

Dress Syndrome - A Rare Presentation of Phenytoin Hypersensitivity

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Abstract: Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare but potentially life-threatening syndrome characterized by skin rash, fever, lymph node enlargement, and involvement of internal organs. It is most commonly induced by aromatic anticonvulsants and antibiotics. Nonaromatic anticonvulsants are rarely encountered as the causes of DRESS syndrome. We report one such case of DRESS syndrome due to phenytoin (Aromatic) anticonvulsant intake in 46 years old male of seizure disorder. He developed symptoms after 4 weeks of start of the treatment. He recovered after change of anticonvulsant and short steroid course.

Keywords: DRESS syndrome; drug-induced hypersensitivity syndrome; eosinophilia; phenytoin hypersensitivity

1. Case Report

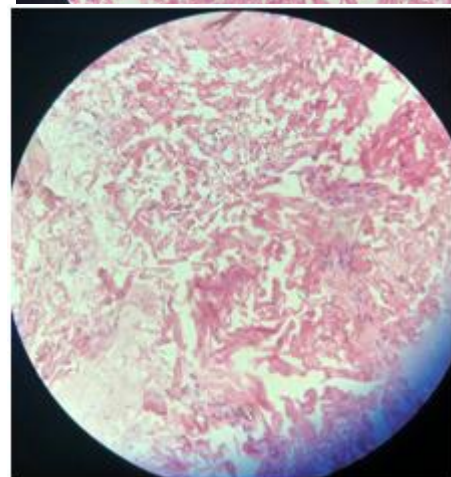
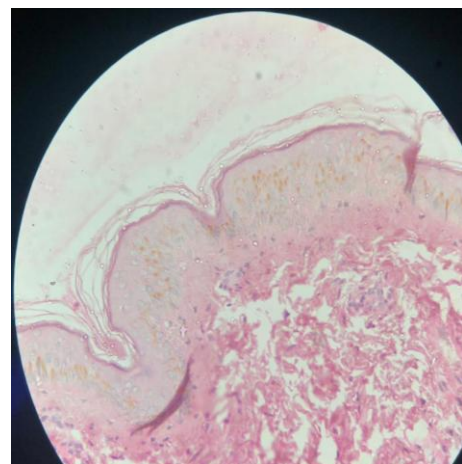
A 46-year-old male was admitted to the emergency department with the complaints of high grade fever, generalised erythematous eruption, oral ulcers, joint pain, itching and burning sensation all over the body. He was known case of seizure disorder. He was on phenytoin treatment for seizure control. No history of animal/insect bites was present.

On examination, he was awake and alert. His temperature was 100.2°F, pulse rate 110 bpm, respiratory rate 18 breaths/min, and blood pressure was 110/70mmHg. Skin showed multiple erythematous plaque all over the face. Multiple maculo-papular rash over bilateral forearm, abdomen, buttocks were present. On oral cavity examination multiple erosive lesion over buccal mucosa gums and tongue was present with whitish deposit over it. On per abdomen examination, there was hepatomegaly without stigmata of chronic liver disease. There was no evidence of lymphadenopathy.

2. Laboratory Investigations

Blood Investigations	Result
Haemoglobin	14.6g/dL
Total WBC count	7700/mm ³
Total RBC count	4.34 Mil/μL
Total platelet count	3.11lacs/cumm
HIV	Negative
HBsAg	Negative
HCV	Negative
AEC(Absolute eosinophil count)	1296 cells/cumm
Aspartate aminotransferase	271U/L
Alanine aminotransferase,	189 U/L
GGT (Gamma-glutamyl transferase)	398U/L
ALP(Alkaline phosphatase)	402 U/L
Lactate dehydrogenase	730U/L
C-reactive protein	88.9 mg/dL
S.Creatinine	0.6 mg%
RBS	147 mg%

ESR	29mm/hr
Chest Xray	Normal
IgE level	223iu/l.
Blood culture	No organism isolated
Throat culture	No organism isolated



Ultrasonography revealed hepatosplenomegaly. Skin biopsy was taken from right forearm. It showed squamous

epithelium with hyperkeratosis and parakeratosis. Basal layer had lymphocytic exocytosis and focal vacuolar interface changes. Dermis showed eosinophils and plasma cell infiltrate and occasional epithelioid granuloma. There was no evidence of dysplasia was present.

Patient was diagnosed as a probable case of DRESS syndrome based on clinical and laboratory and biopsy findings. Previous medication, phenytoin was discontinued and replaced by levetiracetam and clobazam. Antihistamine therapy with pulse methylprednisolone was given at a dose of 10 mg/kg for 3 days, and a good response to the treatment was observed. Fever and rash disappeared in one week. He was discharged from the hospital in good condition with oral prednisolone treatment at a dose of 1 mg/kg/day and changed anti-convulsants. After two weeks, all symptoms completely resolved, laboratory tests were normal, and oral prednisolone was discontinued.

3. Discussion

Drug reaction with eosinophilia and systemic symptoms (DRESS) is very fatal, rarely occurring adverse drug reaction with various skin manifestations and systemic involvement. Also known as Drug Induced Hypersensitivity Syndrome (DIHS). It is categorized as one form of severe cutaneous adverse reactions (SCARs)¹.

Apart from DRESS Syndrome which occurs as a manifestation part of drug reaction, TEN (Toxic epidermal necrolysis), AGEP (Acute generalized exanthematous pustulosis) and SJS (Steven Johnson syndrome) may also occur due to drugs. It may secondarily lead to skin and soft tissue infection and sepsis which may be life threatening too.⁹

The pathogenesis of DRESS syndrome is exactly not understood. According to some hypotheses, there is deficient drug metabolism and reactive metabolites play a major role in the development of DRESS³.

The causes of DRESS are many. The aromatic anticonvulsants drugs like carbamazepine, phenobarbitone and phenytoin, sulphonamides such as dapsone and sulfasalazine, allopurinol minocycline etc. are more frequently found as culprit drugs causing it. Other less commonly cited drugs causing DRESS are strontium ranelate, leflunomide, dapsone, and nonsteroidal anti-inflammatory drugs (diclofenac, celecoxib, ibuprofen, and phenylbutazone) etc. There is long latency period of about 6-8 wks for DRESS to occur. This differentiates it from other drug hypersensitivity syndromes. Although on re-exposure there is rapid development of symptoms.²

Prodromal symptoms of DRESS commonly are itching and pyrexia. The fever precedes cutaneous symptoms. Fever is usually high grade of (101.84°F to 105.44°F) may or may not associated with chills and rigors, continuous, occurring few days before rash and lasting for several weeks. Cutaneous manifestations historically include a morbilliform rash or maculopapular exanthema. It is identified as pink-to-red flat macule or papule. Annular, targetoid, urticaria-like or polymorphous morphology may occur. It typically

involves face, upper aspect of the trunk, and upper extremities first, and later spreads to the lower extremities. Initially discrete lesions that later unite together to form large erythematous patches or plaques. It is also associated with notable facial edema, especially in the periorbital and midfacial region that are often mistaken for angioedema. But this rash evolves over period of time taking more violaceous appearance with diffuse scaling and progress to involve mucosal surfaces causing cheilitis, erosions, erythematous pharynx, and enlarged tonsils. These features disappear after weeks of stoppage of drug⁴.

DRESS is complex syndrome with various organ system involvements. The most commonly involved systems are lymphatic, hematological and hepatobiliary, less commonly renal, pulmonary, and cardiac involvement can also occur. Atypically neurologic, gastrointestinal, and endocrine dysfunctions are also found.

The hematologic system includes leukocytosis (atypical lymphocytosis) with hyper-eosinophilia, fall in hemoglobin levels and thrombocytopenias. Systemic manifestations occur because of eosinophil granule proteins which are toxic to the tissues of the body. Rarely, there can be hemophagocytic syndrome, an uncommon hematologic disorder that manifests as fever, jaundice, and hepatosplenomegaly with hemophagocytosis⁴.

The liver is the most commonly affected internal organ in DRESS syndrome, with variable degrees of hepatitis. It is characterized by elevated liver transaminases and alkaline phosphatase. It often anicteric and without cholangitis^{4,5}.

Cardiac involvement is manifest as myocarditis. Two different forms of myocarditis are recognized in DRESS syndrome, i.e. hypersensitivity and acute necrotizing eosinophilic myocarditis (ANEM)^{4,7} Respiratory system involvement characterized by acute interstitial pneumonitis, lymphocytic interstitial pneumonia, pleuritis, and acute respiratory distress syndrome⁶.

GI tract involvement manifest as nausea, vomiting, bloody, and non-bloody diarrhoea. Histopathological findings range from active colitis with cryptitis, erosion, and ulceration, to eosinophilic infiltrate in the lamina propria, to chronic inflammation with architectural distortion. The long-term sequela associated with DRESS is autoimmune enterocolopathy¹⁰.

Central nervous system involvement manifest as meningitis and encephalitis, which often occur in patients with pre-existing immunocompromised state, occur 2 to 4 weeks after onset symptoms and mostly due to HHV-6 reactivation. Rarely there can be syndrome of inappropriate secretion of antidiuretic hormone (SIADH) due to limbic encephalitis⁴. Endocrine involvement often occur as long-term effect and include thyroiditis or sick euthyroid syndrome, type 1 diabetes mellitus, xerostomia.

The European Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) study groups have developed a scoring system based on clinical findings, the extent of affected skin, the type of organ involvement and the clinical

course to classify DRESS syndrome as defined, probable or possible. It outlines 7 inclusion criteria. Out of that, first 3 criteria are compulsory for diagnosis i.e. acute rash, the suspicion of a drug-related reaction, and hospitalization. Other 4 include systemic features i.e. fever; lymphadenopathy involving at least 2 sites; involvement of at least 1 internal organ (e.g., liver, kidney, heart, pancreas, or other organs) and hematologic abnormalities, including a lymphocyte count above or below the normal limits; an eosinophil count higher than laboratory limits; or a platelet count below laboratory limits⁸. For establishing diagnosis, 3 out of 4 features are required.

The skin biopsy characteristically shows changes in epidermis, dermo-epidermal junction and dermis, including parakeratosis, dyskeratosis, acanthosis, spongiosis, apoptotic keratinocytes, exocytosis, focal or widespread interface dermatitis and dermal inflammation predominantly lymphocytes with an increase in size, irregular nuclear outline and hyperchromatic nuclei (atypical lymphocytes).

The most important challenge in management of DRESS syndrome is early recognition of the hypersensitivity reaction followed immediate withdrawal of the culprit drug. Failure to identify it will result in unwarranted morbidity and mortality. If there are generalised erythematous eruptions then patient should be admitted to an Intensive Care Unit.

Initially adequate supportive therapy to stabilize haemodynamics, antipyretics to reduce fever, and emollient and topical steroids to decrease the cutaneous symptoms should be given. Empirical antibiotics should be not be given because there are chances of cross-reaction between drugs. Mainstay of treatment is systemic steroids at minimum dose of 1.0 mg/kg/day of prednisone or equivalent slowly tapered over 6–8 weeks, upon clinical resolution, to prevent relapse. In more severe cases or cases refractory to oral steroids, patients can be treated with intravenous methylprednisolone, 30 mg/kg intravenously for 3 days. In patient who do not respond to systemic steroids or where steroid was contraindicated Intravenous immunoglobulin (IVIG) was given at dose of 1g/kg for 2 days. Other modalities of treatment that can be tried in DRESS are plasmapheresis and immunosuppressive drugs, such as cyclophosphamide, cyclosporine, interferons, mycophenolate mofetil, and rituximab. N-acetylcysteine found to have effective in drug detoxification and limit reactive metabolites in anticonvulsant-induced DRESS.

4. Conclusion

The diagnosis of DRESS should be suspected if there is presence of skin rash, liver involvement, fever, hypereosinophilia, and lymphadenopathy. Immediate withdrawal of culprit drug, institutional treatment, and supportive measures, standard skin care, multidisciplinary approach, and prompt initiation of systemic steroid as indicated can reduce the morbidity and mortality. Since, good quality of data in DRESS is missing from the Indian subcontinent regarding the causative drug and prognosis more reporting of cases from different offending drugs are

required from the Indian subcontinent to form a consensus statement applicable for this part of the world.

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