STEVEN JOHNSON'S SYNDROME: A BRIEF REVIEW

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ABSTRACT: Stevens-Johnson syndrome (SJS) is a rare immune-complex–mediated type-IV hypersensitivity reaction that primarily affects the skin and the mucous membranes leading to cell death or cell apoptosis. Clinically SJS is characterised by fever, inflammation of the buccal mucosa, and severe purulent conjunctivitis. The etiology of this disorder is multiple, including drugs in almost 75% of cases, infectious agents, genetic predisposition and idiopathic causes account for 25% of cases. The common drugs that can cause SJS are anti-microbials, nonsteroidal anti-inflammatory drugs, antimalarials, anticonvulsants, and allopurinol. The pathology of SJS involves type-IV hypersensitivity reaction that activates cytotoxic T cells leading to apoptosis of keratinocytes. The ultimate effect of SJS is detachment of epidermis from the dermis due to the apoptosis of the keratinocytes that are present at the epidermal-dermal junction. Management of SJS is directed by identification of underlying cause. Therapeutic options include prompt withdrawal of the drug, if drug is the cause, supportive therapy, use of immune modulators and Cyclosporine. Antibiotics were used when the underlying cause is infection. The mortality and disease progression of a particular patient varies with the severity of the disease, age of the patient, the underlying cause and therapeutic options.

Key words: Steven johnson's sundrome, Hypersensitivity reactions, cyclosporine

Introduction :

Stevens-Johnson syndrome (SJS) is an rare immune-complex–mediated type-IV hypersensitivity reaction that primarily affects the skin and the mucous membranes leading to cell death or cell apoptosis [1,9]. Mucosal, conjunctival, and anogenital mucous membranes are prominently affected by SJS [6] . SJS is clinically similar to many severe cutaneous diseases but it differs in some or the other way. SJS and toxic epidermal necrolysis (TEN) are similar clinically and pathologically but differ only by severity of diseases and were within the same spectrum i.e, severe cutaneous adverse reactions (SCAR) [2]. Although different in clinical pattern, prognosis and etiology, erythema multiforme with mucosal involvement, is also part of this spectrum [2]. The other diseases that includes in this spectrum are acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms complex (DRESS). At first in early days (before 1922) SJS was described as an generalised epidermal eruption. These epidermal eruptions may range from transient erythema to life threatening SCAR [4].

The terminology of these different diseases has been conflicted for several years; the differentiation has been made after a consent definition was proposed in 1993. This definition differentiated the EMM from SJS, TEN and SJS overlap TEN [2]. This is also useful in distinguishing the cases clinically that helps in treating the patients appropriately and also as standard for many other studies. This classification categorise the diseases into 5 types like Bullous erythema multiforme, Steven Johnson's syndrome, Overlap SJS-TEN, TEN with spots and TEN without based on some disease characteristics like pattern of lesions, extent of epidermal surface involved or the BSA effected [2,5].

Clinically SJS is characterised by fever, inflammation of the buccal mucosa, and severe purulent conjunctivitis[1]. SJS and TEN are characterized by cutaneous erythema with blister formation of various extent and hemorrhagic erosions of mucous membranes. Fever and malaise are the first symptoms of the disease [2].

In pediatric patients, SJS is usually accompanied or associated with other comorbidities like ocular infections or inflammation, blindness, viral or bacterial infections, pneumonia etc [3].

The etiology of this disorder is multiple, including drugs in almost 75% of cases, infectious agents, genetic predisposition and idiopathic causes account for 25% of cases[1,2]. The different etiological factors will be discussed in later sections of this review. Identification of the cause is important for the individual patient as it reflects the main stay of therapy. Therapeutic outcomes may be poor in severe disease conditions and the mortality rate is usually higher in these cases. The mortality and disease progression of a particular patient varies with the severity of the disease, age of the patient, the underlying cause and therapeutic options [2].

ETIOLOGY:

There were various etiological factors have been proposed for the cause of SJS. However, literally the exact cause was not yet studied. Various previous studies suggest that SJS mainly caused due to the drugs, some infections, and genetical predisposition.

DRUGS:

Drugs were found to be the major cause of SJS in any age group of patients. The common drugs that can cause SJS are anti-microbials, nonsteroidal anti-inflammatory drugs, antimalarials, anticonvulsants, and allopurinol[1,6,7].

Among anti-microbials, sulphonamides, penicillin's and anti-reterovirals were majorly contributed to the incidence while cephalosporins, fluoroquinolones, anti-tubercular were also contributed but to the less extent compared to the others anti-microbials [1,7].

To date, neither a possible interaction of infection and medication nor the interaction of different drugs could be clarified, and a reliable in vitro or in vivo test to determine the link between a specific drug and SJS/TEN in an individual case is not yet available. Other relevant tests to confirm the cause as drug like patch tests were not mainstay of diagnosis due to their irrelevant negative results. Establishment of proper drug causality assessment will only help in conformation of the drug induced SJS. For that an algorithm was published, which provides structured help to identify the responsible drug [2].

The median latency time between the beginning of use and onset of SJS/TEN (also called index-day) was less than 4 weeks for most drugs (15 days for carbamazepine, 24 days for phenytoin, 17 days for phenobarbital and 20 days for allopurinol), whereas it was much longer for drugs with no associated risk (above 30 weeks for valproic acid) [2]

INFECTIONS:

Various bacterial and viral infections have been reported to cause the SJS. However the incidence is very low when compared to the drug induced SJS.

The common virus that cause the SJS were Herpes simplex virus, HIV, Coxsackie viral infections, Influenza, Hepatitis, Mumps [1, 2, 8]. Some studies reported some bacteria were responsible for SJS like group A beta-hemolytic, streptococci, Diphtheria, Brucellosis, Lymphogranuloma venereum, Mycobacteria (*Mycoplasma pneumonia*, Rickettsial infections Tularemia, salmonella typhi etc.

GENETIC FACTORS:

Genetic studies involved case-control studies aimed at identifying associations between SJS/TEN with SOC and genetic loci involved in immune response pathways and the detoxication of drugs and xenobiotics. Alleles of various human leukocyte antigen (HLA) loci were the focus of genetic association studies of SJS/TEN in different populations and ethnic differences in genetic associations have been proposed. [9].

The presence of the following alleles was responsible for the development of the SJS:

- → HLA-B*1502
- → HLA-B*5801
- → HLA-B*44
- → HLA-A29
- → HLA-B12
- → HLA-DR7
- → HLA-A2
- → HLA-B*5801
- → HLA-A*0206
- → HLA-DQB1*0601

The study conducted by Chitra Kannabiran et al., revealed that in Indian population, the haplotype comprised of HLA-B*44:03 and HLA-C*07:01 is strongly associated with occurrence of SJS/TEN. They also suggest that HLA-B*57:01 and HLA-C*06:02 are protective against this disease i.e, these alleles show negative association with SJS [9].

Signs and Symptoms:

Signs and symptoms can be categorised into early and later symptoms which was discussed as follows [10]:

Early signs/symptoms:

• Fever, malaise, fatigue and mucosal lesions, headache, bleeding, orinasal soreness

It is often difficult to decide whether these early symptoms like fever are signs of any other infections or the early stage of SJS/TEN[2]. For this the patients should be completely evaluated for drug and personal history to rule out the other infectious causes.

Later signs/symptoms:

• Marked erythema of skin leading to papules, vesicles and necrosis. These start on the face neck and anterior trunk and may extend over the entire surface of the skin.

This erythema first begins as macules later develops to papules, fluid filled vesicles, bullae which appears as target and contains only 2 zones of colour. After transforming to bullae like lesions they rupture and making the skin ore susceptible to secondary infections.

• Mucosa of GI, GU, genital and upper and the epithelial cells of the lower respiratory tree has been observed to be affected which is characterised by the signs like be erythema, edema, blistering, ulceration followed by necrosis[1,10]. These areas are associated with heavy bleeding, scarring and long-term complications.

Pathophysiology:

It has been postulated that SJS can occur as an delayed hypersensitivity or cell mediated immune reactions in response to certain drugs or their metabolites or infectious organisms. The people with genetic predisposition to a drug hypersensitivity reaction, immunocompromised are at increased risk of SJS [1, 11].

The exact mechanism involved in pathogenesis of SJS has been extensively studied by various authors and many theories have been proposed by them. Here we highlight the two mechanisms that were assumed to be involved in pathogenesis.

The ultimate effect of SJS is detachment of epidermis from the dermis due to the apoptosis of the keratinocytes that are present at the epidermal-dermal junction. These various theories focus on how the apoptosis of keratinocyte is carried out.

According to some hypothesis, this keratinocytes apoptosis have been carried out by the activation of cytotoxic T- lymphocytes in response to the antigens like drugs, infectious organisms etc [12]. first the Ag is up regulate the cell adhesion molecules that promotes the accumulation of leukocytes. Then the engulfed Ag are presented to T cells that were activated and become cytotoxic to keratinocytes. In turn the activated macrophages will release the IL and other lymphocytes. All these together lead to the keratinocytes apoptosis or necrosis.

Additionally some researches has been focused on vitamin A toxicity as the mainstay of development of SJS. According to these studies it has been postulated that the antigens either the drug or the others will damage the liver, the organ that is responsible for the storage of Vit-A. this results in Vit-A toxicity due to increased levels of free Vit-A in the blood circulation. These free Vit-A will eventually activate the cytotoxic T- lymphocytes which is responsible for production of a molecule called granulysin. This granulysin along with Vit- A lead to necrosis or apoptosis of keratinocytes [10].

DIAGNOSIS:

The diagnosis of SJS is done considering the clinical symptoms and the histopathology study. The main stay of the diagnosis of SJS depends on ruling out other diseases (differential diagnosis) that comes under same spectrum.

The clinical symptoms that are considered to confirm the diagnosis are areas of erythematous and macules on skin that shows Nikolsky sky sign upon the mechanical pressure. Epidermal detachment with in few minutes to hours of nikolsky appearance is characterised by development of blisters [2, 13]. These clinical symptoms may also be observed in other diseases hence differential diagnosis helps in ruling out other diseases which is discussed in later section.

Histological observations in SJS include the following:

- ✓ Epidermal necrosis that is reflected by the presence of immediate cryosections or conventional formalin fixed sections of skin confirms the SJS.
- ✓ Keratinocyte necrosis appear as wide spread or dissemination or full thickness of necrosis.
- ✓ Sub-epidermal necrosis blistering is found in basal membrane zone.
- ✓ Lymphocytic infiltrate seen in upper epidermis either superficially or peri-vascularly.
- ✓ No deposition of Ig in epidermis-dermal zone [1].

Both SJS and TEN were same histopathologically.

DIFFERENTIAL DIAGNOSIS:

Differential diagnosis helps in ruling out all other diseases that look like similar in one way or the other. Clinically SJS should be differentiated from the diseases like blistering diseases, EM, Staphylococcus scaled skin syndrome, GBFDE.

Direct immune flouroscent staining helps in ruling out blistering diseases as there should be no Ig or other complement deposition in either epidermis or epidermal-dermal junction in SJS as the deposition is seen in blistering diseases. Varying amount of eosinophil was observed in tissue biopsy infiltrate of patients of SJS, EM and SJS/TEN. Other observations like less epidermal necrosis, more dermal inflammation and more exocytosis in EM observed compared to SJS. At this note the results of biopsies varies with the time of biopsy, onset of disease and from which part of the biopsy taken. Histopathological study of biopsies taken from lesions can distinguish SJS/TEN from other diseases but not from EM as they show the similar results in biopsies.

In early stages of disease maculopapular eruptions may present with or without oral lesions and conjunctivitis. These lesions were hemorrhagic and erosive in SJS but not in EM [2]. In contrast these EMM atypical forms with target lesions appear as wide disseminated with well demarcation and not confluent in children when compared to adult patients which makes diagnosis difficult in those patients [2, 14]. In later stages where the epidermal detachment and blisters were well seen histologically information on the layer of epidermal detachment helps in differentiate the disease from staphylococcal scaled-kin syndrome. Even though macules and target lesions were not seen and mucosal involvement seen rarely in Staphylococcal scaled-skin syndrome, differential diagnosis should always be based on histopathological studies only [2,15].

In Generalised bullous fixed drug eruptions (GBFDE) characterised by well defined, oval/round plaques in brownish or voilaceous and blisters appearing on these plaques frequently similar to SJS but the BSA involved rarely exceeds 10% through which it is differentiated. The other features hat differentiates GBFDE from SJS are less intense of fever, malaise and far better prognosis. But the histopathological observations of both SJS and GBFDE show blisters superficially along with necrosis. Hence the differentiation of SKJS from GBFD should be made clinically rather than histopathologically [2].

Skin peeling by the shedding of membrane observed in diseases like erythoderma or dermatitis is often confused as epidermal detachment seen in SJS clinically [2] .

TREATMENT:

As soon as the diagnosis of SJS has been confirmed, the appropriate treatment modalities depend on the severity and prognosis of disease. A validated SCROTEN disease severity scoring system may be used to assess the progress in patients and based on this score the treatment can be addressed. Patient with a SCORTEN score 3 or above indicates increase in severity and hence the intensive care should be taken and treatment considering infections and other complications should be recommended [15].

WITHDRAWAL OF CAUSATIVE DRUG:

The causative drug is identified as underlying disease then withdrawal of the drug should be done. Predicting the drug as cause it should be based on the time when blisters or erosions appear, as if it occurs during the course of treatment with the respective drug. Some studies reveals that earlier the causative drug withdrawn, better the prognosis be [1, 16] . If the drug causing the disease is with longer half lives then such patients are at increased risk of fatality [16]. Some elements that should be considered to confirm the drug as the cause are time of drug administration of drug and the reports that support the drug can able to cause the SJS.

SUPPORTIVE CARE:

The main supportive therapy includes addressing the fluid electrolyte requirements. This could be achieved by IV fluids supplement [1,2]. The exact requirement should be calculated by the BSA affected. Other supportive approaches include maintaining the room temperature and bedding on an alternating pressure mattress is recommended. Monitoring for the secondary infections should be done in any suspected prophylactic anti-infective treatment should be advised[2].

TOPICAL TREATMENT:

Addressing the blisters and erosions and debriment of skin detached includes in the topical therapy. Blisters should be punctured or else should be left as such in the place. Chlorhexidine**,** polyhexanide solutions, impregnated non adhesive mesh gauze were used extensively for erosions. Skin debriment is carried out in severe cases under general anesthesia followed by the application of allografts. This is often intolerable by elderly patients as they have many underlying causes. Such patients rather benefit from the treatment of underlying disease [17]. Disinfectant mouth wash should be used to treat oral erosions and mild ointment, such as dexpanthenol, should be applied on erosions and bloody crusts of the lips [1, 2].

DRUG THERAPY:

In the treatment of SJS immune modulating drugs like corticosteroids, immunosuppressants can be used. There were many studies including case reports and studies reflecting supportive results with the use of corticosteroids. However, in recent years steroid pulse therapy with dexamethasone has been proposed in the acute stage of SJS/TEN. Mortality was not higher and time of re-epithelialization was not longer than expected [18] . Still to date the available information on pulse therapy is not sufficient to conclude its benefits in the therapy.

IVIg have been tested for the treatment of TEN after the discovery of anti-Fas potential of pooled human intravenous immunoglobulins (IVIG) that blocks the Fas-mediated necrosis of keratinocytes in vitro. Majority of the studies confirm the known excellent tolerability and a low toxic potential of IVIg when used with appropriate precaution in patients with potential risk factors like associated systemic diseases [1, 2, 19, 20].

The use of Cyclosporine is also supported by the positive results of past studies [21] . Patients treated with CsA had significantly shorter time to complete re-epithelialisation, and fewer patients with multi-organ failure and death were observed. The regimen using the high-doses of intravenous dexamethasone followed by CsA showed a stop in disease progression within 72 hrs that was done in a study [22, 23] . Other single case reports also reported a positive effect of the use of CsA in TEN. Recently, an open, phase II trial conducted by Valeyrie-Allanore L to determine the safety and possible benefit of ciclosporin [24]

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