Case Report
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Anesthetic experience: congenital methemoglobinemia due to hemoglobin M

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Methemoglobinemia is rare. It is classified into two types: congenital methemoglobinemia and acquired methemoglobinemia. Methemoglobin is incapable of binding oxygen, leading to complications such as cyanosis, dyspnea, headache, and heart failure. In the present case, a 35-year-old man with congenital methemoglobinemia underwent general anesthesia for thyroidectomy. The patient was diagnosed with hemoglobin M at 7 years of age. Ventilation was performed with FiO_2 1.0. Arterial blood gas analysis showed that the pH was 7.4, PaO_2 439 mmHg, $PaCO_2$ 40.5 mmHg, oxyhemoglobin level of 83.2%, and methemoglobin level of 15.5%. The patient had a stable course, although cyanosis was observed during surgery.

Keywords: General Anesthesia; Hemoglobin M; Methemoglobin; Methemoglobinemia.

INTRODUCTION

Methemoglobin (MetHb) is an altered state of the hemoglobin (Hb) molecule, which is produced by the oxidation of iron in the hemoglobin, from Fe^{2+} (ferrous state) to Fe^{3+} (ferric state). Methemoglobin can lead to hypoxemia because of its inability to bind oxygen, resulting in complications such as dyspnea, headache, and heart failure [1,2].

Acquired methemoglobinemia can be caused by various agents, such as nitrites, sulfonamides, phenytoin, and local anesthetics [1]. Congenital methemoglobinemia occurs in patients with cytochrome b5 reductase deficiency or hemoglobin M (Hb M) disease [3]. Congenital methemoglobinemia is rarer than acquired methemoglobinemia [3-6].

Here, we report a case of a patient with congenital methemoglobinemia who underwent general anesthesia for thyroidectomy.

CASE REPORT

A 32-year-old man was transferred to our tertiary hospital for thyroidectomy due to thyroid cancer. His height and weight were 180 cm and 90 kg, respectively. The body mass index was 27.8. Past medical history revealed that he had visited a pediatrician at 7 years of age because of cyanosis and was diagnosed with Hb M disease. Two days prior to surgery, his arterial blood gas analysis (ABGA) at room air revealed a pH of 7.44, $PaCO_2$ of 39.7 mmHg, partial pressure of oxygen (PaO_2) of 99 mmHg, oxyhemoglobin (OxyHb) level of 87%, and

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Fig. 1. An arterial blood sample showing chocolate brown blood in a patient with methemoglobinemia.

methemoglobin (MetHb) level of 11.9%. Oxygen saturation (SpO_2) measured by pulse oximetry was 75%.

There were no abnormalities on echocardiography, electrocardiography (ECG), pulmonary function test, and chest radiography. The patient worked in a courier service. During routine physical activities, such as walking and climbing stairs, the patient did not experience dyspnea or palpitation.

Premedication was not administered. On arrival in the operating room, ECG and pulse oximetry were performed. SpO_2 was 70% – 75% at room air. Radial arterial catheterization was performed using a 20-gauge catheter before induction of anesthesia. Chocolate brown-colored arterial blood was extracted (Fig. 1). ABGA showed a pH of 7.38, $PaCO_2$ of 40.5 mmHg, PaO_2 of 93.7 mmHg, OxyHb of 86.8%, and MetHb of 12%. The patient was conscious and did not complain of dyspnea. Under manual ventilation with FiO_2 at 1.0, general anesthesia was induced with propofol 200 mg and rocuronium 90 mg. Endotracheal intubation was performed using a size 7.5 endotracheal tube. Anesthesia was maintained with 1.5% – 2.0% sevoflurane with FiO_2 at 0.6, and the target concentration of remifentanil was set at 2 – 3 ng/mL. Volume-controlled ventilation was set at a tidal volume of 8 mL/kg and a respiratory rate of 10 cycles/min to maintain the end-tidal carbon dioxide tension to between 35 and 40 mmHg. Twenty minutes after endotracheal intubation, ABGA showed a pH of 7.4, PaO_2 of 149 mmHg, $PaCO_2$ of 39.4 mmHg, OxyHb of 83.3%, and MetHb of 15.5%. SpO_2 was 65% – 75%, and cyanosis was observed on the patient's lip and fingernails. Therefore, ventilation was performed with FiO_2 at 1.0. After 20 min, ABGA showed a pH of 7.4, PaO_2 of 439 mmHg $PaCO_2$ of 40.5 mmHg, OxyHb of 84%, and MetHb of 15.5%. SpO_2 was 75%, and cyanosis was still observed on the patient's lips and fingernails. The surgery lasted for 2 h, and the patient was stable during the operation. The patient was extubated as he was conscious and spontaneously breathing.

In the postanesthetic care room, the patient received oxygen at 6 L/min via a facemask for 30 min. He remained in a stable condition. After discontinuation of oxygen treatment, he coped well and there was no dyspnea. He was transferred to the ward, where he had an uneventful postoperative course and he was discharged without complications 5 days after surgery. Approval for the publication of this report was obtained from the patient and the Institutional Review Board of our hospital (2021-06-054).

DISCUSSION

MetHb cannot form a bond with oxygen. This leads to insufficient tissue oxygen transport. Nicotinamide adenine dinucleotide phosphate (NADPH) eliminates MetHb, which remains below 1% under normal physiological conditions [1]. However, abnormally increased concentrations of MetHb in the blood can lead to several complications, such as headaches, loss of consciousness, respiratory depression, cardiovascular collapse, and death [1,2]. Cyanosis occurs at methemoglobin levels of over 5% – 15%. Patients with methemoglobinemia generally show a chocolate brown arterial color with normal PaO_2 [4]. Patients become symptomatic at MetHb levels higher than 25% – 30% [2,7].

In the present case, the patient performed routine physical activities, such as walking and climbing stairs, without dyspnea, palpitations, or headaches. Before surgery, his MetHb level was 11.9%. During surgery, his MetHb level

was 15.5%, and cyanosis was observed on his lip. However, vital signs were stable, including heart rate and blood pressure. Metabolic acidosis was not present.

OxyHb absorbs infrared light with a wavelength of 990 nm, and deoxyhemoglobin (deOxyHb) absorbs red light with a wavelength of 660 nm. Pulse oximetry measures oxygen saturation using infrared and red light [8]. However, the accuracy of pulse oximetry decreases in patients with methemoglobinemia [9]. Methemoglobinemia may be clinically suspected when the oxygen saturation measured by pulse oximetry is low in patients with normal arterial blood gases. A co-oximeter is considered to be an accurate device for measuring MetHb and is very useful for the diagnosis of methemoglobinemia [10,11]. It measures absorbance at over 100 wavelengths to construct a continuous absorption spectrum from 450 to 700 nm. Arterial oxygen saturation (SaO_2) was calculated from the measured PaO_2 and an empirical equation for the OxyHb dissociation curve [10,11].

Congenital methemoglobinemia is caused by Hb M disease or cytochrome b5 reductase deficiency. Hb M disease is caused by several abnormal Hb variants with an increased tendency for Hb to oxidize to MetHb, and is referred to as Hb M. Hb M is inherited as an autosomal dominant defect. It occurs because of amino acid replacement of tyrosine for histidine in α, β, or γ globulin chains of the heme pocket, which leads to spontaneous oxidation of heme iron, resulting in methemoglobinemia [3,9,12]. Cytochrome b5 reductase is an enzyme acquired for the reducing system in the body. Methemoglobinemia due to cytochrome b5 reductase deficiency is inherited in an autosomal recessive pattern [12].

Methylene blue is frequently used to treat patients with methemoglobinemia [2,4]. It acts as a reducing agent to reduce MetHb to Hb by activating NADPH diaphorase, which reduces methylene blue to leucomethylene blue [9]. Methylene blue may be indicated in methemoglobinemia in patients with Hb M [6]. Importantly, iron-phenolate complexes, which are resistant to reduction, are formed in patients with Hb M disease [12, 13]. A previous study reported that methylene blue did not improve methemoglobinemia in patients with Hb M [12,13]. Moreover, methylene blue may cause hemolysis [12]. Therapy with vitamin C can be considered when methylene blue is not available, although the effect of vitamin C on the treatment of methemoglobinemia in patients with Hb M is controversial [12].

Inhalation of high concentrations of O_2 can also be used to treat methemoglobinemia. High arterial oxygen pressure should be maintained to decrease tissue hypoxia during induction of general anesthesia [9]. Blood transfusion or exchange transfusion may be useful in patients with severe methemoglobinemia, exceeding 70 % [12,14]. In our case, at MetHb of 15.5 %, ventilation with FiO_2at 1.0 was performed and the intraoperative vital signs, including heart rate and blood pressure, remained stable and the patient did not experience metabolic acidosis. MetHb levels less than 25 % are generally well tolerated [2,7]. Therefore, we did not consider vitamin C infusion.

Methemoglobinemia may be provoked by several oxidizing agents, such as nitroglycerin, sulfonamides, phenytoin, and local anesthetics including lidocaine and prilocaine [1,4,15]. Methemoglobinemia has been reported to occur even at doses lower than the recommended maximum dose of prilocaine in patients who undergo general anesthesia for maxillary sinus elevation and tooth extraction [15]. Therefore, it is important to avoid using oxidizing agents in patients with congenital methemoglobinemia [4,11].

In conclusion, congenital methemoglobinemia is rare but can be fatal. The anesthesiologist should avoid the use of oxidizing agents and maintain O_2 carrying capacity of the arterial blood by ensuring high O_2concentration in the inhaled gas in patients with congenital methemoglobinemia during general anesthesia.

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