

## Toxic Epidermal Necrolysis Associated with High Intake of Sildenafil and its Response to Infliximab

Sadek Al-Shouli<sup>1</sup>, Nabil Abouchala<sup>1</sup>, Maciej J. Bogusz<sup>2</sup>, Mohammad Al Tufail<sup>2</sup> and Kristian Thestrup-Pedersen<sup>3</sup>

<sup>1</sup>Department of Intensive Care <sup>2</sup>Toxicology and Bioanalysis Section and <sup>3</sup>Section of Dermatology, Department of Medicine, King Faisal Specialist Hospital and Research Centre, MBC#46, PO Box 3354, 11211 Riyadh, Saudi Arabia.

E-mail: ktpedersen@kfshrc.edu.se

Accepted March 11, 2005.

Sir,

Toxic epidermal necrolysis (TEN) is a rare, but well-known acute and life-threatening disorder first described by Lyell (1). It is defined as epidermolysis induced most commonly by drugs (1, 2). If the loss of epidermis exceeds 30%, it is called TEN, whereas less than 30% skin affection is called either Stevens-Johnson (SJ) syndrome (<10%) or intermediate SJ-TEN (10–30%). It can involve the internal surfaces of the gastrointestinal tract (1, 2). We describe here a classical case of TEN induced by poly-pharmacy including the intake of aphrodisiac herbal drugs and sildenafil. Treatment with infliximab led to a rapid recovery.

### CASE REPORT

A 67-year-old man was admitted with an extensive mucocutaneous eruption of large erythematous areas and bullae leading to denudation consistent with TEN (Fig. 1a). He had no history of skin disease or allergies. He suffered from cardiac insufficiency, diabetes mellitus, gout, hyperlipidaemia, hypertension, obesity and had 5 months earlier undergone replacement of knee joints due to osteoarthritis. At the time of the skin eruption he took eight drugs for the diseases mentioned above. As he had recently married he took an aphrodisiac drug

of Chinese herbal medicine (2 + 2 capsules over 2 days). Simultaneously, he had also taken 100 mg and 200 mg sildenafil over a 2-day period.

A few days after this intake and approximately 10 days before admission at our hospital he developed oral ulcers and a rash on the upper part of the back. He was admitted to a local hospital and diagnosed as having Lyell's syndrome and started prednisolone 60 mg p.o. daily, which was given for 2–3 days. Due to progressive symptoms, he was admitted to our hospital. We observed a universal skin rash including severe erosions of the oral cavity. Approximately 40–50% of his skin was eroded, especially the back, buttocks and feet. The rest of his skin was also affected. Our clinical diagnosis of TEN was based on his history of poly-pharmacy and confirmed by histological examination, which showed epidermal necrosis of keratinocytes and intra-epidermal blister formation (Fig. 2). Immunofluorescence was negative. Biochemical investigations including liver enzymes were normal.

We stopped all medication except antihypertensive medicine and insulin. He was admitted to our intensive care unit for i.v. fluids and nursing care with sulfadiazine cream on eroded skin. We gave infliximab (Remicade®) 3 mg/kg (total dosage 300 mg) over a 3-h infusion.

Multiple cultures were obtained from skin, and these showed colonization with a sensitive strain of *Pseudomonas aeruginosa*. His course in the intensive care unit was complicated by the development of septic shock secondary to a catheter-related infection, as blood cultures and the femoral central vein line tip grew *P. aeruginosa*. The patient responded

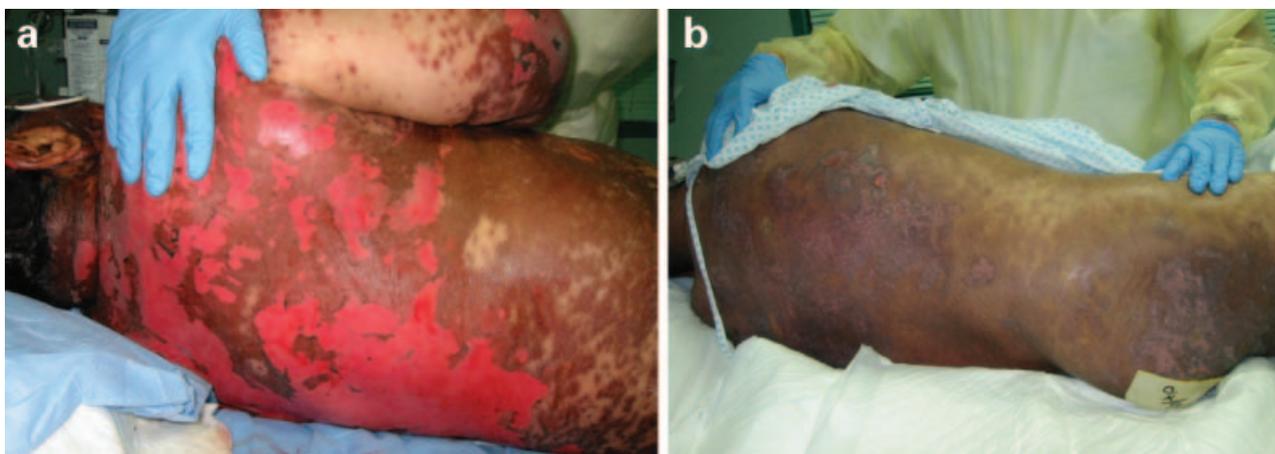


Fig. 1. The patient (a) before and (b) 10 days after injection of infliximab 3 mg/kg during the first day of admission.

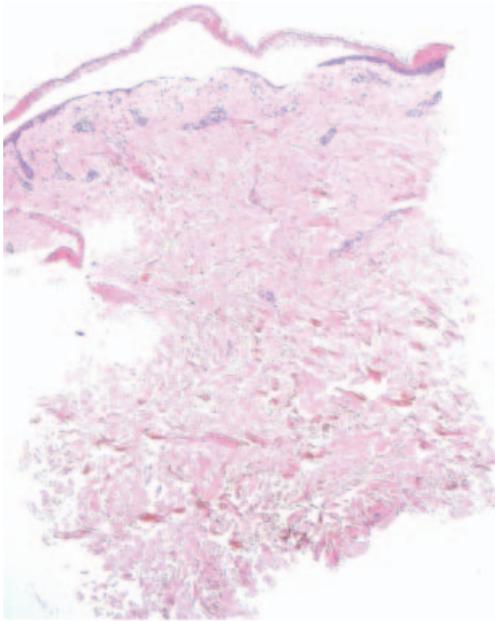


Fig. 2. Histology with necrosis and blister formation of epidermis.

well to meropenem 1 g three times daily, with prompt resolution of septic shock after 48 h.

Within 1 week re-epithelization had started (Fig. 1b) and i.v. administration of analgesics was discontinued. The patient was transferred to a stationary ward after 10 days and recovered fully.

Toxicological investigation of the Chinese herbal medicine (Fu Yauan Chun capsules) revealed that each capsule (0.5 g) contained 95 mg sildenafil. Thus the maximal dosage of sildenafil per day just prior to his skin symptoms may have been close to 300–400 mg. Additionally, each capsule contained *osthole*, which belongs to derivatives of coumarin that are effective in treatment of erectile dysfunction (3).

We measured tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) on his arrival before treatment and after 1 week. The first sample showed 16.5 ng TNF- $\alpha$ /ml (normal range 0–8.5 ng/ml). The second sample was negative for TNF- $\alpha$ .

## DISCUSSION

TEN is the severe form of epidermal necrolysis affecting over 30% of the body surface, whereas SJ syndrome is the less severe form (2). Our patient clearly suffered from drug-induced TEN based on typical clinical and histological findings.

Anti-epileptics are known to be associated with an increased risk of TEN (4), but our patient was not given such drugs. Sildenafil (Viagra<sup>®</sup>) has not previously been associated with TEN. A dosage up to three to four times the maximal recommended dosage may therefore be relevant for the development of TEN. The toxicological investigations could document both sildenafil and *osthole*, a coumarin-like derivative found in *Cnidium monieri* and *Umbelliferae* plants. These compounds occur frequently in Chinese herbal remedies recommended for treatment of erectile dysfunction (5).

TNF- $\alpha$  is considered to be an important mediator in TEN (6, 7). However, a recent study on thalidomide,

which is an inhibitor of TNF- $\alpha$ , showed a deteriorating effect of thalidomide on TEN (8). Infliximab was recently used in a patient with TEN at a dosage of 5 mg/kg as a single infusion leading to a quick recovery, although it took 4 weeks for the oral symptoms to subside (9). We decided on the low dosage (3 mg/kg), as any adverse effect towards infliximab could have been detrimental to this patient's skin condition.

Steroids have been shown not to be helpful in treating TEN (1). Recently, it was also recognized that high-dose intravenous immunoglobulins are not beneficial (10). In the latter study, 11 patients (32%) died despite being admitted on average within 3–5 days. In the survivors on day 11 an average of 17% of the body surface area was not healed, which took on average 18 days (10). The rapid recovery in our patient (see Fig. 1) is therefore supportive of a beneficial effect of infliximab. However, large-scale studies are clearly needed before infliximab may be confirmed as a new 'gold standard' in treating TEN.

## REFERENCES

1. Wolkenstein P, Revuz J. Toxic epidermal necrolysis. *Dermatol Clin* 2000; 18: 485–495.
2. Roujeau JC. Stevens-Johnson syndrome and toxic epidermal necrolysis are severity variants of the same disease which differs from erythema multiforme. *J Dermatol* 1997; 24: 726–729.
3. Chiou WF, Huang YL, Chen CF. Vasorelaxing effect of coumarins from *Cnidium monieri* on rabbit corpus cavernosum. *Planta Med* 2001; 67: 282–284.
4. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Sern R. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Study group of the international case control study on severe cutaneous adverse reactions. *Lancet* 1999; 353: 2190–2194.
5. Bogusz MJ, Al Tufail M, Hassan H. How natural are "Natural Herbal Remedies" – a Saudi perspective. *Adv Drug React Toxicol Rev* 2002; 21: 219–229.
6. Paquet P, Pierard GE. Soluble fractions of tumor necrosis factor- $\alpha$ , interleukin-6 and of their receptors in toxic epidermal necrolysis: a comparison with second-degree burns. *Int J Mol Med* 1998; 1: 459–462.
7. Correia O, Delgado L, Barbosa IL, Campilho F, Fleming-Torrinha J. Increased interleukin 10, tumor necrosis factor alpha, and interleukin 6 levels in blister fluid of toxic epidermal necrolysis. *J Am Acad Dermatol* 2002; 47: 58–62.
8. Wolkenstein P, Latarjet J, Roujeau JC, Duguet C, Boudeau S, Vaillant L, et al. Randomized comparison of thalidomide versus placebo in toxic epidermal necrolysis. *Lancet* 1998; 352: 1586–1589.
9. Fischer M, Fiedler E, Marsch WC, Wohlrab J. Antitumour necrosis factor alpha antibodies (infliximab) in the treatment of a patient with toxic epidermal necrolysis. *Br J Dermatol* 2002; 146: 707–708.
10. Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. *Arch Dermatol* 2003; 139: 33–36.