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Challenges in Managing a Lepromatous Leprosy Patient Complicated with Melioidosis Infection, Dapsone-Induced Methemoglobinemia, Hemolytic Anemia, and Lepra Reaction

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Data Collection B
Statistical Analysis C
Data Interpretation D
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Conflict of interest: None declared

Patient: Female, 22-year-old
Final Diagnosis: Lepromatous leprosy co-infected with melioidosis • complicated by dapsone-induced methaemoglobinaemia and type 2 lepra reaction
Symptoms: Cyanosis • fever • jaundice • pallor • skin rash
Medication: —
Clinical Procedure: —
Specialty: Dermatology • Hematology • Infectious Diseases • General and Internal Medicine • Microbiology and Virology

Objective: Unusual clinical course

Background: Leprosy is an infection caused by *Mycobacterium leprae*. An extensive literature search did not reveal many reports of melioidosis in association with leprosy.

Case Report: A 22-year-old woman, who was diagnosed with multibacillary leprosy, developed dapsone-induced methemoglobinemia and hemolytic anemia, complicated by melioidosis. Methemoglobinemia was treated with methylene blue and vitamin C. Two weeks of ceftazidime was initiated to treat melioidosis, and the patient was discharged on amoxicillin/clavulanic acid and doxycycline as melioidosis eradication therapy. However, she developed drug-induced hypersensitivity. Trimethoprim/sulfamethoxazole, as an alternative treatment for melioidosis eradication, was commenced and was successfully completed for 12 weeks. During the fifth month of multidrug therapy, the patient developed type II lepra reaction with erythema nodosum leprosum reaction, which was treated with prednisolone. Leprosy treatment continued with clofazimine and ofloxacin, and complete resolution of skin lesions occurred after 12 months of therapy.

Conclusions: Our case highlighted the challenges posed in managing a patient with multibacillary leprosy with multiple complications. Clinicians should be aware that dapsone-induced methemoglobinemia and hemolysis might complicate the treatment of leprosy. Our case also highlighted the safety and efficacy of combining ofloxacin and clofazimine as a leprosy treatment regimen in addition to gradual steroid dose titration in the presence of type II lepra reaction.

Keywords: Dapsone • Leprosy • Melioidosis • Methemoglobinemia

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Background

Leprosy is an infection caused by *Mycobacterium leprae*, while melioidosis results from the gram-negative bacterium *Burkholderia pseudomallei*. An extensive literature search did not reveal many reports of melioidosis in association with leprosy. We present a case of a lepromatous leprosy co-infected with melioidosis, complicated by dapsone-induced methemoglobinemia and type 2 lepra reaction.

Case Report

A 22-year-old woman, who was previously healthy, presented with multiple copper-colored macules and patches that showed loss of sensation to pinprick and light touch, dryness, and loss of hair. Physical examination revealed loss of eyebrows and a palpable thickened ulnar nerve without muscle weakness or atrophy. No leonine facies were identified. With leprosy as part of the differential diagnosis, slit skin smear was performed from both earlobes and 6 distinct active sites. A diagnosis of multibacillary leprosy was confirmed with a morphological index of 2.0% and bacteriological index of 3.3.

Further investigations showed normal values for glucose-6-phosphate dehydrogenase activity, complete blood count, and renal and liver biochemistry. The patient was seronegative for HIV, syphilis, and hepatitis B and C. Sputum acid-fast bacilli smears were negative, with no tuberculosis or active infective lung features on chest X-ray. The patient was commenced on standard multidrug therapy (MDT) comprising clofazimine (300 mg once a month and 50 mg daily), rifampicin (600 mg once a month), and dapsone (100 mg daily).

On day 26 after medication commencement, the patient was admitted for dyspnea and high-grade fever with chills. She denied intake of traditional medications or over-the-counter drugs. On examination, she appeared tachypneic and tachycardic. Oxygen saturation (SpO_2) under room air measured by pulse oximeter varied between 75% and 78%, and it did not increase after application of a non-rebreathing mask with 15 L/min oxygen. She appeared pale, jaundiced, and cyanotic. Radial arterial and venous blood was dark colored. Arterial blood gas under room air showed partial pressure of O_2 of 125 mmHg and partial pressure of CO_2 of 88 mmHg. The clinical features were consistent with methemoglobinemia. Due to the resource-restricted setting, the methemoglobin concentration was unavailable.

There was laboratory evidence of severe hemolysis, with hemoglobin of 5.4 g/dL (a drop of 6 g/dL compared with baseline), reticulocyte count of 4.1%, lactate dehydrogenase of 1512 U/L, and predominantly indirect hyperbilirubinemia. A peripheral blood smear was consistent with features of hemolysis with spherocytes. Coombs test was negative. Due to the hemodynamically significant anemia, 1 pint of packed cell transfusion, intravenous (i.v.) hydrocortisone 100 mg 3 times daily, and folic acid were given.

Due to the clinical evidence of sepsis, thorough infective screening, including mycoplasma serology, blood film malaria parasite, and sputum and blood cultures, was conducted. The results were negative. The melioidosis enzyme-linked immunosorbent assay (ELISA) immunoglobulin (Ig)M antibody titer was 1: 640 (reference value ≤1: 320). Abdominal ultrasonography showed multiple splenic micro-abscesses. Melioidosis infection was confirmed and treated with i.v. ceftazidime (2 g every 8 h) for 2 weeks as part of an intensive regimen, followed by amoxicillin/clavulanic acid (1250 mg 3 times daily) and doxycycline (100 mg twice daily) as eradication therapy.

Dapsone-induced methemoglobinemia and hemolytic anemia complicated by melioidosis infection were suspected due to the oxygen-resistant cyanosis without respiratory compromise or abnormalities on chest X-ray and the presence of severe hemolysis. Thus, the patient's MDT was withheld. She was started on methylene blue in addition to hyperhydration, forced alkaline diuresis, and parentrovite, which contained 1000 mg of ascorbic acid. The hemolysis resolved with a gradual increment in SpO_2 level a few days after treatment began.

A few days later, the patient developed drug-induced hypersensitivity, manifesting as pruritic, erythrodermic-like skin rashes with an absence of angioedema and urticarial lesions (**Figure 1A**). Antibiotics were then withheld until complete resolution of skin lesions. Topical emollient and steroid treatment were prescribed in addition to antihistamine. Trimethoprim/sulfamethoxazole (Bactrim) desensitization, as an alternative for the melioidosis eradication regimen, was started successfully and completed over a total of 12 weeks. Repeated serum melioidosis ELISA results were negative with complete resolution of splenic micro-abscesses.

However, after 4 weeks of full-dose Bactrim treatment and 5 months of MDT, the patient developed erythematous nodular skin lesions over her face and bilateral upper and lower limbs (**Figure 1B**). Type II lepra reaction was suspected, and prednisolone 0.5 mg/kg/d was started. A skin biopsy was consistent with lepromatous leprosy with erythema nodosum leprosum reaction (**Figure 2A, 2B**). Symptoms improved with steroid therapy, and anti-leprosy treatment continued with clofazimine and ofloxacin (400 mg daily). Rifampicin was withheld because we were concerned about treatment monitoring and possible risk of hypersensitivity reaction to rifampicin in this patient. Steroid treatment was tapered off over a 6-month period. The patient was well, with complete resolution of skin lesions after 12 months of leprosy treatment.

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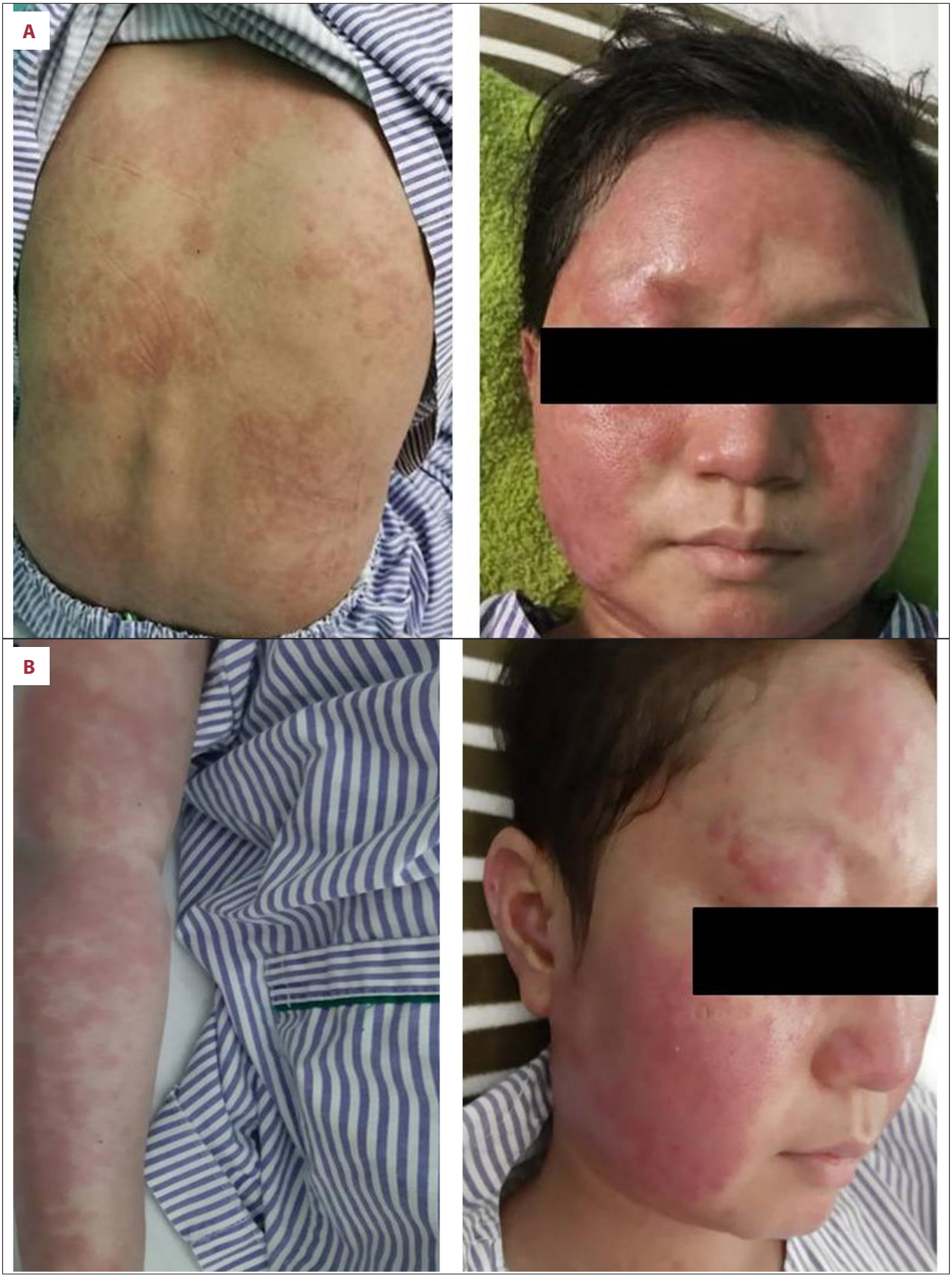

Figure 1. (**A**) Pruritic, erythrodermic-like skin rashes. (**B**) Type II erythema nodosum leprosum reaction.

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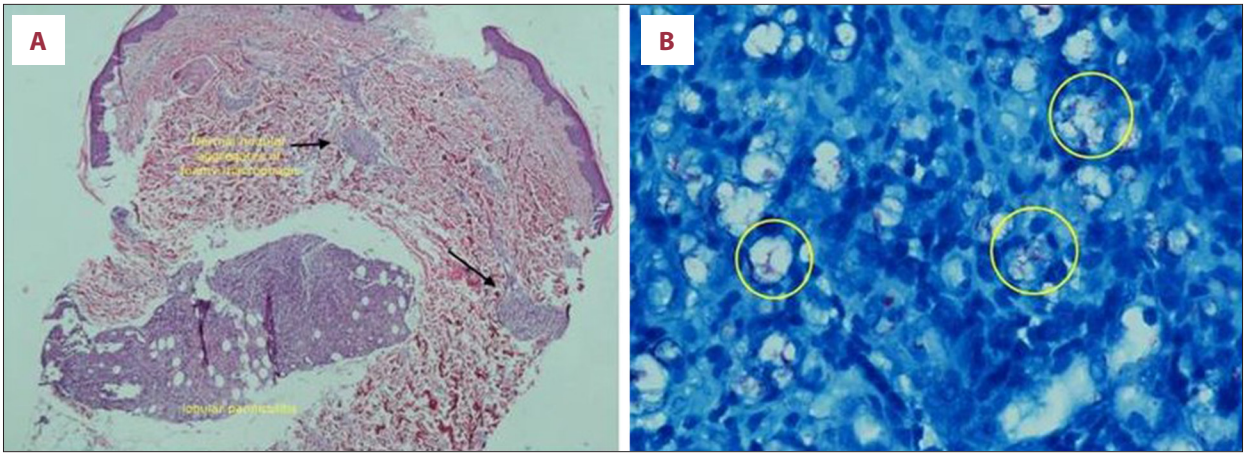

Figure 2. Skin biopsy: (**A**) dermal nodular aggregates of foamy macrophage with lobular panniculitis in part of the subcutaneous layer; (**B**) fite stain showed many intracellular acid-fast bacilli.

Discussion

Methemoglobinemia is often difficult to diagnose and poses a great clinical challenge. Methemoglobin is an aberrant form of hemoglobin arising from oxidation of heme iron to the ferric (Fe^{3+}) form, resulting in a left shift in the oxygen saturation curve [1]. Hemolytic anemia may follow drug-induced methemoglobinemia, especially with exposure to dapsone and sulfonamides [2]. Clinicians should have a high index of suspicion and be able to recognize methemoglobinemia as an adverse effect attributable to dapsone use, particularly when patients present with cyanosis and hypoxemia of unclear etiology and there is a saturation gap (ie, a difference between oxygen saturation measured by pulse oximetry and arterial blood gas analysis) [2]. Our patient demonstrated oxygen-resistant cyanosis with a saturation gap of 37%.

Mild methemoglobinemia can be managed with supportive care and cessation of the offending drug, whereas methylene blue and vitamin C are indicated for moderate to severe forms. Methylene blue is reduced to leukomethylene blue, which acts as an artificial electron donor to methemoglobin, thereby enhancing the ability of erythrocytes to reduce methemoglobin. Vitamin C has antioxidant effects on hemoglobin to prevent conversion to methemoglobin [2,3]. Our patient responded well to methylene blue and vitamin C, as evidenced by the increment in oxygen saturation as well as complete resolution of methemoglobinemia and hemolysis.

It has been reported that methemoglobin levels are significantly higher in patients with sepsis because large amounts of nitric oxide, which is converted to methemoglobin and nitrate, are released in this group of patients [4]. This might explain the severe clinical phenotype in our case in which a concomitant melioidosis infection was present. Thus, a targeted therapy in sepsis is warranted to hasten the clinical recovery. Hemolytic anemia is a serious adverse effect of therapeutic drugs resulting from increased destruction of drug-damaged erythrocytes by macrophages in the spleen and liver [5].

Melioidosis is prevalent in Southeast Asia due to agricultural exposure. Patients have clinical evidence of sepsis with high-grade fever and chills, high titer of melioidosis ELISA IgM antibody (1: 640, reference value ≤1: 320), and multiple splenic micro-abscesses on abdominal ultrasonography, all of which suggested melioidosis in our patient. Melioidosis treatment consists of i.v. intensive phase and oral eradication phase. Ceftazidime and meropenem are recommended for the former, while trimethoprim/sulfamethoxazole is the first-line drug for the latter phase [6]. The rationale for choosing amoxicillin/clavulanic acid and doxycycline as the preferred eradication regimen for melioidosis treatment is due to trimethoprim/sulfamethoxazole, which contains sulfonamides, being known to cause methemoglobinemia similar to dapsone [7]. Due to hypersensitivity reaction to the former antibiotics, we decided to try trimethoprim/sulfamethoxazole using the desensitization protocol, which was successful. Our patient was able to finish a 12-week treatment with complete eradication of melioidosis, as evidenced by negative IgM ELISA titer and resolution of splenic micro-abscesses.

Our patient initially received standard treatment regimen for multibacillary leprosy (rifampicin, dapsone, and clofazimine MDT); however, she developed dapsone-induced methemoglobinemia and hemolysis. She also developed a hypersensitivity reaction to amoxicillin/clavulanic acid and doxycycline, which are penicillin and tetracycline antibiotics, respectively. Various studies have reported that patients with a penicillin allergy might exhibit an allergic response to tetracycline [8,9], thus minocycline might not be a feasible alternative for leprosy treatment. In contrast, ofloxacin, which displays powerful bactericidal activity against *M. leprae*, is the most widely accepted

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fluoroquinolone for treatment of leprosy [10]. A combination of ofloxacin and other agents may considerably shorten the required duration of MDT [11]. Our patient showed remarkable clinical improvement, with attainment of good quality of life.

Conclusions

Our case highlighted the challenges posed in managing a patient with multibacillary leprosy with multiple complications. Clinicians should be aware that dapsone-induced methemoglobinemia and hemolysis might complicate the treatment of leprosy. Our case also highlighted the safety and efficacy of combining ofloxacin and clofazimine as a leprosy treatment regimen in addition to gradual steroid dose titration in the presence of type II lepra reaction.

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Ethics Approval

This article contains a study with a human participant and was registered via National Medical Research Register Malaysia with a Research ID of NMRR-20-1535-55886.

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Conflicts of interest

None.

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