

Intravenous Immunoglobulin in the Treatment of Vancomycin-Induced Toxic Epidermal Necrolysis

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الغلوبولين المناعي الوريدي في علاج انحلال البشرة السمي الناتج عن الفانكوميسين

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الملخص: يتسبب انحلال البشرة السمي (TEN) كثيرا في تفاعل البشرة ، التي من المحتمل أن تهدد الحياة، عن طريق العقاقير. يتميز رد الفعل الجلدي المخاطي بانفصال للبشرة الفقاعية والأغشية المخاطية. نعرض حالة ذكر يباغ من العمر 9 شهور يعاني من احمضاض الدم الميثيل ارتخاء عام، وتأخر في النمو. ذات تاريخ مرضى من الحمى، والسعال، وضيق في التنفس، والتقيؤ لمدة 3 أيام. ظهر طفح جلدي بعد 5 أيام من العلاج بالفانكوميسين. شمل الطفح ما يقرب من 60% من مساحة سطح الجسم الكلية وكتلتا العينين. عولج بنجاح بواسطة الغلوبولين المناعي الوريدي (IVIG)، والمضادات الحيوية، و العلاج المناسب للجروح، وقدم تم الشفاء التام مع مضاعفات لا تذكر على الرغم من شدة مرضه. العناصر الهامة في نجاح العلاج تشمل التعرف المبكر والرعاية المركزة، الانسحاب الفوري للعامل المسبب للمرض، العلاج المبكر بواسطة الغلوبولين المناعي الوريدي (IVIG)، الإنعاش عن طريق السوائل، والسيطرة على العدوى. قد يكون من المفيد استخدام الغلوبولين المناعي الوريدي (IVIG) في علاج انحلال البشرة السمي (TEN)، ولكن هناك حاجة لتقييم الدراسات التي تقارن الغلوبولين المناعي الوريدي (IVIG) بوسائل أخرى.

مفتاح الكلمات: الغلوبولين المناعي الوريدي، انحلال البشرة السمي، العنصر المحفز لخلايا الدم البيضاء، متلازمة ستيفن-جونسن، تقرير حالة، عمان.

ABSTRACT: Toxic epidermal necrolysis (TEN), an uncommon but potentially life-threatening skin reaction, is frequently induced by drugs. The mucocutaneous reaction is characterised by bullous detachment of the epidermis and mucous membranes. We present a 9-month-old male with methylmalonic acidaemia, generalised hypotonia, and global developmental delay. He presented with a 3-day history of fever, cough, shortness of breath, and vomiting. Eruption appeared after 5 days of vancomycin treatment. The eruption involved almost 60% of the total body surface area and both eyes. He was successfully treated with intravenous immunoglobulin (IVIG), antibiotics, and appropriate wound management and made a full recovery with negligible *sequelae* despite the severity of his disease. Important components of successful treatment include early recognition, intensive care, prompt withdrawal of the causative agent, early administration of IVIG, appropriate fluid resuscitation, and control of infection. IVIG might be beneficial in the treatment of TEN; however, controlled studies are needed to evaluate IVIG compared to other modalities.

Keywords: Intravenous immunoglobulins; Toxic epidermal necrolysis; Granulocyte colony-stimulating factor; Stevens-Johnson syndrome; Case report; Oman.

TOXIC EPIDERMAL NECROLYSIS (TEN) IS a severe drug-induced life-threatening disease characterised by fulminant, widespread blisters which become responsible for epidermal sloughing. It is associated with high mortality and the majority of patients die from complications related to infection.¹ Supportive therapies and antiseptics are of paramount importance in the management of patients with

TEN. Recently, a few cases have been treated successfully with intravenous immunoglobulin (IVIG).

Case Report

This case features a 9-month-old male who had been diagnosed with methylmalonic acidaemia with generalised hypotonia and global

developmental delay. He presented with a 3-day history of fever, cough, shortness of breath, and vomiting. At presentation, he was lethargic, tachypneic, tachycardic (heart rate range 150–160 beats/minute), and dehydrated. Subsequently, he desaturated and was transferred to the Paediatric Intensive Care Unit (PICU) with the diagnosis of severe metabolic crisis secondary to sepsis, and impending compensated shock. Initial investigations showed a sodium level of 142 mmol/L (normal range [NR]: 135–145 mmol/L), potassium 4.6 mmol/L (NR: 2.5–5.1 mmol/L), creatinine 23 μ mol/L (NR: 15–31 μ mol/L), urea 9.3 mmol/L (NR: 2.1–7.1 mmol/L), bicarbonate 11 mmol/L (NR: 22–29 mmol/L), albumin 40 g/L (NR: 38–54 g/L), calcium 1.79 mmol/L (NR: 2.1–2.55 mmol/L), alkaline phosphatase 145 U/L (NR: <281 U/L), magnesium 1.1 mmol/L (NR: 0.7–1.05 mmol/L), phosphate 1.67 mmol/L (NR: 1.6–3.5 mmol/L), alanine transaminase (ALT) 654 IU/L (NR: 0–41 U/L), and aspartate aminotransferase (AST) 863 U/L (NR: 0–38 U/L). A complete blood count (CBC) showed haemoglobin (Hb) at 9.6 g/dL (NR: 11.5–15.5 g/dL), white blood count (WBC) 2.7×10^9 /L (NR: $4.5\text{--}14.5 \times 10^9$ /L), absolute neutrophilic count (ANC) 1.9×10^9 /L (NR: $1.4\text{--}9 \times 10^9$ /L), and platelet count 284 (NR: 150–450 10^9 /L). The C-reactive protein (CRP) was elevated at 32 mg/L (normal range: 0–8 mg/L). Initially, he received fluid resuscitation and the acidosis was corrected. Careful fluid resuscitation was guided by central venous pressure (CVP) monitoring to avoid fluid overload. The ammonia level was 149 μ mol/L (NR: 16–60 μ mol/L). Measures to lower the hyperammonemic state were begun as the patient was critically sick. A chest X-ray showed bilateral haziness. Initially, the patient was treated empirically with cloxacillin and cefotaxime while we awaited the results of the cultures.

On the second day, his condition started to deteriorate. He was electively ventilated using pressure-regulated volume control (PRVC). We followed the directed goal therapy of management of shock, keeping the mean arterial blood pressure above normal for both age and sex. Inotropic supports were escalated to dopamine 20 mcg/kg/min, dobutamine 20 mcg/kg/min, and noradrenaline 0.5 mcg/kg/min along with high doses of hydrocortisone. Antibiotics were upgraded to vancomycin, meropenem, and metronidazole. A follow-up CBC showed Hb 8.9 g/dL (NR: 11.5–15.5

g/dL), WBC 0.9×10^9 /L (NR: $4.5\text{--}14.5 \times 10^9$ /L), ANC 0.2×10^9 /L (NR: $1.4\text{--}9 \times 10^9$ /L) and a platelet count of 17 10^9 /L (NR: 150–450 10^9 /L). Granulocyte colony-stimulating factor (G-CSF) was given for neutropaenia (10 mcg/kg once daily for two days) and then stopped when the neutropaenia resolved. His ammonia level increased to 495 μ mol/L, so sodium benzoate and sodium phenyl butyrate were given again as bolus, and then continued as maintenance. His severe metabolic acidosis was corrected with sodium bicarbonate in a continuous infusion over 24 hours. His severe hyperglycaemia, with blood sugar reaching 20 mmol/L, was treated with an insulin infusion. He developed disseminated intravascular coagulopathy, a deranged coagulation profile, thrombocytopenia, haematuria, and bleeding from his stomach and endotracheal tubes. Fresh frozen plasma and a platelet transfusion were administered.

His vancomycin dose was adjusted on the third day, as the drug level was found to be high (pre-dose 23.1 mg/dl (NR: 5–15 mg/dL); post-dose 44.3 mg/dl (NR: 20–40 mg/dL)). In addition, the metronidazole was stopped. His ammonia level came down to 75 μ mol/L. Our aim was to keep his ammonia level below 100 μ mol/L. The G-CSF was restarted at a higher dose as the neutrophils dropped. The metabolic crisis then settled, with stable vital signs and clinical parameters, and no more metabolic acidosis or hyperammonemia. All blood, urine, and endotracheal tube secretion cultures were negative.

On the sixth day, the patient started to have extensive diffuse erythematous skin lesions. These appeared 5 days after starting vancomycin. His fever ranged from 38.5 to 39.2°C as the rash evolved. The rash started on the left axilla and then extended to cover most of his trunk, front, back, and inguinal and perineal regions and, finally, the extremities. At its maximum coverage, the rash covered almost 60% of the total body surface area. The lesions were erythematous and hyperpigmented mainly on flexural sites and below the cardiac monitoring electrodes. There were spots and atypical targets leading to a confluent exanthema. On these lesions, blisters occurred with some of them becoming confluent. Oral mucosal hyperaemia and erosions also appeared. These lesions were diagnosed as vancomycin-induced toxic epidermal necrolysis. Experts in the paediatric field, and a drug reaction and consultant dermatologist confirmed our



Figure 1: Patient's skin with positive Nikolsky's sign.



Figure 2: Patient's skin with target sign.

clinical diagnosis. Vancomycin was stopped and IVIG (0.5 gm/kg) was started to treat the TEN for 5 days. The skin lesions also involved both of the eyelids and interfered with the closing of the eyes. An ophthalmologic examination showed the ocular mucosa was affected by erosions, corneal abrasions, and abnormally directed lashes.

The neutrophil count gradually increased and then stabilised. The entire skin fully recovered, although some pigmentation persisted. Ophthalmological manifestations were managed medically with a good outcome.

The diagnosis of TEN in our patient was based on its classic presentation: 1) prodromal phase with fever and upper respiratory tract symptoms; 2) ophthalmological and oral mucous membrane involvement; 3) typical skin lesions involving more than 10% of the total surface area of the skin with positive Nikolsky's sign;² 4) exclusion of other differential diagnoses, including burns, pemphigus/pemphigoid disease, erythema multiforme (their exclusion depended on which expert or illustrated medical atlas was consulted);³ 5) superficial skin swabs and all septic work-ups were negative; the patient's improvement after the withdrawal of vancomycin made toxic shock syndrome unlikely.

A skin biopsy was not done as our patient was critically ill and immunocompromised. Infection and sepsis are the main causes of death in patients with TEN. It is recommended that all efforts should be made to reduce the risk of infection in order to improve survival.¹ We depended on our clinical diagnosis in the management of the child.⁴

The patient's score of toxic epidermal necrosis (SCORTEN) should be calculated within the first 24 hours of admission and again on day 3. SCORTEN is the sum of 7 measured clinical variables: age; heart rate; the presence of cancer or haematologic malignancy; the percentage of epidermal detachment; and blood, glucose, urea, and bicarbonate levels. Our patient's SCORTEN was as follows: 1) age >40 years? No; 2) heart rate >120 beats per minute? Yes; 3) presence of cancer or hematologic malignancy? No; 4) percentage of epidermal detachment involving body surface area >10% on Day 1? Yes; 5) blood urea nitrogen level >28 mg/dL? No, it was 10 mmol/L; 6) glucose level >252 mg/dL? Yes, it was 14 mmol/L; 7) bicarbonate level <20 mEq/L? Yes. One point is given for each positive variable and the mortality increases sharply with each additional point. Our patient's total score was 4. A SCORTEN of 0 to 1 predicts 3.2% mortality; 2 predicts 12.1% mortality; 3 predicts 35.3% mortality; 4 predicts 58.3% mortality; 5 or greater predicts 90.0% mortality. SCORTEN has proven to be extremely accurate in predicting mortality.

Discussion

TEN is also called Lyell's syndrome, after Alan Lyell who in 1956 described 4 cases of TEN in patients who exhibited eruptions resembling a scalding of the skin.⁴ Despite under-reporting, the incidence of TEN in Oman has been found to be two per million, with a total 4 patients and 5 episodes,

which is just somewhat higher than the incidence reported in other studies (0.5 to 1.2 per million).⁶ TEN is an acute onset, potentially life-threatening, idiosyncratic mucocutaneous reaction which usually occurs after commencement of a new medication. Widespread full-thickness epidermal necrosis develops, producing erythema, large blisters, and detachment of large sheets of skin leaving a raw base.⁷ The skin develops an appearance similar to that which occurs upon receiving a scalding burn. It usually affects the trunk, face, and one or more mucous membranes. It is considered by some to be part of a spectrum of diseases including, in order of severity, erythema multiforme, Stevens-Johnson syndrome (SJS), and TEN. However, others argue that as erythema multiforme is associated with infections such as herpes simplex virus and mycoplasma pneumonia, SJS and TEN are necrolytic bullous reactions to certain drugs. Therefore, erythema multiforme should not be classified as part of the same disease spectrum.⁷

Regional reference in drug prescriptions, the genetic background of patients (e.g. human leukocyte antigen [HLA] and metabolising enzymes), and the coexistence of other diseases can have an impact on the incidence of TEN.⁷

Another classification system is based on the fact that SJS and TEN are related conditions which can be differentiated by the degree of skin involvement. Less than 10% of the epidermis sloughs off in SJS as compared with >30% in TEN.^{1,2,8}

Marcus proposed that a new medication will have been started shortly before the onset of symptoms in all children who develop TEN. The mean duration of medication therapy until onset of symptoms in children with TEN was 11 ± 2 days. TEN occurred after starting antibiotics in 73% of patients in Marcus's study.⁹

An adverse drug reaction is defined as a response to a drug which is noxious and unintended that occurs at doses normally used for prophylaxis, diagnosis or therapy of disease, or for the modification of physiologic function.⁷ Type A reactions are dose-dependent and predictable while type B reactions (idiosyncratic) are dose-independent. A severe cutaneous adverse drug reaction happens when such a response leads to changes in the structure and/or function of the skin, its appendages or mucous membrane,

resulting in outcomes such as death, life-threatening events, hospitalisation, disability or interventions to prevent permanent impairment or damage.^{1,10}

The pathogenesis of TEN is still not fully understood. The widespread epidermal death is thought to be a consequence of keratinocyte apoptosis. A pivotal role of cytotoxic lymphocytes has been suggested.^{1,10} Recent studies indicate that TEN may be a major histocompatibility complex (MHC) class-I-restricted specific drug sensitivity resulting in clonal expansion of CD8+ cytotoxic lymphocytes with potential for cytolysis. The cytotoxicity is apparently mediated by granzymes, which are serine proteinases that are components of cytotoxic cells and natural killer cell granules.¹¹ Chung *et al.* found that granulysin concentrations in the blister fluids were two to four orders of magnitude higher than perforin, granzyme B, or soluble F as ligand concentrations, and depleting granulysin reduced the cytotoxicity. Granulysin in the blister fluids was in a 15-kDa secretory form, and injection of it into mouse skin resulted in features mimicking SJS/TEN. These findings demonstrate that secretory granulysin is a key molecule responsible for the disseminated keratinocyte death in SJS/TEN.¹²

Children with TEN are best managed in burn units; however, as shown by Prendiville *et al.*, children with TEN also can be treated successfully in PICUs. Important strategies of success include meticulous wound care and prevention of all systemic and local infections.¹³

The optimal treatment of the blistering skin is a major issue discussed in the literature. Most centres, including ours, follow recommendations made by Prendiville *et al.*, who advocated removal of only spontaneously blistering skin and did not recommend additional debridement. The group based this recommendation on the fact that the skin re-epithelialises under intact blisters. Open areas were covered with topical antimicrobial agents and 0.5% silver nitrate dressing.¹³ As for adjuvant administration of mediator-neutralising effectors of keratinocyte apoptosis in the form of intravenous immunoglobulin, it has shown beneficial effects on survival in adult patients. However, most studies of this aspect of treatment in TEN lack evidence or are based on prospective studies on large patient groups.¹

The use of IVIG promotes inhibition of Fas-mediated keratinocyte apoptosis by Fas-blocking antibodies contained in IVIG preparations and it also decreases life-threatening infections. We used IVIG in our patient 24 hours after the first appearance of skin lesions. Three days later, epidermal detachment was interrupted and complete skin re-epithelisation was completed within two weeks. We think that poor prognostic factors delayed the skin re-epithelisation in our patient.¹⁴

Neutropaenia is regarded as an important negative prognostic factor.¹⁴ In our case, neutropaenia was related to bone marrow suppression initially to methylmalonic acidemia, and later to the development of TEN. The neutrophilic count improved and reached normal levels within 10 days of G-CSF administration.

Our patient made an excellent recovery despite poor prognostic factors due to the early introduction of IVIG and the immediate removal of the medication thought to be the cause of TEN (vancomycin). We believe that IVIG played a significant role in the recovery of this child. Our experience of using IVIG in the treatment of TEN with a favourable outcome could be useful to those in other Arabian Gulf countries, whose citizens' genetic and environmental circumstances are similar to those of our patient.¹⁵

Conclusion

TEN is an acute, life-threatening, exfoliative disorder with a high mortality rate. High clinical suspicion, prompt recognition, and initiation of supportive care are mandatory. We suspect that IVIG was significantly responsible for this patient's clinical improvement, despite the controversial efficacy of IVIG in treatment of TEN. A thorough investigation of the pathogenetic mechanisms is fundamental. Optimal treatment guidelines are still unavailable. Multi-institutional collaborative efforts to develop better treatment strategies are warranted.

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