

Case Report



Carbamazepine-induced toxic epidermal necrolysis

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Abstract

Toxic epidermal necrolysis (TEN), also known as Lyell's syndrome, is a widespread life-threatening mucocutaneous disease where there is extensive detachment of the skin and mucous membrane. Many factors involved in the etiology of TEN including adverse drug reactions. Here we are reporting a case of toxic epidermal necrolysis in an adult male patient after receiving carbamazepine in a 38 year old male. On the 18th day of carbamazepine, patient developed blisters which first appeared on the trunk, chest and arms. The erythematous rash was covering almost all over the body with epidermal detachment of 70% body surface area. There was loss of eye lashes, congestion of conjunctiva with mucopurulent discharge and exposure keratitis. The clinical impression was TEN induced by carbamazepine. Carbamazepine was stopped immediately. He was treated with high dose intravenous betamethasone and systemic and topical antibiotics. After one month, the progression of the skin lesions halted and he was discharged.

Keywords: Carbamazepine, Stevens-Johnson syndrome, toxic epidermal necrolysis

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Introduction

Toxic epidermal necrolysis (TEN), also known as Lyell's syndrome, is a widespread life-threatening mucocutaneous disease where there is extensive detachment of the skin and mucous membrane characterized by full thickness necrosis of the epidermis. Patients initially develop pain, tenderness or a burning sensation in the skin associated with fever and malaise, which generally begin abruptly. Over the next 1 to 3 days, ill-defined erythematous macules or a diffuse erythema develops over the trunk and extremities. As the red areas enlarge, central dusky necrotic sites develop with subsequent bullae formation. As the disease progresses, sheets of full-thickness epidermis detach, revealing dark red, moist dermis. A positive Nikolsky sign (peeling-off of the epidermis in large sheets caused by a sliding touch) is an important diagnostic clue and precedes the onset of a life-threatening event. Steven-Johnson syndrome (SJS) involves less than 10% epidermal detachment and TEN involves more than 30%

of epidermal detachment. Between 10%–29% epidermal detachment is diagnosed as SJS/TEN overlap.^[1] The most common cause of TEN is the adverse drug reaction. Other causes include acute graft-versus-host disease and cutaneous lupus erythematosus. The drugs blamed includes sulphonamides, aminopenicillins, quinolones, cephalosporins, carbamazepine, phenobarbital, phenytoin, NSAIDs, and allopurinol.^[2] Carbamazepine caused SJS/TEN in a frequency of 14 per 100000 users.^[3] Here we describe a case of toxic epidermal necrolysis in an adult male patient receiving carbamazepine for 3 weeks for complex partial seizures.

Case Report

A 38-year-old Asian Indian male patient presented with a rapidly progressive generalized eruption with fever. Patient was diagnosed as having secondarily generalized complex partial seizures 3 weeks prior to the current illness and was prescribed carbamazepine at the dose of 100mg twice daily with slow up-titration of the dose to 300mg twice daily. On the 18th day of carbamazepine, patient developed blisters which first appeared on the trunk, chest, and arms. It was associated with fever and headache. Patient consulted a local ayurvedic doctor and was prescribed some ayurvedic medication. Later patient developed fluid

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filled lesions all over the body, eyes, mouth and genitales. Patient also had breathlessness. He had no personal or family history of skin diseases.

Physical examination showed hypotension (systolic blood pressure 90mmHg) and tachypnoea (respiratory rate 50/minute). Patient was febrile. Clinical examination of the skin revealed a generalized peeling of the skin with crusting seen almost all over the body including scalp and genitales [Figure 1]. The Nikolsky sign was positive. The erythematous rash was covering almost all over the body with epidermal detachment of 70% body surface area. There was loss of eye lashes, congestion of conjunctiva with mucopurulent discharge and exposure keratitis. There was no hepatosplenomegaly or lymphadenopathy. His total white blood cell count was $4.59 \times 10^9/L$ (normal $4-10 \times 10^9/L$). No atypical lymphocytosis or eosinophilia was noted. Platelet count was normal. Hemoglobin was low (10.8g/dl). Liver function tests showed elevated aspartate aminotransferase (AST) 170 (normal 10–45) U/L and elevated alanine aminotransferase (ALT) 87 (normal 6–48) U/L. Serum creatinine was 1.3gm/dL. Patient had hyponatremia (Na^+ 120mmol/L) and hyperkalemia (K^+ 7.9mmol/L), which was corrected appropriately. Wound swabs of the lesions grew *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

The clinical impression was TEN induced by carbamazepine. Carbamazepine was stopped immediately. He was given high dose intravenous betamethasone and topical mupirocin, fusidic acid. Patient was put on prophylactic mechanical ventilation in view of worsening tachypnoea. The erosions were smeared with fusidic acid and betamethasone combination and covered with sterile paraffin gauze. The patient was made to lie down on sterile banana leaf to prevent sticking of the skin to cotton bed. Eye



Figure 1: Generalized peeling of the skin in toxic epidermal necrolysis

lesions were treated with topical antibiotic preparations (ciprofloxacin, gentamicin, chloramphenicol, moxifloxacin+dexamethasone) and ocular lubricant solution (lacrigel). Eyes were covered with saline soaked sterile pads. Patient was also treated with parenteral piperacillin+tazobactam combination and linezolid. Supportive treatment given includes parenteral opioids (fentanyl, pentazocine) for pain management, intravenous fluids and intravenous albumin. Nutrition was maintained by giving protein powder preparation through Ryle's tube. Patient was started on levetiracetam for complex partial seizures on the fourth day of admission. He was switched over to oral betamethasone once the lesions started healing. Betamethasone was slowly tapered and stopped after 4 weeks. Lesions healed with postinflammatory hyperpigmentation by third week of illness. After one month, the progression of the skin lesions halted and general condition of the patient was improved. As a sequelae, on follow-up patient had developed hypertrophic scars in some areas.

Discussion

Our patient presented with generalized peeling of the skin with mucosal ulceration after initiating the therapy with carbamazepine. Clinical findings were consistent with the diagnosis of TEN. Several case reports have shown that carbamazepine is one of the culprits in inducing TEN.^[4,5] Incubation period for development of TEN after initiating carbamazepine was less than 3 weeks, which is in conformity with earlier reports.^[6] Our patient had a low white cell count, which is more commonly found in TEN.^[1]

Specific epidemiological studies have not been published on the incidence of TEN in developing countries like India. Devi *et al* reported that the most common [53%] group of drugs implicated as the cause of SJS/TEN was anticonvulsants and majority of these cases [81%] were due to carbamazepine.^[5] It is possible that frequency of TEN in countries such as India could be much higher considering the fact that the main etiologic agent of TEN, i.e. drugs such as antibiotics, anticonvulsants, and nonsteroidal anti-inflammatory drugs (NSAIDs) are easily available in these countries without any prescription.

Cytotoxic lymphocyte-mediated immune reaction (CTL) aimed at the destruction of the keratinocyte expressing foreign antigens as the primary causes for development of TEN. Tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) have also been involved in the pathogenesis of TEN as increased amount of these cytokines are found in the blister fluids in TEN

patients. These inflammatory cytokines may play their damaging roles by recruiting the cytotoxic T cells to the epidermis. They may also cause damages directly as cytokines such as TNF- α are known to cause increased apoptosis.^[7] Drugs are considered to be the commonest cause of TEN. Drug metabolites such as hydroxylamines and arene oxides derived from sulfonamides and aromatic anticonvulsants, respectively, bind to cell constituents if they are not rapidly detoxified by epoxide hydrolase. These metabolites act as haptens and render the keratinocytes antigenic by binding to them. A defect in the detoxification system may be the cause of drug eruption.^[8]

A strong association has been reported between human leucocyte antigen (HLA)-B*1502 and carbamazepine-induced SJS in Han Chinese patients. European studies suggested that HLA-B*1502 is not a universal marker but is ethnicity specific for Asians.^[9] Diagnosis is not difficult in advanced phases of the pathology. Biopsy of the specimen shows necrosis of basal layer cells without massive inflammatory infiltration of the dermis; in specimens with mature lesions it is possible to observe necrosis of keratinocytes involving all the epidermis with diffuse detachment of the epidermis at the level of the basal membrane.^[8]

The reported mortality rates for TEN vary from 5% to 70%. Patients benefit from intensive care or management in the burns unit.^[5] The use of corticosteroids is a much debated question. Authors who support the use of corticosteroids recommend high doses of corticosteroids. Other possible medical therapies for the treatment of TEN that are reported in the literature include the use of plasmapheresis, intravenous immunoglobulins, and cyclosporine.^[10] Complete recovery of our patient was probably due to early and effective control of inflammation by treatment with systemic steroids and appropriate topical care of the eroded areas. As reported in the earlier literature, most of the patients with TEN

were treated with systemic steroids along with antibiotics and supportive measures.^[5]

Apart from control of seizures, carbamazepine is being increasingly prescribed for control of pain in neuralgias and diabetic neuropathy. Awareness about the drugs implicated in life threatening drug reactions will help physicians in preventing them by judicious use of the drugs.

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