Toxic epidermal necrolysis (Lyell's syndrome): case report and review of the literature

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Submitted: 16 April 2008
Accepted: 17 July 2008

Arch Med Sci 2008; 4, 4: 480–485

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Abstract

A case is described of a 59-year-old woman, who after oral intake of cefaclor presented with toxic epidermal necrolysis (TEN). Toxic epidermal necrolysis is characterized by widespread erythematous and bullous lesions on the skin caused by keratinocyte necrosis leading to exfoliation of epidermis, formation of erosions on mucous membranes and reactions from other organs. In the case of TEN diagnosis local lesions involve >30% of the body surface area. Appropriate local treatment with hydrogel dressings resulted in total healing of the area of exfoliated epidermis.

Key words: Lyell's syndrome, allergic cross reaction, hydrogel dressings.

Introduction

Toxic epidermal necrolysis (TEN, Lyell's syndrome) is a life-threatening skin and mucous membranes disorder, that is usually drug-induced [1]. The syndrome was first described in 1956 by Lyell [2], who over 20 years later presented the differences between toxic epidermal necrolysis and staphylococcal scalded skin syndrome (SSSS), a syndrome of similar symptoms but different aetiology [3]. Lyell's syndrome is characterized by the occurrence of erythematous and bullous lesions on the skin caused by keratinocyte necrosis leading to exfoliation of epidermis (positive Nikolsky's sign), formation of erosions on mucous membranes and reactions from other organs (frequent erosive lesions within the genitourinary system, cornea, gastrointestinal and respiratory tract) [4]. Besides the most severe form of the disease which is TEN, the spectrum of erythematous diseases with bullous reaction on the skin and/or mucous membranes includes erythema multiforme (EM) and Stevens-Johnson syndrome (SJS). In the case of EM (minor form) the course of the disease is milder and the aetiology is more frequently infection- than drug-induced [5, 6]. Based on the extent of lesions on skin and mucous membranes the above-mentioned entities have been classified. Erythema multiforme is diagnosed when the lesions are local and involve less than 10% of the body surface area. If the lesions do not exceed 10% but epidermal

exfoliation is generalized, Stevens-Johnson syndrome is diagnosed. When the involved area of the body surface is between 10 and 29% TEN overlaps with SJS. When more than 30% of the body surface area is involved TEN is diagnosed [7, 8].

Mortality rate in TEN is high and reaches 70%, mainly due to extensive areas of the affected body surface, fluid loss and electrolyte abnormalities and secondary infections. The patient's clinical state, the time of medication therapy and aggressiveness of the undertaken treatment also contribute to the mortality rate. Furthermore, such factors as age, extensiveness of skin and mucosal involvement, prolonged neutropenia (more than 5 days) hyperazotaemia and hypoalbuminaemia (<2.0 g/l) are not insignificant.

It is also worth noting that the frequency of Lyell's syndrome occurrence differs in the USA and in Europe (2-3 cases/million population/year [9]) and is significantly higher than in Poland, where its prevalence is estimated to be 0.4-1.2 cases/million population/year [10]. The disease is observed in every age group and demonstrates a predilection for female gender (F/M 1.6).

The aetiopathogenesis of TEN still remains largely unknown. At present it is assumed that exposure to drugs is the only documented cause of TEN syndrome. The most frequent groups of therapeutic agents cited in the literature are: sulfonamides, anticonvulsants, nonsteroidal anti-inflammatory drugs, and lactam antibiotics (penicillins, cephalosporins) [11]. It has been recently thought that the main cause responsible for the occurrence of Lyell's syndrome is damage of the metabolic pathway of the used drug, which leads to accumulation in the organism of its toxic metabolites due to enzymatic defects and detoxication disorders [12]. Other authors point to the share of immunological mechanisms in the increased apoptosis of keratinocytes. The role of death receptors (DRs) has been proved in the induction of epidermal cells apoptosis. These receptors are a group of transmembrane glycoproteins within keratinocytes, which after binding with Fas ligand (Fas-L) initiate apoptosis through caspases [13, 14]. A similar effect is exerted by activation of TNF-R1 and TNF-R2 receptors by tumour necrosis factor, a high concentration of which is found in blister fluid in TEN patients [15]. A still different mechanism, described in 1997 by Inach et al., [16] is related to the process of protein release from T lymphocytes (in high concentrations causing necrosis and in low concentrations apoptosis) [17].

At present there is no uniform therapeutic strategy for TEN. The necessity of hospitalisation in intensive care units or in a burn centre has been emphasized because of the appropriate conditions they provide, as well as of possible specialist consultation of a dermatologist, ophthalmologist, pulmonologist, gastrologist, plastic surgeon, gynaecologist, or urologist [18].

Within the range of symptomatic treatment the role of infusion fluids, parenteral nutrition, infection prevention, guided antibiotic therapy, respirator ventilation, and treatment of complications has been indicated. Causal treatment consists in: introduction of cyclosporin, intravenous immune globulin, TNF-α inhibitors, plasmapheresis. Administration of corticosteroids is considered as controversial and according to some authors it is effective only within the first 72 h from the appearance of symptoms of epidermal lesions. However, individual authors are not in agreement in this matter. There have also been described attempts of administration of anti-TNF-α monoclonal antibodies (infliximab) and pentoxyphyllin, but verification of these reports is necessary. ACC is effectively used in the therapy [19-23].

In this manuscript we present a case of a 59-year-old patient with cefaclor-induced severe clinical course of TEN syndrome.

Case report

This 59-year-old woman was brought in an ambulance to the Department of Anaesthesiology and Intensive Care Unit, Bolesław Szarecki University Hospital No. 5 in Łódź with symptoms of epidermal necrolysis. The patient was referred from the Department of Dermatology of the Medical University in Łódź, where the patient was suspected of Lyell's syndrome.

The patient presented with a 5-day history of upper airways infection with fever. A family doctor prescribed her cefaclor (Ceclor MR 500 mg) for 5 subsequent days (every 12 h). The patient's condition deteriorated. Fever continued, followed by itching and burning rash, first purpuric, then blistering. Finally, typical signs of epidermis exfoliation developed. Based on the clinical picture Lyell's syndrome was diagnosed. The history revealed allergy to penicillin and metamizole sodium (Pyralgin). The patient had been treated due to endogenous depression for over 30 years (drugs administered: amitriptyline, chlorprothixene and periodically Relanium).

On admission to the ICU her general condition was evaluated as severe, extensive epidermal exfoliation with surface bleeding in the area of the trunk, buttocks, upper and lower limbs, oral cavity mucosa maroon-red with exfoliation foci. Nikolsky's sign was positive. The patient was conscious, on respiratory efficiency limit, and presented labile circulation. In the ICU the patient required multidirectional treatment: application of passive oxygen therapy, balancing fluid/

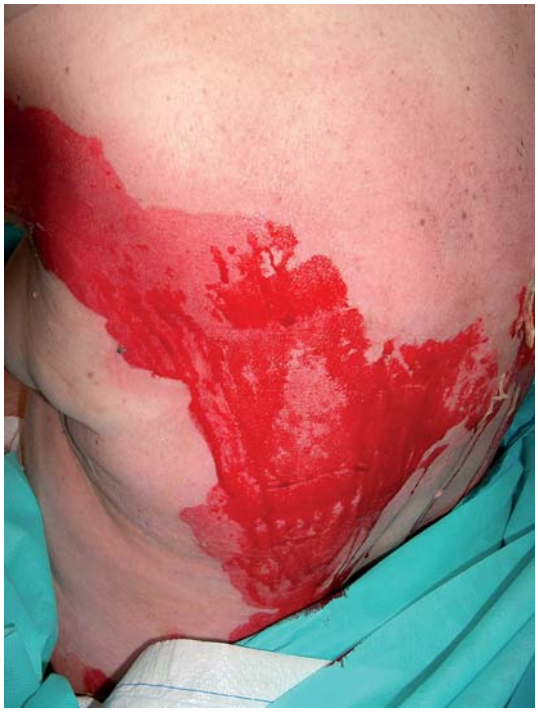

Figure 1. Symptoms of epidermis necrolysis in patient immediately after admission to ICU

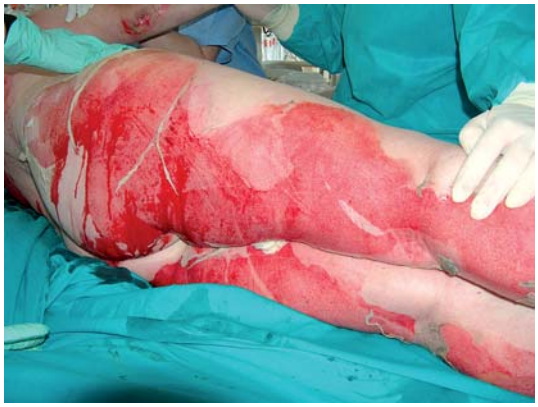

Figure 2. Symptoms of epidermis necrolysis in patient immediately after admission to ICU

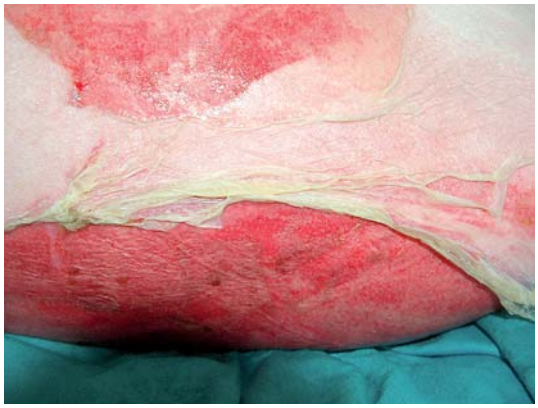

Figure 3. Symptoms of epidermis necrolysis in patient immediately after admission to ICU

electrolyte disturbances, antibiotic therapy. Already on the first day of hospitalisation clinical and laboratory symptoms of renal dysfunction were observed and mannitol and furosemide were administered to force diuresis. After dermatological consultation symptomatic immunosuppressive treatment was introduced (cyclophosphamide – Endoxan, dexamethasone) as well as local treatment.

Despite intensive treatment the patient's condition deteriorated gradually. On the 7th day of the therapy due to increasing symptoms of respiratory failure substitutive ventilation was applied. The patient required high concentrations of oxygen in respiratory mixture. Due to continued hypotension, despite balanced volaemia, catecholamine infusion was introduced. The patient required transfusion because of blood loss from the areas of exfoliated epidermis. Owing to local treatment (daily control of lesions, hydrogel dressings, Solcoseryl) the areas of necrotic epidermis gradually healed (the course of the healing process is demonstrated in Figures 1-5). Broncho-fibroscopy showed bleeding sites and airways mucosa erosions. Due to periodic bronchial obstruction caused by clots and necrotic epithelium the patient required repeated bronchofibroscopic toilet of the bronchial tree. Despite the applied treatment the symptoms of pneumonia continued. Moreover, bleeding from digestive and reproductive systems occurred, which led to significant anaemia.

On the 22nd day of hospitalisation transcutaneous tracheostomy was inserted. Two weeks later tracheo-oesophageal fistula was detected on gastrofibroscopy. The prosthesis was applied in the upper part of the oesophagus. On the 52nd day pleural drainage was performed due to right-side pneumothorax. During therapy the patient's state oscillated, the parameters of mechanical ventilation were modified, the circulatory system was stabilised, antibiotic therapy was modified according to the results of the obtained antibiograms, and homeostasis was maintained. Parenteral and intra-intestinal nutrition was used. Despite healing of the areas of exfoliated epidermis and mucosal epithelium the symptoms of multiorgan failure increased gradually. In consequence the patient died after 2-month treatment in the ICU. Lyell's syndrome was diagnosed as the initial cause of death and multiorgan failure as the direct cause.

Discussion

Toxic epidermal necrolysis is a severe life-threatening pathological syndrome induced by allergic reaction to drugs and/or their metabolites, which as haptens after binding with protein are able to evoke an immune response [24].

An adverse effect of a therapeutic product is each unbeneficial and unintentional effect

of a therapeutic product occurring during application of doses recommended for humans for prophylactic, diagnostic or therapeutic purposes or for modification of physiological functions. A severe adverse effect, meanwhile, is an effect which regardless of the applied dose of a therapeutic product causes the patient's death, threat to life, necessity of hospitalisation or its prolongation, or permanent or severe damage to health. The frequency of occurrence of drug-induced adverse effects is estimated to be about 15-30% of hospitalised patients. Moreover, drugs dependently on the investigated population are the cause of the patients' referral to hospital units from 0.2 to 29.3% [25]. Ulceration and bleeding from the digestive tract, hepatocellular damage, renal failure and anaphylactic shock are the most frequently reported causes of death due to drug-induced adverse effects [26].

In the presented case of epidermal necrolysis there was a direct time relation between the onset of the disease and the administration of an antibiotic from the cephalosporins group – Ceclor MR. As is known, drugs from this group are burdened with high risk of TEN occurrence. Thus, a question arises whether the phenomenon of allergic cross reaction was not the base of such extensive skin lesions in a patient allergic to penicillin in the history.

So far, only antigenic determinants of penicillins have been recognised more closely, which enabled the application of skin and laboratory tests in the detection of the presence of specific IgE antibodies [27]. The main antigenic determinant is used in skin tests which allows only 80% of cases of allergy to penicillin to be detected and thus despite the test performance there is a risk of allergic reaction including anaphylactic shock. Specific immune response to an antigen is a condition for the occurrence of allergic reaction. β-lactam antibiotics are known haptens. Unstable β-lactam ring fused to thiazolidine ring (penicillin) or to dihydrothiazine ring (cephalosporins) is the common feature of their structure. The double ring structure typical for penicillin and cephalosporins is associated with cross reactions. Allergy to penicillin is a risk factor of allergy to cephalosporin. It has been estimated that skin reactions from urticaria to serum disease, cytopenia, or severe skin reactions like Lyell's syndrome are observed in as many as 1-3% of patients treated with cephalosporins [19]. Real allergic reactions to antibiotics are only a small part of reported cases. Allergy to penicillin is diagnosed too often, which leads to unjustified exclusion of other β-lactams from the therapy. It seems obvious that a general practitioner does not always undertake laborious or not always possible (lack of standards) diagnostics of allergy to antibiotics and in the case of any suspicion of an allergic reaction to penicillin eliminates lactams from the therapy. This alarming phenomenon has been proved by the result of a study which reports that the most frequently applied substitutive antibiotics are more expensive and more toxic: erythromycin, quinolones, vancomycin [28]. In a few retrospective studies the frequency of occurrence of cephalosporin-induced allergic reactions in subjects with positive history of allergy to penicillin was estimated to be 4 to 8 times higher than in subjects with negative history of hypersensitivity [29, 30]. The question of whether subjects allergic to penicillin can be treated with cephalosporins is a practical issue. With the current state of knowledge it is difficult to answer this question explicitly. It is only known that in the case of positive history of hypersensitivity to penicillin the risk of cephalosporin-induced allergic reaction increases several-fold. However, it is important to remember that with negative history of allergy to penicillin the development of de novo reaction to cephalosporin cannot be excluded.

Observation and reporting side effects of drugs is of importance out of concern for the safety

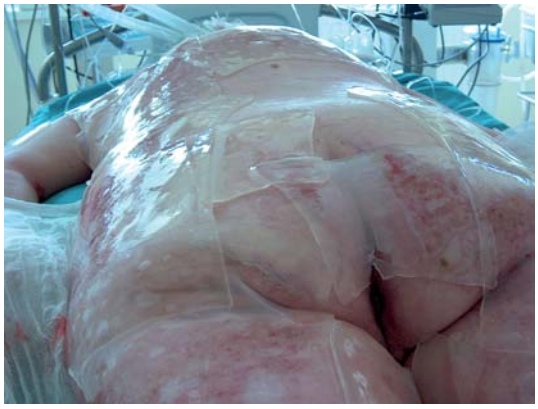

Figure 4. Lyell's syndrome. Patient in the course of treatment. Two weeks after admission to ICU

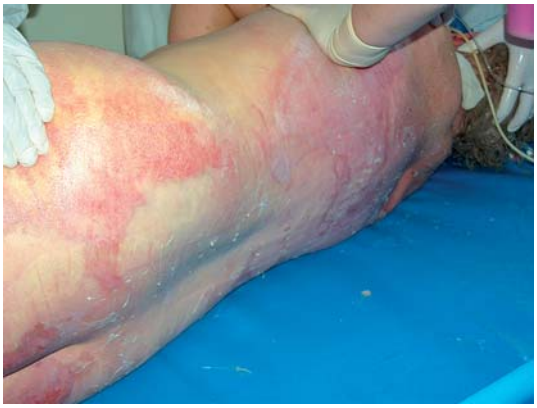

Figure 5. Lyell's syndrome. Patient in the course of treatment. Three weeks after admission to ICU

of patients. In the case of the drug-induced Lyell's syndrome presented in this paper, a protocol was made reporting the adverse effect of a therapeutic product addressed to the Therapeutic Medicinal and Biocidal Registration Office. The protocol included the symptoms which occurred in the patient and all drugs administered prior to the symptoms. An answer was received. The reported case appeared to be particularly valuable because it presented an extremely rare complication: since 1968 only 26 reports have been registered in the World Health Organisation database concerning epidermal necrolysis after cefaclor. The symptoms of Lyell's syndrome which appeared after the applied antibiotic therapy imposed the therapy design within the first few days. It was the same as in the case of patients with IIA degree burns. Intensive fluid therapy predominates with standard guidelines considering the distribution of intravenously administered fluids with the division into hours and volume proportions between colloids and crystalloids. Symptomatic treatment was introduced, while immunosuppressive and organ complications required systemic treatment. The application of local treatment on the surfaces of raw areas of exposed epidermis is an important element of the therapy. Even extensive (100% TBSA) surfaces of epidermal necrolysis can be treated locally by decreasing fluid loss. Hydrogels, collagen dressings and skin substitutes are used [31]. In the case of the described patient a modern method was applied with the use of hydrogel dressings. Their effectiveness has been confirmed in many reports. This type of therapy has found wide application in routine medical practice since the moment of Winter's estimation of the effect of dressings maintaining moisture on the rate of epithelization processes. In recent years much attention has been devoted to studies on the development of hydrogel polymers with the possibility of their application as moistened dressings on wounds. The treatment with a hydrogel dressing under which a moist wound bed is formed has many advantages as compared to traditional gauze dressings. The process of healing is stimulated, they are changed painlessly and fragments of material difficult to remove are prevented from remaining on the wound [32-34]. Moreover, hydrogels inhibit water vaporization from the structure and they themselves are a medium for bacteria which passing from the wound to the gel are stopped in their structures. Furthermore, they protect against excessive loss of systemic fluids, form a barrier against infection, alleviate pain, do not stick to the wound and do not make the exchange of new tissue difficult. They are non-allergizing, and easy to produce and to use [33-35]. Their primary application was to remove necrotic tissues from the wound by donating moisture and initiating autolysis [34, 35]. The loss of water from hydrogel during continuous vaporization is supplemented by wound exudate, and polymer dressing preserves gel consistency. Moreover, the gel structure enables oxygen supply to a wound, facilitates cell regeneration and prevents development of dangerous anaerobes. The use of hydrogel dressings in the local treatment of the patient resulted in faster epithelization of the skin surface and, associated with it, decreased fluid loss through skin layers.

According to the available literature, a very high mortality rate concerns patients in whom symptoms of respiratory failure occurred and substitutive ventilation was necessary [36-39]. Taking into account the level of intensification of skin lesions and accompanying multiorgan dysfunction already in the first few days of the treatment, the prognostication was burdened in this patient with very high risk. Unfortunately the death of the patient presented in this report becomes a part of the unfavourable statistics.

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