**Case Report**

**A CASE REPORT ON DAPSONE INDUCED DRESS SYNDROME**

# ABSTRACT

**Introduction:** Drug reaction with eosinophilia and systemic syndrome is a severe idiosyncratic drug induced reaction. DRESS syndrome should be considered in any patient with skin eruption, fever, eosinophilia or liver and hematological abnormalities. **Case description:** This is a case report of dapsone induced DRESS syndrome of which a 24 years female patient was admitted in hospital with chief complains of low grade fever since one month, yellowish discoloration of eyes since 15 days, giddiness since two weeks, malaise and myalgia since 4 days, painful lesion on tongue since one week, burning sensation of palms and stomach with blurring of vision. Her past history revealed that known case of lepromatous leprosy since one month and for that using dapsone 100 mg, so based on patient signs and symptoms and past history, physicians advised CBC,LFT,RFT and biochemistry, serum electrolytes and retic count, HBSAG, HCV, vitamin b12,serum folic acid, abdomen pelvic sonography and AFB staining. In which CBC,RFT,LFT were abnormal. AFB staining shows AFB morphologically resembling that of mycobacterium leprae seen and confirmed final diagnosis. The treatment initiated with suspected drug dapsone was withdrawn and further supportive treatment was given such as cefotaxime , pantoprazole, Urso deoxy cholic acid, IV fluid, iron folic acid tablets and vitamin b complex tablets and blood transfusion of packed red blood cells was performed to normalize the decreased hemoglobin and red blood cells. For management of leprosy minocycline was included as a alternative drug. After treatment, the outcome of patient condition were improving and her symptoms got reduced. **Conclusion:** The management of this syndrome with prompt discontinuation of the culprit drug and supportive therapy was initiated. Therefore clinicians who are prescribing dapsone for different clinical conditions should have awareness about DRESS syndrome and it’s presentation of potentially becoming fatal.

**Keywords**: DRESS syndrome, Dapsone, Leprosy, Complete Blood Count(CBC) Liver function test (LFT), Acid fast bacilli (AFB), Renal function test( RFT), Hepatitis B Surface Antigen (HBSAG), Hepatitis C virus(HCV), Fatal, awareness.

# INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms(dress) syndrome is a severe idiosyncratic drug induced reaction, usually characterized by rash, fever, lymphadenopathy, hematologic abnormality (eosinophilia and atypical lymphocytes) and single or multi organ involvement. The first exposure to the drug and the onset of symptoms can range from 2 to 8 weeks. This syndrome is also known as drug induced hypersensitivity syndrome (or) drug hypersensitivity syndrome.(1,2) Drugs most commonly causing this reactions are antiepileptic’s, sulpha derivatives, antimicrobials, allopurinol, antidepressants and Nsaids.(2) The letter “R” in the word “DRESS” is used to refer to the “Reaction” instead of “Rash” because some cases of dress can manifest with visceral involvement in absence of cutaneous symptoms.(3)The drug dapsone(4,4'-diamino

diphenylsulfone) is useful for treating a variety of infections, immunological and hypersensitivity disorders. Most commonly encountered adverse effect of this drug include dose related (idiosyncratic)skin hypersensitivity reactions and dose related hemolytic anemia and methaemoglobinemia.(4) Its incidence rate is estimated to be between 1 in 1000 and 1 in 10000 drug exposure and Mortality rate is estimated to be 10% ,It occurs usually in patients with severe multiorgan involvement. Mechanisms involved in this dress syndrome are (a) A genetic component that alters immune response (b) A triggering factor mostly a viral infection (c) Defect in dry metabolism resulting in failure to eliminate drug intermediates. Diagnosis criteria involved in this dress syndrome is (a) Regiscar scoring system (b) Scar J diagnostic criteria.(5) Complications of this disease include limbic encephalitis, thyroid disease, renal failure, eosinophilic colitis, eosinophilic encephalitis.(6)



(7,8)Figure 1-DRESS SYNDROME symptoms such as rashes and lymphedenopathy

# CASE REPORT

A 24 years women admitted to the female medical ward of general medicine in tertiary care hospital, with the chief complaints of low grade fever since 1 month , yellowish discoloration of eyes since 15 days , giddiness since 2 weeks , malaise and myalgia since 4 days , painful lesion on tongue since 1 week , burning sensation of palms and stomach with blurring of vision. Her past history revealed that she was a known case of Borderline Lepromatous Leprosy since 1 month and on MBMDT(Multibacillary- Multi drug therapy) treatment include drugs such as Dapsone(100mg), Rifampicin(300mg) and Clofazimine(100mg). On examination her BP was110/70mm of Hg, Pulse rate was 88bpm and SPO2 was 97%@RA. External examination revealed the presence pallor and icterus , hence physician advised for tests like Complete blood count, Liver function tests , Kidney function tests ,Biochemistry , Serum electrolytes , Retic count , vitamin B12 , Serum folic acid , HCV & HBS AG- Rapid , Abdomen-Pelvic Sonography , AFB ( Acid Fast Bacilli ) staining for the further diagnosis.

# Table 1-LABORATORY PARAMETERS

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **SL. NO** | **TESTS** | **PARAMETERS** | **RESULTS ON ADMISSION** | **RESULTS**  **DURING**  **INWARD** | **REFERENCE RANGE** |
|  | COMPLETE  BLOOD COUNT | Haemoglobin | **7.8** | 13.4 | 12.5-16gm% |
|  |  | Red blood cells | **2.82** | 4.90 | 4.5-  5.5million/cumm |
|  |  | Platelets | **1.06** | 2.05 | 1.5-  4.5lakh/cumm |
|  |  | Neutrophils | **72** | 53 | 40-70% |
|  |  | Packed cell volume | **23.6** | 41.2 | 35-46% |
|  | LIVER FUNCTION  TESTS | Albumin | **3.0** | 2.8 | 3.2-5.4g/dl |
|  |  | Globulin | **3.2** | 3.0 | 2.5-3g/dl |
|  |  | A/G ratio | **0.9** | 0.9 | 1.2-1.5 |
|  |  | Total bilirubin | **4.1** | 2.0 | 0.2-1.2mg/dl |
|  |  | Conjugated bilirubin | **1.4** | 0.8 | 0.1-0.4mg/dl |
|  |  | Unconjugated  bilirubin | **2.7** | 1.2 | 0.2-0.7mg/dl |
|  |  | Alkaline phosphate | **197** | 195 | 20-140U/L |
|  | RENAL  FUNCTION TESTS | Serum creatinine | **0.5** | 1.0 | 0.7-1.4mg/dl |
|  | SERUM  ELECTROLYTES | Sodium | **131** | 140 | 136-146mEq/l |
|  |  | Potassium | **3.0** | 4.4 | 3.48-5mEq/l |
|  |  | Chloride | **94** | 99 | 96-106mEq/l |

* HBSAG Rapid – Negative
* HCV - Negative
* Abdomen-pelvic sonography – Normal
* Retic count – 0.5% ( 0.2-2%)
* Vitamin B12 – 214.5pg/ml (211-911pg/ml)
* Serum folic acid – 12.25 (2.5-20 ng/ml)
* AFB STAINING – AFB morphologically resembling that of Mycobacterium leprae seen.

Based on the External and laboratory examinations , final diagnosis was confirmed as DRESS SYNDROME due to dapsone hypersensitivity

Hence the suspected drug (Dapsone) which caused the above condition was withdrawn and further treatment was suggested.

# Table 2-TREATMENT CHART

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **SL.NO**  **NAME OF THE DOSE ROUTE**  **MEDICATIONS** | | | | **FREQUENCY**  **DURATION** | |
|  | Inj. Cefotaxime | 1gm | IV | 1-0-1 | D1-D4 |
|  | Inj. Pantoprazole | 40mg | IV | 1-0-0 | D1-D4 |
|  | Tab. Urso deoxy cholic acid | 300mg | PO | 1-0-1 | D1-D4 |
|  | I.V. Fluid | 2pintNS | IV | 75ml/hr | D1-D4 |
|  | Tab. Iron folic acid | 333mg | PO | 1-0-1 | D1-D4 |
|  | Tab. B complex |  | PO | 0-1-0 | D1-D4 |
|  | Inj. Vitamin  Bcomplex | 1amp in  100ml NS | IV | 1-0-0 | D1-D4 |
|  | 1Pint PRBC |  |  |  | D1 |

Blood transfusion of packed red cells on the day of admission to normalize the decreased haemoglobin and red blood cells.

The patient was treated with above medications .

# Table 3-DISCHARGE MEDICATION

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **SL.NO**  **NAME OF THE DOSE**  **MEDICATION** | | | **ROUTE** | **FREQUENCY** |
|  | Tab Urso deoxy cholic acid | 300mg | PO | 1-0-1 |
|  | Tab Minocycline | 100mg | PO | 1-0-0 |
|  | Tab Iron folic acid | 333mg | PO | 1-0-1 |
|  | Tab Pantoprazole | 40mg | PO | 1-0-0 |

The suspected drug i.e, Dapsone was withdrawn and Minocycline was included as alternative drug in the MB-MDT treatment to treat Lepromatous leprosy. minocycline is preferred for treating leprosy because it directly combats the infection, while corticosteroids are reserved for managing complications related to the body's immune response.

# DISCUSSION

Drug reaction with eosinophilia and systemic symptoms(DRESS)is indeed a severe and potentially life threating adverse drug reaction .This is mainly caused by certain drugs, as in this case it is caused by dapsone which is used to treat her past disease i.e, Leprosy. Dapsone can cause DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome, a severe adverse reaction. The pathophysiology of DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome is complex and involves the interplay of several factors, including :

**Viral factors:** Viral reactivation, particularly of human herpesviruses (HHVs), plays a crucial role in DRESS pathogenesis. HHV-6 is the most frequently associated virus with DRESS. Viral reactivation may contribute to direct tissue damage, expansion of virus-harboring immune cells, and promotion of anti-drug responses. **Immunological mechanisms:** T-cell responses, including activation and expansion of CD4+ and CD8+ T cells, contribute to the pathophysiology of DRESS.

Drug-reacting cells produce pro-inflammatory cytokines, which may lead to a broad spectrum of inflammatory phenotypes. Immunological mechanisms involve the interaction between drug specific T cells and viral antigens, leading to the activation of immune cells and the release of cytokines. **Other factors:** Genetic predisposition, such as specific HLA alleles, may increase the risk of developing DRESS. Aberrant haptenation of drugs and direct drug-related activation of immune cells may also contribute to the development of DRESS. **Cytokine storm:** The release of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, leads to a systemic inflammatory response, which is a hallmark of DRESS. The cytokine storm may contribute to the development of eosinophilia, a key feature of DRESS. **Drug-related factors:** Recent drug discontinuation is associated with DRESS. Certain drugs, such as anticonvulsants, allopurinol, and antibiotics, are commonly implicated in DRESS. Novel drugs, including anti-cancer targeted therapies and immune-modulators, may also trigger DRESS.(9)

Variations in dapsone metabolism, affecting the production and detoxification of its reactive metabolites, may contribute to individual differences in susceptibility to dapsone-related adverse effects. The metabolism of dapsone via N-hydroxylation to hydroxylamines by the hepatic microsomal cytochrome P-450 system has been associated with hematological toxicity, including methemoglobinemia, hemolytic anemia, and agranulocytosis. However, its role in influencing the risk of Dapsone hypersensitivity syndrome remains uncertain.(10)Dapsone has an elimination half-life of 24 to 30 hours, largely due to its strong protein binding (70-90%) and that of its major metabolite, monoacetyl-dapsone (99%). Hypersensitivity reactions to dapsone can arise between 6 weeks and 6 months after starting treatment, typically manifesting as a triad of fever, skin eruptions, and internal organ involvement, such as liver damage. Diagnostic criteria for Dapsone Hypersensitivity Syndrome (DHS), as outlined by Richardus and Smith, require symptoms to appear within 8 weeks of initiation and resolve upon discontinuation, without being attributable to other drugs, lepra reactions, or underlying diseases. Similarly, DRESS syndrome, as defined by Bocquet et al., involves a drug-induced skin reaction, hematologic abnormalities like eosinophilia or atypical lymphocytes, and systemic involvement such as hepatitis or interstitial nephritis. The RegiSCAR criteria further specify that at least three signs, including acute rash, fever above 38°C, internal organ involvement, lymphadenopathy, or blood abnormalities, must be present for diagnosis.(11)

Where as in this case, a women was admitted with the complaints of low grade fever since start of MB-MDT( Multi bacillary- Multi drug therapy )therapy, yellowish discoloration of eyes since 15 days , giddiness since 2 weeks, malaise and myalgia since 4 days, painful lesion on tongue , burning sensation of palms and stomach with blurring of vision with past history of borderline lepromatous leprosy. As her increased liver parameters and low hemoglobin , red blood cells levels were abnormal

She was treated with Cefotaxime was used to treat nosocomial infection, Pantoprazole was used to treat gastric irritation caused by drugs, Ursodeoxycholic acid was used to treat abnormal liver parameters , IV fluids was given as electrolyte replenisher to treat dehydration , Iron folic acid was used to treat iron and folic acid deficiency ( Anemic conditions) , Vitamin B complex used to treat vitamin b deficiency . After treatment her symptoms like fever, yellowish discoloration of eyes, myalgia, malaise and lesions got reduced, liver and hematological abnormalities were improving. Dress syndrome is caused due to Dapsone drug hence it was withdrawn and further complications were prevented .

**Adverse drug reaction probability Scale(Naranjo Scale)**

It is a method by which to assess whether there is a causal relationship between an identified/suspected reaction and a drug using a simple questionnaire to assign probability score.

WHO Naranjo scale is performed to assess the Adverse drug reaction in this patient it’s Total score is 9 , so it is definite. The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids,(2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on reexposure.

There are many scoring symptoms and criteria to diagnose DRESS SYNDROME , REGISCAR is most widely used and applied. Our diagnosis was based on REGISCAR criteria as its sensitivity to seems to be higher in comparative studies. **According to Regiscar scoring system**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **FEATURES** | **-1** | **0** | **1** | **PATIENT**  **SCORE** |
| Fever>38.5degree celcius |  |  | Y | 1 |
| Enlarged lymph nodes > sites, >1 cm |  |  | Y | 1 |
| Atypical lymphocytes |  | N |  | 0 |
| Eosinophilia  700-1499 or 10%-19.9%  >1500 or >20% |  | N |  | 0 |
| Skin rash  Extent>50%  At least 2: edema , infiltration , purpura, scaling  Biopsy suggesting DRESS | N |  | Y | -1          1 |
| Internal organ involvement  One  Two or More |  |  | Y | 1 |
| Resolution in more than 15 days  At least 3 biological investigation done and negative to exclude alternative diagnosis |  | N/U | Y | 0      1 |
| **TOTAL SCORE** |  |  |  | 4 |

Table 4- Diagnosis was made based on REGISCAR criteria

N=No, U = Unknown, Y= Yes. Final score <2=No , 2-3 = Possible, 4-5= Probable , equal to or

>6 =Definite Based on the above diagnostic criteria ,the Dress syndrome was Probable as per the score .

# CONCLUSION

DRESS syndrome is a serious drug reaction with high mortality due to systemic involvement management of dress syndrome involves early diagnosis is essential and prompt treatment is of utmost importance, as delay in treatment may lead to mortality. Mechanism of DRESS syndrome are not completely understood, numerous cases have been reported in children’s and adults. DRESS syndrome should be considered in any patient with skin eruption,fever,eosinophila or liver and hematological abnormalities because this DRESS syndrome is life threatening multi system ADR.

So, management of this syndrome with prompt discontinuation of the culprit drug, supportive therapy and initiation of corticosteroids may prevent systemic manifestations. Therefore clinicians who are prescribing dapsone for different clinical conditions should have awareness about dress syndrome and it’s presentation potentially becoming fatal.

Ethical Approval:

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

Consent

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

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2.

3.

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