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Case Report

A case of toxic epidermal necrolysis treated with intravenous immunoglobulin

50 歲男患者表皮廣泛脫落：靜注免疫球蛋白治療毒性表皮壞死鬆解症一例

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Toxic epidermal necrolysis (TEN) is a dermatological emergency. Supportive care is the mainstay of treatment in the past. However, there is more and more evidence on the efficacy of intravenous immunoglobulin (IVIG) in the treatment of TEN. We reported below a 50-year-old man developed TEN after taking antibiotics, NSAID and paracetamol. His skin condition dramatically improved after given high dose IVIG.

毒性表皮壞死鬆解症(TEN)是皮膚病學上的急症。在過去，以支持療法為主導。現今有越來越多的証據顯示靜注免疫球蛋白能有效治療此症。本文報告一例 50 歲男患者於服用抗生素，非類固醇抗炎藥及撲熱息痛後出現毒性表皮壞死鬆解症。經高劑量靜注免疫球蛋白治療後，皮膚情況明顯改善。

Keywords: Intravenous immunoglobulin, toxic epidermal necrolysis

關鍵詞：靜注免疫球蛋白治療，毒性表皮壞死鬆解症

Introduction

Toxic epidermal necrolysis (TEN) is a rare, acute, and life-threatening mucocutaneous disease. The incidence is 0.4-1.2 cases per million.[1-2] It is a consequence of extensive keratinocyte cell death that results in separation of large areas of skin at the dermoepidermal junction including the mucous membrane. It is believed to be mediated by Fas/Fas ligand pathway.[3] It is almost always related to drugs. The average mortality rate is 25 -35%.[4-6] Prognosis is affected by the degree of skin detachment, age and underlying medical problem.[7] Rapid identification and withdrawal of the suspected causative agent and intensive supportive care improve the outcome. There is no consensus regarding specific treatment of TEN. The use of intravenous immunoglobulin (IVIG) has been reported in several case series. The following

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case report described the treatment of a patient suffered from toxic epidermal necrolysis with IVIG.

Case report

A 50-year-old gentleman enjoyed good past health without the use of any long-term medication. He had symptoms of upper respiratory tract infection one week before admission and was prescribed paracetamol, amoxycillin-clavulanate, diclofenac and mefenamic acid by his general practitioner. He developed generalised erythematous tender skin lesions four days later and was admitted into the hospital for further management.

He was febrile on admission and his blood pressure and pulse rate were 130/70 and 90 per minute respectively. There were erosions over the trunk and oral mucosa and generalised erythema and maculopapular rash over the limbs (Figures 1 & 2). Twelve percent of skin was involved (including areas of detachment and necrosis). The rest of his physical examination was unremarkable. Blood tests were normal except mild liver function derangement (alkaline phosphatase 134/ alanine aminotransferase 125/bilirubin normal). Septic work-up including chest radiograph, blood culture and wound swab were negative. His skin condition continued to deteriorate and the area of skin detachment and necrosis increased to 20% on day 9 of symptom onset. His clinical course was complicated by hospital acquired pneumonia and acute respiratory distress syndrome. He was admitted into the intensive care unit for ventilatory support. He developed pantocypenia (Haemoglobulin 12.8/platelet 45/white cell count 2.6) and his serum urea was elevated to 12 mmol/L (3.4-8.9 mmol/L). Skin biopsy showed focal denuded skin with the remaining epidermis exhibiting basketweave cornified layers with presence of necrotic keratinocytes. There were superficial and mid-perivascular lymphocytic infiltrate (Figures 3 & 4). The picture was compatible with erythema multiforme.

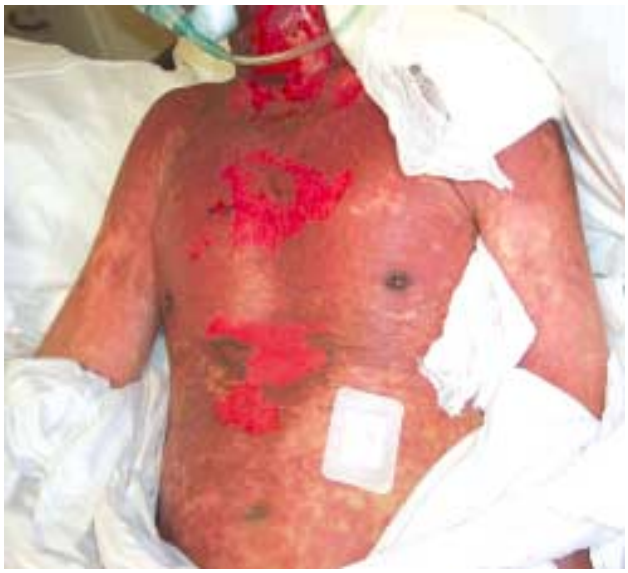

Figure 1. Extensive erosion over the neck and anterior trunk of the patient on admission.

Figure 2. Extensive erosion over the back of the patient.

Intravenous immunoglobulin (IVIG; Intragam P, CSL Ltd. Parkville, VIC, Australia) was started on day 9 after onset of symptom. A total dose of 4 grams per kilogram was given over 4 days without adverse effect. The maximal skin area involved

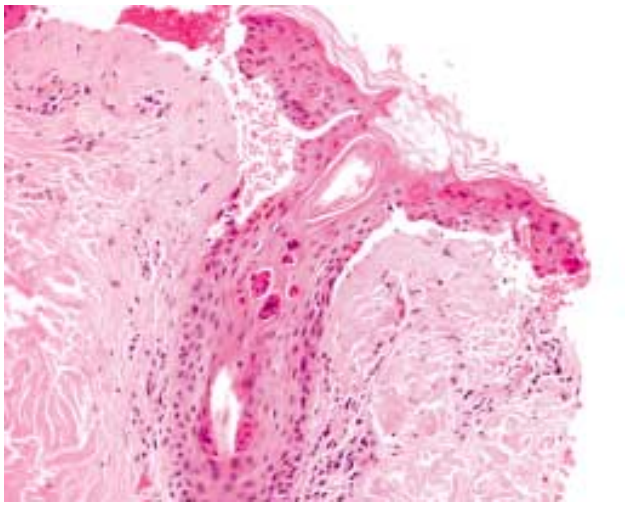

Figure 3. Medium power showed subepidermal clefts containing mainly red cells. Note the solitary units and small aggregates of necrotic keratinocytes. (H&E, original magnification x 10).

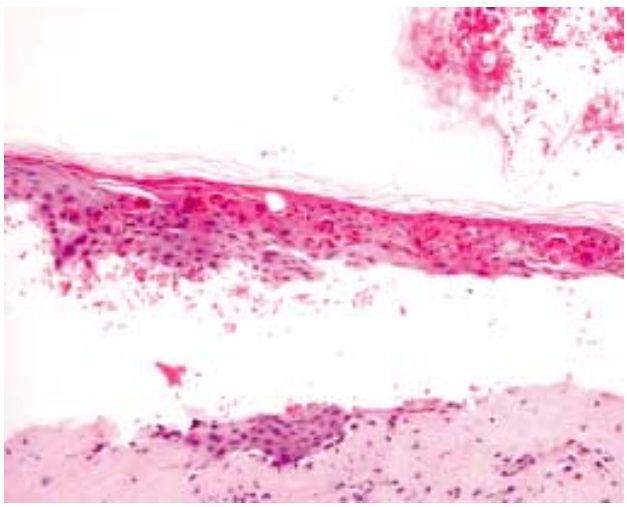

Figure 4. High power showed basketweave cornified layers with quite extensive small aggregates of necrotic keratinocytes (H&E, original magnification x 20).

was 22% on day 10. Re-epithelialisation and cessation of new lesions were evident three days after the commencement of IVIG. He was able to wean off ventilator after intubated for ten days. Complete re-epithelialisation of his integument was observed seventeen days after starting IVIG. Skin dressing with chlorhexidine gauze was performed by burns unit nurses throughout his admission.

Discussion

TEN is a rare but life threatening condition. It is almost always related to drugs. Common offending agents include sulphonamide group of antibiotics, non-steroidal anti-inflammatory drugs and anti-convulsants.[1-2] The underlying mechanism is believed to be the over-expression of the FasL (CD95) on keratinocytes which leads to massive apoptosis.[3] Histologically, there is full thickness necrosis of the epidermis, extensive necrosis of keratinocytes, subepidermal blister formation and sparse lymphohistiocytic infiltrate around the blood vessel. IVIG is believed to work by blocking the Fas receptor binding based on the above hypothesis. Some retrospective series had shown its effectiveness in the treatment of TEN[7-9] while others did not show any benefit at all.[10,11] There was no randomised controlled trial so far to make a conclusion on the effectiveness of IVIG on treatment of TEN.

SCORTEN score (Tables 1 & 2) is often used to predict the severity and hence the outcome of

Table 1. SCORTEN severity of illness score

SCORTEN parameter	Individual score
Age > 40	Yes = 1, No = 0
Malignancy	Yes = 1, No = 0
Tachycardia (> 120/min)	Yes = 1, No = 0
Initial surface of epidermal detachment > 10%	Yes = 1, No = 0
Serum urea > 10 mmol/l	Yes = 1, No = 0
Serum glucose > 14 mmol/l	Yes = 1, No = 0
Bicarbonate < 20 mmol/l	Yes = 1, No = 0

Table 2. The sum of score and predicted mortality

Sum of score	Predicted mortality (%)
0-1	3.2
2	12.1
3	35.8
4	58.3
5 or above	90.0

TEN.[12] The SCORTEN score of our patient was 3 with predicted mortality rate of 35.8%. When compared with patients suffered from TEN in previous large case series,[7] there was delay in commencement of IVIG in our patient (9 days from onset of symptom vs 7.3 days). The age of our patient was also older then the mean age of the survivors (50 vs 39.6 years). However, the initial area of skin detachment was smaller (12% vs 48%). We also used a larger dose of IVIG in our patient (4 g/kg vs 2.7 g/kg) because the therapeutic effect was not apparent on Day 3 which was supposed to be clinically obvious. Also different brand of IVIG was used in our patient. Despite the delay of treatment and relative older age of our patient, the response to IVIG was satisfactory. This may be due to the use of larger dose of IVIG used.

It was difficult to identify the culprit in our patient as he had taken multiple medications at the same time before the onset of symptom. These included both antibiotics and non-steroidal anti-inflammatory drugs which are both well known cause of toxic epidermal necrolysis.[1-2] In fact, it is often difficult to identify the offending agents in many cases of drug allergy as patients often take several kinds of medication together. Balance of 'over-labelling' and risk of exposing patient to another episode of allergy reaction when prescribing the suspected allergens should be made. However, it is better to avoid all the suspected medications which cause TEN in the future as re-challenge is life threatening.

So far there is no clear guideline when IVIG should be started, who should need IVIG, what should be the optimal dosage and how long should it be given. Also, the efficacy of IVIG was only observed in case series but not randomised controlled trial. Clinical decision should therefore be based on severity of disease and response to IVIG. Though there was no life threatening event reported in previous case series, we should be familiarised with all the possible side effects before initiating IVIG. It is contraindicated in patients with known anaphylactic reaction to human immunoglobulin and those with Immunoglobulin A deficiency. Acute renal failure is a serious adverse effect. Patients at increase risk are those with pre-existing renal insufficiency, diabetes mellitus, old age, volume depletion, sepsis and concomitant nephrotoxic drugs. The risk can be reduced by adequate hydration prior to initiation of IVIG. Aseptic meningitis syndrome has been infrequently associated with IVIG infusion. It is usually related to the use of high dose of IVIG (2 g/kg) and remission of symptom after discontinuation of treatment without long term sequalae. Other adverse effects include malaise, abdominal pain, headache, chest tightness, facial flushing, hot sensations, dyspnoea, skin rash, nausea and vomiting. Haemolytic anaemia and neutropenia are rare side effects. Elevation of liver enzymes is also observed. Last but not least, IVIG is made from human plasma, it may contain potentially transmittable disease.

In conclusion, TEN carries a high mortality rate. Management should include rapid identification and withdrawal of the offending agents. IVIG may be an effective treatment for some patients like our patient. However, the use is still controversial as there is no randomised controlled trial to prove its efficacy. Attention should be paid to possible side effects, though rare but some are life threatening. Suspected offending drugs should be avoided in future.

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