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Case Report

Adverse Reactions of Multi Drug Therapy of Leprosy – A Case Series

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WHO recommended multi-drug treatment (MDT) is the standard treatment for leprosy and is the cornerstone for treatment of leprosy since 1982. Rifampicin, Clofazimine and Dapsone even though relatively free of serious adverse reactions, may occasionally cause challenging adverse reactions. Among these three drugs Clofazimine has been known least to cause severe adverse reactions. In this case series we report severe anemia induced by combined effects of Dapsone and type 2 reaction, methemoglobinemia induced by Dapsone, acute renal failure caused by Rifampicin, flu like syndrome due to Rifampicin and severe drug hypersensitivity syndrome (DHS) induced by Dapsone. In all these cases patients needed hospitalization and prompt withdrawal of drugs. Alternative regimens were started and the course thereafter was uneventful in all these patients.

Key words : Methemoglobinemia, Autoimmune Hemolysis, Dapsone Syndrome, Flu like Syndrome, Dapsone, Rifampicin, Leprosy

Introduction

Multi drug therapy (MDT) introduced by World Health Organization and implemented by NLEP (National Leprosy Eradication Programme) of India is the standard treatment of leprosy. MDT is generally devoid of serious side effects. Occasionally there are reports of adverse reactions like drug induced hepatitis, drug hypersensitivity syndrome, acute renal failure and flu like syndrome caused by any one of the components of MDT (Deps et al 2007). In this case series we report major side effects encountered in leprosy patients treated with MDT. In all these patients we stopped MDT and alternative regimens were started. We report these cases as these complications may be life threatening and the physicians should be aware of these serious complications and manage these comparatively rare complications accordingly.

Case Series

Case 1

A 16 year old girl presented with hyperpigmented

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and skin colored papules and plaques over face and upper limbs of 6 months duration (Fig. 1) with associated fever. On examination she had tender subcutaneous nodules over elbows and buttocks which showed ulceration, both ulnar nerves were thickened and touch, pain and temperature sensation impaired over both feet. She was diagnosed as Hansens disease lepromatous leprosy (HD LL) with type 2 reaction (erythema necroticans), and was started on multi-bacillary (MB) MDT with oral Prednisolone and Thalidomide to take care of the Type 2 reaction. Her routine blood test including hemoglobin (Hb) - 10 gms, liver function tests (LFT), renal function tests (RFT), G6PD (glucose 6 phosphate dehydrogenase) levels were normal before starting treatment. Ear lobe slit skin smears (ELS/SSS) showed bacteriological index (BI) of 6+ and morphological index (MI) of 20%. She developed shortness of breath 10 days after starting MDT.

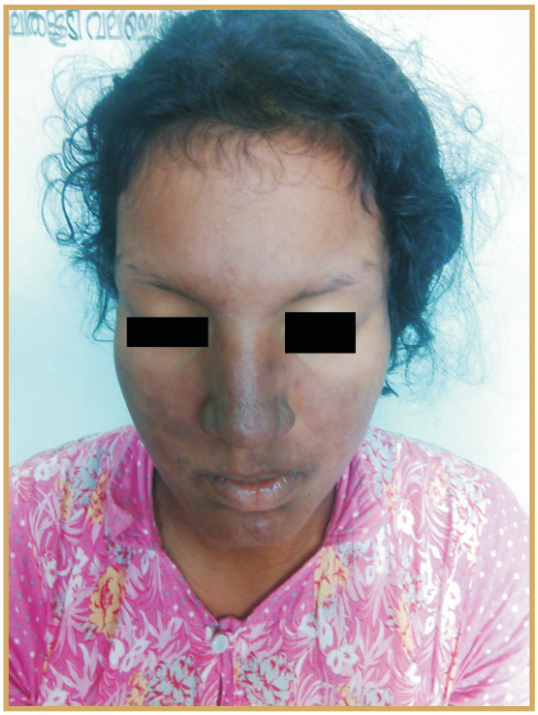

Fig. 1 : Hyperpigmented papules and plaques on face

On examination she had anemia the ulcerative lesions were healing. Her routine blood test showed Hb of 7 gm%, Dapsone was stopped and she was admitted in the hospital. Fever decreased but she developed new ENL lesions and her repeat Hb was 5.5 gm%, and total white blood cell count was 4800/cubic mm two weeks after stopping dapsone. Reticulocyte count was 2% (normal value 2-5%), Lactate dehydrogenase (LDH) levels were 358 (normal range: 230-460) and peripheral smear showed dimorphic blood picture. Direct Coombs test was positive.

Patient was given 5 packed RBC transfusions and her Hb became 10.3 gms. Steroids were tapered and Thalidomide was continued in the dose of 300 mg daily, her fever and ENL lesions subsided and hematological parameters became normal in one week.

Our final diagnosis was HD LL, type 2 reaction, anemia caused by combined effects of Dapsone and Type 2 reaction. The patient did not have features of Dapsone hypersensitivity syndrome. She was treated with alternative regimen consisting of Rifampicin 600 mg once a month, Ofloxacin 400mg and Clofazimine 300mg once a month and 50 mg daily and had uneventful course after that.

Case 2

A 19 year old boy who was the brother of first case on examination of household contacts was found to have hypopigmented macules with sensory impairment over shoulder, elbow and both feet (Fig. 2). Right common peroneal nerve and left superficial peroneal nerves were thickened and sensory impairment was present over left foot. He was a known case of congenital heart disease-atrial septal defect (ASD) and congenital hypo-

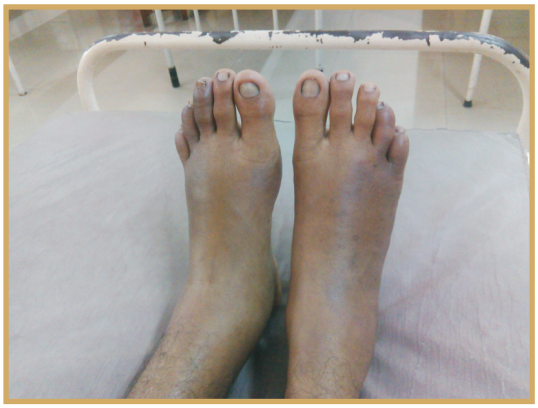

Fig. 2 : Erythematous plaque on foot

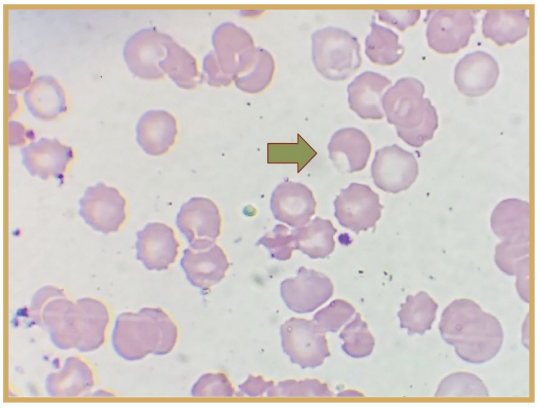

Fig. 3 : Blister cells and Bite cells

thyroidism. Slit skin smear examination showed BI 5+, MI 30%. Diagnosis of HD- Borderline lepromatous (BL) was made and investigations were done.

All the routine investigations were unremarkable, except mild elevation in total bilirubin with unconjugated hyperbilirubinemia and normal liver enzymes. Clinically patient was anicteric.

Gastroenterology consultation was done as the liver function test was deranged and they diagnosed it as a case of Gilberts syndrome. After completing 28 days of MDT patient presented to outpatient department with history of excessive tiredness, breathlessness, fever, redness over the skin lesions, high coloured urine and bluish discoloration of fingers. On examination he had anemia, pedal edema, icterus, central and peripheral cyanosis and the patient was febrile. Existing hypopigmented lesions became erythematous and tender.

Our diagnosis was HD (BL) type 1 reaction, methemoglobinemia and hemolytic anemia induced by Dapsone. Investigations showed Hb 6.7gm%, total counts (TC) 8800/cubic mm, P72, L19, M9, Platelet count – 2.2 lakh/mm^3, ESR 90mm/1hr. Urine had presence of albumin+++, Granular cast+, 24 hour urine protein was 1g. Other tests showed – Serum bilirubin 4.1/0.3 mg/dl, SGOT/SGPT-89/39U/L, ALP-89U/L, Blood urea - 44mg/dl, Serum Creatinine 1mg/dl, Serum sodium 128 meq/L, Serum potassium 4.5 meq/L, LDH-2257U/L (230-460), G6PD level – 260U/L(240-450). Methemoglobin level were 8.7% (<1%) and Reticulocyte count was 2%(0.5-2).

Peripheral smears had Bite cells and blister cells suggestive of hemolysis (Fig 3). ECHO showed large ASD with right to left shunt, mild pulmonary artery hypertension. ECG-Right bundle branch block with right ventricular hypertrophy. Chest X-Ray showed cardiomegaly.

Final diagnosis was Type 1 lepra reaction, Dapsone induced hemolytic anemia and methemoglobinemia and drug induced nephritis.

Dapsone and Rifampicin were stopped immediately and patient was started on Aspirin, Vitamin C and Vitamin E. Three packed RBC transfusions were given. Patient was started on Minocycline 100 mg, Ofloxacin 400 mg and Clofazimine 300 mg once a month and 50 mg daily. Patient is still under follow up and had an uneventful course thereafter.

Case 3

A 16 year old girl presented with a hypo-pigmented anaesthetic patch of size 3x2 cm on forehead and was started on MDT PB from outside. 3 weeks after starting MDT she developed fever and skin rash and was referred to our hospital. On examination erythematous follicular papules over neck, trunk and limbs were present (Fig 4). No nerve thickening was observed. ELS/SSS was negative. Provisional diagnosis of HD BT with Drug hypersensitivity syndrome to Dapsone was made.

Investigations revealed normal bilirubin levels, elevated SGOT/SGPT, USG abdomen showed moderate ascites, Chest X-Ray - mild pleural effusion and 24 hr urine protein was 1g.

In the presence of fever, rash and elevated liver enzymes diagnosis of dapsone syndrome was made and dapsone stopped and was started on 4 mg dexamethasone intravenously. Her hepatic and renal parameters became normal while on treatment.

While tapering her steroids she took the second dose of Rifampicin and on same day developed fever, severemyalgia, headache and erythema all over body. Routine blood examination, renal and liver function tests were within normal limits, and was managed symptomatically, 2 days later her condition improved.

Our diagnosis was flu like syndrome induced by Rifampicin, and the girl was later treated with Ofloxacin 400 mg and Clofazimine 300 mg once a month and 50 mg daily with tapering doses of steroids. On follow up progress was uneventful.

Case 4

A patient from Bihar was diagnosed as lepromatous leprosy from outside and was on treatment with MDT (MB), he developed excessive tiredness after 1 week of treatment, associated with giddiness, exertionaldyspnea, fever and nausea. His urine output was normal. On examination pallor and bilateral pedal edema was present. Multiple erythematous and skin colored discrete and confluent infiltrated papules present over face, trunk and legs. Glove and stockings type of anaesthesia was present and both ulnar nerves and right common peroneal nerves were thickened.

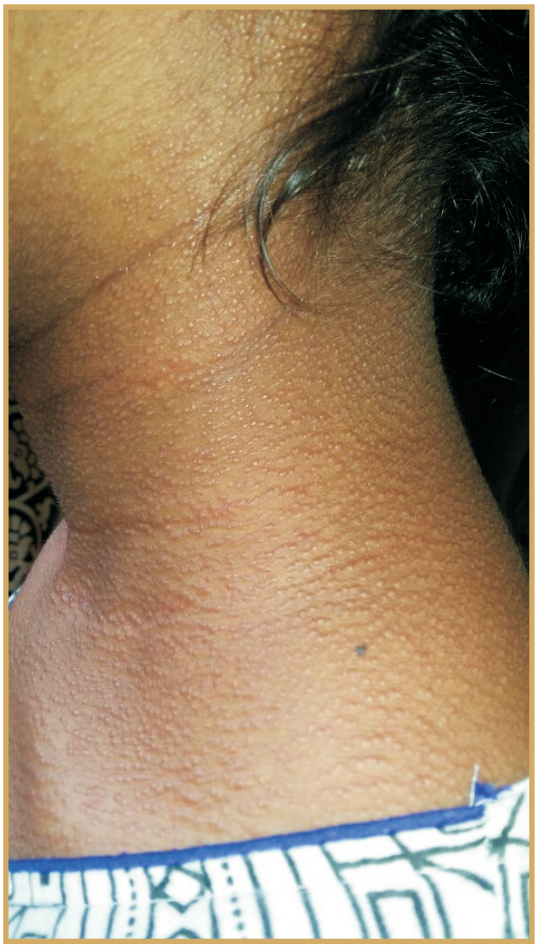

Fig. 4 : Follicular papules on neck

Investigations showed ELS/ SSS = 5+, MI = 20%, Hb 5.8gm%,TC 5600/mm^3 - P59, L22, M18, Platelet 2 lakh/mm^3, Blood urea = 170mg/dl, Serum creatinine = 13.1mg/dl, Serum Potassium = 5 meq

/L, Serum Sodium = 129meq/L,LFT- within normal limits, Serum Lactate dehydrogenase (LDH) levels were 2250U/L and Reticulocyte count 5%. Peripheral smear (PS) was suggestive of Dimorphic anemia. USG Abdomen showed increased echogenicity of both right and left kidneys.

Patient was diagnosed as HD(LL), Drug induced interstitial nephritis probably due to Rifampicin. MDT was stopped and the patient started on COM regimen (Clofazimine, Ofloxacin and Minocycline). As his urine output was normal dialysis was not done and after stopping the drug renal status improved gradually.

Discussion

In some countries like Brazil, the reported incidence of adverse reactions of MDT for leprosy varies from 38% - 44% and most occurred within 6 months of starting treatment (Goulart et al 2002, Deps et al 2007). In the first case of the series lepromatous leprosy patient developed severe anemia and was due to combined effects of type 2 reaction and Dapsone. Her G6PD level was normal, but she had 5 gm decrease in Hb level. Sen et al (1991) reported that Type 2 lepra reaction is associated with acquired hemolytic anemia and this may be due to autoantibody formation or microangiopathy. Frietasand Fleury (1996) have reported anemia, leukocytosis, reticulocytosis, and bone marrow hyperplasia in moderate to severe ENL. So anemia in this patient is due to type 2 reaction and her direct Coombs test was positive. Also patients who have mild iron, folate, or B12 deficiency will not be able to respond with the normal increase in bone marrow activity after starting dapsone, and thus can have drop in Hb.

Type 2 reaction is also associated with increased risk of thromboembolism due to diminution of fibrinolytic activity and activation of coagulation through intrinsic and extrinsic pathway by exposing collagen and secretion of thromboplastin from tissues damaged by inflammatory process (Frietasand Fleury 1996). Usually ENL is associated with leukocytosis but our patient had leukopenia.

The reported incidence of hemolytic anemia induced by Dapsone to be 24.7% and occurred within first 3 months (Deps et al 2012). This data from Brazil can not be extrapolated to Indian population and we need to document our own experiences.

Cardiovascular defect is a relative contraindication to start Dapsone (Edhegard and Hall 2013). Our second patient had ASD and developed severe methemoglobinemia and hemolysis. Hemotoxicity of Dapsone is associated with hydroxyl metabolites, which are potent oxidants. Patients with significant cardiac or pulmonary disease will not be able to tolerate low levels of methemoglobin. Met-Hb is an oxidation product of Hb in which there is an oxidized ferric iron in sixth co-ordination position instead of reduced ferrous iron in normal Hb. This oxidized ferric iron containing site is then bound to a water molecule or to a hydroxyl group. This complex is dark brown and unable to transport oxygen with a leftward shift in oxygen dissociation curve, thus leading to a decreased tissue oxygenation with subsequent hypoxic features (Price 1998). Thus the patients presents with dyspnea on exertion, palpitations and tiredness. Methemoglobin spot test will be positive and spectrophotometric quantitative analysis for met hemoglobin can also be done. The condition can be treated with Vitamin E, oral Methylene blue, Vitamin C. Indication for Methylene blue is methemoglobin levels over 30% and given either oral or intravenously. The renal insult in this patient in the form of proteinuria and cast may be due to Rifampicin or Dapsone. Incidence of Rifampicin nephrotoxicity has been reported to vary from

1.8% to 16% of all acute renal failure - ARF (Covic et al 1998). In a study conducted by (Goulart et al 2002) gastritis was the most common side effect due to Dapsone followed by hemolytic anemia, methemoglobinemia, insomnia and exfoliative dermatitis. Side effects due to Clofazimine 23% and Rifampicin 6.2% with ichthyosis being the most common side effect with Clofazimine and fever with Rifampicin (Goulart et al 2002).

Our third patient was diagnosed to have Dapsone hypersensitivity syndrome with follicular papular lesions on skin, LFT derangement, renal involvement, ascites and plural effusion. Kumari et al (2011) noted similar follicular lesions associated with DHS in their study. While she was improving on treatment with steroids she developed flu like syndrome on taking Rifampicin. The syndrome mostly occurs with the once-weekly or twice-weekly administration of Rifampicin and is rare with once-monthly treatment. However, it can occur with once monthly regimen (Covic et al 1998). The syndrome appears to be due to a hypersensitivity reaction to Rifampicin, and antibodies against it have been demonstrated. Our patient had, fever, myalgia, rash which began 4-5 hrs after administration of Rifampicin and subsided in 24 hrs.

Our fourth patient had acute renal failure induced probably by Rifampicin. He did not have any renal disease previously. Renal toxicity of Rifampicin was first reported by Poole et al (1971). Post Rifampicin ARF can occur in continuous or intermittent therapy. Acute interstitial nephritis (AIN), rapidly progressive glomerulonephritis, acute tubular necrosis and nephrotic syndrome can occur. Post rifampicin ARF is usually associated with autoimmunehemolysis, anemia (96%), thrombocytopenia (50%), hepatic injury (25%), disseminated intravascular coagulation – DIC (Covic et al 1998). Our patient had anemia and hemolysis. Renal function recovery is 96% in 90 days. Severity of immune process and duration of oliguric phase are the prognostic markers. Our patient recovered in 7 days without dialysis.

Conclusion

Although MDT is safe in hands of physicians, we should be aware of the possible adverse reactions associated and patients should be monitored for development of any complications. Dapsone and Rifampicin can cause serious adverse effects and the monitoring guidelines should be strictly followed. It is always better to do G6PD levels before starting Dapsone, and to keep the patients with low levels at close monitoring. The patients should be educated regarding the possible side effects and symptomatology and report accordingly. The treating physicians should be trained regarding the management of complications and use of alternative regimens.

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