Toxic epidermal necrolysis (TEN), also known as Lyell’s disease, is a rare and life-threatening disease with an incidence of 0.5-1.5 cases per million each year in the Czech Republic. Toxic epidermal necrolysis was first described in 1956 by Scottish dermatologist Alan Lyell, who identified it in four patients. In two patients, the diagnosis was subsequently modified to staphylococcal scalded skin syndrome, which was already known by that time; the other two patients indeed had TEN. The syndrome was also described by Lang and Walker in the same year. The condition belongs to a group of diseases called burn-like syndromes. Stevens-Johnson’s Syndrome, as well as TEN, mimics superficial burns. The only difference is that the collection of fluid is only between the epidermis and dermis, unlike the involvement of the dermis in some cases of superficial burns. Toxic epidermal necrolysis is the most severe condition of that group. It is a potentially life-threatening drug-mediated toxoallergic reaction causing extensive skin and mucosal exfoliation in the area of the dermoepidermal junction. The condition is complicated by systemic toxicity. It is an extremely rare disease with an incidence of approximately 0.5-2 cases per million each year. For reasons that are yet to be explained, the patients are predominantly women (in most epidemiological studies, the M:F ratio is about 1:1.5).

Global mortality rates are reported to be somewhere between 40 and 90%. In fact, TEN is an immunological reaction to the presence of a foreign antigen. In 90% of patients, a medication inducing the development of Lyell’s disease can be traced back in their medical history. The drugs associated with highest risk include antibiotics (trimethoprim/sulfamethoxazole, amoxicillin/clavulanic acid), non-steroidal anti-inflammatory drugs, antiepileptics (carbamazepin, valproate, lamotrigine), allopurinol, corticosteroids, antidepressants, anxiolytics, and other substances. However, the causative agent remains unidentified in over 10% of cases.

Successful therapy requires optimization of not only systemic but local therapy, in particular. Our case report presents a young woman who developed TEN, possibly resulting from lamotrigine therapy. Local therapy included a combination of a biological cover and alginate together with a synthetic cover (Aquacel Ag®).

**Case report**

We present the case of a young woman with polyvalent allergy, hospitalized in an alcohol rehab center. Despite her allergy, she deliberately ate a citrus fruit and subsequently developed anaphylactic shock and Quincke’s edema. Emergency medical services provided acute treatment and subsequently transported the patient to the Department of Infectious Disease of the District Hospital in Jihlava. By that time, the patient was breathing spontaneously, there was already no edema involving her face and neck, and...
she showed no signs of shock. The following day, the patient developed a skin rash, likely to have been caused by lamotrigine therapy. A consultant in dermatology, when asked his opinion, said he suspected an exfoliative disease. Corticosteroid (dexamethasone) therapy was subsequently initiated. As the disease progressed despite therapy, the patient was transferred, on day 4, to the Burn and Reconstructive Surgery Center of Brno University Hospital.

On admission, the patient was breathing spontaneously with satisfactory oxygen saturation values. Her clinical picture was dominated by extensive, coalescent bullae, particularly in the upper part of her body; her oral cavity was also involved (Fig. 1). The extent of exfoliation can be seen in Figs. 2 and 3. Because of marked tenderness, the patient had to receive primary treatment in the operating room with a central venous catheter, permanent urinary catheter, and an arterial sensor inserted. As agreed with the anaesthesiologist, the patient was on mechanical ventilation using only a face mask due to the high risk of additional mucosal injury involving the upper respiratory airways. Bronchoscopy on admission did not find injury to the lower respiratory airway lining.

Examination on admission clearly showed the patient had TEN, as Nikolsky's sign was clearly identified; the primary extent of exfoliation was estimated to be 55% of body surface area. The clinical picture deteriorated dramatically within a few hours, with exfoliation increasing to involve up to 85% of the total body surface area (TBSA) together with injury to the mucosa of the oral cavity, upper respiratory airways, vagina, and rectum.

**Systemic therapy**

Upon admission, the patient was already undergoing corticosteroid therapy (Solumedrol 250mg every 8 hours). During hospitalization, the dose was tapered and gradually switched to its oral presentation (methylprednisolone). Because of disease progression, the patient required cyclosporine A at an induction dose of 5mg/kg b.w. per day (the dose was split into two). As the picture progressed dramatically despite the above measure, systemic therapy had to be complemented, at 14 hours post-admission, with high-dose antithrombin (a therapeutic option in TEN not published before). High-dose antithrombin is particularly advantageous in a fulminant amplification phase, as it potently inhibits the production of intracellular adhesive molecules (ICAM) modulated by TNF-α and responsible for deterioration of the disease in this phase. The patient also required the administration of intravenous immunoglobulins (IVIG therapy). A starting dose of 0.2g/kg b.w. per day for 5 days was chosen. There was a gradual reduction in CD14+ monocyte count and the patient was developing immunoparalysis defined as a degree of CD14+ monocyte expression < 66%. After 8 days of hospitalization, CD14+ monocyte expression was 8%.

During the period of hospitalization, the patient also received a combination of parenteral and enteral nutrition, with antibiotic therapy based on the results of microbiological surveillance. After 31 days, with complete re-epithelization, the patient was transferred to a catchment
hospital department because of persisting intensive care unit-acquired weakness (ICUAW), requiring intensive physical rehabilitation and physiotherapy.

Microbiology and antibiotic management

On admission, the patient was on prophylactic therapy with cephalosporin, definitely not the best therapeutic option given her documented hypersensitivity to penicillin and clinical signs. Because of this, cephalosporin was withdrawn until the results of culture tests, conducted using the impression technique (semiquantitative evaluation of the microbiological status in the exfoliated areas), bronchoalveolar lavage, and urinalysis became available. Additionally, although the patient was normothermic, blood samples were obtained for hemoculture (the normothermia may have been masked by the incipient immunoparalysis).

As blood culture revealed the presence of Staphylococcus epidermidis and Escherichia coli, the best possible therapy with tigecycline was initiated on day 3 of hospitalization. As Proteus vulgaris was isolated in the exfoliated areas within the next 5 days of the initiation of tigecycline therapy, a combination of tigecycline and amikacin was considered. However, given the fact the patient still had a booster dose of cyclosporine A, the combination with amikacin was deemed inappropriate because of their marked nephrotoxicity. The tigecycline was complemented with a quinolone (ciprofloxacin), albeit a less convenient combination.

Local therapy

Upon initiation of therapy, a combination of a synthetic and a biological cover was used. Given the unique properties of the biological cover, which may benefit not only burn patients but also those with non-thermal skin cover loss, Xe-Derma®, a novel biological skin cover, was applied on the left forearm. The individual phases of wound healing under Xe-Derma® are shown in Figs. 4, 5, 6, 7, 9, 10, and 11, with alginate and Aquacel Ag® applied on the remaining areas. The patient had her dressing changed ev-
ery other day under general anaesthesia (changing alginate and, also, the partly used Aquacel Ag®).

**Discussion and conclusion**

There has been a growing number of publications with favorable reports on the use of the relatively novel Xe-Derma® biological skin cover in adult and pediatric patients sustaining thermal injury. The publication by Zajiček et al. refers to the possible use of a xenogenic material, that is also a skin cover in local management of patients with skin cover loss due to non-thermal causes. Still, there has been no comprehensive case report on the use of Xe-Derma® in patients with TEN in the relevant international literature to date.

Xe-Derma® represents the ideal cover for acute wounds with a potential to spontaneous re-epithelization. The biological skin cover is applied once to be followed only by regular change of the secondary cover. The skin cover is transparent allowing for monitoring of the status of the skin defect while changing the dressing; after complete re-epithelization, the cover peels off spontaneously. Additionally, the fact Xe-Derma® requires single-only application helps minimize pain and mechanical traumatization in the exfoliated areas. Further, its immediate application reduces the probability of multiplication of potentially pathogenic organisms and development of infectious complications in the skin defects.

Use of a biological cover in patients with non-thermal skin loss is no doubt of advantage; however, its behaviour in interaction with the wound base differs from that with a burn area. What actually matters is the overall concept of therapy, as immunosuppressive therapy also leads to prolonged wound healing. This explains why complete epithelization did not occur until after day 15 of Xe-Derma® application. Comparably deep burn areas with skin loss in the region of the dermoepidermal junction take 7-10 days to re-epithelize.

The cost of Xe-Derma® to cover about 3% TBSA was 165 USD; single-only application was required with no need to repeat it or use additional cover. While the input costs are higher, no additional applications are required. Compared with our current protocol involving the use of alginate or Aquacel Ag®, the input costs are higher yet, overall, therapy with Xe-Derma is financially comparable. To cover 3% TBSA with Flaminal Hydro, about 150 ml was used (10 USD); with 7 dressing changes, the total costs climbed to 70 USD. When using Aquacel Ag, which required 3 changes during therapy to make up for the losses, the costs for covering 3% TBSA totalled USD143. Moreover, each dressing change was performed under general anaesthesia due to the pain experienced by the patient. The above sum does not include costs for anaesthetics and a complete team of anaesthesiologists. The costs of general anaesthesia were in the range of 1,196 USD (overall 8 changes under general anaesthesia for the alginate and Aquacel Ag® covers, with an average time of 60 minutes per change). When including the need for dressing under general anaesthesia, use of the Xe-Derma® biological cover is less expensive. It is also important to consider the risks associated with general anaesthesia, especially in the
critically-ill patient with extensive dermal and mucosal exfoliation.

It should be noted that Xe-Derma® use did not result in acceleration of the individual phases of wound healing, and in the other areas where routine wound management was employed, re-epithelization occurred within the same period of time. The benefits of using this biological cover were simply indisputable. In particular, the minimization of pain experienced by the patient during dressing changes, removing the requirement for general anaesthesia, improves the standard of systemic and local care of patients with this condition.

Xe-Derma® is an acellular porcine dermis made from skin grafts; once all cells have been removed, a matrix is left made up of a mesh of collagenous and elastic fibers. The biological cover is believed to accelerate, thanks to its biological nature and unique structure, the process of healing of acute and chronic defects. It also minimizes the frequency of dressing changes, and prevents the development of infectious complications in burns and/or exfoliated areas. While not containing antibacterial substances, it does suppress the growth of potentially pathogenic organisms under the cover. Xe-Derma® thus prevents a slowing down of the individual phases of wound healing, or even further deterioration of the skin defect; the latter being a most frequent fatal therapy-related complication of patients with TEN.

The main advantages of Xe-Derma® use include its bioactive action (promoting keratinocyte growth and differentiation), though partly modulated in immunosuppressed patients. There are also other advantages identical to those seen when using this cover in burn patients (excellent adherence, transparency, reduced pain, haemostatic effect, single application).

RÉSUMÉ. La nécrolyse épidermique toxique est une maladie rare touchant la peau à la jonction dermo-épidermique, avec inclusion possible des muqueuses. La condition est associée à une toxicité systémique et des taux de mortalité élevés. Le succès du traitement nécessite une optimisation de la thérapie locale ainsi que systémique. Nous rapportons le cas d’une jeune femme qui a développé une nécrolyse épidermique toxique, causée peut-être par un traitement par la lamotrigine. Le traitement local a compris une combinaison d’une couverture biologique et de l’alginate avec une couverture en matière synthétique (Aquacel Ag®).

Mots-clés: Xe-Derma®, nécrolyse épidermique toxique

BIBLIOGRAPHY


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