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Hemodialysis Associated Methemoglobinemia: A Case Report

Hemodiyalize Bağlı Methemoglobinemi: Olgu Sunumu

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Abstract

Aim: Methemoglobinemia develops when ferrous iron (+2) in oxyhemoglobin is oxidized to ferric iron (+3). It can be hereditary or acquired and can develop due to many reasons. Methemoglobin levels between 1-2% in the circulation are considered normal. However, at higher levels, such as acute methemoglobinemia, dyspnea, neurological symptoms, and coma can be observed due to the inability to transport oxygen. This case report describes investigating the etiology of methemoglobinemia in a patient with chronic kidney disease due to hemodialysis.

Case: A 34-year-old male patient with chronic renal failure was admitted to the emergency room with complaints of cyanosis, nausea, and vomiting after routine hemodialysis. The methemoglobin level was determined to be over 5%. The patient did not have any hereditary or acquired disease or history of drug use that would cause methemoglobinemia. However, since rare cases of methemoglobinemia due to chloramine in hemodialysis fluids have been reported in the literature, it was evaluated that the patient's methemoglobinemia was due to dialysis.

Conclusion: Chloramine fluids should be considered the etiological cause in individuals with chronic renal disease who are on dialysis, have no laboratory abnormalities other than high methemoglobin levels, and have no history of inherited or acquired illness or drug use.

Keywords: Methemoglobinemia; chronic kidney disease; hemodialysis; chloramine

Öz

Amaç: Oksihemoglobindeki feröz demir (+2) ferrik demire (+3) oksitlendiğinde methemoglobinemi gelişir. Kalıtsal olabildiği gibi edinsel birçok nedene bağlı olarak gelişebilir. Dolaşımda %1-2 arasındaki methemoglobin seviyeleri normal olarak kabul edilir. Ancak akut methemoglobinemi gibi daha yüksek seviyelerde oksijenin taşınamamasına bağlı olarak, dispne, nörolojik semptomlar ve koma görülebilir. Bu olgu sunumunda hemodiyalize bağlı olarak gelişen kronik böbrek hastalığı olan bir hastada gelişen methemoglobineminin etiyolojisinin araştırılma süreci anlatılmaktadır.

Olgu: Kronik böbrek yetmezliği olan 34 yaşındaki erkek hasta rutin hemodiyaliz sonrası siyanoz, bulantı ve kusma şikayetleri ile acil servise başvurmuş. Yapılan analizlerinde methemoglobin düzeyi %5'in üzerinde saptandı. Hastanın methemoglobinemi oluşmasına yol açacak herhangi bir kalıtsal veya edinsel bir hastalığı ile ilaç kullanım öyküsü yoktu. Ancak literatürde hemodiyaliz sıvılarındaki kloramine bağlı nadir methemoglobinemi vakaları bildirildiğinden hastanın methemoglobinemisinin dialize bağlı olduğu değerlendirilmiştir.

Sonuç: Laboratuvar tetkiklerinde methemoglobin yüksekliği dışında bulgusu olmayan, kalıtsal veya edinsel bir hastalığı ile ilaç kullanım öyküsü bulunmayan, dializ tedavisi gören kronik böbrek hastalarında etiyolojik nedenin kloramin sıvıları olabileceği düşünülmelidir.

Anahtar sözcükler: Methemoglobinemi; kronik böbrek yetmezliği; hemodiyaliz; kloramin

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INTRODUCTION

Hemoglobin is composed of four heme molecules carrying divalent (ferrous) iron and globulin protein. Methemoglobin is formed when ferrous iron (+2) is oxidized to ferric iron (+3). This new molecule has a reduced affinity for oxygen, resulting in the inability to transport oxygen to tissues. This leads to a functional anemia in the body. Methemoglobin levels between 1-2% in circulation are considered acceptable. There are prognostic differences between chronic methemoglobinemia and acute methemoglobinemia due to intoxication. Chronic methemoglobinemia can lead to compensatory erythrocytosis to compensate for the anemia. In this case, only cyanosis that can cause cosmetic concerns may develop, and otherwise, it is asymptomatic. However, in acute methemoglobinemia due to intoxication, compensatory erythrocytosis cannot occur, leading to symptoms such as dyspnea, neurological symptoms, and coma (1).

The mechanisms of methemoglobin formation are reactions related to auto-oxidation, endogenous free radicals, hydrogen peroxide, nitric oxide, hydroxyl radicals, and some exogenous chemical substances (2). The hereditary causes of methemoglobinemia are cytochrome b5 reductase deficiency and hemoglobin M disease. Acquired causes include topical anesthetics (lidocaine, benzocaine), aniline dyes, dapsone, heroin, cocaine, inhaled nitric oxide, rasburicase, and foods, drugs, and additives containing nitrate and nitrite (2).

CASE

Written consent was obtained from the patient that his medical data could be published. A 34-year-old male patient with chronic kidney failure due to renal stone disease referred to the emergency department with nausea, vomiting, and bruising on the body following a hemodialysis session. Except for tachycardia and pulse oximetry, the patient's vital signs were stable. The oxygen saturation was 88 in pulse oximetry. Physical examination revealed icteric sclera and peripheral cyanosis, but no neurological symptoms were observed. No additional pathological features were detected on physical examination and his electrocardiogram showed normal sinus rhythm. An arterial blood gas sample was obtained, which revealed a pH of 7.51, PO_2:96 PCO_2 32.6, lactate 1.4, HCO_3: 17.8, and methemoglobin level is 8.4%. The initial blood sample was considered hemolyzed by the laboratory, and total bilirubin, urea, and transaminase values could not be evaluated due to hemolysis. LDH was 304 mg/dL, and ferritin was 10381 µg/L. The complete blood count showed a WBC: 5600/mm^3, a neutrophil: 4300/mm^3, hemoglobin: 11.6 g/dL, and platelet level: 203,000/mm^3.

Coombs tests could not be evaluated due to hemolysis, and widespread spherocytes were observed on the peripheral blood smear. Heinz body presence could not be demonstrated as Giemsa stain was used for peripheral blood smear. Imaging revealed no pathology except for a few stones in the gallbladder.

The use of medication, administration of such as local anesthesia, acetaminophen, metoclopramide and illegal drug abuse were investigated in the patient's history. He took only antihypertensive medication which was calcium channel blocker. Family history and exposure to well water was also questioned. Additionally, the patient was questioned about occupational exposure to toxic gases. Given the absence of all in the patient's anamnesis and the onset of symptoms following hemodialysis, hemodialysis-related methemoglobinemia was initially considered.

As the patient's methemoglobin level was below 10%, plasma exchange was not planned. Vitamin C, oxygen inhalation, and intravenous hydration were administered. The patient's methemoglobin level was monitored daily, and he was discharged when his methemoglobin level decreased to 1.7%.

DISCUSSION

Methaemoglobinaemia can be inherited or caused by medicines, diet, or harmful substances. Methaemoglobinaemia has two recognized hereditary causes: type 1 and type 2.

Group 1 is associated with a functional deficiency of cytochrome b5 reductase. Patients with this condition have a normal life expectancy and are usually diagnosed at an early age.

There are four reported cases in the literature of individuals diagnosed with type 1 methemoglobinemia after the age of 50 (3). Our patient had no history of previous methemoglobinemia episodes.

Methemoglobinemia can sometimes be seen due to occupational exposure. It can particularly be associated with chronic exposure to copper compounds, nitrogen compounds, and carbon oxychloride. People working in the paint industry, farming, those exposed to exhaust gases, leather tanning, and the construction industry are at risk. (4) Our patient was not employed in a high-risk occupation.

The medications known to cause methemoglobinemia are listed in the table below (Table 1). Our patient was not using any of the medications listed in the table below.

Table 1. The medications known to cause methemoglobinemia.

Analgesics	Acetaminophen, Phenacetin, Celecoxib
Local anesthetics	Benzocaine, Lidocaine, Prilocaine
Antibiotics	Sulfonamides, Nitrofurantoin
Antimalarials	Primaquine, Chloroquine, Sitamaquine
Antineoplastics	Cyclophosphamide, Ifosfamide, Flutamide
Other medications	Nitric oxide, Nitroprusside, silver nitrate, Metoclopramide

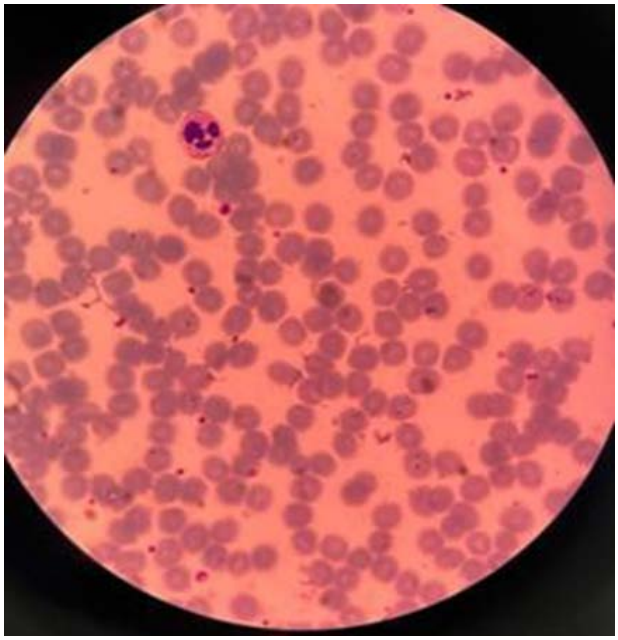
Oxidizing agents like nitrates and nitrites are commonly employed in the food sector to preserve seafood, cheese, and meat. (5) Eating wide beans may also put you at danger. However, the absence of comparable symptoms in other family members rules out this diagnosis for our patient.

Hemolysis associated with hemodialysis is a rare, life-threatening complication. The causes of hemolysis can be presented into three groups: dialysate-related causes (high dialysate temperature, use of hypo-osmolar dialysate, formaldehyde, nitrate, chloramine, glutaraldehyde, sodium hypochlorite, metals such as copper and zinc, nitrite and nitrate-related), hemodialysis equipment-related (use of incorrect-narrow sets, incompatibility between the pump and set, formation of clots in the catheter), or patient-specific causes (hypersplenism, microangiopathy, infections, hypophosphatemia, and inadequate dialysis). In our case's lack of other etiological factors that could cause methemog-lobinemia suggests that the diagnosis is related to hemodialysis induced methemog- lobinemia (6).

Typical symptoms in patients who develop hemolysis include chest pain, shortness of breath, fever, nausea, and vomiting. The appearance of dark red blood in the venous set during hemodialysis should be a warning sign for clinicians (6). The blood smear of patient is shown in the image below (Figure 1).

To decontaminate drinking water, a chemical called chloramine is introduced. Chloramine is removed from the dialysis water in carbon tanks.

Figure 1. The blood smear of patient.



However, if the saturation level of the carbon tanks is exceeded, chloramine cannot be removed and its concentration in the dialysate increases. This can lead to complications such as hemolysis or methemog- lobinemia in patients (6). But in this case, there was no other patient with same conditions referred to us by the patient's hemodialysis center.

Therefore, no sampling could be obtained from dialysis centers for chemical exposure. It is not known if there have been any patient admissions with similar symptoms at nearby centers.

Dark skin color is due to the accumulation of methemoglobin and hemopexin. The patient’s photograph was not included to the article because written consent was not provided.

Haemodialysis should be discontinued right once in this case, and the patient should be constantly watched for hyperkalaemia and respiratory problems. A blood transfusion may also be necessary. Furthermore, in these patients, the arterial blood gas analysis's oxygen saturation and the pulse oximetry's oxygen reading disagree. Calculating the oxygen saturation difference is a quick and inexpensive test used to diagnose methemog-lobinemia.

The difference between oxyhaemoglobin measured by pulse oximetry and oxyhaemoglobin derived by arterial blood gas measurement is known as the oxygen saturation difference.

Standard pulse oximetry calculates the ratio of oxyhaemoglobin to deoxyhaemoglobin by measuring light absorption at 660 and 940 nanometers (nm).

MetHb absorbs light at both wavelengths, upsetting this ratio. Consequently, the saturation value ascertained by pulse oximetry is interpreted as low when MetHb is present (7). Because of the leftward shift of the current oxygen dissociation curve, oxygen intake is advised for these patients even when oxygen saturation in arterial blood gases is normal (8).

When exposed to elevated oxygen concentrations, a drop of blood on filter paper may discolor, which is the basis for the Kronenberg test, a diagnostic technique. If the blood drop does not turn from dark red to light red after being placed on filter paper and exposed to oxygen, it may have a high MetHb value (9). When methaemoglobinemia is suspected, the Evelyn-Malloy test is frequently utilized as a confirmatory test. Cyanide is introduced in this process in order to bind the positively charged MetHb. This binding makes it possible to quantify MetHb as a percentage of the overall hemoglobin concentration by removing absorption at 630 to 635 nm in direct proportion to the quantity of MetHb (9). These tests did not confirm the diagnosis in our investigation. This is among the study's drawbacks.

Two instances of methaemoglobinemia brought on by chloramine poisoning during hemodialysis were documented in 2002. Methaemoglobin levels in these situations range from 4.4% to 6.4%. When methaemoglobin levels are more than 10%, 1-2 mg/kg of 1% methylene blue should be administered intravenously (10). Eight cases were examined in a single center on the day the chlorine was added to the water supply in the research by Iñiguez et al. (2023). Methaemoglobinemia levels in these individuals ranged from 1.3% to 7.9% (11). Two patients in the case described by Medarov et al. (2017) developed methaemoglobinemia while receiving dialysis in the intensive care unit using a portable hemodialyzer.

When chloramine-induced methaemoglobinemia was detected in these cases, the issue was resolved by equipping portable dialysis machines with bigger capacity carbon filters (12). Furthermore, there have been documented instances of methaemoglobinemia in individuals with chronic renal failure linked to the administration of prilocaine and dapsone (13,14) There are, however, very few research on other causes of methaemoglobinemia in individuals receiving regular dialysis.

Ascorbic acid administered intravenously (IV) at a rate of 100 mg/kg/day was used to treat our patient's hemoglobinemia. The cause of methaemoglobinemia could not be identified since the patient was engaged in a hemodialysis program outside of our facility.

CONCLUSION

Internal medicine professionals, on the other hand, should take into account local anaesthesia usage, viral diseases, and glucose-6-phosphate dehydrogenase insufficiency while making a differential diagnosis of these individuals.

Author Contribution

Written consent was obtained from the patient that his medical data could be published.

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The authors approved the final version of the manuscript.

The authors declared that this manuscript has not been published before and is not currently being considered for publication elsewhere.

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