TOXIC EPIDERMAL NECROLYSIS - LYELL'S SYNDROME

Cabral L., Riobom F., Diogo C., Teles L., Cruzeiro C.

Plastic Surgery and Burns Unit Department, Hospitais da Universidade de Coimbra, Coimbra, Portugal

SUMMARY. Toxic epidermal necrolysis (Lyell's syndrome) is a rare but very serious dermatological lesion characterized by the sudden onset of high fever, signs of systemic toxicity, and intense mucocutaneous exfoliation. Its pathophysiology is not yet well determined, although the presence of an immunological basis is almost consensual. It usually appears as a response to the taking of a drug and, in spite of being self-limited in the absence of complications, it is associated if not well managed with high morbidity and high mortality due in most cases to the development of sepsis. The main treatment is the immediate suspension of the inducing drug and early admission of the patient to a hospital facility which is capable of providing intensive support care and minimizing the risk of infection and which also offers conditions for the performance of surgical debridement and the covering of the affected areas, i.e. a burns unit. Several therapeutic measures designed to lower the morbidity and mortality of this syndrome are in the course of study, including the use of plasmapheresis, the administration of high doses of N-acetylcysteine, immunosuppression, and hyperbaric oxygen. The treatment protocol in use at the Coimbra Burns Unit in Portugal is presented and illustrated with three clinical cases from the Unit.

Introduction

Toxic epidermal necrolysis (TEN), also known as Lyell’s syndrome, is a rare but extremely serious nosological entity characterized by high fever, systemic toxicity symptoms, and extensive mucocutaneous exfoliation. It usually occurs in response to certain drugs and accounts for approximately 1% of all hospitalizations due to adverse drug reactions. Some apparently idiopathic cases have been described and can occur as a graft-versus-host reaction.

Although previously described by various researchers, TEN was first made known in the medical literature through the works of Alan Lyell, whose first article, a classic of its genre, was published in 1956 in the British Journal of Dermatology. In that article, the word “necrolysis” was proposed to describe the isolated necrosis of the epidermal layer of the skin and its detachment from the underlying dermis, where there are practically none of the inflammatory changes usually present in toxic erythema conditions.

TEN can affect both infants and adults, but the onset is more frequent at extreme ages, i.e. before 5 years of age and after 64. Like other drug reactions, it is more common in females, with a female/male ratio of 3:2 or even 2:1. No racial differences have been described.

The incidence of TEN in the general population varies from 1 to 1.3 cases per million people per year. The mortality rate is very high, reaching 25 to 70%, according to different sources. In recent years, many works have demonstrated a reduction in the mortality and morbidity of such patients treated in burns units.
Mucosal lesions usually occur prior to epidermal necrosis and are characterized by erosion and sloughing of conjunctival, oropharyngeal, nasal, oesophageal, urethral, anal, vaginal, and perineal mucosae, showing a special predilection for the stratified pavement epithelium. The extent and location of the lesions is patient-specific, and mainly affects the conjunctival, oropharyngeal, and urethral mucosae. The lesions are very painful - mouth lesions may even impair the patients’ correct rehydration and nutrition, urethral lesions may induce urine retention, and conjunctival lesions frequently result in photophobia. The pain induced by mucosal and skin involvement often determines the administration of opioid analgesics.

During this period, fever remains high even in the absence of infectious complications, which has been attributed to the release of pyrogenic agents by the necrotic epidermal tissue, particularly interleukin-1.

In the absence of complications, the recovery phase generally lasts from one to three weeks, allowing for the re-epithelialization of the skin and mucosae. In TEN, the re-epithelialization process is usually faster than in second-degree burns of similar extent (which is understandable, since the dermal layer is not affected) and is even faster in areas not subject to pressure. The mucosae usually require a longer re-epithelialization period than cutaneous areas. Fever may persist until complete healing, even in the absence of infection.

Complications

Given the development phases mentioned above, TEN can be considered a self-limiting disease which, if without complications, would not have any sequela. However, life-threatening complications are unfortunately the general rule, significantly impairing the patient’s quality of life.

The most serious complication, often fatal, is infection. Sepsis is the main cause of death from TEN, accounting for over 50% of all fatal cases. Loss of the skin barrier through epidermal sloughing allows tissue invasion by exogenous and endogenous organisms. Unlike thermal lesions, in which the dermis is also affected, inducing a transient reduction of local micro-organisms, the dermis remains intact, though susceptible to penetration by micro-organisms that are unaffected by the pathological process and grow freely within exudates and the necrotic epidermis. Cutaneous lesions are first colonized by Staphylococcus aureus, followed by Gram-negative bacteria, particularly Pseudomonas aeruginosa. Patients treated with broad-spectrum antibiotics or corticosteroids may also develop a fungal infection, mostly due to Candida albicans. Disseminated intravascular coagulation may occur following sepsis complications. Patients with central venous access catheters show a higher incidence of bacteraemia and sepsis.

Ocular complications are very frequent, ranging from mild conjunctival hyperaemia to purulent conjunctivitis or even fusion of the eyelids and eyeballs (ankylosymblepharon), leading to total blindness. These complications are induced by the erosion and desquamation of the conjunctiva and by subsequent fibrosis; some cases of corneal and lachrymal system (lachrymal duct atrophy) lesions have been described.

Respiratory disorders are a common finding, leading to the necessity of artificial ventilation in 10-20% of the patients. Numerous factors may account for pulmonary function deterioration, such as shallow respiration due to pain, pulmonary oedema caused by increased alveolar-capillary permeability, and aspiration of debris from sloughing of the oropharyngeal (and, according to some researchers, of the tracheobronchial) mucosa, which may pave the way for bronchitis obliterans and pneumonia or even develop into the adult respiratory distress syndrome.

Digestive tract involvement includes not only oropharyngeal sloughing, as already referred to, but also disseminated erosions at a more distal level, particularly lesions in the oesophageal epithelium, which are similar to peptic oesphagitis and may lead to dysphagia and more rarely to increased gastric bleeding; a case of oesophageal rupture has been described. Intestinal lesions are less frequent and may present as bloody diarrhoea. Although 50% of patients show a moderate increase of liver transaminase levels, approximately 10% may develop real hepatitis.

Haematological disturbances are very common, particularly anaemia, which is usually normocytic and normochromic and may be precipitated by several factors, including erythroblastopenia. Leukopenia is also very common: lymphocytopenia occurs in 90% of all patients owing to a transient depletion of CD4 T-lymphocytes, and neutropenia is observed in 30% of cases, generally associated with the appearance of sepsis, which is an unfavourable prognostic sign. Thrombocytopenia is less frequent and occurs in 15% of patients.

Other less frequent complications have also been described, affecting the patient’s morbidity, such as vaginal or urethral stenosis, transient alopecia, loss of nails and eyebrows, keloid formation, and skin hypopigmentation.

Aetiology

As already said, although some researchers accept that TEN may be idiopathic in origin, most cases present as an idiosyncratic response to the administration of a certain medication or drug, irrespective of dosage.
Among the series of medications described as being capable of causing TEN, those most often involved include sulphonamides (the commonest trigger in adults), accounting for approximately one-third of all cases, anti-epileptic drugs (particularly phenytain, the most frequent agent among children, cariba-mazeptine, and phenobarbital), allopurinol, oral penicillins (ampicillin, amoxicillin), and non-steroidal anti-inflammatory agents with a prolonged half-life (especially those derived from pirazolone or oxicam). Sev-
eral other drugs reported less commonly in the literature range from paracetamol to different antibiotics, antifungal agents, cytostatics, and vaccines. The risks associated with drugs responsible for the onset of TEN are diverse, even among similar drugs. It is also likely that TEN results from a synergic activity between different drugs, or between some drugs and other chemical agents that have been related to the disease, such as pesticides, fumigants, herbs, and food additives.

While some viral infections are thought to facilitate the onset of TEN after the intake of the triggering agents (from upper airway infections to the acquired immune deficiency syndrome), some researchers refer to a frequent association with certain conditions, such as systemic lupus erythematosus, leukaemia, lymphomas, graft-versus-host disease (in which cases the TEN mortality rate reaches 100%), ulcerative colitis, and Crohn's disease. Other researchers suggest a genetic susceptibility associated with certain types of antigenic markers of the HLA system (B12, A29, DR7). While these situations of cell destruction, on a reduction in the N-acetylation capacity of patients with TEN, and on the beneficial effect of plasmapheresis in the management of such patients.

Diagnosis

Apart from the presence of the typical clinical manifestations already mentioned (fever, extensive and painful skin necrolysis resembling wet clothes, a positive Nikolsky's sign, oral and conjunctival sloughing, etc.), the confirmation of a TEN diagnosis includes the performance of a skin biopsy - the histological findings reveal the actual vacuolization of the basement membrane, the formation of subepithelial bullae, and the necrosis of epidermal keratinocytes.

While the analysis of a detached skin section reveals only full-thickness epidermal necrosis, there is an alternative method of examining the base of a blister, the so-called Tzanck preparation, which can reveal the presence of eosinophils and basal cells with a high nucleus/cytoplasm ratio.

Differential diagnosis

Erythema multiforme (EM) and the Stevens-Johnson syndrome (SJS) are two skin disorders that share some of the clinical features of TEN, making it sometimes confusing, or even controversial, to tell them apart, particularly because it is not possible to clearly define their histological differences. Some researchers go so far as to claim that they are not three distinct disorders but instead variants of the same nosological spectrum, with EM as the least serious form of the disease and TEN as the most lethal. Chan et al. proposed some criteria to distinguish the three situations: EM would thus be characterized by...
the presence of localized lesions less than 3 cm wide; it may or may not present as targets and cover less than 20% of the body surface; and there may be an absence of mucosal involvement or the involvement of one single area, with minimum symptomatology. In SJS, the initial lesions, which may or may not be target-shaped, are also less than 3 cm wide but may coalesce and involve between 10 and 20% of the body surface; SJS always includes the involvement of two or more mucosal surfaces and fever may be high. In TEN, the affected area covers at least 20-30% of the body surface, including non-exposed areas, presenting as large bullae over an erythematous base that coalesces in large, easily detachable plaques (over 3 cm wide); fever is high and there is always mucosal involvement.

The skin infection caused by a certain strain of Staphylococcus aureus (phase I, group 71), which is responsible for the release of a specific exotoxin, may resemble scaled skin (staphylococcal scalded skin syndrome [SSSS]); this is sometimes misdiagnosed as TEN, despite being much more benign and showing a low mortality rate (0 to 27%, according to sources). This syndrome is commonest in neonates and children, but rare cases in immunocompromised adults have been reported. Although it has a clinical spectrum ranging from localized bullae to extensive exfoliation, with a frequently positive Nikolsky’s sign, its distinctive feature includes the absence of painful experiences or mucosal involvement. The histological differentiation is also simple: while TEN presents as a total necrosis of the epidermal layer and its detachment from the underlying dermis, SSSS is characterized by a partial epidermal necrosis, with intraepidermal cleavage at granular layer level without reaching keratinocytes - hence the absence of scarring sequelae.

Scarlatiniform rash, which is caused by group A Streptococcus or Staphylococcus aureus, can induce widespread erythema, which is more marked at flexion folds, with possible desquamation of the digital pulps, pharyngitis, and a “strawberry-like” tongue.

Another differential diagnosis to be considered is the toxic shock syndrome caused by Staphylococcus aureus, in which a diffuse erythema is accompanied by desquamation (particularly of the palms and soles), fever, and systemic involvement that develops rapidly into a shock situation. Kawasaki disease (mucocutaneous lymph node syndrome) is a multisystemic disease of unknown etiology that affects children under five years old and results in fever, polymorphic rash skin, conjunctivitis, tongue fissures, and adenopathies, which is why it is sometimes mistaken for TEN.

### Treatment

Considering that the onset of a systemic infection, which is favoured by skin denudation and leukopenia, is the primary cause of death in TEN, the first step towards its management consists in promoting, as early as possible, the hospitalization of patients and their treatment in an intensive care unit where such risks can be duly minimized and where medical and surgical procedures can be undertaken according to the clinical condition. Another issue to be addressed, considering the fact that the patients suffer heat loss through skin affected by epidermal necrosis, resulting in discomfort, stress, and increased metabolism, is the need to provide an environment with the correct humidity level and a warm temperature, between 30 and 32 °C. A burns unit is the setting that best offers these conditions - hence the need to transfer patients as soon as possible, a measure that by itself will reduce mortality.

However, the treatment to be instituted should take into account the existence of some major clinical differences compared to burn patients, namely the involvement of the oropharyngeal mucosa (which interferes with adequate rehydration and nutrition), the more diffuse character of skin lesions (impeding venous access), a stronger systemic expression, and a reduced need for fluid and protein-caloric intake.

On the patient’s admission to a burns unit, a detailed clinical history should be elicited, paying special attention to all information regarding the possibility of recent exposure to drugs or chemicals. It is also necessary to perform a thorough physical examination and to determine the extent of the affected skin area (using standard burn charts to assess burn extent). It is crucial to discontinue non-essential medication, obviously including the drug suspected of having triggered TEN, making a decisive contribution to decreasing mortality. Blood samples should be collected as soon as possible in order to perform haemograms, biochemical tests, and coagulation tests on a daily basis, coupled with a regular collection of specimens for bacteriological analysis (swabs of affected areas; sputum or tracheal aspirate; blood and urine). As said, the diagnosis must be confirmed by skin biopsy and histological examination. For the detection of pulmonary complications it is important to perform regular oxymetries and chest X-rays.

After establishing the percentage of burn surface area and the patient’s body weight, the total amount of fluid required for the replacement of water and electrolytes lost through denuded areas can be determined according to one of the standard formulas applied to burn patients (Parkland, Brooke, etc.); however, as already said, one should always bear in mind that in TEN the amount of fluid required is slightly lower than that estimated for the management of burns involving similar skin areas. Particularly during the acute phase, the fluids should be supplied by
an intravenous route, and peripheral catheters should be inserted in areas not affected by necrodermoly-
sis. In order to minimize the risk of infection, pe-
ripheral catheters should be preferred to central catheters, which should be used only in the most se-
cious cases and for as short a time as possible. The
urinary output will allow monitoring of the effective-
ness of fluid therapy, an acceptable minimum being
30-50 ml/h, as in thermal lesions. Vesicular tubes
should be removed as soon as the patient's condi-
tion improves.

Patients should also be encouraged to use an oral
support for their rehydration and nutrition, although
the presence of ophroryngeal lesions may sometimes
determine the necessity of using a nasogastric feed-
ing tube or even total parenteral nutrition, which in-
creases the risk of infection. The risk of the devel-
oment of stress ulcers determines the prescription of
antacids, although these may increase the risk of
bacterial colonization of the stomach - in such cas-
es, the use of sucralfate may represent a beneficial
alternative.

To prevent microbial colonization of denuded ar-
eas, it is fundamental to isolate the patient, adopt strict
aseptic techniques, perform hydrotherapy and apply
local antiseptic agents, remove crusts from oral and
nasal desquamation, and plan surgery carefully. If a
conservative surgical treatment is selected, hydrother-
apy should be performed on a daily basis (or even
twice a day, according to some researchers), supple-
mented by the application of chlorhexidine or 0.5%
silver nitrate solutions over exfoliated areas dressed
with fat gauze. The use of silver sulphadiazine (Sil-
vedene, Flammazine), silver sulphadiazine in asso-
ciation with cerium nitrate (Flammacerium), and
mafenide acetate (Sulfamylon) is contraindicated in
such patients, not only because they slow down the re-
epithelialization process but basically because sulphanamides are the main causative agent of the
syndrome9,29 and tend to induce leukopenia.29

In terms of surgical treatment, there are two cur-
rent schools of thought concerning the measures to
be adopted. One maintains that the patient should be
promptly taken to the operating room, preferably on
the very first day, for debridement of patches of epi-
dermal necrosis that are loose or easily detachable
(with a positive Nikolsky's sign),9,29,38,49 followed by the
immediate coverage of exposed dermis with skin
xenografts, skin allografts, amniotic membrane, or
synthetic skin substitutes,9,49,52 in order to prevent
its excision and microbial colonization,9,49 preclude sys-
temic invasion, reduce fluid and electrolyte loss, re-
lieve pain, and promote re-epithelialization. The sec-
ond current of thought adopts a more conservative
approach, maintaining that only epidermal patches that
are already loose and wrinkled should be removed,9,49
under intravenous sedation, and that the application
of biological or synthetic skin substitutes is not ne-
cessary for the patient's survival or for effective re-ep-
ithelialization since the dermis is intact; it is thus suf-
cient to maintain aeas of affected areas through
hydrotherapy and daily dressings with topical antibi-
ocics until a new epidermal layer is formed.2,29,47 Sup-
porters of this theory also point out the potential risk
from endotracheal intubation (which is necessary for
general anaesthesia in a broader surgical approach)
in a patient whose general condition is serious, with
easy detachable lesions in the oropharyngeal mucosae,
eventually leading to contamination of the bron-
chotraheal tree and the occurrence of pneumonia.7

The administration of corticosteroids in patients
with TEN, which was initially prescribed given the
fact that autoimmunity was considered one of the
main pathophysiological factors of this syndrome, has
been progressively ruled out since it was demonstrated
that their immunosuppressive activity promoted the
appearance of infectious complications and masked the early signs of a possible septic picture, thus postponing the beginning of treatment with all
the risks that this involved. Their use resulted in a
delay of the healing process and an increased risk of
gastrointestinal haemorrhage. Several researchers
have reported increased mortality in TEN patients
treated with these agents and advocate suspension
of any such therapy.8,9,20 Even those who still believe
that their use may have some advantages,10,54 admit that these are limited to administration in the early
stage of TEN, before desquamative lesions occur.8

The prophylactic use of systemic broad-spec-
trum antibiotics is discouraged in such patients,10,46
unless they present leukopenia.7 In the remaining cas-
es, these agents should be administered on first signs
and symptoms of septic complications (fever or hy-
pothemia, oliguria, change in mental state, paralysed
ileum).29 As soon as the results of the bacteriological
analysis are obtained, it is mandatory to adjust anti-
infecctious therapy according to the results of antibi-
otic sensitivity tests. The presence of systemic fun-
gal lesions (usually candidaemia) may require the ad-
ministration of systemic anti-fungal drugs, and the
use of amphotericin B (liposomal) is generally indi-
cated owing to its reduced toxicity and broad spec-
trum of activity.

The judicious use of analgesics (preferably opi-
ates, because of the frequent association of TEN with
the administration of non-steroid anti-inflammatory
drugs) and tranquillizers is indicated for most patients.
The risk of thrombo-embolic complications requires
the propylactic administration of standard heparin18
or its derivatives of low molecular weight.49

The high rate of ocular complications suggests not
only the hourly administration of an ocular antiseptic
and/or antibiotic solutions to avoid the accumulation
of abrasive crusts over the cornea8 but also daily ob-
servation by an ophthalmologist, who will release any synechiae that may have formed.45,46 Similarly, plaques from oral and nasal desquamation should be carefully removed, prior to the application of a topical antiseptic.

Physiotherapy should be initiated on the first day of hospitalization in order to ascertain joint mobility, since regular respiratory kinesiotherapy may effectively contribute to prevent the appearance of atelectasis and subsequent pneumonia.47

Plasmapheresis seems to be a promising therapeutic approach in the treatment of TEN.58,59 Although it requires a venous access, this is a safe method that provides quick pain relief and rapid cessation of necrosis, thus reducing the period of in-patient hospitalization.58 The removal of the offending drug and/or its metabolites, as also of inflammatory mediators, or even of a potential “necrotic factor”, provides the rationale for its use in these patients.58

N-acetylcysteine, which is frequently used as a mucolytic agent and also in the treatment of paracetamol intoxication, shows effective activity when used in high doses in the treatment of patients with TEN. Its activity is thought to be related to the support of the anti-oxidant capability of cells, through the increase of intracellular levels of cysteine required for the production of glutathione (serving as a buffer to oxidant agents), and/or to the inhibition of the production of cytokines that mediate immunological reactions, such as the tumour necrosis factor-α (TNF-α) and interleukin-1 (IL-1), and of oxygen free radicals.59

Some researchers have proposed Pentoxifylline - usually administered as a haemorrhheologic agent to reduce blood viscosity and improve flow conditions - as another drug to be considered for the treatment of TEN.58,59 In this particular case, its activity would be to interfere with the binding of T-lymphocytes to keratinocytes and also to inhibit the production of cytokines by macrophages and keratinocytes, including TNF-, IL-1, and IL-6.59

Given the similarity between TEN and the acute phase of the graft-versus-host disease both in humans and in animal models,60 and also the immunological changes involved, especially the potential role played by the mechanisms of cellular immunity in skin necroepidermolysis, it is only reasonable to consider the use of immunomodulators in its treatment. Several researchers advocate the use of cyclosporin61,62 because of its ability to inhibit the activity of T-lymphocytes and macrophages, the activity of cytokines such as TNF-α and IL-2, and even the apoptosis of keratinocytes, a mechanism that more than any other is responsible for the death of these cells;62 however, they underline the risk involved in the use of an immunosuppressive drug in patients who are already immunocompromised63,64 and they therefore recommend the administration of low doses over during short periods of time that have not been definitely established.64 Following the same rationale, i.e. the inhibition of cellular immunity and cytokine activity, other researchers defend an alternative that consists of the administration of cyclophosphamide,60 a cytotoxic agent commonly used in the treatment of neoplasia that has the same disadvantages as cyclosporin.

Some researchers recommend the use of granulocyte colony-stimulating factors to overcome neutropenia associated with TEN,61 thus reducing the risk of sepsis.

In the literature, there is also a reference to the treatment of such patients with a few sessions in a hyperbaric oxygen chamber, in view of this technique’s capacity to enhance epidermal regeneration and dermal metabolism, associated with an antiseptic activity and a potential immunosuppressive effect;66 however, the effectiveness of this method has yet to be confirmed.

**Prognosis**

Numerous clinical and laboratory factors are related to poor prognosis in TEN patients. These include the involvement of extensive skin areas, delay in withdrawing non-essential medication, old age, a previously bad general condition, the intake of multiple drugs, the need for many blood transfusions, and the prolonged re-epithelialization time of affected areas (more than 9 days). The results of laboratory tests show that persistent neutropenia is the condition most commonly related to higher mortality, revealing reduced ability to resist infectious agents. There is a very important logistic issue also associated with higher morbidity and mortality, namely delay (more than 48 h) in transferring patients to an intensive care unit with adequate conditions for their management, i.e. a burns unit.64,65

**Treatment protocol for toxic epidermal necrolysis**

Extensive bibliographic analyses and discussion between members of the Clinical Staff at the Burns Unit of Coimbra University Hospitals and colleagues from other medical specialties permitted the adoption of a protocol for the treatment of TEN that is currently being applied and has yielded good results.

* Determination of the clinical history, focusing on:
  a) recent exposure to drugs, pesticides, and “natural” products
  b) factors associated with increased risk of TEN (viral infections, lupus, haematological diseases, inflammatory intestinal disease, graft-versus-host disease, X-ray exposure, etc.)
  c) factors determining bad prognosis (delay in referral to a burns unit, involvement of an
extensive body surface area, persistent neutropenia, changes in renal function, old age, poor nutritional status, intake of multiple drugs, etc.)

* Assessment of affected area on admission, based on standard burn charts used in burn patients

* Implementation of plan of action
  a) withdrawal of all non-essential medication and suspension of administration of corticosteroids
  b) skin biopsy (to confirm clinical diagnosis)
  c) intravenous fluid therapy (based on formulas applied to burn patients and on the control of diuresis, which should be kept within a range of 30 to 50 ml/hr)
  d) daily clinical analyses (complete haemogram, complete biochemical test, coagulation test) and regular (at least twice a week) culture of specimens (skin exudates, blood, urine, sputum or bronchial aspirate, tips of central access catheters) for bacteriological analysis and antibiotic sensitivity tests
  e) chest X-rays and oximetries when the patient's respiratory conditions are unclear (at least twice a week)
  f) prevention of stress ulcers with oral sucralfate or, if not possible, intravenous ranitidine
  g) analgesia with opiates
  h) sedation with benzodiazepines
  i) prophylaxis of deep vein thrombosis via subcutaneous administration of heparin with low molecular weight
  j) prescription of a high protein-caloric diet
  k) prevention of ocular problems through daily observation by an ophthalmologist, who will prescribe appropriate ophthalmic medication (artificial tears, antiseptic solutions, topical antibiotics) and release potential adhesions, whenever necessary
  l) joint and respiratory physiotherapy under the supervision of a physiatrist
  m) oxygen therapy through a cannula, or assisted ventilation according to the patient's clinical condition and blood gas analysis
  n) prevention of microbial colonization of denuded areas by means of:
     1. strict aseptic techniques
     2. daily hydrotherapy under intravenous sedation and with the application of a chlorhexidine solution
     3. removal of plaques from oral and nasal desquamation
     4. early surgery with removal of loose epidermal patches
     5. coverage of denuded areas with skin allografts or synthetic skin substitutes
  o) antibiotherapy, but only in the event of clinical and/or laboratory signs of infection (prophylactic use is contraindicated, except in patients presenting persistent neutropenia), with broad-spectrum antibiotics; the corresponding dosage is adjusted in relation to sensitivity tests
  p) administration of inactivated human plasma and intravenous perfusion of heparin (20,000

---

**Fig. 1a, b, c** - Case 1. Aspect of patient on admission to burns unit.

a. Involvement of ocular and oral mucosae.
b. Thorax involvement, with centripetal distribution of skin lesions.
c. Back involvement, showing epidermal sloughing and typical aspect of "wet clothes".
U.I./day) in the event of a sudden increase of FDP values
q) i.v. administration of high doses of N-acetylcysteine
r) therapeutic plasmapheresis - three sessions on alternate days are usually enough

Clinical cases

We will now describe three clinical cases managed in the burns unit of the Coimbra University Hospitals, demonstrating the usual clinical course of such patients and the application of the treatment protocol described.

Clinical case 1

NSGC, a 16-year-old black female, without any significant clinical history, was admitted to the burns unit of the Coimbra University Hospitals presenting eruptive-desquamative skin lesions spreading all over the body except the feet and covering approximately 46% of its surface. The lesions in the upper and lower limbs and the abdomen resembled small bullae with an erythematous outline, whereas the face (Fig. 1a), thorax (Fig. 1b), dorsum (Fig. 1c), and anterior surface of the knees presented easily detachable plaques, with a positive Nikolsky’s sign. The patient’s oral and ocular mucosae were also affected: she was feverish (peaks above 39 °C) and complained insistently.

According to her clinical history, the patient had been prescribed oral paracetamol five days earlier, following headache complaints. The following day she had presented at the emergency service of a district hospital because of the onset of the first skin lesions, fever, and pruritus; she was then discharged, after being advised to increase the frequency of the administration of paracetamol to 1 g every two h. The worsening of her clinical situation led to her hospitalization at Coimbra Hospital Center, where a diagnosis was made of TEN; she was transferred to the burns unit of the Coimbra University Hospitals on the following day. Considering the potential aetiological implications, it should be added that the patient had a meal at a Chinese restaurant eight days before her admission to the burns unit.

The patient received the routine in-patient hospitalization protocol of our burns unit and, apart from the institution of intravenous fluid therapy, was managed with enoxaparin (20 mg, s.c., in d.; sucralfate (1 g, per os, 6 in d); N-acetylcysteine (200 mg, oral, 3 in d); morphine (5 mg, i.v., when necessary), plus an oxytetracycline ointment applied in the eyes (3 in d). On day 2 in the burns unit, the patient, under intravenous sedation, had a hydrotherapy session with a chlorhexidine solution; she was then forwarded to the operating room for removal of all devitalized, detachable dermal tissue, with the application of a synthetic skin substitute (Omiderm®) in denuded areas. The patient subsequently had several more hydrotherapy sessions (average, three sessions a week), with further application of skin substitutes whenever necessary.

On day 3 the patient continued to be febrile, with leukopenia (4000/mm₃) and increased FDP (3.1 lg/ml), which led to an update of the therapeutic plan to high, intravenous doses of N-acetylcysteine (2 g, 4 in d) and the initiation of antibiotherapy with ceftazidime (1 g, i.v., 3 in d). The presence of coughing and moderate dyspnoea, as well as an oximetry with a pO₂ of 56%, supported the institution of oxygen therapy through a nasal cannula with a flow rate of 8 l per min. The first plasmapheresis session was performed on the same day. On day 4 there was a clinical improvement and the patient was given inactivated fresh plasma. The plasmapheresis session was repeated on day 5. On day 6

Fig. 2a - Case 1. Follow-up at 18 months. Facial hypopigmentation and loss of cilia.

Fig. 2b - Case 1. Follow-up at 18 months. Large hypochromic spots in the thorax and upper limbs.
the patient’s oximetry already showed a pO2 of 100%, although the presence of anaemia (with a haemoglobin level of 9 g/dl) and an FDP value of 3.3 g/ml led to the administration of two erythrocyte units and three units of inactivated fresh plasma. On day 7 improvement of the respiratory condition made it possible to reduce the administration of oxygen to 4 l/min (with final definite suspension on day 22). On day 8 the patient had her final plasmapheresis session, by which time she was already subfebrile, with 8,400 leukocytes/mm3, an FDP value of 1.7 g/ml, and a haemoglobin level of 11.8 g/dl.

The patient’s condition continued to improve favourably and the administration of cef-tazidime and N-acetylcysteine was suspended on day 12. Cutaneous tissue (and the oral mucosa) showed a sustained and relatively quick re-epithelialization, which allowed the patient to be discharged home after 26 days of hospitalization.

During the whole hospitalization period, the patient was followed daily by an ophthalmologist, who performed the debridement of the conjunctival cul-de-sac when necessary.

During regular follow-up visits at the out-patient department of the burns unit, the lesions showed a good evolution, although there were some sequelae. The patient presented slight cutaneous hypochromia in the face (Fig. 2a) and marked hypochromic maculae on the affected areas of the anterior trunk (Fig. 2b), dorsum, and limbs. The existence of small hypertrophic scarring areas on the dorsum (Fig. 2c) conditioned the institution of pressotherapy with a pressure vest. The patient was also advised to perform skin hydration with a fat cream and to use sunscreen.

The patient’s eyes presented slight photophobia and epiphora, as well as a rarefaction of the palpebral cilia without any changes in visual acuity. The patient has since been regularly followed at the ophthalmology department of Coimbra University Hospitals.

Clinical case 2

FGC, a 64-year-old Caucasian male with chronic renal failure, dyslipidaemia, and arterial hypertension (usually managed with irbesartan), was admitted to the burns unit of the Coimbra University Hospitals. The patient presented eruptive-desquamative skin lesions, with a positive Nikolsky's sign covering approximately 45% of the body surface, confluent in large plaques on the face (Fig. 3a), thorax (Fig. 3b), abdomen, upper dorsum, and soles, and resembling small bullae scattered over remaining body areas. As in the previous case, the oral and ocular mucosae were affected and the patient was subfebrile.

Two days before the onset of high fever (39 °C), the patient’s clinical history reported purulent conjunctivitis, odynophagia, vesicular lesions in the oral mucosa, and bullae scattered all over the body, which determined his consultation with a general practitioner and the prescription of an oral, long-acting association of amoxicillin with clavulanic acid - oral nimesulide plus chloramphenicol, both as a collyrium and as an ophthalmic ointment. Since there was no improvement, the patient presented to the local health
care centre the following day and was instructed to suspend the medication that had initially been prescribed and to replace it with clarithromycin, as an oral suspension, oral oxatomide, and oxytetracycline as an ophthalmic ointment. The following morning he was observed by a private doctor owing to the worsening of his lesions, and he was prescribed a combination of ammonia liquor, pentamethylenetetrazol, sodium benzoate, sulphadiazine, and balsamic syrup as an oral suspension, oral promelase, oral doxycycline, and oral rifampicin. Finally, he presented at the emergency room of a general hospital later in the evening, where he was immediately forwarded to the Coimbra University Hospitals with a diagnosis of Stevens-Johnson syndrome/TEN. No relation was found between the onset of TEN symptoms and a probable intake by the patient of suspect drugs.

After the patient's admission to our burns unit, the home medication was suspended and replaced with intravenous fluid therapy: ranitidine (50 mg, i.v., 3 in d); enoxaparin (20 mg, s.c., in d) and chloramphenicol (ophthalmic ointment, 3 in d). On day 2 ranitidine was replaced with sucralfate (1 g, oral, 6 in d) and the chloramphenicol ointment was replaced with oxytetracycline ointment plus N-acetylcysteine (2 g, i.v., 4 in d). On day 3 the patient received hydrotherapy, after which he started presenting fever peaks above 38.5 °C and a high FDP value (18.5 lg/ml), necessitating the administration of inactivated fresh plasma and intravenous perfusion of heparin (20,000 U.I./day) instead of enoxaparin, a regimen that was maintained until 18 February 2002. On day 4 he was taken to the operating room for removal of all detached epidermal tissue. In the post-operative period, the patient had high fever peaks (above 39 °C), and the occurrence of moderate dyspnoea led to the institution of oxygen through a nasal cannula (4 l/min). On the same day the patient underwent his first plasmapheresis session. On day 5 oxygen therapy was suspended; the patient remained subfebrile, the FDP value reached 2.2 lg/ml, and a second plasmapheresis session was performed. On day 6 the patient presented a favourable improvement in his skin lesions (Fig. 4a) and we applied a synthetic skin substitute (Omederm®) to his thorax (Fig. 4b) and dorsum; he also had a third and final plasmapheresis session. On day 12 the high febrile peaks recurred, requiring the institution of empirical intravenous antibiotherapy with ceftazidime, replaced by teicoplanin on day 17, following the outcome of the bacteriological analyses and sensitivity tests, which showed the presence of Staphylococcus aureus susceptible only to teicoplanin and vancomycin. On the same day, the observation session.
of an FDP value of 23.6 mg/ml led to a further administration of inactivated fresh plasma and an intravenous perfusion of heparin, which proceeded until day 23. On day 21 there was a complete re-epithelialization of all body surface areas and the patient was subfebrile. On day 23 his clinical condition was good - he was apyretic, presented a normal FDP value, and all medication was suspended. He was discharged on day 24.

As in the previous case, the patient was closely followed by an ophthalmologist, who performed the lysis of ocular adhesions when necessary.

During follow-up visits at our burns unit outpatient department, a number of skin and ocular sequelae (Fig. 5a) were observed. He now presents marked erythema on the thorax (Fig. 5b) and melanic, dyschromic maculae on the remaining affected areas; his facial erythema is milder, without any dyschromic areas. The patient also presents irregularities in the matrices and nail beds of the hands and feet. He has been advised to perform skin hydration with a fat cream and to use sunscreen.

The patient has been regularly followed at the ophthalmology department of the Coimbra University Hospitals; he suffers from photophobia and xerophthalmia (for which he has been prescribed collyrium and artificial tears), rarefaction of the palpebral cilia and also symblepharon in the lower right eyelid.

Clinical case 3

VAC, a 15-year-old Caucasian male, was admitted to our burns unit presenting eruptive-desquamative skin lesions (Fig. 6a) spreading all over the body, with a mixture of fully developed blisters and target lesions covering approximately 70% of its surface. His body temperature was over 39º C; Nikolsky’s sign was positive and the ocular and oral mucosae were involved, and a diagnosis of TEN was pronounced.

With a previous history of allergic rhinitis, the patient had started with a sore throat eight days before admission, for which he was given 1 g of oral paracetamol. The following day he had high fever and myalgia, and the family doctor prescribed oral azithromycin. A few hours after the first administration he developed a cutaneous rash, and two days later he was given oral ibuprofen, prednisolone (oral and i.v.), and an oral anti-histaminic (oxatomide). The same night he noticed the appearance of blisters on the trunk and he was admitted to a regional hospital, where he stayed until being transferred to the burns unit of the Coimbra University Hospitals owing to the deterioration of his clinical status.

During his hospitalization in the burns unit, the patient was put on standard fluid therapy. He received enoxaparin (20 mg, s.c., in d), sucralfate (1 g, oral, 6 in d), N-acetylcysteine (2 g, i.v., 4 in d), ceftazidime (1 g, i.v., 2 in d), morphine, i.v. perfusion of 2 mg/h, and inactivated fresh plasma (average of 3 units per day from day 5 to day 14), as well as cycloplegedol solution and oxytetracycline ointment applied on the eyes (monitored daily by an ophthalmologist). On day 2 all devitalized, detachable dermal tissue was removed, and the patient received daily hydrotherapy until the end of his stay. Also on day 2 he underwent a first session of plasmapheresis, and a second session on day 4. When mild anaemia developed (9.0 g/dl) on day 7, the patient was given two units of whole blood. Microbiological cultures from skin and body fluids were consistently negative.

After day 9, the patient’s temperature dropped to below 38.5 ºC, and he became apyretic on day 11; the value of the leukocytes varied from a maximum of 15900/mm³ on day 3 to a minimum of 5300/mm³.
on day 13. The FDP value fell from a peak of 5.2 μg/ml to a minimum of 2.4 μg/ml on day 13. The re-epithelialization of the denuded areas was very quick and the patient was discharged on day 16. He has been followed up at the burns unit outpatient department. Three months post-discharge his face has a normal appearance, without any ocular sequelae, while there are some zones of mild cutaneous hypochromia on the anterior trunk (Fig. S6), dorsum, and limbs. The patient has no functional limitations, and has been advised to perform skin hydration with a fat cream and to use sunscreen.

**Conclusion**

The high mortality and morbidity associated with TEN make it necessary to familiarize all physicians with this syndrome, in particular those practising in health care centres and county and district hospitals, given the high risk arising from late diagnosis and therapy. In all cases presenting with erythematous or bullous eruptions associated with drug intake, this differential diagnosis should be excluded systematically and at an early point in time. Prompt referral to hospitals possessing a burns unit should be routine practice in suspect cases. The early suspension of all non-essential medication is crucial and this may alter the prognosis. The patients should be regarded as burn patients, and the new treatment procedures described here present promising signs and should be carefully considered and implemented, whenever possible, in patients with TEN. The existence in specialized units of a treatment protocol, which is certainly incomplete and constantly being updated, ensures a minimum standard that is fundamental to enable patients to receive adequate care and, simultaneously, to allow comparison of the results obtained.

**BIBLIOGRAPHY**


This paper was received on 2 December 2003.

Address correspondence to: Dr Luis Cabral, Unidade de Queimados, Hospital da Universidade de Coimbra, Av. Bissaya Barreto, 3000-075 Coimbra, Portugal. Tel: 351 239400669, fax: 351 239482061; e-mail: jlacabra@hotmail.com