EVALUATION OF A CASE FROM LTMMC & LTMGH

Phenytoin induced DRESS syndrome complicated with second drug rash due to Amoxicillin and / or Ibuprofen

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Case Report:

A 26-year-old married woman presented with sudden onset of red colored lesions all over the body associated with low grade fever and malaise since 2 weeks. The patient was on phenytoin 100 mg three times a day for convulsions since 2 month prior to development of rash. For her rash prednisolone 60 mg was initiated, but there was worsening of the lesions with fever. She received oral amoxicillin and ibuprofen from a private practioner for fever. After 3 days of receiving oral amoxicillin and ibuprofen she developed further increase in intensity of rash with pus filled lesions around mouth. There was no mucosal involvement. There was no history of photosensitivity or previous drug allergy.

On general examination there was no pallor, cyanosis or icterus. Generalized bilateral, tender, mobile, firm 1.5 x 1.5 cm cervical, axillary and inguinal lymph nodes were palpable with bilateral pitting pedal edema.

Cutaneous examination showed perioral grouped 1 to 2 mm size pustules with pitting, tender facial edema. (Fig. 1)

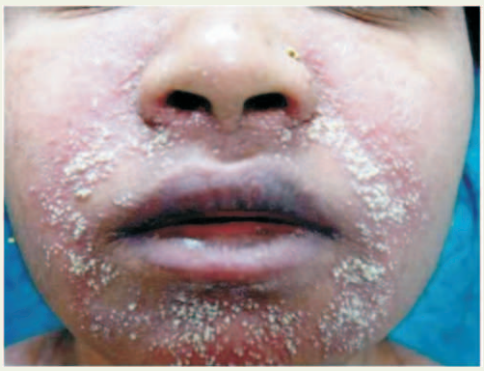

Figure 1: Showing perioral pustules

Generalized, tender, erythematous maculopapular rash was present all over the body sparing palms and soles with erythematous patches over the extremities. (Fig. 2, 3)

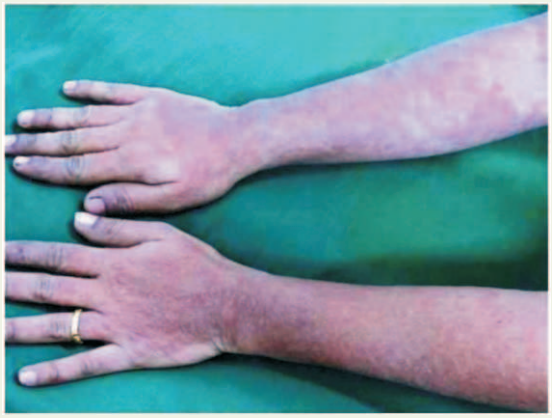

Figure 2 : erythematous rash on hands

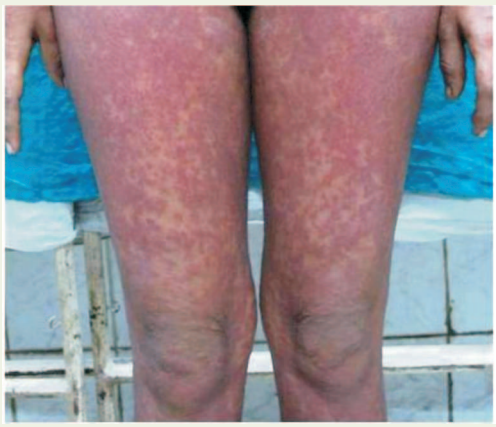

Figure 3 : erythematous rash on legs

Her hematological investigations revealed hemoglobin 10.5 gm/dl; WBC count - 17,900; polymorphonuclear leukocytosis – 80%; lymphocyte – 68; monocytes – 10; eosinophils – 15; absolute eosinophil count – 1500 cells / cmm; increased liver enzymes serum glutamic oxaloacetic transaminase – 76 (Normal range 0-40 IU/L), serum glutamic - pyruvic transaminase – 216 (Normal range 0-40 IU/ L); erythrocyte sedimentation rate 20 mm at the end of hour. Gram staining and pus culture of pustule did not reveal any organisms. Urine microscopy, X- Ray chest were normal and HIV by ELISA were normal / negative.

Fine needle aspiration cytology of left axillary lymph node showed plenty of atypical lymphocytes in varying stages of maturation. Macrophages were also seen which is consistent with drug induced lymphadenopathy. Histopathology of pustular lesion around oral cavity showed basket-weave orthokeratosis, subcorneal blister with moderate spongiosis. There was peri-vascular lymphocytic infiltrate with papillary dermal oedema and extravasation of red blood cells which is suggestive of acute generalized exanthematous pustulosis (Fig. 4)

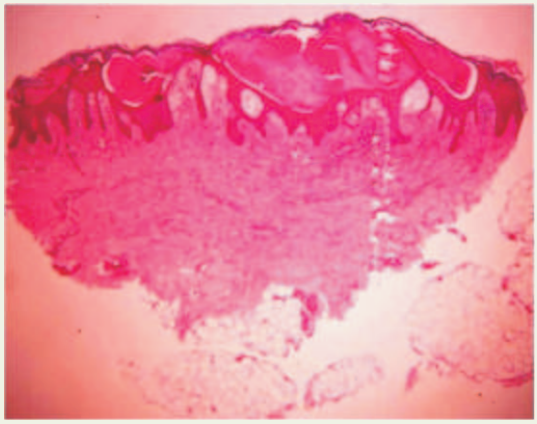

Figure 4 : Histopathology of pustular lesion suggestive of acute generalized exanthematous pustulosis

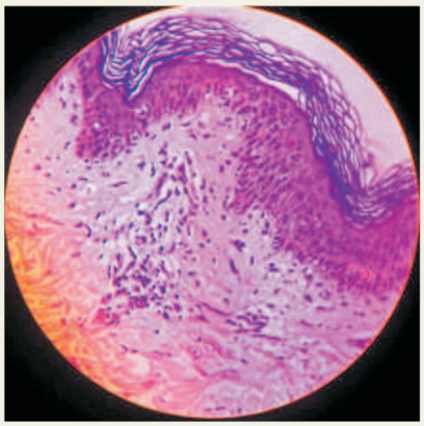

Figure 5 : Histopatalogy of erythematous papule with eosinophils few necrotic keratinocyte

Histopatalogy of erythematous papule showed focal basal vacuolization, superficial and deep perivascular lymphocytic infiltrate with few eosinophils with few necrotic keratinocytes. (Fig. 5)

On the basis of clinicopathological and hematological correlation diagnosis of a combination of two drug reactions were:

1. DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms) secondary to phenytoin
2. Acute generalized exanthematous pustulosis secondary to amoxicillin and / or ibuprofen

The patient was admitted and offending drugs were stopped. She was started on oral Prednisolone (60 mg), tab. Levocetrizine 5 mg and wet compresses four times a day over pustular lesions. The patient improved remarkably over a period of two weeks.

Causality analysis of the ADR

Here, the patient showed 2 ADRs and the causality analysis has been done separately for these drugs.

DRESS syndrome due to Phenytoin: There is a history of taking Phenytoin for 8 weeks prior to development of rash and low grade fever. The ADR is unlikely to be attributed to other disease or drugs and hematological, laboratory and histopathological evidence confirmed DRESS syndrome. There was also improvement in the patient on stopping Phenytoin. In this case, re challenge was not done, and hence as per the WHO scale, causality analysis it can be graded as "Probable".

Acute generalized exanthematous pustulosis due to Amoxicillin and / or Ibuprofen: There is a history of development of pus filled lesions around the mouth after 3 days of starting Amoxicillin and / or Ibuprofen. The AE can occur due to viral infection and either Amoxicillin (more commonly) or Ibuprofen. Hence, it can be explained by disease and other drugs (2 drugs are implicated here).
Hence as per the WHO scale causality analysis it can be graded as "Possible".
In this case, information on drug withdrawal is available and there is improvement on stopping the offending drugs. Re challenge information is not available.

Discussion:

Acute generalised exanthematous pustulosis (AGEP) is characterised by sudden and simultaneous onset of fever with edematous scarletiniform rash. It is soon covered by hundreds of nonfollicular, small, superficial pustules. The disease is self-limiting, fever and pustules lasting for 7 to 10 days, followed by desquamation. Often drugs and viral infections are implicated. Antibiotics are the main class of drugs implicated in the development of AGEP along with anticonvulsants and anti-inflammatory drugs. The most striking feature of AGEP is the short interval between the drug administration and the onset of the disease. [1]

DRESS syndrome is characterized by involvement of various organs and organ systems, particularly the skin, liver and hematologic system. [2]

DRESS syndrome usually occurs on first exposure to the associated offending medication; with a delayed onset classically begin 1 week to 8 weeks after starting drug therapy. In previously sensitized individuals, anticonvulsant hypersensitivity syndrome may occur within 1 day on re-challenge. It has no relationship to dosage or serum concentration of anticonvulsants. The reaction usually starts with low to high-grade fever, and over few days' cutaneous reaction develop. The cutaneous rash is most commonly an exanthema with or without pruritus which starts as a macular erythema and evolves into a red, symmetrical, confluent, papular rash. Initially, the upper trunk and face are affected, with later involvement of the lower extremities. This is followed by involvement of various internal organs, most commonly being the liver. [3]

Careful assessment is necessary as cutaneous changes do not necessarily reflect severity of internal organ involvement. Facial or periorbital swelling is a sign of a systemic and potentially severe reaction and helps in the diagnosis, because the typical erythematous, symmetric drug eruption often involves the body but spares the face. Rash usually resolve with desquamation. Tender local cervical nodes or generalized lymphadenopathy which usually involves axillary, cervical and inguinal nodes is another common feature of DRESS. [4.5]

Multiple drug reactions in an individual may pose challenge for physician as complications of DRESS / AGEP are severe as in this case.
Treatment of these conditions includes discontinuation of the offending drug and systemic steroid 1 to 2 mg/kg/day to avoid potential progression of symptoms. [6]

It is also known that there exists cross reactivity between anticonvulsant drugs for developing DRESS syndrome and hence additional diagnostic methods should be sought to select safer alternative for seizure control.
Although no gold standard exists, in vitro lymphocyte toxicity assay or lymphocyte transformation tests (LTT), and in vivo patch tests may be helpful in such situations. Many studies have showed the usefulness of LTT and patch testing for the diagnosis of hypersensitivity to anticonvulsants. LTT shows similar results with patch test. But false negative reaction of LTT was also noted in patients with simultaneous positive patch test. [7]
Gabapentin and valproic acid could be considered as alternative therapeutic options in few cases. [8]

Finally, one has to take care that the prodromal symptoms of DRESS / AGEP can be misdiagnosed as bacterial or viral infection and a patient can be treated with antibiotics which can sensitise the patient, thereby worsening the existing condition. These prodromal symptoms of DRESS / AGEP should be recognized to avoid further complications as in our case.

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PUBLISHED CASE REPORTS ON DRESS SYNDROME

Drug Hypersensitivity to Previously Tolerated Phenytoin by Carbamazepine-induced DRESS Syndrome

J Korean Med Sci 2006; 21: 768-72

Cheol-Woo Kim, Gwang-Seong Choi, Chang-Ho Yun, Deok-In Kim

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 arena oxide producing anticonvulsant such as phenytoin and carbamazepine. There have been many reports of cross reactivity among the anticonvulsants upon first exposure to the offending drugs. However, there has been few data describing the development of DRESS syndrome after switching medication from previously well-tolerated phenytoin to carbamazepine, and the induction of hypersensitivity to phenytoin by DRESS to carbamazepine. We experienced a case of a 40-yr-old man who had uncontrolled seizure that led to the change of medication from the long-term used phenytoin to carbamazepine. He developed DRESS syndrome after changing the drugs. We stopped carbamazepine and restored phenytoin for seizure control, but his clinical manifestations progressively worsened and he recovered only when both drugs were discontinued. Patch tests with several anticonvulsants showed positive reactions to both carbamazepine and phenytoin. Our case suggests that hypersensitivity to a previously tolerated anticonvulsant can be induced by DRESS to another anticonvulsant, and that the patch test may be a useful method for detecting cross-reactive drugs in anticonvulsant-associated DRESS syndrome.

Drug Neosensitization During Anticonvulsant Hypersensitivity Syndrome

J Investig Allergol Clin Immunol 2006; Vol. 16(5): 321-326

P Gaig, P García-Ortega, M Baltasar, J Bartra

Abstract. Anticonvulsant hypersensitivity syndrome (AHS) is a rare, severe drug hypersensitivity reaction included in the drug-related rash with eosinophilia and systemic symptoms syndrome (DRESS), in which a transient state of immune suppression and reactivation of latent virus infections have been observed. We describe 5 patients who developed neosensitization to different drugs taken during a previous episode of anticonvulsant-related DRESS, in whom skin prick, intradermal and/or patch tests were performed to confirm the diagnosis of drug hypersensitivity. In 1 patient, transient hypogammaglobulinemia was observed during the AHS. Four of the 5 patients developed a delayed skin eruption or a delayed systemic hypersensitivity reaction after intake of a drug that they had also taken during a previous anticonvulsant DRESS which had occurred months or years earlier; in the fifth, a possible reaction was prevented thanks to the allergy workup. The diagnosis of drug allergy was demonstrated by positive delayed reaction to intradermal test with

amoxicillin in 2 cases, positive patch tests to paracetamol and amitriptyline in 2 cases, and by clinical evidence of ceftriaxone erythroderma in one. The possibility of neosensitization to drugs administered during anticonvulsant-related DRESS should be considered. A transient state of immunosuppression induced during the anticonvulsant-related DRESS may trigger latent virus reactivation and massive nonspecific immune system response, which may lead to breakdown of tolerance to other drugs present at that time in the organism

DRESS syndrome associated with carbamazepine and phenytoin

Eur J Dermatol 2004; 14: 339-42

Jean-Pierre Allam, Teresa Paus, Christoph Reichel, Thomas Bieber, Natalija Novak.

Abstract. Drug Rash with Eosinophilia and Systemic Symptoms (*DRESS*) syndrome reflects a serious hypersensitivity reaction to drugs. Its clinical manifestations include diffuse maculopapular rash, exfoliative dermatitis, facial edema, lymphadenopathy, fever, multivisceral involvement and it is associated with a high mortality rate. We report a 62-year-old patient suffering from epilepsia presenting erythroderma following carbamazepine intake. Blood tests revealed eosinophilia, leukocytosis, elevated liver enzymes and high levels of Eosinophil Cationic Protein (ECP). We applied systemic steroids and anticonsulvant therapy was switched to phenytoin, which had been taken previously without adverse reactions. The skin eruptions persisted and the patient developed fever. Anticonvulsant medication was discontinued and skin eruptions finally resolved under steroid application. This case report demonstrates that cross reactivity between carbamazepine and phenytoin may not only lead to the development but also to the worsening of DRESS syndrome. ECP blood levels may represent a sufficient parameter to monitor the development of DRESS syndrome.

DRESS SYNDROME – An update

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The drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, previously referred to as the 'drug hypersensitivity syndrome', is an adverse drug reaction characterized by skin rash, fever, lymph-node enlargement and internal organ involvement.[1]

Many synonymous names and acronyms are attached to DRESS syndrome and includes HSS (Hypersensitivity Syndrome), AHS (Anticonvulsant Hypersensitivity Syndrome), DIHS / DHS [Drug (Induced) Hypersensitivity Syndrome], DIDMOHS (Drug-Induced Delayed Multiorgan Hypersensitivity Syndrome), and Drug-Induced Pseudolymphoma.[2]

The most frequently incriminated drugs are aromatic anticonvulsants (phenytoin, phenobarbital, and carbamazepine), sulfonamides, dapsone, allopurinol, minocycline, and gold salt (Table 1).

Table 1: Medicines more often reported to cause Drug Hypersensitivity Syndrome[3]

Abacavir	Dapsone	Nevirapine
Allopurinol	Diltiazem	Oxicam NSAIDs
Atenolol	Gold salts	Phenobarbitone
Azathioprine	Isoniazid	Phenytoin
Captopril	Lamotrigine	Sulphasalazine
Carbamazepine	Mexiletine	Sulphonamides
Clomipramine	Minocycline	Trimethoprim

The incidence is approximately 1 in 1,000 to 1 in 10,000 exposures. In a recent record-linkage study, the risk for developing hypersensitivity within 60 days of the first or second prescription in new users of phenytoin or carbamazepine was estimated to be 2.3-4.5 per 10,000 and 1-4.1 per 10,000, respectively. Studies have shown 80% cross-reactivity between the anticonvulsants.

Clinical Features:

DRESS syndrome / Drug hypersensitivity syndrome usually occurs on first exposure to the associated medication, with a delayed onset. Reactions classically begin 1 week to 8 weeks after starting drug therapy. In previously sensitized individuals, anticonvulsant hypersensitivity syndrome may occur within 1 day on re-challenge.

The reaction usually starts with low- or high-grade fever, and over the next 1 to 2 days a cutaneous reaction, lymphadenopathy and pharyngitis may develop. This is followed by involvement of various internal organs, as given below, most commonly the liver, although hematologic, renal or pulmonary impairment may occur (Table 2).

Table 2 : Involvement of organs based on severity of disease

Organ Involved (%)	Mild	Moderate	Severe
Skin (90-100)	Maculopapular exanthema	Urticated lesions	SJS-TEN
Liver (50-60)	Mild elevation in LFT	Hepatitis	Fulminant hepatic necrosis
Muscle	Elevated creatine kinase level	Myositis	Rhabdomyolysis
kidney	Hematuria	Nephritis	Acute renal failure
Heart	Pericarditis	Carditis	Congestive cardiac failure
Lung	Mild cough	Pneumonitis	ARDS
Hematological (50-80)	Eosinophilia (80%), neutrophilia, atypical lymphocytosis	Neutropenia, thrombocytopenia, hemolytic anemia	Aplastic anemia

The pathophysiology of DRESS syndrome remains unclear, but a defect in detoxification of causative drug, immunological imbalance, and infections such as human herpes virus type 6 (HHV 6) have been suggested. The overall mortality in DRESS is about 10% and occurs in patients with severe multi-organ involvement.[4]

Differential diagnosis

Patients presenting with skin rash may be attributed to large number of causes however, the presence or absence of eosinophilia and with or without internal organs involved may help in short listing the more likely conditions.

Table 3 gives list of conditions for patients with eosinophilia and maculopapular rashes.[5]

Table 4 gives the list of disorders for patients with or without eosinophilia, drug induced skin eruptions and systemic symptoms (hepatic involvement more common and other organs/systems) whose diagnostic criteria are very similar to those of DRESS syndrome.[6]

Table 3 : Differential diagnosis in skin disorders associated with eosinophilia

	Medical history	Laboratory test	Systemic symptoms	Skin lesion	Skin pathology
DRESS syndrome	Drug initiation or change within the past 2 months	Eosinophilia, leukocytosis, elevated liver enzymes, high ECP levels	Liver failure, renal failure, arthralgia, diarrhea	Maculopapular rash, exfoliative dermatitis, edema of the face	Lymphocytic infiltration, sometimes pseudolymphoma
HES	No association with drugs (without recognizable cause)	Eosinophilia > 6 months, in some cases leukocytosis, elevated liver enzymes, high ECP levels	Endocarditis, congestive heart failure, thrombosis, strokes, peripheral neuropathy, encephalopathy, hepatosplenomegaly, diarrhea, arthralgia	Erythroderma, edema, pruritus	Eosinophilic infiltration, cutaneous microthrombi embolism
Wells' syndrome	In some cases relation to drugs or insect bite at lesional site	Eosinophilia in > 50% of cases, leukocytosis and thrombocytosis may occur	None	Erythema and edema in initial phase, pruritic papular, annular plaques and urticaria-like eruptions, sometimes vesicles and blisters	Dermal infiltration of eosinophils, initially edema, cell debris between collagen bundles forming "flame figures"

ECP - Eosinophil Cationic Protein HES - Hyper eosinophilia syndrome

Table 4 : DRESS syndrome: most common differential diagnosis

	DRESS syndrome	**SJS/TEN**	**Hypereosinophilic syndrome**	**Kawasaki disease**	**Still's disease**
Cutaneomucous features	Facial oedema, morbilliform eruption, exfoliative dermatitis, tight blisters	Blisters, atypical targets, cutaneomucous erosions	Urticaria, angio - oedema, morbilliform eruption, infiltrated papules or nodules	Conjunctival congestion; fissured lips, 'strawberry tongue'; palmar erythema, oedema of the hands, periungual desquamation; polymorphous exanthema	Salmon rash
Haematological abnormalities					
Eosinophilia	+	–	+	–	+/–
Presence of atypical lymphocytes	+	–	+/–	–	–
Systemic involvement					
Adenopathies	+	–	+	+	+
Hepatitis	+	+	+	+/–	+
Other organ involvement	Interstitial nephritis, pneumonitis, carditis	Tubular nephritis, tracheobronchial necrosis	Carditis, pneumonitis, encephalopathy, diarrhoea, vomiting or abdominal pain	Cardiovascular abnormalities, diarrhoea, vomiting or abdominal pain	Pleuritis, pericarditis

+ = Usual; +/– = possible; – = very rare or absent.

There is no gold standard for diagnosis of DRESS, however at least two diagnostic criteria have been proposed for diagnosis. The RegiSCAR criteria[7] and the Japanese consensus group criteria[8] are detailed in the table below.

Table 5 : RegiSCAR criteria and Japanese consensus group criteria for diagnosis of DRESS

RegiSCAR inclusion criteria for DRESS syndrome.	***Japanese consensus group diagnostic criteria*** for DIHS. Seven criteria needed for diagnosis of DIHS or the first five criteria required for diagnosis of atypical DIHS
Hospitalization	Maculopapular rash developing > 3 weeks after starting the suspected drug
Reaction suspected to be drug related	Prolonged clinical symptoms 2 weeks after discontinuation of the suspected drug
Acute Rash*	Fever > 38° C
Fever > 38° C*	Liver abnormalities (ALT > 100 U/L) or other organ involvement
Lymphadenopathy in at least two sites*	Leukocyte abnormalities
Involvement of at least one internal organ*	Leukocytosis (> 11 x 10^9 /L)
Blood count abnormalities (lymphopenia or lymphocytosis*, eosinophilia*, thrombocytopenia*)	
Atypical lymphocytosis (>5%)	
Lymphadenopathy	
Human herpesvirus 6 reactivation	

*- *Three of the four starred criteria required for diagnosis*

Management:

Acute period: DRESS syndrome must be promptly recognized and all potential culprit drugs withdrawn. The typical delay between beginning the administration of a drug and the onset of the reaction is two to six weeks.

Systemic corticosteroids are often used (0.5 to I mg/kg). This therapy rapidly improves symptoms and laboratory measurements, but its impact on the long term disease course is not known. Relapses of rash and hepatitis may occur as corticosteroids are tapered.

When the skin rash results in exfoliative dermatitis supportive care consists of warming the environmental temperature and using local antiseptics and topical corticosteroids.

Prevention of recurrence: Consideration must be given to the likelihood of a particular drug to cause the syndrome when multiple drugs are involved. Patch tests and in-vitro lymphocyte tests have been used, but the sensitivity and specificity of these tests are variable, depending on the drug.

Cross-reactions are frequent between the three main aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital), and all three must be avoided by the patient if one has been causative. It may be difficult to find a safe alternative anticonvulsant therapy.

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