

Research Article

## Fixed Drug Eruption with Exacerbation of Bullous Pemphigoid due to Carbamazepine: A Case Report

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### ABSTRACT

Fixed drug eruptions are one of the most common cutaneous adverse drug reactions reported. Though drugs like analgesics and certain antibiotics are commonly implicated in its causation, yet antiepileptics like carbamazepine can cause a fixed drug eruption by distinct immunological mechanisms, the lesions being so extensive so as to mimic a toxic epidermal necrolysis (TEN). Here we present a case report of a fixed drug eruption with exacerbation of bullous pemphigoid by carbamazepine. The case is reported for its rarity of occurrence and also emphasizes the need for pharmacogenetic and haplotype testing before drug administration, so that individualization of therapy will become the gold standard of treatment in the future.

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### INTRODUCTION

An adverse event is defined as any untoward event that may present during treatment with a medicine, but which does not necessarily have a causal relationship to the treatment<sup>1</sup> Pharmacovigilance has been defined as “the science and activities relating to the detection, assessment, understanding and prevention of adverse drug effects or any other related problems<sup>2</sup>.

A fixed drug eruption (FDE) characteristically recurs in the same site/sites each time the drug is administered, with each exposure, however, the number of involved sites may increase. Usually, just one drug is involved, although independent lesions from more than one drug have been described<sup>3</sup>. Carbamazepine is an iminostilbene derivative with potent anti seizure activity.<sup>4</sup> Here we present an old case of fixed drug eruption with extensive involvement due to carbamazepine along with recently diagnosed bullous pemphigoid, which is a rare presentation.

**Case Report:** A 75 year old man presented to the hospital with history of consumption of one tablet of carbamazepine 5 years back, after which he developed multiple hyperpigmented macules over the trunk and extremities(Fig 1).

There was associated itching and photoallergy. The drug was withdrawn thereafter, but the hyperpigmented lesions persisted. Thereafter he developed multiple bullae all over the trunk and extremities which was present on and off. The patient is a known diabetic for 10 years and has been on Tab. Metformin 500 mg TDS and Tab. Acarbose 25 mg 1 OD and Tab. Glibenclamide 5 mg (2-1-1). He has been taking Tab. Prednisolone 5 mg 4 OD, Tab. Azathioprine 50 mg OD, Tab. Ranitidine 50 mg OD for the past 2 years.

On examination multiple well defined hyperpigmented macules in a rippled pattern were present over the trunk and extremities. Also, multiple discrete vesicles with urticarial,

wheel and erythematous base all over the trunk and extremities were seen (Fig 2).

The biochemical investigations were normal. The biopsy was done, which was suggestive of bullous pemphigoid. On admission, he was diagnosed to have fixed drug eruption due to carbamazepine with associated bullous pemphigoid treated with with Inj. Dexamethasone 8 mg im OD, Tab. Ranitidine 50 mg OD, Cap. Doxycycline 100 mg BD and Tab. Cetrizine 10 mg OD for 5 days. The causality assessment was done using WHO and Naranjo scoring system and was found to have a possible association between the administration of the drug and the adverse drug reaction(Table 1).

Though drugs like analgesics and antibiotics are commonly implicated in the causation of fixed drug eruption, this case is presented for the rarity of its presentation and the probable role of carbamazepine in the exacerbation of bullous pemphigoid.

### DISCUSSION

Fixed drug eruptions usually appear as solid, erythematous, bright red or dusky red macules that may evolve into an edematous plaque, although bullous type lesions may be present. Lesions are solitary at first, but with repeated attacks new lesions usually appear and existing lesions may increase in size<sup>5</sup>. Occasionally, involvement is so extensive as to mimic Toxic Epidermal Necrolysis (TEN)<sup>6</sup>. As healing occurs, crusting and scaling are followed by hyperpigmentation, which may be very persistent and occasionally extensive, especially in pigmented individuals; pigmentation may be all that is visible between the attacks<sup>7</sup>.

Drug induced bullous pemphigoid can encompass a wide variety of presentations, ranging from classic features of large, tense bullae arising from erythematous urticarial

Fixed drug eruption due to Carbamazepine



Fig. 1: The figure shows fixed drug eruption due to Carbamazepine with hyperpigmentation over the thigh.

Fixed drug eruption with bullous pemphigoid



Fig. 2: The figure shows extensive residual hyperpigmentation of the fixed drug eruption over the trunk with multiple bullae. The histopathological examination of the bullae showed lesions typical of a bullous pemphigoid.

Table 1: Assessment of the adverse drug reaction using Naranjo Adverse Drug Reaction Probability Scale

| Question   | Yes | No | Don't know | Score    |
|--|-----|----|------------|----------|
| 1 Are there previous conclusive reports on this reaction?  | 0   | 0  | 0          | 0        |
| 2 Did the adverse event appear after the suspected drug was administered?                                    | +2  | -1 | 0          | +2       |
| 3 Did the adverse reaction improve when the drug was discontinued or a Specific antagonist was administered? | +1  | 0  | 0          | 0        |
| 4 Did the adverse event reappear when the drug was re-administered?  | +2  | -1 | 0          | 0        |
| 5 Are there alternative causes (other than the drug) that could on their own Have caused the reaction?       | -1  | +2 | 0          | 0        |
| 6 Did the reaction reappear when a placebo was given?  | -1  | +1 | 0          | +1       |
| 7 Was the drug detected in blood (or other fluids) in concentrations known To be toxic?                      | +1  | 0  | 0          | 0        |
| 8 Was the reaction more severe when the dose was increased or less severe When the dose was decreased?       | +1  | 0  | 0          | 0        |
| 9 Did the patient have a similar reaction to the same or similar drugs in any Previous exposure?             | +1  | 0  | 0          | 0        |
| 10 Was the adverse event confirmed by any objective evidence?  | +1  | 0  | 0          | +1       |
| <b>TOTAL SCORE</b>   |     |    |            | <b>4</b> |

Scoring

≥ 9 = definite ADR      1-4 = possible ADR  
 5-8 = probable ADR      0 = doubtful ADR

base to scarring plaques, nodules and bullae. The histopathological examination shows perivascular infiltration of lymphocytes with few eosinophils and neutrophils, intraparenchymal vesicles with foci of necrotic keratinocytes, thrombi in dermal vessels, and possible lack of tissue bound and circulating basal membrane IgG<sup>8</sup>. Common drugs implicated in the causation of fixed drug eruption include sulphonamides, tetracycline, salicylates and barbiturates<sup>9</sup>. Carbamazepine was commonly involved

in the occurrence of Steven Johnson's Syndrome (SJS)/TEN<sup>10,11</sup>, though a few case reports report that carbamazepine as a cause for fixed drug eruption<sup>12</sup>. By far, rash is the most common cutaneous manifestation of carbamazepine toxicity<sup>13</sup>, which may act as an early warning to bone marrow toxicity due to the same agent. Carbamazepine was also involved in the causation of drug induced Systemic Lupus Erythematosus (SLE)<sup>14</sup>.

The pathogenesis of carbamazepine induced FDE is poorly understood. Although genetic markers like HLA-B \*1502 and HLA B\*5801 are found to be associated with carbamazepine induced SJS/TEN<sup>15</sup>, the exact mechanism by which carbamazepine causes FDE is still unclear. The FDE caused by carbamazepine differs from other agents in the sense that there is extensive involvement so as to mimic TEN. Also, the perioral provocation test, which is commonly employed to detect an underlying FDE and to elaborate the pathogenesis, is of little value, because it results in re induction of exfoliative dermatitis<sup>16</sup>. Oral therapy with steroids enabled 16 to 20 patients successfully to continue on carbamazepine after development of a rash shortly after introduction of the drug.<sup>17</sup>

Although isolated case reports report an association of bullous pemphigoid with carbamazepine overdose<sup>18</sup> it still remains unclear whether the drug itself remains a cause for the disease, or has actually triggered the idiopathic form of the disease

Carbamazepine induced FDE is a rare occurrence and is peculiar for its extensive involvement. Further elucidation of its underlying pathogenesis and pharmacogenetics will help us treat the condition more efficiently and prevent mortality and morbidity due to the same.

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