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STEVENS-JOHNSON SYNDROME SECONDARY TO DAPSONE SENSITIVITY

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ABSTRACT

Leprosy is a chronic granulomatous infection that affects skin, mucus membrane and peripheral nerves. Where, dapsone is the most commonly used as a part of multidrug therapy. Dapsone being effective, carries the risk of Dapsone Hypersensitivity Syndrome (DHS), a rare but serious adverse reaction characterized by systemic symptoms and severe cutaneous manifestations. Which may rarely progress into Stevens - Johnson syndrome (SJS), the most critical complication. The SJS is presented as widespread mucocutaneous blistering along with multi-organs involvement. The present report is a case of a 35-year-old male with leprosy on dapsone therapy developed DHS progressing to SJS. The patient exhibited mucocutaneous lesions, liver dysfunction, and gastrointestinal symptoms. Laboratory investigations revealed significant haematological and biochemical abnormalities. Immediate discontinuation of dapsone, followed by initiation of corticosteroids, antibiotics, supportive therapy, and plasma transfusion led to clinical improvement. This case highlights on interconnected risk between DHS and SJS during dapsone therapy.

KEYWORDS: ADR (Adverse Drug Reaction), Dapsone, DHS (Dapsone Hypersensitivity Syndrome), Genetic screening (HLA-B*13:01), Multidrug therapy, Mucocutaneous lesions, Liver dysfunction, Leprosy, SJS (Stevens - Johnson syndrome).

INTRODUCTION

Leprosy, also known as Hansen's disease, is a chronic infectious disease caused by the bacterium *Mycobacterium leprae*. It has a primary effect on the skin, peripheral nerves,

mucous membranes of the upper respiratory tract, eyes and other parts. If left untreated, leprosy can lead to progressive and permanent disabilities. For treatment purposes, the WHO classifies leprosy into two categories based on the number of skin lesions and bacteriological findings:

Paucibacillary (PB): Characterised by 1–5 skin lesions without detectable bacilli in skin smears.

Multibacillary (MB): Characterised by more than five skin lesions, detectable bacilli in skin smears, or nerve involvement.[1]

Dapsone, chemically known as 4, 4'-sulfonyldianiline or diamino diphenyl sulfone, is an anti-infective and anti-inflammatory agent that belongs to the class of sulfones compounds. It is used primarily in the treatment of leprosy, dermatitis herpetiformis, and acne vulgaris. It is also used prophylactically in pneumocystis carinii pneumonia and toxoplasmosis in HIV patients as well as an adjuvant in the treatment of malaria. Additionally, dapsone is utilized off-label for various dermatological and infectious conditions.[2] According to the World Health Organization (WHO), dapsone is administered at a dosage of **100 mg daily** for **12 months** in the treatment of **multibacillary leprosy** and for **6 months** in **paucibacillary leprosy**.[3] Dapsone has been a cornerstone in treating both multibacillary and paucibacillary leprosy for over 70 years, since its introduction in the 1940s.[4]

Dapsone exhibits its antimicrobial effects by inhibiting the synthesis of dihydrofolic acid. It competes with para-aminobenzoic acid for the active site of dihydropteroate synthase, thereby interfering with bacterial folic acid synthesis. This mechanism is similar to that of sulphonamides. The anti-inflammatory action of dapsone differs from its antimicrobial activity, and researchers have not yet gained a complete understanding of it. One proposed mechanism involves the inhibition of the myeloperoxidase-hydrogen peroxide-halide system in neutrophils. This system is a part of the neutrophil respiratory burst, produces reactive oxygen species like hypochlorous acid, which can cause tissue damage during inflammation. Dapsone may inhibit this system, thereby reducing tissue damage.[5]

Dapsone hypersensitivity Syndrome (DHS) is a rare and potentially fatal adverse reaction to dapsone. It was first identified in 1949, characterized by exfoliative dermatitis, fever, and hepatitis, and is now understood to be an unpredictable, dose-independent hypersensitivity reaction.[6]

DHS is classified as a Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), characterized by severe skin and systemic involvement. It is a complex condition with an unclear mechanism, potentially involving toxic metabolite production, impaired detoxification, and hapten formation thus triggering an immune response.[4] A genetic link exists with the HLA-B*13:01 allele, which varies across ethnic populations. While pre-initiation HLA typing may be considered in high-risk populations with adequate infrastructure, its practicality and cost-effectiveness require further evaluation. Notably, DHS has a prevalence of 1.4% and a case fatality rate of 9.9%, with increased risk of fatal outcome associated with age and leprosy indication.[6] Dapsone Hypersensitivity Syndrome (DHS) is a potentially life-threatening condition that can arise within a variable timeframe, ranging from 6 hours to 12 weeks, following the initiation of dapsone therapy. This complex syndrome is marked by a constellation of symptoms, including fever, skin rash, and lymphadenopathy, often accompanied by significant organ involvement, particularly hepatitis. Furthermore, patients may exhibit additional systemic manifestations, such as gastrointestinal disturbances (nausea and vomiting), haematological abnormalities (eosinophilia, leucocytosis, and anaemia), and splenomegaly, as well as pulmonary and cardiac complications.[6] [7]

Given the potential severity of DHS, it is crucial to recognize the signs and symptoms at an earliest and manage the condition effectively to prevent serious outcomes, including fatalities. Timely intervention can significantly impact the prognosis and outcome for patients affected by this syndrome.[8] Stevens-Johnson syndrome (SJS) is a rare, serious disorder of the skin and mucous membranes with multi organ involvement. It's usually a reaction to medication that starts with flu-like symptoms, followed by a painful rash that spreads and blisters. Then the top layer of affected skin dies sheds and begins to heal after several days. Stevens - Johnson syndrome (SJS) is severe cutaneous adverse drug reactions (SCARs) that can be associated with DHS.[9]

CASE PRESENTATION

Subjective :- A 35 years old male patient was admitted to hospital with chief complaints of loose stools 6-7 episodes per day since 3 days watery consistency contains mucus and blood in stool since 2 days, B/L crusted plaques over chest , cheeks and peeling of skin all over the face.

Past history: - Patient was having a history of leprosy since 6 months, Chronic Liver Disease (CLD) since 2 months, dapsone hypersensitivity since 1 month and H/o enteric fever and Steven-Johnson Syndrome since 1 week and was admitted to MICU.

Past medication: - Leprosy- T. Dapsone.
For CLD- T. Rifaximin, T. Ursodeoxycholic acid.

Objective: - On examination patient's BP was 70 mm of Hg systolic for which INJ. Nor adrenaline was administered till BP was stabilized, Pulse was 80 bpm, spo_2 was 92% at RA, and PICCLE was negative. On this basis it was diagnosed as Dapsone hypersensitivity syndrome so patient was advised to intake dapsone once daily. On lab examination patient's LFT levels were found to be abnormal so, T. Rifaximin was withdrawn.

The lab parameters were as follows

SL.NO	PARAMETERS	RESULTS	REFERENCE RANGE
1.	Hemoglobin	7.8 g/dl	13- 15 gm
2.	RBC	2.61million/ cumm	5.5- 6.5 million/cumm
3.	PCV	24.7	45- 55%
4.	MCV	95 fl	80 – 100 fL
5.	MPV	10.2 fl	7-11 fl
6.	MCH	29.8 pg	27 – 34 pg
7.	MCHC	30.4%	31-36 %
8.	RDW-CV	17.8%	11.5- 14.5%
9.	WBC	9840	4000 -11000 cells/cumm
10.	Monocytes	02	02 – 10%
11.	Neutrophils	93%	40-70%
12.	Lymphocytes	03%	20- 40%
13.	Eosinophil	02%	3-6 %
14.	Basophils	0	0 – 1
15.	Platelets	0.43lacs/cumm	1.5- 4.5 lakhs/ cumm
16.	PDW-CV	18.8%	10-18 %
17.	ESR	27mm/hr	0-15 mm/hr
18.	Random Blood Sugar (RBS)	65 mg/dl	70- 140 mg/dl
19.	Sodium	130 mEq/L	136-140 mEq/L
20.	Potassium	6.2 mEq/L	3.48- 5 mEq/L
21.	Chloride	95 mEq/L	95- 100 mEq/L
22.	Total protein	5.6g/dl	6-8.3 g/dl
23.	Albumin	2.4 g/dl	3.2- 5.4 g/dl
24.	Globulin	3.2 g/dl	2.5- 3 g/dl
25.	A/G Ratio	0.7	1.2- 1.5
26.	Alanine transaminase	274 U/L	0- 45 IU/L
27.	Aspartate Transaminase	133 U/L	0- 45 IU/L
28.	Alkaline Phosphatase (ALP)	189 U/L	20- 140 IU/L
29.	Total Bilirubin	34.7 mg/dl	0.2- 1.2 mg/dl
30.	Conjugated Bilirubin	20.3 mg/dl	0.1 – 0.4 mg/dl
31.	Unconjugated Bilirubin	13.7 mg/dl	0.2 – 0.7 mg/dl

32.	Blood Urea	28 mg/dl	15 – 45 mg/dl
33.	Serum creatinine	0.9 mg/dl	0.7 – 1.4 mg/dl
34.	INR	2.1	0.8- 1.1
35.	PT	28.5 seconds	11- 16 seconds
36.	APTT	75.1 seconds	30- 40 seconds
37.	Urine Albumin	NIL	-
38.	Urine Microscopy	NAD	-
39.	Urine Sugar	NIL	-
40.	Urine Protein – creatinine ratio	112 mg/g	10 – 150 mg/g

Other investigations

USG: - Mild hepatomegaly with diffuse liver disease, mild splenomegaly. On skin examination B/L M/L crusted plaques were noted over the forehead, chin, cheek; increased desquamation of skin noted over palm and lower limbs.

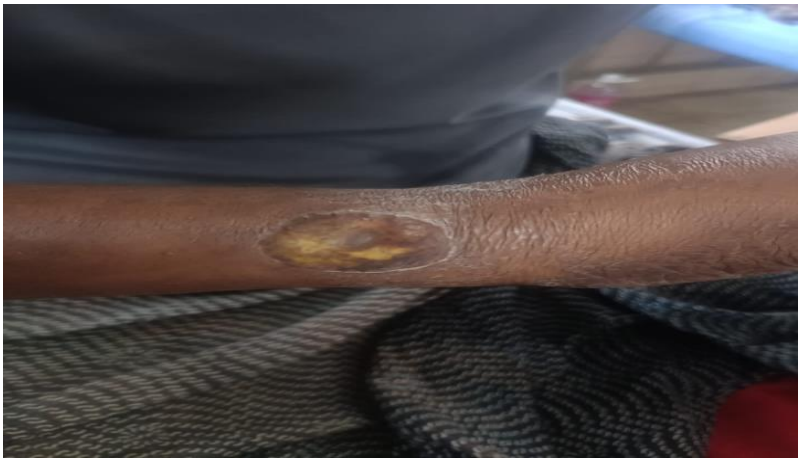

Figure 1: Crusted plaques.

Figure 2a

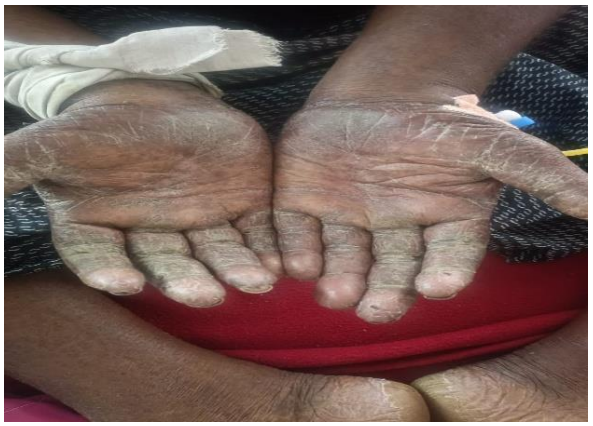

Figure 2b

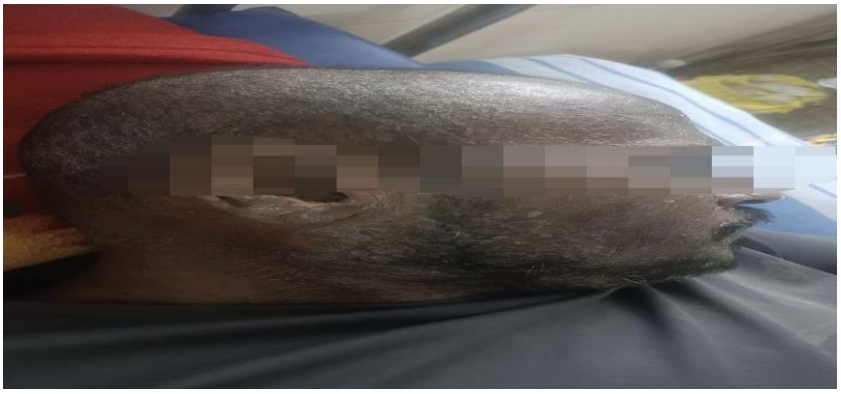

Figure 3

Fig. 2a, 2b and 3 Showing Peeling of Skin On Face B/L Foot and Palms.

Pharmacological Therapy

SL. NO	MEDICATION	DOSE	FREQUENCY & NO OF DAYS
1.	INJ. Ciprofloxacin	500mg	Twice daily for 7 days
2.	INJ. Metronidazole	500mg	TID for7 days
3.	INJ. Pantoprazole	40mg	OD for 7days
4.	T. Sporolac		TID for 7 days
5.	INJ. Noradrenaline	Infusion STAT Continue	2 ampules in 100ml of NS for 2 days
6.	INJ. Vitamin K	10 mg	OD for 7 days
7.	T. Rifaximin	550 mg	BID for 1month later stopped for 15 days Increases ALT, AST levels.
8.	T. Ursodeoxycholic acid	300 mg	BID for 1 month
9.	T. Acetyl cysteine	600mg	BID for 1 month
10.	Liquid Paraffin		
11.	T. Dapsone	100 mg	BD for 5 months and OD for 1 month and stopped from 4 days
12.	INJ. Ondansetron	4 mg	OD for 7 days
13.	Fresh frozen plasma	4 pints	OD for 4 days 1 Pint each day
14.	T. Doxycycline	300mg/ 100 mg	BD for 7 days
15.	Betamethasone cream		Continue
16.	Glycerol gel	SOS	Continue
17.	IV Fluids- NS	@75ml/hour	For 4 days
18.	INJ. Vitamin E		OD for 7 days
19.	INJ. Ceftriaxone	1g	BD for 7 days
20.	PRBC	3pint	Each pint 1 day
21.	T. Prednisolone	30 mg	7 days.

Informed consent was obtained from the patient for being included in the safety and publication of the images.

DISCUSSION

Due to its therapeutic and cost effectiveness the Dapsone is considered as a first line agent for Hansen's disease, dermatitis herpetiform, linear IgA bullous dermatosis etc. however, It is

also associated with serious hypersensitivity reactions including SJS.[10] In the presented case the patient exhibited classic signs of Stevens-Johnson syndrome including widespread erythematous macules, skin detachment involving less than 10% of body surface area, blistering, positive nikolsky sign and mucosal involvement. The temporal relationship between drug intake and symptom onset suggests a drug- induced aetiology which aligns with ***Mockenhaupt M et al*** literature indicating sulphonamides such as Dapsone, antiepileptics and NSAIDs are the most common causative agents of SJS.[10] Upon observing the abnormalities in complete blood count like decreased Hb, RBC, MCHC, platelets along with bicytopenia. In addition, patient`s complaints such as loose blood stained stools, vomiting etc. and by observing abnormal electrolytes level and acute gastroenteritis and hypovolemic shock etc. Hence we imposed used Naranjo causality assessment scale which revealed a total score of **'8'** hence, it was predicted as a dapsone induced Steven's Johnson syndrome with bicytopenia. The cornerstone of management remains immediate withdrawal of dapsone and initiation of supportive care ***Lerch M et al*** studies suggest a potential benefit from early administration of corticosteroids in controlling inflammation and ceasing the disease progression.[11]

CONCLUSION

Stevens-Johnson syndrome (SJS) secondary to Dapsone Hypersensitivity Syndrome (DHS) represents a rare yet serious adverse drug reaction that demands timely clinical attention. In the presented case, the progression of DHS eventually to SJS during leprosy treatment with dapsone highlights on the interconnected risk between these conditions. Early recognition of hallmark features such as mucocutaneous blistering, haematological abnormalities like bicytopenia, and systemic manifestations is crucial, as these signs often overlap and worsen if not promptly addressed. Immediate withdrawal of dapsone, coupled with appropriate supportive measures including corticosteroids, plasma transfusions, and infection control plays a pivotal role in patient recovery. Further, this case also underlines the importance of vigilant monitoring throughout dapsone therapy to detect early warning signs. To minimize such life-threatening outcomes, pre-treatment genetic screening for HLA-B*13:01 may be considered in high-risk populations, to establish suitable preventive strategies with individualized patient care.

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