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Research Article

TOXIC EPIDERMAL NECROLYSIS INDUCED BY CARBAMAZEPINE: A CASE STUDY

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ABSTRACT

Objectives: The objective of this case study is to evaluate the importance of detection, assessment, and reporting of an adverse drug reaction and to improve the medication perseverance.

Methods: This is an observational type of case report which was observed and analyzed in Silchar Medical College and Hospital on regular ward rounds.

Results: A case report of toxic epidermal necrolysis due to carbamazepine (CBZ) administration by a 47-year-old male patient who presented as a follow-up case of ischemic stroke. Causality assessment of the event done with Naranjo' causality assessment scale suggests to be "Probable."

Conclusion: Daily, CBZ is being increasingly prescribed for control of pain in neuralgias and diabetic neuropathy, apart from control of seizures. Awareness about the drugs implicated in life-threatening drug reactions will help physicians in preventing them by cautious use of the drugs. Moreover, proper counseling to the patient regarding the use of medications is of utmost importance, in such life-threatening conditions where treatment guidelines remain indistinct.

Keywords: Toxic epidermal necrolysis, Carbamazepine, Adverse drug reaction, Probable.

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INTRODUCTION

Toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS) affecting approximately 1 or 2/1,000,000 annually, and are considered medical emergencies as they are potentially fatal conditions. Drugs are assumed or identified as the main cause of SJS/TEN in most cases, but *Mycoplasma pneumoniae* and herpes simplex virus infections are also well-documented causes alongside (mostly rare cases) in which the etiology remains unknown [1]. This disease affects the skin and mucous membranes at the skin, mouth, eyes, and genitals. It is severe and highly weakening adverse drug reactions (ADR) [2]. SJS disorder is more likely to occur in people with highly active anti-retroviral therapy regimens [3].

TEN and SJS are two forms of the same life-threatening skin disease induced by an immune complex mediated hypersensitivity reaction. In SJS, a patient has blistering of mucous membranes, typically in the mouth, eyes, and genitalia and widespread small blisters that arise as erythematous or purpuric maculae. There is a similar blistering of mucous membranes, but in addition, the entire top layer of the skin (the epidermis) peels off in sheets forming larger areas in the body of TEN patients [4].

TEN and SJS are rare but critically ill, severe cutaneous ADR. The mortality rates are about 10% in SJS, 10-30% in overlapping SJS/TEN, and 30% in TEN [5].

TEN and SJS are classified into type IVc hypersensitivity reactions according to a modified Gell and Coombs classification by Adam *et al*. [6] The main effector cells are CD8+ cytotoxic T lymphocytes, CD4+ T cells, natural killer cells, and natural killer T cells. Massive release of granulysin, perforin, and granzyme B is involved in the pathogenesis [7].

Patients develop an acute exanthemous lesions, which progresses toward a widespread blistering (TEN) or more limited purpura, vesicles (SJS) and erosion of the skin and mucous membranes, resulting from apoptosis of keratinocytes. The incidence of SJS is estimated to be 1-6 cases per million person-years and of TEN at 0.4-1.2 cases per million person-years. Various drugs are reported to be associated with a high risk for SJS and TEN. These include several antiepileptic agents, especially carbamazepine (CBZ), phenytoin, phenobarbital and lamotrigine, antibacterials, anti-inflammatory drugs of the oxicam family and allopurinol [8,9].

The Pharmacovigilance Working Team recommended key elements of warnings for the product information of CBZ, lamotrigine, phenobarbital, phenytoin, meloxicam, piroxicam, tenoxicam, regarding their rare risk of life- threatening SJS for the early detection of these adverse reactions and subsequent permanent discontinuation of the medicine to improve their outcomes [10]. Certain human leukocyte antigen (HLA) types are sometimes associated with increased risk of SJS, including HLA B1502 [11].

However, recent publications and postmarketing data suggest that CBZ associated SJS/TEN occurs at a much higher rate in some Asian populations, about 2.5 cases per 1,000 new exposures. The early symptoms of fever, malaise, cough, stinging eyes and a sore throat are often confused with an upper respiratory tract infection. This rapidly progresses to erythematous macules and targeted lesions, epidermal detachment, and mucositis. Early painful erythema and blisters of the palms and soles are a hallmark of SJS. Drugs such as anti-epileptics mainly phenytoin and CBZ were responsible for the majority (44%) of the ADR [12].

CBZ is one among the routinely administered medication for the treatment of simple and complex partial seizures, neuralgia and alcohol withdrawal syndrome. The drug has anticonvulsive and anticholinergic properties by reducing excessive nerve signals within the brain and restoring the conventional balance of nerve activity. Side effects include conditions such as ataxia, vertigo, drowsiness, confusion, headache, maculopapular rash, erythema multiforme, SJS, TEN, xerostomia

(gastrointestinal), and aplastic anemia [13,14]. We are reporting such an interesting case of CBZ induced TEN at a tertiary care hospital in the southern part of Assam. The details of this case are discussed and analyzed henceforth.

CASE DESCRIPTION

The patient is a 47-year-old male, a follow-up case of Ischemic stroke who was diagnosed as Rt/middle cerebral artery (MCA) Territory infarction with (Lt) sided Hemiparesis on Jan 2015. He was treated conservatively and was on Tab. Ecosprin AV-75 (clopidogrel - 300 mg and aspirin - 75 mg) one tab once daily after dinner and was advised to continue the same till next follow-up. After about 5 months he visited a neurologist with the residual weakness of the left side of the body. He was prescribed Tab. CBZ (Zeptol CR) 200 mg and was advised to take a half tablet once daily after dinner for 10 days and then one tablet once daily after dinner for next 10 days. After taking the drug CBZ for 11 days (i.e., half tab once daily for 10 days and one tab once daily for just another 1 day) a total of 11 doses, he developed widespread, pruritic, erythematous, papular lesions, and blackish scaly skin all over the body. It was associated with fever and headache. An excess peeling of skin along with intense inflammation of eyes, lips, nose, genitalia, and oral cavity also occurred. On physical examination, the patient presented with a temperature of 39°C and a blood pressure of 100/70 mmHg. On examination, there were ulcerated lesions on the oral mucosa. Extensive erythematous plaques were present over the rest of the body (more than 30% of the body surface). The patient was subsequently admitted in the Department of Dermatology at Silchar Medical College and Hospital with a diagnosis of TEN probably due to CBZ. He had no personal or family history of skin diseases, neither was he an allergic to any known allergens, food or drugs.

Causality assessment of the event was done with Naranjo' causality assessment scale (total score - 7) suggests a causal relationship between the drug and reaction is "Probable."

Physical examination revealed hypotension (B.P-100/64 mm of Hg), tachycardia (pulse rate 110 beats/minutes), and tachypnea (respiratory rate 52/minutes). The patient was febrile. Clinical examination of the skin revealed a generalized peeling of the skin with crusting almost all over the body including scalp and genitalia (Figs. 1-3). The Nikolsky sign was positive. The erythematous rash was present almost all over the body with an epidermal detachment of 70% of the body surface area. Loss of eyelashes, congestion of conjunctiva with mucopurulent discharge and exposure keratitis were also present. Liver and spleen were not palpable. There was no associated lymphadenopathy. Liver function tests showed elevated aspartate aminotransferase 175 (normal 10-45) U/L and elevated alanine aminotransferase 94 (normal 6-48) U/L. His total white blood cell count was 4.25×10^9/L (normal $4\text{-}10\times10^9$/L). No atypical lymphocytosis or eosinophilia was noted. Platelet count was normal. Hemoglobin was low (10.2 g/dl). Serum creatinine was 1.4 g/dL. The patient had hyponatremia (Na^+ 115 mmol/L) and hyperkalemia (K^+ 7.2 mmol/L), which was corrected appropriately.

The clinical impression was TEN induced by CBZ. The suspected medication was stopped immediately. He was given high dose intravenous (iv) dexamethasone (dexona) and pheniramine maleate (avil) intramuscular injection twice daily, iv ondansetron (emigo) SOS, IVF-DNS-RL iv slowly to maintain the fluid and electrolytic balance the fluid topical application of clonate (clobetasone) lotion twice daily, clinical lotion thrice daily, kenacort (triamcinolone) oral paste twice daily, betadine mouthwash once a day was also included in the treatment schedule. The patient was made to lie down on the sterile banana leaf to prevent sticking of the skin to the bed. Eye lesions were treated with topical antibiotic preparations (ciprofloxacin, gentamicin, chloramphenicol, and moxifloxacin + dexamethasone) and ocular lubricant solution (lacrigel). Eyes were covered with saline-soaked sterile pads. The patient was also treated with parenteral antibiotics

Fig. 1: Edema and crusting of the lips, nose, and inflammation of eyes

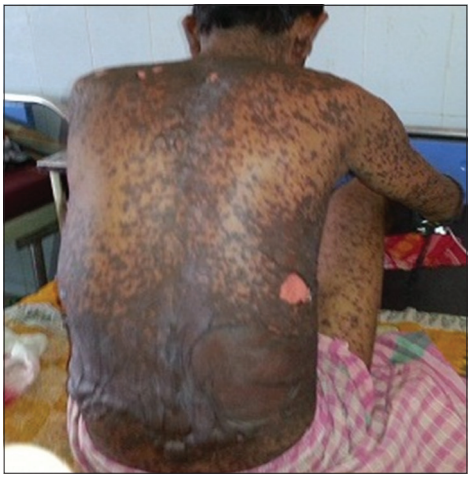

Fig. 2: Peeling of skin and erythematous lesions of skin involving the back

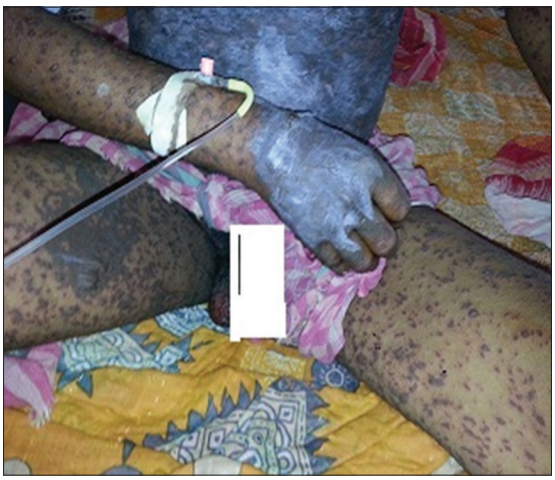

Fig. 3: Erythematous purpuric macular lesions involving the upper limbs, thighs, and genital area

piperacillin+tazobactum combination and linezolid. Supportive treatment included parenteral opioids (fentanyl, pentazocine) for pain management, iv fluids, and iv albumin. Nutrition was maintained by giving protein powder preparation through Ryle's tube. He was switched

over to oral betamethasone once the lesions started healing. Tablet Betamethasone was slowly tapered and stopped after 4 weeks. Lesions healed with post-inflammatory hyperpigmentation approximately by the 16th day. After 1 month, the progression of the skin lesions halted, and general condition of the patient improved significantly.

The following figures depict the actual condition of the patient with CBZ induced TEN.

DISCUSSION

TEN also known as Lyell's syndrome was first described by Lyell in 1956. The word toxic alludes to the constitutional symptoms while necrolysis refers to the necrosis and detachment of the full thickness of the epidermis [15]. TEN and SJS are related mucocutaneous disorders with an estimated incidence of 0.4-1.2 patients per year. Both the diseases are associated with higher rates of morbidity and mortality. Overall mortality for SJS ranges from 5% to 25%, and that for TEN ranges from 15% to 40%. In TEN, maximal skin involvement with a rash is reached within 4 days, and sometimes within hours, whereas the corresponding time for SJS is 1-14 days. About 90% of patients with TEN develop painful erosions in their mucosal membranes, approximately 85% have conjunctival lesions, and about 35% of those who survive experience ocular sequelae [9].

In this case, the patient was admitted to the hospital with severe rashes, peeling of skin as scales all over the body. On physical examination, the patient was dehydrated and poorly nourished. This excess peeled skin was mainly observed on neck, chest, abdomen, lower back, thighs, genitalia, and over the head. The patient dehydrated state was attributed to the detachment of epidermal cells and their secretions. Drugs are the most common cause accounting for about 65-80% of the cases. An immune mechanism is implicated in the pathogenesis, but its nature is still unclear. It is primarily directed at drug modified epidermal cells [16]. In this report, the patient was a follow-up case of Ischemic stroke R/MCA Territory with (L) Hemiparesis diagnosed on January 2015. He came for treatment for his LT sided residual weakness on May 2015. On the 11th day of his follow-up treatment, the patient had his 11th dose on the evening after dinner at around 9 PM. Within a span of 4-5 hrs, he developed severe rashes and blisters all over the body, the patient visited his doctor next morning, who advised him to stop the suspected medication and attend the Dermatology OPD at Silchar Medical College and Hospital. Accordingly, the patient rushed to the dermatology OPD of Silchar Medical College and Hospital, where the physician, on taking a detailed history and through physical examination, suspected it to be a case of TEN, probably due to CBZ administration. The patient was admitted immediately and initiated supportive therapy without further delay.

The following diagnostic criteria must be fulfilled for a case to be labeled as TEN.

1. Bullae or erosions involving more than 20% of body surface area or three different anatomical sites.
2. Skin peeling in sheets of more than 3 cm.
3. Involvement of non-exposed skin.
4. Mucous membranes involvement.
5. Skin tenderness within 48 hrs of rash.
6. Biopsy confirmation within 48 hrs.
7. Fever.
8. Bullae arising on an erythematous background.
9. Exclusion of Staphylococcal scalded skin syndrome.

Investigations usually show leukocytosis, albuminuria, water, and electrolyte imbalance and raised transaminases [17].

Although the pathogenesis of these lesions is unknown, a number of hypothesis has been put forward [18]. Treatment consisted of supportive measures such as removal of precipitating agents, good nursing care, laying down the patient on a ripple bed, care of the eyes and mouth to prevent scarring and infections, along with maintenance of fluid, and electrolyte balance. iv fluids were given for 3 days consecutively. iv fluids were supplemented with ORS. The patient was prescribed antibiotics iv for 3 days and switched over to oral formulations to prevent further infections. The patient was put on a high-protein diet. After several days of treatment, the patient showed signs of improvement and his overall general health conditions also improved.

CONCLUSION

TEN is considered as a life-threatening complication and a medical emergency. Its association with the use of CBZ may have a familial tendency. Moreover, proper counseling regarding the use of medications is of utmost importance, in such life-threatening conditions where treatment guidelines remain unclear. It is also advisable to give information about adverse drug reaction to the patients who suffered from such serious reactions in the past and reporting the same to the concerned authority.

Daily, CBZ is being increasingly prescribed for control of pain in neuralgias and diabetic neuropathy apart from using it as an anti-seizures agent. Awareness about the drugs implicated in life-threatening drug reactions will help physicians as well other health-care providers in early detection and prevention of ADRs by cautious use of such drugs.

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