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Case Report

CASE REPORT

The mystery of 'saturation gap': a case of dapsone-induced methaemoglobinemia in a pregnant mother with leprosy

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Abstract

Limited data regarding methemoglobinemia in pregnancy, particularly secondary to dapsone is available up to date. We report a case of dapsone-induced methemoglobinemia in a pregnant mother with multibacillary leprosy who presented with fever, productive cough and cyanosis of 2 days duration 2 weeks after multidrug therapy was commenced. On examination, she had central cyanosis with low oxygen saturation (SpO_2 = 84–88%). Arterial blood gas analysis showed PO_2 of 111 mmHg and SO_2 of 98 mmHg. Patient was administered 100% oxygen inhalation, but there was no improvement in cyanosis. Vitamin C (1000 mg/day) was prescribed. Dapsone was replaced by ofloxacin 200 mg twice daily. There was a gradual increase in SpO_2 level. She delivered a healthy baby. In conclusion, clinicians should be aware of the side effects of dapsone and know how to promptly manage any undesirable events. Ofloxacin is a safe and feasible alternative in replacement of dapsone in pregnancy.

INTRODUCTION

Leprosy remains a major public health concern in Malaysia despite the fact that it has achieved elimination since 1994 with the advent of multidrug therapy (MDT) [1]. However, the incidence has shown a resurgence over the years although prevalence remains static. This might be attributable to the roles of immigration and globalization. MDT which includes dapsone is the standard treatment for leprosy as per World Health Organization (WHO) guidelines [2]. Dapsone is associated with several side effects and methemoglobinemia is a rare serious adverse effect when patients present with unexplained cyanosis and hypoxemia. Limited data regarding methemoglobinemia in pregnancy, particularly secondary to dapsone is available up to date. We report a case of dapsone-induced methemoglobinemia in a pregnant mother with multibacillary (MB) leprosy.

CASE REPORT

A 36-year-old gravida 2 para 1 woman at 30 weeks' gestation presented to our hospital with complaints of fever, productive cough and cyanosis of 2 days duration. She was recently diagnosed as MB leprosy as evidenced by hypoaesthetic annular plaques on trunk and limbs (Fig. 1), positive slit skin smear (morphological index of 3.2% and bacteriological index (BI) of

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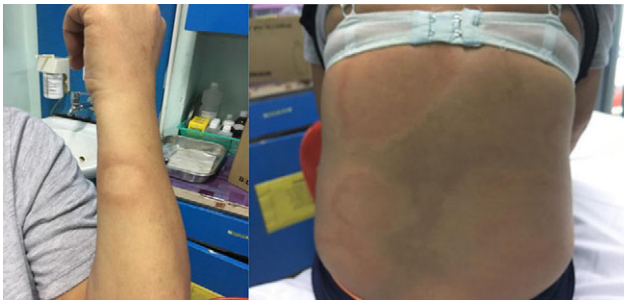

Figure 1: Hypoaesthetic annular plaques on forearm (left) and back (right).

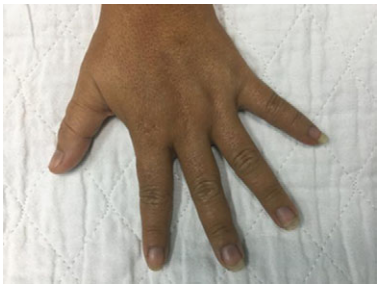

Figure 2: Cyanosis evident on initial presentation.

4.3). Standard MB-MDT consisting of clofazimine, rifampicin and dapsone (100 mg once daily) was commenced 2 weeks prior to such complaints. She had no complaints of headache, chest pain, palpitation, dyspnea, altered consciousness, hemoptysis or syncope. She denied any exposure to chemicals or unprescribed medications.

On examination, she had central cyanosis and one spike of fever on admission. Apart from low oxygen saturation (SpO_2 = 84–88%), her vital signs were stable with no evidence of respiratory distress. Radial artery and venous blood was dark-colored. Arterial blood gas (ABG) analysis under room air showed PO_2 of 111 mmHg and SO_2 of 98 mmHg. There was no laboratory evidence of hemolysis with normal hemoglobin, bilirubin and LDH. Leukocyte count was 7.0 × 10^3/μL. Sputum workup for culture and acid-fast bacilli (AFB) as well as chest X-ray did not reveal any evidence of lung infection. She was not G6PD deficient.

Patient was administered 100% oxygen inhalation, but there was no improvement in cyanosis (Fig. 2) and SpO_2 by pulse oximetry remained around 85%. Repeated ABG revealed almost similar values. Three pairs of intravenous (IV) parentrovite, which contained 1500 mg of ascorbic acid were given at the initial suspicion of methaemoglobinemia. Oral vitamin C (1000 mg/day) was also prescribed. As for MDT leprosy treatment, dapsone was replaced by ofloxacin 200 mg twice daily and patient was closely monitored thereafter. There was a gradual increase in SpO_2 level with value of 90% 2 days later and 99% after 1 week. No cyanosis was evident, and there was a change in color of venous blood by this time. She delivered a healthy baby via spontaneous vaginal delivery 9 weeks later.

DISCUSSION AND CONCLUSION

The elimination of dapsone, particularly in pregnancy, is not completely understood. It remains a great challenge to fully understand the pharmacokinetics of dapsone. One study demonstrated no correlation between dapsone level and methemoglobin in patients, but this did not include pregnant population [3]. The same study also reported that the dosage of dapsone used in leprosy treatment would not promote a significant methemoglobinemia.

Dapsone is metabolized by the liver through the oxidation reactions of N-acetylation and N-hydroxylation. Hydroxylated amine metabolites produced in the oxidation reactions are potent oxidants and are retained in the circulation for a long period as they undergo enterohepatic recirculation. They are taken up by the erythrocytes where they (in particular, dapsone monohydroxylamine) are primarily responsible for the hematologic adverse effects of methemoglobinemia and hemolysis [4, 5]. Methemoglobin is an aberrant form of hemoglobin in which the ferrous (Fe^{2+}) atom is oxidized to a ferric (Fe^{3+}) atom. The latter has higher oxygen affinity but a deceased oxygen binding capacity [6].

Clinicians should have high index of suspicion and be able to recognize methemoglobinemia as an adverse effect attributable to dapsone use as well as the potential factors that precipitate it, including other drugs, aniline dyes, nitrate-containing compounds and others. Patients with cyanosis and hypoxemia of unclear etiology should be evaluated for methemoglobinemia, especially when there is presence of a saturation gap—the difference between oxygen saturation measured by pulse oximetry and ABG analysis. Studies have shown that this saturation gap is typically above 5% in such cases [7]. Similarly, our patient demonstrated a saturation gap of 13%. In addition to methemoglobinemia, the other differential diagnosis of 'saturation gap' includes carbon monoxide poisoning, sulfhemoglobinemia and variant hemoglobinopathy [8]. The presence of dark arterial blood in this case is attributable to the lack of physiologic hemoglobin–oxygen content due to elevated methemoglobin levels in blood [9].

Our patient showed improvement after cessation of dapsone. This result is consistent with a study which demonstrated the resolution of dapsone-induced methemoglobinemia after the withdrawal of the offending agent [10]. Mild methemoglobinemia may spontaneously resolve with cessation of the concerned drug while severe cases would require other supportive therapy when patients are symptomatic. In the setting of pregnancy, methemoglobinemia can pose a significant risk to both mother and fetus. Studies have shown that methylene blue has potential teratogenic effects in early pregnancy and unknown effects in late pregnancy. Pregnancy is a physiologic state of increased oxygen consumption and lower oxygen reserve, and maternal tolerance of methemoglobin levels is likely lower than that of a non-pregnant patient [11]. Therefore, the use of methylene blue in this case might be risky and the use of ascorbic acid could be appropriate. Vitamin C is an endogenous reducing agent within erythrocytes that has antioxidant effects on hemoglobin to prevent conversion to methemoglobin. It is an effective alternative therapy in cases of methemoglobinemia as it increases glutathione production and prevents oxidative damage [12].

The standard MDT regimens are considered safe, both for the mother and the child, as reported by the Action Program for the Elimination of Leprosy, WHO, Geneva [3]. Therefore, the treatment should be continued during pregnancy unless there are other compelling reasons to stop it. Based on Malaysian Leprosy Manual guidelines, the recommended MDT duration is 18 months for MB cases with initial BI of more than 4 [13]. This is in contrast to 12 months as suggested by WHO [3]. As our patient's initial BI was 4.3, replacement of dapsone by ofloxacin is justifiable. Ofloxacin was chosen in this case as it displayed powerful bactericidal activity against mycobacterium leprae

and may be an important component of new multidrug regimens for the treatment of leprosy [14]. The treatment duration may be reduced with the addition of ofloxacin to the standard WHO recommended MDT regime for MB patients [14, 15]. The rate of major birth defects after first-trimester exposure to fluoroquinolones was not increased compared to that for the non-exposed group, which is consistent with the findings of several publications [16–18]. Ofloxacin was commenced at 30 weeks' gestation in our patient, therefore the risk of teratogenicity is likely negligible.

In conclusion, clinicians should be aware of the side effects of dapsone therapy and know how to promptly and effectively manage any undesirable events.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interest.

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ETHICAL APPROVAL

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CONSENT FOR PUBLICATION

Written permission for publication has been obtained from the patient.

GUARANTOR

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REFERENCES

1. Ministry of Health Malaysia. Annual report. Ministry of Health Malaysia, Putrajaya. 2011; pp. 62–3
2. WHO. Model prescribing information: drugs used in leprosy. Chapter: Treatment of Leprosy During Pregnancy and Lactation. 1998. http://apps.who.int/medicinedocs/en/d/Jh2988e/10.html. (16 May 2018, date last accessed).
3. Jose LFV, Juan GBR, Ana NSM, Jorge PS, Claudio GS. Methemoglobinemia and dapsone levels in patients with leprosy. *Braz J Infect Dis* 2010;**14**:3.
4. Turner MD, Karlis V, Glickman RS. The recognition, physiology, and treatment of medication-induced methemoglobinemia: a case report. *Anesth Prog* 2007;**54**:115–7.
5. Tingle MD, Coleman MD, Park BK. An investigation of the role of metabolism in dapsone-induced methaemoglobinaemia using a two compartment in vitro test system. *Br J Clin Pharmacol* 1990;**30**:829–38.
6. Rhodes LE, Tingle MD, Park BK, Chu P, Verbov JL, Friedmann PS. Cimetidine improves the therapeutic/toxic ratio of dapsone in patients on chronic dapsone therapy. *Br J Dermatol* 1995;**132**:257–62.
7. Abu-Laban RB, Zed PJ, Pursell RA, Evans KG. Severe methemoglobinemia from topical anesthetic spray: case report, discussion and qualitative systematic review. *CJEM* 2001;**3**:51–6.
8. Akhtar J, Johnston BD, Krenzelok EP. Mind the gap. *J Emerg Med* 2007;**33**:131–2.
9. Marx JA, Hockberger RS, Walls RM, Biros MH, Danzl DF, Gausche-Hill M, *et al Rosen's Emergency Medicine: Concepts and Clinical Practice*. Philadelphia: Elsevier Saunders, 2014,129–34.
10. Erstad BL. Dapsone-induced methemoglobinemia and haemolytic anemia. *Clin Pharm* 1992;**11**:800–5.
11. LoMauro A, Aliverti A. Respiratory physiology of pregnancy: physiology masterclass. *Breathe (Sheff)* 2015;**11**:297–301.
12. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. *Ann Emerg Med* 1999;**34**:646–56.
13. Manual Pengurusan Kusta Kebangsaan Edisi Kedua. Chapter 2: Pengurusan Klinikal. Ministry of Health. 2014; pp. 24–5. http://www.moh.gov.my. (1 August 2018, date last accessed).
14. Ji B, Grosset J. Ofloxacin for the treatment of leprosy. *Acta Leprol* 1991;**7**:321–6.
15. Ji B, Perani EG, Petinom C, N'Deli L, Grosset JH. Clinical trial of ofloxacin alone and in combination with dapsone plus clofazimine for treatment of lepromatous leprosy. *Antimircob Agents Chemother* 1994;**38**:662–7.
16. Stephanie P, Evelin W, Reinhard M, Mary P, Corinna WS, Mare O, *et al*. Observational cohort study of pregnancy outcome after first-trimester exposure to fluoroquinolones. *Antimicrob Agents Chemother* 2014;**58**:4392–8.
17. Wilton LV, Pearce GL, Mann RD. A comparison of ciprofloxacin, norfloxacin, ofloxacin, azithromycin and cefixime examined by observational cohort studies. *Br J Clin Pharmacol* 1996;**41**:277–84.
18. Bar-Oz B, Moretti ME, Boskovic R, O'Brien L, Koren G. The safety of quinolones—a meta-analysis of pregnancy outcomes. *Eur J Obstet Reprod Biol* 2009;**143**:75–8.