A CHALLENGE IN ESTABLISHING THE ETIOLOGIC OF TOXIC EPIDERMAL NECROLYSIS IN CHILDREN

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Abstract

Background: Toxic epidermal necrolysis (TEN) is a rare especially in children, acute and potentially life-threatening. The etiology of the higher incidence of TEN in various pediatric age groups than in adults is unclear, the cause is multifactorial. TEN have known triggering events, including infections (commonly viral or mycoplasma) drugs/herbs, malignancy, vaccines, and idiopathic.

Case report: We reported a case TEN of a 5 years old boy. There was a history of fever and red rash on the patient's hands 5 days ago and taken paracetamol, amoxicilin, chlorpeniramin maleat(CTM), and vitamin C, then a red patch and blisters appears 12 hours later. Physical examination: composmentis, temperature 38,80C. Dermatological state: erythemathous macules, vesicles, bulla, erosions, excoriations, crusts on the most of body. Hyperemic conjunctiva, on oral mucosa there were erythematous oedem, erosion, excoriation and reddish-blackish crust, and erosion of the genitalia. Epidermolysis was about ± 40%. Laboratory examination :leucocyte 5300/mm3 with lymphocytosis. Serum urea increases, serum bicarbonate decreases. The patient was treated dexamethasone intra venous and decreased dose with prednisone oral, patient improved and healed on day 13.

Discussion: The diagnosis of TEN in patients is made based on history and physical examination. We can establish a typical diagnosis of TEN from clinical symptoms and physical examination, but to find the etiology is sometimes difficult and requires a deep history and other investigations. The etiology in this case cannot be established because of drugs or infection. To find out, it is necessary to do further tests such as serology or PCR

Keywords: *toxic epidermal necrolysis, viral infection, drug eruption.*

1. Introduction

Toxic epidermal necrolysis (TEN) are acute and life-threatening mucocutaneous reaction characterized by extensive necrolysis and detachment of the epidermis. Classification was based on the degree of epidermal detachment. Epidermal more than 30% detachment as TEN. Lyell first introduced the term toxic epidermal necrolysis. The reaction is characterized by involvement of the skin, mucous membranes and eyes.[1]

Toxic epidermal necrolysis is a rare case. The overall incidence is estimated at 1 to 6 cases per million people per year and 0.4 to 1.2 cases per million people per year. Toxic epidermal necrolysis can occur at any age, the risk increases with age after the fourth decade, and more often in women. The incidence of TEN in children ranged from 2 to 2.25 cases per million per year.[2]

Toxic epidermal necrolysis is usually preceded by prodrome including fever, malaise, headache, sore throat, rhinorrhea and cough, followed in 1-14 days by involvement of at least two mucosal surfaces, with extensive erosions followed by mucosal necrosis of the lips and mouth, and a purulent conjunctivitis.[3] The extent of skin involvement is variable. The initial skin lesions are characterized by erythematous, dusky red, purpuric

macules, irregularly shaped, which progressively coalesce evolving into extensive blistering that resembles a second degree burn. A macular, often morbiliform rash appears first on the face, neck, chin, and central trunk area, it may then spread to the extremities and the rest of the body. Blister some flaccid and occasionally haemorrhagic. The lips develop hemorrhagic crusts with denudation of the mucosa and severe stomatitis ensues.[3,4]

Etiology of TEN cannot be explained certainly because TEN can be caused by various factors, but in general TEN arise due to the body's allergic reaction to the drugs consumed. The most common triggers for TEN are anticonvulsant drugs (35.08%), antibiotics (33.33%) and non-steroidal anti-inflammatory drug (NSAID) (24.56%). Beside being cause by allergic reactions, TEN can also be caused by infections such as herpes simplex virus (HSV) infection, and Mycoplasma pneumoniae, food, and vaccination.[5]

Childhood TEN presents several unique aetiological, prognostic and therapeutic challenges, and despite there being an extensive work of literature regarding this topic in paediatric patients, most publications refer to single case reports or a small lnumber of patients, which complicates the possibility of drawing real conclusions.[6][7]

2. Case Report

A five-years-old boy was consulted from Pediatric Department on Emergency Room of dr. M. Djamil Hospital with working diagnosis Toxic Epidermal Necrolysis on November 7th, 2020 with Chief complain of red patches and blistering skin on the most of body accompanied with red and watery eyes, swollen and erosion on lips, and erosion on genitalia since 1 day before hospital admission.

Initially, 5 days before admission the patient had fever accompanied by red patches on both palms that felt itchy, then the patient went to the Medical Center and received powder medicine (paracetamol, chlorpheniramine maleat, Vitamin C) taken 3 times a day and Amoxicillin syrup. Patients have often taken paracetamol since birth when fever. The patient also took amoxicillin twice at the age of 2 years and 3 years, and never had any allergies

Approximately 12 hours after taking the drug, red spots appear with blisters in both arms, his mother continues to give the drug to the patient for 3 days, some blisters burst and become abrasions, laceration and pain. The lesions are spreading to the face, chest, back, stomach, arms and legs, his mother stopped the drug, but the complaints become more extensive and accompanied by abrasions on the genitals and red eyes, then his mother applied turmeric to the patient's neck and chest but the lessions still same. The patient was taken to the Emergency Room Dr. M. Djamil Hospital, Padang.

Physical examination showed the general state of the child was composmentis but irritable, moderate illness with temperature 38,7°C. Dermatological state revealed erythematous macules, flaccid bullae, erosion and excoriation on the most of body. Lip mucosal was erythematous-oedema, erosion, excoriation, accompanied by reddish-blackish crusts. Mucosal of genitalia was erosion. There were Nikolsky sign and epidermal detachment was ±40%. Laboratory examination showed abnormality of liver and renal function test. Thorax xray showed cor and pulmo within normal limit

Table 1. Pediatric SCORTEN

Prognostic Factor	Point on the patient	value in the patient
Malignancy	0	None
Total BSA affected > 10%	1	40%
Heart rate (1-6 years) > 132 bpm	0	130 bpm
Serum urea level > 10mmol/L (27 mg/ml)	1	57 mg/dl
Serum bicarbonate level < 20mmol/L (20 mEq/L)	1	14.1 mmol/L
Serum glucose level > 14mmol/L (252 mg/dl)	0	90 mg/dl
TOTAL	3	Mortality rate = 35 %

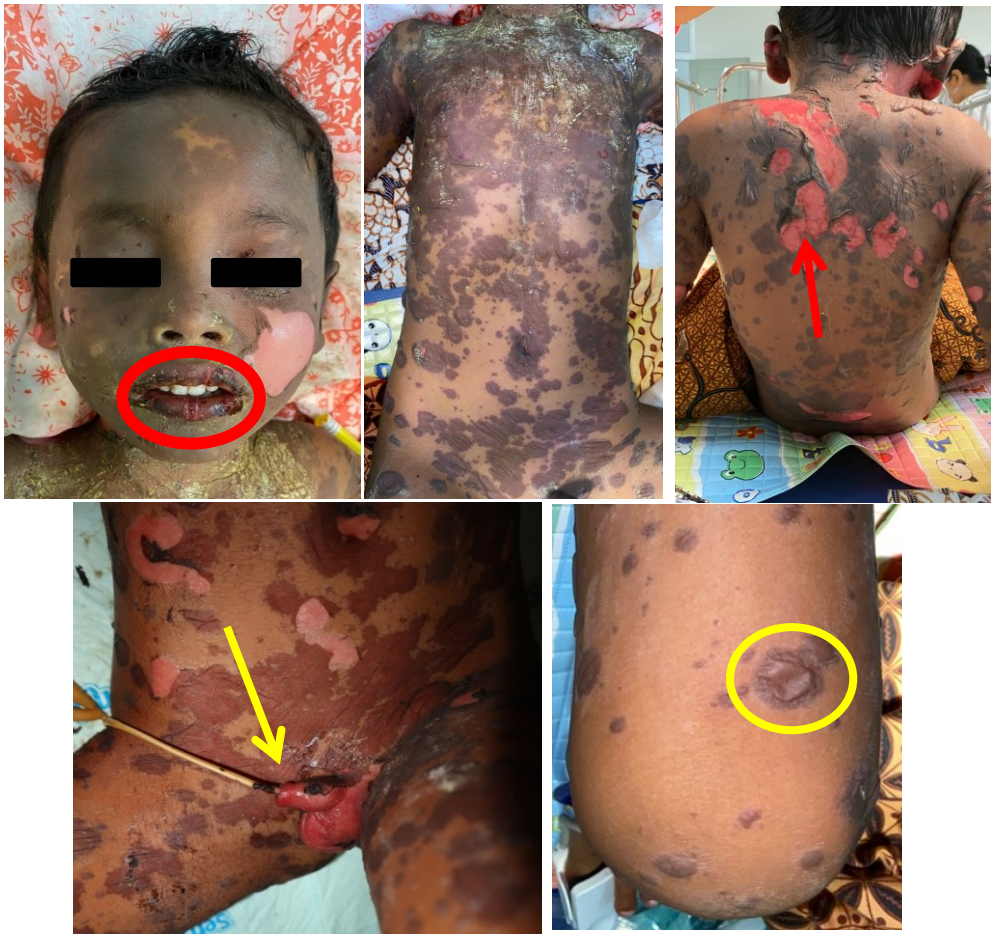

Figure 1. Clinical picture when the patient first arrives. Erosions of the oral mucosa (red circle), epidermolysis which causes ersions (red arrow), erosions on genitalia (yellow arrow), flaccid bullae (yellw circle)

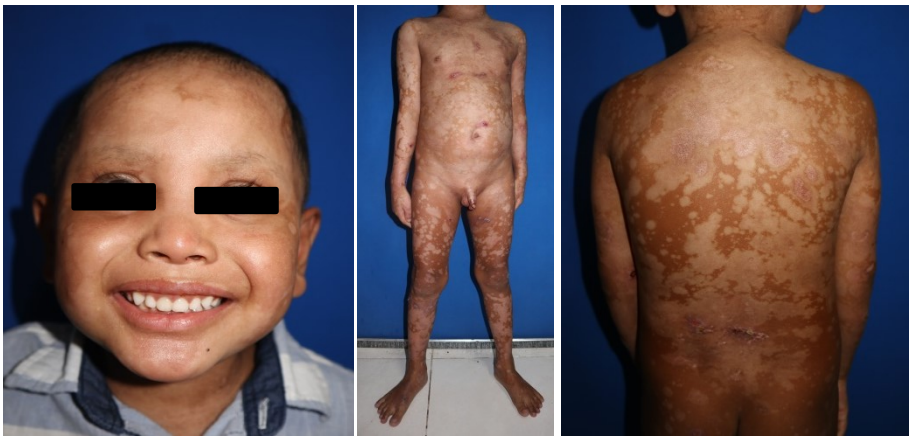

Figure 2. The patient's condition after recovery after 13 days of hospitalization. resulting in residual hypopigmented lesions

3. Discussion

Toxic epidermal necrolysis (TEN) is a rare mucocutaneous reactions, acute and life- threatening characterized with necrolysis and detachment of more than 30% of the body surface area (BSA). In the general population the incidence is 1-6 cases per million people per year, however, incidence in children is 2-2.5 cases per million people per year.[1,2] Data from Cipto Mangunkusumo Hospital found TEN incidence was 29 patients in the year 2009-2011. While Abdul Moeluk hospital in Lampung reported there were 3 cases of TEN in 2010-2015.[2] This case was the seventh case of TEN on a child since 2012 in Dr. M. Djamil Hospital, Padang.

The overall incidence of TEN has been calculated as 1.5–1.8 cases per 1 million inhabitants. However, the exact incidence in children is still unknown. Preliminary data of the German Registry of severe skin reactions show that only 7% of the validated TEN cases collected over 10 years are younger than 18 years of age with an almost equal distribution of gender. The mortality is about 6% and much lower in the pediatric population than in adults, as has been reported in small case series. The most common cause of death is due to complications, especially sepsis. [8]

There has been a dearth of data on TEN in children, because of the rarity of disease and difficulty in performing prospective research in children. The etiology of the higher incidence of TEN in various pediatric age groups than in adults is unclear, but it is likely that it is multifactorial.[9] There are differences between children and adults with respect to possible disease triggers. In adults, a number of drugs have been shown to have the potential to cause TEN. According to a 2008 multinational European study, drugs associated with a high risk include allopurinol, carbamazepine, lamotrigine, antibacterial sulfonamides, sulfasalazine, phenobarbital, phenytoin and nevirapine, as well as oxicam NSAIDs (meloxicam and piroxicam). In under-18-year-olds, TEN is much more commonly triggered by viral infections than by drugs.[10] Many cases seem to be induced by infection. Other causes of TEN that have been reported are due to malignancies, vaccines, herbal medicines and causes that cannot be identified (idiopathic). [6,9]

In TEN induced by an infection, the increase of inflammation parameters may be due to the infection and the reaction itself. In such cases, it has to be clarified whether the infection is viral or bacterial. Although a specific pathogen may often not be detected, examinations for the following pathogens should be done by polymerase chain reaction and/or serology (IgG and IgM): *M. pneumoniae, Chlamydia pneumoniae, Streptococcus pneumoniae, Epstein–Barr virus, Cytomegalovirus, Herpes simplex virus 1 and 2, Human herpes virus 6 and 7,Iinfluenza A and B, Adenovirus, parvovirus and Coxsackie virus*.[11]

Sauteur PM *et al*. reported that *Mycoplasma pneumonia* is the most frequently identified infection cause of TEN (50% of infection). This *Mycoplasma pneumonia* prodromal symptoms, including fever and respiratory symptoms, occurred in all cases with a median duration of 7 days (range 2–21), and documented pneumonia on chest X-ray in 79 %. The diagnosis of *M. pneumoniae* infection was mostly based on serology (94 %), Additionally, throat-swab specimens were obtained from 11 of serology-positive patients identifying *M. pneumonia* with PCR in 64 %. Children are much more likely to have *Mycoplasma pneumoni*-associated mucositis (MPAM) (72 %) than adults, and possible recurrences of TEN due to *M. pneumoniae* infection.[12]

Although the history did not reveal any symptoms suggesting an infection in this patient, this has not been excluded. Demuri G, *et al*. reported that virus is detected in about 80% of upper respiratory tract infections (URTIs) in children and is also detectable in the nasopharynx of 30% of asymptomatic children. The results of this study can be seen from the results of the PCR examination.[13] It is necessary to carry out supporting examinations such as serology or PCR to be able to determine whether an infection is present in this patient or not, but of course it will be very costly.

In patients with no relevant drug history, but an infection directly before reaction onset, it is not easy to distinguish whether the fever is due to the infection or part of the reaction itself. Prodromal symptoms such as fever, sore throat and flu-like symptoms, for which antipyretics, analgesics and secretolytics are taken, appear 1–3 days before the cutaneous and/or mucosal lesions. Frequently, the drugs to treat these prodromal symptoms are accused to have caused the reaction, because they were taken shortly before the mucocutaneous signs appear, which is actually after onset of the disease. This kind of misinterpretation of drug causality is called “protopathic bias”.[11] An infectious origin is considered if the infectious process is noted to take place 1 week prior to the onset of the rash, and titre and/or cold agglutinins (IgM) of the infectious agent are available.[6]

For drugs with a confirmed risk for TEN, the time latency between beginning of drug use and onset of the reaction varies between 4 days and 4 weeks. Furthermore, TEN occurs during the first continuous use of the drug (without prior sensitization), whereas earlier well-tolerated use of the medication does not suggest a causal relationship. In cases where drugs were taken to treat an infection in the corresponding period, the infection, but also the newly introduced drug, may be an etiologic factor.[11]

In this case the patient had a history of fever and rash on the skin, then went to the clinic. Twelve hours after taking the drug, blisters appeared on both hands. In this case the cause of the drug could be ruled out because the patient had taken the same drug before and had no history of allergies. Drug reactions usually occur within 4 days - 4 weeks after the drug is consumed.

Chahal *et al*. in 2018 reported case reports and systematic reviews of vaccine-induced TEN. To summarize, 29 articles reporting erythema multiforme (EM), Steven-Johnsons syndrome (SJS), or TEN following vaccination were included from >5 countries; 23 of these were case reports. 3 postmarketing surveillance studies, along with 3 United States national reporting agency reviews: the US Food and Drug Administration (FDA), the Vaccine Adverse Events Reporting System (VAERS), and the National Communicable Disease Center.[14] Chowdhury AD *et al*. reported a case report a 10 year old male had diagnosed with SJS/TEN who took herbal medicine of plant origin prescribe by traditional healer for remission of his fever.[15] In this case the cause of the vaccine and take herbal medicine can also be ruled out.

A case report has also been reported regarding idiopathic TEN in an adolescents. O'Brien KF *et al*. reported a 10- year- old girl presented with diffuse erythema, tense bullae, Nikolsky- positive desquamation, as well as ulcerations of her oral and genital mucosa. She denied recent travel, sick contacts, or preceding and concurrent use of medications, including over-the-counter and herbal supplements. A comprehensive viral polymerase chain reaction (PCR) panel (*Influenza A, Influenza B, Adenovirus, Coronavirus, Parainfluenza virus, Respiratory syncytial virus A and B, Chlamydia pneumonia, Mycoplasma pneumonia, Human metapeumo virus, Human rhinovirus, Enterovirus*), PCR and IgM, streptococcal molecular antigen test, urine culture, blood culture, and rheumatologic serologies were negative. Based on the patient's clinical presentation and biopsy results, she was diagnosed with idiopathic toxic epidermal necrolysis. The incidence of idiopathic TEN in the pediatric population is estimated to be 5%- 16.6%.[16] In this case it cannot be established as an idiopathic TEN because a complete examination has not been carried out to find the etiology.

Therapy of TEN remains unspecific, and supportive treatment is crucial. In drug-related cases of TEN, the causative drug should be discontinued immediately. In infection-induced cases, the infection requires adequate treatment. For topical treatment, antiseptic solutions or gels should be used, and drug-free, nonadherent wet gauze can be applied to areas affected by blisters and erosions. Adequate analgesia should be started, and if necessary, intravenous fluids should be given, and the room temperature should be raised. Furthermore, for mucosal erosions, local antiseptic treatment is recommended. In case of ocular involvement, a daily ophthalmologic consultation is important, because the eye inflammation may result in long-lasting sequelae.[11] Systemic immunomodulatory therapy with glucocorticosteroids and intravenous immunoglobulins remains controversial, and data for both treatments are ambiguous. Cyclosporine has been used successfully in the treatment of TEN, but further studies are needed, especially in children and elderly patients. [10]

Overall, the principle treatment algorithm of Dermatology and Pediatric Department were similar. In Pediatric Department, intravenous dexamethasone was given 0.2-0.5 mg/BW/6h in 3 consecutive days. After that, dexamethasone therapy can be lowered gradually (tapering off) and replaced with oral prednisone. To overcome the infection, the broad-spectrum antibiotic was given, gentamicin 5 mg/kg/day divided into two doses For the diagnosis of bronchopneumonia, treatment choice in Pediatric Departement is ampicilin and gentamicin,and ceftriaxone.[17] The reported mortality rates are 1-5% in SJS and 25-35% in TEN, and may be higher in older patients and patients with larger areas of the epidermis affected.[11]

Magana BR *et al*. was reported from 20 patients who received corticosteroids during 5 to 7 days, time to objective response was reported in 14 patients ranging from 1 to 4 days, while time to achieve remission since diagnosis was available in only 16 patients and it was 7 to 16 days. Only twopatients reported hospital stays of 12 and 30 days.[17] In this case, pasien got steroids and already had a corrective response from the first day, no new lesions appeared, finished hospitalization on day 12 and he fully recovered.

4. Conclusions

Toxic epidermal necrolysis (TEN) is a rare case reported in pediatric. The disease manifests itself by extensive blistering of the skin with full-thickness necrosis of the epidermis and involvement of mucosal surfaces. TEN in children and adolescents is often not drug induced and probably caused by infections or unknown factors (idiopathic). Fever is present and inflammation parameters are increased in TEN, independent of the etiology (medication, infection and idiopathic). The predictive power of the new pediatric SCORTENs for TEN in children was similar to that of the original SCORTEN developed for adults. Early and prompt recognition, early withdrawal of suspicious causative factors, meticulous supportive care, and an early admission to a specialized unit are the most essential parts of managing these patients.

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