SEVERE CUTANEUS ADVERSE DRUGS EFFECTS MANIFESTED AS TOXIC EPIDERMAL NECROLYSIS (TEN) DUE TO ORAL ANTITUBERCULOSIS DRUGS AND REVIEW OF THE LITERATURE

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Abstract
Introduction Antituberculous drugs has several adverse effects with varying severity manifesting as gastrointestinal symptoms, hepatotoxicity, skin rash, vestibular and auditory nerve, renal damage, peripheral neuropathy, etc. Toxic epidermal necrolysis (TEN) due to oral antituberculous (OAT) (Kombipak Anak A®) drugs was discovered as it was our first experience.

Case A 6-year-old girl was admitted to the emergency room of Dr. Hasan Sadikin Hospital presenting bullous eruption and severe exfoliation of the skin covering approximately 90% body surface area. She had been treating with standard oral antituberculous (OAT) drugs including isoniazid, rifampicin, pyrazinamide (Kombipak Anak A®) by the primary health care which was taken regularly for two weeks without any reported complaint. On the fifteenth day of therapy, she experienced acute fever, pruritus, and diffuse erythema, followed by extensive bullae formation and skin denudation. No respiratory distress nor severe infection occurred. Diagnosis of toxic epidermal necrolysis (TEN) was considered, and she was transferred to the pediatric intensive care unit. The OAT was discontinued and she was treated with intravenous fluid drip, gentamycin, and methylprednisolone. Improvement of her general condition and skin lesions developed within a-week.

Conclusions Severe adverse effect although rare may occur in children treated with OAT. It is difficult to determine which particular drugs in the OAT package that cause this condition.

Key Words: Toxic Epidermal Necrolysis- OAT drugs
INTRODUCTION
Severe adverse drug reactions due to antituberculous drugs is not well known due to lack of notification and underreporting. It seems that many patients have adverse effects which have an influence on treatment outcomes. However, it is difficult to measure the efficacy or toxicity of a particular drugs since anti-TB drugs are usually administered in combination regimens of several drugs. Minor allergic skin reactions such as itching, skin rash, urticaria have been described with these drugs and might requires a quick response. Life threatening adverse effects include anaphylaxis, severe toxic, and allergic reactions (exfoliative dermatitis, Steven-Johnson Syndrome), severe gastritis with bleeding, severe hepatotoxicity, and renal failure can also occurred. Toxic epidermal necrolysis (TEN) is a rare life threatening disorder characterized by sudden development of constitutional symptoms with vesicobullous eruptions involving the hands, feet, with extensive peeling of the skin, ulceration of buccal mucose, ocular lesion and genital involvement, generally induced by drugs. This condition was named as TEN by Lyell in 1956. Separation of the dermal-epidermal junction causes Nikolsky's sign and gives the typical “wet dressing” appearance. It is a rare with antitubercular drugs and only a few cases have been reported with rifampicin, PAS, isoniazid, and streptomycin. Because of the high mortality and morbidity associated with TEN make it necessary to familiarize all physicians with this syndrome, in particular those practising in primary health care centres and district hospitals, given the high risk arising from late diagnosis and therapy. Prompt referral to hospitals possessing a burns unit should be routine practice in suspect cases. The patients should be regarded as burn patients, with careful monitoring to ensure patients receive adequate care. We thus report our experience in a 6-year old girl with TEN whose taking oral antituberculous drugs, and she had good response with corticosteroids and supportive treatment.

CASE REPORT
A 6-year-old girl was transferred to the Hasan Sadikin Hospital because of bullous eruption and severe exfoliation of skin. The patient had been well until two months before admission, when she diagnosed as having pulmonary tuberculosis by primary health care doctor and was given standard package oral antituberculous drugs (KOMBIPAK ANAK A) which consists of 1 tablet Isoniazid @ 100 mg, 2 capsules Rifampicin @ 75 mg, and 2 tablets Pyrazinamide @ 200 mg. Drug compliance was satisfactory and no adverse effects to therapy were seen until she developed fever and skin rash two weeks after starting the treatment. A diffuse pain erythematous morbiliform rash with extensive confluence was present, most intensely visible on the trunk, back, upper arms and thighs. Over the course of the next 24 hours, increased additional vesicular skin lesions developed. There was no history of diarrhea, seizure, dyspnea, or decrease of consciousness.

The patient had no other medical problems, no known food or drugs allergies.. His father was diagnosed to have pulmonary tuberculosis 5 years ago, but after taking antituberculosis drug for one month, he discontinued the treatment.
On examination the patient was alert, the blood pressure 100/60 mmHg, the pulse 136 beats per minute, the respiratory rate 30 breaths per minute, and the axillary temperature was 37.8°C. The weight was 16 kg and height was 110 cm (89% NCHS). A diffuse, erythematous, raised lesions involved the face, trunk, back, arms, and legs. Nikolsky’ sign was positive, and few flaccid bullae were seen. There were multiple vesicles on her skin and mild ulcers on her lips. The lungs were clear, and the heart sounds were normal. The abdomen was diffusely tender, no abnormalities were found on genital examination. Laboratory findings revealed mild anemia, polymorphonuclear leucocytosis, mild increase in blood transaminase, blood glucose, electrolytes, ureum and creatinine were within normal value. No bacterial growth shown in blood culture. Chest radiography appeared no abnormalities.

A clinical diagnosis of toxic epidermal necrolysis was made, and the patient shifted to Pediatric Intensive Care Unit (PICU) with burns management setup. All the antituberculosis drugs were discontinued. She was given gentamycin, dexamethasone intravenously. Blistered wounds were compressed with saline solution and hydrocortisone cream 2.5% was applied, and then the patient was consulted to dermatology and ophtalmology department. From ophtalmology department, they found no ocular abnormality. Diagnosis from dermatology department was also toxic epidermal necrolysis. During the next day after admission, the skin was denuded, with the appearance of a second-degree burn, there was involvement of approximately 90 percent of the epidermis, sparing only the vertex of the scalp. The temperature rose to 37.9°C, respiratory rate increase to 40 breaths per minute, others were within normal limits. Significant improvement was seen after 3 days, with stabilitation of vital signs, absence of fresh bullae, reduction of erythema and exudation from the skin. Hypopigmentation on the arms and lower abdomen were noted as residual sequelae of the disease process. Steroid was switched to oral methylprednisolone. She was discharged on 5th of hospital day.

DISCUSSIONS

Adverse effects or side effects are the most common adverse reactions that is undesirable but sometimes unavoidable pharmacologic actions of the drugs at the usual prescribed dosage. Cutaneus adverse drug reactions of varying severity can be caused by many antituberculous drugs. Pruritus with or without rash may occur in many as 6% of patients taking rifampicin, and skin reactions requiring discontinuation of the drug are reported in 0.2-0.7% of patients on ethambutol. If a rash is localized or presents as itching alone, it may be managed symptomatically with anti histamine without discontinuing TB therapy. Petechial rash may indicate thrombocytopenia in patients taking rifampicine, and if confirmed on platelet counts, rifampicine should be discontinued and not restarted. A generalised erythematous rash warrants immediate discontinuation of all TB drugs, particularly if associated with fever or mucous membrane involvement, due to the risk of Stevens-Johnson syndrome.

Eventhough accurate diagnosis of drug eruptions can be challenging because we have to distinguish drug eruptions from viral exanthems or preexisting skin diseases, but in this case the diagnosis can be straight forward because rash develop after 2 weeks starting antituberculous drugs, while she did not take other medications,
and no known history of viral illness symptoms. More over, it is difficult to determine which drugs in Kombipak Anak A® package that cause this reaction. Perhaps the most sensitive and specific diagnostic for drug eruptions is the rechallenge. In fact, with some adjustments, such as elimination of drug interactions or changing the dose to accommodate impaired metabolism, many drugs can be safely readministered. Obviously, drugs suspected to have caused severe reactions should never be given again.¹⁰

Eventhough very rare, TEN is a disease of interest because of a high impact on the evaluation of the benefit/risk ratio of medicines and because of the mechanism of acute and severe destruction still poorly understood. Several lines of evidence support the cytotoxic lymphocyte (CTL) mediated pathogenesis of TEN. These include (1) link to some specific HLA haplotypes to increased susceptibility to TEN, (2) characteristic lag between the exposure and disease onset, (3) increased inflammatory CD8+ T cells in the epidermis, and (4) increased apoptosis of the keratinocytes in TEN patients. Although a specific link between the drug metabolite and the immunologic hypothesis is still lacking, drug-reactive T-cells have been shown in the skin and blood of patients with various types of cutaneous drug eruptions, demonstrating that CTL mediated immune response against drugs occur. Cytokines that also were found in the blister fluids play their damaging role by recruiting the cytotoxic T cells to the epidermis. Recently, it has been also clearly shown that the tissue damage as epidermal necrolysis is due to massive keratinocyte cell death via apoptosis. Certain important cytokines (TNF-α, IFN-γ, FasL, IL-6 and IL-18, granzyme B, perforin) by binding to their specific cell-surface receptors (death receptors), have the ability to induce apoptosis. The presence of IL-5, a cytokine whose role is to regulate the maturation, differentiation and activation of eosinophils, may explain eosinophilia in most of these patients.¹²

A few years ago, an international group of investigators began a large case-control study, the Severe Cutaneous Adverse Reactions (SCAR) study. A group of experts proposed a classification based on the pattern of erythema multiforme-like lesions (categorized as typical targets, raised or flat atypical targets, and purpuric macules) and on the extent of epidermal detachment. The body surface area plus localized "typical targets" or "raised atypical targets"; Stevens-Johnson syndrome (SJS), detachment below 10% of the body surface area (BSA) plus widespread erythematosus or purpuric macules or flat atypical targets; overlap Stevens-Johnson syndrome-toxic epidermal necrolysis, detachment between 10% and 30% of the body surface area plus widespread purpuric macules or flat atypical targets; toxic epidermal necrolysis with spots, detachment above 30% of the body surface area plus widespread purpuric macules or flat atypical targets; and toxic epidermal necrolysis without spots, detachment above 10% of the body surface area with large epidermal sheets and without any purpuric macule or target). Thus, patients with < 10% BSA of epidermal detachment are considered to have SJS, a 10% to 30% detachment is classified as SJS/TEN overlap, and detachment > 30% plus purpuric macules, or > 10% with large epidermal sheets, is considered TEN.¹³ We diagnosed TEN because there is involvement 90% of BSA. The diagnosis of toxic epidermal necrolysis can be confirmed by skin biopsy, although one was not performed in this case. When obtained, skin-biopsy specimens show that the epidermis is necrotic and detached from the underlying
dermis. The dermis shows a mild superficial perivascular lymphocytic infiltrate, the feature that was later referred to as “dermal silence”\textsuperscript{14}.

Initial symptoms can be fever, malaise, myalgia, headache, stinging eyes, and pain upon swallowing, any of which can precede cutaneous manifestation by 1 to 3 days. Skin lesions tend to appear first on the trunk, spreading to the neck, face, and proximal upper extremities. The epithelium of the respiratory tract is involved in 25\% of cases of TEN, which was not occurred in this patient. The skin lesions are usually tender, and mucosal erosions are very painful. As the epidermal involvement progresses toward full-thickness necrosis, epidermis then detached from the underlying dermis, and fluid fills the space between the epidermis and dermis, giving rise to blisters. The blisters have special features: they break easily (flaccid) and can be extended sideways by slight pressure of the thumb as more necrotic epidermis is displaced laterally (Nikolsky sign)\textsuperscript{4}.

Blood tests are usually of limited importance in the diagnosis of TEN, but they are important in an attempt to identify a specific etiology, the presence of associated disease, and the degree and type of systemic involvement. A normocytic anemia characterized by a progressive drop in hemoglobin, accompanied by a moderate reduction in serum iron, seems to be a common finding in TEN patients. Leukocytosis is often present in TEN, and thrombocytopenia appears less frequently. Investigations in this patient revealed mild anemia, polymorphonuclear leukocytosis, and mild increase in blood transaminase. Blood culture was negative. Chest radiography appeared no abnormalities.

Optimal medical management of TEN requires early diagnosis, immediate discontinuation of the offending agent (in this case was Kombipak pediatric\textregistered{}), supportive care, and specific therapy (Lars). Numerous recent reports have clearly demonstrated highly improved prognosis when TEN patients are treated through multidisciplinary management in a Burn Center. When Burn Centers are not available, management of patients should be undertaken in the Intensive Care Unit (ICU) with reverse-isolation nursing techniques\textsuperscript{14}.

The large area of denuded skin in TEN patients allow continuous loss of massive amount of body fluids through oozing and evaporation very much like second-degree burn patients. The fluid requirements of TEN patients are about 2/3 to ¾ of these patients with comparable second-degree burns. The BSA affected using the “rule of nine” or “modified Lund-Browder Chart”: Strict urinary output maintained through a catheter. Meticulous monitoring with daily lab associated with laboratory examinations, and bacterial culture are mandatory. Massive nutritional support by nasogastric feeding initiated as soon as possible to minimize protein losses and to promote healing. Environmental temperature raised to 30\(^\circ\)C to 32\(^\circ\)C to reduce caloric loss through the exposed skin and the resultant shivering and stress\textsuperscript{15}.

Sepsis is the most common cause of death in TEN patients. Therefore, sterile handling of the patients is a must and can not be over emphasized to minimize nosocomial infection. Routinely patients are bathed and painted with topical antiseptic solutions or antibacterial agent. However, prophylactic systemic antibiotics (gentamycin) was given. Historically, corticosteroids had been used routinely for the treatment of TEN patients until the early 1980s. Many early case reports have acclaimed the benefits of steroid therapy in accordance with the hypothesis of an allergic reaction and that such interventions were meant to stop progression of TEN. But more recent studies
have described prolonged wound healing and higher morbidity and mortality due to sepsis with the use of corticosteroids. Indeed, in the widely reported SCAR study, it appears to be an important risk factor for TEN. On the basis of these reports, most authorities are no longer routinely recommend steroids for patients with TEN. In spite of several studies demonstrated no benefit for steroids, many of the experts still use corticosteroids in the early course of the disease. However, when it is used, it should be given very early (within the first 24 to 48 hours) in a relatively high dose (1-2 mg/kgBW) of oral prednisolone or intravenous methylprednisolone for only a brief period of time (not more than 3 to 5 days). But in this case we gave dexamethason intravenously, and she had rapid response to steroid.

Many other therapies have been attempted to treat TEN patients, such as some immunosuppressants (cyclophosphamide, cyclosporine) to prevent progression of the disease. Plasmapheresis had also been used successfully in some studies. The recent discovery that Fas-FasL interactions are directly responsible for apoptotic death of the keratinocytes in TEN has opened up a specific mode of treatment. The ability of FasL to induced apoptosis is blocked in vitro by intravenous immunoglobulin (IVIG). A large case series describe favorable results when using IVIG (0.2-2.9 g/kgBW for 1 to 5 days) to treat TEN. In the near future, the use of IVIG as a specific therapy in TEN should improve even further the prognosis of this previously dreadful acute skin condition.

Published mortality rate for patients with TEN vary widely between 40 and 70 percent. With the objective of being able to precisely predict patient mortality, Batuji-Garin et al proposed a scoring system for TEN named the SCORTEN severity of illness score (Table 1).

Table 1. The SCORTEN Scoring System

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Individual Score</th>
<th>SCORTEN</th>
<th>Predicted Mortality(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 40 years</td>
<td>Yes = 1, No = 0</td>
<td>0-1</td>
<td>3.2</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Yes = 1, No = 0</td>
<td>2</td>
<td>12.1</td>
</tr>
<tr>
<td>Tachycardia (&gt;120/min)</td>
<td>Yes = 1, No = 0</td>
<td>3</td>
<td>35.3</td>
</tr>
<tr>
<td>Initial surface of epidermal detachment &gt; 10%</td>
<td>Yes = 1, No = 0</td>
<td>4</td>
<td>58.3</td>
</tr>
<tr>
<td>Serum urea &gt; 10 mmol/L</td>
<td>Yes = 1, No = 0</td>
<td>≥ 5</td>
<td>90</td>
</tr>
<tr>
<td>Serum glucose &gt; 14 mmol/L</td>
<td>Yes = 1, No = 0</td>
<td></td>
<td></td>
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<tr>
<td>Bicarbonate &lt; 20 mmol/L</td>
<td>Yes = 1, No = 0</td>
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Although retrospective and limited by small simple size, case ascertainment, and uniformity of therapy, survivors of TEN often experience ophtalmologic and dermatologic complications. The psychological and functional consequences of these sequelae are not inconsequential and, although poorly detailed, will require long-term care. 17

CONCLUSIONS
Adverse reactions to drugs most often affect the skin, but only a small fraction are life-threatening or lead to disabling sequelae. Because of the low frequency of such severe reactions (usually less than 1 reaction per 5000 exposed patients), they are unlikely to be detected. For many severe cutaneous reactions to drugs including toxic epidermal necrolysis, medical intervention is limited to the early recognition of the symptoms and the withdrawal of the offending drug. Even for other reactions that may benefit from therapy, early recognition of the symptoms and prompt withdrawal of suspect drugs are usually the most important steps.

References


14. Lars
15. John Hopkins
16. Saha