Case Series

A Rare Case Series of Cutaneous Adverse Drug Reaction Presenting with Stevens Johnson Syndrome in A Tertiary Care Rural Hospital of Western Maharashtra

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ABSTRACT

Adverse drug reactions pose a major health problem worldwide. Drug reactions range from minor maculopapular rash to erythema multiforme to severe Stevens Johnson Syndrome (SJS) or Toxic epidermal necrolysis (TEN). SJS is a life threatening vesicobullous disease characterised by an acute eruption that involves skin and mucous membranes. Here we present 4 cases of Stevens Johnson Syndrome which came to Pravara Rural Hospital, Loni, Ahmednagar, Maharashtra. First case is a 65 year old female presenting with severe mucocutaneous bleeding with exudative haemorrhagic ulcers on the back and chest next day after ingestion of ceftriaxone. Second case is a 74 year old elderly female presenting with peeling of the skin, blisters on neck, face, mouth, groin, chest region with ulcers in the oropharynx. The patient had history of consumption of ceftriaxone after which the skin lesions started. Third case is a 69 year old female presenting with dry scales with itching all over the body after taking ceftriaxone leading to Stevens Johnson Syndrome. The fourth case is a 22 year old female with history of ingestion of unknown medication from a local doctor and presented to our hospital with severe exudative ulcers on the mouth, lips and chest diagnosed to be Stevens Johnson syndrome. This case series highlights the importance of prescription of commonly used antibiotic like ceftriaxone with extreme caution. Early identification of severe adverse drug reactions can reduce the morbidity and mortality in these patients.

Keywords: Stevens Johnson Syndrome, Ceftriaxone, rare case series, management, rural hospital.

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INTRODUCTION

Adverse drug reactions (ADRs) are the most common cause of hospital admission and the fourth or sixth leading cause of death, thus leading to significant impact on health care costs.[1]

Stevens Johnson syndrome is a rare, severe cutaneous condition considered to be most life threatening dermatologic disease with a mortality incidence of 15% overall, and up to 50% in the elderly.[2, 3]

The prevailing understanding of the pathophysiology is that an immune reaction mediates the apoptosis of keratinocytes.

Drugs are found to be one of the important causes. More than 100 drugs have been implicated in causing SJS.[4] The most common offending agents are allopurinol, non-steroidal anti-inflammatory drugs (NSAIDs) like piroxicam, antibiotics, immune modulators like sulfasalazine, and anticonvulsants. The highest rates of cutaneous drug reactions occur due to antibiotics, particularly sulfonamides. Anticonvulsants can include Lamotrigine, phenytoin, and carbamazepine. Immunizations and infections such as mycoplasma pneumonia, cytomegalovirus, herpes simplex virus (HSV), coxsackievirus, and echovirus are less common causes.[5-7]

Immediate cessation of an offending drug and adequate supportive care in intensive care unit remain the mainstay of management of SJS. There is no specific treatment strategy available for this condition. Systemic corticosteroids, intravenous immunoglobulin therapy (IVIG), and other immunosuppressive therapy are used for its management.[8]

CASE SERIES

Case report 1

A 65 year old female patient came to casualty of Pravara Rural hospital with complains of warty lesions on the perioral area, axilla, neck, genitals and back, peeling of the skin with generalised weakness since 8 days and burning sensation all over the body since 2 days. The patient was apparently normal eight days before when she developed red haemorrhagic lesions followed by pustules which progressed into warty lesions after 8 days which were localised around mouth, neck, axilla and genitals and back bilaterally. Patient was admitted in district civil hospital, Ahmednagar and was then referred to our hospital for further management. On careful history of the patient, we came to know that patient had history of ingestion of ceftriaxone 8 days back from a local doctor, after which her

symptoms started. Ulcers were also present in the nasal and oral cavity.

On examination, detachment of the epidermis on the face, axilla, back and chest, (fig 1, 2) haemorrhagic crusts over the lips and erosions of the mucous membrane over the mouth and nose were observed. She was treated with injection hydrocortisone pulse therapy, broad spectrum antibiotics, cyclosporine twice a day. She was given Neosporin powder and glycerine ointment for external application on the lesions. Intravenous fluids to correct the electrolyte imbalance and high protein diet was advised. Causality assessment using Naranjo Causality algorithm was probable.

Figure 1 & Figure 2 shows detachment of the epidermis on the neck and back with excoriation and haemorrhagic crusts.

Case report 2

A 74 years old female patient from rural area of Ahmednagar district in Maharashtra presented to the emergency department of Pravara Rural Hospital with epigastric pain and blisters, peeling of the skin and burning sensation on lips, face, neck, mouth , groin, chest region with difficulty in swallowing since 30 days. One month before her presentation, patient had history of taking ceftriaxone prescribed by a local doctor, after which she started developing skin lesions, which were ignored by the patient. The patient had also complained of epigastric pain for one month, for which she consulted a local doctor. Upper GI endoscopy was done before 15 days which revealed esophagitis with small ulcer at the oropharynx. This was also ignored by the patient. The skin lesions gradually became scaly, tender and there was extensive mucocutaneous blistering (fig 3) with exudative ulcers over the back and flexors after which she presented to our emergency department and was immediately admitted for further management. The Naranjo Adverse Drug Reaction Probability Scale score of 6 was derived suggesting **Probable** association between ceftriaxone and the adverse drug hypersensitivity reaction. The patient was not taking any other medication prior to ingestion of ceftriaxone. A diagnosis of Stevens Johnson Syndrome was made.

The patient improved after initiation of intravenous methylprednisolone along with fluid replacement as supportive therapy. Corticosteroid dose was gradually tapered from sixth day of the treatment. Cyclosporine was also given to the patient twice daily. For congestion in eyes and eye lesions, moxifloxacin eye drops with lubricant drops were given thrice daily. Broad spectrum antibiotics were given to cover the gram positive and gram negative infections. Topical Mupirocin ointment was given to apply on the skin lesions thrice daily. High protein diet and plain water compresses on the lesions were advised to the patient. Xylocaine for symptomatic improvement in mouth ulcer along with multivitamins to aid wound healing were given.

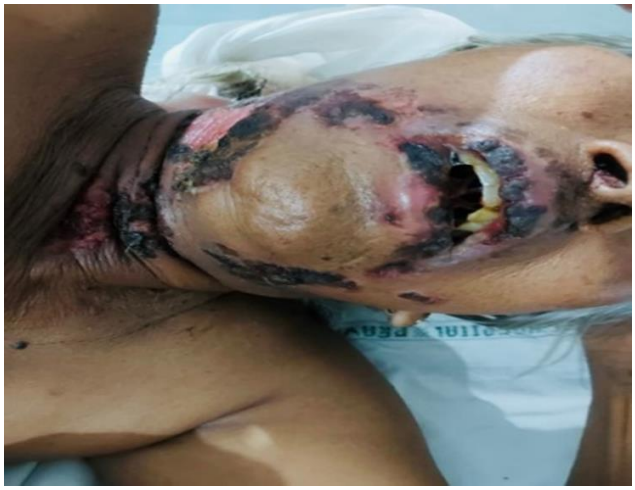

Figure 3: Extensive mucocutanous blistering and crusting on lips, face, mouth and neck

Case report 3

A 69 year old female came to casualty department of Pravara Rural hospital with complains of swelling over the face, dry flaky scales and itching all over the body since 15 days. Initially the scales were present on the face and gradually spread to the extremities. The patient had history of taking ceftriaxone for fever a month ago from a local doctor. After which, the symptoms started but they were ignored by her.

On examination, multiple dry scales with reddish lesions were present on the face, abdomen and the extremities (Fig 4, 5). The scales were non itchy and not oozing. She was started with methylprednisolone pulse therapy and broad

spectrum antibiotics along with intravenous fluids for correction of electrolyte imbalance and nutritional support. Mupirocin ointment was given for external application over the lesions. On causality assessment using Naranjo causality algorithm was probable.

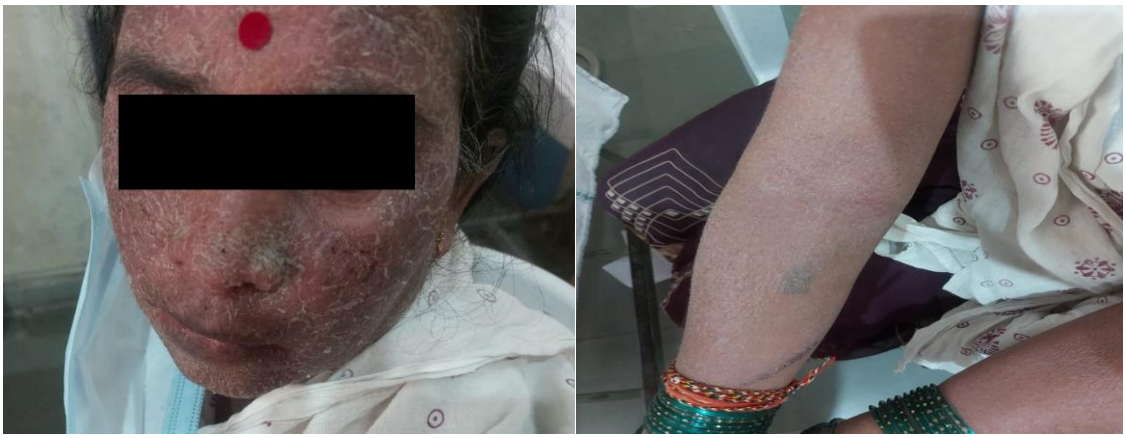

Figure 4 & Figure 5 shows dry flaky scales over the face and extremities

Case report 4

A 22 year old female presented to the casualty of our hospital with mucocutaneous blisters since 1 month. The blisters gradually ruptured and excoriated since 2 weeks. On careful history, it was learned that the patient had past history of ingestion of unknown medication intake from a local doctor a month ago, which led to the development of these skin lesions. On examination, ulcers were present on the lips, around the mouth and around the eyes. The ulcers were haemorrhagic and tender on palpation. The ulcers were excoriated and ruptured on the lower lips (Fig 6). She was treated with dexamethasone pulse therapy, broad spectrum antibiotics, Intravenous fluids (normal saline), analgesics to relieve the pain and symptomatic treatment for her ulcers with mupirocin ointment. Moxifloxacin eye drops were given for congestion in the eyes. Causality assessment using Naranjo algorithm was probable.

Figure 6: Mucocutaneous blisters with crusts, excoriated lesions on the lower lips

DISCUSSION

SJS is a rare and unpredictable delayed type of hypersensitivity reaction to medication. However, the mechanism has still not been understood and is complex, evidence has shown complex of various pathological mechanisms like drug metabolism, immunity, specific CD8+ cytotoxic lymphocytes, natural killer cell activation, cytokines including perforin /granzyme, Fas-Ligand, granulysin and Tumour Necrosis Factor (TNF) alpha involvement.[9]

A few individuals have a genetic predisposition to develop such disorders. Slow acetylators are deficient in enzymes involved in the destruction of toxic drug metabolites. Slow acetylators, especially immunocompromised patients and whose liver cannot completely detoxify reactive drug metabolites are at most risk.[10]

Drug or drug-peptide complexes are recognized by T-cell receptors. This results in downstream CD8 cytotoxic T-cell and NK-cell-mediated cytotoxicity and cytokine expression [especially of tumor necrosis factor (TNF)-alpha and interferon (IFN)-gamma]. These effects drive and perpetuate the pathogenesis of SJS.[11]

There has been a huge role of cytotoxic molecules in the pathogenesis of SJS which is an important topic of research. Fas-Fas ligand (FasL) interactions were initially thought to be integral to keratinocyte apoptosis.[12] There has been reporting of increased levels of perforin and granzyme B along with those of TNF-alpha and FasL correlated with SJS in the early studies in 2000.[13] Granulysin released by drug-specific cytotoxic CD8 T cells and natural killer cells has been identified as the ‘‘key mediator’’ for keratinocyte death in SJS. It is also reported that depleting granulysin reduces the cytotoxicity.[14]

People of specific ethnic groups with certain human leukocyte antigen subtypes have an increased incidence of SJS/TEN when exposed to specific drugs.[15] Ceftriaxone is a widely used third generation cephalosporin in our country. SJS due to ceftriaxone is a matter of concern due to its high efficacy and cost effectiveness in our population. Whether there is a genetic predisposition to the effects of these antibiotics in the rural population is a matter of research.

SJS is a fatal condition characterised by widespread erythema and tenderness followed by diffuse excoriation. If the patient is not immediately treated, it can lead to life threatening Toxic Epidermal Necrolysis (TEN). Careful history of such patients is important so that the offending drug can be avoided later. The management of such cases includes the sudden stoppage of the offending drug, short course corticosteroid therapy, cyclosporine, intravenous immunoglobulins, maintaining the haemodynamic of the patients, preventing and treating the secondary bacterial infections and symptomatic treatment of the lesions with the electrolyte balance and nutritional support. Sepsis and multiorgan failure are the most common causes of mortality in these patients.

Due to high risk of mortality in SJS patients, early diagnosis and prompt rigorous management with rapid identification and interruption of the culprit drug can drastically affect the prognosis. In our case series of four cases, the offending drug was removed at the time of admission of the patient in the hospital. Awareness about the adverse drug reactions among the physician and the patients in recognising the early signs and symptoms of Stevens Johnson Syndrome is a MUST to prevent its consequences. In the present case series, all our patients ignored the initial symptoms and presented late to the hospital, which affected the treatment outcomes.

CONCLUSION

Any drug can lead to drug reaction. Antibiotics should be prescribed judiciously and cautiously. There are currently no data to support specific guidelines for the treatment of SJS patients. Supportive care remains the most widely accepted intervention in SJS. Adjuvant therapies are debatable and the outcomes varies in patients depending on the age, gender and other co morbid conditions. More studies are needed in India to strengthen the database on the pathogenesis and treatment modalities of SJS to improve the prognosis in these patients. All the patients should receive appropriate medication at the right dose at the right time in the right amount at the right cost to meet their requirements.

REFERENCES

1. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies.JAMA. 1998;279(15):1200-1205
2. Phillips EJ, Bouchard CS, Divito SJ. Stevens - Johnson syndrome and toxic epidermal necrolysis-coordinating research priorities to move the field forward. JAMA Dermatol. (2022). doi: 10.1001/jamadermatol.2022.0484. [Epub ahead of print].
3. Chang W-C, Abe R, Anderson P, Anderson W, Ardern-Jones MR, Beachkofsky TM, et al. SJS/TEN 2019: from science to translation. J Dermatol Sci. (2020) 98:2–12. doi: 10.1016/j.jdermsci.2020. 02.003
4. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med 1995; 333:1600-7.
5. Chong I, Chao A. Stevens-Johnson syndrome/toxic epidermal necrolysis and treatment with a biologic: A case report. Perm J 2017; 21:16–060.
6. Khan FA, Vishwakarma K, Shah IA. Drug-induced Stevens-Johnson syndrome in a 21 year male patient: A case report. Adv Med Dent Res 2015; 1(1):31–2.
7. Castana O, Rempelos G, Anagiotos G, Apostolopoulou C, Dimitrouli A, Alexakis D. Stevens-Johnson syndrome: A case report. Ann Burns Fire Disasters 2009;22(3):147–51
8. Kardaun SH, Jonkman MF. Dexamethasone pulse therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis. Acta Derm Venereol 2007; 87:144-8.
9. Stevens Johnson Syndrome & Toxic Epidermal Necrolysis[http://dermnetnz.org/reactions/sjs- en.html]
10. Ovivera OA, Sanches M, Selores M. [Stevens-Johnson syndrome and toxic epidermal necrolysis]. Acta Med Port. 2011; 24(4):995-1002.
11. Schneider JA, Cohen PR. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Concise Review with a Comprehensive Summary of Therapeutic Interventions Emphasizing Supportive Measures. Adv Ther. 2017 Jun; 34(6):1235-1244. doi: 10.1007/s12325-017-0530-y. Epub 2017 Apr 24. PMID: 28439852; PMCID: PMC5487863.
12. Abe R, Shimizu T, Shibaki A, Nakamura H, Watanabe H, Shimizu H. Toxic epidermal necrolysis and Stevens-Johnson syndrome are induced by soluble Fas ligand. Am J Pathol. 2003;162(5):1515–20. doi:10.1016/S0002-9440(10)64284-8 (PMID: 12707034)
13. Posadas SJ, Padial A, Torres MJ, Mayorga C, Leyva L, Sanchez E, Alvarez J, Romano A, Juarez C, Blanca M. Delayed reactions to drugs show levels of perforin, granzyme B, and Fas-L to be related to disease severity. J Allergy Clin Immunol. 2002;109(1):155–61. doi:10.1067/mai.2002.120563 (PMID: 11799383)
14. Chung WH, Hung SI, Yang JY, Su SC, Huang SP, Wei CY, Chin SW, Chiou CC, Chu SC, Ho HC, Yang CH, Lu CF, Wu JY, Liao YD, Chen YT. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. Nat Med. 2008; 14(12):1343–50. Doi: 10. 1038/nm.1884 (PMID: 19029983).
15. Dao RL, Su SC, Chung WH. Recent advances of pharmacogenomics in severe cutaneous adverse reactions: Immune and nonimmune mechanisms. Asia Pac Allergy 2015; 5:59-67.[Google Scholar]

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