International Journal of Research in Dermatology
Mawenzi RL et al. Int J Res Dermatol. 2018 Nov;4(4):600-604
http://www.ijord.com

DOI: http://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20184469

Case Report

Management of carbamazepine induced drug reaction with eosinophlia and systemic symptoms in Mediheal hospital-Nakuru, Kenya: a case report

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Received: 19 August 2018
Accepted: 22 September 2018

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ABSTRACT

Adverse drug reactions (ADR) are undesirable events occurring as consequences of an ingested, injected or applied drug. Their spectrum can range from mild to severe reactions. Severe Cutaneous Adverse Reactions (SCARs) are diverse in presentation and in consequence. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a type of life-threatening SCAR which affects the skin as well as the internal organs. Various drugs can cause DRESS, but aromatic anticonvulsants, especially carbamazepine are considered the major culprits. The diagnosis of DRESS requires a high index of suspicion followed by an intense sign-searching clinical examination guided by established criteria. We report a previously healthy 53 year old man of Kenyan ancestry who developed fever, widespread maculopapular rash, swollen eyelids and cervical lymphadenopathy three weeks after carbamazepine. Liver enzymes were markedly elevated and he had lymphocytopenia and a positive serology for human herpes virus type 6 (HHV6). Using the RegiSCAR criteria a probable diagnosis of DRESS secondary to carbamazepine was made. His treatment involved discontinuation of the drug, intravenous hydrocortisone together with mild topical steroids. He remarkably improved and was discharged on oral prednisone and followed up for three consecutive months. The length of his hospitalisation was ten days. Carbamazepine has potential to provoke DRESS in patients of Kenyan ancestry. DRESS should be anticipated before and during use of carbamazepine for early recognition. Treatment of DRESS should involve the immediate withdrawal of offending drug and rapid initiation of systemic corticosteroids as well as application of diluted topical steroids to sooth the skin.

Keywords: Carbamazepine, Drug reaction with eosinophilia and systemic symptoms, Human herpes virus, Kenya

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe, unpredictable side effect of a drug. It is characterized by a constellation of signs and symptoms of cutaneous, hematologic and systemic origin. Various drugs can initiate DRESS, however, aromatic anticonvulsants, especially carbamazepine are currently considered the major culprits.[1] Recently, human leucocyte antigen (HLA-B) gene and human herpes viruses have been advocated as potential facilitators of DRESS among those using culprit drugs.[2] The epidemiology of DRESS is still being determined. Its incidence is estimated to range from 1 to 10 per 10,000 drug users per year.[3] People of African descent are reported to be especially vulnerable to develop DRESS.[4] The disorder does not discriminate gender or age.

The cutaneous manifestations of DRESS are characteristically protean; intense pruritus,

maculopapular eruptions, generalized urticarial papules, desquamation, erythema, swollen eyelids, infiltrated and edematous skin are some of skin signs that occur commonly.[4] These manifestations however, can occur typically or atypically. Haematologic manifestations commonly associated with DRESS include eosinophilia, thrombocytopenia and lymphocytic aberrations.[5] DRESS is a multisystem disease characterised by the involvement of many organs. The liver, lungs, kidneys and lymph nodes are the organs frequently involved[5]. Others include the pancreas, heart and brain.[5] The multi-systemic effects of DRESS make it one of the leading sources of morbidity and fatality recorded in drug reactions.

The diagnosis of DRESS is currently guided by criteria generated by a group of European experts designated as European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR).[6] The RegiSCAR criteria lists the presence of fever >38^{0}C, enlarged lymph nodes, involvement of at least one internal organ, and abnormal blood picture, as mandatory for the diagnosis of DRESS. Another set of diagnostic criteria suggested by a Japanese group of experts (SCAR-J) lists positive serology for HHV-6 as an additional element among its items.[7]

Most patients with DRESS are managed conservatively. The capstone of management is the immediate withdrawal of offending drug and use of systemic corticosteroids.[8] Use of new generation antihistamines and enhanced nursing care are suitable adjunctive approaches**.** Patients with severe organ dysfunction may need to be managed in intensive care unit.

CASE REPORT

A 53 years old man consulted a general practitioner due to a first time episode of nocturnal convulsions. He was treated with carbamazepine. After three weeks, he developed an extremely itchy skin rash but was reassured and advised to continue with the drug. However, his condition progressively deteriorated following which he sought a consultation in a midtown dermatology clinic in Nakuru town. His history and clinical manifestations were consistent with severe cutaneous adverse reaction (SCAR). He was therefore admitted in Mediheal Hospital for close observations and management.

On examination, he had generalized erythema, thin walled pustules on the upper chest, neck and upper back. His skin was hot and characteristically inflamed. There was acral and facial edema, swollen eyelids and a fever of 38^{0}C. His blood pressure was 140/85; pulse rate was 102beats/min and respiratory rate was 32/min. There was no palpable organomegally or lymphadenopathy. Following these observations, a diagnosis of SCAR due to carbamazepine was sustained.

Carbamazepine was stopped forthwith and patient was commenced on intravenous hydrocortisone 100 mg twice daily. A twice daily application of topical betamethasone ointment diluted in white soft paraffin and liquid paraffin was begun. Additionally, levocetirizine-montelukast combination was administered two times per day. No substitute of the anticonvulsant was given, instead, the patient was observed for seizures but none occurred.

Investigations were ordered to rule out definable SCAR entities such as acute generalized exanthematous pustulosis (AGEP) and DRESS. The results of the tests were as shown in Table 1.

Table 1: Results of initial laboratory investigations.

Test	Result	Reference
Liver function tests		
Total bilirubin	0.83 mg/dl	0–1.0
Direct bilirubin	0.63 mg/dl	0–0.20
AST	34.3 u/l	0–40.0 u/l
ALT	321.9 u/l	0–41.0 u/l
Alkaline phosphatase	53.6 u/l	0–105 u/l
GGT	240.9 u/l	0–55.0
Full haemogram		
WBC count	17,000 u/l	4,000–11,000 u/l
Neutrophil count	78%	40–60%
Eosinophil count	6%	2–6%
Monocytes	2%	3.0–9.0%
Lymphocyte count	14%	20–40%
Hemoglobin	15.1 g/dl	14–17.5
Platelet count	348000 u/l	150,000–50,000 u/l

The initial results as observed were consistent with a SCAR but not specific to AGEP or DRESS. The initial treatment for SCAR was therefore continued and by the second day of intravenous and topical corticosteroids the patient had improved remarkably. The temperature normalised, the itching abated, the skin less infiltrated and the facial edema significantly regressed. On the third day, there being no new complaints and the patient in fair general condition, he was discharged on twice daily application of the topical preparation and a daily intake of levocetirizine-montelukast combination. However, his condition deteriorated three days post discharge and he was readmitted. He complained of extreme fatigue, throbbing headache, and a new eruption of intensely itchy body rashes and upper abdominal discomfort.

On examination, he looked quite ill and had a hyperpyrexia of 42^{0}C, a pulse rate of 122 beats/min, and a respiratory rate of 38breaths/min. His face was puffy and eyelids were swollen. Prominent and palpable lymph nodes (>2 cm in diameter) were noted below the angles of both jaws and cervical area. There was tenderness on his right upper quadrant and the epigastrium but no palpable organomegally. On auscultation, there were bounding rapid heartbeats and fine basal rales on both lungs. His lower arms, hands and legs were swollen. The entire skin was erythematous, infiltrated and inflamed.

Urticarial plaques, papules, dusk-red patches and macules, and exfoliation were also noted. The new manifestations were consistent with DRESS. Consequently, relevant lab tests were ordered to confirm or rule out DRESS; the results are as shown in Table 2.

Table 2: Lab results on readmission.

Test	Result	Reference
Urea	45.8 mg/dl	15.0–39.0
Serum creatinine	1.1 mg/dl	0.7–1.20
Liver function tests		
Total bilirubin	1.42 mg/dl	0–1.0
Direct bilirubin	0.84 mg/dl	0–0.20
AST	264.7 u/l	0–40.0 u/l
ALT	321.9 u/l	0–41.0 u/l
Alkaline phosphatase	945.7 u/l	0–105 u/l
GGT	883.8 u/l	0–55.0
Full haemogram		
WBC count	7100 u/l	4.0–11000 u/l
Neutrophil count	70%	40–60%
Eosinophils	5%	2–6%
Monocytes	8%	3.0–9.0%
Lymphocyte count	15%	20–40%
Hemoglobin	12.5g/dl	14–17.5
Platelet count	148000 u/l	150,000 u/l–450,000 u/l).
Human herpes virus type 6	Positive	Negative

Table 3: Levels of hepatic enzymes 90 days after DRESS.

Test	Result	Reference
Total bilirubin	1.51 mg/dl	0–1.0 mg/dl
Direct bilirubin	0.68 mg/dl	0–0.20 mg/dl
AST was normal	28.4 u/l	0–40.0 u/l
ALT was normal	35.4 u/l	0–41.0 u/l
Alkaline phosphatases	85.8 u/l	0–105 u/l
GGT was normal	88.8 u/l	0–55.0

Based on the RegiSCAR criteria scoring system, he scored 5 points making him a probable case of DRESS. He was restarted on intravenous hydrocortisone 100 mg twice daily for three days then switched to prednisone 60 mg daily with a weekly taper by 5mg until a dose of 10 mg per day was reached. A topical preparation comprising betamethasone valareate ointment 200G in 100 g of white soft paraffin and 100 mls of liquid paraffin was compounded for twice daily application. Although there was no clinical evidence of herpetic disease, acyclovir was given in anticipation of herpes virus reactivation based on positive HHV-6 antibodies titers.

The patient improved progressively and was discharged after seven days of hospitalization. His subsequent follow up was done after every three weeks for a period of three consecutive months. All other parameters normalized within the first three weeks but hepatic enzymes levels were slow to normalize. As shown in Table 3, some hepatic enzymes were still marginally high on the 90th day post event.

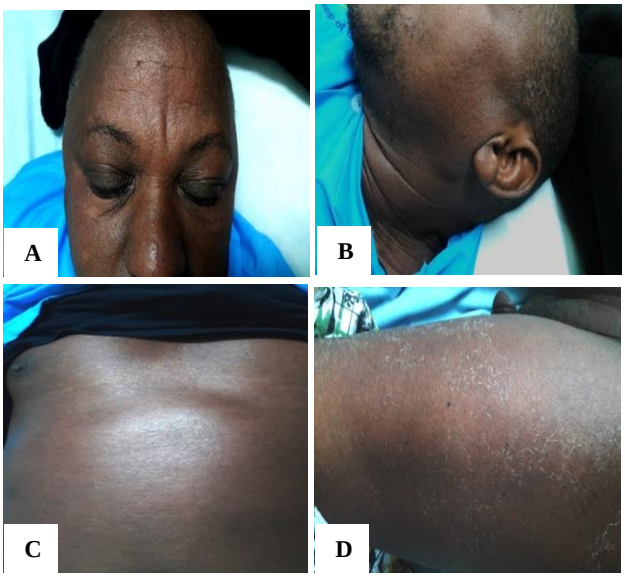

Figure 1: (A) Swollen eyelids; (B) swollen lymph node; (C) infiltration of skin; (D) exfoliation of skin.

DISCUSSION

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe form of drug reaction associated with an avarage mortality of 10 to 20 people in every 100.[9] These signifcant levels of mortality call for enhanced diligence before and during the use of drugs commonly implicated in DRESS. Though DRESS can occur secondary to many drugs, it is commonly associated with use of aromatic anticonvulsants chief among them being carbamazepine. Other implicated drugs include but are not limited to allopurinol, dapsone, minocycline and sulphur based drugs.[10]

The pathomechanism of DRESS is complex and only partially understood. It is currently unknown why some individuals do suffer DRESS while others don't. However, genetic factors associated with poor metabolism of enzymes responsible for drug breakdown such as cytochrome P450 and variability in genes encoding HLA molecules have been implicated.[11] These varied factors could be linked to the observation that people of African descent are reported to be especially vulnerable to DRESS.[4] DRESS has been observed to occur more frequently in the black race than the causcasians.[7] This observation calls for heightened preparedness among clinicans handling African patients on aromatoc anticonvulsants. Viral infections, especially by the herpesviruses have also been linked to the etiopathogenesis of DRESS.[12] However, as was seen in

this case, a postive antibody HHV type 6 test did not have any clinical significance.

DRESS is considered to be rare, its incidence is estimated to be between 1 in 1000 and 1 in 10 000 drug exposures.[3] Nevertheless, the apparent low prevalence could be a result of under diagnosis or underreporting. The scarcity of data on DRESS form Africa is a case in point. Published data on DRESS in Kenya could not be found despite a rigorous search, this case report could actually be the first published from Kenya. Lack of published reports does not indicate absence of DRESS. The incidence of DRESS is therefore expected to rise with increased reporting of cases, enhanced alertness and improved diagnostic capabilities.

The natural progress of DRESS from exposure to clinical manifestations is about three weeks in the majority of patients. The patient described in this case report also developed symptoms on the third week post exposure. This relatively long incubation period separates DRESS from other SCARs majority of which occur after 72 hours. It is prudent therefore that any patient who develops fever and skin rashes on or around the third week of suspect drug intake should be evaluated and managed as a case of DRESS. Clinicians need to be alert to minimize undue delay in diagnosis. As was seen in this case, the patient's first contact encouraged the patient to continue with carbamazepine when the initial tale sign were evident. This is indicative of low awareness levels of DRESS among clinicians. Besides, this case was managed as a case of ordinary ADR and was therefore discharged prematurely. Such mishaps need to be rectified through continuous medical education through publication of cases.

Diagnosis of DRESS is based on two criteria- the RegiSCAR[6] and the SCAR-J[7] criteria. For this particular case, the diagnosis was based on total scores calculated from the RegiSCAR criteria where a point each is awarded to a selected feature commonly associated with DRESS. The following scores were awarded to this case:

- 0 point for having fever.
- 0 points for not having eosinophilia ≥0.7 X 109/L or ≥10% if WBC <4.0 X 109/L
- 1 point for having skin rash covering >50% of body surface area.
- 1 point for having skin rash suggesting DRESS.
- 1 point for having atypical lymphocytes
- 2 points for having two organs involved (lung and liver).

The total RegiSCAR score in this patient was five, making it a probable case of DRESS. However, as alluded to by other experts, positive HHV-6 antibodies and puffy eyelids seen in this case lends credence to a definite diagnosis of DRESS.[7,13] Other reinforcing features include persistence of symptoms long after the offending drug was discontinued. This symptom persistence distinguishes DRESS from close mimickers.[14] Contrary to what is commonly seen in DRESS, this patient did not have eosinophilia. Eosinophilia was also not observed in another African country.[15] This provides fertile grounds for more research to investigate the prevalence of eosinophilia among Africans with DRESS. Nevertheless, the patient in this study exhibited lymphopenia, neutrophilia and thrombocytopenia. These hematologic aberrations occurring without eosinophilia have also been experienced in other settings.[16] Lack of eosinophilia should therefore not sway the diagnosis of DRESS. We suggest that the 'E' in the acronym DRESS should probably represent two effects- Eosinophilia and or 'Erratic' white blood cells.

The rapid improvement of systemic symptoms in this patient following the administration of intravenous hydrocortisone reaffirms the central role of systemic steroids in the management of DRESS. Although other experts aver that topical steroids alone may resolve DRESS, this should be avoided because topical steroids cannot effectively control inflammation of internal organs. However, use of diluted topical steroids is required to mitigate secondary skin changes such as excoriation and desquamation. The rapid defervescence of fever following administration of intravenous hydrocortisone alone reflects the central role of systemic steroids in DRESS. Antipyretics are therefore unnecessary in the management of fever in DRESS instead systemic steroids especially when given intravenously, should be prioritised in all cases of DRESS. Topical applications, such as bland emollients or mild topical corticosteroids can be used as adjuvants to mollify the skin. Hospitalisation of patients with DRESS is recommended for proper monitoring and good nursing care. Despite long term prednisolone therapy, adverse effects associated with long term corticosteroid administration were not observed in this patient. Nevertheless, long term corticosteroid administration should be cautiously monitored for short and long term side effects. This particular patient did not require intensive nursing care; nevertheless, patients with life-threatening severe systemic disease should probably be nursed in intensive care units.

In order to detect any organ specific sequelae of DRESS, follow up of patients is necessary. During the follow up of this patient, liver derangement was still evident three months later. It is pragmatic therefore to advise all patients recovering from DRESS to abstain from any diets or drugs that can impact on the liver. According to the criteria advanced by the International Consensus Meeting Criteria to classify types of liver injury in DRESS, the R ratio of this particular case was 0.87, assigning it the cholestatic type of liver injury. Cholestatic liver injury is described as the most common type of hepatic damage especially in older patients. Others are - hepatocellular and the mixed type.

CONCLUSION

DRESS is a multi-organ disease occasioned by a use of carbamazepine and other related drugs by vulnerable persons. It should be anticipated among individuals in Kenya who are taking aromatic anticonvulsants. It manifests with cutaneous, hematologic and organ-specific symptoms at least three week after use of the offending drug. Cutaneous symptoms and fever occurring around the third week of administered drug should arouse suspicion of DRESS. Its diagnosis is made by clinical means supported by laboratory findings and specific criteria. It is managed by prohibiting further use of suspected drug and their associates, use of systemic steroids in conjunction with mild topical steroids. As a preventative strategy, we recommend that where alternatives to carbamazepine exist, priority should be to use them other than carbamazepine where indicated.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Mawenzi RL, Parikh D. Management of carbamazepine induced drug reaction with eosinophlia and systemic symptoms in Mediheal hospital- Nakuru, Kenya: a case report. Int J Res Dermatol 2018;4:600-4.