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STEVENS–JOHNSON SYNDROME ASSOCIATED WITH VALPROIC ACID: A CASE REPORT

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ABSTRACT

Stevens-Johnson syndrome (SJS) is a rare vesiculobullous disease of the skin and mucosa. Without proper management, it can be life threatening. Very strong associations of sodium valporate –induced SJS werereported in this case report. Medical history revealed that SJS developed following a change in medication for epilepsy from phenytoin to valproic acid (300 mg bid) by a local physician. Our authors suggested that, to overcome this problem, early diagnosis and implementation of interdisciplinary approach for management of SJS and careful monitoring for complications with regards to morbidity and mortality of life threatening cutaneous disorders. This report should alert the physicians to this severe cutaneous reaction of valproic acid.

INTRODUCTION

The erythema multiforme (EM) spectrum of diseases comprises a cluster of closely related acute exanthematic intolerance reactions of the skin which are clinically characterized mainly by target lesions, and by satellite cell necrosis of the epidermis in histopathology. These symptoms represent the morphologic expression of an archetypicpolyetiologic reaction pattern of the skin, the EM-like reaction pattern, which is caused by cytotoxic cells attacking epidermal cells expressing foreign antigens [e.g. viral, bacterial, drugs, non-self-major histocompatibility complex (MHC)]. The EM-spectrum [1,2] comprises fairly frequent and mild variants [e.g. the herpes simplex-associated EM (HAEM)] [3] and infrequent and life-threatening variants which are most often drug induced: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)[4].

Stevens-Johnsonsyndrome(SJS) is a rare vesiculobullous disease of the skin and mucosa. Without proper management, it can be life threatening. The characteristic target-like skin lesions consist initially of macules, which then develop into central necrosis to form vesicles and bullae, which lead to the denudation of the face, trunk, and extremities, and which are accompanied by the involvement of two or more mucosal surfaces [5]. Although the pathophysiology of SJS is not entirely understood, increased susceptibility has been observed in patients with immune-associated conditions [6]. We are showing few drugs causes of SJS, are reported below the table 1. List of suspected drugs to cause the Stevens-Johnson syndrome [7,31].

CAUSATIVE DRUGS	CATEGORY
Phenytoin Carbamazepine Phenobarbital Valproic acid Lamotrigine	Anti-epileptic drugs

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NSAIDs Aspirin Paracetamol Diclofenac	Anti-inflammatory drugs
Penicillins Amoxicillin Ciprofloxacin Azithromycin	Antibiotics (Sulfa based drugs)
Chloroquine Doxycycline	Antimicrobial drugs
Co-trimoxazole	Antifungal drugs
Nevirapine Stavudine + lamuvudine+Nevirapine	Anti retrovirals drugs
Isoniazid Rifampicin Pyrazinamide	Anti-tuberculosis drugs

SJS are immunologic in origin, but their exact etiology is not known. Young Researchers have to determined that apoptosis of keratinocytes occurs; this cell destruction is thought to be mediated or triggered by a cytokine, such as tumor necrosis factor. Antigen-antibody immune complexes are formed that trigger cytokine release. CD4 and CD8 T lymphocytes also are present in patients with SJS or TEN [8,9] . The patho-mechanisms of drug induced SJS/TEN are only partially understood. Clinical observations (the lag period between exposure and the onset of the eruption, shortening of the lag period and the increasing severity of SJS/TEN with repeated exposures) as well as the presence of predominantly CD8+ T lymphocytes and activated macrophages in the epidermis, [10-12] and additionally CD4+ T cells in the dermis, indicate a cytotoxic cellular immune reaction directed at keratinocytes; the latter, in turn, express adhesion molecules and MHC II. There is a drastic overexpression of tissue necrosis factor-α (TNFα) in the epidermis,[13] derived from macrophages as well as from keratinocytes, which is obviously linked to extensive apoptosis. TNF-α may both directly induce apoptosis and attract more effector cells. The pivotal role of TNF-α is underscored by the observation that TNF-α inducing agents like ultraviolet B light [14] or x-rays [15] have a potentiating effect on SJS/TEN. It has been recently shown that, in TEN, keratinocytes express lytic Fas ligand (FasL, CD95L) and soluble FasL is present in high levels in the peripheral blood.[16] It appears that FasL expression which triggers apoptosis by interaction with Fas (CD95, a cell surface death receptor physiologically expressed by keratinocytes) is the critical step in the genesis of SJS/TEN. Causative drugs or their metabolites are thought to act as haptens and to render keratinocytes antigenic by binding to their surfaces, being presented on both MHC I and II molecules.[17] Propensity for drug eruptions, including SJS/TEN, has been linked to defects of the detoxification systems of the keratinocytes:[18] their incidence is increased in the slow acetylator phenotype[19] and in HIV-infected patients who are deficient in glutathione, an important scavenger of toxic compounds. Also, SJS/ TEN may arise in the context of the carbamazepine or hydantoin hypersensitivity syndrome which is characterized by defective cytochrome P450 detoxification of aromatic compounds. [20]

CASE REPORT -1

A 28-year-old epileptic women with Valproic acid induced SJS of four day duration was referred to the Department of dermatology of a tertiary care hospital, for the management of oral mucous membrane erosions and wide spread erythematous macules extending over her both limbs since two days. Medical history revealed that SJS developed following a change in medication for epilepsy from phenytoin to valproic acid (300 mg bid) by a local physician. After 4 days of administration of the medication, the patient developed blisters preceded by high grade fever and headache. They ruptured to form painful erosions in oral cavity. Subsequently she reported to the hospital, where the offending drug was withdrawn immediately. The laboratory investigations, reveals that, haemoglobin 11.5g/dL, Platelet count 1,40,000/cmm, and WBC 5,500/cmm. Neutrophil was 68%, lymphocyte 19% and RBC 33-35/HPF, Pus cells 5-6/HPF; Serum electrolytes were found to be normal, urine culture showed no growth and causality assessment score of 7 (Naranjo's criteria) were indicative of probable Valproic acid-induced SJS. Systemic corticosteroid (Dexamethasone, 1 mg once daily intravenously for ten days) along with tablet chlorpheniramine maleate 5mg/OD/bed time, Paracetamol 500 mg/TID and emollient cream were prescribed I.V fluids were given as a supportive therapy. Examination in the Department of Dentistry revealed erosive ulcerations in the oral cavity. The lips were encrusted [Figure A,B,C,D]. Figure A. Haemorrhagic of encrustations on both lips, Figure B & C. Epidermal keratinocytes and a subepidermal blister in hands and toes. Figure D. Macules and patches on limbs. The mucosal ulcerations and Haemorrhagic of crusts of both lips were observed. After two weeks of the treatment skin rashes started to fade away, no fever, relief from pain and improved general well being. She was discharged on medication and asked her consult the physician regularly till she come back to a normal, without manifestations of SJS.

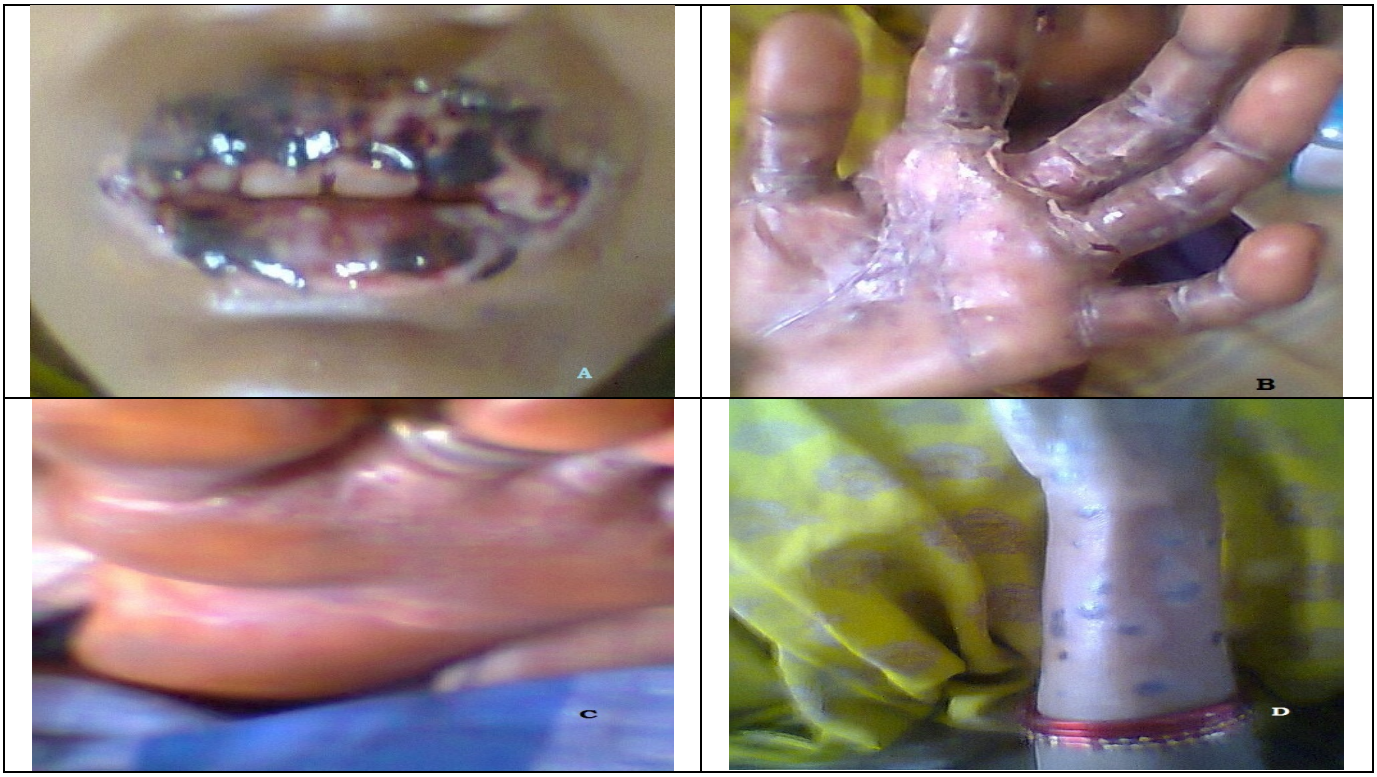
DISCUSSION

Stevens- Johnson syndrome is an acute mucocutaneous disease. Most of the authors have proposed that SJS be referred to as " erythemamultiforme major" to differentiate it from erythema multiforme of Von Hebra, the so –called erthemamultiforme minor [26]. Since the description of Thomas [27] there has been much confusion in the literature between SJS and erythema multiforme

ofVon Hebra, often due to herpes simplex infection and where cutaneous disease is characterized by symmetrical fixed, red, round, target like lesions [28]. Inorder to clarify these clinical descriptions, Bastuji- Garin et al [29] proposed a classification in 1993.

Stevens - Johnson syndrome is most often associated with drug reactions and less frequently with infections. Among infections.*M.Phenumoniae* is the most common agent responsible for SJS [26]. Oral lesions are present in patients and ocular lesions are present in two-thirds and genital lesions may be present: these can be maculopapular and sometimes vesticulobullous, as they initially were in our patient. Target like lesions are present in approximately 50% of patients. Pustualar lesions are very rare, especially in the term of hypopion –like pustules. We agree that our case is similar to that of Tay Y.K et al 1996 &Barbaud A 1998.

Naveen KN et al reported that SJS was caused by valproate when it was used in combination with other drugs [30]. Similar findings was observed in our present case report.



Patients must be treated with fluid management, nutritional support, and infection control measures. Skin, eye, and mouth care are a priority. Pain management also is a major consideration. Many hospitals without a burn unit may lack essential supplies and staffing resources to provide complex skin care. Improving the outcomes for patients with SJS depends on early recognition as well as early appropriate interventions. Prompt withdrawal of the suspected offending agent should occur, which can mean stopping all but life-sustaining drugs to eliminate the suspected agent. Increased survival has been observed in patients who stopped taking offending agents with short half-lives early [21]. Patient education must take place when beginning any new drug, including stopping a drug immediately and calling healthcare providers at the first sign of rash or skin discoloration. The use of corticosteroids in treating SJS and TEN is controversial. Evidence suggests that corticosteroids cause SJS and TEN [8], although some researchers support the use of corticosteroids in the treatment of SJS but not TEN. Many patients with cancer are on prednisone or dexamethasone as part of their treatment; therefore, a physician or an advanced practice nurse must determine whether these medications should be continued. Currently, no specific treatment modality has been established as standard for SJS patients. But in the University of Florida management guidelines for toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) [22] has been established and follow care should be taken for the patients.

- ❖ Admit patient directly to the burn intensive care unit (BICU) or an intensive care setting
- ❖ Discontinue corticosteroids if they are being used to treat the eruption
- ❖ Discontinue unnecessary medications and suspect medications

❖ Obtain baseline laboratory tests, such as complete blood count, liver function tests, metabolic panel, chest X-ray films, and any other appropriate imaging or serologic tests, including an immediate (stat) immunoglobulin A (IgA) serum level
❖ Look carefully for evidence of infection
❖ Obtain punch biopsies of skin for diagnosis confirmation. An alternative for rapid diagnosis is removal of a bulla roof for immediate frozen sections to differentiate between TEN and staphylococcal scalded skin syndrome (SSSS)
❖ Culture skin, blood, body orifices (as appropriate), and urine daily to monitor for early infection, and keep abreast of changing antibiotic sensitivities
❖ Use systemic antibiotics only for documented infections or signs of sepsis
❖ Place large-bore intravenous lines or a central venous line in an area of uninvolved skin to ensure adequate intravenous access
❖ If within 48–72°h of bulla onset, use intravenous immunoglobulin (IVIG), sucrose depleted, 1 g/kg/day for 3 days infused over 4 h. If 72 h have passed, but the patient is still actively progressing with new lesions, IVIG may still be useful
❖ Monitor fluid and electrolytes closely and begin total parenteral nutrition (TPN) in patients unable to take nourishment. Fluid replacement need not be as aggressive as for burns of same extent
❖ Debridement of necrotic and desquamating areas may be performed
❖ Consult ophthalmology to assess ocular involvement
❖ Consult otorhinolaryngology to evaluate extent of upper respiratory tract involvement
❖ Further consultations driven by patient condition (i.e. internal medicine to manage comorbidities, pulmonary medicine for airway involvement, gastroenterology for alimentary involvement, and gynecology or urology for genitourinary involvement)
❖ Physical therapy daily to preserve limb mobility
❖ Pain relief measures, such as patient-controlled analgesia (PCA) pump
❖ Hydrotherapy (whirlpool) if needed
❖ Nonstick dressings to denuded areas, saturated with 0.5% silver nitrate impregnated every 3–8 h as needed. Pre-impregnated dressings with silvernitrate are an alternative
❖ Avoid sulfa-containing topical or systemic preparations
❖ Oral care with chlorhexidine rinses and white petrolatum to lips
❖ Air-fluidized bed to minimize shearing force
❖ Keep room warm to prevent hypothermia
❖ Foley catheter and nasogastric tube placement only when necessary
❖ Avoid unnecessary manipulation of skin. Adhesive tape should not be applied directly to involved skin when possible

❖ Baby shampoo for cleansing hairy areas daily
❖ Mineral oil or petrolatum for dry skin
❖ Skin substitute grafting (porcine xenografts or artificial skin) based on BICU protocol

SOME OTHER SUPPORTIVE MEASURES

SKIN

Patients should be placed on an aluminum foil. Loose sheets of detached skin may cautiously be removed, but early aggressive debridement as performed in burns is not indicated because it is painful and increases the extent of the erosions; also, the necroses are only superficial and represent no obstacle for re-epithelization. Erosions should be covered with gauze or hydrocolloid dressings. Sulfonamide containing topical treatments should be avoided. When using topical antibacterials or antiseptics, the possibility of systemic absorption has to be considered. Fresh-frozen or cryopreserved cadaver allograft [23] and porcine xenograft skin, [24] as well as biosynthetic dressings [25] have been advocated, but their value is questionable because – unlike in burns – the dermis is largely uninvolved and re-epithelization is not a problem.

Alimentation

Patients are often unable to eat and drink due to their oral and/or esophageal mucosa involvement, or to their poor general condition. Local anesthetics, in the form of a mouth wash used before the meals, may be helpful. High calorie and high protein diet or intravenous administration is recommended, taking into account the risk of septicemia by intravenous lines. [25].

CONCLUSION

To overcome this problem, early diagnosis and implementation of interdisciplinary approach for management of SJS and careful monitoring for complications with regards to morbidity and mortality of life threatening cutaneous disorders. This report should alert physicians to this severe cutaneous reaction of Valproic acid.

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DECLARATION OF INTEREST

The authors report no conflict of interest. The authors alone are responsible for the content and writing the paper.

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