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CASE REPORT ON DICLOFENAC INDUCED STEVENS-JOHNSON SYNDROME

G Venkata Nagaraju, SK. Mariyabi
Department of Pharmacy Practice, Hindu College of Pharmacy, Guntur.

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***Corresponding author**
G Venkata Nagaraju

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Abstract
Stevens-Johnson Syndrome (SJS) is a rare, severe hypersensitivity disorder affecting the skin and mucous membranes. It is primarily triggered by adverse reactions to medications or infections and is considered a medical emergency. The syndrome initially presents with flu-like symptoms, including fever and fatigue, followed by a painful, widespread rash, blistering, and detachment of the skin and mucosal surfaces. Common causative agents include antibiotics, anti-seizure drugs, NSAIDs, and infections such as Mycoplasma pneumoniae or herpes simplex. Diagnosis relies on clinical evaluation and skin biopsy when needed.

Keywords: Stevens-Johnson syndrome, Skin and mucous membrane disorder, Drug reaction.

Introduction
Previously known as Lyell syndrome, Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are variants of the same condition and are distinct from erythema multiform major staphylococcal scalded skin syndrome and other drug eruptions [1-3].

Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis is a rare, acute, serious, and potentially fatal skin reaction in which there are sheet-like skin and mucosal loss accompanied by systemic symptoms. Medications are causative in over 80% of cases.

Stevens - Johnson syndrome/ Toxic Epidermal Necrolysis are classified by the extent of the detached skin Surface area.

- Stevens-Johnson syndrome: less than 10% body surface area.
- Overlap Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis: 10% to 30% body surface area.
- Toxic Epidermal Necrolysis: 30% body surface area.

Pathogenesis
1. Triggering factors
Drugs: Commonly implicated drugs include sulfonamides, carbamazepine, phenytoin, NSAIDs, and allopurinol [4-6].

Infections: Mycoplasma pneumoniae and Herpes simplex virus are significant triggers, especially in children [5, 7].

HLA Genotypes

HLA-B*15:02: Associated with carbamazepine-induced SJS, prevalent in Southeast Asians.

HLA-B*58:01: Linked to allopurinol-induced SJS/TEN.

HLA-A*31:01: Associated with increased risk of carbamazepine hypersensitivity in non-Asians [4, 7, 8].

2. Immune Response Activation
- **Drug hapten Formation:**
  Drugs or metabolites bind to host proteins, forming hapten-protein complexes. These complexes are presented to cytotoxic T-cells by HLA molecule, triggering an immune Response [4, 5].
- **T-cell Activation:**
  HLA restricted presentation leads to the activation of CD8+ T-cells which release inflammatory cytokines. (e.g., TNF- alpha, IFN – gamma) [6, 9].

3. **Keratinocyte Apoptosis:**
   Fas-Fas Lignad interaction: Binding of FasL on immune cells to FasL on Keratinocytes initiates apoptosis via the extrinsic pathway [6, 11].
   Granzyme B and performing release: CD8+ T-cells and natural killer (NK) cells release Granzyme B and perforin, directly inducing Keratinocyte apoptosis [10, 11].
   Cytokine storm: Pro Inflammatory cytokines like TNF-alpha and IL-6 amplify Inflammation, contributing to widespread tissue necrosis [6, 11].
4. **Epidermal damage and Systemic effects:**
   - **Keratinocyte Necrosis:** Apoptosis and necrosis of Keratinocytes results In extensive Epidermal detachment and blistering [5, 11].
   - **Mucosal involvement:** The mucosal membranes are heavily affected, causing ulceration and pain [9, 11].
   - **Systemic Inflammation:** Cytokine release, contributes to systemic symptoms, Including fever, multi-organ damage [10, 11].

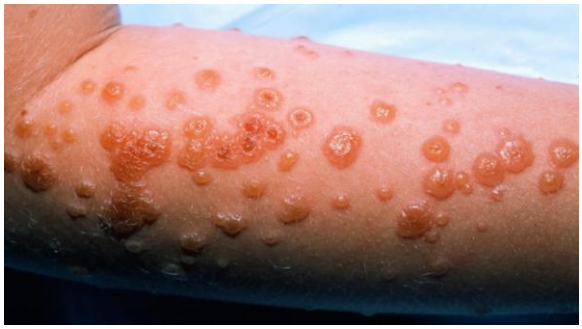

Figure 1 Stevens–Johnson syndrome – Bullous erythema multiforme

Symptoms

1. **Prodromal Symptoms:**
   - Fever, malaise, and fatigue [12, 13].
   - Flu-like symptoms (cough, rhinorrhea and sore throat) [13, 14].
2. **Skin Manifestations:**
   - Painful erythematous macules or purpuric spots may coalesce [14, 15].
   - Blisters on skin, mouth, eyes, nose, ears and genitals [5].
   - Shedding the skin after blisters form [8, 9].
   - Unexplained pain in the skin [5, 6].
   - Swelling of the lips, mouth, throat, tongue or face·
   - Painful red or purplish skin rash that spreads and blisters [6].
   - Detachment of the upper layer of the skin (epidermis).
   - Painful sores on mucous membranes, including the mouth, eyes, and genital area
   - Eye inflammation, which can lead to vision problems if untreated.

Causes:

The most common cause of SJS is an adverse drug reaction. Almost any drug can result in SJS include

- Antibiotics (e.g., sulfonamides, penicillin)[16,5].
- Anti-seizure drugs (e.g., carbamazepine, lamotrigine) [8, 10].
- NSAIDs (e.g., ibuprofen, diclofenac) [5].

SJS is more common in children and younger adults, but can develop at any age. Typical problems associated with SJS can include [9].

- Conjunctivitis [11].
- Ulceration of the eye lids [9,11].
- Inflammation inside him eyes (iris) [17].
- Corneal blisters [13, 17].
- Corneal perforation, a hole in the cornea that can lead to permanent vision loss [9, 13].

Diagnosis

SJS is primarily diagnosed as clinically, supported by histopathology and identifying potential triggers.

Clinical Criteria

Prodromal Symptoms: Fever, malaise, and upper respiratory symptoms.

Widespread erythematous or purpuric macules evolving to bullae and necrosis.

Mucosal involvement: Oral, ocular, genital lesions are present in >90% of cases.

Skin detachment <10% body surface area for SJS,> 30% for Toxic Epidermal Necrolysis (TEN)

Diagnostic tests

Skin Biopsy: Demonstrates Keratinocyte necrosis, sub epidermal blistering, and sparse lymphocytic infiltrates [16, 18].

Patch testing: useful in identifying drug triggers after delivery [5, 17].

Genetic testing: HLA typing for specific at risk alleles. (e.g., HLA-B*15:02 for carbamazepine) [8, 19].

Treatment

Treatment of SJS involves immediate cessation of the offending agent and prompt medical intervention.

Drug withdrawal:

Immediate discontinuation of the suspected medication reduces mortality risk [13, 20].

Pharmacological Interventions:

Corticosteroids: Controversial but often used in early-stage disease; may reduce inflammation and half progression.

Intravenous immunoglobulin (IVIG): High dose IVIG has been used for immunomodulation, although evidence is inconsistent.

Cyclosporine: Shows promise in modulating T – cell activity and reducing progression [9].

Case Study

A 39 Year old male patient was admitted in the department of dermatology with chief complaints of erythematous leisions with scaling on face, upper trunk and back since 5 days due to abnormal administration of diclofenac. His past history was stroke 2 months back, and he is alcoholic and smoker since 20yrs. His ultra sound abdomen reveals cholelithiasis. His lab data were Haemoglobin : 12.7g/dl, platelet : 3.75lakh/mm^3, Total WBC : 13200 cells/mm^3, SGPT : 69IU/dl Total Bilirubin : 1.3mg/dl, E : 05%, L : 15%, M :05%, N : 75%, ALP : 129IU/dl, Direct bilirubin : 0.3mg/dl, Indirect bilirubin : 1.9mg/dl, SGOT : 30IU/dl. His hospital medication includes : Inj. Dexamethasone 2cc, Inj. Pantop 40mg, Inj. Avil 2cc, Inj. Linezolid 600mg, 2% Miconazole cream over groin TC leisions, Fusidin+0.1%beta methadone E/A over lips, Tab. Fluconazole 200mg, Tab. Azee 500mg, Nyapalin forte, T. BC, Glycerine mix with water and apply,0.1%beta methadone cream, Tab. Cyclosporine 50mg, Syp. Potchlor 10ml in glass water TID.

His discharge medication includes:

- Pantop 40mg
- Tab linezolid 600mg
- 2%miconazole cream
- Tab fluconazole 200mg
- Tab. Niacinamide

Discussion

Stevens - Johnson syndrome (SJS) is a severe and life-threatening mucocutaneous disorder requiring urgent medical attention. Its rarity and potential for significant morbidity and mortality highlight the importance of understanding its pathogenesis, clinical features, treatment, and prevention strategies. SJS not only affects the skin but also has a profound impact on mucous membranes, vision, and overall quality of life. Many patients experience long-term sequelae such as chronic ocular damage, corneal scarring, dry eye syndrome, and even blindness, significantly affecting their daily activities. Additionally, scarring of the genital mucosa can lead to complications such as painful intercourse and urinary tract issues. These long-term effects emphasize the need for multidisciplinary care, including dermatologists, ophthalmologists, and pain specialists, to ensure holistic treatment.

Conclusion

Stevens - Johnson syndrome is a critical condition with high morbidity and mortality. Early recognition, prompt discontinuation of causative agents, and supportive care are essential to improving patient outcomes. Ongoing research and preventive strategies, including genetic screening and pharmacovigilance, are vital in addressing this severe condition effectively.

Ethical permission

Authors took prior consent from patient before taking this case and also taken ethical permission from head of the department and Superintendent of government General Hospital Guntur.

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Conflict of Interest

Authors are declared that no conflict of interest.

Inform consent

Inform Consent has taken from the patient. .

Author Contribution

All authors are contributed equally.

References

1. Jha N, Alexander E, Kanish B, Badyal DK. A Study of Cutaneous Adverse Drug Reactions in a Tertiary Care Center in Punjab. Indian Dermatol online J. 2018 Sep-Oct;9(5):299-303 [PMC free article] [PubMed]
2. Auyeng J, Lee M. Successful Treatment of Stevens-Johnson Syndrome with Cyclosporine and Corticosteroid. Can J Hosp Pharm. 2018 Jul-Aug; 71(4):272-275 [PMC free article] [PubMed]
3. Iyer G, Srinivasan B, Agrawal S, Ravindran R, Rishi E, Rishi P, Krishnamoorthy s. Boston Type 2 Keratoprosthesis-mid term outcomes from a tertiary eye care Centre in India. Ocul Surf. 2019 Jan; 17(1):50-54 [PubMed]
4. Chung, W. H., et al. (2004). Medical genetics: A marker for Stevens-Johnson syndrome. Nature, 428(6982), 486.
5. Mockenhaupt, M., et al. (2008). The risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with NSAIDs. Epidemiology, 19(2), 303-309.
6. Bellón, T., et al. (2009). Immunopathogenesis of Stevens-Johnson syndrome and toxic epidermal necrolysis. Current Opinion in Allergy and Clinical Immunology, 9(4), 294-300.
7. Shi, Y. W., et al. (2012). HLA genotype and carbamazepine-induced cutaneous adverse drug reactions: A meta-analysis. Epilepsia, 53(3), 517-525.
8. Hung, S. I., et al. (2005). Genetic susceptibility to carbamazepine-induced cutaneous adverse drug

reactions. Pharmacogenetics and Genomics, 15(4), 297-306.
9. Bastuji-Garin, S., et al. (1993). Toxic epidermal necrolysis (Lyell syndrome): Incidence and drug etiology in France, 1981–1985. Archives of Dermatology, 129(1), 37-42.
10. Pichler, W. J. (2003). Delayed drug hypersensitivity reactions. Annals of Internal Medicine, 139(8), 683-693.
11. White, K. D., et al. (2015). Understanding the pathogenesis of Stevens-Johnson syndrome and toxic epidermal necrolysis. Allergy, 70(9), 938-949.
12. Choudhary, S., et al. (2016). Clinical manifestations of Stevens-Johnson syndrome and toxic epidermal necrolysis: A review. Indian Journal of Dermatology, 61(3), 290-295.
13. Cacoub, P., et al. (2000). Severe cutaneous adverse reactions: Clinical features, management, and prognosis. International Journal of Dermatology, 39(8), 543-548.
14. Fagot, J. P., et al. (2001). Incidence and risk factors for Stevens-Johnson syndrome and toxic epidermal necrolysis in the French population. Pharmacological Research, 43(5), 237-243.
15. John, A., & Diamond, G. (2011). The clinical spectrum of Stevens-Johnson syndrome and toxic epidermal necrolysis: An update. Journal of Clinical Medicine, 5(2), 142-148
16. Roujeau, J. C., & Stern, R. S. (1994). Severe adverse cutaneous reactions to drugs. New England Journal of Medicine, 331(19), 1272-1285.
17. Fritsch, P. O., & Sidoroff, A. (2000). Severe drug-induced skin reactions. Allergy, 55(12), 1216-1225.
18. High, W. A., et al. (2006). Stevens-Johnson syndrome and toxic epidermal necrolysis: Pathogenesis, clinical presentations, and treatment. Journal of the American Academy of Dermatology.
19. Wang, C. W., et al. (2013). Immunopathogenesis and risk factors for allopurinol severe cutaneous adverse reactions. Current Opinion in Allergy and Clinical Immunology.
20. Kim, K. J., et al. (2016). Management of Stevens-Johnson syndrome and toxic epidermal necrolysis. Journal of Clinical Dermatology.