Diagnosis and Management of Drug-induced Stevens-Johnson Syndrome: Report of Two Cases

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ABSTRACT

Erythema multiforme (EM) is a typically mild, self-limiting and recurring mucocutaneous reaction characterized by target or iris lesions of the skin and mucous membranes. It is most often a recurring phenomenon with great variability in the interval between episodes. It is much more common in persons under 40 years of age. In contrast, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are less common and more severe conditions that typically occur in adults. SJS and TEN are severe variants of EM usually caused by a drug exposure. We report two cases of Stevens-Johnsons syndrome following drug intake. There is an increased incidence of SJS and TEN in the HIV-infected population.1 Herewith, we report two cases of Stevens-Johnson syndrome in one patient following drug intake and other in a HIV-infected patient.

Keywords: Erythema multiforme, Stevens-Johnson syndrome, Atypical target lesions.

INTRODUCTION

Physicians writing prescriptions for their patients must warn them about possible side effects. One such potential complication of drugs, like paracetamol, carbamazepine and tetracycline, is Stevens-Johnson syndrome, a potentially fatal condition that manifests mainly on the skin and mucosal surfaces but also affects other vital organs. Many types of therapy have proved efficacious for treating the syndrome, but use of steroid agents for this purpose remains controversial. Stevens-Johnson syndrome, otherwise known as erythema multiforme majus, is thought to represent a continuum of disease, the most benign type of which is erythema multiforme, whereas toxic epidermal necrolysis is the most severe. The condition was first described in 1922 by Stevens and Johnson as a febrile illness with stomatitis, purulent conjunctivitis and skin lesions. The syndrome is generally described as vesiculobullous erythema multiforme of the skin, mouth, eyes and genitals.2

CASE REPORTS

Case 1

A 30-year-old male patient (Fig. 1) presented to the emergency department with a 3 days history of malaise, high-grade fever associated with sore throat since 10 days. The medication used by the patient was paracetamol for fever. Four days later he developed severe rash on the face with multiple, painful red raw lesions in the mouth and multiple fluid-filled lesions over the body (Figs 2 and 3). Vital signs were normal except for a temperature of 102.8ºC. He appeared ill and had copious amounts of blood drooling saliva with difficulty in swallowing and speech. Solid lesions initially over the hands later spread to trunks, legs, palms and soles. Vesicles were also noticed in the eyes and genitalia with bilateral conjunctival congestion with mucopurulent discharge from eyes and erosions, oozing seen over the shaft of penis and scrotum (Fig. 4). Multiple, poly-sized, erythematous based central necrotic areas and edema surrounding it described as atypical target lesions are seen bilaterally, predominantly over extremities, dorum of hands, flexor and extensor aspect, arms, shoulders, abdomen, thighs, etc.
cells and few neutrophils and histiocytes. At places the inflammatory infiltrate also involving the epidermis. Focal basal cell vacuolation also observed. In dermis, there is moderate perivascular lymphoplasmocytic inflammatory infiltrate in superficial and deeper dermis and consistent with Stevens-Johnson syndrome.

A serological evaluation of the patient was also done for HSV and the titers were not significantly elevated thus ruling out the possibility of HSV infection in etiopathogenesis in this case.

Patient was admitted and treated with intravenous fluids (ringer’s lactate, dextrose normal saline), systemic administration of corticosteroid (8 mg/ml), mouth washes, eye lubricants and topical application of steroids intraorally patient showed positive improvement in the treatment and 1 week later the severity of the lesions subsided. Patient is under close monitoring and follow-up.

**Case 2**

A male patient aged 38 years (Fig. 6) reported to the department of oral medicine and radiology with painful lesions in mouth and lips since 4 days. He also noticed dark brown colored legs sparing trunk (Fig. 5). Yellow greasy scales were seen over scalp. Considering the clinical features presented by the patient a provisional diagnosis of Stevens-Johnson syndrome was arrived at.

A skin biopsy was performed which revealed subepidermal bullous lesion composed of collections of lymphocytes, plasma
itchy skin lesions (Fig. 7), swelling of eyelids and discharge from eyes since 4 days, difficulty in mastication and speech. History revealed that he was asymptomatic 5 days back then first noticed a rash on the face following with dark brown colored lesions on the chest, stomach and back. Patient had no history of fever. Patient had an episode of epileptic seizures 10 days back for which he was given tegrital 200 mg, patient is a known HIV positive. After taking tegrital (carbamazepine) patient developed severe oral, cutaneous, eye and genital lesions with atypical target eye lesions on skin suggestive of Stevens-Johnson syndrome.

Cutaneous examination revealed multiple, polysized, purpuric macules on face, neck, chest, abdomen with very few lesions on upper limbs (Fig. 8). Oral examination showed multiple erosions with white patches on buccal mucosa, lateral borders of tongue, hard palate. Dryness of lips with crusting noticed on lower lip (Fig. 9). Nikolkys sign was positive in clavicular area. Bilateral congestion is seen in both the eyes with swelling of eyelids and mucopurulent discharge. Erosions with discharge were noticed from the shaft of penis with burning micturition (Fig. 10). Vital signs were under normal parameters. Considering the clinical features and history of drug intake and positive immunocompromised status of the patient a provisional diagnosis of Stevens-Johnson syndrome was arrived at.

Patient was admitted and treated with intravenous fluids, systemic administration of corticosteroid, mouth washes, eye lubricants and topical application of corticosteroid preparation for intraoral application. Patient is still under treatment and the severities of the lesions have decreased after 1 week of treatment. Patient is being monitored closely.

DISCUSSION

Stevens-Johnson syndrome is a severe, episodic mucocutaneous intolerance reaction described by Hebra in 1866 and Albert Mason Stevens and Frank Chambliss Johnson in 1922. Erythema multiforme (EM) and Stevens-Johnson syndrome are part of a clinical spectrum. EM minor is defined as typical targets or raised edematous papules acrally distributed, whereas EM major consists of EM minor with involvement of mucous membranes. By contrast, Stevens-Johnson syndrome is a severe yet similar illness with widespread blisters predominant on the chest, presenting with erythematous or purpuric macules with mucous membrane erosions. The annual incidence of EM major is estimated at 1-2:1000 000³. When there is very extensive skin detachment and a poor prognosis (death rates of 30 to 40%), the condition is usually called toxic epidermal necrolysis. Milder forms are known as Stevens-Johnson syndrome or overlapping Stevens-Johnson syndrome and toxic epidermal necrolysis. Toxic epidermal necrolysis is usually drug-related. Drugs are an important cause of Stevens-Johnson syndrome, but infections or a combination of infections and drugs has also been implicated.⁴ There is no ethnic preponderance and reports of gender differences are conflicting. Whereas Lind’s series reported equal gender involvement, Tay noted a male predominance, with a sex ratio of 2:1.5. As expected, the incidence is increased in the immunocompromised, HIV-infected population. Some authors believe that Stevens-Johnsons syndrome in children usually is not associated with
medication hypersensitivity but mainly with infectious agents.\textsuperscript{3} The common pathogenesis of cytotoxic immunologic attack against exogenous antigens on the keratinocytes further unified these entities.\textsuperscript{1}

**ETIOLOGY**

A comprehensive review of Stevens-Johnson syndrome identifies an extensive and multifactorial etiology.\textsuperscript{3} EM is almost always infectious in origin; herpes simplex virus (HSV) is the infectious agent in 70 to 80\% of cases. HSV-1 and HSV-2 are known to trigger EM. In contrast to EM, drugs precipitate 80 to 95\% of the cases of TEN and more than 50\% of cases of SJS. These drugs are all forms of sulfonamides; in descending order of incidence, they are: Trimethoprim-sulfamethoxazole, nonsteroidal anti-inflammatory agents, penicillins, anticonvulsants, such as barbiturates and carbamazepine, hydantoins, valproic acid, allopurinol and terbinafine chlormezanone, a minor tranquilizer has been suspected of inducing severe cutaneous reactions. Presumably, the cytotoxic T-cell response is against keratinocytes expressing drug antigens. The remaining 10\% of cases may be caused by infections, such as *Mycoplasma pneumonia* by vaccination or by graft-versus-host disease. The condition is idiopathic in a small fraction of cases.\textsuperscript{1}

**PATHOLOGY**

SJS exhibits much more widespread necrosis of the epidermis and little vascular inflammation of the dermis. Presumably, the drug antigens are expressed only on the keratinocytes, not the blood vessels. In fact, there is a remarkable absence of significant lymphocytes around the vessels and few are seen in the epidermis.\textsuperscript{1}

**CLINICAL PRESENTATION**

With SJS/TEN there is considerable variability in the interval between exposure to the offending agent and onset of skin eruptions, severity of symptoms, surface area and region of involvement and associated constitutional symptoms. SJS/TEN may occur within 45 days of a drug treatment being started or within a few days after repeat exposure. In many patients a nonspecific prodrome occurs 7 to 14 days in advance of lesion development. Symptoms may include fever, malaise, headache, cough, rhinitis, sore throat, myalgia, arthralgia, nausea and vomiting. Initially a macular, morbilliform rash develops on the face, neck, chin and central trunk making the presenting appearance and distribution of the lesion different from that seen in EM. In SJS/TEN lesions spread rapidly over much of the body. Target lesions are seen but are larger and less well defined than in EM. The lesions tend to coalesce. The skin is tender and some lesions exhibit the Nikolsky sign. Large areas of fragile skin involving more than 30\% of the body surface define TEN. Many mucosal surfaces are severely affected.\textsuperscript{1} The characteristic findings of Stevens-Johnson syndrome are mucosal erosions and widespread distribution of flat atypical targets or purpuric macules.\textsuperscript{2} The lips, buccal mucosa and palate may be involved. Sometimes the extensive hemorrhagic sloughing tissue extends to the whole oral cavity, larynx, esophagus and respiratory tree. The bulbar conjunctiva can be involved, and sometimes corneal ulceration and uveitis develop. Eye lesions consist of photophobia; a characteristic of the disease referable to the conjunctivitis, panophthalmitus, keratoconjunctivitis sicca also have been described.\textsuperscript{1} Late scarring of the conjunctiva (symblepharon formation), corneal ulcerations and intercurrent bacterial infection can result in blindness.\textsuperscript{6} Genital ulcerations can develop leading to urinary retention, phimosis, nonspecific urethritis and balanitis. Sepsis from widespread skin infection, respiratory tract involvement, such as tracheobronchial ulceration, pneumonia, renal failure and cardiac complications, can lead to death in a significant percentage. In contrast to EM, repeat attacks do not occur, if the offending drug is strictly avoided. Reexposure to the same agent can again precipitate SJS/TEN, often with a more severe clinical course.\textsuperscript{1}

The varied nature of this disease may present difficulty in diagnosis, particularly when the occurrence of cutaneous lesions is minimal. In the presence of oral lesions, the differential diagnosis which can be considered are aphthous stomatitis, contact dermatitis or stomatitis, acute necrotizing gingivitis, pemphigus, dermatitis herpetiformis, bullous lichen planus, herpes zoster, chickenpox and toxic epidermal necrolysis (Lyell’s disease).\textsuperscript{5}

**DIAGNOSTIC TECHNIQUES**

In SJS/TEN there is an elevation in the blood sedimentation rate. Moderate leukocytosis, fluid and electrolyte imbalances, microalbuminuria, hyponatremia, elevated liver transaminase, hypoproteinuria and anemia also may be present. A transient decline in CD4\textsuperscript{+} T-lymphocyte counts may also be seen during the acute phase of TEN. Numerous other laboratory abnormalities may also be identified depending on organ involvement or the presence of secondary infection.\textsuperscript{1} The primary cytokine involved is tumor necrosis factor (TNF)-\alpha.\textsuperscript{7}
TREATMENT OPTIONS

There are no standardized guidelines for treatment of SJS/TEN. Recognition and prompt discontinuation of the offending agent is a priority. Use of all drugs should be stopped as quickly as possible, especially those taken within 8 weeks before the onset of TEN symptoms. In SJS, oral intake may be limited, so patients may need to be hospitalized to receive replacement intravenous fluids. Ophthalmologic consultation is imperative. Ocular lubricants and elimination of new lid adhesions should be a priority. Patients with SJS benefit greatly from admission to a burn unit where dressings, fluid and electrolyte replacement, and antibiotics are best administered. Otherwise, protein loss, electrolyte imbalance, and infection can result in death up to 60% of cases. It is sometimes difficult to choose an antibiotic to fight secondary infection. The use of systemic steroids is controversial because the steroid may stop the immune reaction against the drug but may favor the infection after the epidermis sloughs. Most argue strongly against the use of systemic steroids. The dosage of systemic steroids, if used, should be in the range of 100 mg prednisone; use of systemic steroids should be discontinued within 48 hours once the disease stops progressing. Unfavorable signs in TEN are advanced age, extensive skin lesions and neutropenia. It is imperative to counsel the patient about avoiding the responsible drug in all of its forms in the future. In the future, treatments tailor-made to the pathogenesis may be available, such as antibodies against CD95 or FasL, the ligand that results in apoptosis or keratinocytes.\(^1\)

Intravenous immunoglobulin (IVIG) prepared from pooled plasma that interferes with the apoptotic pathway mediated by the Fas ligand and receptor are given within 24 to 72 hours from the first appearance of bullae.\(^8\)

Immunosuppressive agents, like cyclosporin A (3-4 mg/kg/day), have shown favorable outcomes in short-term cases.\(^8\)

Removal of the offending medication, its metabolites or cytokines by plasmapheresis or hemodialysis can also be considered.\(^8\)

Sepsis is the most important cause of mortality.\(^8\)

CONCLUSION

Two interesting cases of Stevens-Johnson syndrome are reported and their clinical manifestations, pathogenesis and treatment options discussed. EM and SJS/TEN are distinct entities that lead to clinical to different investigations and management. With EM the investigative focus is on identification of an infectious cause, particularly an HSV. With SJS/TEN the effort is to identify the causative drug. Identifying the offending drug and avoiding the implicating drug in future are important in treatment and management of SJS syndrome.

REFERENCES