DRUG-INDUCED STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

Dalia Dop, Desdemona Stepan, Cristian Gheonea, Elena Carmen Niculescu
1rd Clinic of Pediatrics, University of Medicine and Pharmacy, Craiova

ABSTRACT

Steven-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare diseases that appear following the administration of risk drugs. Both are severity grades of the same condition and are considered medical emergencies, because they are potentially lethal. They are characterized by mucocutaneous tenderness, erythema, necrosis and bullous detachment similar to extended burns. We report 3 cases of SJS/TEN in which the etiology was probably drug-related (Paracetamol, Atomoxetinum, Sulfamethoxazolum + trimethoprinum), with *restitutio ad integrum* following the administration of intravenous immunoglobulins.

Keywords: Steven-Johnson syndrome, toxic epidermal necrolysis, drug-related etiology, intravenous immunoglobulins

The Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severity variants of a rare multi-organ, immune-mediated disease that affects especially the skin and the mucosa. The drug-related etiology is the main cause of these conditions, but other causes include Mycoplasma pneumoniae and viral infections with Herpes simplex. In some cases, the etiology remains unknown (1). Because of the high risk of mortality, patients with SJS require fast diagnosis, identification and suspension of the responsible drug and specialized treatment in an intensive care unit (2). We would like to present 3 cases of SJS/TEN diagnosed in the 1st Pediatric Clinic at the Craiova District Emergency University Hospital in the period between 01.01.2009 and 30.03.2016, on the basis of medical history, clinical and paraclinical criteria.

CASE PRESENTATION

Case no. 1

We present the case of a female patient, aged 1 year and 5 months, from the rural background, who is admitted by transfer from the Hospital in Caracal for altered general status, generalized erythematous papular rash, edema of the eyelids and face, cough.

The family history is insignificant. The patient history revealed that she is the first child from a pregnancy that was followed-up, with imminence of abortion at 3 months, treatment during pregnancy that she cannot state, full-term pregnancy, natural delivery, head presentation. Weight at birth was 3,200 g, she was natural fed for 4 months, then with cow milk, incorrectly diversified at 4 months, vaccinated.

Past medical history revealed at the age of 1 year and 3 months a streptococcal and staphylococcal skin infection, treated with skin topical medication.

The *onset of the present illness* was 7 days prior to admission, with respiratory symptoms for which she receives treatment with Albuterol, Fluticasonum propionat inhaler and Paracetamol. Shortly after, she presents erythematous macules disseminated on the face and lower limbs, which were interpreted as allergic contact dermatitis. She is admitted at the Hospital in Caracal, where she follows a treatment with Ceftriaxonum, Gentamicin, Hydrocortisone Hemisuccinate, Albuterol and Fluticasonum propionate inhaler, for 3 days, with a favorable progression of the respiratory symptoms. The skin rash became accentuated and generalized.

The physical examination upon admission revealed the following pathological elements: altered general status, erythema with edema of the face, purple patches and phlyctenae in the mental area, in the region of the deltoids and arms, generalized er-

Corresponding author:
Dalia Dop, University of Medicine and Pharmacy, 2 Petru Rares Street, Craiova
E-mail: dalia_tastea@yahoo.com

ythematous papular and petechial rash with rapid expansion, in the course of a few hours, dry, chapped lips, local bleedings and haematic crusts, edema of the eyelids bilaterally, minimal serous conjunctival secretions, lung auscultation: rhonchi bilaterally. Meningeal syndrome is absent.

The *laboratory tests* performed upon admission reveal: microcytic, hypochromic anemia (Hb 10.1 g/dl, MCV 78.3 fL, MCH 26.9 pg/dl), elevated transaminases (GOT 70 UI, GPT 62 UI), hyponatremia (Na 134.2 mmol/L), hypokalemia (K 2.9 mmol/L) and ESR = 20/42 mm. The blood culture was negative, the immunogram was normal, and the chest radiography presented no alterations. The eye physical examination revealed normal anterior pole, pupillary reflexes present bilaterally and well-contoured papillae which can be seen on the fundus oculi. The dermatological examination raises the suspicion for Stevens-Johnson syndrome. Virus Herpex Simplex (HSV1, HSV2) IgM antibodies were negative, anti human immunodeficiency virus HIV 1, 2 antibodies – negative, Mycoplasma pneumonia IgM and IgA antibodies – negative.

We began *treatment* in order to reestablish the hydroelectrolytic balance – Aminoven 10%, SMOFlipid for 3 days, followed by oral feeding, antibiotic (Meropenemum), systemic corticosteroids, antihistamines, antipyretics, local dermatological and ophthalmological treatment, local surgical treatment.

Initially, the *progression* of the skin lesions was a generalization of the exanthema, with vesicular-bullous elements with a tendency to fuse, ruptured bullae in the area of the mouth, nose and genitals. Subsequently, the progression was slowly favorable, with skin scaling in strips that left behind clean erythematous areas. However, 10 days after admission, the fever syndrome reappears, with a 3-4^{o}C rise, in temperature a day. The patient is polypneic in the fever period, lung auscultation: no alterations, is cardiovascular balanced, receives oral feeding, plays with the mother and is agitated only during the examination. At this moment, she is transferred to the ICU, where she receives iv Immunoglobulins 2 g/Kg for 5 days, with favorable progression; she is discharged 2 weeks later, with *restitutio ad integrum*.

The *particularities of the case* are represented by the development of Stevens-Johnson syndrome in a patient with lower respiratory tract infection and treatment with nonsteroidal anti-inflammatory drugs (Paracetamol), with prolonged progression but with *restitutio ad integrum* after the administration of iv Immunoglobulins.

Case no. 2

We present the case of a child aged 7, male, who is admitted for fever, altered general status, generalized maculovesicular rash, edema of the lips, oral aphthae, conjunctival secretion. From the family history, we note that the grandfather and maternal aunt are diagnosed with epilepsy. Patient history is insignificant. Past medical history reveals that at the age of 1 year and 6 months he was diagnosed with Reflex epilepsy (complex partial seizures that began in the bathroom), for which he initially received Valproic Acid; four weeks before admission, Atomoxetinum is added. We also mention that at the age of 3 he is diagnosed with hyperkinetic syndrome and enuresis, for which he doesn't receive any treatment.

The onset of the present illness was 24 h prior to admission, by edema of the lips for which he receives treatment with antihistamines, Calcium. A few hours later, he develops conjunctival hyperemia and an erythematous vesicular rash on the limbs, which subsequently expanded in the cervical area; he also presents sialorrhea and aphthae in the oral cavity. He comes to the Craiova Infectious Diseases Hospital, where the suspicion of Stevens-Johnson syndrome is raised and he is directed to the Craiova District Emergency University Hospital.

The physical examination upon admission revealed the following pathological elements: altered general status, edema of the lips, aphthae in the oral cavity, sialorrhea, conjunctival hyperemia, purulent secretions in both eyes, erythematous vesicular rash on the face, in the cervical area, and on the limbs, erosions in the left malleolus. Meningeal syndrome is absent.

The *laboratory tests* performed upon admission reveal leukocytosis (L 18,200/mmc) with neutrophilia (N 79%) and negative acute phase reactants. Urine culture and blood culture were negative. The eye physical examination revealed bilateral conjunctival secretion, in the right eye the cornea retains the dye at 1-2 o'clock, the remaining anterior pole is normal, and in the left eye the cornea does not retain the dye. Virus Herpex Simplex (HSV1, HSV2) IgM antibodies, anti human immunodeficiency virus HIV 1, 2 antibodies and Mycoplasma pneumonia IgM and IgA antibodies – negative. The oral and maxillofacial surgery examination revealed Necrotizing ulcerative stomatitis secondary to the primary disease.

The administration of Atomoxetinum was interrupted and we began volume support *treatment*, Aminoven, antibiotic (Ampicillin), systemic corti-

costeroids, antihistamines, antipyretics, local dermatological and ophthalmological treatment and we continued to administer valproic acid. Initially, the skin erythematous maculovesicular rash was generalized, some bullous elements appear that fuse and break, leaving behind erosions covered in bleeding haematic crusts on the lips, jugal mucosa, tongue, and genital mucosa, edema of the scrotum; subsequently, there is fine skin scaling or in strips, gradual skin and mucosa reepithelialization.

The patient is discharged in the 17th day since admission, without fever, with fine scaling on the torso, no crusts on the body skin, detaching crusts on the lips, in cardiorespiratory balance, soft abdomen, appetite is present.

The particularities of the case consist in the onset of the Stevens-Johnson syndrome a few weeks after the beginning of treatment with Atomoxetinum in a schoolboy with epilepsy. Progression was favorable, no complications arose.

Case no. 3

We present the case of a 5-year-old child, female, who is admitted for edema of the lips, erythematous papules and plaques on the face, palms and soles, dysuria, pollakiuria. She had insignificant family and patient history. Past medical history reveals recurrent episodes of urinary tract infections (UTIs), vesicoureteral reflux.

The onset of the present illness was 10 days prior to admission, through dysuria, pollakiuria. A urine culture is performed and it is positive for Escherichia Coli, for which she receives treatment with Sultamicillinum for 5 days and subsequently with Sulfamethoxazolum + Trimethoprinum. Three days prior to admission, she developed conjunctival hyperemia, for which she received local treatment with Azitromycinum. 12 h before admission she developed erythematous macular rash in the cheeks, soles, and palms, and subsequently in the torso; for this reason, she is admitted.

The physical examination upon admission reveals the following pathological elements: altered general status, excess weight, edema of the lips, edemas of the eyelids, conjunctival secretions in both eyes, erythematous macular plaques on the face, torso and limbs, more intense in the palms and soles, vesicular lesions on the gums and lips, diffusely sensitive abdomen, dysuria, pollakiuria, meningeal syndrome is absent. The *laboratory tests* performed upon admission reveal leukocytosis (L 18,900/mmc) with neutrophilia (N 77%), positive acute phase reactants (ESR = 18/32 mm; fibrinogen 410 mg/dl) and glycemia 120 mg/dl. Liver samples were altered (GOT 806 UI, GPT 864 UI), with normal values of bilirubin. She presented hyponatremia (Na 153 mmol/L), with normal potassium levels and alkaline reserve of 18.6 mEq/l. Urine culture positive for Escherichia Coli, and the eye physical examination revealed bilateral acute conjunctivitis. The immunogram was negative, just like the hepatic markers for viral hepatitis (Atg HBS, Anti HAV Ig M, anti-HCV Ig M). Virus Herpex Simplex (HSV1, HSV2) IgM antibodies, anti human immunodeficiency virus HIV 1, 2 antibodies and Mycoplasma pneumonia IgM and IgA antibodies were negative.

The administration of Sulfamethoxazolum + Trimethoprinum was interrupted and we began *treatment* for the reestablishment of hydroelectrolytic and acid-base balance, Aspatofort, antibiotic (cefoperazonum + sulbactanum), systemic corticosteroids, antihistamines, antipyretics, local skin, eye and oral cavity treatment.

The *progression* was not favorable, with a generalization of the skin rash, bullous lesions with citrine-colored serous contents, ruptured on the face, soles and palms, ulcerative lesions covered by false membranes in the oral and genital cavity, congestion and OU conjunctival secretions, sialorrhea, difficulties swallowing, dysuria. We began intravenous Immunoglobulin treatment 2 g/Kg for 5 days, subsequently the progression was favorable.

The particularities of the case consist in the development of the Stevens-Johnson syndrome, complicated by reactive hepatitis, in a 5-year-old patient with urinary infection, who was administered treatment with Sulfamethoxazolum + Trimethoprinum.

DISCUSSIONS

TEN and SJS affect approximately 1 or 2/ 1,000,000 each year and are considered medical emergencies, because they are potentially lethal (1). Both are severity grades of the same condition. Thus, if less than 10% of the skin surface is affected, it is called SJS, if between 10 and 30% is affected, it is called overlap SJS/TEN, and if more than 30% is affected, it is called TEN (3). Case no. 1 presented the involvement of approximately 20% of the skin surface, therefore it is an overlap. Case no. 2 presented the involvement to less than 10% of the skin surface, therefore it is a case of Stevens-Johnson syndrome and case no. 3 presented the involvement of over 30% of the skin surface, therefore it is a case of toxic epidermal necrolysis.

The main cause of SJS is represented by the administration of risk drugs, which include allopurinol, sulfonamides, aminopenicillins, macrolides, tetracyclines, quinolones, cephalosporins, carbamazepine, phenobarbital, phenytoin, nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (2-7). Mycoplasma pneumonia infections or viral infections (herpex simplex or HIV), recent radiotherapy, neoplasms and collagen diseases are suspected to have a role in inducing SJS (8).

The pathophysiology of SJS/TEN remains unknown, but immunological mechanisms, cytotoxic reactions and late hypersensitivity seem to be involved (9). Onset manifestations are uncharacteristic, subsequently there are erythematous macular elements on the torso and face that become generalized and then there is necrosis and bullous detachment similar to extended burns. Aside from the epidermis, there is also damage to the oral, genital, anal, conjunctival, digestive and respiratory mucosae (2).

The diagnosis is based mainly on the clinical signs, together with the histological analysis of skin biopsy, which shows typical epidermal necrolysis caused by extended keratinocyte apoptosis.

The interruption of the triggering medication should be a priority when SJS is suspected. Garcia-Doval and collab. showed that the rapid interruption of the incriminated drug determines a better prognosis and patients exposed for a longer period to the causative pharmaceuticals have a high risk of death (1,12). In order to identify the incriminated drug, it is important to take into consideration the chronology of administration and the reported capacity to induce SJS/TEN. The development of SJS secondary to the administration of a treatment is produced at 1 up to 8 weeks since the beginning of the treatment (2,11). In the presented cases, the manifestation of the first lesions occurred 1 week after the beginning of therapy in cases no. 1 and 3 and 4 weeks after in case no. 2. In all 3 cases, the suspect drug was interrupted as soon as the suspicion of SJS arose.

Sequelae are generally characteristic in TEN and are represented by skin damage, hypo- or depigmentation, nail dystrophies, eye complications, more rarely complications of the urethral or digestive mucosa (10,12,13). Mortality is reported to be 1-5% in the case of SJS and 25-35% in the case of TEN (1,14).

The treatment for SJS/TEN is similar to that for major burns and it includes treatment for wound support and care, maintaining the blood volume, broad-spectrum antibiotics, treatment with immunosuppressives. Although the parenteral administration of corticosteroids and immunoglobulins (ivIg) is used for the treatment of SJS/TEN, studies are contradictory (9,15). In our case, parenteral corticosteroids were administered since the onset and progression was favorable in case no. 2. In the other two cases, complicated by infections, we used i.v immunoglobulins which determined a favorable progression with *restitutio ad integrum*.

CONCLUSIONS

The Stevens-Johnson syndrome is a rare condition that raises problems of differential diagnosis in the initial phase of the disease. The initial diagnosis in all three cases was allergic contact dermatitis and the etiology was probably drug-related (Paracetamol, Atomoxetinum, Sulfamethoxazolum +/- trimethoprinum), while in 2 cases it occurred on the background of infections (respiratory and urinary, respectively). The progression was favorable in case no. 2, without complications, while the cases of Stevens-Johnson syndrome that had their onset on the background of infections grew complicated, with prolonged progression (6-9 weeks), but with *restitutio ad integrum* following the administration of ivIg.

REFERENCES

1. **Harr T., French L.E.** Toxic epidermal necrolysis and Stevens-Johnson syndrome. *Orphanet J Rare Dis*. 2010 Dec 16; 5:39. doi: 10.1186/1750-1172-5-39.
2. **A.K. Yapici, M.K. Fidanci, S. Kilic, N. Balamtekin, M. Mutluay Arslan, S.T. Yavuz, S.** Kalman Stevens-Johnson Syndrome triggered by a combination of clobazam, lamotrigine and valproic acid in a 7-year-old child. *Ann Burns Fire Disasters.* 2014 Sep 30; 27(3): 121–125.
3. **Bastuji-Garin S., Rzany B., Stern R.S., et al.** Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol.* 1993;129:92–6.
4. **Blanca-López N., Cornejo-García J.A., Pérez-Alzate D., Pérez-Sánchez N., Plaza-Serón M.C., Doña I., Torres M.J., Canto G., Kidon M., Perkins J.R., Blanca M.** Hypersensitivity Reactions to Nonsteroidal Anti-inflammatory Drugs in Children and Adolescents: Selective Reactions. *J Investig Allergol Clin Immunol.* 2015; 25(6):385-95
5. **Levi N., Bastuji-Garin S., Mockenhaupt M., Roujeau J.C., Flahault A., Kelly J.P., Martin E., Kaufman D.W., Maison P.** Medications as risk factors of Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a pooled analysis. *Pediatrics.* 2009 Feb; 123(2):e297-304. doi: 10.1542/peds.2008-1923. Epub 2009 Jan 19

6. **Forman R., Koren G., Shear N.H.** Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a review of 10 years' experience. *Drug Saf.* 2002; 25(13):965-72.
7. **Bohan K.H., Mansuri T.F., Wilson N.M., et al.** Anticonvulsant hypersensitivity syndrome: Implications for pharmaceutical care. *Pharmacotherapy.* 2007; 27:1425–39.
8. **Mockenhaupt M., Viboud C., Dunant A., et al.** Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCARstudy. *J Invest Dermatol.* 2008; 128:35–44.
9. **Gerull R., Nelle M., Schaible T.** Toxic epidermal necrolysis and Stevens-Johnson syndrome: a review. *Crit Care Med*. 2011; 39:1521–32.
10. **Garcia-Doval I., LeCleach L., Bocquet H., Otero X.L., Roujeau J.C.** Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol.* 2000; 136:323–327. doi: 10.1001/archderm.136.3.323.
11. **Lissia M., Mulas P., Bulla A., et al.** Toxic epidermal necrolysis (Lyell's disease). *Burns*. 2010; 36:152–63.
12. **Sheridan R.L., Schulz J.T., Ryan C.M., Schnitzer J.J., Lawlor D., Driscoll D.N., Donelan M.B., Tompkins R.G.** Long-term consequences of toxic epidermal necrolysis in children. *Pediatrics*. 2002 Jan;109(1):74-8.
13. **Saeed H., Mantagos I.S., Chodosh J.** Complications of Stevens-Johnson syndrome beyond the eye and skin. *Burns.* 2016 Feb; 42(1):20-7. doi: 10.1016/j.burns.2015.03.012. Epub 2015 Apr 9.
14. **French L.E.** Toxic epidermal necrolysis and Stevens Johnson syndrome: our current understanding. *Allergol Int.* 2006 Mar; 55(1):9-16.
15. **Schneck J., Fagot J.P., Sekula P., et al.** Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR Study. *J Am Acad Dermatol.* 2008; 58:33–40.