Black Urine and Methemoglobinemia in the Setting of Sepsis Due to Clostridium Perfringens

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ABSTRACT: Clostridium Perfringens is an anaerobic gram-positive bacillus able to produce different types of toxins and can cause septicemia. The mechanism is through translocation from a previously colonized gastrointestinal or genital tract. Massive intravascular hemolysis induced by this bacterium is a rare presentation reported in only 7% to 15% of cases of Clostridium Perfringens bacteremia with a mortality rate reaching 90%.We present the case of a middle-aged man with metastatic melanoma having black-colored urine as the first sign of massive hemolysis along with mild methemoglobinemia. Despite timely management, the patient progressed into septic shock with severe hypoxia and passed away. Postmortem, blood cultures grew clostridium perfringens. Black-colored urine and blood samples, sepsis-induced mild methemoglobinemia and acute massive hemolysis should raise concern for Clostridium Perfringens sepsis in the appropriate clinical settings.

KEYWORDS: Clostridium Perfringens, hemolysis, methemoglobinemia, melanoma, immunocompromised host

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Background

Clostridium Perfringens (C. Perfringens) is an anaerobic gram-positive bacillus that can be present in the human gastrointestinal and genital tracts.[1] C. Perfringens septicemia most commonly occurs in patients who are immunocompromised. There are 5 biotypes of C. Perfringens, based on the type of toxin that is produced: type A, B, C, D, and E.[2] Alpha toxin, which is produced by all C. Perfringens types, is responsible for gas gangrene and myonecrosis in infected tissues; this toxin also possesses hemolytic activity by functioning as an enzyme that splits lecithin into phosphocholine and diglyceride, leading to the development of spherocytosis and interference with the functional integrity of the red blood cell (RBC) membrane and resulting in anemia, jaundice, and in rare cases, massive hemolysis.[3,4] This causes impairment in the oxygen transport function of the red blood cell (RBC), and subsequent death from tissue hypoxia.[5]

Massive intravascular hemolysis is a rare but described complication of C. Perfringens septicemia.[1] The disease can be deceptive as patients may not appear to be severely ill, and may be hemodynamically stable, yet decompensate very quickly. Without early detection, source control, and antibiotics administration, the course of C. Perfringens septicemia can be rapidly fatal.[1,3,4]

We present a case of an unfortunate 50 years old man who was found to have C. Perfringens septicemia early after he died from massive hemolysis and highlight the importance of early consideration of massive hemolysis as part of the differential diagnosis when faced with a critically ill patient presenting with a remarkably black-colored urine and mild methemoglobinemia.

Case Report

A 50-year-old man presented to our Emergency Department (ED) with the chief complaint of diffuse body pain. Past medical history is notable for hypothyroidism and skin melanoma, with metastasis to the brain, lung, liver, and bone. He had completed 7 cycles of chemotherapy with Carboplatin/Paclitaxel, few months prior to presentation, with recent evidence of disease progression. The pain was mainly abdominal, but also involved his usual metastasis-related pain sites and included his jaw, bilateral scapula, chest wall, and left inguinal region. The pain increased over the last 2 hours, reached 10 over 10 in intensity level, and was not relieved by his usual doses of analgesics.

Physical examination revealed an ill-appearing man, in pain. He was alert and oriented to person, place, and time His heart rate was regular with no murmurs. His lungs were clear to auscultation and he had diffuse abdominal tenderness. His vital signs were as follows: blood pressure, 126/96 mmHg; heart rate, 105 beats per minute; temperature, 37.3°C (Oral), and a pulse oximeter reading of oxygen saturation (SpO2) of 95% on room air.

His home medications included the following: temozolomide, esomeprazole, acetylcysteine, atorvastatin, dexamethasone, gabapentin, levetiracetam, levothyroxine, magnesium lactate-pyridoxine, metoclopramide, ondansetron, oxycodone, and sitagliptin-metformin.

He had a white blood cell (WBC) count of 8824/mm^3 (reference range 4000-11 000/mm^3), with 64% neutrophils and 24% lymphocytes, RBC count of 2.84 million/mm^3 (reference

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range 4 - 6.5 million/mm^3), a hemoglobin (Hb) of 9.1 g/dL (decreased from 12.5 g/dL 1 month prior), hematocrit of 25% (reference range 37%-54%), MCV of 89.7 fl (reference range 80-94 fl) and platelet count of 107 000/mm^3 (reference range 150 000-400 000/mm^3).

His peripheral blood smear revealed many left-shifted granulocytes, polychromasia, many spherocytes, rare target cells, elliptocytes, and schistocytes, with a low platelet count. A note was also made about the presence of multiple dehemoglobinized "ghost cells" (Figure 1). Indirect and direct antiglobulin tests (DAT or Coombs) were both negative.

The first blood sample revealed a serum creatinine of 1.2 mg/dL (reference range 0.6-1.2 mg/dL), which was similar to his baseline, and a blood urea nitrogen of 37 mg/dL (reference range 8-25 mg/dL). Other data were as follows: Total bilirubin, 5.9 mg/dL (reference range 0-1.2 mg/dL); direct Bilirubin of 2.1 mg/dL (reference range 0-0.3 mg/dL); Alkaline phosphatase, 235 IU/L (reference range 35-120 IU/L); AST, 662 IU/L (reference range 0-50 IU/L); ALT, 24 IU/L (reference range 0-65 IU/L); lipase <3 U/L (reference range 13-60 U/L). Activated partial thromboplastin time (aPTT), 42 seconds (reference range 27-39 seconds), prothrombin time (PT), 25.7 seconds (reference range 10-13 seconds) and international normalized ratio (INR) 2.1 (reference range 0.9-1.2). His lactic acid was reported as 11.6 mmol/L (reference range 0.55-2.20 mmol/L).

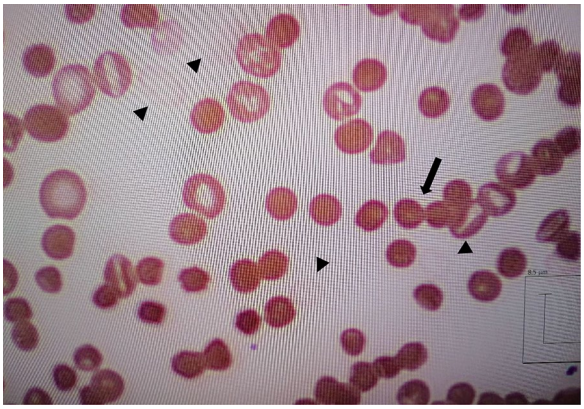

Figure 1. Peripheral smear showing many spherocytes (black arrow) and multiple ghost cells (arrow heads).

A Foley catheter was inserted, and his urine was found to be dark red/black in color (Figure 2). His blood samples were also noted to have a dark red/black color (Figure 3). In addition, his blood tests were reported as excessively hemolyzed and on multiple occasions.

An arterial blood gases (ABGs) was ordered to investigate this color change and it showed a pH of 7.20, a partial pressure of carbon dioxide (PaCO2) of 34.8 mmHg, a partial pressure of oxygen (PaO2) of 87.1 mmHg, bicarbonate of 13 mmol/L, an O2 saturation of hemoglobin (SaO2) of 99%, carboxyhemoglobin of 4.4% (reference range 0 %-0.8%), methemoglobin of 4.9% (reference range 0.2%-0.6%), hemoglobin of 6.1 g/dL, and a lactic acid of 10.9 mmol/L.

At this stage, in view of this acute drop in hemoglobin reported on the ABGs and the repetitively hemolyzed venous blood samples obtained, and the discoloration of his urine, severe intravascular hemolysis was suspected rather than just blood draw artifact, and packed red blood cells were ordered for urgent transfusion. Furthermore, the presence of methemoglobin and lactic acid prompted the initiation of broad-spectrum antibiotic coverage for severe sepsis with vancomycin, amikacin and piperacillin-tazobactam.

CT scan of the abdomen and pelvis with intra-venous contrast revealed new metastatic hepatic lesions, peritoneal and lymph node disease. No intraabdominal collections or bleed were seen (Figure 4).

About 4 hours later, a new measured Hb level showed a significant drop to 4.4 g/dL and hematocrit to 18%, despite ongoing packed red blood cell transfusion.

Six hours after the patient arrival to the ED, he suddenly deteriorated, became disoriented and was intubated. He then became pulseless, and resuscitation was attempted but was unsuccesful.

The definitive diagnosis of C. Perfringens sepsis was made after the patient's death as it grew in two sets of blood cultures after 4 and 14 hours, respectively.

Discussion

A wide variety of causes leading to a remarkably black colored urine exist, and these include cresol substance poisoning, commonly used medications (ie, metronidazole, nitrofurantoin,

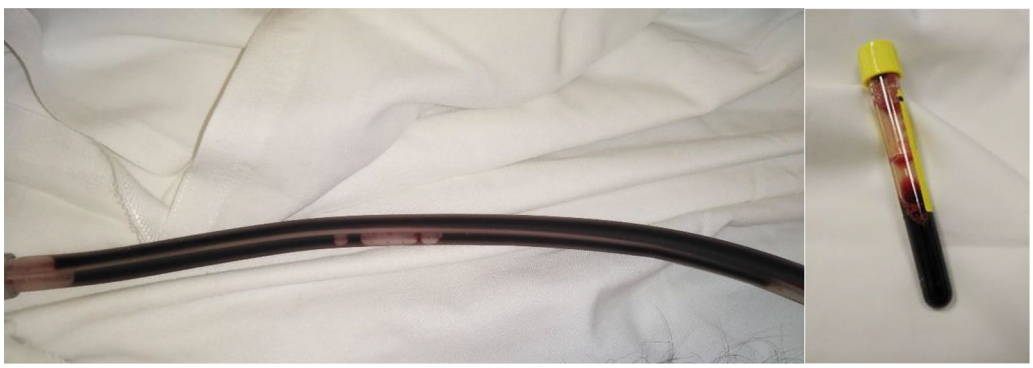

Figure 2. Urinary catheter (left) and urine sample (right) showing a remarkable dark red/brown color.

Figure 3. Fresh blood sample with a dark red/brown color.

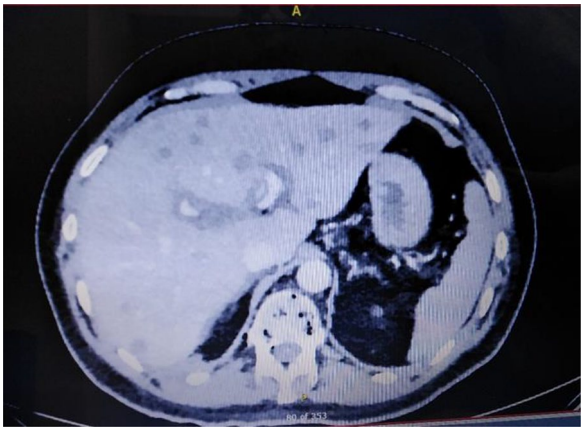

Figure 4. Computed tomographic scan of the abdomen showing metastatic hepatic lesions and no evidence of intra-abdominal collections.

sorbitol, and intramuscular iron) and some medical conditions like rhabdomyolysis and alkaptonuria. Additionally, a similar deep red-colored urine can be seen in hemoglobin structural or functional abnormalities leading to hemolysis or following transfusion hemolytic reactions. Melanuria has also been reported to rarely cause black urine in patients with disseminated melanoma and is explained by the presence of melanoma cells in the urine.[6-8]

None of the mentioned patient's home medications listed above is known to cause hemolysis or methemoglobinemia. And although we could not totally rule out rhabdomyolysis and melanuria (due to the unavailability of the corresponding tests), the significant acute drop in hemoglobin, presence of many spherocytes and ghost cells on peripheral smear,[9] finding of C. Perfringens bacteria in blood cultures, along with the absence of melanoma cells in the urine analysis taken 1 month earlier, allows us to justify the dramatic and acute clinical deterioration of our patient by the massive hemolysis due to C. Perfringens bacteremia, with the resulting remarkable dark red/black urine discoloration noted.[10]

C. Perfringens infections are often linked to poorly controlled diabetes, genitourinary or gastrointestinal solid tumors, hematological malignancies, and secondary to radiation, chemotherapy, post-embolization, post-hematopoietic cell transplant and rarely, are of unknown origin. Being in an immunocompromised state, as in our case, due to concomitant diabetes, metastatic melanoma and oral chemotherapy treatment probably constituted a strong risk factor for C. Perfringens translocation into the blood stream from a previously colonized gastrointestinal tract, especially in the presence of increasing hepatic and peritoneal metastasis.[11]

The mild methemoglobinemia witnessed in our case was brought into attention after the remarkable finding of dark colored blood samples, and was found to be mild with a level of 4.9%. This can be explained by the presence of sepsis, as shown in previous studies, with increasing levels reflective of disease severity.[12,13] Regarding the oxygen-Hb dissociation curve, increased methemoglobin level is known to cause a left shift in the oxygen-Hb dissociation curve, leading to decreased oxygen carrying capacity by heme, along with decreased oxygen unloading to tissues.[14] Moreover, the presence of spherocytosis secondary to C. Perfringens sepsis might also be responsible for a left shift in the oxygen-Hb dissociation curve, after a similar mechanism was reported in cases of hereditary spherocytosis where a lower level of 2,3-diphosphoglycerate was found.[15,16] This co-presence of both methemoglobin and spherocytes results in severe tissue hypoxia. Correction of this severe tissue hypoxia by either simple or hyperbaric oxygen administration and massive timely blood transfusion, would help in breaking the vicious cycle of anaerobic C. Perfringens proliferation, a bacterium known to possess a remarkably short doubling time estimated as low as 7 minutes.[17]

Other important interventions consist of early administration of antibiotics (a regimen of penicillin/clindamycin is recommended), prior to onset of the massive hemolysis, defined as hemoglobin <8 g/dL or hematocrit <24%, and surgical intervention with drainage of any identifiable source (liver abscess, cholecystitis or any abscess or gas in tissues that suggest gas-forming anaerobic infection) has been shown to improve survival and prolong time to death.[18,19]

Conclusion

Dark red/Black urine and blood samples, acute hemolysis, along with the presence of sepsis-induced methemoglobinemia, may be the only early sign of C. Perfringens septicemia and should prompt immediate administration of antibiotics, control of the source of infection, oxygen supplementation and massive blood transfusion.

Author Contributions

IB and ZI were responsible for conceptualization and management of the project. SK and RA were responsible for manuscript preparation and interpretation of findings. All authors have read and approved the manuscript.

Informed Consent

The consent form to publish the findings of this case study was signed by the patient's son.

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