

## **Case study**

### A Case Study of Oxcarbazepine-Induced Stevens-Johnson Syndrome

#### **Abstract**

An eight-year-old girl was admitted to hospital with complaints of seizure episodes that occurred during sleep, characterized by drooling, jerky stiff upper limbs, throat sounds, and blue lips. Patient had suffered a series of three seizures, all lasting for less than five minutes. Patient was given rectal diazepam to abort seizures. EEG results confirmed that focal epilepsy was the underlying cause of seizures. Patient was born with severe intrauterine growth retardation and microcephaly and was diagnosed with congenital cytomegalovirus (CMV).

After confirming diagnosis of epilepsy, patient was recommended an anticonvulsant medication, oxcarbazepine, and a follow up examination in two to three months. However, after two weeks of treatment, patient developed rashes and skin lesions over arms and legs. Later, these spread to the mouth, and then ulcerated, leading to admission to the hospital. The patient had rashes all over her body except hands, which were red and tan in color, swollen, itchy, scaly, dry, popular, macular and patchy. The severity of symptoms was rated a seven out of ten on the pain scale. The rash lasted for six days and occurred after infectious exposure. It was exacerbated by scratching. Lotion and medication were effective in relieving effects.

The skin detachment was less than 10% of BSA (body surface area) and purpuric macules were present in patient. Hence, patient was diagnosed as a case of Stevens-Johnson syndrome. The naranjo algorithm was used to check the probability of a drug reaction and through the WHO-

UMC criteria for causality it was decided that oxcarbazepine induced the syndrome. Oxcarbazepine is a structural analog of carbamazepine, the most common cause of drug induced SJS (Stevens-Johnson syndrome).

Upon findings and investigation, this was diagnosed as a case of drug-induced Stevens-Johnsons Syndrome and the patient recovered after a week.

Keywords: Oxcarbazepine, seizures, Stevens-Johnson syndrome, congenital Cytomegalovirus

## **INTRODUCTION**

Stevens-Johnson Syndrome is a fatal and rare skin disorder with prominent manifestation in the form of skin loss, blistering, and multi-organ damage. It is a type of autoimmune disorder that usually invades skin, mucous membranes, and can potentially cause damage to the eyes. In its symptoms, it is very much like epidermal necrolysis but is distinct from erythema multiforme. It is considered a rare complication after medication and occurs in one to two million individuals annually. Eye complications occur in almost 80% of hospitalized patients and chronic ocular changes are present in about 35%.<sup>(1,2)</sup>

Frank Chambliss and Albert Mason Stevens first described this syndrome in 1922. It is distinct from toxic epidermal necrolysis and less severe. In SJS, less than 10% of bodily surface is affected, while in toxic epidermal necrolysis it can be more than 30%. If more complications don't occur, then the lesions heal in 1-2 weeks and the patient recovers without any long-term issues. However, a severe form of skin sloughing, and secondary bacterial infections can lead to a less positive prognosis for the disease.<sup>(3)</sup>

The syndrome is diagnosed based on the character of the affected skin. Clear signs of SJS include more than 10% affected skin in first 48 hours of symptoms, specifically iris lesions with

a diameter of less than 3cm, involvement of at least two mucous membranes, a positive biopsy specimen, and fever. It is seen that there are also rises in the concentrations of several human leucocyte antigen markers, including HLA-B12, HLA-B44, HLA-Aw33, and HLA-DRw53.

Although the exact mechanism of disease prognosis is poorly understood, early blister fluids may contain drug-specific CD8+ cytotoxic cells that show natural killer activity. Detected cytokines include tumor necrosis factor alpha, Fas-L, granulysin, and perforin. At molecular levels, two pathways are important. The apoptosis of keratinocytes by Fas-Fas ligand pathway is a key step in the prognosis of TEN (Toxic epidermal necrolysis). The Fas-ligand is secreted by lymphocytes that bind to keratinocytes via death receptors. On the other hand, granzyme B and perforin can induce granule mediated exocytosis, leading to cytotoxicity.<sup>(4)</sup>

### **EXAMINATION/CASE PRESENTATION**

An eight-year-old girl was admitted to hospital with complaints of a seizure episode in October 2021 that occurred during sleep, characterized by drooling, jerky stiff upper limbs, throat sounds, and blue lips. Patient suffered a series of three seizures from October 2021 to December 2021. The last seizure episode was on 9<sup>th</sup> December 2021. All seizures lasted for less than five minutes and patient was given rectal diazepam to abort seizures. Episodes of seizures made the girl stay at home and dependent on caregivers for feeding.

#### **Patient History:**

The eight-years-old female was born with severe intrauterine growth retardation and microcephaly and was diagnosed with congenital CMV. A brain MRI showed patchy delayed myelination of the deep white matter on both brain hemispheres with evidence of cortical atrophy. She used a wheelchair and was fully dependent on her caregivers to support her for life

activities. She had significant developmental milestone delay with mental retardation, hence the child was considered in the category of People of Determination.

Patient had following problem:

1. Congenital CMV infection
2. Delayed neuronal myelination with brain atrophy
3. Global developmental delay, including gross and fine motor skills
4. Speech delay
5. Mental retardation
6. Hypotonia
7. Wheelchair user

**Initial Examination and Medication:**

Electroencephalography was performed to determine any underlying reasons for seizures. Recordings were taken at 50-minute intervals. Patient was partly drowsy and then brief periods of sleep were observed, as well as:

- Unremarkable photic stimulation
- No focal slowing or voltage asymmetry
- Short strains of rhythmic spikes were recorded in the left temporal occipital without any clinical change
- Posterior dominant rhythm was recorded as 8-9 Hertz during wakefulness

- While in the centro temporal parietal region, discharges of synchronous spike waves, bilateral in nature, were seen during wakefulness.

EEG findings supported the diagnosis of epilepsy.

For seizures, anti-convulsant oxcarbazepine was recommended with following doses with follow up plan for 2-3 months.

- Week 1 : 60 mg BID
- Week 2: 120 mg BID
- Week 3: 180 mg BID
- Week 4: 240 mg BID
- Buccal Midazolam 7.5 mg x PRN for seizure > 5 min

Although medication showed positive results for preventing seizures, it resulted in severe kind of rash after two weeks of prescribing.

**Diagnosis and Treatment:**

Patient developed rash over arms and legs. Later, it spread to the mouth, and ulceration led to admission to the hospital. The patient had rashes all over the body except hands, which were red and tan in color, swollen, itchy, scaly, dry, popular, macular and patchy. The severity of symptoms was rated at a seven out of ten on the pain scale. The rash lasted for six days and occurred after an infectious exposure. It was exacerbated by scratching. Lotion and medication were effective in relieving symptoms.

An integumentary examination gave following information:

Rash	Macular, papular
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Shape	Symmetric
Characteristic	Blanching, indurated, raised
Margin	Discrete
Color	Red, tan

As per case reports,<sup>(5, 6)</sup> the abovementioned symptoms clearly indicate the presence of Stevens Johnsons Syndrome.



Figure 1: Red and crusted lips and mouth with ulceration



Figure 2: Red rashes on foot



Figure 3: Scaly, dry, patchy, and macular rash

The naranjo algorithm was used to check the probability of drug reaction and through the WHO-UMC criteria for causality it was determined that oxcarbazepine induced the syndrome. Then medication plan was changed to topiramate as follows:

Week 1: 25 mg BID

Week 2 :50 mg BID

Week 3 : 75 mg BID

For symptomatic treatment: **Calamine lotion**/ Chlorphenamine 2mg twice a day was recommended. It had relieving effects and the rash disappeared after a week.

## DISCUSSION

Stevens-Johnson syndrome is typically viewed as medical emergency induced by certain drugs, although microorganisms such as *mycoplasma pneumoniae* can be the basis of atypical cases of SJS. <sup>(5)</sup>

Malaise and a prodrome of fever are initials signs of Stevens-Johnson syndrome, and are followed by progression of mucosal and cutaneous lesions. Urogenital and ocular lesions are also prevalent. In pure SJS cases, the affected bodily surface area is less than 10%. Patients recover easily but certain skin infections can occur due to absence of intact skin barriers that may lead to complications or even death. <sup>(6)</sup>

The onset of SJS is unpredictable and it may occur in anyone on medication, regardless of age and race. However, it has higher incidence in females and studies suggest that human immunodeficiency virus is closely associated with SJS. Common causes of SJS are drug reactions to penicillin, salicylate, sulfonamides, isoniazid, phenytoin, or barbiturates. Infections

such as adenovirus, streptococcus, mycoplasma, HSV can also be potential causes. About 200 drugs have been found to be associated with the onset of Steven Johnson Syndrome. Genetic factors in some cases also play a role. Some races have HLA associations with allopurinol and anticonvulsants, while polymorphism has also been detected in some genes. Despite diverse causes, 50-60% of cases are due to drug toxicity. The most common drug which causes SJS are sulfonamides.<sup>(7)</sup>

Clinical manifestations of the syndrome overlap with many other disorders that affect the mucous membranes and skin, such as toxic epidermal necrolysis, erythema multiforme major, and erythema multiforme minor,<sup>(8, 9)</sup> while staphylococcal scalded skin syndrome and other drug hypersensitivity reactions also cause other differential diagnosis with SJS.<sup>(10, 11)</sup>

So in differential diagnosis, different problems were suggested, but a keen examination of lesions and rashes proved the SJS as skin detachment was less than 10% of BSA and purpuric macules were present in patient. It was not a case of overlapping SJS/TEN and TEN because the detachment area is between 10-30% in overlap SJS/TEN and more than 30% in TEN.

Although no biopsy was done, a comparison of all symptoms and the nature of the lesions with other case studies of Stevens-Johnson syndrome confirmed the diagnosis, as confirmed by other case studies.<sup>(5, 6)</sup>

A SJS case in a patient with a history of taking SJS-inducing drugs in the eight weeks before the onset of symptoms is classified as secondary to drug-induced SJS. On the other hand, it is considered infectious if onset of symptoms is one week before the rash appears and serology results are positive.<sup>(12)</sup> In this case, SJS was drug-induced as patient was on medication, oxcarbazepine. In literature, several research and case studies point towards rare cases of the

involvement of oxcarbazepine in development of SJS . Oxcarbazepine is structurally similar to carbamazepine, the most common Steven- Johnson syndrome-inducing anticonvulsant drug.<sup>(13,</sup>

14)

## CONCLUSION

Stevens-Johnsons Syndrome is rare autoimmune disorder that affects one to two million individuals annually in the United States. Reactions to drugs are responsible for 40-60% of SJS cases. Genetic factors can also play a role.

The given case was of Stevens-Johnson syndrome in an eight-year-old girl who developed a rash in response to medication for epilepsy treatment. The case was termed as secondary to drug-induced SJS.

### COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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