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Case study

Unveiling Paracetamol's Dark Side: The Stevens-Johnson Syndrome Saga

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Abstract - *Introduction: Acetaminophen is a common drug belonging to the broader category of Non-Steroidal Anti-inflammatory Drugs with analgesic and antipyretic properties. The potential side effects of paracetamol can range from mild drug reactions to severe life-threatening emergencies. Case History: 67-year-old female consumed paracetamol and amoxicillin for fever, upon consumption of paracetamol for 2 days on an empty stomach, she developed oral ulcers with dysphagia and eye redness. Tablet was withdrawn and she recovered from the episode. Discussion: Although the liver toxicity of acetaminophen is well known, a lesser-known side effect of this drug is Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These dermatological emergencies are associated with similar pathological processes, including epidermal apoptosis and detachment of the dermis and mucosa from the underlying layers. Conclusion: Currently, adverse drug effect of paracetamol such as SJS and TEN are extremely rare and are immune-mediated type IV hypersensitivity reactions involving primar ily CD8+ T lymphocytes. Other immune mediators are thought to be involved, including regulatory T cells, natural killer cells, interleukins, and drug metabolites, but their mechanisms are not fully defined. Genomic variations in human leukocyte antigen (HLA) genes have been associated with susceptibility and severity of acetaminophen induced SJS/TENS, but the details of these interactions remain unclear. The widespread use of acetaminophen and the associated morbidity of skin pathologies (SJS and TENS) require a thorough investigation of the causal processes involved in their pathogenesis.*

Keywords - *Adverse effects, Paracetamol, Skin lesions, Steven Johnson, Toxic Epidermal Necrolysis.*

I. INTRODUCTION

Stevens-Johnson syndrome and toxic epidermal necrolysis are acute, rare and potentially fatal skin reactions with systemic symptoms and loss of skin and, in some cases, mucous membranes are involved too.[18][35] In more than 80 percent of cases, medications are the leading cause.[10][23][26] Paracetamol (acetaminophen) is one of the leading cause of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), accounting for 5.2% of cases falling behind antibiotics (sulfonamides).[7][27][32] However, side effects of paracetamol are rare in India and there are few detailed reports of paracetamol-induced SJS.[8][10][12] It can present with multiple symptoms, the most common being nonspecific febrile illness that can cause malaise, headache, cough, rhinorrhoea, and polymorphic lesions of the skin and mucous membranes characterised by acute blisters and erosions.[26] The incidence of SJS is estimated to be approximately 1-6/1,000,000 persons

per year, with a mortality of 1-5%.[2][31][39]. One feature to distinguish between the two is based on involvement of total body surface area where less than 10% of skin epidermis is involved in SJS while more than 30% is involved in TEN. Borderline SJS/TEN is better 11-29% involvement of skin. [2][11][34]The most reported cases of analgesic-induced SJS were due to the presence of oxicams or propionic acid metabolic derivatives [27][32][37].

II. CASE HISTORY

67 year old female came with complaints of fever with dry cough since 4 days for which she received tab. PARACETAMOL and tab. AMOXICILLIN 500mg twice daily along with some injection and syrup (contents unknown) . After 2 days of paracetamol intake on empty stomach, she developed oral ulcers with difficulty in swallowing solid food and bilateral eye redness. She had no history of vomiting/loose stools. She had similar history in past on consumption of paracetamol for 2 episodes, 3 years ago, but milder without hospitalisation. No previous history of Tuberculosis, Diabetes mellitus, Hypertension, Hepatitis B&C, HIV nor any previous history of immunocompromised state. Obstetric History: She's married for 40 years with score P4L4, normal delivery, deliveries were uneventful for each pregnancy.

A. Head to Toe Examination

a. Eyes

- **Right Eye**: Ulcer (1×1 cm) on medial margin of eyelid with widespread conjunctival redness. Gregory DG scoring of 4(very severe) was made.
- **Left Eye**: Severe conjunctival hyperemia of grade 4.
- **Neck (outer surface)**: Multiple erythematous rashes, more seen on the left side extending up to sternocleidomastoid region.

b. Oral cavity

- **Lips**: Ulcer with irregular margin (1×2cm) with irregular fashion spread across the margin.
- **Tongue**: Linear ulcer with whitish discoloration (mucocutaneous candidiasis) – confirmed by swab.
- Unable to retract mouth fully.

c. Vitals (As measured on day of arrival)

- **Pulse Rate**: 138/min, measured on right upper arm, normal rate, rhythm, volume, character, no radio-radial and radio-femoral delay.
- **Blood Pressure**: 138/98 mm Hg, measured on right upper arm.
- **Respiratory Rate**: 23 cycles/min, Abdominothoracic type.
- **Glasgow Coma Scale**: 15/15 (normal)
- **Oxygen saturation**: 94%
- **Random Blood Sugar**: 140mg/dL
- **Temperature**: 98.8°F

d. Investigations

- **ESR**: 95mm/hr (≤10)
- **C Reactive Protein**: 13mg/L (<10)
- **Oesophagus imaging**: Normal
- **C-reactive protein**: 15%
- **Complete Blood Count**: WBC count: Absolute Monocyte count: 1.39 10^3/uL (0.2-0.95)
- **Serology (HIV, HbSAg)**: NEGATIVE
- **Swab culture**: Positive for Candida albicans infection.
- **Urine routine**: Normal

e. Treatment

1. Initial (before onset): Tab. Paracetamol, Tab. Amoxicillin 500mg B.D for 4 days along with some injection and syrup.
2. For conjunctivitis: (each given for 1 week duration)
Moxifloxacin eye drops, Tobramycin eye drops, Triamcinoline gel.
3. Tab. Montelukast & Desloratadine OD.
4. Inj. Acyclovir 400mg TID.
5. Inj. Ceftriaxone 1g IV BD.
6. Inj. Metronidazole 100mL IV TID.
7. Tab. Doxycycline 100mg BD.
8. Inj. Pantaprazole 40mg BD
9. Inj. Ondansetron 4mg (As and when required).
10. Tab. Fluconazole 150mg BD.
11. Clotrimazole mouth paint (done 3 times before stopping).
12. IV Fluids (Ringer Lactate, Dextran Normal Saline).
13. Syrup Sodium Alginate, Sodium Bicarbonate, Calcium Carbonate oral suspension 15mL TID.
14. Inj. Methylprednisolone 40mg IV OD.
15. Patient was reviewed in one week.

III. RESULTS AND DISCUSSION

The first step in achieving control was immediate withdrawal of the offender, followed by supportive treatment. Garcia-Doval et al reported that the sooner the drug is stopped, the better the prognosis, while exposure to drugs with longer half-lives increases the risk of death. [1] Supportive care should include regulation of fluid and electrolyte requirements. [19][24] A study by Khawaja et al reported a case of acetaminophen-induced SJS and TEN with generalized macular-papular rash, hyperaemic conjunctivitis, oral mucosal ulcers, and high fever, similar to the present case study. [16] The use of corticosteroids in SJS treatment is controversial. Some believe that their use can lead to delayed wound healing, increased risk of infection, masking the early signs of sepsis, gastrointestinal bleeding and increased mortality. [25][36][40] If steroids are required, it should be started early and tapered off quickly. [3][6][22]Very few cases of SJS have been reported after ingestion of paracetamol [15][16][23].

In publications between 1995 and 2011 describing SJS and TEN in the Indian population, Patel et al. published a study referring to Central electronic databases PubMed, Medline, Embase and UK PubMed indicated that 6.17% of SJS and TEN cases were associated with paracetamol intake.[4] Amongst NSAIDs, Paracetamol and nimesulide are the most commonly used drugs. [14][17][23] In the Serious Cutaneous Adverse Reactions (SCAR) study, an overall risk of SJS was observed with the use of oxicam derivative drugs. reported an increased risk with paracetamol use in Germany, Italy and Portugal, in addition to France, but very rarely from India. [24] [26] The presence of constitutional features, atypical target lesions with a tendency to coalesce, positive Nikolsky sign, involvement of more than one mucosa and residual signs. In the oral cavity, SJS causes extensive ulcerative lesions. [28][30] Prodromal symptoms occur in about 30% of cases and may begin 1-3 weeks after starting a new drug and last 1-2 weeks and include flu-like symptoms, sore throat, headache, arthralgia, myalgia, fever, and other rashes [27][6][9].

In some cases, eye changes such as dry eyes may be seen, similar to the symptoms of mucosal pemphigoid. Urethritis and external genital ulcers may occur. [38][13] Although many factors have been proposed as risk factors for SJS, including drug-induced infections, malignancy, and graft rejection, most have been attributed to adverse drug reactions. The most common medications are nonsteroidal anti-inflammatory drugs (NSAIDs), antipsychotics, antibiotics, allopurinol, and anticonvulsants. [16][37] SJS can be distinguished from other skin

diseases by three clinical criteria: (i) the pattern of individual skin lesions, (ii) the distribution of lesions, and (iii) the extent of epidermal detachment. [8][36] Characteristic findings of SJS include generalised erythematous or purplish macular lesions that form flat, atypical focal lesions as the disease progresses, causing full-thickness epithelial necrosis [2][41][7].

IV. CONCLUSION

SJS is a severe immune-mediated hypersensitivity reaction. In 90% of cases, mucosal erosion is observed, which is painful and especially responsible for eating difficulties. The most common drugs are nonsteroidal anti-inflammatory drugs, antipsychotics, antibiotics, allopurinol and anticonvulsants. However, some rare cases of SJS have been reported in the past and are thought to be related to the use of paracetamol. This case was diagnosed as SJS caused by paracetamol and a discovery correlation was made. Self-medication with paracetamol is common, due to it's over the counter status. Its most common side effect is liver toxicity. Except in cases of overdose, acetaminophen is relatively safe, so it can be used regularly. Additionally, 5.2% of SJS/TEN cases are due to acetaminophen-related reactions, making it the third leading cause of SJS/TEN. Although these cases do not usually occur, clinicians should be aware of the apparent risk in different individuals, especially those with a genetic predisposition. In addition, genetic variations of certain HLA types in different ethnic groups have been shown to react with acetaminophen, which can cause serious, life-threatening side effects. Although public opinion is very favourable to the use of acetaminophen, patients and doctors must recognize the risks involved. Awareness of these adverse effects may lead physicians to make more informed decisions to effectively respond to cases of SJS/TEN. Acetaminophen is a basic drug with antipyretic and pain-relieving effects, but doctors must consider the potential risks and consequences in order to provide comprehensive patient care and respond quickly in an emergency.

V. REFERENCES

1. Garcia-Doval I et al., "Toxic epidermal necrolysis and Stevens-Johnson syndrome: Does Early Withdrawal of Causative Drugs Decrease the Risk of Death?" *Archives of Dermatology*, vol. 136, pp. 323-327, 2000. Google Scholar | Publisher Link
2. Jha N et al., "A Study of Cutaneous Adverse Drug Reactions in a Tertiary Care Center in Punjab," *Indian Dermatology Online Journal*, vol. 9, no. 5, pp. 299-303, 2018. Google Scholar | Publisher Link
3. Auyeung J, and Lee M, "Successful Treatment of Stevens-Johnson Syndrome with Cyclosporine and Corticosteroid," *Canadian Journal of Hospital Pharmacy*, vol. 71, no. 4, pp. 272-275, 2018. Google Scholar | Publisher Link
4. Geetha Iyer et al., "Boston Type 2 keratoprosthesis- Mid Term Outcomes from a Tertiary Eye Care Centre in India," *Ocular Surface*, vol. 17, no. 1, pp. 50-54, 2019. Google Scholar | Publisher Link
5. Noel Frey et al., "Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Association with Commonly Prescribed Drugs in Outpatient Care Other than Anti-Epileptic Drugs and Antibiotics: A Population-Based Case-Control Study," *Drug Safety*, vol. 42, no. 1, pp. 55-66, 2019. Google Scholar | Publisher Link
6. Sato S et al., "Clinical Features of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis," *Pediatrics International*, vol. 60, no. 8, pp. 697-702, 2018. Google Scholar | Publisher Link
7. Yang SC et al., "Corrigendum to 'The Epidemiology of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in China'," *Journal of Immunology Research*, vol. 2018, no. 1, pp.1-3, 2018. Google Scholar | Publisher Link
8. Velasco-Tirado V et al., "Life-threatening Dermatoses: Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis," *PLoS One*, vol. 13, no. 6, pp. 1-12, 2018. Google Scholar | Publisher Link

9. Safiri S, and Ashrafi-Asgarabad A, "The Risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in New Users of Antiepileptic Drugs," *Epilepsia*, vol. 59, no. 5, pp. 1083-1084, 2018. Google Scholar | Publisher Link
10. Wolf R, and Marinović B, "Drug Eruptions in the Mature Patient," *Clinical Dermatology*, vol. 36, no. 2, pp. 249-254, 2018. Google Scholar | Publisher Link
11. Tangamornsuksan W, and Lohitnavy M, "Association Between HLA-B*1301 and Dapsone-Induced Cutaneous Adverse Drug Reactions: A Systematic Review and Meta-analysis," *JAMA Dermatology*, vol. 154, no. 4, pp. 441-446, 2018. Google Scholar | Publisher Link
12. Richard EB et al., "Variability in Management of Patients With SJS/TEN: A Survey of Burn Unit Directors," *Journal of Burn Care & Research*, vol. 39, no. 4, pp. 585-592, 2018. Google Scholar | Publisher Link
13. Khawaja A, Shahab A, and Hussain SA, "Acetaminophen Induced Steven Johnson Syndrome-Toxic Epidermal Necrolysis Overlap," *Journal of the Pakistan Medical Association*, vol. 62, pp. 524-527, 2012. Google Scholar | Publisher Link
14. Ramineni HB et al., "Phenobarbital Induced Stevens-Johnson Syndrome: A Case Report," *International Journal of Research in Medical Sciences*, vol. 3, 2015. Google Scholar | Publisher Link
15. French LE, "Toxic Epidermal Necrolysis and Stevens Johnson Syndrome: Our Current Understanding," *Allergology International*, vol. 55, no. 1, pp. 9-16, 2006. Google Scholar | Publisher Link
16. Deore SS et al., "Drug Induced-Stevens Johnson syndrome: A Case Report," *International Journal of Science Studies*, vol. 2, pp. 84-87, 2014. Google Scholar | Publisher Link
17. Kvedariene V et al., "The Accuracy of the Diagnosis of Suspected Paracetamol (Acetaminophen) Hypersensitivity: Results of a Single-Blinded Trial," *Clinical and Experimental Allergy*, vol. 32, pp. 1366-1369, 2002. Google Scholar | Publisher Link
18. Patel TK et al., "A Systematic Review of the Drug-Induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Indian Population," *Indian Journal of Dermatology, Venereology and Leprology*, vol. 79, pp. 389-398, 2013. Google Scholar | Publisher Link
19. P Farthing, J-V Bagan, and C Scully, "Number IV Erythema Multiforme," *Oral Diseases*, vol. 11, pp. 261-267, 2005. Google Scholar | Publisher Link
20. Patel PP et al., "An Analysis of Drug Induced Stevens-Johnson Syndrome," *Indian Journal of Medical Research*, vol. 136, no. 6, pp. 1051-1053, 2012. Google Scholar | Publisher Link
21. Ignacio Garcia-Doval et al., "Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome: Does Early Withdrawal of Causative Drugs Decrease the Risk of Death?" *Archives of Dermatology*, vol. 136, no. 3, pp. 323-327, 2000. Google Scholar | Publisher Link
22. Roujeau JC et al., "Medication Use and the Risk of Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis," *New England Journal of Medicine*, vol. 333, no. 4, pp. 1600-1608, 1995. Google Scholar | Publisher Link
23. Budania RJ et al., "Fatal Stevens-Johnson Syndrome Induced by Phenytoin: A Case Report," *International Journal of Basic & Clinical Pharmacology*, vol. 2, pp. 843-845, 2013. Google Scholar | Publisher Link
24. Patterson R, et al., "Stevens-Johnson Syndrome (SJS): Effectiveness of Corticosteroids in Management and Recurrent SJS," *Allergy Proceedings*, vol. 13, pp. 89-95, 1992. Google Scholar | Publisher Link
25. Sasmita Biswal, and Swayam Sourav Sahoo, "Paracetamol Induced Stevens-Johnson Syndrome - Toxic Epidermal Necrolysis Overlap Syndrome," *International Journal of Dermatology*, vol. 53, pp. 1042-1044, 2014. Google Scholar | Publisher Link
26. Ortonne N, "Histopathology of Cutaneous Drug Reactions," *Annales de Pathologie*, vol. 38, no. 1, pp. 7-19, 2018. Google Scholar | Publisher Link

27. Plachouri KM, Vryzaki E, and Georgiou S, "Cutaneous Adverse Events of Immune Checkpoint Inhibitors: A Summarized Overview," *Current Drug Safety*, vol. 14, no. 1, pp. 14-20, 2019. Google Scholar | Publisher Link
28. Lerma V et al., "Care in Patients with Epidermal Necrolysis in Burn Units: A Nursing Perspective," *Burns*, vol. 44, no. 8, pp. 1962-1972, 2018. Google Scholar | Publisher Link
29. Kumar R, Das A, Das S, "Management of Stevens-Johnson Syndrome-Toxic Epidermal Necrolysis: Looking Beyond Guidelines!" *Indian Journal of Dermatology*, vol. 63, no. 2, pp. 117-124, 2018. Google Scholar | Publisher Link
30. Schneider JA, and Cohen PR, "Stevens - Johnson syndrome and Toxic Epidermal Necrolysis: A Concise Review with a Comprehensive Summary of Therapeutic Interventions Emphasizing Supportive Measures," *Advances in Therapy*, vol. 34, no. 6, pp. 1235-1244, 2017. Google Scholar | Publisher Link
31. Zhang S et al., "Biologic TNF-Alpha Inhibitors in the Treatment of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Systemic Review," *Journal of Dermatological Treatment*, vol. 31, no. 1, pp. 66-73, 2020. Google Scholar | Publisher Link
32. Schwartz RA et al., "Toxic Epidermal Necrolysis: Part II. Prognosis, Sequelae, Diagnosis, Differential Diagnosis, Prevention, and Treatment," *Journal of the American Academy of Dermatology*, vol. 69, no. 2, 2013. Google Scholar | Publisher Link
33. Hsu DY et al., "Morbidity and Mortality of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in United States Adults," *Journal of Investigative Dermatology*, vol. 136, no. 7, pp. 1387-1397, 2016. Google Scholar | Publisher Link
34. Bettuzzi T et al., "Trends in mortality rates for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Experience of a Single Centre in France between 1997 and 2017," *British Journal of Dermatology*, vol. 182, no. 1, pp. 247-248, 2020. Google Scholar | Publisher Link
35. Marianne Lerch et al., "Current Perspectives on Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis," *Clinical Reviews in Allergy & Immunology*, vol. 54, no. 1, pp. 147-176, 2018. Google Scholar | Publisher Link
36. Papp A et al., "Treatment of Toxic Epidermal Necrolysis by a Multidisciplinary Team: A Review of Literature and Treatment Results," *Burns*, vol. 44, no. 4, pp. 807-815, 2018. Google Scholar | Publisher Link
37. James W. Antoon et al., "A Retrospective Cohort Study of the Management and Outcomes of Children Hospitalized with Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis," *Journal of Allergy and Clinical Immunology: In Practice*, vol. 7, no. 1, pp. 244-250, 2019. Google Scholar | Publisher Link
38. Antoon JW et al., "Incidence, Outcomes, and Resource Use in Children with Stevens-johnson Syndrome and Toxic Epidermal Necrolysis," *Pediatric Dermatology*, vol. 35, no. 2, pp. 182-187, 2018. Google Scholar | Publisher Link
39. Rajput R et al., "Paracetamol induced Steven-Johnson Syndrome: A Rare Case Report," *Contemporary Clinical Dentistry*, vol. 6, no. 1, pp. 278-281, 2015. Google Scholar | Publisher Link
40. Fakoya AO et al., "Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis; Extensive Review of Reports of Drug-Induced Etiologies and Possible Therapeutic Modalities," *Open Access Macedonian Journal of Medical Sciences*, vol. 6, pp. 730-738, 2018. Google Scholar | Publisher Link
41. Biswal S, and Sahoo SS, "Paracetamol induced Stevens-Johnson Syndrome-Toxic Epidermal Necrolysis Overlap Syndrome," *International Journal of Dermatology*, vol. 53, pp. 1042-1044, 2014. Google Scholar | Publisher Link