

## A Case of Dapsone-induced Mild Methemoglobinemia with Dyspnea and Cyanosis

Dear Editor,

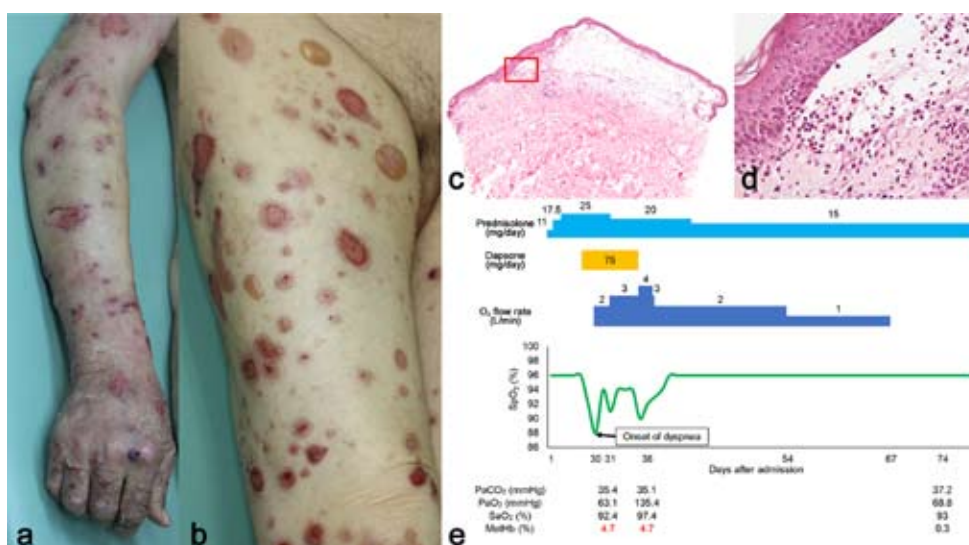
Dapsone is a dual-function drug with antimicrobial and antiprotozoal effects and anti-inflammatory features (1). In dermatology, it is a first choice for conditions such as leprosy, IgA pemphigus, dermatitis herpetiformis, and linear IgA bullous dermatosis, or an adjunctive treatment for, e.g. bullous pemphigoid (BP) and pemphigus vulgaris (1). However, dapsone is associated with some adverse effects, including methemoglobinemia (1).

Methemoglobin (MetHb) concentrations of less than 15% usually cause no symptoms in patients with normal hemoglobin concentrations (2). Herein, we report the case of a patient with BP who developed dyspnea because of dapsone-induced methemoglobinemia that was as mild as 4.7%.

A 93-year-old man was diagnosed with BP based on skin manifestations (Figure 1, a and b), histopathological findings (Figure 1, c and d), and anti-BP180 NC16A antibody titer determined by chemiluminescence enzyme immunoassay (279 U/mL) 3 years

earlier. His comorbidities included diabetes mellitus, chronic heart failure, right pleural effusion, and brain infarction. The patient had been successfully treated with oral prednisolone, so the steroid was tapered to 4 mg/day. The blisters recurred, however, and new ones kept developing even though the prednisolone was increased to 25 mg/day. Dapsone (75 mg/day) was begun as adjunctive treatment, and new blister formation ceased. At one week from dapsone initiation, the patient developed dyspnea, and his oxygen saturation as measured by pulse oximetry decreased to 88% on room air.

At presentation, his blood pressure was 118/78 mmHg, the heart rate was 95 beats/minute, and axillary temperature was 36.3 °C. Neurological examination and consciousness findings remained unchanged compared with findings before dyspnea onset. Chest examination showed normal breath and heart sounds, but lip and peripheral cyanosis was present. Blood tests revealed a white blood cell count



**Figure 1.** (a, b) Skin manifestations with tense blisters and erythema on the trunk and limbs. (c, d) Histopathological examination of the skin on the left thigh revealed subepidermal blistering with eosinophil infiltration (hematoxylin and eosin,  $\times 20$  and  $\times 200$ , respectively). (e) Clinical course.

of 12,920/ $\mu$ l; red blood cells,  $370 \times 10^4$ / $\mu$ l; hemoglobin, 11.7 g/dl; and CMV antigenemia (or C7-HRP), negative. Chest CT and echocardiography indicated no remarkable change compared with imaging from one year earlier. Arterial blood gas analysis showed a pH of 7.454, PaO<sub>2</sub> 63.1 mmHg, PaCO<sub>2</sub> 35.4 mmHg, HCO<sub>3</sub><sup>-</sup> 24.3 mmol/L, SaO<sub>2</sub> 92.4%, and MetHb of 4.7%. These findings indicated a saturation gap (difference between SpO<sub>2</sub> and SaO<sub>2</sub>) induced by MetHb. Upon cessation of dapsone, MetHb levels and SpO<sub>2</sub> returned to normal and the dyspnea resolved, implicating dapsone in the methemoglobinemia (Figure 1, e).

Differential diagnoses were pulmonary disease, heart disease, neuromuscular disease, sepsis, and drug intoxication. These possibilities were ruled out by the physical examination, drug history, vital signs, blood tests, and chest CT and echocardiography.

In normal individuals, MetHb levels are less than 1% (2). Healthy patients with normal hemoglobin concentrations develop cyanosis at MetHb level of 15-20%, dyspnea at 20-50%, and coma at 50-70%, and die at more than 70% (2). However, patients with hematologic disease, acidosis, or cardiopulmonary diseases, for example, present with symptoms even with MetHb levels less than 15% (2,3). We inferred that our patient presented with dyspnea even under mild methemoglobinemia because he had anemia, chronic heart failure, and right pleural effusion.

The occurrence of dapsone-induced methemoglobinemia with obvious symptoms is rare (1,4). Clinicians should be aware that methemoglobinemia symptoms are influenced not only by MetHb concentrations but also by comorbidities.

### References:

1. Wozel G, Blasum C. Dapsone in dermatology and beyond. *Archives of dermatological research*. 2014;306:103-24.
2. Price D. Methemoglobin Inducers. In: Hoffman R, Howland M, Lewin N, Nelson L, Goldfrank L, eds. *Goldfrank's Toxicologic Emergencies*. tenth ed. New York: McGraw-Hill Education; 2014. pp. 1622-30.
3. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. *Annals of emergency medicine*. 1999;34:646-56.
4. Das J, Katyal A, Naunwaar D. Dapsone-induced Methemoglobinemia in a Patient of Leprosy. *Indian journal of dermatology*. 2015;60:108.

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Received: June 11, 2019

Accepted: November 16, 2020