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Agranulocytosis as an Adverse Effect of DAPSONE in Leprosy Pateints: A Case Report

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ABSTRACT:
Multidrug therapy (WHO/MDT) in leprosy consists of treatment with rifampicin, dapsone and clofazimine. We report on a patient who presented with agranulocytosis and haemolytic anaemia associated with the 2 drug MDT regime for borderline tuberculoid leprosy.
Dapsone although well tolerated, widely used for leprosy but has been reported to cause rare adverse effects such as agranulocytosis, Haemolytic anaemia, Meth-hemoglobinemia.
These side effects are idiosyncratic reactions to dapsone and can be life threatening if not detected at right time.Febrile neutropenia secondary to dapsone intake should be treated promptly before the development of sepsis, which can lead to shock and death.
Our aim is to increase clinical awareness of Dapsone induced agranulocytosis risk by regular complete blood count monitoring to detect and treat agranulocytosis early and thus enhancing patient prognosis.

PRESENTATION OF THE CASE:

We reported a 53 year old female patient with nil comorbidities, resident of Kolar, Bangalore who was recently diagnosed with Tuberculoid leprosy 2 months back and was started on 2 drug MDT regime. (Dapsone 100mg daily plus Rifampicin). She presented to our casualitywith fever, breathlessness and hypotension (80/50 mmHg). She was started on IVF resuscitation, ABG and routine blood samples were sent for workup. She remained hypotensive despite fluid resuscitation, started on Noradrenaline support and empirical antibiotic cover after sending blood and urine cultures. Initial laboratory workup at casuality revealed Severe Neutropenia with agranulocytosis (TLC= 380/cubic mm , ANC =0%) , Indirect hyperbilirubinemia with evidence of hemolysis (Raised LDH = 666 IU/L, Increased indirect bilirubin, Anaemia -Hb =8 gm/dl) . Initial ABG showed Lactic acidosis and methemoglobinemia (methb level in ABG = 21%). Considering initial provisional diagnosis of neutropenic sepsis with shock, she was started on empirical Meropenem with vancomycin and was shifted to ICU with Oxygen support and Noradrenaline support .for further evaluation and care .

In ICU, she was continued on vasopressor support and MDT regimen for Leprosy was withhold. Dermatology opinion taken and Further workup to evaluate neutropenic sepsis was sent. In view of severe agranulocytosis, Filgrastim 300mcg once daily was added to ongoing treatment. All workup (Nutritional, Autoimmune, Infective workup) reported to be negative**.** G6PD deficiency was also not found to be present. We concluded at end of our workup dapsone to be the culprit drugleading to severe agranulocytosis. Serial monitoring of Complete blood count, Liver function test and ABG were done during her stay in the ICU.

Serial blood test revealed a typical case presentation of Agranulocytosis

Date	TLC (10^3/µL)	ANC (10^3/µL)	Hb (g/dl)	Platelet (10^3/µL)	LDH IU/L	S.MetHb	T.B/D.B	
22/3	0.38	0.00	8.0	129	680	21%	6.4/2.2	
23/3	0.72	0.00	9.3	146	-			
24/3	0.49	0.00	7.8	135	-	20%	6.4/1.9	
25/3	0.60	0.01	7.3	127	504			
26/3	770	0.00	7.2	140		18%	4.5/2.3	
27/3	0.46	0.00	5.3	149				
28/3	0.86	0.14	8.2	189	222	5%	3/1.3	
29/3	1.62	0.61	8.2	215				

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30/3	**2.81**	**1.50**	**8.7**	**246**				
31/3	**3.95**	**1.72**	**8.4**	**207**	**120**		**1.7/1.0**	
01/04	**5.50**	**1.80**	**8.6**	**257**				

Gradually Noradrenaline support was tapered and stopped over the next 3 days in ICU. She clinically became afebrile and was off oxygen support.Laboratory blood parameters improvement was delayed relative to clinical improvement. Neutropenia with agranulocytosis started showing improvement by day 5 of withholding dapsone and starting filgrastim and antibiotic cover , serum methemoglobinemia levels showed a decreasing trend,hence not treated .All cultures revealed no growth. She remained hemodynamically stable and was shifted toward on Day 8. Her all blood parameters stayed in normal range after day 7, antibiotics and Filgrastim was stopped and she was discharged on day 10 to home with alternative regimen for leprosy containing Clofazimine and Rifampicin.

DISCUSSION:

Leprosy also known as Hansen's disease caused by Mycobacterium leprae, an obligate intracellular acid-fast bacillus. Typically manifests as anaesthetic skin lesions and peripheral nerve enlargement and/or impairment[1]. **Leprosy classified into two forms**: **Paucibacillary leprosy** patients are being given two-drug MDT regimen; rifampicin and dapsone for 6 months. **Multibacillary leprosy** patients are being given three drug MDT regimen ; rifampicin dapsone and clofazamine for 12months .[2]

Dapsone , a sulfone compound exhibiting both antimicrobial and anti-inflammatory properties. It is structural analogue of para-aminobenzoic acid (PABA). It inhibits folate pathway by competitive inhibiting dihydropteroate synthase . It is widely used for leprosy since 1948 and also used for other infections, including toxoplasmosis and Pneumocystis jiroveci pneumonia; dermatitis herpetiformis, linear IgA dermatosis, bullous systemic lupus erythematosus, and pemphigus vulgaris; and immune thrombocytopenia[3]

Adverse effects associated with dapsone use :

1. **Dapsone Hypersensitivity Syndrome (DHS):** An idiosyncratic dose-independent reaction. Typically seen 4–6 weeks after initiation of Dapsone use , classically presents with the triad of fever, skin rash, and internal organ involvement, most frequently hepatitis. It carries high fatality rate. [4]

2. **Rare Adverse effects:** Also idiosyncratic effects of dapsone use -Methaemoglobinaemia , cyanosis, agranulocytosis and haemolytic anaemia. Typically seen in the first six weeks , reported up to six months after starting dapsone.[4,5,6]

Agranulocytosis seen in 0.2-0.4% of patients who were treated with dapsone . One of the mechanism of dapsone induced agranulocytosis is attributed to the formation of antibodies against neutrophil progenitor cells leading to agranulocytosis . Another mechanism - Dapsone is metabolised to hydroxylamine, a toxic metabolite of dapsone which depresses the synthesis of granulocytes in the bone marrow leading to severe agranulocytosis[5] .Dapsone induced agranulocytosis is an idiosyncratic dose independent reaction [7]

According to Mishra and Chhetia (2006),[8] **Carneiro et al. (2011)**,[9]and our report, agranulocytosis occurs between 3 weeks and 3 months after the onset of the MDT.

Strong Suspicion, Early detection and effective treatment with adequate antibiotic cover, Granulocyte - CSF, withholding MDT regimen in this case accounted for the faster recovery and survival of the patient.

Any patient on Dapsone treatment should be given proper information about adverse effects of dapsone and should remain cautious with respect to any signs of infection like fever, breathlessness. To detect rare side effects of Dapsone therapy, complete blood count should be done weekly for the first month of Dapsone therapy, twice monthly for the next two months, and periodically thereafter.[10]

REFERENCES :

[1]. Boggild AK, Keystone JS, Kain KC, 2004. Leprosy: a primer for Canadian physicians. Can Med Assoc J 170: 71–78.
[2]. World Health Organization. Global Leprosy Strategy 2016–2020; 2017.doi:978-92-9022-509-6
[3]. Lowe J, 1950. Treatment of leprosy with diamino-diphenyl sulphone by

mouth. Lancet 1: 145–150. [PubMed] [Google Scholar].

[4]. VineethaM, CelineMI, SadeepMS Adverse reactions of multi drug therapy of leprosy - a case series. Indian J Lepr, 2017;

[5]. ZhangF-R, LiuH, IrwantoA HLA-B*13:01 and the Dapsone hypersensitivity syndrome. N Engl J Med, 2013

[6]. Vinod KV, Arun K, Dutta TK, 2013. Dapsone hypersensitivity syndrome: a rare life threatening complication of dapsone therapy. J PharmacolPharmacother 4: 158–160

[7]. Jacobus DP. Dapsone. In: Drug therapy in dermatology. Millikan LE, editor. Marcel Dekker Inc: 2000. p. 445-75.[Google Scholar]

[8]. Mishra M, Chhetia R. Dapsone induced agranuilocytosis in a patient of leprosy. Indian J Dermatol VenereolLeprol. 2006;72:456–457

[9]. Carneiro JA, Poswar FO, Ramos MIA, Nassau DC, Veloso DC. Agranulocitoseinduzidapordapsonaempaciente com hanseníase. Relato de caso. Rev Bras Clin Med. 2011;9:242–244.

[10]. Katz SI. Sulphones. In : Freedberg IM, Eisen AZ, Wolff K, Austen F, Goldsmith L, Katz S, editors. Fitzpatrick's Dermatology in General Medicine. 6th ed. New York: Mc Graw Hill; 2003. p. 2388-91.