

## **Acetaminophen induced Steven Johnson Syndrome-Toxic Epidermal Necrolysis overlap**

Ali Khawaja,<sup>1</sup> Ahmed Shahab,<sup>2</sup> Syed Ather Hussain<sup>3</sup>

Medical College,<sup>1,2</sup> Section of Nephrology, Department of Medicine,<sup>3</sup> Aga Khan University Hospital, Karachi, Pakistan.

**Corresponding Author: Syed Ather Hussain. Email: ather.hussain@aku.edu**

### **Abstract**

Steven Johnson Syndrome and Toxic Epidermal Necrolysis are rare but severe form of hypersensitivity inflammatory reactions to multiple offending agents including drugs. Acetaminophen is extensively used due to its analgesic and anti-pyretic properties. It is rendered to be relatively safe, with hepatotoxicity considered to be the major adverse effect. However, very few cases of Steven Johnson Syndrome and Toxic Epidermal Necrolysis have been reported with acetaminophen usage in the past. We present the case of a 40 years old lady who developed an overlap of the two condition after taking several doses of

acetaminophen for fever. She presented with widespread maculopapular rash, stinging in the eyes, oral mucosal ulcerations and high grade fever. She was successfully treated with corticosteroid therapy along with the supportive treatment. This case addresses the fact, that severe hypersensitivity reactions can occur with acetaminophen which can be potentially life threatening.

**Keywords:** Steven Johnson Syndrome, Toxic Epidermal Necrolysis, Acetaminophen, Corticosteroids.

### **Introduction**

Steven-Johnson Syndrome (SJS) is an infrequent but

a severe form of adverse hypersensitivity reaction to drugs which results in skin and mucosal eruptions that can be potentially lethal. It is considered to be a less severe form of Toxic Epidermal Necrolysis (TEN), the difference being the extent of epidermal detachment; <10% and >30% of the total body surface area, respectively while 10%-30% is known as SJS-TEN overlap.<sup>1</sup> The incidence of SJS has been estimated to be around 1-6 per 1,000,000 persons per year with a mortality rate of 1-5% which rises up to 30% in TEN.<sup>2</sup> Multiple drugs have been identified to cause SJS and TEN, antibiotics (sulfonamides) being the most common.

Acetaminophen is amongst the most extensively used analgesic and anti-pyretic because of easy availability and cost-effectiveness. Despite being considered relatively safe, adverse reactions including cutaneous hypersensitivity reactions have been reported.<sup>3</sup> However, very few cases of SJS and TEN have been reported as being associated exclusively with acetaminophen usage.<sup>4-6</sup>

We present the case of a previously healthy lady who developed SJS-TEN overlap after acetaminophen ingestion.

### Case Report

A 40-year old lady, with no co-morbid developed



Figure-1: Shows oedema and crusting of the lips with erythematous purpuric macular lesions involving the neck.



Figure-2: Shows dusky red cutaneous lesions on the back with some of them coalescing to form plaques.

high grade fever of 39°C (102.2°F) one evening. She took TWO tablets of Acetaminophen after which the fever subsided but recurred next morning. The dose of Acetaminophen was repeated and the condition started worsening with oedema of lips, oral mucosal ulcerations and stinging in eyes. Rashes appeared later that evening. She consulted a physician who continued her on Acetaminophen and added Cetrizine which she did not take.

She reported to our emergency department next morning. She was diagnosed as having a self-limiting hypersensitivity reaction and administered a dose of intravenous Ketorolac (30mg) for pain and fever and was discharged. She returned in 24 hours with spread of rashes, bilateral conjunctivitis, oedema and crusting of lips (Figure-1), pruritus, oral ulcerations, salivation, myalgia and fever of 39°C. Acetaminophen was stopped immediately and IV Clemastine (1mg) and IV Hydrocortisone (100 mg) together with Ringer Lactate solution were administered. She was later shifted to the ward.

According to the patient, the rashes started as dusky red macular lesions in the palms and later extended symmetrically involving her arms, forearms, eyes, trunk, neck, soles and legs in the order of sequence. Some of the lesions became papular. On examination, she was vitally stable. Erythematous maculopapular lesions were observed covering around 25% of total body surface area. The rashes

had coalesced to form plaques in the arms, back and head and neck region (Figure-2). The genitals were spared and no blister formation was seen. Other systemic examination was unremarkable. Based on the case history and examination, she was diagnosed clinically with SJS-TEN overlap by a consultant dermatologist.

The patient reported to have had complaints of diarrhoea and vomiting after acetaminophen usage in the past. Similar complaints were also associated with intake of wheat products, potatoes, beef and several vegetables. Her child had fever and flu like symptoms since one week. Other personal and family history was unremarkable.

Baseline investigations revealed a Haemoglobin level of 11.3g/dl, leukocytes  $4.7 \times 10^9/L$  with neutrophils of 82%, lymphocytes 11.0% and eosinophils 0.2% followed by a normal count the next day. Platelets were reduced to  $129 \times 10^9/L$  (150-400) initially. Sodium was observed to be 140 (135-145) mmol/l, Potassium 3.3 (3.6-5.0) MEQ/L, Chloride 108 (101-111) and Bicarbonate 18.8 (21-31) mmol/L. Renal and liver function tests were normal. Blood and urine culture were sent which were negative after 5 days. Mycoplasma pneumonia serology and Malarial ICT were negative. Urine analysis and chest x-ray were normal.

The following medications were administered: Hydrocortisone (100mg) every 8 hours and Clemastine (1mg) every 12 hours intravenously for 5 days along with supportive treatment. Topical application of Gentamicin drops (1ml) for conjunctivitis, Clobetasol ointment (5grams) for cutaneous lesions and Fluticasone Propionate cream (0.05%) for lesions on the face were prescribed. Nystatin oral drops and a mouthwash were started for oral hygiene. Pregabalin (75mg) per-oral twice a day was also added to counter the burning sensation particularly on palms and soles.

During her hospital stay, she complained of dysphagia which indicated the esophageal involvement of SJS-TEN overlap. Her mouth opening was limited and she was kept on soft diet due to ulcerations. She also complained of dryness and irritation in eyes. Laboratory evaluation revealed hypokalaemia (3.3 mmol/l) and reduced bicarbonate levels (19 mmol/l) that normalized after potassium and fluid resuscitation (28 mmol/l). She responded to the treatment and was significantly better after 5 days. She remained afebrile and generalized subsidence in rashes was observed with improved salivation and swelling of lips. She was discharged on oral Prednisolone, Cetrizine, Pregabalin and topical medications. The dose of steroids was gradually tapered over two weeks. On two weeks follow up, there was considerable resolution of rashes and oedema of the lips. Sloughing off of skin was noted in palms and soles with

new skin formation. Last follow up was at two months.

## Discussion

SJS and TEN are life threatening immune complex hypersensitivity reactions. They are progressive, severe variants of Erythema multiforme spectrum with drugs being the most common associations.

SJS can be differentiated from other skin conditions on 3 clinical criteria: the pattern of individual skin lesions, distribution of lesions and the extent of epidermal detachment.<sup>7</sup> The characteristic findings in SJS are widespread erythematous or purpuric macules which form flat atypical target lesions as the disease progresses to cause full thickness epithelial necrosis.<sup>2</sup> Our patient had developed erythematous macules but did not progress to form vesicular and target lesions. This suggests either a prevention of the development of full thickness epithelial necrosis due to early effective treatment or an atypical presentation. The lesions were widespread as compared to Erythema Multiforme which is localized. No epidermal detachment was seen which is more suggestive of TEN due to greater severity. The degree of confluence of lesions was higher in our patient than found in SJS alone but lesser as compared to TEN. It was diagnosed as drug induced based upon the fact that a temporal relationship with acetaminophen was established and the patient could correlate the increased exposure with increased severity of symptoms. The fever which preceded the appearance of the rash was most probably due to viral infection since her son was suffering from fever and flu like symptoms.

The first step in the management of patients with drug induced SJS is immediate withdrawal of the offending agent followed by supportive care, as done in our patient. Garcia-Doval et al.<sup>8</sup> report that earlier the drug is withdrawn the better the prognosis while exposure to drugs with longer half-lives increases the risk of death. Supportive care must include management of fluid and electrolyte requirements.<sup>8</sup> Our patient was administered corticosteroids as they reduce the inflammatory process which is the major cause of skin necrolysis. Management of SJS patients with steroids however, remains debatable as steroid use may also increase wound healing time, the risk of infection and cause gastrointestinal bleeding. Patterson et al highlighted its effectiveness in treating SJS in which none of the patients suffered any side effects.<sup>9</sup> However, no well controlled trials have been conducted to support the claim. Another efficacious option available in treating SJS and TEN is the use of intravenous Immunoglobulins. Several retrospective studies have shown it to be effective in SJS management when used in combination with corticosteroids.<sup>10</sup> However, being expensive its use is limited, particularly in developing countries like Pakistan.

## Conclusion

As per our experience, the causative agent is highly suggestive to be acetaminophen since no other drug was used and a temporal relationship between acetaminophen use and severity in symptoms was proven. However, other causes particularly viral infection could not be ruled out since oral provocation test to confirm acetaminophen involvement was avoided due to associated risks. It is hence important for the clinicians to be alert to severe hypersensitivity reactions even with drugs which are considered to be potentially safe such as acetaminophen.

## References

1. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol* 1993; 129: 92-6.
  2. French LE. Toxic epidermal necrolysis and Stevens Johnson syndrome: our current understanding. *Allergol Int* 2006; 55: 9-16.
  3. Kvedariene V, Bencherioua AM, Messaad D, Godard P, Bousquet J, Demoly P. The accuracy of the diagnosis of suspected paracetamol (acetaminophen) hypersensitivity: results of a single-blinded trial. *Clin Exp Allergy* 2002; 32: 1366-9.
  4. Trujillo C, Gago C, Ramos S. Stevens-Johnson syndrome after acetaminophen ingestion, confirmed by challenge test in an eleven-year-old patient. *Allergol Immunopathol (Madr)* 2010; 38: 99-100.
  5. Halevi A, Ben-Amitai D, Garty BZ. Toxic epidermal necrolysis associated with acetaminophen ingestion. *Ann Pharmacother* 2000; 34: 32-4.
  6. Bygum A, Gregersen JW, Buus SK. Acetaminophen-induced toxic epidermal necrolysis in a child. *Pediatr Dermatol* 2004; 21: 236-8.
  7. Rzany B, Hering O, Mockenhaupt M, Schröder W, Goertler E, Ring J, et al. Histopathological and epidemiological characteristics of patients with erythema exudativummultiforme major, Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol* 1996; 135: 6-11.
  8. Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol* 2000; 136: 323-7.
  9. Patterson R, Miller M, Kaplan M, Doan T, Brown J, Detjen P, et al. Effectiveness of early therapy with corticosteroids in Stevens-Johnson syndrome: experience with 41 cases and a hypothesis regarding pathogenesis. *Ann Allergy* 1994; 73: 27-34.
  10. Chen J, Wang B, Zeng Y, Xu H. High-dose intravenous immunoglobulins in the treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis in Chinese patients: a retrospective study of 82 cases. *Eur J Dermatol* 2010; 20: 743-7.
-