A CASE OF TOXIC EPIDERMAL NECROLYSIS (TEN) WITH SEVERE CHRONIC OCULAR COMPLICATIONS IN A HEALTHY 46-YEAR-OLD WOMAN

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SUMMARY. Toxic epidermal necrolysis (TEN), also known as Lyell’s syndrome, is a severe drug reaction characterized by extensive destruction of the epidermis and mucosal epithelia. The eyes are typically involved in TEN. The precise pathomechanisms involved remain unknown. We present a case of toxic epidermal necrolysis in a healthy 46-yr-old female patient who had inhaled glyphosate (herbicide) and was treated with paracetamol, aspirin, and chlorpheniramine. Thirty-five per cent of the skin area was affected by the syndrome, with involvement of conjunctival, gastrointestinal, and respiratory mucous membranes. Topical treatment was performed every day and the patient did not undergo surgery. Complete wound healing was achieved in 47 days. There were acute complications, consisting of infection of the skin areas (Candida), gastrointestinal bleeding, pleural effusion, and severe ocular mucous membrane damage. The most serious chronic complication was the presence of significant opacity of the corneal epithelium, causing almost complete loss of vision. According to the data in the literature, ocular complications in TEN are frequent and are present in the majority of the patients studied, but are not often severe. Risk factors for the development of ocular complications are not known. Ocular sequelae may appear after the acute period and they can be extremely disabling, even causing almost complete loss of vision. Treatment includes corticosteroids and topical antibiotic therapy in the acute phase and if necessary corneal transplantation in the event of chronic damage to the corneal epithelium.

Keywords: toxic epidermal necrolysis, severe ocular involvement, chronic complication

Introduction

Toxic epidermal necrolysis (TEN), also known as Lyell’s syndrome, is a severe adverse drug reaction characterized by extensive destruction of the epidermis and mucosal epithelia. This entity was first described by Lyell in 1956, who termed the condition “toxic epidermal necrolysis”, pointing out that drug sensitization was generally considered to be the mechanism leading to this syndrome. Although the incidence of TEN is very low, i.e. approximately 1 to 6 cases per million persons, it can affect anyone at any time at any age, usually as a consequence of an adverse idiosyncratic drug reaction.

The mortality rate for TEN is still high (approximately 25-35%), mainly due to secondary sepsicaemia and ionic and metabolic disturbances following loss of epidermal integrity.

Drugs appear to be the predominant causative agent, particularly antibacterials, anticonvulsivants, and nonsteroidal anti-inflammatory agents. More than 220 medications have been implicated, of which a few are those most commonly involved.

The generally proven cause of TEN is an adverse drug reaction resulting from a specific formation of toxic drug metabolite, perhaps in the skin itself. Reactive metabolites generated from cutaneous sources can exert a direct cytotoxic effect. They also stimulate stress signals promoting the cell surface expression of stress molecules, as well as the release of cytokines and the expression of adhesion molecules initiating lymphocyte and macrophage infiltration and activation.

However, the precise pathomechanisms involved remain unknown. The majority of studies focus on the role of T cells, but recently, there is growing evidence that in the pathogenetic scenario of TEN, T cells, particularly CD4+ in the dermis and CD8+ in the epidermis, monocytes, macrophages, and keratinocytes play different important roles directly or with the mediation of cytokines.

Dysregulation of the tumour necrosis factor (TNFα)
system is also likely to be involved in TEN pathogenesis. Functional studies showed that Fas-L was typically active on keratinocytes in TEN. The expression of Fas-L on human keratinocytes is upregulated by cytokines including IL-1β, IL-15, IFN-γ, and TNF-α released by keratinocytes themselves and also by skin-infiltrating immunocompetent cells.10,15,19

The eyes are typically involved in TEN. The ten disease spectrum remains an important cause of severe visual loss in a significant number of patients.20

According to the data in the literature, ocular complications occur in more than 50% of the patients affected, with ocular surface inflammation developing rapidly in the acute stage.6,10,11

The common clinical course after the acute stage includes persistent epithelial defects, ulceration, and perforation, finally developing into corneal cicatricial changes such as neovascularization, opacification, keratinization, and symblepharon.6,22,23

Even when the acute stage impairments subside, permanent visual impairment or blindness remains and conjunctival inflammation becomes chronic.

After the acute period, ocular sequelae may appear. These are not rare but only a few outcome studies have been published. About 40% of survivors of TEN have residual potentially disabling lesions that in some cases cause blindness.11,15,17

Case report

An otherwise healthy 46-yr-old woman was admitted to Padua Burns Unit (Italy) with the following history. A few hours after exposure to a glycolphosphate herbicide she developed the sensation of slight sore throat together with conjunctival hyperaemia, eyelid oedema, lacrimation, and fever. During the night she took a drug based on acetylsalicylic acid, paracetamol, and chlorpheniramine, with scarce relief. The following morning, noticing aggravation of her symptoms and an itchy skin rash in her the face and trunk, she went immediately to the nearest hospital. She was first treated with corticosteroids, antihistamines, and liquid infusion with mild relief and she returned home. After worsening of symptomatology and increasing of fever (>38 °C), she was hospitalized in an intensive care unit and vigorous antibiotic therapy was set up. She was assessed by a specialist dermatologist and otorhinolaryngologist for multiple lesions of the skin and mucosal epithelia of the respiratory tract and, in the end, a diagnosis of toxic epidermal necrolysis was confirmed.

Three days after the onset of her symptoms, the woman was admitted to our burns unit and all general and topical measures were established.

When the patient was admitted to the burns unit, 35% of the skin area was affected by the syndrome, with in-
The patient was immediately positioned on an air-fluidized therapy unit. Drugs suspected of being inciting agents were immediately discontinued. Intravenous replacement of fluid losses, administration of high-title IgM enriched intravenous immunoglobulin (Pentaglobin®) at a dosage of 0.2g/kg daily for three days, and enteral nutrition were initiated. Antibacterials were administered on the basis of the results of microbiological exams performed on blood, urine, and skin lesions. A blood culture taken on day 14 after admission resulted positive for Staphylococcus Warneri and Staphylococcus saprophyticus and treatment with gentamicin, vancomycin, and piperacillin was established (after consulting an infectious diseases specialist). Microbiological tests performed on skin lesion serum resulted once positive for Escherichia coli.

Topical treatment was performed every day and the patient did not undergo surgery. Medical dressing was performed by washing with saline solution, application of paraffin gauze on eroded skin areas, and ointment with oils and vitamin E preparations. Dressings were changed daily. We preferred not to use aggressive agents such as silver sulphadiazine, clorhexidine, or other topical antimicrobial agents. We did not use skin substitutes (keratinocytes, homografts, xenografts, etc.).

Fig. 4 - Typical lesions on right arm.

Fig. 5 - Maximum involvement of face, four days after admission.

Fig. 6 - Positive Nikolsky sign on patient’s back. The skin appeared to have suffered a second-degree burn.

volvement of conjunctival, gastrointestinal, and respiratory mucous membranes.

Flaccid bullae developed on the patient’s trunk, face, and upper and lower limbs (Figs. 1-5). These lesions exhibited a positive Nikolsky sign with spreading of the bullae on pressure. The patient’s skin took on the appearance of a second-degree scald (Fig. 6).
A skin biopsy was taken and histological tests confirmed the diagnosis of TEN. A cytological examination of the serum of the lesions showed the presence of typical inflammatory cells such as macrophages and lymphocytes. On admission of the patient we had already carried out toxic investigations in haematics, which were positive for paracetamol and chlorpheniramine but not for alcohol or other drugs.

Respiratory mucous membrane involvement was confirmed by bronchoscopy, which revealed acute inflammation of the upper respiratory tract, with moderate bleeding of mucous membranes, while the trachea and bronchial tube, in the tract visible with endoscopy, were open.

The patient soon started assisted physiokinesitherapy in the upper and lower limbs and to both eyelids in order to prevent symblepharon.

Three weeks after the onset of the symptoms, skin re-epithelialization of the face and anterior part of the trunk was almost complete (Figs. 7, 8) and wound healing of the back was beginning (Fig. 9).

Anamnestic. The patient, a healthy housewife, married with two healthy children, did not report any previous pathology or allergy, she had never undergone surgery, and she was not receiving any home pharmacological therapy at the time of admission.

Ocular involvement. The first examination of the eyes by a specialist oculist on admission found the presence of copious conjunctival secretions and disepithelialization of the borders of the eyelids, while the corneal epithelium was still in good condition (Fig. 10). Artificial tear replacement to prevent keratoconjunctivitis sicca syndrome and daily washing with saline solution were initiated.

Six days after hospitalization, the patient developed conjunctival synechiae with partial corneal disepithelialization in both eyes and was therefore treated daily with washing with saline solution, debridement of the fornices with a sterile spatula, and topical antibiotic therapy.
Fifteen days after the onset of the symptoms corneal opacity occurred. Five days later, a diagnosis was made of bilateral corneal leucoma (Fig. 11).

The final examination by an oculist found severe ocular impairment, conjunctival synechiae still present, and bilateral neovascularized corneal opacity.

**Fever pattern.** From admission, and for 24 days, the patient had high fever, with a temperature of over 39 °C and peaks above 40 °C. The fever abated on day 24, and all antibiotics were stopped, the patient being treated only with fluconazole for *Candida esophagitis* with a good response. On the following days the patient was feverless and remained so until she was discharged.

**Acute complications.** Ocular damage was the first acute complication the patient developed, followed by *Candida esophagitis*, gastrointestinal bleeding, and pleural effusion.

**Chronic complications.** Complete wound healing was achieved in 47 days. The most serious chronic complication was significant opacity of the corneal epithelium, which caused almost complete loss of vision. The patient is now waiting to undergo surgery for corneal membrane transplantation.

**Discussion**

Toxic epidermal necrolysis is a rare but potentially fatal skin disorder. Even if much has been learned in the last fifty years about the management of TEN, the difficulty of making a prompt and accurate diagnosis at the onset of the disease and the controversy about a treatment regimen that could be universally accepted represent an important limitation on the correct approach to this severe pathology.

TEN is a severe adverse drug reaction, characterized by low incidence but high mortality (25-50%). Elderly patients and patients with extensive lesions have a higher mortality rate. Septicaemia is the commonest cause of death in patients, usually due to *Staphylococcus aureus* or *Pseudomonas aeruginosa*. TEN is heralded by a prodromal phase (48-72 h) progressing into the acute phase.

A typical feature of TEN is epidermolysis, characterized by the presence of flaccid bullae formed by the necrosis of epidermal cells, determining a positive Nikolsky sign.

After the acute phase, cutaneous and ocular sequelae may appear. According to the data in the literature, ocular complications in TEN are frequent and are present in the majority of the patients studied. They result in entropion, symblepharon, and synechiae.

The skin lesions usually completely heal in 4 to 10 weeks, but up to 40% of survivors have residual potentially disabling lesion that may cause blindness. However, the exact percentage of blindness as a chronic complication among the population of survivors is unknown.

The pathomechanism that leads to severe ocular complications has been variously hypothesized. Some reports maintain that the loss of corneal epithelial stem cells located in the limbal region plays an important role in the pathophysiological mechanism of the ocular damage. When the corneal epithelial stem cells are lost, the corneal epithelium no longer regenerates, resulting in conjunctival epithelial invasion into the cornea (conjunctivalization) and cicatricial changes in the ocular surface. It is also believed that severe and prolonged acute ocular inflammation promotes the development of late ocular complications. A continued inflammatory reaction involving the ocular surface destroys goblet cells and results in decreased secretion of mucin, which impairs tear distribution and stability. Cicatrization may lead to dry eye, corneal opacification, and eyelid deformities.

The risk factors for the development of ocular complications are not known. Early ophthalmological consultation is recommended for ocular lesions.

Treatment must be prompt and accurate to prevent severe complications - it includes general and local measures. The patient is usually admitted to a burns unit and treated with systemic corticosteroids, although the benefits of this are controversial. The patient should be placed in a warm environment, avoiding any skin trauma. Supportive therapies and antiseptics used in burn patients are similarly applied to TEN patients.

General measures include control of fluid and electrolyte balance, nutritional support, and close monitoring to detect any signs of internal organ failure and systemic
infection. Antibacterials should be administered only in case of infection. Local measures for skin involvement include dressings for wound coverage, performed every day in order to prevent infectious sequelae.

In patients affected by this syndrome, skin loss is usually superficial and spontaneous re-epithelialization occurs in a few weeks. However, it has been suggested that surgical treatment should be performed with skin allografts to prevent infection and protein/fluid loss and provide immediate pain relief. However, it has also been found that keratinocyte allografts offered no improvement in re-epithelialization and did not prevent abnormal scarring.

Local measures for ocular involvement include corticosteroids and topical antibiotic therapy in the acute phase and if necessary corneal transplantation for chronic damage to the corneal epithelium.

It is universally accepted that as long-term ophthalmic sequelae can be catastrophic, early recognition and therapy of this acute oculocutaneous disease spectrum are critically important.

Local measures should be instituted at the very onset of ocular involvement. First, tear replacement and frequent irrigation of the conjunctival fornices have to be performed with a preservative-free solution. The superior and inferior fornices must be debrided daily in order to remove membranes. Despite early local measures, late surgical therapy is often required to correct structural defects such as symblepharon, entropion, ectropion, and lagophthalmos.

The outcome of TEN, not only as regards the eyes, is in all cases difficult to predict because it depends on age, co-morbidity, and the extent of skin involvement.

**Conclusion**

As in the literature and in our own experience, the majority of patients affected by TEN suffer acute ocular complications. Between 2000 and 2008, 26 patients (17 female, 9 male) were admitted to our burns unit with a confirmed diagnosis of TEN. Of these, nineteen (73%) developed acute ocular complications but no chronic sequelae.

To our knowledge, in our burns unit, the patient described in this paper is the first reported case of TEN among all the patients affected by the syndrome presenting severe ocular complications, with almost complete loss of vision. Given the limited data in the literature, mainly due to the syndrome’s rarity, we think it is important to publicize the individual experiences of various burns units as a way of improving our knowledge of this severe pathology.

We decided to present this case because of the particular manner of the onset of the disease (exposure to herbicide and drugs) and because of the severe damage to the corneal epithelium, which was the worst chronic complication.

While the importance of a prompt and accurate diagnosis and of correct and rapid therapy to prevent severe chronic complications is generally known, the pathological mechanism that causes the progression from acute to chronic lesions is still unknown.

We are convinced of the need to increase as much as possible the amount of information available in the literature about toxic epidermal necrolysis if we are to improve diagnosis and therapy, together with help and suggestions from the experience of others.

RÉSUMÉ. Le syndrome de Lyell, également appelé l’épidermolyse nécrosante suraiguë, est une grave réaction pharmacologique caractérisée par la destruction étendue de l’épiderme et des épithéliums muqueux. Les yeux sont généralement atteints. Les mécanismes pathologiques précis impliqués restent inconnus. Nous présentons un cas du syndrome de Lyell chez une patiente saine de 46 ans qui avait inhalé glyco phosphate (herbicide) et a été traitée avec paracétamol, aspirine, et chlorphéniramine. Trente-cinq pour cent de la surface cutanée a été atteinte par le syndrome, avec l’implication des membranes muqueuses conjonctivales, gastro-intestinales et respiratoires. Un traitement topique a été administré tous les jours et la patiente n’a pas été opérée. La guérison complète des lésions a été obtenue après 47 jours. Nous avons observé des complications aiguës, c’est-à-dire infection des surfaces cutanées (Candida), hémorragie gastro-intestinale, effusion pleurale, et de graves dommages aux membranes muqueuses oculaires. La complication chronique la plus grave a été la présence d’une opacité importante de l’épithélium cornéen, qui a provoqué la perte presque complète de la vue. Selon les données de la littérature, les complications oculaires sont fréquentes dans les cas de syndrome de Lyell et sont présentes dans la majorité des patients étudiés, mais elles ne sont pas souvent très graves. Les facteurs de risque qui portent au développement des complications oculaires ne sont pas connus. Les séquelles oculaires peuvent se manifes ter après la période aiguë et peuvent être extrêmement invalidantes, causant même la perte presque complète de la vue. Le traitement comprend les corticostéroïdes et la thérapie antibiotique topique dans la phase aiguë et, si nécessaire, la transplantation cor neenne en cas de dommages chroniques de l’épithélium cornéen.

Mots-clés: syndrome de Lyell, atteinte oculaire sévère, complication chronique
BIBLIOGRAPHY


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