solution and fresh frozen plasma. Total parenteral nutrition was initiated.

The wounds were blistered and produced moderate amounts of clear drainage fluid. Bland petroleum dressings were applied to cover the raw exposed dermis, while the denuded hands were covered with the patient's own detached epidermis in a glove-like manner. Chlortetracycline eye ointment was applied on the mucosal surfaces of the perianal region and vaginal labia and lips



FIGURE 1 Epidermal sloughing exposes bare dermis. Coalescing violaceous macules can also be observed. There is widespread involvement of the face and upper trunk. Erosions with hemorrhagic crusts on the lips can also be seen.



FIGURE 2 Extensive necrolysis results in the detachment of sheets of epidermis and exposure of large areas of denuded dermis of one hand.

to avoid synechia formation. Advice on ocular care was obtained by consulting the ophthalmology department. Treatment involved daily removal of mucosal strands and adhesions between the lids and between the lids and the globe and the application of topical antimicrobial drops to prevent infection and topical corticosteroids to reduce inflammation and scarring.

On the fourth hospitalization day, body temperature was normal and the rash did not deteriorate. By day 6, oxygen saturation was maintained at 95% after the NCPAP treatment was terminated. On the eighth hospitalization day, the patient could eat some rice soup and noodles and parental nutrition was stopped. There was strong resolution of the rash and pain medications were slowly discontinued. During the third week, the skin wounds began to heal, followed by gradual healing of ocular, oral, and anogenital mucosal lesions without scarring. The patient was discharged on the twentieth day after hospitalization. Four months after discharge, the patient had almost completely recovered, except for persisting variegated skin pigment changes (Figure 3). The skin of the hands and the fingernails



FIGURE 3 After 4 months, the patient's face had almost completely recovered, except for persisting variegated skin pigment changes.



FIGURE 4 After 4 months, the skin of the hands and the fingernails were essentially normal.

TABLE 1 Laboratory analyses of the patient

Laboratory analyses	D1 [*]	D2 [*]	¹ D3	² D6	D7	D9	D10	D12	D16
Sodium (mmol/L)			128.0	130.5		130.0			N
Albumin (g/L)			23	24		29			N
Aspartate aminotransferase (U/L)			671	N		N			N
Alanine aminotransferase (U/L)			51	N		N			N
Creatine kinase (U/L)			988	N		N			N
Creatine kinase-MB (U/L)			176	N		N			N
Blood glucose (mmol/L)			9.21	N		N			N
White cell count ($\times 10^9/L$)	8.0	7.0	5.0		15.1		14.7	10.5	9.7
Hemoglobin (g/L)	119	103	100				106	115	103
Platelet count ($\times 10^9/L$)	137		315				599	475	
C-reactive protein level (mg/L)	< 8		29		22			< 8	< 8
Chest radiograph			Patchy infiltrates				N		N

D1^{*} and D2^{*}: Hospital day 1 and day 2

¹D3: patient transferred from the department of dermatology to the intensive care unit

²D6: patient transferred from the intensive care unit to the department of dermatology

TABLE 2 Treatment options of the patient in detail

Medications	D-3 [*]	D1	D2	¹ D3	D4	D5	² D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16	D17	D18	D19
Dexamethasone (mg/d)		12.5	15	15						10	10	7.5	7.5	5	5	4	4	3	2	1
Methylprednisolone (mg/d)	40				560	560	560	270	60											
IVIg (g/d)		25	25	25																
Blood plasma (ml/d)					300	300		200												
Albumin (g/d)									10	10										
Azithromycin (mg/d)		250	250	250	250	250	250	250												
Vancomycin (mg/d)									500	500	500	500	500	500	500					
Midazolam				+	+	+	+													
Morphine				+	+	+														
Cedilanid				+	+	+	+													
Dopamine					+	+	+	+												

D-3^{*}: 3 days before admission

¹D3: patient transferred from the department of dermatology to the intensive care unit

²D6: patient transferred from the intensive care unit to the department of dermatology

Weight of the patient: 27kg

were essentially normal, having recovered under the protection of the patient's own detached epidermis (Figure 4). Laboratory analyses and medications are presented in detail in Tables 1 and 2.

DISCUSSION

SJS and TEN are drug-induced, immune-mediated blistering disorders, which are characterized by different extents of full-thickness epidermal necrosis and detachment of the mucosal and skin surfaces. According to the severity and extent of widespread epidermal detachment, SJS/TEN is classified as SJS, SJS/TEN overlap and TEN when involving <10%, 10–30%, and 30% of the body surface area, respectively. An important feature of SJS/TEN is the varying degrees of detachment of the epidermis and wound formation, leading to multiple organ dysfunction and infection. Generally, the more severe the epidermal necrolysis, the greater the mortality risk. Therefore, patients require early transfer to an intensive care or burn unit, where wound care can be optimally managed, fluid and electrolyte losses can be corrected, infection surveillance can be conducted, and multidisciplinary consultation can be performed.¹ A multicenter review found that delayed referral of TEN patients to a burn center was associated with a significantly lower survival rate.²

Several retrospective studies^{3,4} noted that a new epidermal layer developed after approximately 12–16 days, which was produced by the residual dermal appendages, provided the exposed dermis was maintained moist and viable. Before epidermal re-population proceeds, covering of the exfoliated skin to protect and preserve the dermis with an appropriate dressing or skin substitute is pivotal, because there are potential advantages, including accelerating dermal re-epithelialization, preventing transcutaneous fluid, protein, and heat loss from the wound, establishing a barrier to exogenous microbial colonization, and helping pain control. However, there is a lack of evidence for which wound covering to apply. Experiences from burn centers favor the use of a biological skin substitute, including porcine xenograft and cadaveric allograft,⁵ or biosynthetic dressings, for example, Biobrane, after aggressive cleansing and irrigation of the wound and debridement of any loose or imminently detached epidermis.⁶ Harr et al. stressed that wounds should be treated conservatively, without skin debridement, because the epidermis should remain as intact as possible to act as a natural biological dressing, aiding re-epithelialization of the exposed dermis and avoiding scar formation.⁷ We propose preserving any loose epidermis and blistered skin carefully to act as biological membranes as well as covering the exfoliated area with non-adhesive wound dressings, including silver nitrate, silver-containing synthetic material, and Vaseline gauze with a gauze overlay soaked in povidone iodine solution. Moreover,

when surface infection is present, topical antimicrobial agents are necessary, but topical sulfa-containing medications should be avoided. It is essential that such wounds are managed in a bacterial-controlled environment that minimizes the risk of sepsis.

Care of the mucosal surface is important to maintain normal functions, prevent infections, and avoid sequelae, including among others synechia, scarring, and dysfunction. Special mention should be made of ophthalmologic care management. Inflammation of the mucosal surfaces of the eye and eyelids may result in chemosis, conjunctivitis, pseudomembrane formation, and corneal and conjunctival epithelial sloughing, which are very painful and prone to desiccation, corneal ulceration, and local infection. It is imperative to consult an ophthalmologist for assistance with eye care in patients with SJS/TEN, to prevent or mitigate acute blinding, corneal and conjunctival scarring, symblepharon, severe dry eyes, and trichiasis.^{8,9} Acute management normally includes ocular-surface lubrication and conjunctival hygiene, for example, two-hourly application of a lubricant to prevent desiccation, daily saline irrigation, and removal of the conjunctival fornices with a glass rod to break down mucosal strands, to maintain ocular hygiene and prevent adhesion. Furthermore, the use of topical antimicrobial drops and corticosteroids to avoid infection and reduce inflammation and scarring is recommended.^{10,11} An amniotic membrane transplantation should be considered for patients with extensive loss of ocular surface epithelia as an effective means to temporarily protect the corneas.¹² In the presented patient, throughout the acute illness, oculoject gel (Hypo Fears Gel), levofloxacin eye drops, and tetracycline cortisone eye ointment was administered topically. The patient's eyes recovered completely without any complications.

Other mucosal management strategies include regular application of emollients and lubricants on the raw mucosal surfaces, including the lips, glans, perianal region, and between the vaginal labia, to keep these mucous membranes separated, of topical corticosteroids to reduce mucosal inflammation, and of topical analgesia and antiseptics to prevent severe pain and infections.^{5,13} In the presented patient, chlortetracycline eye ointment was applied on the lips and urogenital area as a lubricant, petrolatum gauze was placed between the vaginal labia, and a urethral catheter was worn during the acute period, and the patient healed without and sequela.

In addition, management of epithelium-lined structures related to visceral wounds is essentially supportive, treating infections as they occur, replacing fluid, protein, and blood losses, and supporting failing organ systems, while awaiting re-epithelialization of these inaccessible surfaces. Special attention should be paid on admission to the evaluation of any involvement of the airway. When a

related problem is present, the patient should be promptly transferred to an ICU or burn center, where mechanical ventilation is likely to be applied. When necessary, bronchoscopy should be undertaken to prevent atelectasis and airway obstruction by the removal of sloughed bronchial epithelium.¹⁰

In summary, improving the management of SJS/TEN patients requires attention both to the process of the wound management and to individual supportive care and active therapeutic interventions. Only through this can standardized care, including both muco-cutaneous and visceral wound care, be delivered to provide high-quality care with improved clinical prognosis and quality of life.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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