World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(CASE REPORT)

Check for updates

Drug associated steven Johnson syndrome/ toxic epidermal necrolysis: A case report

Denisa Dwi Rahmayani *

Faculty of Medicine, Airlangga University, Surabaya, Indonesia.

World Journal of Advanced Research and Reviews, 2024, 24(02), 1208–1213

Publication history: Received on 02 October 2024; revised on 10 November 2024; accepted on 12 November 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.24.2.3443

Abstract

Steven-Johnson Syndrome (SJS)/ TEN (Toxic Epidermal Necrolysis) is a rare cutaneous adverse drug reaction and one of the most life-threatening dermatologic cases. It is characterized as rashes, blisters, and epidermolysis of the dermis and mucosa tissue, and it may also be followed by systemic symptoms. SJS/TEN presents a mortality rate of 9%. The most popular method for predicting fatality rates and assessing prognosis in individuals with SJS/TEN is the severity of sickness score for Toxic Epidermal Necrolysis (SCORTEN) scale. In this case report, we present a case of a patient who presented with SJS/TEN following consumption of antibiotic medication.

Keywords: Steven Johnson syndrome; Toxic epidermal necrolysis; Drug reaction; Hypersensitivity; Case report

1. Introduction

Steven-Johnson Syndrome (SJS)/ TEN (Toxic Epidermal Necrolysis) is a rare cutaneous adverse drug reaction and one of the most life-threatening dermatologic cases [1]. These diseases may manifest in the skin as rashes, blisters, and epidermolysis of the dermis and mucosa tissue, and it may also be followed by systemic symptoms. According to the percentage of the skin detachment, SJS/TEN may be classified to SJS with <10% of skin involvement, SJS-TEN overlap with 10-30% of skin involvement, and TEN with >30% skin involvement [1, 2].

Prior to the appearance of cutaneous involvements, SJS is often preceded by prodromal symptoms. Late cutaneous lesions manifest as erythematous macules or unusual target lesions on the trunk, which develop into sheets of denuded epidermis and flaccid blisters with a positive Nikolsky sign [3]. Mucosal involvement manifests as mucositis and ulceration in the oral, orbital, or genital [3, 4].

Several factors are found to be able to trigger SJS, such as medications and infection, whether it is bacterial, viral, or fungal. Previous research shows that medications are the leading causative agent of SJS, accounting for up to 95% [2, 4, 5, 6]. Following exposure to the drug(s) or drug metabolites, a potentially antigenic drug-tissue complex forms that triggers the secretion of granulysin, perforin, and granzyme-B by cytotoxic CD8 T-cells and natural killer cells along with increased interaction between FAS ligand and FAS death receptor on keratinocytes, leading to massive keratinocyte apoptosis [7]. The most common SJS inducing medications are antibiotics, followed by non-steroidal anti-inflammatory drugs (NSAIDs), anti-epileptic drugs, and gout medication [2, 5]. The antibiotics with the highest rate of SJS cases are trimethoprim-sulfomethoxazole and other sulfonamide group antibiotics, followed by chlormezanone, cephalosporine, quinolone, and aminopenicillins [1].

Although there is not one single treatment that is agreed on as the gold standard for SJS/TEN, supportive care and therapy targeted to minimizing long-term sequelae are imperative [8]. Identification and discontinuation of the causal factor is the first step in the comprehensive management of SJS/TEN [3]. Due to the immunologic nature of the disease, it is believed that immunosuppressive therapies will aid in treatment, and many case reports have reported positive

* Corresponding author: Denisa Dwi Rahmayani

results with varying treatment regimens involving different combinations of corticosteroids, IVIg, cyclosporine, and TNF-alpha inhibitors [3].

Systemic corticosteroids are one of the treatments used in SJS-TEN instances. High doses should be administered as soon as feasible and for a brief period of time; treatment for three days may be chosen and modified based on the patient's clinical response. The prognosis of patients will improve if therapy is initiated as soon as possible [2].

Prior reports of SJS fatality rates showed a range from 4.8 to 9% [3] and 6.3% [6]. The most popular method for predicting fatality rates and assessing prognosis in individuals with SJS/TEN is the severity of sickness score for the Toxic Epidermal Necrolysis (SCORTEN) scale. The mortality rate is typically between 1 and 5% when BSA sloughing is less than 10%. The mortality rate ranges from 25 to 35% when there is more than 30% BSA sloughing [4]. Prognostication is an important step in the management of SJS/TEN since it may guide the management and placement of SJS/TEN patients in an intensive care or burn unit [3].

2. Case report

A 29-year-old female came to the emergency department of Slamet Martodirjo Hospital, Pamekasan, Indonesia, with a chief complaint of blisters all across her body since 3 days prior to admission. The patient first complained about having some red, itchy insect bites looking like spots in her arms and chest 10 days before admission. She had gone to a general practitioner and had been given 3 medications: cetirizine, dexamethasone, and cefadroxil. She had consumed 3 packs of those medicines prior to her coming to the emergency department. She had developed small, fluid-filled blisters (vesicles) on her fourth day of medication; they first appeared in her shoulder before spreading to her arm, back, palms, and feet. She had experienced pain and a hot sensation in those vesicles. She also complained about having swollen lips and having difficulty swallowing since three days prior to her arrival in the emergency room; her lips are covered with traces of dried, dark yellowish fluid, causing her pain and making it difficult for her to eat. She also had a mouth ulcer. The patient's eyes had become red and discharged white, yellowish fluid; she also developed fever and shortness of breath one day prior to her admission. She had no problem with defecation and urination, and there was no lesion in her genital area.

The patient had a history of a similar symptom after consuming a medication for mastitis, but she had forgotten about the name of the medication. There was no history of food allergies, diabetes mellitus, hypertension, or other systemic diseases. She had no family with an allergic history or similar symptom. She spent her days as a housewife.

Her physical examination showed weak general condition, with a Glasgow Comma Scale of 456, blood pressure of 129/62 mmHg, heart rate of 87 bpm, respiratory rate of 24 x/m, axillar temperature of 38.7 ^{o}C, oxygen saturation of 94%, body weight of 75 kg, body height of 158 cm, and body mass index of 30.04 kg/m^2. Head and neck physical examination showed dyspnea and hyperaemic conjunctiva with yellowish discharge. Her thorax and abdomen physical examination showed normal results.

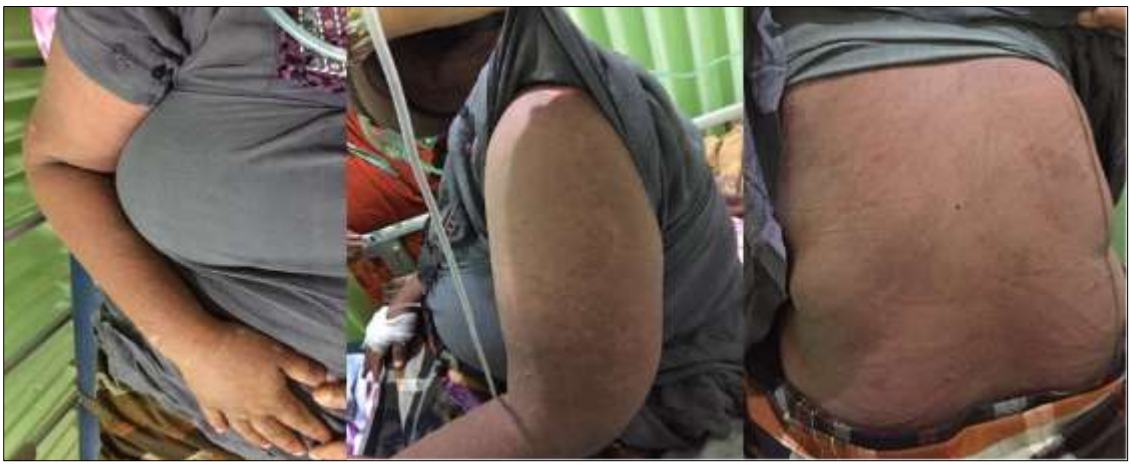

Figure 1 Upper extremities and thorax posterior

Figure 2 Lower extremities and palms

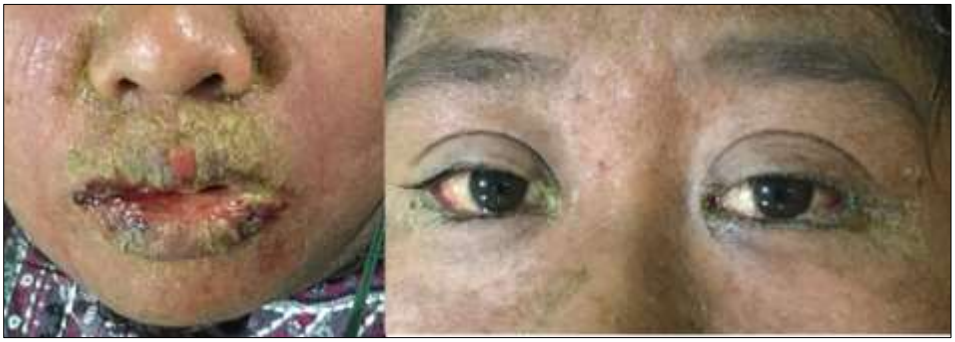

Figure 3 Mucosal involvement

Dermatological examination in the anterior and posterior of her thorax, upper and lower extremities, and facial region showed purpuric macules confluent with multiple loose-walled bullae filled with clear fluid on erythematous skin with varying diameters from 5 cm to 15 cm. Nikolsky sign showed positive result in the bullae in her left shoulder. In the labial region, multiple erosions with clear geographical boundaries were found with sizes varying from 0.2x0.5cm to 0.5x1cm covered in blackish yellow crust. The area of skin peeling was 10%.

Laboratory examination in the emergency room showed haemoglobin level of 12.4 g/dL, leucocyte level of 14.100/uL, thrombocyte level of 203.000/uL, haematocrit level of 36.1%, blood sugar level of 118 mg/dl, blood urea nitrogen level of 33 mg/dL, serum creatinine level of 1.04 mg/dL, sodium level of 129.2 mEq/L, potassium level of 4.03 mEq/dL. Chloride level of 99.1 mEq/dL, SGOT level of 51 U/L, SGPT level of 19.2 U/L, total cholesterol level of 170 mg/dL, and triglyceride level of 208 mg/dL.

The patient was being treated by giving an oxygen mask with a flow of 6 lpm, an infusion of normal saline with 1000 mL/24 hour, injection of methylprednisolone 125 mg/24 hour, injection of ranitidine ampule/12 hour, diphenhydramine injection/12 hour, and intravenous gentamycin 80 mg/12 hour with a skin test prior to injection. An aspiration had been done for the bullae in her foot; normal saline compression and topical intraoral triamcinolone acetonide were given to the labial area. The patient had undergone treatment for two days before being referred to a tertiary hospital for further treatment.

3. Discussion

Steven Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are forms of acute and severe cutaneous reactions [2]. SJS may manifest as a nonspecific prodromal symptom (malaise, headache, cough, rhinorrhea) accompanied by a polymorphic lesion of the skin and the mucous membrane [1]. In SJS/TEN, the lesions may start as an erythema to blackish-red macules, purpuric macules, or irregularly shaped lesions, which later may enlarge and merge with each other. There's also another atypical lesion of SJS that comes in the 'target' lesion [2]. These lesions will progress into

flaccid blisters with a positive Nikolsky sign and sheets of denuded epidermis [3]. Over 50% of SJS patients developed mucosal damage in two distinct areas: conjunctivitis, vaginal erosion, and oral ulcers, which are typically characterized by hemorrhagic lip crusting [3,4,5]. The significant wound area induces severe pain, substantial loss of fluid and protein, bleeding, evaporative heat loss, and infection, which may result in complications like respiratory distress and sepsis [1, 2].

SJS and TEN are both induced by type IV hypersensitivity reaction which is mediated by cytotoxic T cell lymphocytes [2]. SJS/TEN is classified regarding the percentage of the skin detachment with SJS having <10% of skin involvement, SJS-TEN overlap with 10-30% of skin involvement, and TEN with >30% skin involvement [1,2]. There are a number of hypotheses about how medication may develop an immunological response that causes SJS/TEN. The first hypothesis is the hapten/pro-hapten concept, which defined that small-molecule drugs will bind to the proteins in serum, forming a complex that is perceived by certain HLA molecules and presented to T-cells, generating an immune response. The second hypotheses is the pharmacological interaction concept, which says that the chemically inert drugs bind HLA molecules directly, leading to T cell activation. The last hypothesis is the changed peptide notion, which postulates that medications attach inside HLA binding spaces in a way that changes how self-proteins are presented to T cells, making them unrecognizable as self and triggering an immune response. Although the precise mechanism is unknown, the final effect is T-cell activation in response to an infection or medication, followed by epidermal necrosis [3].

In this case report, the drugs mentioned were obtained based on the patient's treatment history prior to the appearance of the SJS/TEN symptoms, not through the results of drug patch tests. Previous research shows that medications are the leading causative agent of SJS, accounting for 50-95% [2, 3, 6]. The most common SJS-inducing medications are antibiotics, followed by anti-inflammatory agents, anti-epileptic drugs, and gout medication [1, 2, 5, 6]. The antibiotics with the highest rate of SJS cases are trimethoprim-sulfomethoxazole and other sulfonamide-group antibiotics, followed by chlormezanone, cephalosporine, quinolone, and aminopenicillins [1, 6]. Other studies defined antipyretic analgesic drugs, specifically paracetamol, as the most common trigger of SJS/TEN, followed by antibiotics, with cefadroxil as the most common SJS/TEN trigger [2]. The high incidence number of paracetamol induced SJS/TEN is possibly due to its common use, its ease to obtain, and how relatively affordable it is [2].

Numerous studies have investigated potential diagnostic markers of SJS/TEN, with early studies focusing on the role of granulysin and CCL-27 [3]. The increase of granulysin and CCL-27 levels in SJS and TEN patients had been reported in several studies. However, elevated granulysin levels were also found in all cytotoxic T-lymphocyte-mediated bullous blistering disorders, such as erythema multiforme, bullous fixed drug eruption, and patients with drug reactions with eosinophilia and systemic symptoms. On the other hand, CCL-27 level increase were also found in non-bullous drug-induced exanthems. Therefore, elevated levels of granulysin and CCL-27 in both serum and blister fluid are not a specific marker for SJS/TEN [3].

Recent research found that galectin-7 and receptor-interacting kinase-3 (RIP3) are important biomarkers for diagnosis and potential mediators of SJS/TEN [3]. However, these tests are not regularly performed. Meanwhile, suspected medications of SJS and TEN were typically tested using patch tests and drug-induced lymphocyte stimulation tests (DLSTs), also called lymphocyte transformation tests (LTTs). Sunaga et al. discovered positive patch test and DSLT results for antibiotics and anti-inflammatory drugs in both SJS and TEN cases [5].

SJS patient shows separation of the epidermis at the dermal-epidermal junction of the skin, extracutaneous epithelium, and mucous membranes in their histopathological examination. Clinically, this finding can be detected by a positive Nikolsky sign, which is defined as detachment of the full-thickness epidermis when light lateral pressure is applied by the examining finger [1]. Despite its importance, biopsy to obtain histopathological results was not done in many SJS/TEN patients.

Supportive care is the main treatment for SJS/TEN patients, which includes discontinuation of the possible causative drug, fluid and electrolyte management, infection control, and wound care [3]. Identification and discontinuation of the causative drug is the most important aspect of SJS/TEN treatment [1, 3]. A thorough history taking is important to identify the causative agent, as symptoms typically present within 8 weeks of beginning therapy, with most cases appearing between 4 days and 4 weeks of starting a medication [3]. Due to skin detachment, the patient's thermoregulatory function is at loss, making the maintenance of environment temperature very important (30-32^{o}C) [3, 8]. Fluid replacement therapy should be based on urine output, with a goal of 0.5-1 mL/kg/h [3]. Enteral feeding should be done as early as possible, and nasogastric tube feeding is done when indicated [3, 7]. Ophthalmology should be consulted for management of ocular disease to prevent long-term complications [8].

This patient has a high level of leucocytes (14.100/uL) and fever. Septicemia is a leading cause of morbidity and mortality in SJS/TEN patients. The high percentage of positive blood culture was found to be correlated with the delay of admission to a specialized burn unit in 7 or more days [lerch]. Most SJS/TEN patients have also developed multi-organ involvement with varying degrees of severity [9]. This patient had a slightly elevated blood urea nitrogen level of 33 mg/dL and a SGOT level of 51 U/L. Comorbidities that are found to be associated with SJS/TEN cases are acute kidney injury and hypertension [2, 9]. Patients with AKI tend to develop more severe complications, requiring a longer hospital stay and a higher mortality rate [2].

Surgical debridement remains a controversial treatment for SJS/TEN; a recent study showed that the decision for this treatment largely depends on where the care is being delivered [3]. In anti-shear therapy, the blister fluid is being aspirated and the denuded epidermis is being left in place to act as a biological skin graft. It has been found that it could reduce hospital costs as well as pain. Patients who received this treatment presented a mortality reduction of 11 percent compared to the expected mortality [3].

Corticosteroid medication, especially methylprednisolone, is considered to be able to reduce the pro-inflammatory cytokines level [2], which will improve the patient survival rate [2, 9]. Our patient received a high dose of intravenous methylprednisolone from 125 mg/24 hours and later being tapered off according to the patient's treatment response and length of stay. The role of corticosteroids and IVIg as monotherapy remains a controversy [3]. Some studies showed that a combination of IVIg and corticosteroids produces statistically significant improvements in outcome [3, 8]. Meanwhile, Sunaga et al. presented that all cases of SJS/TEN improved with corticosteroid monotherapy, IVIg monotherapy, as well as a combination of corticosteroid and IVIg [5]. Our patient also received topical therapy of normal saline compression and triamcinolone acetonide for her hemorraghic crusting of her lip area.

The SCORTEN calculation has been found to be the most prognostically accurate on the third day of care. As the extent of the disease progresses, so does the mortality rate, with 30% for SJS/TEN overlap and up to 50% for TEN [8]. Another study by Sunaga et al. showed that the mortality rate of SJS is 4.5% and 32.5% for TEN. The leading cause of death in SJS and TEN cases was pneumonia, sepsis, or underlying malignancy [5]. Pneumonia is a major SJS/TEN complication, with almost half of the patients requiring mechanical ventilation. Half of SJS/TEN patients develop mild pulmonary dysfunction as a long-term complication [8]. Multiorgan failure in SJS/TEN patients is often caused by skin or peripheral line infection. Hypovolemia can also increase the risk of early morbidity. Mucosal involvement can lead to oral, ocular, or genitourinary strictures [8].

4. Conclusion

Stevens-Johnson syndrome is a life-threatening disease induced mostly by medication. Identification and discontinuation of the causal factor is the first step in the comprehensive management of SJS/TEN. Physicians therefore should instruct the patient to avoid any identified drugs or chemicals that may be responsible. A holistic approach is needed in the treatment of SJS/TEN patients to prevent complications and worsening of the condition. Prognostication is crucial in the management of SJS/TEN; it may guide the management and placement of SJS/TEN patients, whether the patient is placed in intensive care or not, and whether the patient is supposed to be referred to tertiary care.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from the patient included in the study.

References

[1] Deore SS, Dandekar RC, Mahajan AM, Shiledar VV. Drug induced-Stevens Johnson syndrome: A case report. International Journal of Scientific Study. 2014;2(4):84-7. Available online at https://www.researchgate.net/publication/265852452

[2] Putri OE, Oktavriana T, Octarica SG, Anandita BL, Pradestine S, Oktaviani T. Profile And Risk Factors of Stevens Johnson Syndrome–Toxic Epidermal Necrolysis on Adult Patients in Dr. Moewardi General Hospital Surakarta from January 2019–December 2022. Health and Medical Journal. 2024 Apr 30;6(2):135-44.

[3] Frantz R, Huang S, Are A, Motaparthi K. Stevens–Johnson syndrome and toxic epidermal necrolysis: a review of diagnosis and management. Medicina. 2021 Aug 28;57(9):895.

[4] Castana O, Rempelos G, Anagiotos G, Apostolopoulou C, Dimitrouli A, Alexakis D. Stevens-Johnson syndrome: a case report. Annals of Burns and Fire Disasters. 2009 Sep 9;22(3):147.

[5] Sunaga Y, Kurosawa M, Ochiai H, Watanabe H, Sueki H, Azukizawa H, Asada H, Watanabe Y, Yamaguchi Y, Aihara M, Mizukawa Y. The nationwide epidemiological survey of Stevens-Johnson syndrome and toxic epidermal necrolysis in Japan, 2016-2018. Journal of Dermatological Science. 2020 Dec 1;100(3):175-82.

[6] Wang L, Varghese S, Bassir F, Lo YC, Ortega CA, Shah S, Blumenthal KG, Phillips EJ, Zhou L. Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review of PubMed/MEDLINE case reports from 1980 to 2020. Frontiers in Medicine. 2022 Aug 24;9:949520.

[7] Manvi S, Mahajan VK, Mehta KS, Chauhan PS, Vashist S, Singh R, Kumar P. The clinical characteristics, putative drugs, and optimal management of 62 patients with Stevens-Johnson syndrome and/or toxic epidermal necrolysis: a retrospective observational study. Indian Dermatology Online Journal. 2022 Jan 1;13(1):23-31.

[8] Owen CE, Jones JM. Recognition and management of severe cutaneous adverse drug reactions (including drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, and toxic epidermal necrolysis). Medical Clinics. 2021 Jul 1;105(4):577-97.

[9] Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, Harr T. Current perspectives on Stevens-Johnson syndrome and toxic epidermal necrolysis. Clinical reviews in allergy & immunology. 2018 Feb;54:147-76