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Case Report

Plasmapheresis in severe methemoglobinemia following occupational exposure

Wassim Shatila[a], Amanda Verma[b], Soheir Adam[b,*]

[a] Department of Medicine, Baylor College of Medicine, Texas Heart Institute, United States
[b] Department of Medicine, Duke University Medical Center, United States

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ABSTRACT

Ferrous iron can be converted to ferric iron by oxidative stress which results in the formation of methemoglobin. Consequently, the oxygen dissociation curve is shifted to the left, which leads to tissue hypoxia and ultimately may cause death. Acquired methemoglobinemia can be due to a host of offending agents and chemicals including nitrites, local anesthetics, aniline and antimalarial drugs.

There are several approaches to the management of methemoglobinemia. The first step is to stop the offending agent and initiate supportive measures. Methylene blue can be used successfully provided the patient has no evidence of glucose 6 phosphate deficiency. Hyperbaric oxygen and intravenous ascorbic acid are other treatment options.

We present a case of unusually severe methemoglobinemia (82% methemoglobin) secondary to occupational exposure that failed to respond to several lines of management including methylene blue, red cell exchange, intravenous ascorbic acid, and hyperbaric oxygen. However, the patient responded swiftly to plasmapheresis started upon suspicion of concomitant thrombotic thrombocytopenic purpura, and he subsequently recovered completely.

Thus, plasmapheresis may have a role in severe methemoglonbinemia unresponsive to standard treatment options.

1. Introduction

Routinely used in industry, aromatic compounds are volatile and lipophilic which makes them a potential occupational hazard. There have been reports of aromatic compound-induced methemoglobinemia, hemolytic anemia, liver failure, and renal failure. There are only a few cases in the literature describing such toxicity and most are reported outside the United States. Here, we report a case of severe methemoglobinemia with multi organ failure in a male patient secondary to occupational exposure to aromatic compounds.

2. Case presentation

A previously healthy young male presented to an outside hospital emergency department two hours after onset of headache, nausea, fatigue, left sided body pain and weakness, and notable change in skin color. In the emergency department there, the patient's vital signs showed an oxygen saturation of 83% on room air, heart rate of 115, respiratory rate of 20, and blood pressure of 153/85. Arterial blood gas showed pH 7.407, pCO2 43.2 mmHg, pO2 26.7 mmHg, and arterial methemoglobin level of 70.4%. He was given methylene blue 70 mg twice without significant improvement in the methemoglobin levels. Patient was thus transferred to Duke University Medical Center and admitted to the medical intensive care unit for further care. On physical examination, the patient had pale mucous membranes, dusky skin, cyanotic tongue, and cyanotic, cool extremities. The methemoglobin level continued to rise despite an additional 70 mg of intravenous methylene blue, peaking at 82.3% following the third dose. The patient then underwent hyperbaric oxygen therapy for 4 h, following two additional doses of methylene blue (70 mg, 80 mg) and 1 g of ascorbic acid. He developed sinus tachycardia with a heart rate of 150, diaphoresis, altered mental status, and shortness of breath with increased oxygen requirement, requiring supplemental oxygen. The hematology team was consulted and upon review of his blood film, there were remarkable red cell changes with the presence of a large number of bite cells and contracted hemoglobin, consistent with methemoglobin-induced hemolysis (Fig. 1). The

* Corresponding author at: Department of Medicine, Duke University Medical Center, Durham, NC 27710, United States.
E-mail address: soheir.adam@duke.edu (S. Adam).

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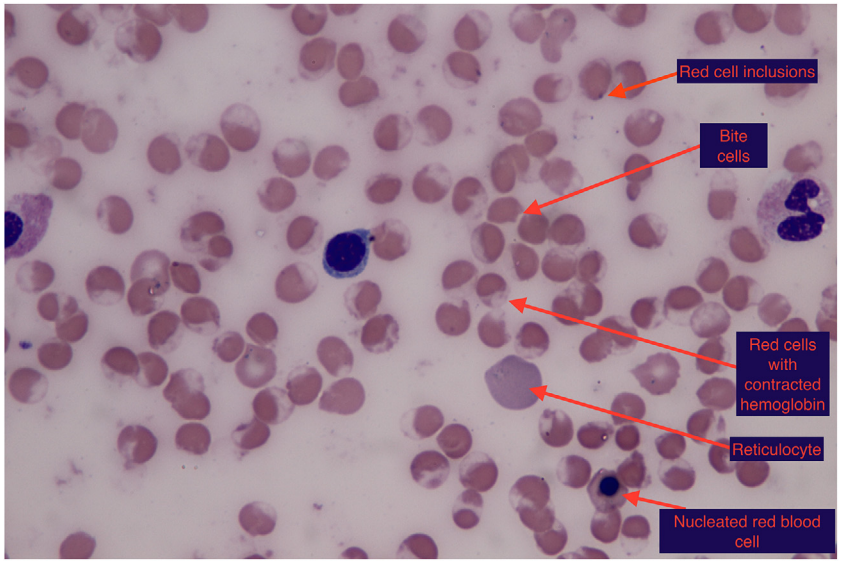

Fig. 1. Peripheral blood film on day 2 of admission showing numerous red cells with contracted hemoglobin, bite cells, polychromatic calls and nucleated red cells.

patient underwent red cell exchange on day 1 of admission, and he received a total of 3543 ml of packed red blood cells (PRBCs). G6PD assay performed was 20.8 units/gram hemoglobin (normal range 7.0–20.5 units/gram hemoglobin) and was interpreted as normal. While reticulocytosis associated with hemolysis may result in a false negative test result, the patient denied any past history of G6PD-associated symptoms. Investigation for high affinity hemoglobins like hemoglobin M was negative. Computed tomography (CT) imaging of his brain and electroencephalography (EEG) were also performed and were unrevealing. The patient was thoroughly scrubbed and bathed to remove any possible contaminants on the skin.

On the second day of admission, the patient's clinical status continued to deteriorate with only a modest reduction in methemoglobin levels. He then developed evidence of thrombotic thrombocytopenic purpura (TTP), based on a picture of microangiopathic hemolysis in the peripheral blood smear, elevated lactate dehydrogenase (LDH), thrombocytopenia and oliguria. While it was not clear whether the patient's altered mental status was a manifestation of TTP or a sequel of methemglobinemia, a high index of clinical suspicion was maintained and plasmapheresis was initiated. On the first day, a volume of 5434 ml fresh frozen plasma (FFP) was used for the exchange, followed by 3735 ml, 5000 ml, 3800 ml, 3554 ml and 3675 ml on 6 consecutive days. Of note, upon separation of blood during plasmapheresis, the plasma was chocolate colored (Fig. 2). The methemoglobin level subsequently dropped with a corresponding improvement in oxygen saturation (Fig. 3). On day six of plasmapheresis, methemoglobin level normalized, and the patient was transferred to the floor.

Hemodialysis was started to manage volume status as he became oliguric and his renal functions deteriorated. He continued to require hemodialysis at the time of discharge on day 18 of hospitalization. However, his renal function normalized, and dialysis was discontinued approximately five months from the date of presentation. He also required packed red blood cell transfusions in addition to the exchange transfusion. He continued to have mild hemolysis requiring transfusion, which resolved gradually.

Upon further inquiry into his chemical exposure history, we learned that the patient worked with nitrobenzene, aniline, sulfuric acid, and other catalysts. He reported an exposure to a benzene spill approximately 15 h prior to the onset of symptoms. The patient was wearing protective clothing at the time of the spill.

Further investigation by poison control showed a significant occupational exposure to aminophenol, a compound related to aniline, which was thought to be the underlying cause of methemoglobinemia.

3. Discussion

The iron moiety in hemoglobin exists in the "ferrous" state and undergoes oxidization to the "ferric" state forming methemoglobin at a rate of ~3% per day [1]. The body has multiple different pathways to reduce the ferric moiety back to its ferrous state to keep the methemoglobin level less than 1% of the total body hemoglobin. The main mechanism by which this is accomplished is through the cytochrome b reductase pathway [1]. Another reduction pathway involves the NADPH methemoglobin reductase pathway which requires an electron donor.

Methemoglobin interferes with oxygen delivery to the tissues by two different mechanisms. First, it has limited capacity to bind oxygen thus reducing the oxygen carrying capacity of red blood cells [2]. Secondly, it alters the structure of hemoglobin, increasing oxygen affinity of the unaffected heme molecules and reducing oxygen release to tissues.

Methemoglobinemia can either be congenital or acquired. Congenital methemoglobinemia may be caused by structurally-abnormal hemoglobins like hemoglobin M, or due to metabolic abnormalities caused by deficiencies in either G6PD, pyruvate kinase or erythrocyte methemoglobin reductase [3]. G6PD is more common in individuals of African or Mediterranean descent and thus was initially pursued as possible etiology in our patient. Acquired methemoglobinemia can be caused by oxidizing agents such as anesthetics, antibiotics like dapsone, or analgesics like phenazopyridine [3]. These compounds can overwhelm the body's natural reduction mechanisms resulting in signs and symptoms of methemoglobinemia.

A common cause of methemoglobinemia also includes occupational exposure to aromatic amino and nitrogen-containing compounds such as nitrobenzene and aniline, as shown in a recent review [4], from China on 1240 cases of acute aromatic amino and nitro compound poisoning. Methemoglobinemia was reported in a total of 1146 cases, and poisoning was caused by occupational exposure in 939 cases. Other clinical manifestations included

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