

CASE REPORT

PROLONGED USE OF MULTIDRUG THERAPY FOR LEPROSY LEADING TO MULTIPLE COMPLICATIONS

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ABSTRACT: Multidrug therapy (MDT) for leprosy was recommended by WHO with a triple drug regimen of Dapsone, Rifampicin and Clofazimine, which is still the best treatment for leprosy. Side effects of these are commonly seen in clinical practice. Herein we present to you a case of 63 year old male patient who presented to the OPD with gastro-intestinal symptoms, paresthesias and difficulty in walking. It was only by proper history taking (he has been continuing MDT for the past 43 years), the diagnosis could be made. Further workup revealed presence of methemoglobinemia, atrophic gastritis, peripheral neuropathy and subacute combined degeneration of spinal cord. Prompt treatment and withdrawal of the drug lead to improvement of the symptoms.

KEYWORDS: Clofazimine, Dapsone, Gastro-intestinal symptoms, Methemoglobinemia, Peripheral neuropathy.

INTRODUCTION: Dapsone (4,4'-diaminophenyl sulfone) is the primary drug for Leprosy,¹ and is also often prescribed in the management of several inflammatory dermatoses like dermatitis herpetiformis, erythema elevatum diutinum, acne conglobata, bullous lesions in lupus erythematosus and infections like actinomycetoma, P. carinii pneumonia and Falciparum malaria.^{2, 3} It is a potent anti – inflammatory and anti-parasite compound .

Clofazimine (Lamprene/B663) is a prototype lipophilic riminophenazine antibiotic⁴ which has both anti-mycobacterial and anti-inflammatory action. It has been primarily used in multibacillary leprosy as a component of WHO recommended triple drug regimen, since 1962.⁵ Clofazimine accumulates in the skin and nerves because of its lipophilicity, while its anti-inflammatory activities control harmful erythema nodosum leprosum and reverse immunity reactions, which may complicate antimicrobial chemotherapy. It is also used as a second line treatment along with other drugs for drug-resistant TB. WHO recommends clofazamine as Group 5 medicine. i.e an agent with unclear efficacy, for use in patients with XDR TB.⁶ Both the drugs have adverse effects if taken for a prolonged period of time.

CASE REPORT: A 63 year old male patient presented to the outpatient department one day after he had one episode of hematemesis. He complained of difficulty in swallowing, loss of appetite due to persistent nausea and loss of weight (approx. 5kgs) since past 3 months which were progressively increasing. He had a history of difficulty in writing, buttoning the shirt, tingling and numbness in both the feet, inability to walk in narrow pathways and decrease in muscle mass since past 3 years which was progressively increasing in nature.

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He had a past history of leprosy diagnosed at the age of 20 years for which he is on dapsone and clofazamine since 43years. No significant family history. No other co morbidities. Physical examination revealed that patient was well nourished with gross pallor. Local examination revealed diffuse ichthyotic changes present all over the body (Figure 1). On systemic examination he had no lung signs, a pansystolic murmur heard in the mitral area, abdomen was soft, non-tender and mild splenomegaly was present. CNS examination revealed both cord involvement and peripheral neuropathy (Bilateral ankle jerk absent with bilateral extensor plantar response and sensory loss in both upper and lower limbs).

The patient's medical history and physical examination suggested possibility of valvular heart disease, peripheral neuropathy and dapsone/clofazamine overdose. Laboratory investigations (Table 1) revealed dimorphic anemia, eosinophilia, raised ESR and LDH, low Vitamin B12 levels, and radiological investigations were done (Table 2).

In view of dimorphic anemia two unit packed cells are transfused, post transfusion haemoglobin increased but he was found to be cyanotic. Suspecting dapsone overdose, serum methemoglobin levels was done which was raised.

INVESTIGATION	VALUE	NORMAL VALUE
CBC		
HB	4.6 gm/dL	13.5-17.5 gm/dL
TC	5400 mcl	4, 500-10, 000 mcl
Platelet count	1.5 lakh/mL	1.5-4 lakh/mL
ESR	52 mm/hr	0-22 mm/hr
LDH	443 u/L	140-280 u/L
Sr. Ferritin	10 ng/mL	12-300 ng/mL
Sr. iron	34 µg/dL	65-176 µg/dL
TIBC	273 µg/dL	262-474 µg/dL
Reticulocyte count	3.4%	0.5-1.5%
Vit B 12	132 pg/mL	200-800 pg/mL
Methemoglobin levels	2%	<1%
Stool for occult blood	Negative	
PERIPHERAL SMEAR		
RBC	Microcytic hypochromic with anisopoikilocytosis (tear drop cells, occasional target cells, fragmented RBC)	
WBC	Eosinophilia	
Platelets	Adequate	
TABLE 1		

TABLE 1

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CHEST X RAY	Suggested mediastinal widening
CT THORAX	Normal study
USG ABDOMEN	Mild splenomegaly
2D ECHO	Shown mildly dilated left atrium PML belly calcification Mitral regurgitation with PAH (EPAP: 42mmHg) EF: 63%
UGI SCOPY	Shown lax LES flattened mucosal folds and gastric nodule Biopsy revealed chronic atrophic gastritis with intestinal metaplasia (Figure 2& 3)
NCS OF BOTH LL	Severe sensory motor neuropathy of LL

TABLE 2



Fig. 1: Diffuse ichthyosis over the legs

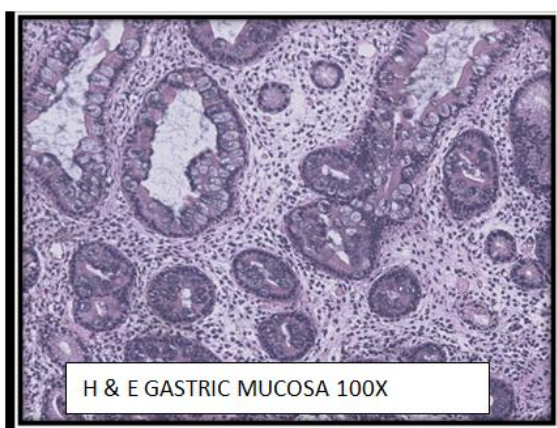


Fig. 2

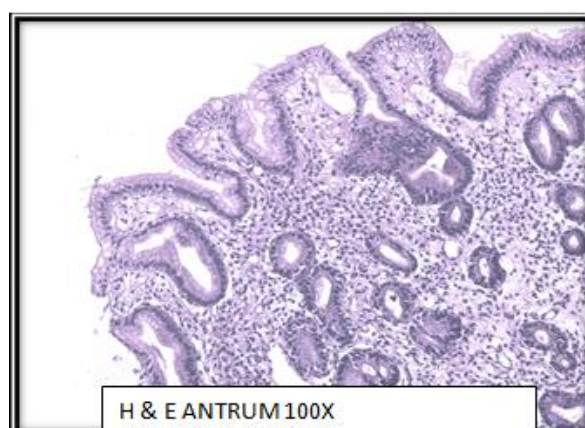


Fig. 3

Figure 2 and Figure 3 revealing chronic atrophic gastritis with intestinal metaplasia.

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He was diagnosed as dapsone and clofazimine overdose, in view of methaemoglobinemia, peripheral neuropathy, dimorphic anemia, ichthyotic skin changes, chronic atrophic gastritis and Vitamin B 12 deficiency causing subacute combined degeneration of spinal cord. (Table 3). The barium study and jejunal biopsy could not be done.

DAPSONE OVERDOSE	Peripheral neuropathy Methemoglobinemia Hemolytic anemia
CLOFAZIMINE OVERDOSE	Ichthyotic skin changes Malabsorption syndrome and chronic atrophic gastritis causing iron deficiency and Vitamin B12 deficiency. Severe Vitamin B12 deficiency can lead to sub-acute combined degeneration of spinal cord

TABLE 3

Dapsone and Clofazimine was stopped, started on Vitamin B12 and Iron supplementation, within one week there was an improvement on paraesthesia of both LL. He was discharged with Vitamin B12 and Iron therapy and remained in remission with regular follow up.

DISCUSSION: MDT for leprosy has been the best treatment over the past six decades, recommended by WHO, which includes triple regimen – Dapsone, Rifampicin and Clofazimine. Adverse effects of these drugs are well known especially with dapsone and clofazimine after prolonged use.

Dapsone hypersensitivity syndrome, dose dependent hemolytic anemia, methemoglobinemia and agranulocytosis are the predominant adverse effects of dapsone.^{7, 8} Recent studies at several tertiary centers have shown dapsone to be the major cause of drug induced methemoglobinemia. The oxidation reactions produce hydroxylated amine metabolites which are potent oxidants, causing dapsone's hematological adverse effects, including hemolytic anaemia and methemoglobinemia. The other mechanism causing agranulocytosis could be the formation of antibodies for neutrophil progenitors in bone marrow and the resultant destruction.⁹ Though dapsone induced methemoglobinemia is a dose dependent toxicity seen in patients with chronic use, it has been reported with short term use also.¹⁰

In the presented case, patient did not have symptoms of methemoglobinemia, like dyspnea, lethargy, dizziness, lightheadedness, weakness, headaches, impaired consciousness, seizures, coma or cardiac arrhythmia. Hence the patient was not started on intravenous methylene blue and was monitored for features prompting for treatment.

Dapsone can also be associated with peripheral neuropathies with loss of fine motor skills and gait disturbances, thenar eminence atrophy, foot/toe drop and glove and sock sensation loss¹¹ Motor neuropathy being more predominant than sensory, and affecting more in the lower limbs than upper limbs.¹²

Clofazimine causing adverse effects is generally dose related. Skin, Eyes and Gastrointestinal tract being primarily affected¹³ Reddish discoloration of the skin as well as ichthyosis are well known on administration of the drug.

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Malabsorption, periodic epigastric distress with occasional vomiting unrelated to meals, episodic and prostrating abdominal pain, generalized abdominal pain, and rebound tenderness without localization are the identified gastro-intestinal toxicity of this drug.¹⁴ The abnormal laboratory findings include eosinophilia, hypoalbuminemia, hypocholesterolemia and hypotriglyceridemia. The radiological abnormalities include coarsening of the mucosal pattern and segmentation of barium in the ileum and distal jejunum. Biopsy of jejunum demonstrates red crystals in the lamina propria accompanied by a moderate number of plasma cells (clofazimine-induced crystal-storing histiocytosis). The histologic findings mimic B-cell neoplasms including multiple myeloma and lymphoplasmacytic lymphoma or immunocytoma.

Clofazimine induced malabsorption for prolonged periods can predispose to iron deficiency and B12 deficiency anaemia. B12 deficiency causing sub-acute combined degeneration is seen in the present case. Sub-acute parasthesias in the hands and feet, loss of vibration and position sensation, and a progressive spastic and ataxic weakness are the presenting features of sub-acute combined degeneration. The important diagnostic clue is presence of Babinski's sign, with loss of reflexes due to an associated peripheral neuropathy. It is generally symmetric and involves predominantly the posterior and lateral tracts, including Romberg's sign. This is a treatable myelopathy, reversed by replacement therapy.¹⁵

CONCLUSION: This is so far the first case to be reported to have prolonged use of dapsone and clofazimine for a period of 43 years. It is quite unusual to take MDT for such a long time and it was interesting how he had been getting the drugs for so long (History revealed that he was getting the medicines from the hospital with regular follow up). It can be said that there is a need to give more significance for detailed history and physical examination to diagnose a patient with MDT induced toxicity. It can also be emphasized that the toxicity for MDT for leprosy is common and one should be cautious to rule out the same by looking for methemoglobinemia, agranulocytosis, hemolytic anemia and neurological manifestations in dapsone toxicity and gastro-intestinal toxicity and sequelae in clofazimine toxicity. The patient has been taking the drugs for a long time without severe side effects until it was detected and it was worth mentioning that his symptoms started improving after withdrawal.

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