Case Report

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TANAFFOS

A Rare Mechanism of Hypoxemia: A Case Report

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The leading causes of hypoxemia and acute respiratory failure commonly observed in the intensive care unit setting are ventilator/perfusion mismatch and intrapulmonary shunt. The main objective of the current report was to describe the treatment and the diagnostic procedures in a patient with methemoglobinemia.

A 66-year-old woman arrived at the emergency department after suddenly losing coordination while walking and reported having experienced increased cough and sputum in the previous days. The patient, a current smoker with 35 pack–years, had comorbidities and chronic obstructive pulmonary disease, requiring long-term oxygen therapy. Extensive laboratory analyses revealed elevated methemoglobin (MetHb) levels, increasing from 10% upon admission to 25% of total hemoglobin (Hb), and the onset of post-surgical anemia (Hb 9.6 g/dL).

In the present case, the hypoxemia was caused by an increase in MetHb levels, in addition to anemia due to surgical intervention and overhydration. Antibiotic and diuretic therapy for treating infection and right heart failure was effective, leading to a favorable postoperative course.

Keywords: Acute respiratory failure; Cough; Dyspnea; Intensive care unit; Methemoglobinemia

INTRODUCTION

The main causes of hypoxemia and acute respiratory failure (ARF) observed in the intensive care unit (ICU) are ventilation/perfusion (VA/Q) mismatch and intrapulmonary shunt (1). A higher shunt (zero VA/Q ratio), caused by collapsed or flooded alveoli, results in lower arterial oxygen partial pressure (PaO2). Conversely, in VA/Q mismatch, PaO2 increases nearly linearly as the fraction of inspired oxygen (FiO_2) rises. However, an extremely low VA/Q ratio closely resembles a shunt. Hypoxemia depends on both intrapulmonary factors such as VA/Q mismatch, intrapulmonary shunt, and limitations in alveolar to end-capillary oxygen diffusion and extrapulmonary factors, including FiO_2, total ventilation, cardiac output, and oxygen consumption, as shown in Table 1 (2,3). Understanding these key factors is essential for effectively treating patients with ARF. This case report was written following the CARE guidelines (4).

The main objective of the current report was to describe the treatment and the diagnostic procedures in a patient with methemoglobinemia.

CASE SUMMARIES

A 66-year-old woman, who gave consent for the use of anonymized data in the present report, arrived at the emergency department after suddenly losing coordination while walking. The patient mentioned an increase in cough and sputum in the previous days; the patient is a current smoker (35 pack-years) with a history of depression,

alcohol consumption, mild kidney failure, hypertension, and chronic obstructive pulmonary disease requiring long-term oxygen therapy.

Medications included prednisone, pantoprazole, diuretics, and antihypertensive agents. Upon examination, the patient had no fever, but peripheral oxygen saturation (SpO_2) was 83% in ambient air, while blood pressure and cardiac frequency were normal. It was observed that there was swelling in both lower limbs, and auscultation revealed diminished breath sounds over the right lung base. The laboratory tests showed high levels of inflammatory markers, acute renal failure, and hypoxemia. A contrast-enhanced computed tomography (CT) scan revealed massive right pleural effusion with pleural thickening, which is consistent with empyema (Figure 1A, 1B). The patient was given piperacillin/tazobactam (18 g/day), but emergency pleural decortication via video-assisted thoracoscopic surgery was necessary due to the severity of the condition. Two liters of purulent material were drained, and two thoracic drainages were placed to drain any remaining fluid. After a short postoperative stay in the ICU, the patient was transferred to the Respiratory ICU because of persistent refractory hypoxemia. Peripheral oxygen saturation on admission was 89%, and the patient was immediately adapted to nasal high-flow (NHF) therapy with a flow rate of 60 L/min and an initial FiO_2 of 60%. The reported PaO_2 was 40.9 mmHg; therefore, FiO_2 was increased to 85% with a poor response. A trial of non-invasive ventilation showed no improvement in oxygenation, so it was discontinued. Antibiotic therapy was maintained; the inflammatory markers and pleural effusion decreased, and the drainage was removed. The patient's diuretic therapy was increased to 125 mg/day of furosemide due to worsening lung congestion, with an appropriate response to treatment. Despite feeling better and not reporting dyspnea, the patient's respiratory rate remained high at 20-25 breaths per minute with persistent hypoxemia. Atelectasis and mucus retention were present, leading to suspicion that intrapulmonary shunt was the main cause of hypoxemia. Respiratory physiotherapy was initiated, including chest expansion, recruiting exercises with positive airway pressure (15 cmH_2O) (5), and an active cycle of breathing techniques performed in a sitting position (6). Respiratory physiotherapy was performed daily for 30 minutes over 3 days. Despite improvements in lung congestion, the resolution of atelectasis, and the enhancement of secretion clearance, oxygenation did not improve.

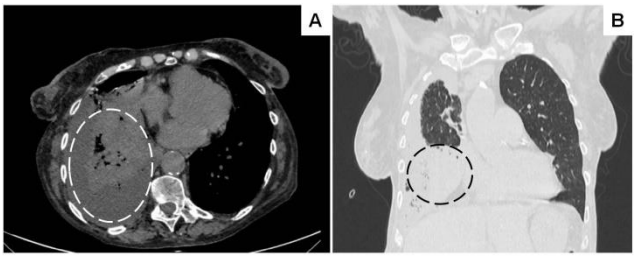

Figure 1. Right empyema (dotted circled area) causing compression of the lung parenchyma. (A) Contrast-enhanced CT scan transverse section, mediastinal window. (B) Contrast-enhanced CT scan, coronal section, lung window

Such a clinical frame led to investigating different causes of hypoxemia other than respiratory. Extensive laboratory analyses revealed an elevation in Methemoglobin (MetHb) levels, rising from 10% upon admission to 25% of total hemoglobin (Hb), and the onset of post-surgical anemia (Hb 9.6 g/dL). After contacting the poison control center, 1 mg/kg (50 mg) of methylene blue was administered, which resulted in a sudden decrease of MetHb to 3% of total Hb. One hour after the infusion, SpO_2 increased to 95% and PaO_2 to 69 mmHg while the patient was on NHF with a FiO_2 of 40%. The patient was diagnosed with congenital methemoglobinemia as there was no evidence of exposure to hemoglobin-oxidizing agents. At discharge, the patient was referred for genetic testing. Figure 2 summarizes the key events during the hospitalization.

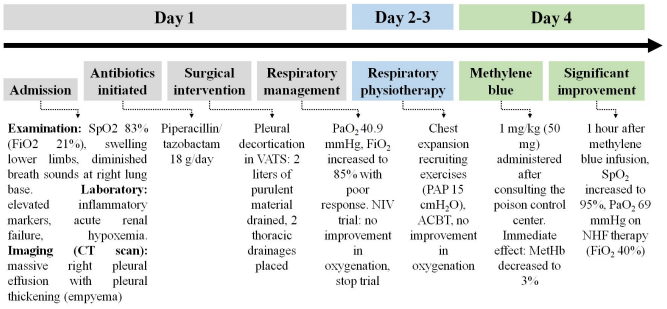

Figure 2. Timeline

FiO_2: fraction of inspired oxygen; CT: computed tomography; VATS: video-assisted thoracic surgery; PaO_2: arterial oxygen partial pressure; NIV: noninvasive ventilation; PAP: positive airway pressure; ACBT: active cycle of breathing techniques; MetHb: methemoglobin; NHF: nasal high-flow

DISCUSSION

The present case emphasizes that commonly used tools for monitoring gas exchange, like SpO_2 and PaO_2, may not always be reliable, especially when dealing with rare conditions such as methemoglobinemia. This can lead to confusion, particularly when multiple coexisting conditions could explain hypoxemia, making it difficult for clinicians to determine an effective management strategy.

Regardless of the cause, patients with methemoglobinemia are often placed into the diagnostic process due to initial discrepancies between blood gas analysis values and pulse oximetric readings, and they are effectively treated with intravenous methylene blue (7,8). In a retrospective study conducted among a cohort of patients exhibiting methemoglobinemia, different causes were described, including nitric oxide, sepsis, smoke inhalation, lidocaine, benzocaine, sulfasalazine, and contaminated food, among others (9).

The literature documents spontaneous recovery from methemoglobinemia after stopping external hemoglobin-oxidizing agents (10). In some instances, treating patients with methylene blue or vitamin C is not necessary; rehydration and supportive therapy can be sufficient. For example, the literature includes cases where, despite the severity of the clinical situation, patients responded well to oxygen therapy and intravenous crystalloid solutions, eliminating the need for antidotes (11). In the present case, however, methylene blue was administered to address the symptoms due to the absence of clinical improvement.

The increase in MetHb levels in hospitalized patients may be caused by various drugs and sepsis (12,13), but a specific causative agent could not be identified. MetHb is a modified version of Hb in which the heme group's iron atom is in the ferric (Fe 3+) state as opposed to the ferrous (Fe 2+) state and is, therefore, unable to bind oxygen. In addition, as Hb is a tetramer, the presence of Fe 3+ in the heme group of one or more tetramers results in allosteric changes that increase the O_2 affinity in the normal non-oxidized tetramers, producing a left shift in the oxygen-hemoglobin saturation curve (14). Therefore, when present, MetHb leads to impaired Hb capabilities of carrying and releasing O_2 to the peripheral tissues (12,15). As Hb is always exposed to oxidizing agents, such as O_2, MetHb is continuously produced. Endogenous oxidizing mechanisms produce MetHb; however, several mechanisms contribute to keeping MetHb levels low. The primary mechanism involves the cytochrome-b_5 reductase enzyme, which converts MetHb to normal Hb. In typically healthy individuals, MetHb makes up less than 1% of total Hb. When there is an imbalance between oxidizing and reducing processes, which may occur due to low activity of reducing enzymes (primary methemoglobinemia) or exposure to oxidizing agents (secondary methemoglobinemia), MetHb levels increase, resulting in methemoglobinemia (12). Chronic methemoglobinemia may cause low SpO_2 refractory to oxygen therapy, simulating a hypoxemic status. SpO_2 and PaO_2 become unreliable and insufficient as MetHb disrupts the pulse oximeter's ability to read the correct SpO_2, and high levels of PaO_2 do not indicate adequate oxygenation due to Hb-impaired O_2 release to peripheral tissues (15).

Detection and prevention of methemoglobinemia require a multimodal strategy. Avoiding identified triggers, such as certain drugs and environmental elements, and safeguarding vulnerable groups, such as newborns and people with G6PD deficiency, are the main goals of preventive efforts. In addition to careful monitoring of oxygen saturation levels, which can be deceptive in cases of methemoglobinemia, and the use of specialist laboratory tests, including co-oximetry, to confirm the diagnosis, detection mostly depends on clinical suspicion. To avoid serious consequences, it is crucial to be aware of the hazards connected with methemoglobinemia, especially in susceptible groups and when administering certain drugs. Particularly in severe cases of methemoglobinemia, early detection and timely care can greatly improve prognosis.

Patients with chronic methemoglobinemia typically develop a compensatory mechanism, namely polycythemia, to prevent hypoxia (16). Cyanosis, which

becomes visible when MetHb levels are higher than 1.5 g/dL, is actually a pseudocyanosis or a non-hypoxic cyanosis (17). Other manifestations include dyspnea, weakness, seizures, and even death. The severity of the disease depends on Hb levels, MetHb percentage of total Hb, and disease progression (15,18,19).

When evaluating a patient with suspected methemoglobinemia, significant symptoms to look for include cyanosis (particularly if pulse oximetry shows no desaturation), shortness of breath, dizziness, lethargy, headache, disorientation, tachycardia, and tachypnea. In severe cases, venous sampling may reveal lethargy and chocolate-brown blood. Recent usage of oxidizing chemicals such as local anesthetics, dapsone, sulfonamides, and nitrites, as well as G6PD deficiency and infancy (especially under six months of age), are also risk factors. During the initial evaluation, pulse oximetry may falsely reflect normal or high oxygen saturation despite hypoxia. If pulse oximetry measurements do not match clinical findings, an arterial blood gas should be performed to determine oxygen saturation and confirm the diagnosis. Early identification of symptoms and risk factors is essential for appropriate diagnosis.

The management of the condition depends on its cause. High MetHb levels in symptomatic individuals can be treated with ascorbic acid or methylene blue. Methylene blue is particularly effective at reducing MetHb by activating NADPH-dehydrogenase (20).

Furthermore, respiratory physiotherapy is not a primary treatment for methemoglobinemia. However, in the present case, it contributed to the improvement of pulmonary congestion and facilitated airway secretion clearance.

The present study has several limitations. Firstly, the findings reported here come from a single case; therefore, extending them to a broader context is impossible. On the other hand, the specificity of the case described here may help to recognize similar conditions in daily clinical practice, facilitating the decision-making process during patient evaluation. Furthermore, another limitation is represented by the absence of a follow-up, as the study was limited to the acute/sub-acute context. In this regard, a more extended observation period would have returned a more robust construct; nevertheless, we are confident that the clinical frame illustrated here can contribute to the early detection of methemoglobinemia in critical settings and increase awareness of such a condition.

As highlighted here, methemoglobinemia could complicate recovery from a critical clinical condition; therefore, additional research areas could be explored to prevent and recognize methemoglobinemia early in patients with refractory hypoxemia.

CONCLUSION

In the present case, the hypoxemia was predominantly caused by increased MetHb values, which were worsened by anemia due to surgical intervention and overhydration. While antibiotic and diuretic therapy effectively treated the underlying infection and right heart failure, resulting in a favorable surgical outcome, the patient's oxygenation remained inadequate. This emphasized the significance of a thorough clinical evaluation, with respiratory physiotherapy playing a vital role in recognizing the lack of significant improvement in oxygenation and, therefore, proving the extrapulmonary cause of the hypoxia.

As previously outlined, the primary respiratory mechanisms behind hypoxemia in patients recovering in the ICU are VA/Q mismatch and intrapulmonary shunt. However, this instance highlights the critical necessity to widen the diagnostic approach to include extrapulmonary variables when treating refractory hypoxemia. Clinicians must stay alert in investigating other potential causes of hypoxemia, particularly when standard treatments for intrapulmonary causes fail to produce good results. Early detection and treatment of extrapulmonary factors can considerably enhance patient outcomes under challenging contexts.

Conflicts of interest

The authors have no conflicts of interest to declare.

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