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RARE CASES OF METHEMOGLOBINEMIA IN CANCER PATIENTS: CLINICAL CASES

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ABSTRACT

Relevance: *Methemoglobinemia is a serious disease characterized by impaired oxygen binding to iron in hemoglobin, followed by impaired oxygen delivery to body tissues. Various drugs, including antacids containing benzocaine, can cause acquired methemoglobinemia. The presented clinical cases describe methemoglobinemia that arose in connection with the use of the antacid Almagel A in a 32-year-old woman who underwent surgery on the laryngopharynx, suffering from T3NxM0 St III hypopharyngeal cancer and in a 45-year-old woman diagnosed with cancer of the left kidney St I. Condition after resection of the left kidneys.*

The study aimed to *describe clinical cases of acquired methemoglobinemia induced by Almagel A (antacid), widely used in post-antitumor therapy treatment of cancer patients with digestive system diseases.*

Methods: *We present clinical cases of methemoglobinemia in patients (32 and 45 years old) hospitalized at JSC "Kazakh Research Institute of Oncology and Radiology." Complaints, anamnesis of the disease, clinical picture, and clinical, laboratory, and instrumental test results were analyzed retrospectively.*

Results: *This article reports on the clinical picture of our patients, discusses the causes and mechanisms of possible poisoning, and reviews the latest recommendations for the treatment of methemoglobinemia. Treatment with intravenous methylene blue led to a rapid improvement in the patient's respiratory status.*

Conclusion: *Acquired methemoglobinemia is an acute condition that most often results from poisoning with certain drugs and compounds, which can be fatal. These clinical cases demonstrate the difficulties of diagnosing methemoglobinemia, highlight the value of taking anamnestic data, studying the acid-base state and blood gases, and the effectiveness of using methylene blue as an antidote drug in treatment.*

Keywords: *Methemoglobinemia, methylene blue, hypoxia, cyanosis, acrocyanosis.*

Introduction: Methemoglobinemia is a rare disease characterized by elevated levels of methemoglobin (MetHb), a hemoglobin (Hb) molecule containing an oxidized form of iron that cannot bind oxygen and leads to an insufficient supply of tissues by oxygen. Methemoglobinemia has two forms – genetic and acquired [1].

Genetic methemoglobinemia is a chronic disease that leads to numerous complications, and patients present cyanosis without other accompanying symptoms. On the other hand, an acquired methemoglobinemia is an acute condition most commonly due to poisoning after intake of certain drugs and compounds, which can lead to a fatal outcome [2].

The manifestation of symptoms depends on the percentage of MetHb in blood, and the clinical picture varies from fatigue, anxiety, dizziness, and cyanosis to qualitative disorders of consciousness, epileptic seizures, arrhythmia, and coma. Unexplained symptoms of refractory hypoxia, cyanosis-saturation, and chocolate-colored blood may raise suspicion of methemoglobinemia, but a definitive diagnosis is made by Co-oximetry and determination of MetHb levels in the blood. Treatment of methemoglobinemia is based on supportive care and withdrawal of the drug or substance that caused that condition. Although acquired methemoglobinemia is a rare disease, it can be a life-threatening condition, so emergency services should be provided with antidotes such as methylene blue and vitamin C [3].

The study aimed to describe clinical cases of acquired methemoglobinemia induced by Almagel A (antacid), widely used in post-antitumor therapy treatment of cancer patients with digestive system diseases.

Materials and Methods: The paper presents clinical cases of methemoglobinemia in patients (32 and 45 years old) who underwent inpatient treatment at "Kazakh Institute of Oncology and Radiology" JSC. Registered complaints, medical history, clinical picture, and clinical, laboratory, and instrumental test results were analyzed retrospectively. The PubMed Electronic Database (NCBI) was searched to identify the randomized controlled and prospective observational studies, systematic reviews and meta-analyses, and the scientific articles published in English in 2015-2023.

Description of the clinical case No. 1

Patient information: Female A., born in 1975, diagnosed with "Left kidney cancer, stage I," 6 days after planned left kidney resection.

Anamnesis: The patient mentioned she was taking Almagel A containing benzocaine at 1 dosing spoon TID, which could cause an increase in MetHb levels.

Clinical findings:

During the initial examination at the Urologic Oncology Department, the patient complained of acute malaise, dizziness, headache, and cyanosis of the nasolabial triangle, fingers, and toes, which appeared at night on the 6th day after surgery.

Diagnostics:

Normal consciousness, adequate, easy to contact. The patient maintained normal blood pressure (BP – 134/88 mm Hg) and heart rate (heart rate – 74/min); normothermia (T – 36.5°C), but tachypnea and hypoxia (SpO_2 – 78%) were observed. Over the lungs, the respiration is vesicular, with no pulmonary rales.

For severe conditions, the patient was transferred to the Anesthesiology, Resuscitation, and Intensive Care Department of "Kazakh Institute of Oncology and Radiology" JSC to determine the causes of respiratory failure and acute hypoxia, perform clinical, laboratory, and instrumental tests, and provide intensive care.

Chest CT scan: no pathology. Spirometry: VC – 82%, within the conditional norm. On the ECG: sinus rhythm, heart rate – 78 beats per minute. QRS axis – not deviated. Incomplete RBBB. Impaired repolarization processes along the anterior wall of the left ventricle. Echocardiogram: EF – 75%. The heart cavities were not dilated, with no areas of hypokinesis; the heart LV contractility and EF LV function were satisfactory.

Laboratory parameters: General and biochemical blood count and coagulogram were normal. The test for D-dimer, an active thrombosis marker, showed 217 ng/ml, a norm. Procalcitonin, the earliest and most reliable "blood inflammation" (sepsis) indicator, was normal at 0.1 ng/ml.

The arterial blood sample was dark brown. Analysis of arterial blood gases (acid-base balance) at normal room air showed pH – 7.44, normal partial pressure of oxygen (pO_2 – 212), normal oxygen saturation (SO_2 – 97.4%), MetHb fraction elevation to 24.4%, and oxyhemoglobin fraction A decline (FO_2Hb – 74.1%).

A clear correlation between the appearance of cyanosis of the nasolabial triangle, fingers, and toes with the intake of Almagel A, the signs of respiratory failure (RR – 20 per minute), acute hypoxia (SpO_2 level – 78%), and FMetHb high level (24.4%) revealed during physical examination made it possible to establish the diagnosis of Acute acquired methemoglobinemia of moderate severity.

Treatment:

The prescribed antidote therapy included the 1% methylene blue infusion at a dose of 1 mg/kg IV, oxygen therapy, and the monitoring of MetHb, SpO_2, and skin color.

Results: Against the infusion of methylene blue, the patient's lips, fingers, and toes turned pink, the headache stopped, and SpO_2 elevated to 96%. There was a gradual decrease of the MetHb fraction of FMetHb to 14.3%, then to normal FMetHb values of 3.0%. The oxyhemoglobin content (FO_2Hb) increased to 93.6%.

The patient with positive dynamics was transferred to a specialized department.

Description of the clinical case No. 2

Patient information: Patient B., born in 1991, was diagnosed with "Laryngeal cancer T3NxM0, stage III. Status after chemotherapy. Progression. Esophagopharyngotracheostoma" on Day 11 after the planned surgery in the scope of "Laryngopharyngoectomy with esophageal-pharynx-tracheostomy, with IJV ligation on the left side, and leftward hemithyroidectomy."

It was also known from the patient's history that the antacid drug Almagel A, containing benzocaine, had been taken uncontrollably for several days, which could have caused the MetHb elevation.

Clinical findings:

Upon examination in the department of head and neck tumors, the patient had the following symptoms: weakness, pronounced dyspnea, and cyanosis of the nasolabial triangle, lips, fingers, and toes.

The patient is hyposthenic, available for contact, hypotension (BP 90/60 mm Hg), tachycardia (heart rate – 102/min), tachypnea (RR – 22/min), and hypoxia (SpO_2 – 74%). Auscultatively: vesicular respiration over the lungs, no rales. The patient was transferred to the Anesthesiology, Resuscitation, and Intensive Care Department of "Kazakh Institute of Oncology and Radiology" JSC" to determine the causes of respiratory failure and acute hypoxia, perform clinical, laboratory, and instrumental tests, and provide intensive care.

Diagnostics:

The complete blood count and blood biochemistry, electrocardiogram, plain chest X-ray, ultrasound examinations of the heart and blood vessels, veins of the lower extremities, abdominal organs and kidneys, computed tomography of the chest cavity with contrast-enhanced, and doctor counseling excluded acute coronary syndrome, pulmonary embolism, respiratory obstruction, and acute surgical pathology.

The analysis of arterial blood gases (acid-base balance) at normal room air showed the following: pH – 7.47, normal partial pressure of oxygen (pO_2 – 85.5), normal oxygen saturation (SO_2 – 95.4%), elevation of the level of MetHb fraction (FMetHb – 49.3%), decline of oxyhemoglobin fraction (FO_2Hb – 47.8%), dark-brown color of the blood sample was noted.

Visible signs: cyanosis of the nasolabial triangle, lips, fingers, and toes revealed signs of respiratory failure (RR – 22 beats/min), acute hypoxia (SpO_2 – 74%), and high level of FMetHb (49.3%), as well as anamnestic data on the use of Almagel A, made it possible to establish the diagnosis: Acute acquired methemoglobinemia of moderate severity.

Treatment:

The patient was prescribed antidote therapy with 1% methylene blue at 1 mg/kg as an infusion, oxygen therapy, MetHb, SpO2, and skin color monitoring.

Results: Over time, against a positive effect of methylene blue infusion, the patient showed clinical improvement with the disappearance of cyanosis, the MetHb level returned to normal value (FMetHb – 1.8%), and the oxyhemoglobin fraction increased (FO_2Hb – 93.8%). The patient with positive dynamics was transferred to a specialized department.

Discussion: Methemoglobinemia is characterized by ferrous iron oxidation from divalent to trivalent form in a Hb molecule. Oxygen can bind with Hb only in the divalent (glandular) form, and as a result of binding, oxygen is temporarily oxidized to the trivalent form. The various substances listed below can lead to the state when Hb will remain permanently in the trivalent form and thus no longer be able to bind the oxygen. Consequently, the symptoms of methemoglobinemia directly result from inadequate oxygen transportation.

The specific mechanism is the Hb molecule allosteric change. Besides, due to further changes in the oxygen-hemoglobin dissociation curve (change in oxygen dissociation to the left), peripheral oxygen excretion, hypoxia, and functional anemia are reduced without a Hb level decline [1-4].

The Medline search revealed 71 cases of benzocaine-induced methemoglobinemia. The review of the listed links revealed 18 additional case reports. The earliest publication about benzocaine-induced methemoglobinemia was made by Ocklitz in 1949. He reported methemoglobinemia in two children treated with benzocaine powder sprayed into the mouth for symptomatic relief of stomatitis [5].

Benzocaine (ethylamine benzoate) is widely used as a local anesthetic and recognized as a cause of methemoglobinemia. Although this complication is uncommon, it can be potentially serious and even fatal. However, methemoglobinemia is not listed as a complication in the instructions for use or in the package inserts for some benzocaine-containing products. Benzocaine is also found in various over-the-counter medications (such as Almagel A), and methemoglobinemia can occur in case of their use. This can present a challenging diagnostic problem if the physician is not aware of the effect of benzocaine, resulting in a delay in establishing the correct diagnosis and initiating appropriate treatment [5].

Various common medications can lead to the development of methemoglobinemia (Table 1).

Table 1 – Drugs and substances that can lead to methemoglobinemia

Drug group	Represented by
Local anesthetics	Benzocaine (often used in endoscopic procedures) Prilocaine, tetracaine, lidocaine
Nitrates	Nitroglycerin Inhaled nitrogen oxide Nitroprusside, oral nitrates, amyl nitrate
Antibiotics	Dapsone Rifampicin, sulfonamides, antimalarials
Other drugs	Rasburicase (especially in G6PD deficiency) Oncology drugs: cyclophosphamide Metoclopramide Various preparations that use an oxidizing substance in their production
Environmental causes	Fertilizers, herbicides Plastics (various kinds) Paints & Rubber

The clinical picture of methemoglobinemia is diverse and depends on the percentage of methemoglobin, the patient's usual Hb level, and cardiovascular reserve. The normal percentage of MetHb is below 25%. Patients with levels between 3% to 15% are usually asymptomatic, and cyanosis is rare. Patients with a 20-30% MetHb fraction are always symptomatic, with mild symptoms such as fatigue, tachypnea, dyspnea, tach-

ycardia, anxiety, dizziness, qualitative disturbance of consciousness, nausea, and vomiting. When the MetHb level is above 40%, such serious and life-threatening symptoms as epileptic seizures, coma, arrhythmias, and elevated lactate levels, to the extent of death, are observed (Table 2) [1, 3].

Table 2 – Signs, symptoms, and causes of methemoglobinemia

MetHb level	Clinical indicators	Symptoms	Causes
<10%	Low pulse oximeter readings, skin discolora-tion (pale, gray, bluish)	Asymptomatic	Acquired
10%-30%	Cyanosis, dark-brown blood	Asymptomatic course / confused consciousness	Enzymopenic methemoglo-binemia, M-group variants of Hb acquired
30%-50%	Dyspnea, dizziness, faintness	Confused consciousness, chest pain, palpitations, headache, fatigability	Acquired, hereditary
50%-70%	Tachypnea, metabolic acidosis, arrhythmias, convulsions, delirium, coma	Confused consciousness, chest pain, palpitations, headache, fatigability	Acquired, hereditary
>70%	Severe hypoxemia, fatal outcome	-	Acquired, hereditary

The diagnosis of methemoglobinemia is confirmed by arterial or venous blood gas composition with Co-oximetry that determines the Hb for identification of concentration and percentage of methemoglobin; SpO_2 measurements cannot be used to directly determine the methemoglobinemia severity. However, the clinical suspicion itself can be made based on the following three objects [1, 2, 5]:

– Refractory hypoxia: methemoglobinemia can usually be suspected in a patient with an oxygen saturation of 82% to 86%, who is on high oxygen flow (FiO_2 100%), and there is no other explanation of hypoxia [5].

– "Cyanosis-saturated rupture": methemoglobinemia leads to central cyanosis (attention to the tongue's color). Oxygen saturation of 80-90% usually does not lead to cyanosis. Hence, methemoglobinemia is clinically suspected in patients with 80-90% saturation with central cyanosis [5].

– The brown color of blood: methemoglobinemia causes the blood color to change to chocolate. In addition, if the patient's blood is placed on white gauze, the blood will remain brown when it dries, unlike the deoxygenated blood, which will absorb the oxygen from the air and turn red again [5].

Treatment of methemoglobinemia involves the removal of the provoking agent and consideration of treatment with the antidote methylene blue (tetramethylthionine chloride). The high-velocity oxygen delivered through nasal cannulas or masks increases the oxygen delivery to tissues and enhances the natural degradation of MetHb [1, 3].

The methylene blue generally works quickly and efficiently due to its interaction with the aforementioned secondary MetHb recovery pathway, where NADPH-MetHb reductase reduces the methylene blue to leucomethylene blue using NADPH from G6PD-dependent hexose-monophosphate shunt. Subsequently, the leucomethylene blue acts as an electron donor, recovering the MetHb to Hb [1, 3, 5].

In cases of acquired methemoglobinemia, treatment with methylene blue should be given when MetHb levels are greater than 20-30% or lower if the patient has symptoms. Treatment decisions should be made based on clinical manifestations rather than delayed until confirmed laboratory findings. The dose of methylene blue is 1-2 mg/kg (0.1-0.2 ml/kg of 1% solution) intravenously for 5 minutes. The dose may be repeated after 30-60 minutes if significant symptoms or levels remain above the treatment threshold [1, 2, 5].

Practitioners should be aware of the side effects of methylene blue. Benign side effects include staining the urine to a green or blue, which patients should be alerted about. Caution should also be followed in treating newborns, as they are also very sensitive to oxidants. Besides, methylene blue is contraindicated for pregnant women [1].

When treatment with methylene blue is ineffective or not recommended, additional options may include ascorbic acid, substitution transfusion, and hyperbaric oxygen therapy [2, 4, 5]. High doses of ascorbic acid (vitamin C), up to 10 g/dose intravenously, may be considered for treating MetHb. However, it is generally ineffective and not considered the standard of treatment. High doses of ascorbic acid are associated with increased urinary excretion of oxalates. In the presence of renal insufficiency, high doses of ascorbic acid may predispose to renal failure due to hyperoxaluria [4].

Conclusion: Acquired methemoglobinemia is an acute condition that is most often the result of poisoning with some drugs and compounds and can lead to

a fatal outcome. The described cases could be unique since both patients presented tachycardia, tachypnea, and hypoxemia, with no other common manifestations. The only clinical symptom reported by both patients was general tiredness.

However, measurements of PaO_2, SpO_2, and MetHb concentrations indicated that both patients suffered from methemoglobinemia caused by benzocaine, a component of Almagel A.

Many patients and practitioners assume that over-the-counter medications (Almagel A) pose no risk. The presented clinical cases of acquired methemoglobinemia in cancer patients show that using the antacid drug Almagel A against the background of antitumor treatment for a long time without medical supervision leads to serious complications. These clinical cases demonstrate the complexity of diagnostics of methemoglobinemia and highlight the value of the anamnestic data collection, acid-base and blood gas studies, and the efficacy of methylene blue as an antidote for treating methemoglobinemia.

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АНДАТПА

ҚАТЕРЛІ ІСІКПЕН АУЫРАТЫН НАУҚАСТАРДАҒЫ МЕТЕМОГЛОБИНЕМИЯНЫҢ СИРЕК КЕЗДЕСЕТІН ЖАҒДАЙЛАРЫ: КЛИНИКАЛЫҚ ЖАҒДАЙЛАР

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Өзектілігі: *Метемоглобинемия – гемоглобиндегі оттегінің темірмен байланысуының бұзылуымен, одан кейін дене тіндеріне оттегінің жеткізілуінің бұзылуымен сипатталатын ауыр ауру. Әртүрлі препараттар, соның ішінде бензокаин бар антацидтер жүре пайда болған метгемоглобинемияны тудыруы мүмкін. Ұсынылған клиникалық жағдайлар жұтқыншақ ісігімен ауыратын, көмейге операция жасалған 32 жастағы әйелде және сол бүйректің қатерлі ісігімен диагнозы қойылған 45 жастағы әйелде сол бүйрек резекциясынан кейінгі Алмагель А антацидті препаратын қолданумен байланысты метгемоглобинемияны сипаттайды.*

Зерттеудің мақсаты *– Ісікке қарсы терапиядан кейін ас қорыту жүйесінің аурулары бар қатерлі ісікпен ауыратын науқастарды емдеуде кеңінен қолданылатын Алмагель А (антацид) индукцияланған метгемоглобинемияның клиникалық жағдайлын сипаттау.*

Әдістері: *Біз «Қазақ онкология және радиология ғылыми-зерттеу институты» АҚ ауруханасына жатқызылған науқастарда (32 және 45 жаста) метгемоглобинемияның клиникалық жағдайларын ұсынамыз. Шағымдар, ауру анамнезі, клиникалық көрінісі, клиникалық, зертханалық және аспаптық зерттеу әдістерінің нәтижелері ретроспективті түрде талданды.*

Нәтижелері: *Бұл мақалада науқастарымыздың клиникалық көрінісі туралы баяндалады, ықтимал уланудың себептері мен механизмдері талқыланады және метгемоглобинемияны емдеуге арналған соңғы ұсыныстар қарастырылады. Көктамырішілік метилен көкпен емдеу науқастың тыныс алу жағдайының жылдам жақсаруына әкелді.*

Қорытынды: *Жүре пайда болған метгемоглобинемия – бұл көбінесе өлімге әкелуі мүмкін белгілі бір препараттармен және қосылыстармен уланудан туындайтын өткір жағдай. Бұл клиникалық жағдайлар метгемоглобинемияны диагностикалаудың қиындықтарын көрсетеді, анамнестикалық мәліметтерді алудың, қышқылдық-негіздік күйді және қан газдарын зерттеудің маңыздылығын, сонымен қатар емдеуде метилен көкін антидот ретінде қолданудың тиімділігін көрсетеді.*

Түйінді сөздер: *Метгемоглобинемия, метилен көк, гипоксия, цианоз, акроцианоз.*

АННОТАЦИЯ

РЕДКИЕ СЛУЧАИ МЕТГЕМОГЛОБИНЕМИИ У ОНКОЛОГИЧЕСКИХ ПАЦИЕНТОВ: КЛИНИЧЕСКИЕ СЛУЧАИ

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Актуальность: *Метгемоглобинемия представляет собой серьезное заболевание, характеризующееся нарушением связывания кислорода с железом в гемоглобине с последующим нарушением доставки кислорода к тканям организма. Различные препараты, включая антацидные средства, содержащие в составе бензокаин, могут вызывать приобретенную метгемоглобинемию. Представленные клинические случаи описывают метгемоглобинемию, которая возникла в связи с использованием антацидного средства Алмагель А у 32-летней женщины, перенесшей операцию на гортаноглотке, страдающей раком гортаноглотки T3NxM0 St III и у 45 летней женщины с диагнозом рак левой почки St I. Состояние после резекции левой почки.*

Цель публикации *– описать клинические случаи приобретенной метгемоглобинемии, индуцированной Алмагелем А – антацидным средством, которое широко используется в лечении онкологических больных с заболеваниями органов пищеварения после проведения противоопухолевой терапии.*

Методы: *Представлены клинические случаи метгемоглобинемии у пациентов (32 и 45 лет), находившихся на стационарном лечении в АО «Казахский научно-исследовательский институт онкологии и радиологии». Проанализированы ретроспективно жалобы, анамнез болезни, клиническая картина, результаты клинико-лабораторных и инструментальных методов исследований.*

Результаты: *В данной статье описана клиническая картина у пациентов с метгемоглобинемией, обсуждаются причины и механизмы возможного отравления, а также рассматриваются последние рекомендации по лечению метгемоглобинемии. Лечение внутривенным введением метиленового синего привело к быстрому улучшению респираторного статуса пациента.*

Заключение: *Приобретенная метгемоглобинемия, представляет собой острое состояние, которое чаще всего является результатом отравления некоторыми лекарствами и соединениями и может привести к летальному исходу. Представленные клинические случаи демонстрируют сложность диагностики метгемоглобинемии, подчеркивают ценность сбора анамнестических данных, исследования кислотно-основного состояния и газов крови, а также эффективность использования метиленового синего в качестве антидотного препарата при лечении метгемоглобинемии.*

Ключевые слова: *Метгемоглобинемия, метиленовый синий, гипоксия, цианоз, акроцианоз.*

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