A CHALLENGES AND CLINICAL IMPLICATION IN DAPSONE-INDUCED HYPERSENSITIVITY SYNDROME IN BORDERLINE TUBERCULOID HANSEN'S DISEASE

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ABSTRACT:
An essential sulfone medication, dapsone was created in 1908 and is mostly used to treat leprosy and other dermatological disorders**.** 0.2% to 0.5% of users have dapsone hypersensitivity syndrome (DHS), which was initially identified in 1949. If left untreated, DHS can cause severe systemic symptoms that could result in organ damage or even death. DHS is characterised by a delayed onset that can happen anywhere from two hours to six months after exposure. It involves processes such as the creation of inflammatory cytokines. Skin hypersensitivity responses and haemolytic anaemia associated to dosage are important adverse effects.
A 42-year-old housewife with borderline tuberculoid leprosy showed up with extensive red lesions that turned into yellowish pustules over the course of four days, as well as hand and foot oedema, pain, and itching. A trophic ulcer on her right sole, hyperpigmented patches, and non-blanchable erythema and pustules on her face, upper and lower limbs, chest, and belly were all found during the examination. She had steady vital signs and no systemic symptoms.
Keywords: Dermatological Disorders, Borderline Tuberculoid Leprosy, Dapsone Hypersensitivity Syndrome (DHS), Hyperpigmented Patches.

INTRODUCTION: -
First synthesised by Fromm and Wittmann in 1908, dapsone (4,4, -diaminodiphenylsuphone) is a member of the sulphone drug category. Allday and Barnes coined the name "dapsone syndrome" in 1951[1] after Lowe and Smith in 1949[2] in Nigeria first described dapsone hypersensitivity syndrome (DHS). A drug-induced hypersensitivity syndrome (DIHS), dapsone 4'4'-diaminodiphenylsulfone (DDS) is the cause of DHS. DHS is found in 0.2% to 0.5% of people. In previously sensitised patients, the symptoms may appear as early as 2–6 hours or as late as 6 months [3]. Many dermatological diseases, including dermatitis herpetiformis, vesicobullous dermatoses, cutaneous vasculitis, polyarteritis nodosa, nodulocystic acne, and cutaneous mycetoma, are treated with dapsone, the medicine of choice for Leprosy (Hansen's disease) [4]. Because of its antibacterial and anti-inflammatory properties, it is a good choice for treating the illnesses listed above [5]. Dose-related haemolytic anaemia and methemoglobinemia, as well as dose-unrelated (idiosyncratic) skin hypersensitivity reactions, are frequent side effects of this medication. Other significant side effects include psychosis and sleeplessness. Dapsone medication may be complicated by dapsone hypersensitivity syndrome (DHS), an uncommon and potentially fatal idiosyncratic systemic hypersensitivity syndrome that manifests as fever, skin rash, eosinophilia, lymphadenopathy, hepatic, pulmonary, and other systemic symptoms [6-10]. DHS can result in mortality or irreparable organ damage if it is not identified and treated promptly [7,10].
DHS's precise mechanism is unknown, although it is thought to be mediated by inflammatory cytokine production and immunological activation (figure:1) [11]. One potential form of DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) disease is Dapsone Hypersensitivity disease (DHS). There are numerous medications that can cause DRESS, including dapsone, sulfonamides, allopurinol, cyclosporine, azathioprine, minocycline, antiviral medications, anticonvulsants, and gold salt [12]. Because DHS can happen up to six months after exposure to the offending substance, it is different from other drug reactions. DHS is a complex condition with distinct features. It occurs 0.2-0.5% of the time in patients receiving dapsone medication [12]. The dermatological effects of DHS are highlighted in this case study. An outline of DHS manifestations, the disease, diagnosis, and treatment are given in the sections that follow.

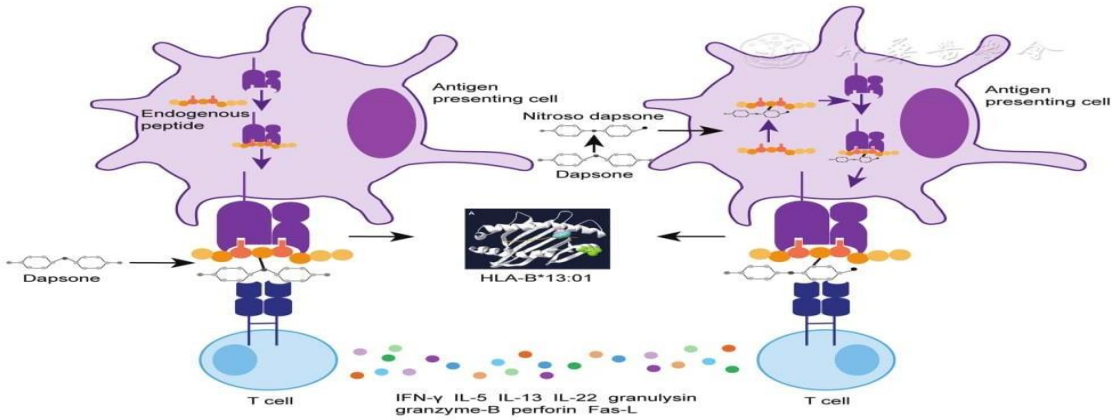

Figure 1: Mechanism of DHS. Dapsone (left) could interact directly with HLA-B∗13:01 resulting in activation of T cell, whereas nitroso dapsone (right) binds covalently to endogenous peptide then subjected to antigen processing and presented by HLA-B∗13:01 to T cell. (DHS: Dapsone hypersensitivity syndrome)

CASE REPORT: -

A 42-year-old housewife with a significant medical history of borderline tuberculoid leprosy presented with lesions on her hands, feet, and face. She was evaluated, and based on the presumed diagnosis of borderline tuberculoid leprosy, she was treated with dapsone (100 mg), clofazimine (50 mg), and rifampicin (600 mg) for 32 days.

On admission, the patient reported skin lesions associated with itching all over her body for the past 3 to 4 days, mild pain in both her hands and feet for the same duration, and swelling in both hands for the last 2 to 3 days. When further exploring the origin, duration, and progression of her symptoms, it was noted that she had been relatively asymptomatic until 4 days prior, when she developed red flat lesions on her left upper limb, followed by similar lesions on her abdomen, face, back, and both lower limbs(figure:2). These lesions gradually increased in size and number. After one day, the lesions filled with yellowish pus and spread to other parts of her body. There was no history of abdominal pain, vomiting, pallor, bleeding diathesis or cardio respiratory symptoms. On examination, she had normal vitals and oxygen saturation. There were no pallor, jaundice, lymphadenopathy, or cyanosis.

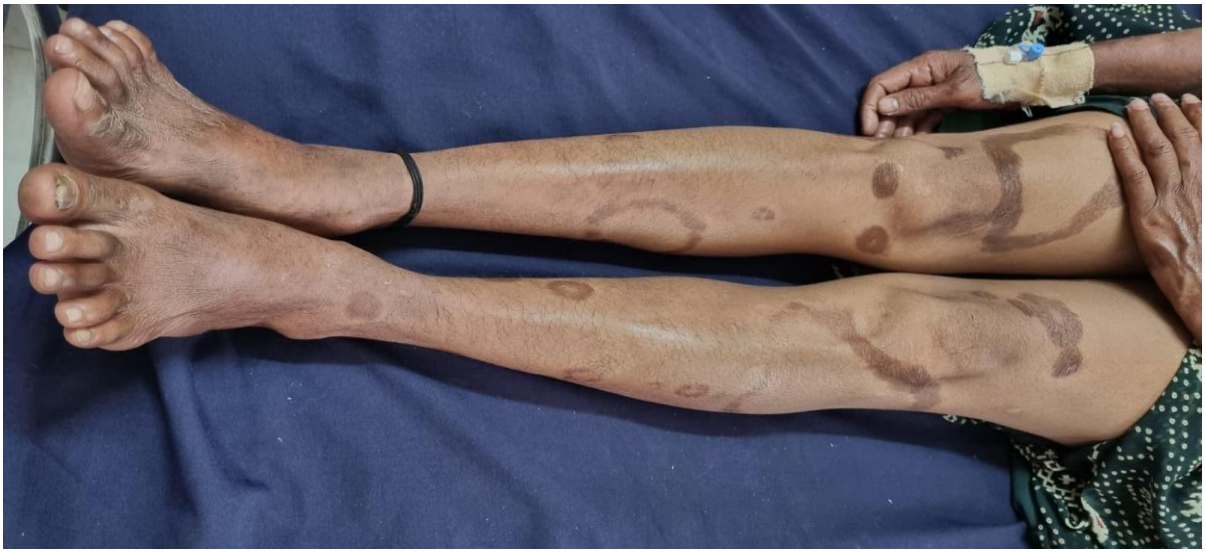

Figure 2: Both lower limbs

Table 1: Cutaneous examination

CUTANEOUS EXAMINATION	
HEAD & NECK	Few tiny yellowish pustules that over forehead, jawline, B/L ear, neck diffuse, non-blanchable erythema over face and neck.
B/L UPPER LIMB	Diffuse, ill-defined, non- blanchable erythema and well defined tiny yellowish pustules that over B/L upper limb and B/L palm.
CHEST AND ABDOMEN	Diffuse, ill-defined, non- blanchable erythema and well defined tiny yellowish pustules that over chest and abdomen. Few hypopigmented patch with central hyperpigmentation that over abdomen.
BACK AND BUTTOCK	Diffuse, ill-defined, non- blanchable erythema and well defined tiny yellowish pustules that over back. Few well defined hyperpigmented annular patches over buttock
B/L LOWER LIMB	Diffuse, ill-defined, non- blanchable erythema and well defined tiny yellowish pustules that B/L leg and feet. Few well defined hyperpigmented annular patches over B/L leg and feet.
NAIL	Blackish discoloration of left great toe.
PALM AND SOLE	Diffuse, ill-defined, non- blanchable erythema and well defined tiny yellowish pustules that B/L palm. Single trophic ulcer that over right sole.

LABORATORY FINDINGS: -

Table 2: Hemogram

PARAMETER	09/10/24	10/10/24	BIOL.REF.RANGE
HEMOGLOBIN	11.90	11.32	13-17gm/dl
ESR	15.00	13.00	0-12mm
RBC	4.01	3.84	4.5-5.5*1o^6/cmm
PCV	36.00	33.67	40-50%
MCV	90.00	87.59	83-101fL
MCH	29.60	29.46	27-32pg
MCHC	33.00	33.63	31.5-34.5gm/dl
WBC	11700	12000	4000-10000/cmm
PLATELETS	449000	428000	150000-410000/cmm
NEUTROPHILS	16.04%	69.00	40-80%
LYMPHOCYTES	15%	23.00	20-40%

Table 3: Biochemistry

PARAMETER	RESULT	BIOL.REF.RANGE
S.ALT(SGPT)	13.00IU/L	0-4IU/L
S.AST(SGOT)	14.00IU/L	0-37IU/L
S.ALP	118.00U/L	64-306U/L
S. GLOBULIN	2.8gm/dl	2.3-3.6gm/dl
S. ALBUMIN	4.17gm/dl	3.2-5gm/dl
S.C REACTIVE PROTEIN	9.34mg/L	0-6mg/L

TREATMENT GIVEN: -

SR.NO	DRUG	DOSE	FREQUENCY	ROUTE
1.	Inj. Dexamethasone	4gm	Once in morning	I.V
2.	Inj. Pantoprazole	40mg	1-0-1	I.V
3.	Tab.MVBC+ calcium carbonate		1-0-1	PO
4.	Continue 5th MBALD pack without dapsone (clofazimine+ rifampicin)	50mg+ 600mg	0-0-1, Once a month	PO
5.	Tab.FA/ FE		0-1-0	PO
6.	Tab. Cefadroxil	500mg	1-0-1	PO
7.	Tab.MBSON-SL (Mecobalamin)	1500mcg	0-1-0	PO
8.	Tab. levocetirizine	5mg	1-0-1	PO
9.	Tab. paracetamol	500mg	SOS(1tab)	PO
10.	Tab. ibuprofen	400mg	SOS(1tab)	PO
11.	Vitamin-D3 Sachet		Once a week	
12.	White paraffin		LABD	
13.	Soframycin cream		LABD	

DISCHARGE MEDICATION: -

Sr.no	DRUG	DOSE	FREQUENCY	ROUTE	DURATION
1.	Continue 5th MBALD pack without dapsone (clofazimine+ rifampicin)	50mg+ 600mg	0-0-1+ Once a month	PO	
2.	Tab. Prednisolone	5mg	OB	PO	15days
3.	Tab.Augmentin	625mg	1-1-1	PO	5days
4.	Tab.FDSON-12SL (folic acid+ methylcobalamin)	5mg+75 0mcg	0-1-0	PO	15days
5.	Tab. paracetamol	500mg	SOS(1tab)	PO	15days

DISCUSSION: -

DHS is defined as a hypersensitive reaction to the sulfone medication dapsone. To treat skin conditions brought on by bacteria and fungi, dapsone (4,4'-Diaminodiphenyl sulphone) is primarily utilised as an anti-inflammatory and antibacterial agent. Dapsone's ability to inhibit neutrophil chemotactic migration and adhesion is primarily responsible for its anti-inflammatory actions [8]. Dapsone successfully kills organisms but may harm surrounding tissues by suppressing neutrophil recruitment and preventing the production of inflammatory mediators. Hepatitis and haemolytic anaemia can develop as early as 7–10 days or as late as 6 months after beginning treatment. The traditional triad of dapsone hypersensitivity syndrome (DHS) consists of fever, skin eruptions, and internal organ involvement. Plaques, pustules, and erythematous papules are examples of cutaneous lesions. There is no correlation between the degree of cutaneous alterations and the degree of internal organ involvement, which can be asymptomatic or even fatal [13]. When medication is stopped, cutaneous lesions from dapsone hypersensitivity syndrome (DHS) usually go away in two weeks. However, in severe cases, toxic epidermal necrolysis or Stevens-Johnson syndrome might develop, which can cause serious morbidity and death. Oral erosions, eczematous eruptions, exfoliative dermatitis, and photosensitivity are among the dermatological signs of DHS. The patient in this instance displayed symptoms that were typical of DHS and a marked clinical reaction to glucocorticoids, suggesting a hypersensitivity to the medicine. Extended observation for complications is essential, particularly in situations of extreme severity. If DHS is left untreated or not identified, the quick clinical decline that occurs can result in renal failure and perhaps death [14].

Table 4: Treatment approaches to DHS

Interventions	Comments
1. Withdrawal of offending medication (dapsone)	Drug discontinuation
2. Supportive therapy	
• Volume replacement	• Intravenous fluid replacement
• Nutritional support	• Enteral/parenteral nutrition
• Antibiotics	• Early antibiotics in case of concomintant sepsis.
• Skin care	• Preventing skin superinfections
3. Specific therapy	
• Glucocorticosteroids	• Recommended dose 1mg/kg/day

The mainstay of treatment for dapsone hypersensitivity syndrome (DHS) is stopping dapsone very away and starting glucocorticoids, such as prednisone, to control inflammation. Due to the lengthy existence of dapsone in the body, these steroids should be reduced gradually over a period of more than one month. On the other hand, glucocorticoids have the potential to cause adverse consequences such as osteoporosis, hypokalaemia, and hyperglycaemia. Patients who have any of these problems' risk factors should be closely watched. Blood sugar measurements, bone mineral density assessments, regular electrolyte measurements, and comprehensive ophthalmologic examinations are crucial [15]. The literature indicates that patients with viral hepatitis (B, E) are more likely to develop DHS, indicating that a hepatitis B screening test should be conducted prior to beginning dapsone [16]. Nutritional assistance, hydration and electrolyte management, and infection avoidance are all essential supportive therapy for severe cases of dapsone hypersensitivity syndrome (DHS). Cimetidine can decrease methemoglobinemia, while vitamin E may help with haemolysis. Alternative therapies should be explored if glucocorticoids are contraindicated because of severe adverse effects. Other treatment alternatives including methotrexate, azathioprine, cyclosporine, or hydroxyl chloroquin have not been thoroughly investigated because this is a rare disorder. The same patient may benefit from these medications [17]. Pneumonia, colitis, hepatitis, and pericarditis are examples of severe internal organ involvement that can be fatal. Because they can happen at any time, these patients need to be closely watched. Recall that a chronic and recurrent course may occur in certain patients despite steroid therapy and medication discontinuation. Given that genetic factors play a role in the pathophysiology of DHS, family should get education regarding DHS and their increased vulnerability to comparable unfavourable reactions.

CONCLUSION: -

DHS requires a high index of suspicion to be diagnosed early. Patients who are started on dapsone for a variety of reasons must be closely monitored to detect the onset of DHS. DHS may be confused with the advancement of the underlying illness if and when this happens. Significant organ dysfunction could result from the drug's harmful and possibly lethal consequences if it is not stopped.

Treatment for Dapsone Hypersensitivity Syndrome (DHS) In K/C/O Borderline Tuberculoid Leprosy (Hansen's Disease) included a multifaceted strategy that included:

1. IV Dexamethasone (4 gm): Administered once in the morning to manage severe inflammation.
2. IV Pantoprazole (40 mg): Given to prevent gastric irritation from corticosteroids.
3. Oral Medications:
   - MVBC + Calcium Carbonate: Supports nutritional needs.
   - Clofazimine + Rifampicin: Continued monthly for leprosy management.
   - Cefadroxil (500 mg): Antibiotic for potential infections.
   - Mecobalamin (1500 mcg): Supports nerve health.
   - Levocetirizine (5 mg): Manages allergic symptoms.
4. Pain Management: Paracetamol and ibuprofen are available as needed for pain relief.
5. Supportive Care: Weekly Vitamin D3, along with topical treatments (white paraffin and Soframycin cream) for skin care.

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