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Drug-related Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis: A Review

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Abstract

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, life-threatening, allergic reactions affecting the skin and mucous membranes. SJS is considered to be a milder form with less than 10% of body surface area (BSA) involvement. We report successful management of two cases of SJS and TEN. Firstly, a case of a 24-year-old female who presented with rashes over face, chest, and upper limbs after the oral intake of ciprofloxacin and local application of moxifloxacin eye drops. She developed high-grade fever and difficulty in breathing requiring intubation and lung-protective mechanical ventilation and was treated with high-dose methylprednisolone, azithromycin, soframycin skin dressings, and topical ocular antibiotics. Secondly, another case of a 16-year-old female who developed bullous eruptions over the trunk, arms, hands, face, and sole involving 60% of BSA, after oral intake of albendazole. She was diagnosed as TEN and successfully managed with sterile silver nitrate, soframycin dressings, and antibiotics.

Key message

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening, allergic reactions affecting the skin and mucous membranes. Early identification, withdrawal of the suspected drug, and early transfer to a specialized center decrease mortality.

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Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are both rare and life-threatening conditions caused by a hypersensitivity reaction involving the skin and the mucous membranes. SJS is a milder form of TEN with the involvement of less than 10% of body surface area (BSA), and the condition is called TEN if the affected BSA is more than 30%. The involvement of 10 to 30% of BSA is considered to be SJS-TEN.[1] We report two cases—SJS by fluoroquinolones and TEN caused by albendazole. TEN caused by albendazole to the best of our knowledge has not been reported previously.

Case Descriptions

Case 1

A 24-year-old female developed erythematous rashes over the face, chest, and upper limbs after the oral intake of ciprofloxacin and local application of moxifloxacin eye drops. The patient presented with high-grade fever and breathing difficulty necessitating endotracheal intubation and ventilation. She was put on pressure control mode with lung-protective strategy. Skin involvement was found to be approximately 10% of BSA with extensive damage to the conjunctiva and symblepharon formation. A diagnosis of fluoroquinolone-induced SJS was made based on the clinical findings.

The patient was given high-dose methylprednisolone for 3 days and azithromycin. The erosions were covered with a sterile paraffin gauge and mometasone cream. The patient developed hospital-acquired pneumonia and sepsis, which were treated with appropriate antimicrobial therapy. Supportive treatment included sedatives, analgesics, and intravenous fluids. The patient improved significantly by day 10 and was weaned from the ventilator and shifted to ward on day 15.

The patient developed symblepharon, which was released successfully. She later developed painful deglutition due to glossitis and oral ulcers that was treated with local glycerin application.

Case 2

A 16-year-old female presented with bullous eruptions over her face, trunk, arms, hands, genitals, and sole covering about 60% of BSA, following oral intake of albendazole (Figs. 1 to 3). A diagnosis of TEN was established based on purplish lesions over the trunk, which were more than 30%. She had tachycardia that was managed with fentanyl infusion. The patient was managed with crystalloid and albumin infusion given through the central line, early enteral feeding with a high protein diet, appropriate antibiotics, and methylprednisolone. She developed sepsis early requiring escalation of antibiotics and withdrawal of steroids. Wound care was provided with soframycin dressings (Fig. 4). and wet dressing of silver nitrate that maintains a moist wound environment. Eyes cared for with saline-soaked pads. The skin lesions improved by day 20 after which they got converted to hyperpigmented scars, and the patient was discharged home.

Discussion

Both SJS and TEN are rare, life-threatening acute allergic drug reactions affecting the skin and mucous membranes. SJS affects less than 10% of BSA, while TEN involves more than 30% of BSA, and between 10 and 30% is SJS/TEN overlap. The mortality rate of TEN can be up to three times higher than that of SJS because of the extensive skin involvement and secondary complications.[2]

Drug reactions are the most common cause of SJS/TEN. Drugs like antibacterial, allopurinol, sulfonamides, anticonvulsants, and steroids are found to be associated with an increased risk of SJS/TEN.[3] Among these drugs, sulfonamides, penicillin, and anticonvulsants are the commonest implicating agents for SJS/ TEN.[4,5]

Among nondrug infectious causes, mycoplasma pneumonia in adults and herpes simplex virus infections in children are known to cause SJS/TEN.[6,7] A rare occurrence of TEN in a patient with severe aplastic anemia after allogeneic hematopoietic stem cell transplantation has also been reported.[8] Lastly, vaccination is also implicated as an inciting factors like human papillomavirus, mumps, measles, rubella, hepatitis B, influenza, anthrax, and tetanus vaccines.[9]

The primary cause for the development of TEN is massive T-lymphocyte-mediated immune reaction causing destruction of the keratinocytes-expressing foreign antigens. An increased amount of inflammatory cytokines like tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are found in blister fluid.[10] They recruit the cytotoxic T-cells to the epidermis causing cell death by inducing apoptosis. A cascade of intracellular enzymes called caspases is activated when cytotoxic T-lymphocytes come in contact with target cells.

The patient may present with a prodromal phase of fever, malaise, cough, stinging eyes, and sore throat. Other symptoms include erythematous rash, bullae, and separation of large sheets of epidermis from the dermis. Cutaneous lesions include diffuse erythema with target-like lesions, blisters, and erosions. "Target lesions"[11] are less than 3 cm in diameter, round, and have three concentric zones; a central area of dusky erythema, a middle paler zone of edema, and an outer ring of erythema with a defined edge. Target lesions plus involvement of at least two mucous membranes comprise SJS.

The condition can be associated with multi-organ failure, sepsis, gastrointestinal hemorrhage, and pulmonary embolism. Ocular involvement[12] of TEN occurs in 50% to 88% of cases and includes a purulent form of conjunctivitis, corneal ulceration, anterior uveitis, entropion, dry eye syndrome, and severe visual loss.[13,14]

Pulmonary involvement is common but usually mild in nature,[15] and only 10 to 20% requires ventilator support.[16] Our first case had pulmonary involvement and developed hospital- acquired pneumonia. Reported pulmonary complications include tracheobronchial mucosal necrosis, pulmonary edema, acute respiratory distress syndrome, and pneumonia in 20–50% of cases. Erosive and ulcerative vaginitis and vulvar bullae are seen in genital involvement.

Long-term Sequelae Complications

Long-term complications include xerophthalmia, ectropion, entropion, symblepharon, corneal opacity, pannus formation, nasolacrimal duct obstruction, punctal stenosis, vaginal synechiae,[17] obliterative bronchitis or bronchiolitis, bronchiectasis, esophageal stricture, recurrent cystitis, lingual ulcerations, recurrent oral aphthae, etc.[18]

The presence of extensive necrolysis, idiopathic nature of diseases, old age, elevated urea, creatinine and glucose levels, neutropenia, lymphopenia, and thrombocytopenia are linked to a bad prognosis. SCORTEN scale[19] (Table 1) has been validated to determine the mortality rate and is considered to be the gold standard for prognosis. Our first patient had a SCORTEN score of 1, corresponding to a reported mortality of 3.2%. Our second patient had SCORTEN score of 3, with a reported mortality of 35.3%. Drug provocation tests[20] (DPTs) are often needed when evaluating these patients for the correct causative agent and for the preparation of a list of drugs to be given to these patients. Since DPT may itself cause reactions, it has to be done under proper medical supervision.

Management

TEN behaves like a superficial dermal burn with fluid shifts, hypermetabolism, and high nutritional requirements. The initial aim is the prevention of secondary infection by good wound care as this is the most common cause of death.[21] Early diagnosis, early withdrawal of the suspected drug,[22] and early transfer and management of these patients in a specialized unit like intensive care or burn unit[23] are associated with survival benefit.[24]

Wound management with nonadhesive wet silver nitrate dressings maintains a moist wound environment, speeds re-epithelialization, minimizes the pain, and decreases infection rates.[25] Wounds should be treated conservatively as much as possible,[26] as blistered skin acts as a natural biological dressing and favors re-epithelialization. Biological or biosynthetic temporary skin replacements[27] (e.g., porcine xenografts), Biobrane (skin substitute), and Aquacel Ag (a moisture-retentive hydrofiber dressing that releases silver within the dressing) are the latest modalities of skincare. Umbilical cord mesenchymal stem cell

transplantation[28] is an attractive and promising tool for skin regeneration in patients with severe denudation due to their self-renewal capacity, multilineage differentiation potential, paracrine effects, and immunosuppressive properties.

Pain control is a very important part of the management of SJS/TEN, as these patients experience low-intensity background pain. Longer-acting opioids and paracetamol should be given for pain.

It is important to encourage oral feeds to avoid adhesions in the upper gastrointestinal tract, but parenteral feeding may be considered when the nutritional requirement cannot be met with oral intake.

SJS/TEN patients have impaired temperature control due to loss of the integument and should be cared for in rooms with temperature and humidity control. Careful monitoring of fluid balance with strict input and output chart is essential because of significant insensible fluid losses, resulting in dehydration and renal impairment.

Eye care includes 1- to 2-hourly eye lubrication and early involvement of an ophthalmologist. Nonhealing corneal ulcers may be treated with bandage contact lenses and amniotic membrane transplantation for severe persistent corneal damage.[29]

Specific Management

The use of corticosteroids is debatable and remains controversial. Corticosteroids have an antiapoptotic role in the skin tissue, inhibit the initiating pathways,[30] and down-regulate fas ligand (FasL) in the apoptotic tissue. Studies support the early use of high-dose corticosteroids[30] (1–2 mg/kg/day of prednisolone for 3–5 days).

Dexamethasone 8 to 16 mg/day is recommended;[31] however, the dose can be increased by 4 mg the next day if considered necessary and the recovery is not adequate. On the other hand, the opponents to corticosteroids suggest an increased risk of sepsis, prolonged hospital stay, and increased mortality.[32]

Other reported medical therapies for the treatment of TEN include plasmapheresis, intravenous immunoglobulins (IVIG), and cyclosporine. Literature supports early use of IVIG,[33] which is a safe therapy even for children with severe cutaneous drug reactions.[34] However, there are conflicting reports as well.[35]

Cyclosporine if given early in the disease arrests the progression of the disease without increasing the risk of sepsis.[36] The mean duration of re-epithelialization and duration of hospital stay were significantly lower in patients receiving cyclosporine in comparison to those patients who were managed using supportive treatment only, without increasing mortality.[37,38]

Plasmapheresis therapy[39] to remove drug metabolites and cytokines from circulation remains controversial.

Although beneficial effect of cyclophosphamide[40] and tacrolimus[41] is suggested by some authors, larger studies are needed to clarify these results.

Other treatments that have been tried include chimeric anti-TNF-α antibody (infliximab)[42,43] and thalidomide (TNF-alpha inhibitor) as cytokines such as IL-6 and TNF-alpha are found in higher quantities in the skin of patients of TEN. Recombinant granulocyte colony-stimulating factor in a dose of 5 μg/kg/day for 5 days leads to rapid re-epithelialization of skin as reported in some case reports. But still their use remains controversial, and more robust data are required to make these treatments as a standard of care.[44–47]

There are still gaps in our understanding of the pathophysiology of SJS/TEN and the available treatment options. Good quality multicenter studies are needed to understand the disease better and explore the treatment options further.

Conclusion

Life-threatening SJS and TEN present a challenge in early detection and subsequent management. Evidence-based practice related to the care of patients with SJS is still evolving. Management includes early identification, withdrawal of the suspected drug, and early transfer to a specialized center. Further research and clinical evidence are needed to develop appropriate and cost-effective treatment guidelines for optimal care of these patients.

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Footnotes

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Figures and Tables

Fig. 1

Initial skin lesions involving trunk and face (Case 2)

Fig. 2

Initial skin lesions over chest and abdomen (Case 2)

Fig. 3

Crusting (Case 2)

Fig. 4

Wound care and use of barrier precautions (Case 2)

Table 1A

Scorten scale

Risk factor	*0*	*1*
Age	<40 years	>40 years
Associated malignancy	No	Yes
Heart rate (beats/min)	<120	>120
Serum BUN (mg/dL)	<27	>27
Detached or compromised body surface	<10%	>10%
Serum bicarbonate (mEq/L)	>20	<20
Serum glucose (mg/dL)	<250	>250

Table 1B

Percentage of mortality

No of risk factors	*Mortality rate (%)*
0–1	3.2
2	12.1
3	35.3
4	58.3
5 or more	>90

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