

Case Report

A Case of Aniline Poisoning Manifesting as Cyanosis with Unknown Cause

Kenichi Taguchi^a, Kazuya Nishii^{b*}, Sakura Hata^a, Shoichi Kuyama, and Shoichi Tanaka^a

Department of^aGastroenterology,

^bRespiratory Medicine, NHO Iwakuni Clinical Center, Iwakuni, Yamaguchi 740-8510, Japan

A 38-year-old man was brought to the hospital for emergency treatment of cyanosis. The patient exhibited generalized cyanosis and impaired consciousness despite adequate oxygen therapy. Arterial blood was black, and arterial blood gas analysis revealed an abnormally high methemoglobin level of 67.8%. We later interviewed his colleagues regarding his exposure to aniline while working at the factory and diagnosed him with methemoglobinemia due to aniline poisoning. The patient was administered methylene blue (MB) after being transferred to another hospital, where this treatment was available, resulting in an improvement in symptoms. Although rare, methemoglobinemia is serious. A good understanding of the circumstances at disease onset, characteristic findings, and abnormal values of methemoglobinemia is important. In addition, MB is an important therapeutic for the treatment of methemoglobinemia; if MB is not available at a particular hospital, transfer of the patient to a hospital that stocks MB should be considered.

Key words: methemoglobinemia, aniline, methylene blue, cyanosis

Methemoglobinemia is a disease that causes tissue hypoxia due to the oxidation of trivalent iron from divalent iron in blood hemoglobin [1]. The most common causes of acquired methemoglobinemia are drug ingestion and toxic exposure, such as to aniline. The main symptoms of acquired methemoglobinemia include cyanosis, pallor, fatigue, headache, central nervous system depression, metabolic acidosis, seizures, arrhythmias, and coma [2]. The severity of symptoms depends on the concentration of methemoglobin, which becomes fatal at concentrations exceeding 70%.

Generally, aniline poisoning and severe methemoglobinemia are rare. However, because they are serious diseases, clinicians must not overlook them and should provide prompt treatment. Here, we report the case of a man who presented at our emergency department with cyanosis of unknown cause. Based on blood gas analy-

sis and medical history, he was diagnosed with methemoglobinemia due to aniline intoxication, for which he underwent a 16-day treatment course that was complex but ultimately successful.

Case Report

A 38-year-old man was transported to our hospital for emergency treatment of respiratory distress and hypothermia. When we first received the emergency transport request from the emergency medical service (EMS), we were informed that the patient had fallen sick while working at a factory handling chemical intermediates. He was also taking regular medication (30 mg/day of thiamazole) for hyperthyroidism.

When the EMS reached him at the factory, his pulse oximetry saturation (SpO₂) level was 90% and his body temperature was 34.1°C. Upon arrival at the hospital, he presented with a bluish-black skin color and cold

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*Corresponding author. Phone: +81-827-34-1000; Fax: +81-827-35-5600
E-mail: kazuya.nishii.2112@gmail.com (K. Nishii)

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extremities. He had a Glasgow Coma Scale of E3V5M6, blood pressure of 87/52 mmHg, respiratory rate of 28 breaths/min, heart rate of 105 beats/min, body temperature of 34.1°C, and SpO₂ level of 81% (O₂: reservoir mask 10 l/min), and he was in a state of shock. Lung sounds were normal, and no heart murmurs or obvious neurological abnormalities were detected. Electrocardiogram, transthoracic echocardiography, and whole-body computed tomography showed no abnormalities. Upon admission, the patient's arterial blood was black in color (Fig. 1). Laboratory data showed no major abnormalities in blood counts, coagulation, or biochemistry (Table 1). Arterial blood gas (ABG) analysis showed a partial pressure of oxygen (PaO₂) of 280 mmHg and an arterial oxygen saturation (SaO₂) of 100%, indicating a discrepancy between SpO₂ and SaO₂, and his methemoglobin level was highly elevated at 68.7%. Acute methemoglobinemia due to toxic exposure was suspected based on the results of the ABG analysis. Since the patient was unconscious and had difficulty speaking, we asked his colleagues about his exposure to chemical agents and sought details of the working conditions, such as the clothing he was wearing and the chemicals he was handling at the time of onset.

The scenario presented by his colleagues was as follows. Four hours before arriving at the hospital, the patient was working indoors and accidentally spilled a drum containing a large amount of aniline. The chemical adhered to his clothing, which he wiped off by himself. He was wearing work clothes, safety glasses, rubber gloves, and a gas mask and helmet. He subsequently felt sick and experienced respiratory distress. Although he changed his clothes, he did not decontaminate his body. His symptoms did not improve; his colleague



Fig. 1 Photograph showing the black-colored arterial blood drawn from the patient.

found him lying in a fetal position and called for an EMS.

Based on this interview, we diagnosed the patient with aniline poisoning and immediately performed a decontamination. For treatment, methylene blue (MB) was considered the best option, but it was not available at our hospital. Therefore, we decided to transfer the patient to another hospital where MB was available. In preparation for the transfer, we administered ascorbic acid intravenously, but his condition did not improve. His consciousness level deteriorated, and he developed convulsions and was intubated and ventilated.

The patient was then transferred by helicopter and immediately admitted to the intensive care unit (ICU). He was administered 1 mg/kg MB twice, which lowered his methemoglobin levels (Fig. 2). He was weaned from

Table 1 Laboratory data of the patient

WBC	$14,810 \times 10^2/\mu\text{l}$	pH	7.375
RBC	$537 \times 10^4/\mu\text{l}$	pCO ₂	42.5 mmHg
Hb	15.5 g/dl	pO ₂	280 mmHg
PLT	$22.6 \times 10^4/\mu\text{l}$	HCO ₃	24.3 mmHg
PT%	11.5 %	SaO ₂	100.3 %
CRP	0.09 mg/dl	COHb	0.6 %
Total Protein	7 g/dl	MetHb	68.7 %
Albumin	4.5 g/dl	p50	15.57 mmHg
Total Bilirubin	0.91 mg/dl	ctO ₂	3.1 mmol/l
ChE	499 U/l		
T-Bil	0.91 mg/dl		
AST	22 U/l		
ALT	24 U/l		
γ-GTP	43 U/l		
LDH	207 U/l		
CK	110 U/l		
Na	145 mmol/l		
K	3.5 mmol/l		
BUN	21.6 mg/dl		
Creatinine	0.54 mg/dl		
Glucose	174 mg/dl		

No major abnormalities in blood counts, coagulation, or biochemistry were observed. Arterial blood gas analysis showed PaO₂ of 280 mmHg and SaO₂ of 100%, indicating a discrepancy between SpO₂ and SaO₂. Methemoglobin level was highly elevated at 68.7%. WBC, white blood cell count; RBC, red blood cell count; Hb, hemoglobin; PLT, platelet count; PT, prothrombin time; CRP, C-reactive protein; ChE, cholinesterase; T-Bil, total bilirubin; AST, aspartate transaminase; ALT, alanine transaminase; γ-GTP, gamma glutamyl transpeptidase; LDH, lactate dehydrogenase; CK, creatine kinase; BUN, blood urea nitrogen; pCO₂, partial pressure of carbon dioxide; pO₂, partial pressure of oxygen; SaO₂, arterial oxygen saturation; COHb, carboxyhemoglobin; MetHb, methemoglobin; p50, 50% saturation; ctO₂, concentration of total oxygen.

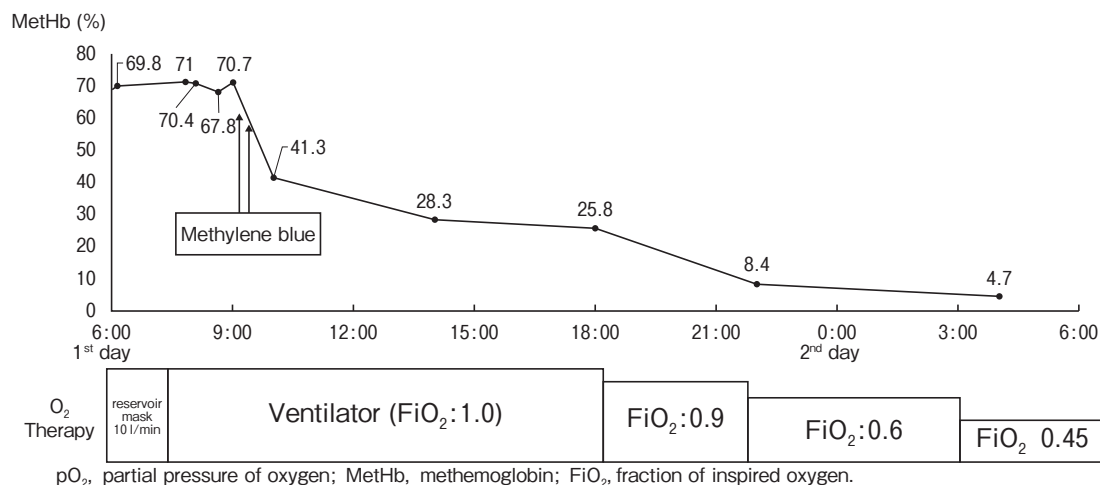


Fig. 2 Treatment progression of the patient. The patient was administered 1 mg/kg of methylene blue twice. Methemoglobin levels subsequently decreased.

the ventilator on the 2nd day. On the same day, he developed a fever of 40°C and tachycardia over 140 beats/min. His blood test showed decreased thyroid-stimulating hormone levels of <0.005 μ IU/ml, free triiodothyronine (FT3) levels of 10.9 pg/ml, and FT4 levels of 4.2 ng/ml, and he was diagnosed with thyroid crisis due to methemoglobinemia and treatment stress. We commenced treatment with 60 mg/day thiamazole, 200 mg/day inorganic iodine, 300 mg/day hydrocortisone, and 2.5 mg/day bisoprolol. On the 4th day, his FT3 and FT4 levels improved to 3.9 pg/ml and 2.3 ng/ml, respectively, and the doses of thiamazole and inorganic iodide were reduced. Hydrocortisone, bisoprolol, and inorganic iodide were phased out, and the patient was maintained on 15 mg/day of thiamazole.

In addition, anemia became apparent from the 3rd day, and the hemoglobin level dropped to 6.2 g/dl on the 6th day, necessitating red blood cell transfusion for 3 days. The elevated levels of ruptured erythrocytes, serum indirect bilirubin, and lactate dehydrogenase and reduced levels of serum haptoglobin below 10 mg/dl led to the diagnosis of hemolytic anemia. Anemia began to improve on the 8th day. Both direct and indirect Coombs tests were negative on the 9th day, and no other drug administered could have caused hemolytic anemia; therefore, MB was considered the cause of the hemolytic anemia. The anemia did not worsen after the 9th day. The patient was discharged from the hospital on the 16th day with ongoing treatment of oral thiamazole 15 mg/day, and no relapse has occurred since.

Discussion

We report a case in which the process leading to the diagnosis of methemoglobinemia was instructive. The patient was brought to the hospital with cyanosis of unknown cause. He presented with a bluish-black skin color and blackish-colored blood. Despite the administration of high levels of oxygen, his SpO₂ did not increase, whereas his SaO₂ and PaO₂ values were sufficiently high. These are the typical features of methemoglobinemia [3]. Fortunately, we did not miss the abnormally high methemoglobin level in the ABG test, and a diagnosis was promptly made.

Although we had limited information at the time of the initial examination, we suspected the possibility of poisoning based on physical and laboratory findings and interviews with the colleagues of the patient regarding working conditions.

The patient developed aniline poisoning despite wearing a gas mask. The cause of this poisoning was thought to be the absorption of aniline from contaminated clothing, since aniline may be absorbed both orally or percutaneously [4]. The patient was promptly decontaminated to prevent secondary aniline exposure by medical personnel.

MB is crucial for the treatment of methemoglobinemia [5]. However, since it was not available at our hospital, the patient was transported to a hospital that stocked MB. Before transportation, we administered ascorbic acid as an alternative therapy [6], but it was not

effective. Cyanosis does not improve unless methemoglobinemia is corrected, despite adequate oxygen therapy. However, since the patient's consciousness level deteriorated due to cyanosis, he was ventilated to ensure stable administration of high-flow oxygen, which was decidedly the best treatment strategy available to us at that point. The patient was transported by helicopter for rapid transport. Therefore, in addition to underscoring the advisability of wearing chemical-resistant clothing while handling aniline, our case argues for the availability of MB at any hospital that might be required to treat cases of aniline poisoning.

Our case had an unusual course, including thyroid crisis and hemolytic anemia. Although neither aniline poisoning nor methemoglobinemia has been reported as a cause of thyroid crisis, a common cause is stress from infection, acute illness, or surgery in patients with a background of hyperthyroidism [7,8]. In our case, physical stresses such as methemoglobinemia, ventilator therapy, and management in the ICU may have been factors in the development of thyroid crisis. The patient's condition improved after treatment with thiamazole and inorganic iodine to suppress thyroid function as a trigger, beta blockers for tachycardia, and glucocorticoids to prevent relative adrenal insufficiency, following the general protocol of thyroid crisis treatment.

MB is metabolized into leucomethylene blue in erythrocytes, and leucomethylene blue treats methemoglobinemia as a reducing agent [1,2]. However, high doses of MB can paradoxically worsen methemoglobinemia and Heinz body hemolytic anemia due to the increased concentration of MB as an oxidizing agent. A previous case report described that hemolytic anemia was improved by discontinuation of MB and blood transfusion [9]. In the present case, the hemolytic anemia that occurred after MB administration also improved with blood transfusion.

Conclusion

This case study demonstrates that, when treating a patient with severe methemoglobinemia, understanding the features of this condition and the circumstances of its onset are important for prompt diagnosis. In addition, the patient with methemoglobinemia should be administered MB as soon as possible. In the event MB is not available, immediate transfer to a hospital where MB is available should be considered.

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