ABSTRACT

Background: In Toxic Epidermal Necrolysis (TEN), age has been reported to be not only a risk factor but also associated with increased mortality. The presence of underlying illness and comorbidities also increased the burden of TEN in elderly patients.

Case: A 70-years old male patient was consulted with a history of pulmonary tuberculosis and skin detachment. Symptoms started since four weeks before admitted to the hospital with redness in the face and extremities that spread to the chest and back accompanied by fever and malaise. The patient was admitted with a wound in the lips and genitalia. Physical examination found multiple erosion, geographical shape, varicose veins, and positive nail signs. On the laboratory, a result showed a decrease in hemoglobin, blood glucose, albumin, and potassium. The patient was diagnosed with TEN, treated in the burn care unit, given supportive care and intravenous dexamethasone 10 mg every 8 hours, and then tapered off. The mortality rate from SCORTEN count was 12.1%.

Discussion: The incidence and mortality of TEN were higher in the elderly than among younger adults. Supportive care was the key feature of management with various adjunctive therapy, including systemic corticosteroids, intravenous immunoglobulin, and other immunosuppressant agents. Giving more comorbidities, more observation, and a multidisciplinary approach for TEN in elderly patients might be needed.

Conclusion: In the elderly, the risk and mortality of TEN were even higher, and the presence of comorbidities require more observation and supportive care.

Keywords: toxic epidermal necrolysis, elderly, comorbidities

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INTRODUCTION

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are acute life-threatening mucocutaneous reactions characterized by extensive necrosis and detachment of the epidermis and mucosal epithelium. Both of these entities share the same clinical pattern, histopathologic findings, etiology, risk factors, and the mechanism they are considered as severity variants of one disease entity. The term TEN first was introduced by Lyell in 1956 to describe a syndrome of extensive epidermal loss with mucous membrane involvement. It is considered as a rare severe drug reaction, with an estimated annual incidence of SJS/TEN ranges from 2-7 cases per million. In Sanglah General Hospital Denpasar Bali, from January 2014 until April 2018 was found 40 patients with SJS and 14 patients with TEN. TEN has been described in all age group, but the increased incidence in the elderly population has been described, and thought was 2.7 times more common than in younger adult population. Old age not only increases the incidence but also associated with increased mortality in the TEN condition. The overall mortality rate associated with SJS/TEN is 22% - 27%, varying from approximately 10% for SJS to almost 50% in TEN. Here, we present a case of TEN in an elderly patient with underlying comorbidities that are challenging in treatment and management, even with a multidisciplinary approach.

CASE

A 70-years old male patient was consulted with a history of pulmonary tuberculosis and skin detachment. Symptoms started since four weeks before admitted to the hospital with redness in the face and extremities that spread to the chest and back accompanied by fever and malaise. The patient was admitted with a wound in the lips and genitalia (Figure 1). The patient had a history of prolonged coughing and was diagnosed with pulmonary tuberculosis since one year ago, had taken a category I anti-tuberculosis drugs, which consist of Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol for four months and then ceased the therapy by himself. Any reaction during this period of medication was denied. Because coughing persists, the patient was advised to take category II...
anti-tuberculosis consist of Rifampicin, Isoniazid, Pyrazinamide, Ethambutol, and Streptomycin injection. The patient started to take this treatment regime since five weeks before symptoms appeared. History of the previous allergy to any medication was denied. History of other chronic illnesses such as asthma, diabetes mellitus, or hypertension was denied.

On physical examination, the patient looked severely ill but still conscious. Blood pressure 100/70 mmHg, pulse rate 102 times/minute, temperature 38.0°C, and VAS score 2/10. The patient was in severe malnutrition conditions. From dermatologic examination on the back, chest, abdomen, and extremities were found multiple erosion, geographical shape varied in sized with positive nickolsky sign. On the lips and genitalia were found multiple erosion geographical shapes covered with black crusts. The detachment covered 40% of the body surface area. On the thorax, X-Ray found an old active specific lesion and minimal pleural effusion on the left lung. From the laboratory, a result found a slight increase in basophil and monocyte with a decrease in hemoglobin, blood glucose, albumin, and potassium. From histopathology examination were found a lichenoid drug reaction with extensive inflammation. The patient was diagnosed with TEN et causa suspect Streptomycin, Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol, with lung TB, severe malnutrition, hypoglycemia, hypoalbuminemia, and hypokalemic. The patient was treated in the burn unit, elimination of suspected drugs, IVFD with NaCl 0.9%, and Dextrose 5%, given intravenous dexamethasone 10 mg every 8 hours and then tapered off, drip KCL, and albumin transfusion. Wound care was done with NaCl 0.9% dressing with tulle and sterile gauze every two days. The mortality rate from SCORTEN count was 12.1%.

On follow up treatment, the lesion on the lips and genitalia was improved, and there was no progression on the skin lesion. However, the healing process was very slow due to the underlying condition and immobility (Figure 1-3).

The result of sputum examination for TB acid-fast bacilli was negative TB gene expert showed *Mycobacterium tuberculosis* was detected low and resistance to rifampicin was not detected. Until the evaluation of the third weeks of treatment and steroid therapy was already stopped, the skin lesion has not been improved. The patient was still under observation for wound care and was complicated with decubitus ulcers. Therapy for lung TB was still postponed.

**DISCUSSION**

Stevens-Johnsson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) form a spectrum of immune-mediated disease, typically triggered by medications and characterized by cutaneous and mucous membrane sloughing during the acute phase.\(^3\) SJS affects <10% of total body surface area (BSA) while TEN involves > 30% BSA.
SJS/TEN overlap is defined by involvement 10-30% BSA. Affected individuals may develop severe inflammation of mucosal surface, including the respiratory, gastrointestinal, and genitourinary tracts. Metabolic imbalance, sepsis, pulmonary embolism, renal failure, hematologic abnormalities, and gastrointestinal hemorrhage can also occur. The exact pathophysiology of EN is still unclear; however, drugs are the most important etiologic factors. More than 100 different drugs have been implicated; high-risk drugs include antibacterial sulfonamides, aromatic antiepileptic drugs, allopurinol, oxicam nonsteroidal anti-inflammatory drugs, lamotrigine, and nevirapine. TEN is likely to be more common in elderly patients. As the elderly population increases, the number of elderly patients with TEN can also be expected to increase. It is not surprising since the elderly typically prescribed more medication than other population groups, and TEN is often drug-induced. The highest incidence was found in older adults after 65 years old. TEN is also more often associated with high mortality, especially in the elderly population. Reports for people age over 65 years old suggest that adverse drug reactions are more likely to have a serious or even fatal outcome. The presence of underlying illness and comorbidities with multiple drugs consumption in elderly people also increased the risk of developing TEN. Study by Honari et al., in 52 elderly patients with TEN, showed that every patient had multiple premorbid conditions such as diabetes, alcoholism, cirrhosis hepatitis, coronary disease, heart failure and renal failure. In our patient the age was 70 years old, with history of pulmonary tuberculosis, no history of medication allergy before and suspected drugs were anti-tuberculosis drugs.

The diagnosis of TEN mostly done by doing a clinical assessment. Skin biopsy for routine histologic and possibly immunofluorescence studies are recommended, especially if there are alternative diagnoses to consider. From history, TEN usually begins with unspecific prodromal symptoms such as sore throat, runny nose, malaise, cough, headache, and fever 1 to 3 days before the lesions appeared. The history of risky medication seems confined to the first eight weeks of treatment, and most inducing drugs revealed the first continuous exposure between 4 and 28 days before reaction onset. Skin lesion usually started as erythematous macules and atypical target lesions that may be confluent and on which blisters occur. Burning or stinging of the eyes and pain when swallowing or urinating showed mucous membrane involvement. Nikolsky sign or dislodgement of the epidermis by lateral pressure is positive on the erythematous zone, showing necrotic epidermis that is easily detached, revealing vast areas of exposed, red, sometimes oozing dermis. In our patient, the history of medication was anti-tuberculosis drugs consist of rifampicin, isoniazid, pyrazinamide, and ethambutol. Also, streptomycin injection started five weeks before symptoms appeared. The patient complained of redness that spread all over the body accompanied by fever and malaise, followed by a detachment of the skin and erosion on lips, and genitalia. On physical examination, found positive Nikolsky sign and detachment covering 40% of BSA. Assessment of prognostic scoring system using SCORTEN evaluate age, heart rate, BSA, comorbidities including cancer or hematologic malignancy, and also laboratory results of serum urea, bicarbonate, and glucose. In this patient SCORTEN assessment yielding a score 2 with mortality rate approximately 12.1%. The improvement was hampered by age, comorbidities including lung TB, severe malnutrition, hypoglycemia, hypoalbuminemia, hypokalemia, and also immobilization.

Despite the significant acute and chronic morbidity associated with this disease, recent advances in treatment still limited and optimal therapy remain unclear. Most recommendation emphasize in early recognition and withdrawal of the offending drugs with supportive care in the appropriate setting. The study showed early referral to the special intensive unit such as burn care unit decrease mortality of patient with TEN. A multidisciplinary collaboration between a specialist from disparate fields of medicine were indicated in acute TEN treatment. Generally, patients benefit from careful management of fluid balance, electrolyte disturbance, respiratory function, nutrition, infection control, and pain. Nevertheless, beyond supportive measures, management varies between centers and physicians. Various systemic interventions, particularly systemic corticosteroids, human intravenous immune globulin (IVIG), and plasmapheresis, have been suggested. Systemic corticosteroid that was the first-line therapy is considered a controversy because of the heightened risk of infection but yet still more commonly used. The use of systemic corticosteroids was thought could prevent the extension of disease when administered in the early phase, especially as an intravenous pulse during a few days. Our local guidelines suggest the use of Dexamethasone 10 mg every 8 hours for three days and then tapered off as the skin lesion improved. For wound care, there is currently no gold standard, and treatment often follows local trends in the local burn unit. The most common dressing used was saline-soaked gauzed. Our patient was treated in burn unit care with the collaboration of dermatologist, plastic surgeon,
internalist, pulmonologist, clinical nutritionist, and medical rehabilitation specialist. We eliminated anti-tuberculosis drugs as the suspected drugs, given IVFD with NaCl 0.9% and Dextrose 5%, intravenous dexamethasone 10 mg every 8 hours, and then tapered off, drip KCL, and albumin transfusion. Wound care was done with NaCl 0.9% dressing with tulle and sterile gauze every two days.

Anti-tuberculosis drugs, mainly ethambutol, rifampicin, and isoniazid have been associated as the causal agent of TEN. This complication is problematic in case of active pulmonary TB, bringing the dilemma of management whether to continue the treatment or not. Streptomycin, on the other hand, was an infrequent cause of TEN. However, Hmouda et al. report a case of TEN in an active TB patient proven caused by streptomycin.12 Our patient was diagnosed with pulmonary TB and already taken category I anti-tuberculosis drugs for an intensive phase but have not completed TB treatment. When resuming TB therapy with category II he suffered TEN and suspected TB treatment as the causal agent. Upon treatment of TEN patients also evaluated for TB and gene expert showed a low level of M.tuberculosis with negative acid-fast bacilli in twice sputum examination. Until now, anti-tuberculosis drugs for this patient was still postponed.

CONCLUSION
Toxic epidermal necrolysis (TEN) is a severe mucocutaneous reaction most commonly induced by drugs. As in the elderly population, the incidence and mortality of TEN were increased. The presence of comorbidities brings several considerations when treating TEN, especially in older patients. There are still no universal guidelines for the management of TEN. Supportive care was the key feature of management, and some author suggests a more observation and multidisciplinary approach for TEN in elderly patients.

CONFLICT OF INTEREST
There is no competing interest regarding the manuscript.

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AUTHOR CONTRIBUTION
All the authors are responsible for the study from the conceptual framework.

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