Review Article

Stevens-Johnson Syndrome

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Background

Stevens-Johnson syndrome (SJS) is an immune complex mediated hypersensitivity complex that typically involves the skin and mucous membranes. While minor presentations may occur, significant involvement of oral, nasal, eye, vaginal, urethral, gastrointestinal, and lower respiratory mucous membranes may develop in the course of the illness. GI and respiratory involvement may progress to necrosis. Stevens-Johnson syndrome is a serious systemic disorder with the potential for severe morbidity and even death. The syndrome was first described in 1922, when the American pediatricians Albert Mason Stevens and Frank Chambliss Johnson reported the cases of 2 boys aged 7 and 8 years with "an extraordinary, generalized eruption with continued fever, inflamed buccal mucosa, and severe purulent conjunctivitis". Both cases had been misdiagnosed by primary care physicians as hemorrhagic measles. Erythema multiforme (EM), originally described by Von Hebra in 1866, was part of the differential diagnosis in both cases but was excluded because of the 'character of skin lesions, the lack of subjective symptoms, the prolonged high fever, and the terminal heavy crusting". Despite the presence of leucopenia in both cases, Stevens and Johnson in their initial report suspected an infectious disease of unknown etiology as the cause. In 1950, Thomas divided EM into 2 catagories: erythema multiforme minor (Von Hebra) and Erythema multiforme major (EMM). Since 1983, erythema multiforme major and Stevens-Johnson syndrome had been considered synonymous. In the 1990s, however, Bastuji and Roujeau each proposed that Erythema multiforme major and Stevens-Johnson syndrome are 2 distinct disorders. Several investigators propose that Stevens-Johnson syndrome and Toxic epidermal necrolysis (TEN) represent the same disease at different levels of severity. Although several classification schemes have been reported, the simplest breaks the disease down as follows:

** Stevens-Johnson syndrome-A "minor form of TEN", with less than 10% body surface area (BSA) detachment.*

** Overlapping Stevens-Johnson syndrome/Toxic epidermal necrolysis (SJS/TEN)-Detachment of 10-30% BSA.*

** Toxic epidermal necrolysis-Detachment of more than 30%BSA.*

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Epidemiology

Over a period of 20 years, Bastuji's classification has successfully been in several large epidemiological studies (including RegiSCAR) which have provided reliable information on the incidence of SJS and TEN[3]

Incidence is estimated at 2-3 cases/million population/year in Europe[1]

It is much more common in individuals with HIV (Estimated 1-2/1,000 in Canada)[2]

It is more common in female than males[4]

Most patients are aged 10-30 but cases have been reported in children as young as 3 months

Etiology

Various etiologic factors have been implicated as causes of SJS. Approximately 75% of SJS/TEN are caused by medications and 25% by infectious and'other'causes. The 4 etiologic categories are as follows:-

Drug induced

Infections

Malignancy related

Idiopathic

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Drugs most commonly associated with SJS and TEN:

Allopirunol
Carbamazepine
Sulfonamides
-Trimethoprim-Sulfamethoxazole
-Sulfadiazine
-Sulfasalazine
Antiviral agents
-Nevirapine
-Abacavir
Anticonvulsants
-Phenobarbital
-Phenytoin
-Valproic acid
-Lamotrigine
Others
-Imidazole antifungal agents
-Non-steroidal anti-inflammatory drugs (oxicam type such as meloxicam)
-Salicylates
-Sartraline
-Bupropion (rarely).

Stevens-Johnson syndrome is idiopathic in 25-50% of cases. Drugs and malignancies are most often implicated as the etiology in adults and elderly persons. Pediatric cases are more related more often to infections.

Infection

Viral: includes Herpes simplex virus, Epstein-Barr virus, Enteroviruses, HIV, Coxsackie virus, Influenza, Hepatitis, Mumps and variola.

Bacterial: Includes Group A beta -hemolytic streptococci, Diphtheria, Brucellosis Mycobacteria, Mycoplasma pneumoniae[5,6]. Lymphogranuloma venerium, Tularaemia, Typhoid, Rickettsia

Fungal: includes Coccidioidomycosis, dermatophytosis, and histoplasmosis.

Protozoal: Malaria and trichomoniasis.

Immunization

Associated with immunization-e.g, measles, Hepatitis B

Genetic factors

There is a strong evidence for a genetic predisposition to sever cutaneous adverse drug reactions such as SJS.Carriage of the following HLA has been associated with increased risk:HLA-B1502, HLA-B5801, HLA-B 44, HLA-A29, HLAB12, HLA-DR7, HLA-A2, HLA-A0206, HLA-DQB1 0601

Clinical features[7,8]

Symptoms

It often starts with a nonspecific upper respiratory tract infection, which may be associated with fever, sore throat, chills, headache, arthralgia, vomiting and diarrhea, and malaise. Mucocutaneous lesions develop suddenly and clusters of outbreaks last from 2-4 weeks. The lesions are usually not pruritic.

Mouth: severe oromucosal ulceration. Respiratory involvement may cause a cough productive of thick purulent sputum. Patients with genitourinary involvement may complain of dysuria or an inability to pass urine.

Ocular symptoms: Painful red eye, purulent conjunctivitis, photophobia, blepharitis.

Signs

General examination: fever, tachycardia, hypotension: altered level of consciousness, seizures, coma Skin lesions may occur anywhere, but most commonly affect palms, soles, dorsum of the hands and extensor surfaces. The rash may be confined to any one area of the body, most often the trunk. The rash can begin as macules that develop into plaques, vesicles, bullae, urticarial plaques, or confluent erythema. The center of the lesion may be vesicular, purpuric, or necrotic. The typical lesions have the appearance of a target, which is considered pathognomonic. Lesions may become bullous and later rupture. The skin become susceptible to secondary infection. Urticarial lesions are usually not pruritic. Nikolsky sign is positive (mechanical pressure to skin leading to blistering within minutes to hours). **Mucosal involvement:** Erythema, edema, sloughing, Blistering, ulceration and necrolysis. **Eye:** conjunctivitis, corneal ulcerations. **Genitalia:** Erosive vulvovaginitis or balanitis.

Differential diagnosis:

Acute generalized exanthematous pustulosis
Bullous pemphigoid
Bullous phototoxic reactions
Chemical or thermal burns
Erythroderma
Exfoliative dermatitis
Maculopapular drug rashes
Paraneoplastic Pemphigus acantholysis
Staphylococcal scalded skin syndrome
Lyme disease

Investigations

Serum electrolytes, glucose and bicarbonate are essential to assess clinical severity and level of dehydration7

Diagnosis is based on clinical picture and histopathology

Minimal dermal inflammatory cell infiltrate and full-thickness necrosis of the epidermis are typical histologic findings in patients with SJS.

Histopathologic examination of the skin can also reveal the following:

Changes in the epidermal-dermal junction ranging from vacular alteration to subepidermal blisters.

Dermal infiltrate: superficial and mostly perivascular

Apoptosis of keratinocytes

CD4+T lymphocytes predominating in the dermis; CD8+T lymphocytes predominating in the epidermis; the dermoepidermal junction and epidermis is infiltrated mostly by CD8+T lymphocytes.

Ocular examination can demonstrate the following:

Conjuctival biopsies from patients with active ocular disease show subepithelial plasma cells and Lymphocyte infiltration; lymphocytes are also present around vessel walls; the predominant infiltrating lymphocyte is the helper T cell.

Immunohistology of the conjunctiva reveals numerous HLA_DR positive cells in the substantia propria, vessel walls, and epithelium.

Management

Management of patients with Stevens-Johnson syndrome is usually provided in intensive care units or burn centers. No specific treatment of Stevens-Johnson syndrome is noted; therefore, most patients are treated symptomatically. In principle, the symptomatic treatment of patients with Stevens-Johnson syndrome does not differ from the treatment of patients with intensive burns. Patients should be treated with special attention to airway and homodynamic stability, fluid status, wound/burn care, and pain control. Therapy for SJS proceeds as follows:

Withdrawal of any agent suspected of causing the condition is critically important.

Oral lesions are managed with mouth washses; topical anaesthetics are useful in reducing pain and allowing the patient to take in fluids.

Areas of denuded skin must be covered with compresses of saline or Burow solution.

Tetanus prophylaxis must be addressed.

Extensive debridement of nonviable epidermis followed by immediate cover with biologic dressing is among the recommended treatments.

Treat secondary infection with appropriate antibiotics

The use of systemic steroid remains controversial. Prolonged treatment with systemic steroids has been associated with an increased prevalence of complications. The currently advocated approach for corticosteroid use suggests the early use of short term (4-7 days), high dose Intravenous corticosteroids9,10.

Plasmapheresis, immunosuppressive therapy, and intravenous immunoglobulin (IVIG) have been used with variably successful results.

Ocular therapy

The treatment of acute ocular manifestations usually begins with aggressive lubrication of the ocular surface. The ophthalmology literature contains several papers that advocate systemic and topical steroids to minimize ocular morbidity[11,12]. As inflammation and cicatricial changes ensue, most ophthalmologists use topical steroids, antibiotics, and symblepheron lysis. In the case of mild chronic superficial keratopathy, long-term lubrication may be sufficient. In case of severe involvement, treatment includes the following:-

Removal of keratinized plaques from the posterior lid margins.

Mucous membrane grafting and/or amniotic membrane grafting

Limbal stem cell transplantation and amniotic membrane grafting.

Superficial keratectomy removing conjunctivalized or keratinized ocular surface.

Prognosis and sequelae

Individual lesions typically should heal within 1-2 weeks, unless a secondary infection occurs. Most patient recover without sequelae. Mortality is determined primarily by the extent of skin sloughing. When body surface area (BSA) sloughing is less than 10%, the mortality rate is approximately 1-5%. However, when more than 30% BSA sloughing is present, the mortality rate is between 25% and 35%, and may be as high as 50%[31,26]. The overall mortality rate is up to 10% for SJS and at least 30% for TEN. Many patients surviving SJS and more than 50% surviving TEN experience long term sequlae involving the skin, mucous membrane or eyes.

These include:

Skin: hyperhidrosis, xeroderma, reversible hair loss, heat and cold sensitivity, scarring and irregular pigmentation (hyper/hypo-62.5%)

Nail dystrophy (37.5%)
Mucous membranes: vaginal, urethral and anal strictures. Persistant mucosal erosions.
Ocular: xerophthalmia, photophobia, symblepharon, synechiae, entropion, meibomian gland dysfunction, sight impairment The SCORTEN score (a severity -of - illness score for toxic epidermal necrolysis) calculates the risk for death in both SJS and TEN on the basis of the following variables:
Age >40 years
Malignancy
Heart rate >120
Initial percentage of epidermal detachment >10%
Blood urea nitrogen level (BUN)>10mmol/L
Serum glucose level>14mmol/L
Bicarbonate level<20mmol/L
Each variable is assigned a value of 1 point.
Mortality rates area as follows:
0-1 point, >=3.2%
2 points, >=12.1%
3 points, >=35.3%
4 points >=58.3%
5 or more points, >=90%
Other negative prognostic factors include persistent neutropenia (defined as neutropenia lasting more than 5 days), hypoalbuminemia(usually <2g/dl), and persistent azotemia.

Complications

Dehydration and acute malnutrition
Shock and multiorgan failure
Thromboembolism and disseminated intravascular coagulation
Gastrointestinal ulceration, necrolysis, strictures and perforation
Skin: secondary infection and scarring
Mucosal pseudomembrane formation may lead to mucosal scarring and loss of function of the involved organ system
Lung: mucosal shedding in the tracheobronchial tree may lead to respiratory failure
Eye complications include corneal ulceration and anterior uveitis. Sight impairment may develop secondary to severe keratitis or panophthalmitis in 3-10% of patients
Vaginal stenosis and penile scarring have been reported
Renal complications are uncommon but renal tubular necrolysis and acute kidney injury may occur.

Conclusion

SJS is a rare, serious disorder of skin and mucous membranes. It is usually a reaction to a medication or an infection. Often, SJS begins with flu-like symptoms, followed by a painful red or purplish rash that spreads and blisters. Then the top layer of the affected skin dies and sheds. SJS is a medical emergency that usually requires hospitalization. Treatment focuses on eliminating the underlying cause, controlling symptoms and minimizing complications. Recovery after SJS can take weeks to months, depending on the severity of condition.

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