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Case Report

Carbamazepine-induced Stevens Johnson syndrome: a case series of three case reports

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ABSTRACT

Carbamazepine is an iminostilbene derivative that was initially used as an antiepileptic but has been used with increased frequency for different indications including chronic pain, trigeminal neuralgia, and herpetic neuralgias. This has resulted in increased incidence of carbamazepine related adverse effects such as nausea, vomiting, and serious hematological toxicities such as aplastic anemia, agranulocytosis, eosinophilia, lymphadenopathy, and splenomegaly. Life-threatening hypersensitivity reactions such as Steven Johnson syndrome (SJS) and toxic epidermal necrolysis can also occur. We hereby present a series of three cases that were prescribed carbamazepine for different indications and presented with SJS.

Keywords: Carbamazepine, Stevens Johnson syndrome, Toxic epidemal necrolysis

INTRODUCTION

Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), defined by widespread blisters arising on macules and/or flat atypical targets, are diseases with homogenous clinical characteristics and a potentially lethal outcome.[1] SJS involves less than 10% of the area, and TEN involves more than 30% of epidermal detachment.[2] The most common cause of the SJS is adverse drug reactions. SJS is usually associated with some types of anticonvulsants, including carbamazepine,

lamotarigine, phenobarbital, phenytoin, and valproic acid.[3] Clinically, these diseases present as erythema, necrosis, and extensive sloughing of the epidermis; mucous involvement; and systemic symptoms. Carbamazepine is an iminostilbene derivative and is one of the common drugs used for the treatment of seizures, trigeminal neuralgia, and bipolar affective disorder.

With long-term therapy, it can cause drowsing, vertigo, ataxia, diplopia, and blurred vision. Other adverse drug effects are nausea, vomiting, and serious hematological toxicities such as aplastic anemia, agranulocytosis, eosinophilia, lymphadenopathy, and splenomegaly. Hypersensitivity reactions are dangerous skin reactions. Late complications are retention of water with decreased osmolality and hyponatremia. These reactions are commonly associated with human leukocyte antigen-B 1502 in Indian population. Carbamazepine is very commonly associated with TEN/SJS with the incidence of 14/100,000.[4] We hereby present a case series of three cases that were prescribed carbamazepine for different indications and presented with SJS.

CASE REPORTS

Case 1

An 18-year-old female, a known case of microcephaly with mental retardation with history of seizures was admitted to the hospital around one and a half month back and was started on tablets phenytoin 100 mg TDS, tablets acyclovir 100 mg, and tablets cefixime.

After 15 days, patient was prescribed tablets carbamazepine 100 mg BD. After 10 days of treatment, she developed pea head sized, reddish raised skin lesion over upper arm which was sudden in onset and rapidly progressed to involve whole of the body. Rash first appeared on upper limb and spread rapidly to lower limb, chest and trunk, lastly involving palm and sole. There was a history of decreased appetite. The patient was then admitted to our institution.

On examination patient was febrile (101°F). Pallor +, Edema +, and eyes were congested, lips were edematous.

Laboratory tests shows:

- Hemoglobin (Hb) - 9.0 g%
- Total leukocytes count (TLC) - 32,300
- Differential leukocyte count (DLC) showed eosinophilia with N45/L23/M02/E30
- Platelet count adequate - 105/cumm
- S. Na^+ - 132 mEq/l
- S. K^+ - 4.9 mEq/l.

Renal function test showed urea - 69 mg/dl, creatinine - 1.4 mg/dl.

Liver function test showed alkaline phosphate - 220 IU, SGOT/PT - 68 IU/122 IU.

Urine for routine and microscopic examination showed albumin +.

Local examination

Mucocutaneous examination showed generalized involvement of body including face, trunk, upper limb, lower limb including palm, soles and scalp in form of multiple well to ill-defined discrete to confluencent erythematous purpuric macules to papular lesions of size varying from 0.5 to 1.0 cm to 1.0 cm × 2.0 cm with diffuse blanch able erythema. Diffuse involvement of face in the form of exfoliation is shown in Figures 1-3.

A typical target lesion and pustular lesions present at few places. Pitting edema presents over hand and legs. Nikolsky's sign is positive. The diagnosis of STS was made, and carbamazepine stopped and patient given intravenous (IV) fluids, injection dexamethasone 12 mg in the morning and 4 mg in the evening intramuscularly, can free (clotrimazole 1% + beclomethasone 0.01% + benzocaine 1% + glycerine) mouth paint for local application, mucaine gel 2 TSF thrice daily orally, tablet paracetamol 500 mg SOS, injection

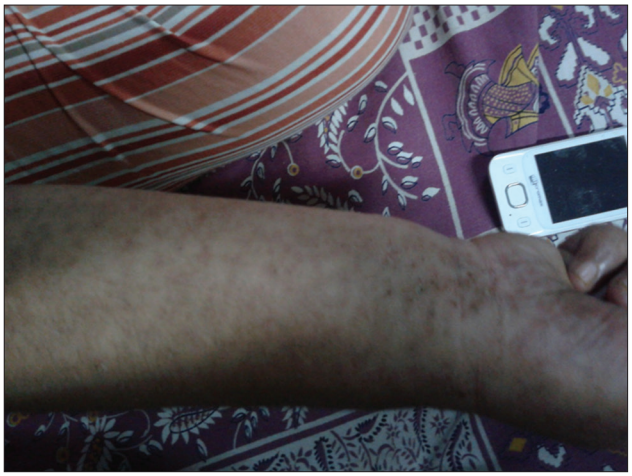

Figure 1: Carbamazepine induced lesions on forearm and palm of the 18-year-old female being treated for epilepsy.

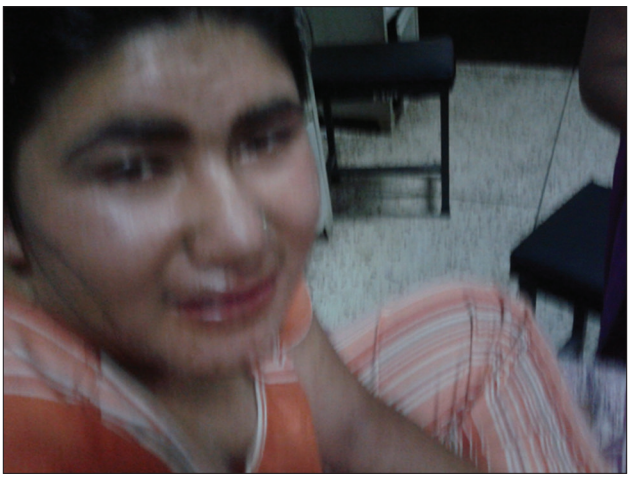

Figure 2: Drug-induced maculopapular lesions on face along with swelling lips and face in the 18-year-old female being treated for epilepsy.

pantoprazole 40 mg IV before meals twice daily and antibiotics. Later on patient shifted on oral T. Prednisolone, which was one tapered slowly and stopped. The patient improved and discharged after 10 days.

Case 2

A 32-year-old female presented with a history of vesiculopapular rashes on scalp, forehead and occipital region, and burning sensation. There was history of fever on and off. The patient was diagnosed with herpes zoster in a private clinic and put on tablet carbamazepine 200 mg HS and injectable vitamins B1, B6, and B12. After taking treatment for 3 weeks, patient started complaining of vomiting, epigastric discomfort, and itching on whole of the body. There was swelling post-auricular region and face and red skin lesions. There was history of passage of orange-colored stools.

General physical examination was normal. Non-invasive blood pressure (NIBP): 128/82 mmHg, heart rate (HR): 78/min.

Bilateral inguinal lymphadenopathy: 2-3 lymph nodes, 1-3 cm size not attached to underlying skin. On local examination, there were fluid filled lesions on left side of face, swelling forehead and periorbital area bilaterally and left hand (Figures 4 and 5). There was mild splenomegaly.

Investigations showed Hb - 13 g%, DLC - N58, L 33, E9 M0, B0, Platelets - 2,91,000/mm^3, ESR - 28 mm 1st hr., RBS - 89 mg%, S. Electrolytes - Na^+/K^+ - 128.8 mEq/l/4.9 mEq/l, S. urea – 35 mg/dl, S. creatinine - 0.68 mg/dl.

Red blood cells are normocytic, normochromic. Reactive lymphocytosis with increased eosinophil count. 40% of lymphocytes are large with ovoid to folded nucleus showing moderately condensed chromatin with few showing prominent nucleolus s/o drug hypersensitivity reaction.

Urine analysis - NAD

USG showed mild splenomegaly.

Patient was diagnosed to have hypersensitivity reaction to carbamazepine and was put on treatment with tablet omnacortil 40 mg at 8 am after breakfast and 20 mg in the evening, along with tablet pantoprazole 40 mg, tablet hydroxyzine 25 mg. The patient improved symptomatically and discharged.

Case 3

A 41-year-old male adult presented to Orthopedics Department for chronic pain left hip and knee for past 2 years and was under treatment. He was referred to Neurology Department due to the neuropathic nature of the pain 6 months back and was given tablet carbamazepine 100 mg twice daily which was increased to 200 mg BD and for last 1 month it was increased to 200 mg thrice daily. After 1 month, patient reported to skin department with history of fever with chills and rigors for 1 week associated with reddish skin rash all over the body which started from face and rapidly progressed to the neck, trunk, back, lower extremities and legs. The rash was associated with burning sensation in oral cavity and body. History of itching on and off was present.

On general physical examination: NIBP: 108/70 mm Hg, PR: 88 bpm.

Local examination showed well to ill-defined, discrete, erythematous blanch able erythemas and papules all over the body including upper limb, lower limb, trunk, and back (Figures 6-8).

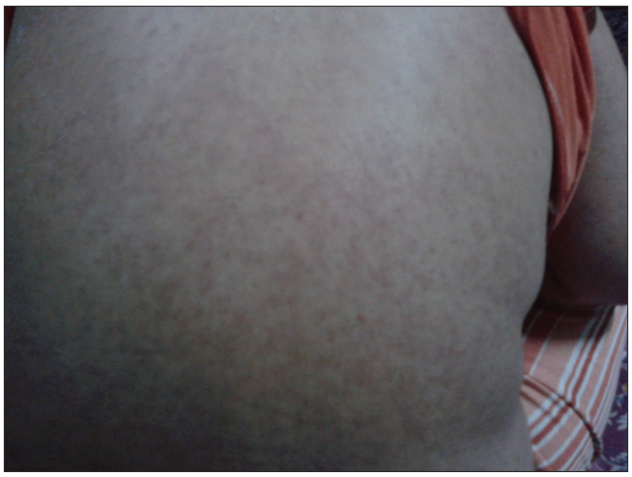

Figure 3: Maculopapular lesion due to carbamazepine hypersensitivity of the18-year-old female being treated for epilepsy.

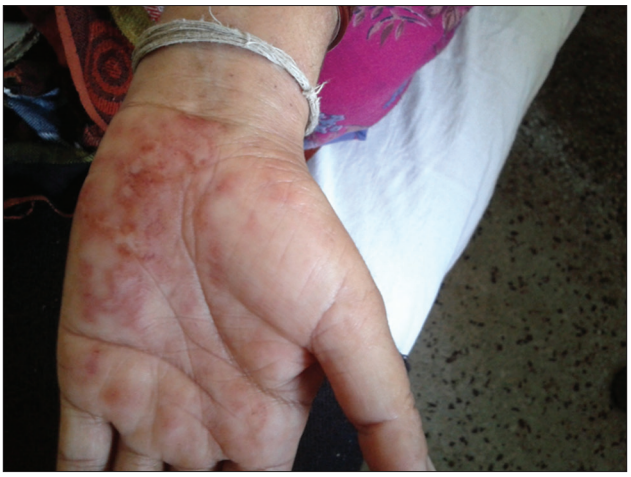

Figure 4: Resolving lesions on the forearm and palm of the patient who was being treated with carbamazepine for post herpetic neuralgia.

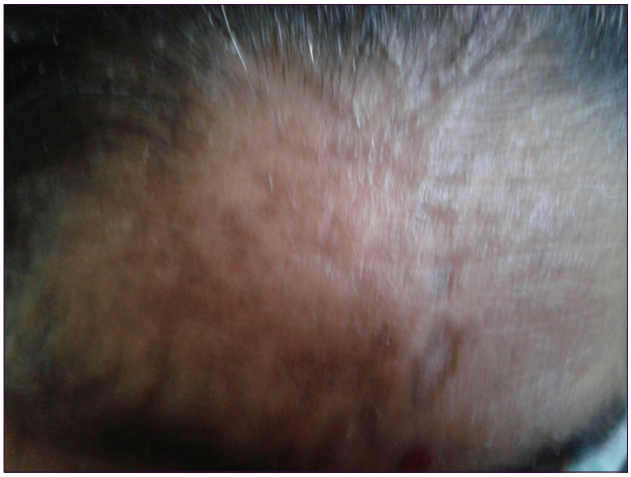

Figure 5: Healing lesions on forehead of the patient who was being treated with carbamazepine for post herpetic neuralgia.

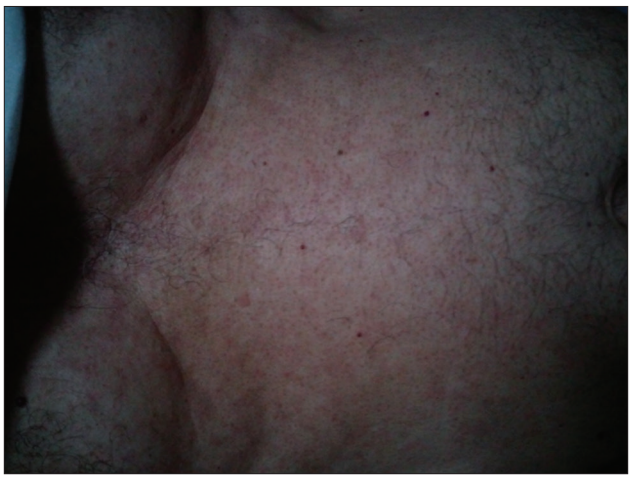

Figure 6: Maculopapular and target lesions on the trunk of the patient being treated with carbamazepine for chronic neuropathic pain.

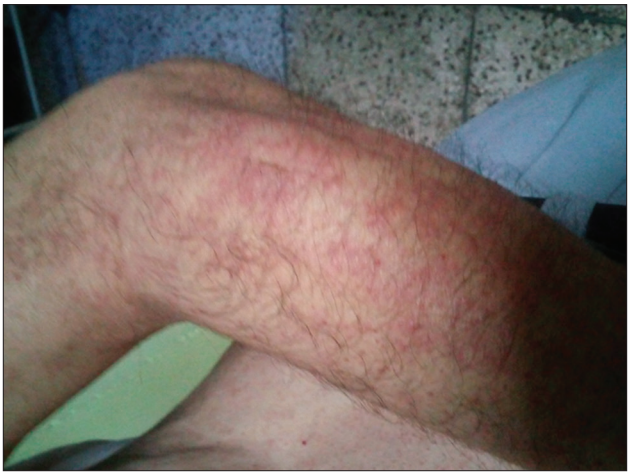

Figure 7: Maculopapular and target lesions on the arm and forearm of the patient being treated with carbamazepine for chronic neuropathic pain.

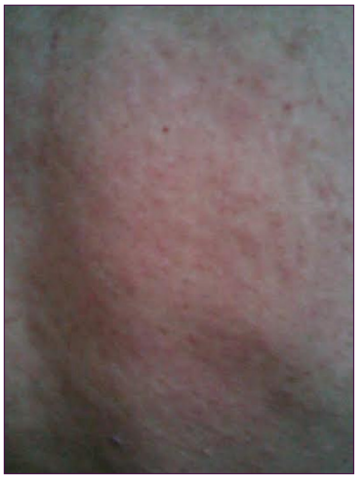

Figure 8: Maculopapular and target lesions on the back of the patient being treated with carbamazepine for chronic neuropathic pain.

Investigations: Hb - 12 mg%, TLC: 12,000/dl, DLC - N58, L35, E2, M5, B0, S Na^+ - 135.56 mEq/l, S. K^+ - 4.5 mEq/l, SGOT/SGPT - 186 IU/294 IU, Alk. PO_4 - 509 IU, RFT - normal.

The drug was stopped immediately, and the patient was given IV fluids, injection dexamethasone 8 mg in the morning and 4 mg in the evening along with injection pantaprazole 40 mg twice daily. The patient was later on shifted to tablet omnacortil 40 mg in the morning and 20 mg in the evening and then slowly the drugs were tapered down and stopped.

DISCUSSION

Carbamazepine was initially approved in the US for use as an antiseizure agent in 1974. It has been employed since 1960 for treatment of trigeminal neuralgia. There is no simple relationship between dose of carbamazepine and concentration of drug in plasma. Therapeutic concentrations are reported to be 6-12 µg/ml although considerable variations occur.[5] It is one of the common drugs associated with hypersensitivity reactions. Carbamazepine has been strongly associated with SJS.

Although SJS has multiple etiologies, it is commonly triggered by viral infections (herpes simplex virus is the infectious agent more commonly involved) and neoplasias (carcinomas and lymphomas). However, the most common cause is the use of medications. Among the drugs, implicated more often are allopurinol, antibiotics, anticonvulsants and non-steroid anti-inflammatories.[6] Devi et al.[7] conducted a 7 years study and found out that anticonvulsants were the cause implicated most in SJS especially in the first 8 weeks of treatment, and the main drug responsible (more than 80%) was carbamazepine.

The increased number of prescriptions of carbamazepine for the control of herpetic and neuropathic pain may be the reason for the increased frequency of SJS due to

carbamazepine. A similar association has been found by us where the drug-related rash has appeared in our patients within 10-40 days. Also, the patients were being treated with carbamazepine for different indication - as antiseizure drug in first case, for post herpetic neuralgia in second case and neuropathic pain in the third case. All three patients showed the maculopapular rash involving the body, upper limbs, lower limbs, palms, and sole. Mild hyponatremia was seen in all patients whereas eosinophilia was present in two of the patients, and mild splenomegaly was present in one of them. The liver functions were mildly deranged in all the patients.

The mechanism of the hypersensitivity reaction is not clear but according to Wu et al.[8] There is lymphocyte and T-cell clone proliferation with the exposure to carbamazepine. The T- cell proliferation time varies from 5 min to 4 h.

The presentation is usually history of fever, along with the appearance of maculopapular rash, usually on upper body and limbs which then rapidly progresses to involve the entire body. The diagnosis is usually clinical, but skin biopsy is helpful in confirmation of diagnosis.

The mainstay of treatment is early recognition of the rash and immediate stopping of the drug along with the symptomatic treatment. It has been seen that the higher drug dose is usually associated with the reactions as compared to the low dose[9] as occurred in our case 3 who developed lesion when he increased the dose from 100 mg twice daily to 200 mg thrice daily.

CONCLUSION

Carbamazepine is increasingly used for different indications, hence the careful titration of the drug and early recognition of the side effects will help in avoiding the life-threatening conditions such as SJS and other side effects associated with the drug.

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