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DRESS Syndrome; Just a Rash or Much More?? Time to Rethink.

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ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe multiorgan drug induced idiosyncratic reaction. As the name suggests it is characterized by peripheral eosinophilia and systemic symptoms like fever, rash, lymphadenopathy, liver failure. Incidence is around 1:1000 to 1:10,000 drug exposures and has a high mortality if not diagnosed and treated timely. Diagnosis is difficult and challenging due to the diversity of symptoms this syndrome has, hence scoring systems like the RegiSCAR and Japanese criteria may be used. Mortality rate is around 10-20% and mostly due to liver failure. Most important step in treatment is withdrawal of the offending drug and supportive line of therapy with corticosteroids forming the mainstay of therapy. This paper reports two such cases which were a diagnostic dilemma and timely withdrawal of the offending drug and corticosteroids changed the course of the condition completely.

Keywords: DRESS Syndrome, Drug Reaction, Eosinophilia.

INTRODUCTION

Rashes are always a dilemma for a clinician and when systemic symptoms are present its all the more challenging and demand for an early diagnosis and treatment. Drug reaction with eosinophilia and systemic symptoms (DRESS) is a potentially life threatening syndrome associated with rash, eosinophilia, fever and internal organ involvement secondary to a hypersensivity reaction to a drug.

The main culprit drugs known are Carbamazepine and Allopurinol but any drug from a list of around 50 drugs or any other drug outside the list can give rise to this fatal condition. One has to be extremely vigilant and suspicious while diagnosing this syndrome as delay in diagnosis can be fatal. Mortality being as high as 20%.

Diagnosis is difficult due to the varied symptoms and complications this syndrome presents with and also there being no gold standard test for diagnosis. A good clinical history, examination, investigations and using the RegiSCAR criteria can grade DRESS as "no", "possible". "probable" or "definite". A skin biopsy may also help to reach the diagnosis. Studies have also shown a genetic predisposition and association with Human Herpesvirus 4,6 and 7 infection.

Treatment mainly depends on withdrawal of the said drug with corticosteroids and supportive measures.

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CASE REPORT

A 25 year old male, presented with high grade fever of around 103^0 F, of one week duration with skin rash and abdominal pain. He denied any history of nausea, vomiting, diarrhea, headache, joint pain, weight loss, cough, breathlessness, chest pain. On physical examination temperature was 103^0 F , heart rate 120/min, blood pressure 132/82 mm Hg, respiratory rate 20/ min SpO2 97% and a maculopapular erythematous rash which were remarkable on his neck, trunk, upper arm, forearm, hand, thigh, leg and foot. On systemic examination he had mild abdominal distension and air entry was decreased bilaterally. Other systems were normal.

A 32 years female, recently diagnosed to have Spondyloarthropathy, started on Sulfaslazine for same came with high grade fever with diarrhea, vomiting and abdominal pain. She also complained of dry cough and mild chest pain but no breathlessness. She reported headache and generalized weakness too.

The male described in the vignette was investigated and was found to have total leucocyte count 21000 cells / cu mm(normal range 4000-11000 cell/ cu

mm) with eosinophilia of 10 %,(normal range 2%-6 %) and atypical lymphocytes on peripheral smear. Dengue NS1 and malaria antigen were negative. Liver enzymes were raised (Alanine transaminase (ALT) 240 mg/dl, Aspartate transaminase (AST) 350 mg/dl), serum creatinine 1.9 mg/dl, CRP 204 mg/l (normal <5 mg/l).His PCT, serum amylase and lipase was normal. C3 complement level 37mg/dl (normal range 66-185mg/dl). Chest x ray was suggestive of bilateral pleural effusion with no signs of consolidation. Ultrasound examination of abdomen showed hepato splenomegaly with acalculous cholecystitis and moderate ascites, with para aortic lymph node of size around 1.5 X 2 cm. CT scan of abdomen confirmed USG findings without any signs of perforation. A clinical suspicion of enteric fever was considered and after sending blood cultures patient was started on intravenous cefipime.

His blood cultures were sterile, ascitic fluid tapped which was transudative fluid with lymphocyte predominance- 6500 cell, with 90% lymphocyte and 3.5 gm protein. Aerobic culture, TB gene xpert and AFB smear were negative in ascitic fluid.

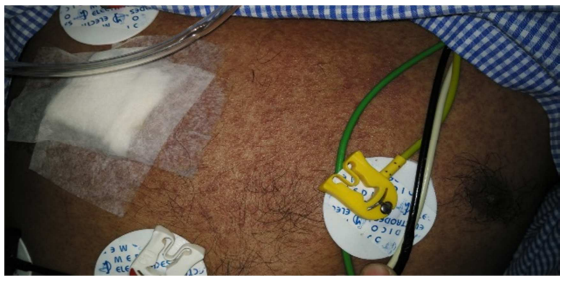
Patient's total leukocyte counts continued to rise with persistent fever of 103-104^0 F. His fever was non responsive and antibiotics were upgraded to meropenem and teicoplanin. He was managed in intensive care unit and Noninvasive ventilator support was given for his rapid shallow breathing. His ANA, ANCA, dsDNA were negative.

Skin biopsy picture was taken from the anterior chest wall. Histopathology report showed focal mild vacuolization of keratinocytes at dermal epidermal junction. Mild to moderate perivascular and peri appendageal lymphocytic infiltrates in upper epidermis seen. Several extravasted erythrocytes were also seen. These Features were consistent with DRESS syndrome.

Patient's antibiotics were stopped and he was started on methyl prednisolone, fever subsided after 24 hours of starting methyl prednisolone which was switched to iv hydrocortisone in due course, patient's clinical condition improved, rashes disappeared, liver enzymes and creatinine returned to normal, chest Xray became clear. He was discharged on tapering dose of oral prednisolone.

The female gave history of being started on Sulfasalzine 3 weeks prior to admission. On investigating she was found to have counts of 21,000 with 8%eosinophils and atypical lymphocytes. She had deranged liver transaminases. Her ultrasound was suggestive of ascites, bilateral pleural effusion and acalculous cholecystitis. Her blood and urine cultures were negative. She also had left sided cervical lyphadenopathy which on ultrasound showed fatty hilum and looked to be reactive. Her serology for Dengue, Measles, Rubella were negative. Ascitic fluid tapping was s/o 500 cells, 1.6 gm proteins and normal sugars with negative ascitic fluid cultures and TB gene Xpert. After ruling all possible etiologies of infection a diagnosis of DRESS syndrome was made. She was started on methylprednisolone and responded both clinically and biochemistry wise too.

Both these cases were diagnosed as Drug reaction with eosinophilia and systemic symptoms (DRESS) which is a drug induced hypersensitivity reaction involving leucocytes, lymph nodes and one or more systemic organ. Although DRESS mostly manifests with anticonvulsant drugs and allopurinol but sometimes it can present without any obvious exposure with any drug.[1] Here we are presenting a case of 25 year old male without any obvious exposure with any listed drug. And a 32 years female with DRESS due to Sulfasalazine.



Rashes present on anterior chest wall.

DISCUSSION

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a drug induced hypersensitivity reaction with a variety of clinical manifestations. In most of the cases Allopurinol, Carbamazepine, Lamotrigine, Phenytoin, Sulfasalazine, Vancomycin, Minocycline ,Dapsone, and Sulfamethoxazole are associated temporally with the disease onset.[1]

Pathgogenesis

Some pharmacogenetic studies have shown the association of HLAB* 5801 and HLAA* 31:01 with allopurinol and carbamazepine induced DRESS respectively.[2,3] In some studies reactivation of herpes virus specially HHV6 was found to be specific to DRESS syndrome.[4,5] Other herpes viruses like HHV-7, EBV and cytomegalovirus have been associated with DRESS.

Clinical features

Fever, malaise, lymphadenopathy, and rash are the most common initial symptoms with the initiation of the first symptom,[1,2] usually 2-6 week after exposure with offending medication.[1] In other drug reactions the latency between drug exposure and appearance of symptom is, 4 to 9 days for morbilliform eruptions and 4 to 28 days for SJS/TEN. Cutaneous manifestations may consist of urticarial maculopapular eruptions, vesicles, bullae, pustules, purpura, target lesions, facial edema and erthroderma.[6] Systemic involvement in the form of hepatitis, pneumonitis, myocarditis, pericarditis,

nephritis and colitis are the major cause of morbidity and mortality.

Laboratory abnormalities

Leukocytosis with eosinophilia (90%) and/or mononucleosis(40%). Low complement level,[7] atypical lymphocytosis with large activated lymphocytes, lymphoblasts, or mononucleosis like cells, Increased serum aminotransferase.

The most frequent histopathologic pattern was an interface dermatitis often involving the pilar units, followed by eczematous, erythema multiforme like,and Acute generalized exanthematous pustulosis(AGEP) like pustulosis.[8]

Differential diagnoses

Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), hypereosinophilic syndrome, Kawasaki disease and Still's disease.

Disgnostic criteria

Diagnosis is mainly clinical with a high degree of suspicion and ruling out other causes of similar non drug induced conditions.

Various criteria are laid down for the diagnosis of DRESS like RegiSCAR criteria,[9] Japanese group's criteria.[10] As per RegiSCAR a score more than 5 is considered as diagnostic in hospitalized patients with a drug rash.

Regi SCAR criteria for diagnosis of DRESS
Hospitalization
Reaction suspected to be drug related
Fever>38^{o}C*
Enlarged lmph nodes at a minimum of 2 sites*
Involvement of at least one internal organ*
Blood count abnormalities*
Lymphocytes above or below normal limits
Eosinophils above the laborator limits
Platelets below the laborator limits
3 out of the 4 asterixed criteria are required to make the daignosis

Japanese group's criteria for diagnosis of DRESS
Maculopapular rash developing >3 weeks after starting with the suspected drug
Prolonged clinical symptoms, 2 weeks after discontinuation of suspected drug
Fever>38^{0}C
Liver abnormalities(alanine aminotransferase >100U/L)
Leucocyte abnormalities
Leucocytosis
Atpical lymphocytosis
Eosinophilia
Lmphadenopathy
Human herpes virus 6 reactivation
Diagnosis is confirmed by presence of 7 criteria

Management: The main management of DRESS is withdrawal of offending drug and supportive line of therapy. The earlier the drug withdrawal, better is the prognosis. Severe hepatic damage may lead to acute hepatic failure; in this condition hepatic transplant will be the only therapeutic option. Systemic corticosteroid can be use in severe organ involvement especially pulmonary and renal involvement. Other immunosuppressants like cyclosporin may also be involved.[11] Hepatic failure is the most common cause of mortality. Mortality is estimated to be around 10%.[9,12]

CONCLUSION

The identification of the offending drug is an important prerequisite of DRESS management. Also timely withdrawal of drug and avoidance in future is also of paramount importance.

Systemic involvement has to be monitored by basic laboratory parameters like AST, ALT, total bilirubin , creatinine, and radiological investigations like chest Xray ,USG abdomen along with pulse oximetery . The other causes of fever have to be ruled out before reaching to the final diagnosis. Corticosteroids can be switched to the oral form once clinical stability achieved.

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