

A case of carbamazepine-induced toxic epidermal necrolysis in an Afghan woman

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ABSTRACT

We present a case of a 55-year-old diabetic woman who presented to the clinic with an erythematous, scaly, itchy rash and generalized abdominal pain with vomiting. Owing to the symptoms of peripheral neuropathy, she had been prescribed carbamazepine 100 mg twice daily. Initially, the patient presented with the rash on her face along with sticky eyelashes, which later spread to chest, abdomen, and thighs. Blood cultures and wound swabs were taken, carbamazepine was stopped, a working diagnosis of toxic epidermal necrolysis (TEN) with prerenal acute kidney injury was made. Her renal functions were deranged with a serum urea of 170 mg/dL, serum creatinine 3.3 mg/dL, lactic acid 43 mg and estimated glomerular filtration rate (eGFR)15.3 ml/min/1.73 m². There was no biochemical improvement observed, postdialysis. She developed left leg arterial ischemia with numbness, bluish discoloration of the skin, and hypotension. Ultimately, the patient went into multi-organ failure and unfortunately passed away. Serious and, sometimes, fatal dermatological reactions have been reported during the treatment with carbamazepine. Although carbamazepine-induced TEN is not a rare presentation, other similar drugs with a safer side effect profile could be used instead as in the case of our patient.

Key words: Anticonvulsants, drug reactions, toxic epidermal necrolysis

INTRODUCTION

Cutaneous reactions are a common type of adverse drug reactions (ADRs). They hold a special importance in healthcare because they add to the patient's suffering, increase hospital stay, incur more expenses, and can occasionally be fatal.^[1] Among the various cutaneous adverse reactions, itching, skin rashes, urticaria, fixed drug eruptions, angioedema, and contact dermatitis are all common.

Toxic epidermal necrolysis (TEN) also known as Lyell's syndrome is a rare but life-threatening,

immune-mediated, severe cutaneous adverse reactions.^[2] TEN is characterized by a macular exanthema ("atypical targets") which predominantly presents on the face, neck, and the central trunk regions. Lesions show a rapid confluence, a positive Nikolsky's sign, and quickly result in widespread detachment of the epidermis with erosions.^[3] Mucosal, conjunctival, and anogenital mucous membranes are prominently involved. Antimicrobials, analgesics, and antiepileptics are common groups of drugs involved. However, the pattern and the drugs causing cutaneous

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reactions can vary due to different prescribing habits, use of newer drugs, and referral bias.^[4]

Carbamazepine is an antiepileptic drug which is also used for trigeminal neuralgia, post-herpetic neuralgia, and bipolar mania. It is rarely prescribed for peripheral neuropathy due to the availability of safe alternatives, such as amitriptyline, gabapentin, pregabalin, and most recently, duloxetine which has recently been approved by the Food and Drug Administration for peripheral neuropathy. We present a case of carbamazepine-induced TEN in an Afghan woman who was prescribed carbamazepine for her peripheral sensory neuropathy due to her long-standing diabetes mellitus. Written informed consent was obtained from the patient for the publication of this case and the accompanying images.

CASE REPORT

A 55-year-old woman from Afghanistan, previously diagnosed with type 2 diabetes mellitus and hypertension 8 years ago, presented to the outpatient department with a 4-day history of a generalized rash, abdominal pain, and vomiting. The rash initially appeared on the face and gradually involved the entire body. It was erythematous, scaly, itchy, and involved 50–55% of the total body surface area, resulting in skin loss as shown in Figure 1.

The patient also has sticky eyelashes associated. Moreover, the patient complained of odynophagia due to oral mucosal involvement and generalized abdominal pain which was gradual in onset with no aggravating or alleviating factors. The patient also had a history of loose, watery stools for the last 4 days. The stools were small in volume, and there were 4–5 episodes/day. However, there was no blood or mucus in the stool. According to the patient, she had neither nocturnal symptoms nor any association with any specific food.



Figure 1: Blisters of the left arm and forearm

The patient was a housewife and lived a good standard of life before the onset of her symptoms. The patient was on lisinopril 10 mg for hypertension, premixed insulin 70/30 (insulin isophane and insulin regular) for diabetes, and clopidogrel 75 mg.

A week ago, she was started on carbamazepine 100mg twice daily for her new complaint i.e peripheral sensory neuropathy. On arrival to the outpatient department, the patient was noted to be of normal build, dehydrated, afebrile with a blood pressure of 110/70 mmHg, pulse of 14/min which was regular and of normal volume, and a respiratory rate of 15 breaths/min. Her systemic examination was unremarkable, including the respiratory, cardiovascular, gastrointestinal tract, and nervous systems. Her initial laboratory results showed hemoglobin 13.6 mg/dL, total leukocyte count $10.67 \times 10^9/L$, platelet count $136.90 \times 10^9/L$, serum sodium 132 mmol/L, potassium 5.4 mmol/L, chloride 107 mmol/L, serum bicarbonate 15 mmol/L, serum urea was 126 mg/dL, serum creatinine was 2.6 mg/dL, and eGFR 15.3 ml/min/1.73 m². Her random blood sugar was 243 mg/dL, serum alanine transaminase was 38 μ/L , and C-reactive protein was 26 mg/dL.

Blood cultures and wound swabs were taken; a working diagnosis of TEN with prerenal acute kidney injury was made. She was given intravenous (IV) fluids, adjusted dose IV meropenem, insulin, IV heparin, topical moisturizing gel, oral analgesics, and IV omeprazole. Due to her gradual deterioration of renal function, a decision of hemodialysis was made.

Meanwhile, the plastic surgeon's opinion was sought, who advised topical emollients and dressing with debridement. Her laboratory test results after dialysis showed a serum urea of 170 mg/dL, serum creatinine of 3.3 mg/dL, lactic acid 43 mg/dL, and a prolonged activated partial thromboplastin time of 62 s. No biochemical improvement was noted postdialysis. Moreover, the patient developed left leg pain, numbness, and bluish skin discoloration. Blood culture and wound culture were both sterile. The vascular surgeon was consulted for her left leg pain, and the patient was found to have left lower limb arterial ischemia. A conservative approach was adopted, as the patient was hypotensive despite being on the vasopressor norepinephrine, after failing a fluid challenge in the Intensive Care Unit. Her shock worsened, and she passed away due to multi-organ failure.

DISCUSSION

TEN, was first described by Lyell in 1956.^[5] The word “toxic” alludes to the constitutional symptoms while the word necrolysis refers to the necrosis and detachment of the full thickness of the epidermis.^[6] Drugs are the most common cause and account for about 65–80% of the cases. The patient has TEN, which is characterized by the destruction and detachment of the skin epithelium and mucous membranes. In the majority of cases the causative factor is a drug and this can be identified if a proper medication history is taken, as the manifestations of the syndrome usually appear within 2 days to 8 weeks of starting the medication. Infectious and idiopathic etiologies are also possible.^[6,7] It typically presents with an influenza-like prodrome of abrupt onset, including high-grade fever, systemic toxicity, nausea or vomiting, conjunctivitis, and pharyngitis lasting days to weeks.^[8] TEN is a clinical diagnosis with no definitive laboratory test. The skin manifestations are scalp-sparing and involve the trunk, extremities, and face.^[9] Hemorrhagic, crusty erosions on the oral mucosa and ocular pseudomembrane formation are also common. Regarding our patient, the symptoms appeared a week after the start of carbamazepine. Abdominal symptoms such as nausea and vomiting were associated with the facial and oral mucosal involvement. However, the typical influenza-like prodromal symptoms were not there initially, but features of systemic toxicity appeared later on in the course of her disease.

The assessment according to Naranjo ADR probability scale showed a score of five (probable ADR). Thus keeping in view the temporal association between the recent start of therapy with carbamazepine and onset of the rash in our patient, the drug was stopped. IV fluids and steroids were commenced. This is because of the beneficial role of steroids in halting the process of skin necrolysis.^[4]

At times, TEN may be confused with staphylococcal scalded skin syndrome, pemphigoid, pemphigus vulgaris, acute graft-versus-host disease, and acute generalized exanthematous pustulosis. TEN can be differentiated from these by the presence of fever, mucositis, acute onset with a rapid course, and morphology of cutaneous manifestations. Cutaneous eruptions in TEN are classically preceded by mucositis of the oropharynx, eyes, or genitalia, which begins as a warm, dusky, erythematous, maculopapular rash, followed by painful blistering and epidermal

sheet detachment leaving a denuded dermis. The actual etiopathogenesis is not known; however, it is hypothesized that some noxious metabolites, inflammatory mediators, as well as cytotoxic T-lymphocytes, and dermal dendrocytes could provoke apoptosis and necrosis of epithelial cells.^[10-12]

Early discontinuation of the suspected agents and hospital admission with intensive supportive care are directly related to survival.^[13]

Sepsis-associated multi-organ failure is a major cause of death; therefore, blood cultures are recommended with the initiation of directed antibiotic therapy on early signs of sepsis.^[14] Overt necrotic epidermises can be debrided and should be covered with an antibacterial dressing. In our case, blood cultures were taken and antibiotics were started. In line with the general recommendations, the patient also had a plastic surgery review.

The frequent administration of eye lubricants and lysis of ocular adhesions is sometimes necessary. No specific treatment has been proven to be effective in a randomized controlled trial; however, some studies suggest that plasmapheresis, tumor necrosis factor- α inhibitors, or IV immunoglobulin may improve outcomes.^[8]

The SCORTEN level^[15] is used to predict disease severity and mortality, and is calculated within 24 h of admission and on day 3. The score is the sum of seven variables, each contributing one point, including the following:

1. Age >40 years
2. Heart rate >120 beats/min
3. Positive cancer history
4. Epidermal detachment >10% body area on day 1
5. Blood urea nitrogen >28 mg/dL
6. Glucose >252 mg/dL
7. Bicarbonate <20 mEq/L.

A score of two or less predicts 12% mortality or less, while a score of four predicts 58% mortality, and five or more is associated with a 90% death rate. Leukopenia, thrombocytopenia, delay in hospital admission, and prehospital treatment with corticosteroids or antibiotics are also poor prognostic factors.^[8]

Although carbamazepine-induced TEN is not uncommon, the reported frequency of serious carbamazepine hypersensitivity reaction is between 1/1000 and 1/10,000 new exposures to the drug.^[16]

However, our patient's case is unique as the patient was given carbamazepine for peripheral neuropathy, which is not in line with recommendations; this emphasizes on the fact that guidelines are not practiced in the third world countries, and there is a lack of knowledge related to it. The continuous medical education and refresher courses for clinicians are the key tools in preventing such mishaps.

CONCLUSION

In our patient, the most probable causative drug was carbamazepine as the onset of symptoms coincided with the introduction of this drug. The point that needs to be highlighted is that the ADR could have been avoided if the right drug was chosen for the patient's peripheral neuropathy as per the National Institute for Health and Care Excellence guidelines.

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Conflicts of interest

There are no conflicts of interest.

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