Study of genital manifestations of Stevens Johnson Syndrome/Toxic Epidermal Necrolysis

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Abstract

Background: Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (SJS/TEN) are severe mucocutaneous reactions, considered as variants of same pathologic process. It is characterized by epidermal blisters, necrosis and sloughing predominantly of drug induced etiology. Due to severe cutaneous reactions, the genital manifestations associated with SJS/TEN are less studied. The chronic sequelae of genital manifestations results in severe gynecological, urological and sexual related complications, and have a great impact on the quality of life of patients. Aims And Objectives: To study the genital manifestations associated with SJS/TEN. Materials and Methods: Patients of SJS/TEN attending the Out-patient and In-patient Department of Skin and VD in a tertiary care hospital, having genital manifestations were included in the study. Genital examination of all patients were observed and recorded with a follow up for 6 months. Results: A total of 30 patients, twelve males (40%) and eighteen females (60%), were included. Genital manifestations were observed in 18 (60%) patients, with a male:female ratio of 1:2, i.e. males 6 (36.66%) and females 12 (63.33%). All patients presented in the acute stage of the disease. Four female patients (33.3%) developed chronic manifestations in the form of labial synechiae in 2 (16.66%), vaginal synechiae in 1 (8.33%), vaginal strictures in 1 (8.33%) patient. None of the male patients developed chronic sequelae. Conclusion: SJS/TEN are rare diseases, but the mucocutaneous involvement, especially of genitourinary system and their long-term sequelae have a major impact on the quality of life of affected patients. The genital manifestations are largely preventable by means of proper awareness and early intervention.

Key words: Genital manifestations, scrotal bullae, scrotal erosions, Stevens–Johnson syndrome, toxic epidermal necrolysis, urethral erosions, vaginal discharge, vaginal erosions, vaginal synechiae

Introduction

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) are rare, potentially life-threatening conditions triggered by drug administration and infections.[1,2] SJS and TEN are now recognized as variants of the same condition with differing severities. It is characterized by epidermal blisters, necrosis, and sloughing due to dermoeidermal interface dermatitis resulting in the apoptosis of keratinocytes. By definition, changes affecting <10% of body surface area are seen in SJS and >30% of body surface area seen in TEN, while the involvement of 15%–30% body surface area is considered as SJS/TEN overlap. The most common cause is drugs, over 50% cases in SJS and up to 90% cases in TEN.

SJS/TEN affects about 1–5 people/million/year with a mortality rate of 7.5% in children and 20%–25% in adults.[3,4] It begins with a prodrome of fever, malaise, headache, and anorexia lasting for 2–3 days, sometimes up to 10–11 days. Mucosal lesions precede cutaneous lesions. The pathogenesis of epidermal necrosis in SJS/TEN remains unknown. Various theories have been implicated that includes drug-specific T-cells and/or monocytes/macrophages, Fas/Fas ligand, function of regulatory T-cell, and perforin/granzyme B. One theory suggests altered drug metabolism (e.g., failure to clear reactive metabolites) as a triggering factor to T-cell-mediated cytotoxic reaction.[5] Recently, the role of granulysin produced by natural killer cells and proinflammatory cytokines in keratinocyte death is suggested.[6] About 25% cases are believed to have infectious etiology.

The skin and mucous membrane are affected in SJS/TEN, and mucosal involvement can be more severe than
cutaneous involvement. Healing of ulcerative mucosal lesions may result in extensive scarring, which can interfere with the organ function. Genital long-term sequelae may occur and affect patients’ quality of life, emphasizing the need for long-term follow-up of patients after the resolution of SJS/TEN.

Genital manifestations and their sequelae include erosive and ulcerative vaginitis, vulvar bullae, vaginal synchieae in females and scrotal erosions, urethritis, phimosis, and urethra meatal stenosis in males. Genital manifestations of SJS and TEN are preventable, but the prevention requires an awareness of the disease process. In this study, we attempt to study the genital manifestations seen in patients of SJS/TEN.

**Materials and Methods**

Thirty patients of SJS/TEN, attending the Outpatient/Inpatient Department of Skin and VD in MGM Medical College and Hospital were included in the study. After obtaining consent, the demographic information and clinical pictures were recorded. Genital examination of all patients was done in association with the department of gynecology. Patients were followed up regularly for a period of 6 months.

**Results**

A total of 30 patients were included in the study during the study, of which 12 were males and 18 were females. Of these, 22 were SJS or SJS/TEN overlap, and eight were TEN patients. Genital manifestations were observed in 18 patients (60%), with a male-to-female ratio of 1:2 [Table 1]. All cases were drug induced, except one, in which no history of any drug intake before the appearance of lesions could be elicited [Table 2].

All the patients with genital involvement presented in the acute phase with symptoms such as pain, burning sensation, discharge, redness, peeling of the skin, and ulcerative lesions that were observed over the mons pubis, labia, vagina, and perianal area in females and scrotum, penis, prepuce, and urethra in males.

Genital examination in females revealed vulval erosions and sloughing of skin over mons pubis and perineal area to be the most common finding, as observed in 11 (91.6%) patients each. Of these, four patients developed chronic sequelae in the form of labial synchieae, vaginal synchieae, and vaginal stricture formation [Table 3 and Figures 1-6].

Among the male patients, scrotal erosions, ulceration, and sloughing of skin were observed as the most common findings, seen in 4 (66.6%), 4 (66.6%), and 3 (50%) patients, respectively. Other findings noted were balanitis/balanoposthitis, urethral erosions, and ulceration over perineal areas. None of the male patients developed chronic sequelae [Table 4; Figures 7 and 8].

**Discussion**

SJS and TEN are overlapping cutaneous drug reactions that differ from the extent of the body surface area involved in epidermal detachment. It presents clinically as severe mucocutaneous erythema, blisters, and sloughing of the epidermis by necrosis caused due to dermoepidermal interface dermatitis resulting in the apoptosis of keratinocytes. The most common cause is drugs, over 50% cases in SJS and up to 90% cases in TEN.

In spite of documented involvement of genitals in the patients with SJS/TEN, there is a paucity of published data describing genitourinary symptoms, their management, and the prevention of long-term sequelae. In a retrospective case series evaluating the vulvovaginal involvement and acute genital manifestations of SJS/TEN were observed in 70% patients. Chronic sequelae developed in 28% of these patients.[7] Similar to these findings, our study reported a 60% occurrence of acute genital manifestations in SJS/TEN, 22.2% of which developed chronic sequelae. As observed, patients having genital involvement presented with symptoms of pain, erythema, burning micturition, sloughing of skin, etc. Genital manifestations and their chronic sequelae include vulval bullae, erosive and ulcerative vaginitis, vaginal or labial synchieae, vaginal strictures in females while urethritis, scrotal erosions and ulceration, phimosis, and urethra meatal stenosis are the findings in males.

| Table 1: Gender distribution |
|-----------------------------|
| Gender | Frequency | Genital lesions | Percentage |
| Male | 12 | 6 | 36.66 |
| Female | 18 | 12 | 63.33 |
| Total | 30 | 18 | 100 |

| Table 2: Causative agent |
|--------------------------|
| Drug | Frequency (%) |
| Aceclofenac | 4 (22.2) |
| Carbamazepine | 2 (11.1) |
| Nimesulide | 6 (33.3) |
| Ofloxacin | 1 (5.5) |
| Phenytoin | 4 (22.2) |
| No history of drug intake | 1 (5.5) |
| Total | 18 (100) |

| Table 3: Genital manifestations in females (12 patients) |
|-----------------------------|
| Features | Frequency (%) |
| Acute manifestations | |
| Vulval bullae | 4 (33.3) |
| Vulval erosions | 11 (91.6) |
| Skin sloughing | 11 (91.6) |
| Secondary infection | 5 (41.6) |
| Ulceration | 6 (50) |
| Vaginitis/discharge | 6 (50) |
| Chronic manifestations | |
| Labial synchieae | 2 (16.6) |
| Vaginal synchieae | 1 (8.3) |
| Vaginal strictures | 1 (8.3) |

| Table 4: Genital manifestations in males |
|-----------------------------|
| Features | Frequency (%) |
| Acute manifestations | |
| Scrotal bullae | 3 (50) |
| Scrotal erosions | 4 (66.6) |
| Urethral erosions | 1 (16.6) |
| Balanitis/balanoposthitis | 1 (16.6) |
| Skin sloughing | 3 (50) |
| Secondary infection | 2 (33.3) |
| Ulceration | 4 (66.6) |
| Chronic manifestations | |
| Phimosis | 0 (0) |
| Urethritis | 0 (0) |
| Urethral meatal stenosis | 0 (0) |
Genital lesions heal with extensive scarring that lead to long-term consequences. Vaginal adhesions and stenosis occur as a result of scarring. In these cases, the patients have complaints of itching, dryness, dyspareunia, postcoital bleeding, cyclic abdominal pain, and amenorrhea in some cases. Significant vulvovaginal stenosis, once developed,
can be extremely challenging to manage, even with appropriate surgical intervention. There has been a report of hematocolpos secondary to SJS in a case, which occurred due to the obstruction flow of menstrual blood. Vaginal adenosis and endometriosis after SJS/TEN episodes have also been reported.

Genital lesions, when in the acute phase, if treated promptly and properly with great care, can decrease the long-term complications of the genital manifestations. Importantly, scars can continue to mature for up to a year after injury, so a successful treatment plan should include long-term follow-up and longitudinal management strategies.

The primary goal of management in the genital sequelae of SJS/TEN is to protect vaginal function by decreasing the formation of adhesions and scarring. The application of intravaginal corticosteroids, such as betamethasone valerate 0.1%, betamethasone dipropionate 0.05%, and hydrocortisone acetate 10%, in patients with ulcerative lesions of SJS and TEN has been proposed as an effective preventive strategy. A rare side effect of super potent topical steroids is tachyphylaxis, which may occur as early as day 4 of treatment. However, this tachyphylactic effect usually weans off on stopping the application of steroids, hence, on and off protocol of steroids may be used. Topical steroid treatment should be continued until the resolution of the acute phase of illness.

Soft vaginal molds in addition to topical steroids may be used prophylactically to prevent adhesion formation. Daily insertion of molds for up to 24 h can be done, such as soft silicone vaginal molds, i.e. Milex dilator or inflatable vaginal dilators coated with high-potency corticosteroids. They prevent fibrous band formation till complete re-epithelialization of ulcerated surfaces occurs. In virgin patients, vaginal molds are not advisable. Instead, a steroid formulation which is suitable can be applied every other day with a standard vaginal applicator.

The use of topical calcineurin inhibitors such as tacrolimus has been shown to prevent vaginal stenosis in patients of erosive lichen planus. However, their use in SJS/TEN has not been studied.

Regular follow-up and effective pediatric, dermatological, and urological interventions can avoid the long-term genital complications of SJS/TEN patients.

Conclusion

SJS/TEN are rare diseases, but the mucocutaneous involvement, especially of genitourinary system and their long-term sequelae have a major impact on the quality of life of affected patients. The genital manifestations are largely preventable by means of proper awareness and early intervention. Prudent measures to treat acute manifestations lead to the prevention of chronic sequelae.

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Conflicts of interest

There are no conflicts of interest.

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