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DRESS Syndrome in ICU: A Diagnostic Dilemma

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Abstract

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome can be severe and life-threatening specially in critical care setting if not diagnosed and treated in time. DRESS syndrome is an idiosyncratic drug reaction characterized by rash, fever, eosinophilia, lymphadenopathy and involvement of internal organ. Regi SCAR (European Registry of Severe Cutaneous Adverse Reaction) scoring system is used for its diagnosis. Diagnosis of this syndrome can be challenging in critical care setting due to nonspecific clinical features, multiple confounding factors, use of polypharmacy, and its resemblance with sepsis and septic shock of varied etiologies.

We report a case of 15-year-old boy who developed this syndrome after starting sulfasalazine, HCQ and NSAIDS all together, one month back for treatment of ankylosing spondylitis. This case report focuses on early suspicion and identification of this syndrome in critical care setting. This in turn should help in effective treatment of the illness by stopping offending drugs and timely initiation of steroid therapy. Further it may help in judicious use of antibiotics by holding irrational use of these drugs.

Introduction

15-year-old boy presented with complaints of high-grade fever, throat pain, generalized erythematous rash over face, hands, legs and abdomen for 7 days. He consulted a local practioner and took some symptomatic medications with no relief. His rashes got worsened and involved the entire body with increasing throat pain and facial swelling. He was diagnosed as a case of ankylosing spondylitis one month back and started on HCQ 200 mg twice and sulfasalazine 500 mg once and NSAIDs. He had no history of any other OTC medicines intake. There is no other significant past history, use of alcohol, smoking or any drug allergy.

He was admitted for further evaluation and management. At the time of admission, patient was conscious and oriented. Patient was febrile with temperature of 102^0 F, heart rate of 133/minute, respiratory rate 30/minute, BP 110/60 mm of Hg and SPO2 89% on room air which improved to 97% with 2 lit oxygen through nasal prongs. His rash was maculopapular and diffuse initially which started desquamating over next few days and changed to exfoliative dermatitis as shown in Figure1. His bilateral inguinal lymph nodes were palpable and tender. Systemic examination was with in normal limits.

Significant investigations include leukocytosis-(TLC: 28340 per mm^3, DLC: N 29%, L 39.2%, M 9.1%, B 0.8% E 21.8%). His absolute eosinophil counts were 6178 per mm^3.Peripheral smear did not show atypical lymphocyte. Liver functions revealed transaminitis (SGOT561U/L and SGPT234U/L), cholestatic jaundice (Total Bilirubin 5.6mg/dl, Direct Bilirubin5.5mg/dl), Alkaline phosphatase 761U/L, Albumin 2.7gm/dl

and INR of 1.6). His Procalcitonin was 10.2 ugm/L. Antinuclear antibody was negative. Viral markers negative for HIV, HBSAG, and HCV antibody. IgM HAV and HEV antibody were negative. Kidney function tests including electrolytes, Thyroid function tests, urinalysis, and stool routine were within normal limits. IgM Leptospira and Dengue serology was negative. No diagnostic workup was done for Chlamydia and Mycoplasma. Bone marrow, skin and lymph node biopsy could not be done. CECT abdomen revealed hepatomegaly with periportal edema and pericholecystic edema, borderline splenomegaly, mild to moderate ascites and multiple enlarged epigastric, mesenteric and inguinal lymph nodes. MRI sacroiliac joint showed mild juxta articular STIR hyper intensities involving left sacroiliac joint s/o active sacroiliitis.

Diagnosis of drug rash with eosinophilia and systemic symptoms (DRESS) syndrome due to sulfasalazine/HCQ was made. Regi SCAR score of our patient was 7, which was suggestive of definite case of DRESS. Injection methylprednisolone was started at dose of 1mg/kg/day in divided dosages along with supportive care. HCQ and sulfasalazine was stopped. The patient developed GTCS on the evening of his admission for which injection midazolam and levetiracetam was given and patient was taken on mechanical ventilator. In view of his worsening status, relatives shifted him to another center and we could not keep further follow up on his treatment and recovery status.

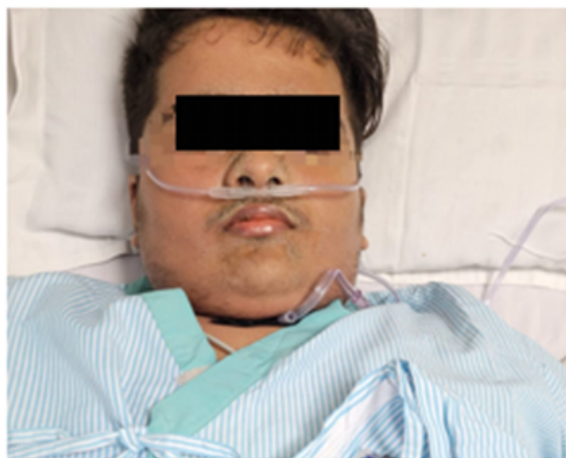

Figure1: Peculiar rash of DRESS with facial puffiness and characteristic psoriasiform desquamation.

Table 1: (Patient's investigations report with reference values)

Parameter	Reference Range	Result of the Test
HAEMOGLOBIN	12.0-15.0 gm/dl	10 gm/dl
TLC	4000-10000 /cu.mm	28340/cu.mm
TOTAL RBC COUNT	3.8-4.8 millions/cu	4.88 millions/cu
PLATELET COUNT	1.5-4.1 millions/cu	3.44 millions/cu
D.L.C		
POLYMORPH	40-80 %	29%
LYMPHOCYTES	20-40 %	39%
MONOCYTES	2-10 %	9.1%
EOSINOPHILS	1-6 %	21.8%
BASOPHILS	0-01 %	0.8%

S. UREA	14.98-36.38 mg/dl	37 mg/dl
SERUM CREATNINE	0.52-1.04 mg/dl	0.4 mg/dl
S. SODIUM	135-155 mmol/L	138 mmol/L
S. POTASSIUM	3.5-5.5 mmol/L	4.3 mmol/L
LIVER FUNCTION TEST		
SERUM TOTAL BILIRUBIN	0.2-1.3 mg/dl	3.1 mg/dl
SERUM DIRECT BILIRUBIN	0.00-0.4 mg/dl	3.0 mg/dl
SERUM SGOT	14-36 U/L	102 U/L
SERUM SGPT	9-52 U/L	87 U/L
SERUM ALKALINE PHOSPHATASE	38-126 U/L	579 U/L
SERUM TOTAL PROTEINS	6.3-8.2 gm/dl.	5.8 gm/dl.
SERUM ALBUMIN	3.5-5 gm/dl.	3.1 gm/dl.
URINE PROTEIN		
LDH	120-246 U/L	4638 U/L
CPK	55-170 U/L	67 U/L
TSH	0.465-4.68 ulU/ml	3.884 ulU/ml
PROCALCITONIN	<0.5- see Below ugm/L	10.5 ugm/L
IGM HAV ANTIBODY		Negative
IGM HEVANTIBODY		Negative
IGM LEPTOSPIRA ANTIBODY		Negative
DENGUE NSI ANTIGEN		Negative
DENGUE IGM ANTIBODY		Negative
HBS Ag		Negative
ANTI HCV ANTIBODY		Negative

Discussion

A combination of rash, lymphadenopathy, and multiorgan failure after use of phenytoin was diagnosed as Dilantin hypersensitivity syndrome. It is first defined by Bocquet et al[1]. Later, the similar reaction was noted with other drugs as well. Fever with rash and MODS has multifactorial etiology. It is essential to suspect and diagnose DRESS in early phase to halt the progression of disease in time by stopping the offending drug and timely initiation of steroid therapy.

Our case report is focused on establishment of early diagnosis in critical care setting where multiple confounding factors and its close mimics are dealt on daily basis. Fever, maculopapular generalized erythematous skin rash, increased eosinophil counts, lymphadenopathy and the multiorgan dysfunction organs is characteristic of DRESS. Rash associated with this syndrome has some peculiar features like facial oedema, resolution with psoriasiform desquamation, infiltrated skin lesions, and purpuric lesions. Presence of two out of the four of these features of rash are suggestive of DRESS associated rash[2].Our

patient had very peculiar rash of dress with facial puffiness and characteristic psoriasiform desquamation shown in the picture. (Figure 1). DRESS syndrome usually begins several weeks after exposure to the offending drug in contrast to various other drug related eruptions which have low latency. In most patients the reaction occurs 2 to 6 weeks after starting the offending drug. Approximately 44 medications have been associated with DRESS. Most commonly culprit drugs are anticonvulsants (phenytoin, carbamazepine, and phenobarbital); sulphonamides; sulfones (dapsone); nonsteroidal anti-inflammatory drugs (piroxicam, ibuprofen, and diclofenac); beta lactam antibiotics, vancomycin, allopurinol; minocycline and antiretrovirals[3]. Table2 is showing the list of drugs associated with DRESS. This includes sulfasalazine, HCQ and NSAIDS. In our case patient was using sulfasalazine, HCQ and NSAIDS for ankylosing spondylitis and patient started developing fever and peculiar rash after 3 weeks of starting these medications.

Pathogenesis of DRESS syndrome is not well understood and it consists of complex interaction between certain factors like genetic susceptibility in relation to certain human leukocyte antigen (HLA) and drug hypersensitivity, alteration in certain metabolic pathways and genetic deficiency of certain detoxifying enzymes. Virus-drug interaction may lead to certain viral reactivation and can precipitate DRESS. Reactivation of HHV6is being observed in cases of DRESS caused by antiepileptics[4].

The liver is the most frequently involved internal organ. Liver dysfunction characterizes with hepatomegaly, transaminitis, cholestatic jaundice and coagulopathy. Kidney, lung, central nervous system, heart, and other organs can also get involved. In our case, the level of transaminases was initially elevated >10 x above the upper limit of normal (ULN) and the very next day increased to > 25 times above normal limit. INR was with in normal limit. The hematological manifestations in DRESS include leukocytosis (preceded by leukopenia and lymphopenia), the presence of atypical (reactive) lymphocytes, thrombocytopenia, and anemia. Eosinophilia occurs in 60–70% of cases. Our patient had leukocytosis with marked increased in eosinophils with absolute eosinophil count of6178 per mm^3. Rest of CBC was grossly OK. Neurological manifestations though are infrequent but our patient developed GTCS on next day of ICU admission. This was suggestive of presence of meningitis and encephalitis and poor prognosis. Headache, cranial nerve palsy, and muscle weakness are some other features of neurological involvement[5]. Rest of the systemic examination was with in normal limit. The overall mortality in DRESS syndrome is about 10% and most patients die from liver failure.

In our case DRESS was suspected on the basis of history, use of culprit drugs which are major offenders mentioned in the literature, diffuse erythematous desquamating typical dress related rash, eosinophilia and liver involvement. Though there is no diagnostic test to confirm the diagnosis of DRESS but awareness of illness led to early suspicion and detailed workup and use of Regi SCAR scoring system led to diagnose and grade DRESS in our case. On the basis of this scoring system diagnosis is either “excluded,” “possible,” “probable,” or “definite”. Our patient was a definite case of DRESS because his final score was 7 as calculated and shown in Table 3.

It is important to differentiate DRESS from other diseases that involve the skin with systemic involvement such as Stevens-Johnson syndrome/toxic epidermal necrolysis, vasculitis like systemic lupus erythematosus, Kawasaki disease, hypereosinphillic syndrome and tropical infections with multiorgan involvement[7].This kind of presentation in critical care setting specially during the rainy and post rainy season can easily be contributed to tropical fever syndrome, sepsis and MODS. Hence presence of characteristic rash, eosinophilia and drug related history along with awareness of illness is important to make early diagnosis with conviction.

In our case DRESS syndrome developed in 15-year-old kid with use of these drugs. Withdrawal of these drugs, together with injection hydrocortisone along with supportive care was started. The French group headed by Descamps et al given the treatment algorithm as per the severity

of illness of this syndrome. They have summarized entire treatment algorithm in 4 case scenarios. The first scenario occurs in mild illness, requires treatment with topical corticosteroids with use of emollients and antihistamines and interruption of the suspected drug. The presence of organ involvement such as transaminases 5 times higher than the normal value, kidney failure, lung disease, hemophagocytosis, or cardiac abnormalities define the second scenario, its management should include systemic steroids such as prednisolone in dosages of 1 mg/kg per day. The third scenario is in the presence of any life-threatening sign, hemophagocytosis, spinal cord failure, encephalitis, liver failure, respiratory failure, it should be treated with corticosteroid as well as intravenous immunoglobulin (IVIG) at a dose of 2 g/kg for five days. Finally, in fourth scenario suggested by presence of severe disease along with the confirmation of viral reactivation HHV6 should be treated with corticosteroids, IVIG and antivirals such as ganciclovir. Finally, a fourth scenario is given by the presence of signs of severity together with the confirmation8.

Table 2: Medications associated with DRESS

Group	Drugs
Antiepileptics	Aromatic antiepileptic drugs (Carbamazepine, lamotrigine phenobarbital, phenytoin, oxcarbazepine)
Antibiotics	Amoxicillin, ampicillin, azithromycin, levofloxacin, Minocycline, Sulfamethoxazole- Trimethoprim, Vancomycin
Antituberculosis agents	Aspirin, celecoxib, diclofenac, ibuprofen, piroxicam
Others	Allopurinol, amitriptyline, dapsone, hydroxychloroquine, imatinib, nevirapine, omeprazole, sulfasalazine

Adopted from Cho Y-T[3].

Table: 3 Regi SCAR Scoring system for classifying DRESS cases as Definite, Probable, or no case from Kardaun et al

Criteria (Score)	-1	0	+1	+2	Patient score
Fever greater than or equal to 38.5 ^{0}C	No	Yes			0
Lymph node enlargement		No/ U	Yes		+1
Eosinophilia		No/ U			
Eosinophils			700-1499/mm^3	≥1500mm^3	2
Eosinophils,if leukocytes are 4,000/mm^3			10-19.9%	≥20%	
Atypical (or reactive) lymphocytes		No/U	Yes		0
Extensive rash (>50% TBSA)		No/U	Yes		+1
Rash suggestive of DRESS	No	U	Yes		+1
Biopsy suggestive of DRESS	No	Yes/U			0
Hepatic impairment		No/U	Yes		+1
Renal impairment		No/U	Yes		0
Lung manifestations		No/U	Yes		0
Muscle/Heart manifestations		No/U	Yes		0
Pancreatic impairment		No/U	Yes		0
Impairment of other organs		No/U	Yes		+1
Resolution in ≥ 15 days	No/U	Yes			-1
Evaluation of other potential causes: ✓ ANA ✓ Blood Cultures			Yes		+1

✓ **Serology for hepatitis A/B/C** ✓ **Chlamydia/Mycoplasma pneumonia** ✓ **Other serologies/PCR/cultures** **If none is +0 and ≥3 of those mentioned are (-)**					
Patient final score	7				
DRESS-Drug Reaction with Eosinophilia and Systemic Symptoms; U=unknown/unclassifiable ANA=Antinuclear antibody; HAV=hepatitis A virus, HBV= hepatitis B virus, HCV= hepatitis C virus, *After exclusion of other explanations: 1, one organ; 2, two or more organs. Final score<2, no case; final score2-3; possible case; final score4-5, probable case; final score>5, definite score					

Adopted from S H Kardaun[2].

Conclusion

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a life-threatening adverse effect of certain drugs. Most commonly implicated drugs are anticonvulsants like phenytoin, phenobarbital and carbamazepine. HCQ, sulphasalazine and NSAIDS are common offenders in genetically predisposed individuals. Clinicians should have a high index of suspicion for the DRESS syndrome in patients being treated with these drugs. Fever, characteristic drug related rash, eosinophilia and transaminitis are important clue for early diagnosis. Management includes stopping the offending drug, use of steroids and IVIG depending on the severity of illness.

References

1. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). *Semin Cutan Med Surg*. 1996;15(4):250-257. doi:10.1016/s1085-5629(96)80038-1
2. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist?. *Br J Dermatol*. 2007;156(3):609-611. doi:10.1111/j.1365-2133.2006.07704.x
3. Cho YT, Yang CW, Chu CY. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): An Interplay among Drugs, Viruses, and Immune System. Int J Mol Sci. 2017 Jun 9;18(6):1243. doi: 10.3390/ijms18061243. PMID: 28598363; PMCID: PMC5486066
4. Choudhary S, McLeod M, Torchia D, Romanelli P. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome. *J Clin Aesthet Dermatol*. 2013;6(6):31-37.https://pubmed.ncbi.nlm.nih.gov/23882307/
5. Lin IC, Yang HC, Strong C, et al. Liver injury in patients with DRESS: A clinical study of 72 cases. *J Am Acad Dermatol*. 2015;72(6):984-991. doi:10.1016/j.jaad.2015.02.1130
6. Chen YC, Chang CY, Cho YT, Chiu HC, Chu CY. Reply to: "Using a diagnostic score when reporting the long-term sequelae of the drug reaction with eosinophilia and systemic symptoms". *J Am Acad Dermatol*. 2013;69(6):1060-1062. doi:10.1016/j.jaad.2013.08.026
7. Bachot N, Roujeau JC. Differential diagnosis of severe cutaneous drug eruptions. *Am J Clin Dermatol*. 2003;4(8):561-572. doi:10.2165/00128071-200304080-00006
8. Descamps V, Ben Saïd B, Sassolas B, et al. Prise en charge du drug reaction with eosinophilia and systemic symptoms (DRESS) [Management of drug reaction with eosinophilia and systemic symptoms (DRESS)]. *Ann Dermatol Venereol*. 2010;137(11):703-708. doi:10.1016/j.annder.2010.04.024.