Toxic epidermal necrolysis in an 8-year-old girl successfully treated with cyclosporin A, intravenous immunoglobulin and plasma exchange

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Adv Dermatol Allergol 2018; XXXV (2): 217–221
DOI: https://doi.org/10.5114/ada.2018.75247

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are two rare, acute and severe dermatoses. They are characterized by different extent of epidermal necrolysis. Toxic epidermal necrolysis is associated with high mortality and it is one of the most severe disorders in dermatology. The most frequent and predominant triggers of TEN are drugs. The annual risk of TEN in the general population is calculated as 0.4–1.2 per million [1, 2]. The prevalence of this toxic reaction is unknown in children. It looks likely to be less frequent than in the adult population [1, 2]. The treatment of TEN is difficult and there is no optimal management established. Several therapy modalities have been proposed and analyzed [2]. We present a case of very severe TEN in an 8-year-old child successfully treated with combination therapy of cyclosporin A, intravenous immunoglobulin and plasma exchange. We would like also to draw attention to the difficulties in diagnosing TEN in such young patients.

An 8-year-old girl in a very serious condition was admitted to the Pediatric Intensive Care Unit (PICU).

Before admission she had been hospitalized in the Department of Infectious Diseases. On the basis of clinical manifestations (high fever, cough, photophobia, blistering skin eruptions on erythematous background) and laboratory tests (C-reactive protein 209 mg/dl, norm: > 5 mg/dl; procalcitonin 11.03, norm: 0.05, aspartate aminotransferase 106 IU/l, norm: 0–45 IU/l, alanine aminotransferase 141 IU/l, norm: 0–40) staphylococcal scalded skin syndrome was diagnosed and therapy with amoxicillin 90 mg/kg/day was initiated.

On admission to the PICU the girl was conscious with efficiency of circulatory and respiratory systems. Erythematous and blistering eruptions on the face, trunk

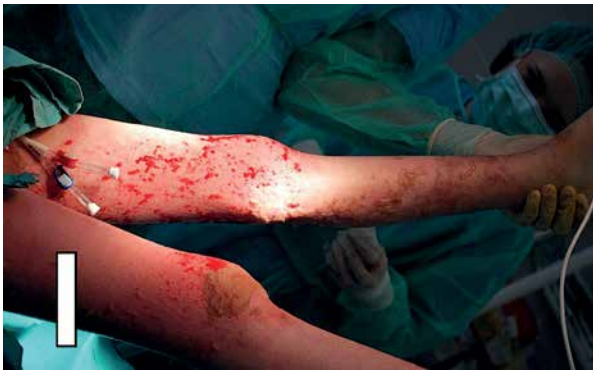

Figure 1. Skin lesion on the legs

Figure 2. Skin lesions on the face

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Received: 21.01.2017, **accepted:** 25.03.2017.

Table 1. Review of literature

Authors (year)	Number of patients in study	Pediatric patients with TEN	Involvement (% TBSA)	Mortality (%)	Treatment for the pediatric case
Adzick *et al.* (1985)	4	4	86 ±6	25	Adjuvant therapy
Ruiz-Maldonado (1985)	5	5	> 70	N/A	Adjuvant therapy
Heimbach *et al.* (1987)	19	3	75 ±5	16	Adjuvant therapy
Revuz *et al.* (1987)	87	N/A	39 ±3	25	Adjuvant therapy
Jones *et al.* (1989)	9	9	60 ±6.5	11	Adjuvant therapy
Taylor *et al.* (1989)	6	6	72.5	17	Adjuvant therapy and topical xenograft (pig skin)
Prendiville *et al.* (1989)	7	7	N/A	0	Adjuvant therapy
Murphy *et al.* (1997)	44	N/A	52 ±5	36	Adjuvant therapy
Szepietowski *et al.* (1997)	3	1	73	0	Cyclosporin A and corticosteroids
McGee *et al.* (1998)	36	N/A	63 ±5	31	Adjuvant therapy
Sheridan *et al.* (1999)	10	10	76 ±6	0	Adjuvant therapy
Magina *et al.* (2000)	1	1	95	0	IVIG and adjuvant therapy
Spies *et al.* (2001)	15	15	76 ±5	7	Adjuvant therapy and human allograft skin or xenograft
Inamo *et al.* (2002)	2	2	N/A	0	Adjuvant therapy and intravenous ulinastatin
John *et al.* (2002)	2	2	80	0	Adjuvant therapy and amniotic membrane transplantation
Lee *et al.* (2002)	1	1	N/A	0	Adjuvant therapy
Sheridan *et al.* (2002)	11	11	76 ±6	0	Adjuvant therapy
Uzum *et al.* (2002)	1	1	N/A	100	Adjuvant therapy
Metry *et al.* (2003)	8	8	N/A	0	IVIG and adjuvant therapy
Tristani-Firouzi *et al.* (2002)	8	8	67	0	IVIG and adjuvant therapy
Mayorga *et al.* (2003)	1	1	N/A	0	IVIG and adjuvant therapy
Beerhosrt *et al.* (2003)	1	1	N/A	100	Adjuvant therapy
Al-Mutairi *et al.* (2004)	12	4	57.5	100	IVIG and adjuvant therapy
Bygum *et al.* (2004)	1	1	50–60	0	IVIG, intravenous steroids and adjuvant therapy
Kalyoncu *et al.* (2004)	1	1	90	0	IVIG, granulocyte colony-stimulating factor and adjuvant therapy
Yildizdas *et al.* (2005)	1	1	30	0	Adjuvant therapy
Lam *et al.* (2005)	1	1	N/A	N/A	N/A
Ziora *et al.* (2005)	1	1	90	0	IVIG, intravenous corticosteroids and adjuvant therapy
Mangla *et al.* (2005)	10	10	66.7	0	IVIG and adjuvant therapy
Kobayashi *et al.* (2006)	1	1	40	0	IVIG, intravenous steroids, adjuvant therapy and amniotic membrane transplantation
Elkharaz *et al.* (2006)	7	5	N/A	0	IVIG, intravenous steroids and adjuvant therapy
Aihara *et al.* (2006)	1	1	> 30	0	Cyclosporin A, intravenous corticosteroids and adjuvant therapy
Chiossi *et al.* (2007)	1	1	N/A	0	IVIG, intravenous steroids and adjuvant therapy
Clayton *et al.* (2007)	1	1	80	0	Adjuvant therapy

Table 1. Cont.

Authors (year)	Number of patients in study	Pediatric patients with TEN	Involvement (% TBSA)	Mortality (%)	Treatment for the pediatric case
Gerdts *et al.* (2007)	19	3	N/A	21	Adjuvant therapy
Serati (2007)	1	1	90	0	IVIG and adjuvant therapy
Fine *et al.* (2008)	1	1	N/A	0	Systemic steroids and adjuvant therapy
Sevketoglu *et al.* (2009)	1	1	60	0	IVIG and adjuvant therapy
Mamishi *et al.* (2009)	7	3	N/A	0	IVIG and adjuvant therapy
Dillon *et al.* (2010)	6	3	> 50	0	IVIG, Versajet system with allograft and adjuvant therapy
Koh *et al.* (2010)	1	1	N/A	100	IVIG and adjuvant therapy
Yang *et al.* (2010)	36	6	N/A	0	IVIG, intravenous corticosteroids and adjuvant therapy
Ferrándiz-Pulido *et al.* (2011)	14	6	88	16	IVIG or/and intravenous steroids and adjuvant therapy
Bouziri *et al.* (2011)	1	1	40	0	Adjuvant therapy
Finkelstein *et al.* (2011)	55	5	N/A	20	IVIG, corticosteroids and adjuvant therapy
Norris *et al.* (2012)	1	1	60	0	Adjuvant therapy
Aihara *et al.* (2012)	1	1	70	0	Plasma exchange, intravenous steroids, IVIG and adjuvant therapy
Barvaliya *et al.* (2012)	1	1	66	100	Intravenous steroids and adjuvant therapy
Calka *et al.* (2013)	1	1	> 30	0	Intravenous steroids and adjuvant therapy
Scott-Lang *et al.* (2014)	1	1	N/A	0	IVIG, infliximab and adjuvant therapy
Kreft *et al.* (2014)	1	1	N/A	0	IVIG, infliximab and adjuvant therapy
Sethuraman *et al.* (2012)	20	8	N/A	37	Intravenous steroids in 7 patients, 1 patient received cyclosporin A, adjuvant therapy
El-Naggari *et al.* (2013)	1	1	60	0	IVIG and adjuvant therapy
Calvano *et al.* (2013)	1	1		0	IVIG, plasma exchange, intravenous steroids and adjuvant therapy
Gogia *et al.* (2013)	1	1	N/A	100	Adjuvant therapy
Atanasković-Marković (2013)	1	1	> 70	0	Intravenous corticosteroids, IVIG and adjuvant therapy
Yi *et al.* (2014)	1	1	90	0	IVIG and adjuvant therapy
Klosová *et al.* (2014)	1	1	90	0	Adjuvant therapy and biological xenograft
Kumar Das *et al.* (2014)	29	6	60–90	66	Systemic steroids and adjuvant therapy
Romero-Tapia *et al.* (2015)	2	1	N/A	0	IVIG and adjuvant therapy
Sniderman *et al.* (2015)	1	1	N/A	0	Systemic corticosteroids and adjuvant therapy
Quirke *et al.* (2015)	41		N/A	0	Adjuvant therapy
Rizzo *et al.* (2015)	21	14		9.5	IVIG and adjuvant therapy
Hinc-Kasprzyk *et al.* (2015)	1	1	N/A	0	Plasma exchange
Yamane *et al.* (2016)	35	3	N/A	0	Systemic steroids or/and other treatment and adjuvant therapy
Çekiç *et a*l. (2016)	11	4	N/A	0	3 patients: IVIG, systemic steroids, antihistaminic drugs, 1 patient: IVIG, systemic steroids, antihistaminic drugs and cyclosporin
Techasatian *et al.* (2016)	30	6	N/A	33	5 patients: systemic steroids and adjuvant therapy 1 patient: IVIG and adjuvant therapy

and extremities (encompassing about 90% of total body surface area) were observed (Figure 1). Nikolsky's sign was highly positive. Bloody erosions on all mucous membranes (in the oral cavity, genital region and eyes) were also visible (Figure 2).

During the first day of hospitalization in the PICU the girl was still treated as having staphylococcal infection. The cultures of the skin, throat and blood were taken. Antibiotic therapy was continued. However her clinical condition worsened. Cultures were negative. The biopsy from the skin lesion was taken. Because of the respiratory and circulatory insufficiency, the girl was intubated and pharmacological treatment with pressor amines was introduced.

Astute medical anamnesis from parents revealed that 4 weeks before this acute disorder, ambulatory therapy with carbamazepine because of generalized epileptic seizures without loss of consciousness was initiated. On the basis on clinical manifestations, anamnesis and histological examination, toxic epidermal necrolysis was diagnosed. Immunoglobulin intravenous in a dose of 2 g/kg in total (for 5 days) and cyclosporin A (CsA) in a dose of 3 mg/kg/day intravenously (for 20 days) were administered. Because of the severe condition of the girl, six plasma exchange cycles (Prismaflex/Gabro®) were performed.

After 40 days of endotracheal intubation and mucous membranes epithelization the girl was extubated. During these forty days the child's life was constantly threatened. She required aggressive intravenous hydration, parenteral nutrition, broad-spectrum antibiotics (because of a few sepsis events confirmed by various blood cultures), transfusions of blood and albumins, supportive topical therapy (with gauze wound dressing), active ophthalmological service, rehabilitation and surgical help.

This combination therapy was successful. Persisting complications of severe TEN and its treatment in this patient are a secondary nutritional disturbance, loss of muscle mass, reduced mobility and anxiety-depressive syndrome. The girl is also still under ophthalmological control because of corneal abrasion.

The diagnosis of toxic epidermal necrolysis is made on the basis of the clinical condition, anamnesis and histological examination of a skin biopsy [3, 4]. The presented case shows that clinical symptoms of TEN can resemble staphylococcal scalded skin syndrome. However, staphylococcal scalded skin syndrome is very uncommon in populations over 5 years old [3, 4]. What was also typical of toxic epidermal necrolysis was a correlation with initiation of carbamazepine therapy 4 weeks before the skin reaction. Pooled analysis of risk factors for SJS and TEN in children confirmed that carbamazepine is one of four highest-risk factors. The other suspected drugs are: lamotrigine, phenobarbital and anti-infective sulfonamides [5–7]. We confirmed clinical diagnosis with histological examination. There is some research on possible indicators which can help in early diagnosis of TEN. The first results show that an elevated level of serum granulysin may be a helpful biomarker for the early phase of SJS/TEN [8].

A child with skin necrosis involving more than 30% of its surface must be treated in the PICU due to the massive loss of fluids through the body shell, electrolyte imbalance, and the seizure of the mucous membranes of the mouth and respiratory tract. In cases similar to ours, it is necessary to perform a tracheotomy because of mucous changes in the respiratory tract. Deprivation of the immunological barrier (epidermis) exposes to an elevated risk of severe infections, associated also with the use of immunosuppressive therapy of TEN. The treatment of drug-induced toxic epidermal necrolysis is always a huge challenge. There are no guidelines established. The systemic review of treatment of SJS/TEN in children showed that the four most frequent treatment options were: intravenous immunoglobulin (IVIG), systemic steroids, dressings with or without the surgical approach, and support treatment [2] (Table 1). The usage of steroids is still controversial but they are often used by clinicians in the treatment of children with TEN (Table 1). Therapy with cyclosporin A (CsA) is usually effective in adults [9] but has numerous side effects [9, 10]. In the literature we found only limited reports of children with TEN successfully treated with cyclosporin A [10] and cyclosporin in conjunction with corticosteroids [11]. Use of off-label intravenous immunoglobulin seems to be not as risky as immunosuppressive agents [12–14]. In the literature we found numerous reported cases of children with TEN who were successfully treated with IVIG [12–15] (Table 1). Plasma exchange in patients with toxic epidermal necrolysis is still an infrequent method of therapy because of the costs. However, the results are very promising, especially in pediatric patients with TEN [16–18].

We are presenting our TEN patient because to the best of our knowledge it is the first case in the child population when such combination of treatment modalities was used.

Conflict of interest

The authors declare no conflict of interest.

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