Phenytoin-induced Lyell's syndrome

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SUMMARY

Lyell's syndrome or toxic epidermal necrolysis (TEN) is a rare dermatological disease that causes serious morbidity and mortality. It is most commonly drug induced. The authors report the case of a 57-year-old woman who was admitted to our hospital with severe rash all over the body. She had been previously submitted to brain surgery for total resection of a large meningioma and medicated with phenytoin for seizures prophylaxis. During this treatment, erythematous lesions and blisters were observed first on her face and trunk and then spreading to the entire body. Detachment of the skin, as well as mucous involvement especially of mouth and conjunctiva, was also observed. TEN was diagnosed, and phenytoin was discontinued. Intravenous fluids, systemic steroids and tightened infection control measures were implemented. After 10 days, skin recovery and re-epithelialisation were established, temperature decreased and mucosal complications stabilised. The patient was discharged after 1 month of hospitalisation.

BACKGROUND

Lyell's syndrome or toxic epidermal necrolysis (TEN) is a rare, severe and potentially life-threatening disorder.

It is most commonly drug induced; however, other aetiologies including infection, malignancy and vaccinations may exist. In 90% of the cases, it is triggered by an immune-allergic reaction to medication.¹ The most frequent groups of therapeutic agents cited in the literature are sulphonamides, anticonvulsants, non-steroidal anti-inflammatory drugs and lactam antibiotics (penicillin, cephalosporins).²

The objective of this report is to describe a rare case of phenytoin-induced severe clinical course of TEN syndrome.

The authors think it is important for clinicians to be familiar with the recognition of this syndrome's clinical features, and with the fact that TEN is almost invariably drug induced. Early recognition and immediate withdrawal of any potentially causative agents are critical first steps in the management and prognosis of TEN.

CASE PRESENTATION

A 57-year-old woman was brought to the hospital emergency room, after progressive onset of facial oedema with a rash, which progressively extended to the extremities and trunk, with severe oral and ocular involvement. She also complained of fever and malaise (figure 1).

She had a recent history of total surgical excision of a large fronto-temporo-parietal meningioma. She was being treated with phenytoin, 100 mg three times daily, for seizures prophylaxis. She claimed that symptoms appeared after the seventh

day of treatment with phenytoin. There was no history of any other kind of recent medication.

On admission, the patient presented with a generalised itching erythema with purpuric macules more prominent upon the face and trunk, but spreading to the entire body and becoming confluent and then blistering with an area of vesicles and bullae on the back and shoulder. According to Parkland's formula, 72% of the body surface was affected.

At this point, there was oral mucosa involvement with painful haemorrhagic crusting of the lips and mucosal erosions. She had ocular hyperaemia with signs of synechiae between the eyelids and conjunctiva.

The blood pressure was 110/60 mm Hg, heart rate 110/min, respiratory rate 17/min and tympanic temperature 39.4°C. Pulse oxymetry revealed oxygen saturation 99%.

The rest of the examination was unremarkable.

After two days, typical signs of extensive epidermis exfoliation developed upon more than 30% of the affected areas of her body. Vesicles and bullae then formed and the skin began to slough. We could then identify a positive Nikolsky sign. Two different mucous membranes were involved (mouth and conjunctiva). Based on the clinical picture, Lyell's syndrome was diagnosed. She was then transferred to an isolation room in the Internal medicine intermediate care unit, where she had continuous monitoring and observation as well as a nursing staff that are trained and focused on providing consistent care.

INVESTIGATIONS

The laboratory exams revealed: leukopaenia (3400/ μ l) with 2000 neutrophils, elevated C reactive protein (18 g/dl, normal range <0.01 g/dl), levels of phenytoin in blood were within its normal therapeutic levels. Hepatic and renal function tests were normal.

Chest x-ray was unremarkable. Arterial blood gas analysis was unremarkable.

Blood and urine cultures and mucocutaneous swabs were sterile.

TREATMENT

First, we promptly withdrew the causative drug, in this case phenytoin.

The patient required monitoring of various parameters used in burn patients paying special attention to urine output and balancing fluid/electrolyte disturbances.

Treatment consisted of fluid infusion, systemic steroids, prophylactic broadspectrum antibiotics (vancomycin and meropenem) and pain management. Infection control measures with sterile handling and reverse-isolation procedures, daily

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Figure 1 Oral and ocular involvement in toxic epidermal necrolysis.

dressings and repeated cultures of the skin, as well as blood and urine, were performed.

Ocular and conjunctiva disorders were managed with extensive lubrication of the eyes and local antibiotics, and management of synechiae between the eyelids and conjunctiva.

Oral ulcers were treated by applying local sucralfate.

OUTCOME AND FOLLOW-UP

After the seventh day of treatment, facial oedema diminished, the patient became afebrile and epidermisation occurred.

During admission, she was regularly observed by doctors from the departments of ophthalmology, dermatology and plastic surgery. Also, doctors from immunoallergology were also

brought in to further the discussion of clinical features and relation to the culprit drug.

The patient was discharged after a month of hospitalisation with cutaneous scarring and irregular pigmentation. There were no oral or ocular sequelae.

DISCUSSION

Toxic epidermal necrolysis is a life-threatening skin and mucous membranes disorder.

The syndrome was first described in 1956 by Lyell.³ The incidence is estimated between 0.4 and 1.2 cases per million each year (figures 2–4).^{4 5}

It is characterised by the occurrence of sloughing of greater than 30% of the body surface area. It begins with a prodrome of fever, often exceeding 39°C and malaise. Mucous membranes are involved in nearly all cases. Involvement of the buccal, genital and/or ocular mucosa occurs in more than 90% of patients, and in some cases, the respiratory and gastrointestinal tracts are also affected.^{6 7} Ocular involvement at the onset of disease is frequent, and can range from acute conjunctivitis, eyelid oedema, erythema and crusts, to conjunctival membrane or pseudomembrane formation. The skin lesions are widely distributed erythematous macules and patches, although 50% of cases begin with diffuse erythema.^{3 8 9} The skin lesions progress to vesicles and bullae formation and the skin begins to slough within days. Nikolsky sign (detachable skin) may be positive. Sloughing progresses rapidly for 2 or 3 days and then usually stabilises.

Haematological abnormalities, particularly anaemia and lymphopaenia are common. Neutropaenia is noted in about one-third of patients, and is correlated with a poor prognosis.^{1 10} Mild elevations in serum aminotransferase levels are present in about one-half of patients.

Suggestive history of antecedent drug exposure and clinical course support diagnosis of Lyell's syndrome. Histology findings are neither specific nor diagnostic.

The aetiopathogenesis of TEN still remains largely unknown. At present, some authors assume that exposure to drugs is the only documented cause of TEN because of allergic reaction to drugs itself and/or their metabolites, which happens when binding with protein is able to evoke an immune response.¹¹ There are still many ongoing researches in order to understand the pathogenesis of TEN. Currently, it appears that CD8 T cells, as well as the cytotoxic molecules FasL and granzyme, seem to play a major role in the pathogenesis of TEN.^{12–15}

Figure 2 Widespread erythema and confluent vesiculation leading to sloughing of the skin in toxic epidermal necrolysis.

Figure 3 Diffuse erythema and large areas of desquamation in toxic epidermal necrolysis.

Figure 4 Multiple bullae overlying diffuse erythema in toxic epidermal necrolysis.

The most frequently involved groups of therapeutic agents cited in the literature are sulphonamides, anticonvulsants, non-steroidal anti-inflammatory drugs and lactam antibiotics.²

Mockenhaupt *et al* were able to show that almost all cases of TEN developed within 63 days of starting of antiepileptic drugs, and that the risk of developing TEN per 10 000 new users significantly increased for carbamazepine (1.4 cases/10 000 users), lamotrigine (2.5), phenobarbital (8.1) and phenytoin (8.3).¹⁶ Furthermore, studies in different populations indicate that the risk of developing TEN is the highest when the drug has been recently initiated and subsequently declines within 8 weeks or more of administration.^{17 18}

In our case, we report a phenytoin-induced TEN. Gómez-Criado *et al*¹⁹ reported some factors linked to a higher risk of TEN related to phenytoin. They concluded that there is an increased risk of TEN when phenytoin is associated with cranial radiotherapy, as well as, when associated with other known antiepileptics, as cross-sensitivity of carbamazepine and barbiturates with phenytoin has been observed.

The case we report appears to be particularly valuable, because not only did our patient have a rare condition, but it was also related to phenytoin without any association with the described risk factors.

Treatment includes prompt recognition and withdrawal of suspected drugs and hospitalisation. Garcia-Doval *et al* have shown that earlier the causative drug is withdrawn, better the prognosis. In order to identify the culprit drug, it is important to consider the chronology of administration of the drug and development of TEN.

Cutaneous isolation and aseptic measures, control of infection and the management of cutaneous coverage improve the symptoms and facilitate evolution of the injuries towards epithelialisation.

Intravenous fluid should be given to maintain urine output of 50–80 ml/h.

There is still no specific treatment for TEN. However, high-dose intravenous immunoglobulin, cyclosporine and Tumour necrosis factor alpha antagonists have been used. The role of systemic steroids is controversial. Some authors advocate their important role in the first days of disease, whereas others claim their potential harm related to increased risk of sepsis. In our patient, we administered prednisolone 1 mg/kg daily, and associate a prophylactic broadspectrum antibiotic despite no evidence

of infection. We noticed a favourable evolution with no sepsis evidence. Nevertheless, steroids were soon tapered.

More than 50% of patients surviving TEN suffer from long-term sequelae of the disease. These include conjunctival synechiae, ingrowth of eyelashes, cutaneous scarring and irregular pigmentation.

In our case, the patient presented a very favourable evolution and sequelae resumed to cutaneous scarring and irregular pigmentation. Despite the moderate-to-severe involvement of oral and conjunctival mucosa, there was an outstanding recovery.

Death rate in TEN is high and can reach 25–35% 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 neutropaenia (more than 5 days) hyperazotaemia and hypoalbuminaemia (<2.0 g/dl) are not insignificant.

This case emphasises the importance of a multidisciplinary clinical approach as it brought together internal medicine, dermatology, Plastic surgery, ophthalmology and immunoallergology.

We conclude that special attention to skin rash in the first month after starting on an epileptic drug is needed. As soon as TEN is suspected, immediate withdrawal of the drug must be done and treatment should be started.

Learning points

- ▶ Toxic epidermal necrolysis (TEN) is, almost, invariably drug induced.
- ▶ Early recognition and immediate withdrawal of any potentially causative agents are critical first steps in the management of TEN.
- ▶ Sepsis is the major cause of death. Sterile handling, infection control measures, topical antibiotic agents and surveillance cultures of possible sites of superinfection are important components of prevention.
- ▶ Supportive care should be the primary focus of management of TEN. Beyond this, there is insufficient evidence to establish the benefit of any adjunctive therapies. Systemic glucocorticoids and intravenous gammaglobulin are commonly used at many centres, although not all.
- ▶ The mortality of TEN ranges from 25% to 35%. Predictors of mortality include older age at onset and greater extent of skin involvement. Long-term sequelae of the skin and eyes are common among survivors.

Competing interests None.

Patient consent Obtained.

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