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Stevens - Johnson Syndrome: Review Of The Subject

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SUMMARY

Erythema multiforme (EM) is an acute, self limited, inflammatory disorder of the skin and mucous membranes which is characterized by "Target Lesions" which can develop in a severer form called Stevens-Johnson Syndrome (SJS) characterized by vesicles and bullae formation which can be fatal. Various causes have been described including infectants, ingestants, contactants, malignancies and connective tissue diseases along with physical agents. Drugs and infections are the commonest causes. The literature is reviewed on Stevens-Johnson Syndrome (SJS) describing the management and outcome. In this article the controversies about corticosteroid therapy have also been discussed.

In 1866, Von Hebra grouped several of the previously described cutaneous erythemas as variants of the same process and then termed them erythema exudativum multiforme (EEM). The disease is now considered a spectrum varying from mild mucocutaneous form to a severe multisystem disorder which is potentially fatal.

The disease is defined as an acute inflammatory disorder of unknown aetiology (probably immune mediated) of the skin and mucous membranes of eyes, nose, mouth, respiratory, gastrointestinal and genito-urinary tract, characterized by a rash with "target" or "iris" lesions on the skin, palms and soles, and vesicles and bullae formation on the skin and mucous membranes. In Stevens-Johnson Syndrome, there is a serum sickness type reaction with mucosal involvement more than the skin involvement[1]. Toxic epidermal necrolysis (TEN) is a life threatening condition which results in scalded appearance of skin and its severer form is also called scalded skin syndrome (SSS) or now a days staphylococcal scalded skin syndrome (SSSS) but all these modalities constitute a part of the erythema multiforme spectrum. A number of causes have been described but drugs, viral and mycoplasma infections constitute most of them[2].

As regards incidence of SJS, a hospital based study[3] analysis to show which drug is notorious to cause high incidence of EM, SJS and TEN requiring hospitalization, the overall incidence of hospitalization for EM, SJS, and TEN due to all causes was 4.2 per 10^6/persons per year. The incidence of EM was 7 per 10^6 persons per year, SJS 1.8 per 10^6 persons per year and TEN was 9 per 10^6 persons per year. The respective ages were upto 24 years (for EM), 25-64 years (for SJS) and 65 and above (for TEN). The drugs responsible included phenobarbitone (20 per 100,000), nitrofurantoin (7 per 100,000), Sulphamethoxazole and trimethoprim (3 per 100,000) and amoxicillin (2 per 100,000). The incidence is about 2 cases per million inhabitants per year in another study from Germany[4].

The aetiology is unknown. It is however an immune mediated pathological phenomenon. Serum-sickness like features have lead to a search for circulating immune complexes. Most investigators find exclusively lymphocytic histology. Viral antigens and keratinocytes of the skin may be the triggering mechanisms. Autoantibodies directed against them have been documented[5]. The lymphocytes damage both dermal vessels and epidermal target cells. The dermo-epidermal portion shows changes ranging from vacuolar alteration upto sub-epidermal blisters. This is sparse in SJS and TEN but more common in erythema exudativum multiforme major (EEMM). Eosinophils are uncommon in TEN in which there

is detatchment of more than 30% of the skin. This dermopathological study[6] of patients with EEMM, SJS and TEN indicates that the epidermal type of erythema multiforme is the pathological correlate of these diseases.

Some of the actual causes or associated factors are grouped as under;

1. Infectants
   a. Viruses e.g. herpes simplex, HIV
   b. Mycoplasma and Chlamydia.
   c. Fungi e.g. coccidioidomycosis and histoplasmosis.
   d. Bacteria e.g. Streptococci, Salmonella, Yersinia
   e. Parasites e.g. Trichomonis, Spirochetes.

2. Ingestants.
   a. Drugs e.g. penicillins, barbiturates sulphonamides, phenytoin and phenolphthalene.
   b. Food additives and dyes.

3. Contactants: e.g mefanide acetate and 9-bromofluorane.
4. Physical agents: e.g. cold, heat and x-radiation.
5. Collagen vascular diseases:- e.g systemic lupus erythematosus, mixed connective tissue diseases.
6. Malignancy: e.g leukemia, lymphoma.
7. Pregnancy:

Mycoplasma pneumonia is the most common infective agent associated with SJS. It is not associated with EM of Von Hebra[7]. Most commonly males are affected and there is an upper respiratory tract infection. In another report, mycoplasma was associated with anti-phospholipid antibodies which might play a role in the development of SJS[8]. In a review[9] of epidemiological aspects of mycoplasma pneumonia and its complications especially the dermal involvement, it has been suggested that not only the rise in serological titers but isolation of the actual organism is required before a syndrome is attributed to mycoplasma pneumonia infection. Recurrent herpes simplex virus infections have been implicated[10] as a cause of SJS. A case of SJS and HIV infection has been reported in the "Pedro Kouri" institute of tropical medicine in Spain[11]. Drugs like phenytoin and sulphonamides are notorious and so is irradiation. Rarely drug treatment of carcinoma of cervix with cisplatin and bleomycin results in fatal pneuomnitis and Stevens-Johnson Syndrome[12].

Antimalarials[13] due to increased photosensitivity can lead to subsequent progression of Stevens-Johnson Syndrome especially Fansidar which contains chloroquine and sulphadoxin-pyrimethamine. This unusual combination of two different patterns of adverse cutaneous drug reaction is most probably caused by the sulphonamide component of the drug.

A study[14] from Italy, reveals such drug and their related risks in causation of Stevens Johnson Syndrome.

The severe form of Stevens-Johnson Syndrome with erythema multiforme, intrahepatic cholestasis, pulmonary infiltrates and acute renal failure can be induced by non-ionic contrast medium[15], Iopamidol. It is therefor recommended that contrast media should be used with extreme caution especially in patients with immuno-compromised status. In a study comprising eight cases, in whom brain was irradiated and phenytoin was administered to prevent convulsions in space occupying lesions (SOL), the patients developed Stevens-Johnson Syndrome[16]. The picture differed from the classical form of erythema multiforme, in that the erythema begins on scalp and spreads to the extremities and progresses to formation of extensive bullae. No SJS-like lesions were found in patients with phenytoin or radiotherapy alone. In the absence of seizures, it is thus recommended that anticonvulsants should not be administered routinely to patients with brain tumors. However, if anticonvulsants are required and the patient is scheduled for brain radiotherapy, then phenytoin[17] should not be selected as drug of choice.

The clinical features are variable[18,19]. However there is characteristic and severe illness. Onset of disease is usually sudden although there may be prodromal illness lasting from 1-13 days before actual eruptions. A number of organs are affected. In a review of 81 cases[20], changes were found in the following frequency: mouth 100%, eyes 91%, skin 83%, genitals 57%, anal mucosa 5%, bronchitis 6% and pneumonitis in 23%. Mouth and lips show characteristic haemorrhagic crustings. Severe glossitis, epiglottitis and inflammation of the upper respiratory tract with laryngeal oedema is also described, which can cause acute respiratory

obstruction leading to death. SJS has been associated with pneumonia of many aetiologies. This "mucosal respiratory syndrome" was first reported by Stanyon and Warner in 1945. Normally pneumonia occurs early and resolves in 2-3 weeks after the onset of rash[21]. Generally pulmonary sequelae are not permanent but a case has been described where severe obstructive pulmonary disease following SJS was thought to be a permanent sequela.[22] Bronchiolitis obliterans can be diagnosed with high resolution CT without open lung biopsy.[23] Oesophageal strictures and webs are also described in SJS.[24] Oesophageal stenosis secondary to Stevens-Johnson Syndrome is very rare and during the last 40 years only two cases have been described[25]. Rarely the gastric mucosa and mucosa of small and large bowel can be involved in the pathological process.

Eye is an important structure and can be involved with conjunctivitis, palpebral oedema, iritis, uveitis, corneal vesicles, erosions and then perforation[26]. Synechae and corneal opacities are also common ocular manifestations[27]. With ocular involvement SJS has been associated with the class-I human leukocyte antigen (HLA BW44). HLA-DQ B1*0601 is found in significant numbers in patients with SJS who have ocular complications. The presence of this allele may confer an increased risk for the development of SJS with ocular complications and provides further evidence for an underlying immunogenetic susceptibility to the development of this disease[28]. Skin lesions are variable from maculo-papular to bullous pustular lesions however, there is little correlation between the extent of the skin lesions and constitutional symptoms.

Psychosis following SJS has been reported which is quite rare, however, a previously undiagnosed neurological impairment should be searched[29].

Vaginal stenosis after SJS can complicate pregnancy[30]. Other vaginal complications can occur depending upon the degree of vaginal mucosal damage e.g. vaginal adenosis and endometriosis[31]. In a review, cutaneous reaction to non-steroidal anti-inflammatory drugs have been highlighted[32]. Severe haematuria and renal tubular necrosis can lead to renal failure. Less common symptoms are diarrhoea, paronychia, shedding of nails, polyarthritis and otitis media.

There have been new concepts about the classification based on the pattern and distribution of cutaneous lesions to separate erythema multiforme from Stevens-Johnson Syndrome[33]. Erythema multiforme is mainly related to the herpes virus infection while Stevens-Johnson Syndrome and toxic epidermal necrolysis are associated with drug reaction. It has been suggested that erythema multiforme (EM) and Stevens-Johnson Syndrome (SJS) can be separated as two distinct clinical disorders with similar mucosal but different patterns of cutaneous lesions[34].

The lesions of EM are raised, typical target shaped and are located on the extremities and face whereas lesions of SJS are flat, atypical target or purpuric maculae that are widely distributed on the trunk. However the preliminary diagnostic criteria for EM is based primarily on clinical features[35].

There are many entities to differentiate from erythema multiforme which include polycyclic urticaria, toxic erythemas resulting from infections or drug hypersensitivity, septicaemia, vasculitides, blistering diseases e.g. impetigo, pemphigus, bullous pemphigoid, dermatitis herpetiformis, toxic epidermal necrolysis and herpes gestationis and mucocutaneous disorders. The differential points of few such conditions are shown in the Table 1.

Other differential diagnosis include Behcet's disease, Reiter's disease and hand foot and mouth disease. Immunofluorescence is helpful in distinguishing erythema multiforme from other sub-epidermal blistering diseases.

As regards management of the disease, the diagnosis and treatment of the underlying cause is most important. Milder form of the disease requires symptomatic treatment. Elimination of suspected aetiological factors is of prime importance. Non essential drugs should be discontinued immediately. In severe cases good nursing care is of paramount importance. Fluid and electrolytes balance is imperative including oral hygiene. Warm saline mouth washes, topical anaesthetics and topical steroids might be helpful[36]. Ocular care is also of importance in concordance with the ophthalmologist. The use of systemic corticosteroids is still controversial because of the lack of controlled prospective studies[37,38]. Undoubtedly some systemic manifestations are relieved with steroids but there is no convincing evidence yet that they influence the overall mortality or long term morbidity. Nevertheless, they are used in every severe case of SJS in a dose

Table 1: Differential diagnosis of common bullous eruptions.

Criteria	*Dermatitis herpetiformis*	*Pemphigus*	*Pemphigoid*
1. Age	Any	Usually 40-60 years	Over 60 years
2. Sex	Both	Both	Both
3. Typical eruptions	Vesicles and bullae	Bullae	Bullae
4. Site	Lumbosacral, buttocks and posterior axillary folds.	Face, neck, trunk and limbs	Thighs, arms and trunk
5. Nature	Grouped lesions	Non-grouped lesions	Scattered
6. Mucous membranes	Oral mucosa some times affected	Commonly affected	20%
7. Itching	Always present, may be very severe.	Rare	Rare
8. Pathological lesions	Sub-epidermal bullae, no acantholysis	Intra-epidermal bullae with acantholysis	Both types, no acantholysis
9. Eosinophilia	10-40 percent	Usual but low count	Unusual
10. Immunofluorescence	None	Intracellular zone	Basement membrane
11. Type of Ig	IgA	IgG	IgG
12. Compliment fixing	None	Yes	Yes
13. Treatment	Dapsone	Steroids and methotrexate	Steroids and methotrexate
14. Course	Chronic	Chronic	Chronic
15. Prognosis	5-20 years	Fairly good with modern therapy	Quite good.

of 30-60 mg/day for 4-5 days and then reduced over the next 3-4 weeks. Antibiotics are also used for infection. In a few large studies on corticosteroid therapy, no fatalities or adverse effects due to corticosteroids were noted[39,40,41]. SJS due to a drug or a drug metabolite or viral infection may mimic a graft versus host reaction in which the patient rejects skin, mucous membrane, kidney or liver cells to which the drug metabolite or virus has bound. Corticosteroids suppress the inflammatory rejection until the activating agent has been eliminated. The frequently suggested "controlled trials of corticosteroids therapy" can probably never be done for ethical reasons, although such a study will have to establish the standard of therapy.

In a group of patients, rapid wound closure with xeno-graft and supportive care resulted in rapid re-epithelialization and decreased mortality and morbidity[42]. Xeno-graft from porcine sources have been used successfully as immediate grafting for upto 75% of the denuded skin[43].

Anti-viral therapy with acyclovir for erythema multiforme with overt herpetic infection is disappointing once the eruption has appeared. However, long term prophylactic use may be helpful and justifiable in recurrent herpetic infections[44,45]. A dose of 200 mg twice daily may be appropriate but it can be fluctuated.

Vitamin A has been reported to be beneficial in helping regeneration of conjunctival goblet cells[46].

Rehabilitation for patients with SJS is also important because there is similarity to partial thickness burn injuries and benefit from treatment in a multi disciplinary way is valuable[47].

Amnion in the form of biological dressing has been tried as it is non-antigenic, for covering of denuded skin in SJS and TEN. Successful treatment of this syndrome is reported in upto 95% of denuded skin and upto 6.5-8.5 square feet of amnion can be used[48].

Ocular involvement may require early and appropriate management in collaboration with an experienced ophthalmologist especially in recurrent type of SJS.

Relapses tend to occur when the drug is omitted. Interestingly, some cases of recurrent

erythema multiforme without overt herpetic infections may be helped by prophylactic acyclovir, implying that recurrent herpetic infection may nevertheless be responsible.

In a hospital based study comprising 123 patients it was found that improvement with steroid therapy occurred and average length of stay in the hospital was 4.2 days longer than that for the patients not treated with steroids[49].

Overall mortality is 5-10%. In cases that recur, the rate of recurrence is more if there is herpes simplex virus infection.

For mild illness medicines are prescribed but any one of them can cause lethal eruptions, therefore use of these agents should be very carefully considered.

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