SUMMARY. Toxic epidermal necrolysis is a rare, potentially fatal disorder that involves large areas of skin desquamation. Patients with toxic epidermal necrolysis are frequently referred to burn centres for expert wound management and early comprehensive critical care as this has been shown to improve patient outcome and mortality. The authors describe the first report of medication-induced toxic epidermal necrolysis occurring in a patient during acute burn management in a tertiary burn care facility. The patient sustained a 17% total body surface area flame burn to her face, chest, bilateral upper limbs and bilateral lower limbs while escaping from a wildfire. She required extensive debridement and allografting to manage burn injured areas and additional areas of epidermal loss from subsequent toxic epidermal necrolysis, amounting to a total body surface area of 90%. Definitive burn wound closure was achieved using autologous split-thickness skin grafting once donor sites healed and became suitable for harvest 3 weeks after the onset of toxic epidermal necrolysis. Grafts achieved complete take and the patient was discharged home following rehabilitation.

Keywords: toxic epidermal necrolysis, Lyell’s syndrome, Stevens-Johnson syndrome, allograft, burn

RÉSUMÉ. La nécrolyse épidermique toxique est une pathologie rare potentiellement mortelle entraînant des desquamations cutanées étendues. Ces patients sont fréquemment hospitalisés dans un CTB, en raison de leur expertise des soins locaux et de la réanimation, ce qui contribue à l’amélioration du pronostic et à la baisse de la mortalité. Nous rapportons le premier cas de nécrolyse épidermique toxique liée à un médicament survenu au cours du traitement en CTB d’une patiente brûlée. Elle souffrait d’une brûlure sur 17% SCT intéressant le visage, le thorax et les 4 membres, ayant nécessité excision et greffes. Celles-ci n’ont pu être réalisées que tardivement, en raison d’un défaut de site donneurs car la patient a développé une nécrolyse épidermique toxique sur 90% SCT ne les ayant laissé utilisables que 3 semaines plus tard. Les greffes se sont bien intégrées et la patiente a pu retourner à domicile après rééducation.

Mots-clés: nécrolyse épidermique toxique, syndrome de Lyell, syndrome de Stevens-Johnson, allogreffe, brûlure
Introduction

Toxic epidermal necrolysis (TEN), also known as Lyell’s syndrome, and Stevens-Johnson syndrome (SJS) are rare, potentially fatal disorders characterized by high fever, widespread blistering of varying severity, macules and target-like lesions with mucosal involvement. SJS, TEN and SJS/TEN overlap are distinct entities on a spectrum of disease whereby SJS refers to epidermal detachment of less than 10% body surface area and TEN refers to more extensive epidermal detachment, generally greater than 30% body surface area. The incidence for SJS/TEN is one to two cases per million each year. Mortality rates are high from both conditions, greater than 30% reported for TEN and 10% for SJS. Although the exact mechanism is unknown, TEN is thought to represent an immune complex mediated hypersensitivity disorder whereby apoptotic keratinocyte cell death causes separation of epidermis from dermis. Medications are most commonly implicated and more than 200 medications have been associated with SJS/TEN, although 20% of cases are not medication related.

Case presentation

A 46-year-old lady was repatriated to a tertiary burn care centre 30 days after she sustained 17% total body surface area flame burns to left face, anterior chest, upper and lower extremities (Fig. 1). Initial emergency management was provided by a local hospital in Southeastern Europe after she was injured there due to uncontrolled wildfires that engulfed the resort where she was vacationing, with major loss of life. The patient had no significant past medical history, took no regular medications and had no known drug allergies.

Acute surgical management included emergency escharotomy for full thickness circumferential left hand burn and three surgical debridements, carried out thereafter, of all burn affected areas. There was no inhalational component and no other injuries were detected. Microbiology from burn tissue excised had polymicrobial growth with multi-drug resistant pseudomonas aeruginosa and carbapenemase-producing enterobacteriaceae (CPE) klebsiella pneumoniae and enterococcus faecalis for which 10 days of intravenous Cefuroxime and Vancomycin had been administered up to the time of international transfer. Treating physicians arranged transfer of the patient to the National Burns Unit at St James’ Hospital, Dublin for definitive surgical management, where she had access to a wider psycho-social support network following the traumatic nature of her injury.

On arrival in Ireland the patient showed signs of sepsis for which antimicrobial advice was sought pending further investigation of infection source, taking into consideration known multi-resistant polymicrobial growth from burn tissue. Broad-spectrum antimicrobial coverage was instituted with Colistin, Meropenem, Vancomycin and Tigecycline.

Debridement of all burn tissue affecting bilateral upper and lower limbs was carried out on Day 1 of admission following antibiotics, fluid resuscitation, change of central access and septic work-up. The burn wounds themselves appeared to be critically colonised and sloughy if not overtly infected. Cadaveric allografting was performed to bilateral upper and lower limb burn wounds due to heavy colonisation of the burn wounds, ongoing sepsis and deranged coagulation profile.

On Day 1 post-operatively the patient was noted to have developed new areas of epidermal loss with positive Nikolsky’s sign in addition to

![Fig. 1 - Burn wounds on admission following repatriation, 30 days post flame injury](image-url)
oral mucosal ulceration and ocular chemosis (Fig. 2). Including the burn affected areas this new epidermal loss amounted to greater than 90% of the patient's total body surface area. All antimicrobials were promptly stopped following thorough medication review and the diagnosis of toxic epidermal necrolysis (TEN) was confirmed on skin biopsy, which demonstrated full thickness epidermal necrosis. A severity of illness score for TEN (SCORTEN) of 5 was calculated, corresponding to a predicted mortality of 90%.

Multi-disciplinary critical care management followed with Ophthalmology and Dermatology consultation. The patient returned to theatre for hydrosurgical debridement and further allografting to areas of skin most severely affected by TEN (namely the back, buttocks and thighs). The patient’s post-operative course was complicated by respiratory sepsis requiring judicious antimicrobial use with avoidance of beta lactam antibiotics, presumed to have been the causative medication responsible for the onset of TEN. Deteriorating renal function attributed to acute tubular necrosis necessitated renal replacement therapy for a period of 5 days. She responded well to treatment and her skin re-epithelialised within 14-21 days. Autografting to bilateral lower legs and bilateral upper limb burn wounds was carried out 21 days after the onset of TEN at which time split-thickness skin graft donor sites (namely right circumferential thigh and right lower leg) previously affected by TEN, were now fully healed and intact. Graft take was excellent with 100% adherence of autograft (Fig. 3). The patient underwent intensive physiotherapy and occupational therapy for stiffness from early burn scar contracture affecting her left hand and bilateral knees before discharge home 9 weeks after admission, with plans for further outpatient scar management. No long-term sequelae secondary to TEN were noted at last follow-up.

Discussion

This article describes the first reported case, to the best of the authors’ knowledge, of toxic epidermal necrolysis (TEN) occurring in a patient with acute burn injury. Donor site preservation and expedited healing were paramount in this case in order to facilitate definitive burn wound closure.

Fig. 2 - Toxic epidermal necrolysis (positive Nikolsky’s sign) affecting left antecubital fossa and thigh proximal to previously allografted burn wounds

Fig. 3 - Healed burn wounds and donor sites, Day 16 post autografting
with autologous split-thickness skin graft harvest following the acute critical care management of this life-threatening complication. Cadaveric allograft is a versatile and reliable temporary skin substitute which was employed in the management of this patient’s burn wounds and further epidermal loss secondary to TEN. Several case reports have described the use of allografting in management of exfoliative skin disorders in pediatric and adult populations since the 1980s.\textsuperscript{4,5} Potential advantages of allografting skin affected by TEN includes prevention of wound desiccation, reduction of fluid and heat loss from the wound, establishment of a barrier to exogenous microbial contamination, reduction in pain and facilitation of movement in the involved parts. The host epidermis regenerates rapidly from adnexae, and displaces viable allograft along the plane of the host/graft interface. Other synthetic and biosynthetic skin substitutes have also been described in the treatment of TEN,\textsuperscript{6,7} although infection risk is a feared complication and time to healing using such skin substitutes compared to dressing only has not been shown to be significantly different. Due to the rarity of this condition, large randomised controlled studies to determine the optimum skin substitute in the treatment of SJS/TEN are lacking. One criticism of allograft is that it may become firmly embedded into native skin, requiring further wound care. This was not evident in this patient’s case. Where allografted skin took well to TEN affected skin initially, it was easily removed once the underlying skin re-epithelialized within 2-3 weeks, making it amenable to autograft harvest.

Acute kidney injury is a common complication in SJS/TEN, reported in 20%-30% of cases, 5% of whom require dialysis.\textsuperscript{8} The cause of renal dysfunction in TEN is multi-factorial and any of the following may lead to acute tubular necrosis: increased fluid loss from mucosal and skin surface involvement, drugs, diarrhoea and sepsis. Acute kidney injury has been shown to represent an independent risk factor for mortality in patients with SJS/TEN, increasing the risk of mortality 5 fold.

This patient demonstrated a high severity of illness score for TEN (SCORTEN) at the time of her diagnosis, with a predicted mortality of 90%. A recent study has shown that this scoring system overestimates mortality of patients with TEN,\textsuperscript{9} likely due to improvements in critical care and wound care since the SCORTEN was first devised in 2000.\textsuperscript{10} Withdrawal of the suspected offending drug early has been shown to decrease mortality rates and complications from TEN.\textsuperscript{3} A large number of medications have been implicated in the aetiology of TEN/SJS: the most common include sulphonamides such as co-trimoxazole, beta-lactam antibiotics including penicillins and cephalosporins (as identified in our patient’s case), anti-convulsants, allopurinol, acetaminophen and non-steroidal anti-inflammatory drugs.\textsuperscript{2} Early transfer of patients with TEN/SJS to burns units with specialist intensive nursing care also improves survival, reduces infection and shortens hospital stay,\textsuperscript{11} particularly when there is greater than 30% body surface area involved. Supportive care, wound management, temperature maintenance, and nutritional and fluid replacement are key aspects of TEN/SJS management, as well as early ophthalmology consultation for sight threatening ocular sequelae.\textsuperscript{2} Variability in treatment and management of TEN/SJS among burn units has led to a call for standardized guidelines,\textsuperscript{12} particularly with regard to systemic immunomodulation therapy such as intravenous immunoglobulin and cyclosporine.

Conclusion

Described is a unique, previously unreported case of toxic epidermal necrolysis complicating acute burn injury, leading to a 90% total body surface area injury and high predicted mortality, managed successfully using sequential allografting and autografting. The standard of care for TEN management in our unit is hydrosurgical debridement of de-epithelialised tissues followed by wound closure using biosynthetic skin substitutes in wounds uncomplicated by infection, or cadaveric allograft in cases where there is high risk for infection or where delay to definitive wound closure is expected.
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