Case Report

Toxic Epidermal Necrolysis in Children Caused by Bulbus Fritillariae Cirrhosae: Identification of Causative Drug Based on Alden Score

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Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe, potentially fatal illnesses marked by widespread necrosis and separation of the epidermis and mucosal epithelium. A 10-year-old girl presented with blisters and whole-body rashes worsening since two days before admission, which developed after taking herbal medicine containing Bulbus Fritillariae cirrhosae (BFC) two days prior to the symptoms. The patient was diagnosed with TEN affecting 32.5% of body surface area and hospitalized for further treatment. Infection and drugs hypersensitivity are among the etiologies of SJS/TEN in children. The patient took herbal medicine containing BFC, which contains acetic acid, a substance reported to cause severe cutaneous adverse reactions. Since reports on SJS/TEN in children caused by herbal medicine remains scarce, vigilance towards the use of herbal medicine and further studies are needed.

Keywords: Bulbus Fritillariae cirrhosae, Pediatric, Stevens-Johnson syndrome, Toxic Epidermal Necrolysis.

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Introduction

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe acute mucocutaneous reactions that are typified by separation of the mucosal epithelium and exten-sive necrosis. These circumstances are due to cell-mediated type IV hypersensitivity reaction according to the Coombs and Gell classification, resulting in the spread of keratinocyte apoptosis.[1,2] The condition occurs in 1-6 per one million persons each year.[3] Although the risk of SJS/TEN rises with age, it can occur at any age. It affects women more often than men, at a ratio of 0.6.[1]

The most common etiology of SJS/TEN is medications. There are more than 100 types of drugs suspected to cause SJS/TEN, such as non-steroidal anti-inflammatory drugs (NSAIDs), sulfonamides, anti-epileptic medications, allopurinol, lamotrigine, and nevirapine. In addition, SJS/ TEN can be caused by non-drug factors, such as *Mycoplasma pneumonia* infection, viral infections, and vaccinations in children.[1] Utilizing the Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN) score is one method of determining the drug responsible for SJS/TEN**.** The ALDEN score contains six criteria classifying probable cause for SJS/TEN as 'very likely,' 'likely,' 'possible,' 'unlikely,' and 'very unlikely'. The final score is calculated based on the values assigned to each category. These criteria also help to eliminate drugs that are unlikely to cause SJS/TEN.[4]

Increasing age, significant comorbidities, and higher levels of skin detachment correlate with a poor prognosis.[1] A prognostic grading system for individuals with epidermal necrolysis, known as SCORTEN has been developed to determine the

mortality percentage. The mortality rate varies from around 10% for SJS to nearly 50% for TEN.[1] The overall mortality rate associated with epidermal necrolysis is 25-35%.[2] This case reported a rare case of TEN in a child caused by herbal medicine containing *Bulbus Fritillariae cirrhosae* (BFC), which can enhance understanding of this disease.

Case Report

A 10-year-old Indonesian girl was brought to the emergency room (ER) presented with blisters and rashes all over her body, which worsened two days before admission. Six days prior, the patient had a fever accompanied by rashes on the back, chest, and abdomen. The patient had taken paracetamol from the first day of fever. On the fifth day, the patient was given herbal medicine containing BFC twice daily for two days. The patient

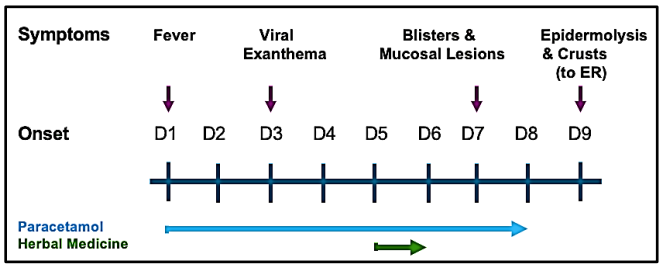

Figure 1: *Chronology of symptoms onset and patient's medication history*

had never taken the herbal medicine before. Two days after herbal medicine consumption, blisters with rashes appeared on the patient's face, mouth, trunk, back, hands, and feet. The patient also had difficulty opening her mouth and decreased appetite due to pain and blisters in the mouth. History of consuming other herbal medicine and medications was denied. History of drug allergies in the patient and family members was also denied. The patient had never experienced the same complaint before. The chronology can be seen in the figure below (Figure 1).

The patient weighed 19.5 kg, and her vital signs were within normal range. Dermatological assessment revealed that the patient had multiple erythematous maculopapular plaques in the facial, oral, anterior and posterior thoracic, abdominal, and lower extremity regions, with atypical target

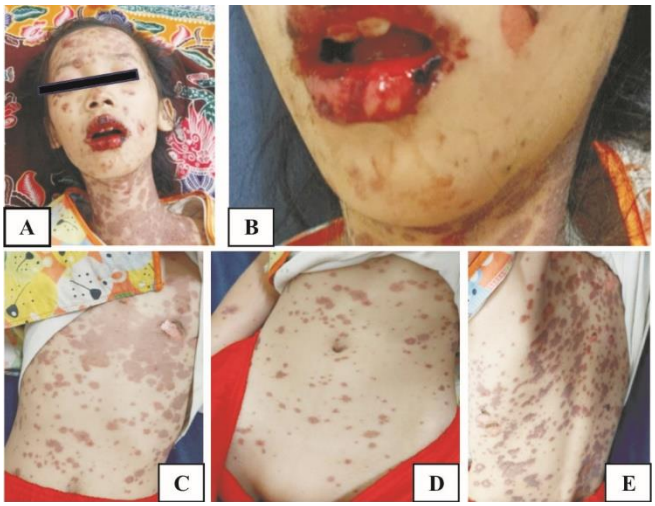

Figure 2 (A-E): *Multiple erythematous plaque with epidermolysis and atypical target lesion.* ***(B)*** *Erosion and haemorrhagic crusts.*

lesions accompanied by epidermolysis with a positive Nikolsky sign (Figure 2: A-E). In the superior and inferior oral regions, there were erosive lesions and blackish crusts accompanied by mucositis (Figure 2. B). Upon examination of the body surface area (BSA), the lesions in the facial and neck regions accounted for approximately 5.5% of the total body surface area (TBSA). The lesions in the anterior thoracic and abdominal regions accounted for 13% of TBSA. Likewise, those in the posterior thoracic region also accounted for 13% of TBSA. The lesions in the lower extremities accounted for 1% of TBSA. No lesion was observed in the genital region. Both eyelids had yellowish-white secretions. Significant laboratory tests showed increased potassium (6.1 mmol/L), urea (161 mg/dL), and CRP (3.27 mg/L) levels, as well as a decrease in sodium level (134 mmol/L). Routine blood tests, albumin, liver function, and blood sugar were within normal limits. The total SCORTEN score was 2, but the bicarbonate level was not included in the calculation due to limited laboratory facilities. The ALDEN score was 3. The patient was diagnosed with TEN with an epidermolysis area affecting 32.5% of TBSA. The patient was given Ringer's lactate (RL) infusion of 10 cc/ kg body weight, approximately 195 cc over 1 hour, and the administration of methylprednisolone injection of 15.6 mg/day for 6 days. On the lesions, Vaseline album and mupirocin ointment were

applied twice daily. Cold compress with 0.9% NaCl fluid was applied 3 times a day on the lesion, accompanied by aseptic care. The patient was then admitted to the hospital for further examination and treatment.

Discussion

SJS and TEN are classified according to the BSA involved. SJS is diagnosed when the epidermolysis area is less than 10% of BSA, while overlap SJS/TEN affects 10-30% of BSA, and TEN affects more than 30% of BSA.[1] Atypical target lesions with epidermolysis and erythematous maculopapular plaques are the hallmarks of SJS/TEN lesions.[2] In the present case, the facial, oral, anterior and posterior thoracic, abdomen, as well as lower extremity regions showed several erythematous plaques with epidermolysis and unusual target lesions spanning 32.5% of BSA, along with a positive Nikolsky sign. Erosive lesions and blackish crusts with mucositis were also present at the orifices.

In children, SJS/TEN is typically caused by *Mycoplasma pneumonia* and other viral infections, such as herpes simplex (5–31%). However, it can also be caused by drugs, like anti-epileptics (60%), NSAIDs, and antibiotics from the sulfonamide and cephalosporin groups (26.6%). *Mycoplasma pneumonia* in children causes SJS/TEN in about 5-31% of cases with characteristic symptoms of mucositis with or without minimal skin lesions, while the percentage of herbal medicines causing SJS/TEN remains scarcely reported.[5] However, in the present case, herbal medicine is highly suspected to induce TEN based on the patient's ALDEN score of 3. ALDEN score is a widely used tool to determine the medication responsible for SJS/TEN cases.[6]

Herbal medicine containing BFC, known as chuanbeimu in Chinese, has been widely used for relieving cough and eliminating phlegm for thousands of years in China. The herbal medicine contains peimine induced from acetic acid, which exhibits similar properties to NSAIDs.[1,7] A study in Korea reported that acetic acid can cause a severe cutaneous adverse reaction (SCAR), such as SJS/ TEN, with an incidence rate of approximately 22%.[8]

Identifying the causative drug is important to prevent recurrent drug allergies. There are several procedures to evaluate adverse drug reactions (ADR) and identify the causative drug, such as skin allergy tests (*in vivo*), *in vitro* tests, and oral provocation tests.[9] The "gold standard" for the majority of drug reactions is usually oral provocation test with the causative agent; however, this approach is not advised for severe and hazardous reactions such as SJS/TEN. Patch tests may be used.[8] However, due to the limitations of laboratory facilities, a drug patch test could not be conducted in this case to prove the causative drug.[9]

Based on the patient's history and supporting examinations, the patient was diagnosed with TEN caused by herbal medicine containing acetic acid with properties similar to drugs of the NSAID class, with an epidermolysis area affecting 32.5% of BSA. Fluid therapy is the mainstay management of SJS/TEN because the erosive lesions cause significant fluid loss, leading to hypovolemia, electrolyte imbalances, and renal insufficiency.[10] Accordingly, laboratory results showed hyperkalemia, hyponatremia, and increased urea levels.

The administration of antibiotics is recommended if secondary infection signs are present.[1] Antibiotic therapy is also one of the causes of SJS/TEN and has the potential to increase allergic reactions; thus, allergy tests need to be conducted before the medication is administered. In the present case, antibiotics were not administered because they could trigger further epidermolysis since a patch test for the drug had not been conducted.

In the present case, the patient's SCORTEN score was 2, indicating a low mortality rate. Therefore, quick and accurate administration of fluid therapy, nutrition, and aseptic skin care without debridement can prevent the occurrence of sepsis, thus lowering the mortality rate in the management of SJS/TEN in children.[1,2]

Conclusion

SJS/TEN in children is commonly caused by infections such as *Mycoplasma pneumonia* and other

viral infections. Reports of SJS/TEN caused by herbal medicine are limited; thus, herbal medicine should be used with caution and further research is needed.

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Author's Contribution

RRN: Conceived, designed, collected data, patient assessment & edited manuscript, is responsible for integrity of research, critical review and final approval of manuscript.

GH: Literature search and manuscript writing.

FQS: Literature search and manuscript writing.

WKB: Did critical review and final approval of manuscrip.

TA: Manuscript writing, final approval of the version to be published.

References

1. Fitzpatrick's Dermatology," 9th edition, volume 1, published in the United States by McGraw-Hill Education in 2019:734-44.
2. Effendi EV. Sindrom Stevens-Johnson dan Nekrolisis Epidermal Toksik. In: Menaldi SLSW, Bramono K, Indriatmi W, editors. Ilmu Penyakit Kulit dan Kelamin. 7th Edn. Jakarta: Badan Penerbit FKUI; 2016. p.199. Indonesian.
3. Hsieh PP, Nurwatin, Khalisah N, Nurjannah, Tantu OI, Pikatan O, et al. Sindroma Steven Johnson Terinduksi carbamazepine: laporan kasus. Intisari Sains Medis. 2021;12(3):948-51.
   Doi: https://doi.org/10.15562/ism.v12i3.1198.
4. Chen T, Zhong F, Yao C, Chen J, Xiang Y, Dong J, et al. A Systematic Review on Traditional Uses, Sources, Phytochemistry, Pharmacology, Pharmacokinetics, and Toxicity of Fritillariae Cirrhosae Bulbus. Evid Based Complement Alternat Med. 2020;2020:1-26. Doi: 10.1155/2020/1536534.
5. Lin A, Prabhu N. Conservative management of Mycoplasma pneumoniae-induced Stevens Johnson syndrome in a paediatric patient: A case report. Pediatric Dental Journal. 2023;34(1).
6. Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, Bork K, et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis: comparison with case-control analysis. Clin Pharmacol Ther. 2010;88(1):60-8. Doi: 10.1038/clpt.2009.252.
7. Xu J, Zhao W, Pan L, Zhang A, Chen Q, Xu K, Lu H, Chen Y. Peimine, a main active ingredient of Fritillaria, exhibits anti-inflammatory and pain suppression properties at the cellular level. Fitoterapia. 2016;114:75-83.
   Doi: 10.1016/j.fitote.2016.03.018
8. Lee SY, Nam YH, Koh YI, Kim SH, Kim S, Kang HR, et.al. Phenotypes of Severe Cutaneous Adverse Re-actions Caused by Nonsteroidal Anti-inflammatory Drugs. Allergy Asthma Immunol Res. 2019; 11(2):212-21. Doi: 10.4168/aair.2019.11.2.212.
9. Oakley AM, Krishnamurthy K. Stevens-Johnson Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. [Updated 2023 Apr 10]. Available from:
   https://www.ncbi.nlm.nih.gov/books/NBK459323
10. Patel RV, Goldenberg G. Drug Eruptions. In: Buka B, Uliasz A, Krishnamurthy K, editors. Buka's Emergencies in Dermatology. New York: Springer; 2013. p. 43-9.