A CASE REPORT ON CARBAMAZEPINE INDUCED DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS), KERATOCONJUNCTIVITIS AND HEPATIC INJURY

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ABSTRACT

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome associated with anticonvulsant drugs is a rare but potentially life-threatening disease that occurs in response to arene oxide producing anticonvulsant such as Phenytoin and Carbamazepine. In this article a case report on Carbamazepine induced DRESS is discussed. A 35 year of female patient admitted with the complaints of maculopapular rash, erythema multiforma, blephitis and keratoconjunctivitis of both eye and mucositis. The patient is a known case of epilepsy for the past 10 years and is on Valproic acid. On previous hospital visit the patient was refilled with Carbamazepine 300mg due to continuous seizure episodes which showed no response on Valproic acid therapy. Following which she developed the above adverse drug reactions to the drug. Liver function tests including LDH=615 U/L, SGOT=132U/Land SGPT=137U/L revealed mixed cholestatic and hepatitis changes, which along with a raised INR (1.7) confirmed liver toxicity. Serological tests for hepatitis A, B, C and Epstein-Barr virus (EBV) were negative. All the physical examination and laboratory finding aid in supporting the diagnosis of Carbamazepine induced DRESS. The patient was managed conservatively in a hospital setup using topical and systemic corticosteroids and also managed appropriately for hepatic damage due to the offending agent.

KEYWORDS: Drug rash with eosinophilia and systemic symptoms; Carbamazepine; erythematous rash; keratoconjunctivitis; cholestatic and hepatic changes.
INTRODUCTION
Hypersensitivity syndrome is an idiosyncratic, serious drug reaction that consists of a rash, fever, involvement of multiple visceral organs, and hematological abnormalities such as eosinophilia. To individualize the drug hypersensitivity reaction and to distinguish the hypersensitivity reaction from drug-induced pseudolymphoma, Bocquet et al., have recently introduced the term drug rash with eosinophilia and systemic symptoms (DRESS) syndrome.[1] DRESS syndrome reflects a serious hypersensitivity reaction, especially during therapy with antiepileptic drugs. Clinical features include cutaneous eruption, fever, multiple peripheral lymphadenopathy, and potentially life-threatening damage to one or more organs, such as nephritis, hepatitis, or myocarditis. Skin rash, suggestive of DRESS syndrome, includes maculopapular rash or generalized erythematous rash is usually associated with facial edema. Reversion of systemic manifestations is very slow, ranging between 1 and 6 months. DRESS syndrome is most commonly induced by aromatic anticonvulsants and antibiotics. Nonaromatic anticonvulsants are rarely encountered as the causes of DRESS syndrome. In this report, a discrete case with DRESS syndrome developing due to an antiepileptic drug, Carbamazepine and the treatment modalities were aimed to be discussed in light of the literature.[2]

CASE REPORT
A 35 year old female patient was admitted in the hospital with the complaints of headache for the past two months, fever, blurred vision, conjunctivitis and vomiting on and off. The patient also had the complaints of redness of eye, dysphagia, oral ulcer and facial puffiness. She is a known case of epilepsy for the past 10 years on Valproic acid and hysterectomy done before 4 years. The patient also had also history of arthritis and parasinusitis and hemorrhagic crusting on lip with erosion in buccal mucosa for which she was on treatment for a week. Due to continuous seizure episodes even after administration of Valproic acid, on previous discharge the patient was prescribed with Carbamazepine 300mg, Diclofenac 150mg and Domperidone. Following which the patient developed maculopapular rash, erythema multiforma, blephitis and keratoconjunctivitis of both eye and mucositis which was noted on physical examination. The patient is allergic to Pantoprazole, Phenytoin, Aceclofenac, Phenobarbitone and Lamotrigine. On examination the patient was conscious, disoriented and had seizure attack twice after admission. Full blood examination showed mild eosinophilia, thrombocytopenia and mild microcytic anemia. Liver function tests including LDH=615 U/L, SGOT=132U/L and SGPT=137U/L revealed mixed cholestatic and hepatitis changes, which
along with a raised INR (1.7) confirmed liver toxicity. Serological tests for hepatitis A, B, C and Epstein-Barr virus (EBV) were negative. All the physical examination and laboratory finding aid in supporting the diagnosis of Carbamazepine induced Drug Reaction (or Rash) with Eosinophilia and Systemic Symptoms (DRESS).

Management in the first week entailed cessation of Carbamazepine, bed rest, and general fluid and nutritional support. Topically she was treated with liquid paraffin emollient all over, with Fluticasone propionate ointment and T. Desloratidine 5mg per oral twice a day to combat the pruritus. For mucositis a topical antifungal and topical antibacterial/corticosteroid combination was used, in addition to chlorhexidine gluconate mouthwash. Despite this, specific liver parameters continued to deteriorate and from day 7 of admission, he was treated with intravenous (IV) hydrocortisone 50ml (2mg/ml) six hourly for 3 days, concurrently with oral Ursodeoxycholic acid 900mg daily. This led to rapid reversal of both abnormal liver function and clinical symptoms. The patient was administered with Tablet Paracetamol 1g and Tablet Piperacillin-Tazobactam combination 4.5g eight hourly for fever and parasinusitis. No further systemic steroids were given by mouth or IV, and no rebound of symptoms or laboratory parameters were seen. The patient was managed conservatively and discharged to outpatient services 10 days after intervention.

**DISCUSSION**

The Drug Reaction with Eosinophilia and Systemic symptoms (DRESS) is a severe adverse drug-induced reaction. The estimated incidence of this syndrome ranges from 1 in 1000 to 1 in 10,000 drug exposures. \(^{[3]}\) The acronym designated by Bocquet et al., describes a potentially life-threatening syndrome including a severe skin eruption, fever, hematologic abnormalities (eosinophilia or atypical lymphocytes) and internal organ involvement. The other noteworthy features are a delayed onset, usually 2-6 weeks after the initiation of drug therapy, and the possible persistence or aggravation of symptoms despite the discontinuation of the culprit drug. \(^{[1,4]}\) The pathogenesis of DRESS syndrome is partially understood. Different mechanisms have been implicated in its development, including detoxification defects leading to reactive metabolite formation and subsequent immunological reactions, slow acetylation and reactivation of human herpes, including Epstein-Barr virus and human herpes virus (HHV)-6 and -7. \(^{[5,6]}\) The detection of HHV-6 reactivation has even been recently proposed as a diagnostic marker for DRESS. The diagnosis of DRESS is challenging because the pattern of cutaneous eruption and the types of organs involved are various. In addition,
the multitude of denominations for this syndrome, such as drug hypersensitivity, drug induced delayed multiorgan hypersensitivity syndrome.\textsuperscript{[7]} and recently, drug-induced hypersensitivity syndrome (DIHS).\textsuperscript{[8]} is confusing. However, recognizing this syndrome is of particular importance, as the mortality rate is up to 10%. DRESS syndrome can manifest 1-8 weeks after starting the anticonvulsant therapy with a mean of 3 weeks. In previously sensitized individuals, DRESS may occur within 1 day upon rechallenge. In our case, DRESS syndrome developed 7 after the introduction of Carbamazepine. The patient had no known exposure to other medications that have been implicated in development of the DRESS syndrome.\textsuperscript{[9]} Although rare, it is seen with lots of commonly used drugs like Phenobarbitone, Phenytoin, Lamotrigine, Minocycline, Sulphonamide, Allopurinol, Dapsone, Ethambutol, Celecoxib, etc. It is important to recognize this entity early because it can mimic other pathologies; is potentially serious (with mortality as high as 10% and withdrawal of the incriminating drug being the only definitive treatment.\textsuperscript{[10]}

As in the management of adverse drug reactions, it mostly involves discontinuing the suspected drug and treating the systemic manifestations and symptoms associated with the reaction. In this patient the drug was discontinued and the patient was managed conservatively by emollients and topical corticosteroid preparations for subsiding pruritus and also to reduce flaring up of the symptoms. In this case all other drugs administered prior was discontinued and the patient was started on systemic corticosteroids, with rapid resolution of her fever and eosinophilia and progressive improvement in skin rash and multiorgan system dysfunction. Use of the Naranjo adverse drug reaction probability scale and WHO-UMC assessment scale showed a probable relationship between the patient’s development of DRESS syndrome and treatment with Carbamazepine. As a part of management of the reaction and to manage the seizure episodes the patient can be treated using Oxcarbamazepine, Phenytoin or Phenobarbitone. Since the patient is allergic to Phenytoin ad Phenobarbitone, Oxcarbamazepine would be a better choice.

CONCLUSION

In conclusion, the diagnosis of DRESS should be highly suspected with the presence of skin rash, liver involvement, fever, Hypereosinophilia and lymphadenopathy. The high rate of HHV-6 and other herpes viruses reactivation associated with DRESS implies that HHV-6 and other herpes viruses should be detected in routine clinical practice. Clinicians and pathologists must take special care to recognize the heterogeneous clinical and histologic
symptoms of these conditions. They must also consider the possibility of finding hypersensitivity syndrome to Carbamazepine, which may histologically mimic mycosis fungoides and systemically present as a true lymphoma, as in our case. After drug discontinuation, complete remission of the condition, in addition to the results of Carbamazepine allergy tests, will help clinicians make the correct diagnosis and therefore, avoid unnecessary aggressive chemotherapy. Patients with Carbamazepine hypersensitivity syndrome require regular follow-up examinations for years to prevent what is known as a pseudo-pseudolymphoma—which, in time, becomes true lymphoma. Besides the prompt withdrawal of causative drug as standard of care, further studies are needed to recommend specific treatment guidelines. All health care professionals must understand the necessity of reporting such adverse drug reactions and thereby educating other health care members of the team in developing necessary strategies to detect, evaluate and treat adverse drug reaction at the earliest thereby reducing significant burden to hospital and the patients economically and physically.

REFERENCE
