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Original

Stevens-Johnson syndrome and toxic epidermal necrolysis: a report of six cases

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Stevens-Johnson syndrome and toxic epidermal necrolysis are severe cutaneous adverse reactions commonly caused by exposure to drugs and can end up with significant morbidity and mortality. We reported our experience with six patients who were diagnosed with Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis with a different clinical presentation. In patients, drugs and *Mycoplasma pneumoniae* infection were implicated as a trigger. Intravenous Immunoglobulin treatment was given to all patients, and intensive treatment was applied for skin and mucosal lesions. The median period of stay in hospital was 13.5 days. The most common long-term complication was ocular involvement. Among six patients, corneal epithelial defects occurred in one patient. Consequently, ophthalmological evaluation should be performed both at the time of diagnosis and before hospital discharge.

Key words: drug reaction, mycoplasma, Stevens-Johnson syndrome.

Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening diseases associated with significant morbidity and mortality. They are considered to be part of a spectrum of cutaneous drug reactions, differentiated only by their extent of skin detachment following keratinocyte apoptosis. Drugs are assumed to be the leading cause of SJS and TEN in most cases.[1] Pathogenesis includes immediate or delayed immunologic mechanism, usually independent from the dosage of the drug, and pharmacologic/toxic mechanism.[2,3] The mainstay of the diagnosis is generally clinically based together with the histological analysis.[1] Rapid withdrawal of the probable causative drug(s) (if detected) is essential. Use of Intravenous Immunoglobulin (IVIG) and corticosteroids are reported as the most commonly recommended therapy in childhood.[4,5]

Material and Methods

We reported our experience with six patients who were diagnosed with SJS or TEN with a different clinical presentation. We followed-up these patients in our hospital in the Pediatric Infectious Diseases Unit between 2014 and 2016. We noted their sex, age, symptoms, affected areas, suspicious agents and laboratory results. Institutional approval was obtained from the Ethics Committee of Dr. Behçet Uz Children's Hospital (Ethics Approval Number: 2017/150). Written consent obtained from all participants' parents.

Results

Six patients, ages between 2.5 to 14 years, were admitted to our center with various complaints. Three (50%) of the patients were female.

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Numerous lesions were seen on the body which gave the typical appearance of "target lesions." Ulcerative lesions were present in the oral cavity and lips. Some images of lesions of patients are shown in Figure 1. There was redness and bilateral purulent discharge in some of the patients' eyes. The demographic characteristics and clinic outcomes of patients are summarized in Table I. There were no significant changes in biochemistry and hematology (complete blood count) laboratory examinations. Plasma *Mycoplasma pneumoniae (M. pneumoniaee)* IgM titers were evaluated by using indirect immunofluorescence method and was positive in two patients, which have been validated via Polymerase Chain Reaction for *M. pneumoniae* from the samples gathered from the nasopharyngeal wash. Details of the laboratory examinations of the patients are shown in Table II. Skin biopsy was performed in only two patients. Two patients were diagnosed with SJS, three patients TEN and one SJS/TEN overlap. Suspected drug was discontinued in all cases. IVIG treatment was given to all patients. Patients were laid on fluidized air beds. The skin of the patients was washed with saline solution daily. Topical care (mupirocin pomade and netilmicin sulphate eye drop) was applied to eyes, lips, and skin lesions 3-8 times daily. Eye drops with ofloxacin and netilmicin sulphate was applied to bilateral eyes of one patient with a corneal defect. In addition, clarithromycin therapy was started for *M. pneumoniae* in two patients. The lesions gradually diminished and healed up in 12-21 days (median 13.5 days) and resolved with mild hypo or hyperpigmented spots. Patients were informed about suspected drugs and were advised to avoid taking it or any drugs like it. The patient with corneal defect was evaluated regarding long-term complications for a year at 3-month intervals. A detailed eye examination was performed at each visit. There were no long-term complications during one-year follow-up. Diagnosis, therapy, and prognosis of patients are summarized in Table III.

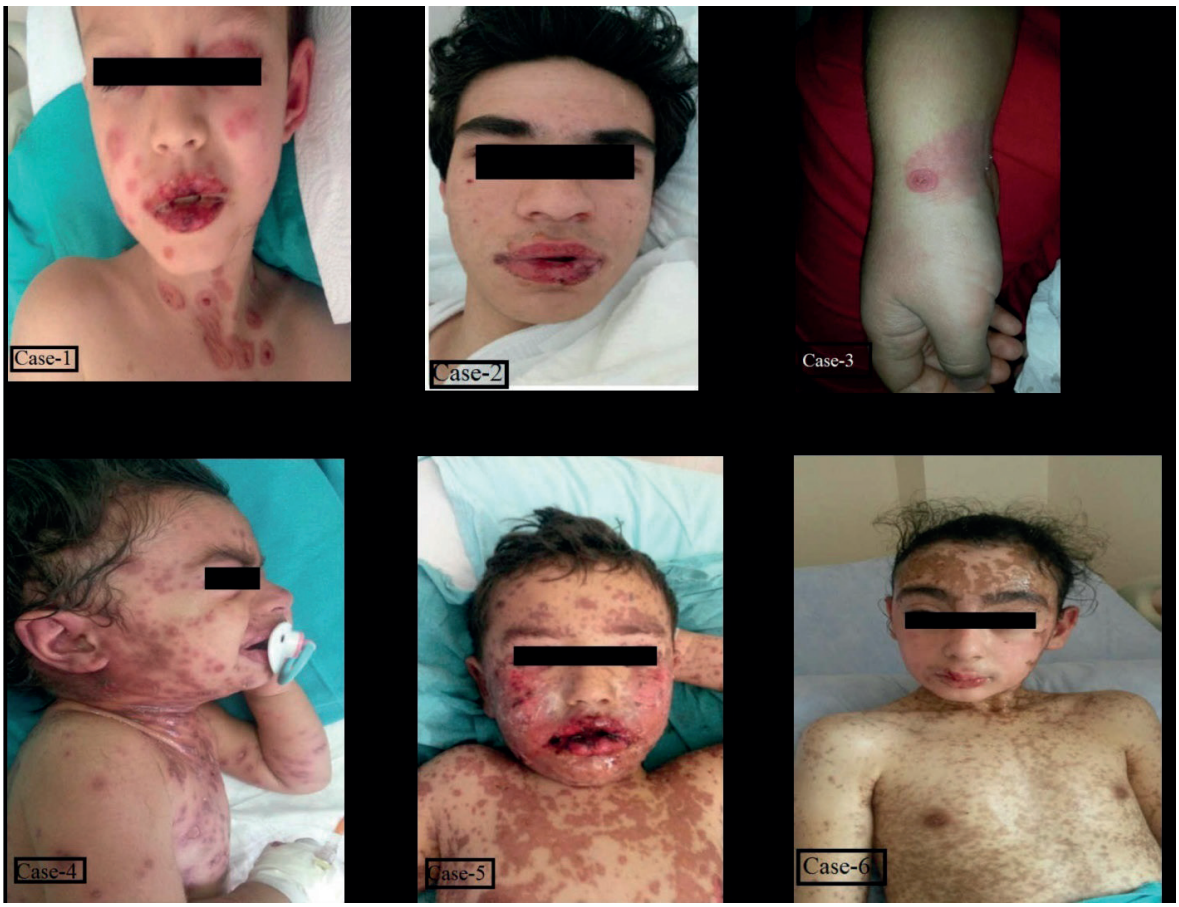

Fig. 1. Some images of lesions of patients.

Table I. The Demographic Characteristics and Clinic Results of Patients.

Case	Sex	Age (year)	Symptom	Duration of rashes (day)	Time between use of suspicious drug and rashes (day)	Affected areas	Suspicious agent
1	Male	9	Fever, rash	8	2	Body, mouth, eyes	Amoxicillin clavulanate / paracetamol
2	Male	14	Rash, oral ulcer	5	1	Body, mouth, genital	Amoxicillin clavulanate/ paracetamol or M. pneumoniae
3	Female	14	Fever, rash	1	1	Body, mouth, eyes	Amoxicillin clavulanate
4	Female	2.5	Fever, rash, oral ulcer	3	2	Body, mouth, genital	Paracetamol/ ibuprofen
5	Male	5	Fever, rash	1	1	Body, mouth, eyes	Amoxicillin clavulanate/ paracetamol or M. pneumoniae
6	Female	11	Fever, rash	1	30	Body, mouth	Paracetamol or lamotrigine

Table II. Laboratory Tests of Patients.

Case	White blood cell (WBC)	Thrombocyte count	Albumin	C-reactive protein (CRP)	Mycoplasma pneumoniae PCR
1	18,690/mm^3	243,000/mm^3	3.5 mg/dl	11.7 mg/dl	Negative
2	10,450/mm^3	382,000/mm^3	3.9 mg/dl	10.5 mg/dl	Positive
3	8,740/mm^3	162,000/mm^3	4.5 mg/dl	7.97 mg/dl	Negative
4	13,790/mm^3	42,000/mm^3	4.0 mg/dl	5.9 mg/dl	Negative
5	4,500/mm^3	281,000/mm^3	2.1 mg/dl	5.13 mg/dl	Positive
6	8,210/mm^3	157,000/mm^3	3.6 mg/dl	0.25 mg/dl	Negative

WBC reference value: 4,000−11,000/ mm^3
CRP normal value: <0.5 mg/dl
Thrombocyte reference value: 150,000-400,000/mm^3
Albumin normal value: 3.2-4.6 mg/dl
PCR: Polimerase Chain Reaction

Discussion

Stevens-Johnson syndrome is an immune-complex-mediated disease that typically involves the skin mucous membranes.[6] Although several classification systems have been proposed, the simplest classification breaks the disease down as follows 6:

- SJS: A minor form of toxic epidermal necrolysis, with less than 10% body surface area (BSA) detachment
- Overlapping SJS/TEN: Detachment of 10-30% of the BSA
- TEN: Detachment of more than 30% of the BSA

Mucosal involvement happens in more than 90% of patients, predominantly affecting the mouth, genitalia, and/or ocular region. In our case series, oral mucosa involvement was standard however ocular and anogenital involvement was present in 3 and two patients consecutively.

Erythema and erosions usually characterize the morphology of lesions.[7] During the disease, the lesions rapidly coalesce and become tense bullae. As the disease progresses, the lesions form large concurrent areas of epidermal detachment. The degree of skin involvement is a highly important prognostic factor. Skin involvement should be determined including only already detached necrotic (e.g., blisters

Table III. Diagnosis, Therapy and Prognosis of Patients.

Case	Biopsy	Diagnosis	Affected body surface (%)	Therapy	Lenght of stay in hospital (day)	Prognosis
1	Yes	SJS/TEN overlap	12	IVIG 2g/kg/day 3 days	21	Referred to university hospital for corneal epithelial defect
2	No	SJS	4	IVIG 1g/kg/day 6 days + Clarithromycin 15 mg/kg/ day divided 2 doses	12	Cure
3	No	SJS	3	IVIG 2g/kg/day 3 days	13	Cure
4	No	TEN	72	IVIG 2g/kg/day 3 days	12	Cure
5	No	TEN	85	IVIG 2g/kg/day 3 days + Clarithromycin 15 mg/kg/ day divided 2 doses	18	Cure
6	Yes	TEN	75	IVIG 2g/kg/day 3 days	14	Cure

IVIG: Intravenous immunoglobulin, SJS: Stevens-Johnson Syndrome, TEN: Toxic epidermal necrolysis

or erosions) or detachable skin (Nikolsky positive). A classification system for SJS and TEN according to the extent of skin detachment has been suggested by Bastuji-Garin et al.[8] In our experience skin biopsy was done in two patients and the pathology has shown extensive epidermal necrosis, focal subepidermal necrotic blisters, and separation of the epidermis from the dermis.

Stevens-Johnson syndrome may occur idiopathically in 25-50% of cases. Pediatric cases are related more frequently to infections (viral, bacterial and fungal). More than half of the patients with Stevens-Johnson syndrome reports a recent upper respiratory tract infection. Mycoplasma investigation was performed in all cases. In two patients, *M. pneumoniae* IgM and Polymerase Chain Reaction from nasopharyngeal wash was positive. SJS is an uncommon occurrence in *M. pneumoniae* infection (1-5%) and has been mainly reported in children and young adults.[9,10] Drugs and malignancies are usually implicated as the etiology in adults and elderly persons. More than 100 drugs can cause SJS/TEN. Antibiotics are the most prevalent cause of SJS/TEN, followed by analgesics, cough and cold medication, non-steroid anti-inflammatory drugs (NSAID), psycholeptics, and antigout drugs. Patient history in our study revealed use of antibiotics [Amoxicillin clavulanate (4 patients)], lamotrigine (1 patient) and/or NSAIDs (5 patients). Mockenhapupt et al.[11] stressed that most anticonvulsant-induced SJS occurs in the first 60 days of use. The syndrome generally begins 4–14 days after the initiation of medication therapy.[12] Five of our patients first symptom started 1-2 days after the trigger. In only one patient, the first symptoms started 30 days after the drug (lamotrigine). Although the first symptoms in our patients appeared to be much earlier than in the literature, there are also cases whose symptoms occur two days after the administration of the culprit.[13]

Immediate discontinuation of the suspected agent which is assumed to be the cause of the situation is critically important. The primary treatment is usually supportive and symptomatic. Patients should be managed with special attention to airway and hemodynamic stability, fluid status, wound/ burn care, and pain control.[5] Oral lesions are treated with mouthwashes; topical anesthetics are useful in reducing pain and allowing the patient to take in fluids. Special types of types of equipment such as fluidized air beds are recommended if a substantial piece of the skin area on the patient's posterior is affected. Patients with SJS/TEN are at tremendous risk for infection. The careful approach of healthcare stuff including sterile handling or reverse-isolation techniques are crucial to decreasing nosocomial infection risk. Cultures from blood, catheters, nasogastric, and urinary tubes must be performed regularly. Areas of denuded skin must be covered with

compresses of saline or Burow solution.[1-3] Because of the relationship between SJS and sulfonamides, use of silver sulfadiazine should be avoided, which is generally used in burnt skin areas. Alternatively, another antiseptics such as 0.5% silver nitrate or 0.05% chlorhexidine should be applied to the affected skin areas. Our patents were bathed daily with saline. Nitrofurazone 0.2% were allocated to patients with severe and deep skin lesions three times a day. Extensive debridement of nonviable epidermis followed by an immediate cover with biologic dressings is among the recommended treatments.[5,14] Underlying diseases, and secondary infections should be treated. Primarily, in our patients, the drugs that caused SJS/TEN were discontinued. A patient's anticonvulsant therapy (lamotrigine) was changed. In two patients, *M. pneumoniae* was detected, and clarithromycin therapy was an addition to the therapy.

Early administration of high-dose IVIG (2 g/kg) is recommended for patients with SJS/TEN, even though its mechanism of action remains unclear. All of the patients in our study received IVIG (2 g/kg/day-3 days). No side effects were observed during their treatment. According to a recent meta-analysis of observational studies, IVIG at dosages of ≥2g/kg appears to decrease mortality in patients with SJS or TEN significantly.[4,15-17] A Canadian review about SJS in children showed that the use of IVIG and corticosteroids had similar outcomes regarding infection-related complications and length of hospital stay and that both of these treatments were better when compared with supportive therapy alone.[18]

Younger patients are known to have a shorter course of hospital stay (<30 days) compared to adults.[9] In our experience median length of stay in the hospital was 13.5 days. The most common long-term complication was ocular involvement. Of patients with SJS, 27-50% progress to severe ocular disease.[19,20] Among our patients, corneal epithelial defects occurred in one patient; and he was referred to the Ophthalmology Clinic of a University Hospital for treatment. The treatment of acute ocular manifestations of SJS normally starts with aggressive lubrication of the ocular surface. As inflammation and cicatricial changes happen, most ophthalmologists use topical steroids, antibiotics, and symblepharon lysis. About one year after the patients were discharged, none of the patients, including the patient with a corneal defect, had any deformation.

The ocular findings of one patient was worse even though the affected area was smaller when We believe this was probably due to delayed referral and therefore late treatment. Although more than 70% of the body surface was affected in three of our patients, no complications developed due to the fact that they were diagnosed shortly after the onset of the symptoms (1-3 days) and treatment was started immediately. In patients receiving treatment for the first 4-6 days from skin rash, the assumed drug stops the progression of the disease rapidly and accelerates epithelization.[21] In our cases, we concluded that late diagnosis and treatment were a factor that adversely affected the clinical course of the disease even if the affected body area was small.

In order to evaluate prognosis of patients affected by SJS and TEN, there is a scoring system called SCORTEN. SCORTEN is composed of 7 parameters: age >40 years; neoplasms; tachycardia (>120 bpm); epidermal detachment >10%; serum urea >10 mmol/l; serum glucose >252mg/dl; and serum bicarbonate ≤20 mmol/l. These parameters determine a better or worse prognosis of the patient. For each of these items, 1 point is given if the item is present or 0 point if the item is absent. When the patient scores 3 or more, he/she should be managed in an intensive care unit. A score ≥5 predicts a mortality rate of approximately 90%. Risk of death is higher in the elderly and in those with larger affected body surface.[22] It is recommended to use this scale in the first 24 hours and on the 3rd day after the patient's application. The value in the pediatric age group is not known yet.

In conclusion, SJS/TEN is a severe disease which in some cases can be fatal despite adequate therapy. Ophthalmology evaluation should be performed both at the time of diagnosis and before hospital discharge. Secondly, work-up for *M. pneumoniae* should be done because patients may benefited from specific anti-bacterial treatment.

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