CASE REPORT

Delayed Diagnosis in Army Ranger

Postdeployment Primaquine-Induced Methemoglobinemia

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ABSTRACT

Presumptive antirelapse therapy (PART) with primaquine for *Plasmodium vivax* malaria postdeployment is an important component of the US military Force Health Protection plan. While primaquine is well tolerated in the majority of cases, we present a unique case of an active duty Army Ranger without glucose-6-phosphatase dehydrogenase or cytochrome b5 reductase (b5R) deficiencies who developed symptomatic methemoglobinemia while taking PART following a deployment to Afghanistan.

KEYWORDS: *presumptive antirelapse therapy; Plasmodium vivax; primaquine; methemoglobinemia*

Introduction

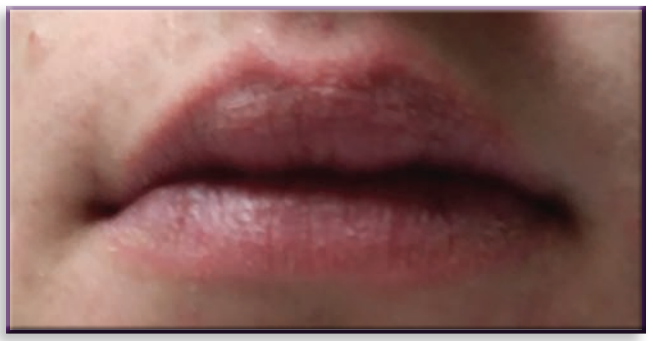
Prevention of plasmodial infection remains an important concern among deployed US Servicemembers and encompasses both primary prophylaxis and PART.[1] Both *Plasmodium vivax* and *Plasmodium ovale* can cause delayed infection due to activation of dormant hypnozoites in the liver. The primary goal of PART is the eradication of intrahepatic *P vivax* hypnozoites. First licensed in 1952, primaqine (PQ) was the only US Food and Drug Administration (FDA)-approved medication for this purpose until the recent FDA approval of tafenoquine in 2018.[2] The Centers for Disease Control and Prevention (CDC) recommends that providers consider prescribing PQ to travelers with prolonged exposure to endemic areas where *P vivax* accounts for >80% of malaria cases.[3] Afghanistan, North Korea, and Iran are among the countries with highest risk of *P vivax* exposure; the Armed Forces Health Surveillance Center has identified PART as a key component in the US military Force Health Protection plan.[4]

Prescribing considerations for PQ include ruling out an underlying glucose-6-phosphatase dehydrogenase (G6PD) deficiency, the screening for which is now mandated for all military personnel. PQ can precipitate both severe hemolysis and methemoglobinemia in individuals with G6PD deficiency. Reports of symptomatic methemoglobinemia related to malaria prophylaxis with PQ are particularly rare in the absence of G6PD deficiency, with the last cases published during the Vietnam Conflict among a group of soldiers heterozygous for b5R deficiency.[5] Our review of current English-language literature identified fewer than 10 published cases of symptomatic PQ-induced methemoglobinemia, which were all described in HIV-positive patients treated for *Pneumocystis jiroveci* pneumonia. Additionally, only two of these cases required treatment with methylene blue.[6–8] We present a unique case of a PQ-induced methemoglobinemia diagnosed in an otherwise healthy, postdeployment, active duty Army Ranger without G6PD deficiency.

Case Presentation

A 22-year-old white Army Ranger presented to our emergency department (ED) with concern for contrast-induced allergic reaction following computed tomography pulmonary angiography (CTPA). On arrival, we noted both labial cyanosis (Figure 1) and an initial oxygen saturation (SpO_2) of 90% without any evidence of anaphylaxis or other allergic reaction. Our patient reported persistent shortness of breath, dry cough, and "blue lips" for the past 2 weeks, which originally began 1 week after returning from a several-month–long deployment to Afghanistan. He reported dyspnea at home after climbing a single flight of stairs and had been unable to resume any of his typical work-out routines. He was otherwise healthy and denied any chest pain, palpitations, leg swelling, hemoptysis, fever, or history of clotting disorder. Medical workup 6 days earlier was inconclusive with a normal electrocardiogram, chest radiography, venous blood gas, complete blood count, and basic metabolic panel. CTPA at that time was negative for large

FIGURE 1 *Labial cyanosis pretreatment.*



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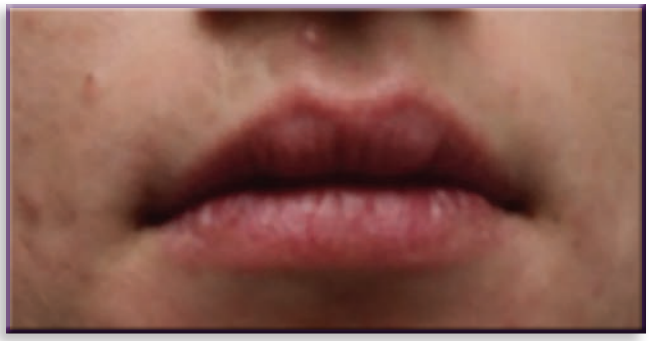
central pulmonary embolus (PE); however, the report noted suboptimal contrast bolus timing. Repeat laboratory results and imaging ordered earlier in the day by the patient's primary care physician were significant for D-dimer 0.54µg/mL FEU, creatinine 1.27mg/dL, and anion gap 17mmol/L. Repeat CTPA was negative for central or segmental PE.

Despite not taking any prescriptions or supplements at the time of our assessment, further history revealed that he had completed a 14-day course of PQ (15mg base daily) 1 week earlier. Venous co-oximetry confirmed an elevated methemoglobin (MetHb) level of 8%. Military medical records showed that the patient's G6PD deficiency screening was negative. After consultation with the Poison Control Center and discussion with the patient, we initiated treatment with methylene blue intravenous infusion at a dose of 1mg/kg. Within minutes of beginning treatment, we observed complete resolution of lip cyanosis (Figure 2), and Spo_2 levels improved to 100%. He remained asymptomatic on reevaluation in clinic 13 days later. Subsequent hemoglobin electrophoresis and genomic testing for the *CYB5R* gene were normal.

FIGURE 2 *Labial cyanosis resolution posttreatment.*



Discussion

The differential diagnosis for dyspnea in a Soldier returning from deployment is broad (Table 1) and distinct from the most common diagnoses encountered in civilian EDs, such as cardiogenic pulmonary edema, community-acquired pneumonia, and acute exacerbation of chronic respiratory disease.[9] Specifically, postdeployment considerations should be tailored to include pathogens more common to the region where the Soldier was recently deployed (e.g., tuberculosis, Avian influenza), job-related exposures, animal contacts, side effects of any new medications, and increased risk of venous thromboembolism secondary to venous stasis during prolonged travel.

Methemoglobinemia occurs when >1% of red blood cells contain iron in the ferric (Fe^{3+}) form, causing a leftward shift of the oxygen–hemoglobin dissociation curve. In the ferric form, hemoglobin affinity for oxygen increases, preventing oxygen delivery to tissues regardless of the concentration of oxygen inhaled. This diagnosis should be considered in patients with dyspnea or cyanosis when relatively low Spo_2 levels fail to respond to oxygen supplementation. Venous blood samples may exhibit a chocolate-colored appearance, and a thorough history may reveal exposure to one of several medications known to increased MetHb levels. Although asymptomatic elevations of MetHb levels have been measured in patients in South America receiving 2 to 5 times the recommended treatment dose of PQ for *P vivax*, none of these patients reported

TABLE 1 *Sample Differential Diagnosis for Life-Threatening Causes of Dyspnea*

Cardiac Output/Vascular • Ischemia • Arrhythmia • High-output heart failure • Tamponade • Valve dysfunction • Pulmonary embolism • Acute blood loss	**Respiratory Muscle Weakness** • Guillain-Barré syndrome • Myasthenia gravis • Multiple sclerosis • Botulism • Chest wall trauma • Increased abdominal pressure
Lower Respiratory Tract Abnormality • Infection • Potential bioterrorism agents (e.g., anthrax, tularemia, Hantavirus) • Asthma • Bronchitis • Aspiration • Pneumothorax • Inhaled toxins, such as organophosphates • Pulmonary edema • Pulmonary contusion	**Upper Airway Obstruction** • Inhaled foreign body • Abscess • Anaphylaxis **Hemoglobin Abnormality** • Anemia • Hemoglobinopathies (e.g., thalassemia) • Methemoglobinemia
Central Nervous System • Injury to brainstem or spinal cord	**Metabolic/Toxins** • Methanol • Ethylene glycol • Ketoacidosis (diabetes, alcohol) • Cyanide • Salicylates • Carbon monoxide
Oxygen Supply Abnormality • High altitude • Failure of oxygen source	

symptoms typically associated with methemoglobinemia.[10–13] Risk of clinically significant methemoglobinemia increases significantly with G6PD or b5R deficiency. Treatment with methylene blue in these patients can lead to hemolytic anemia.[141] Our patient did not have either of these deficiencies, and we did not identify any additional factors apart from his recent PQ course which would have otherwise increased his risk for elevated MetHb levels.

The 2017 World Malaria Report specifically identifies Afghanistan as an area of increasing *P vivax* infection. PART with PQ remains an important intervention to reduce delayed malarial infections following deployment. Soldiers returning from deployment to endemic areas may have received PQ, and providers should be alert to the development of adverse effects including both hemolytic anemia and methemoglobinemia. Although only recently approved and not yet widely used, tafenoquine has also been shown to increased MetHb levels. Treatment thresholds should be tailored individually and may be considerably lower in Soldiers requiring rapid return to high performance levels compared to the chronically ill patients described in most published cases.

Conclusion

This case emphasizes the importance of considering a broad differential particularly in patients with repeated health care visits. Specifically, when evaluating shortness of breath in a patient who has recently travelled internationally, careful history regarding potential infectious exposures and new medications must be considered. Our case also suggests that, although symptomatic methemoglobinemia following PART is rare, PQ alone can induce symptomatic methemoglobinemia, even among soldiers previously screened negative for G6PD deficiency.

Disclosure

The authors have no conflicts of interest to report.

GLOSSARY OF KEY TERMS

Co-oximetry. Blood test that reports percentages of various forms of hemoglobin including hemoglobin bound to carbon monoxide (carboxyhemoglobin) and hemoglobin containing ferric iron (methemoglobin).

Cytochrome b5 reductase. Also known as NADH-cytochrome **b**5 reductase 3, a soluble enzyme found in red blood cells that protects the cell from oxidative stress by reducing methemoglobin (containing ferric iron) to normal hemoglobin (containing ferrous iron).

Force Health Protection Plan. "All measures taken by commanders, supervisors, individual Servicemembers, and the MHS to promote, protect, improve, conserve, and restore the mental and physical well-being of Servicemembers across the full range of military activities and operations."[15]

Glucose-6-phosphatase dehydrogenase. An enzyme found in red blood cells essential to protecting against oxidation and hemolysis through the regeneration of the molecule NADPH and reduction of glutathione stores.

Hemolytic anemia. An abnormally low hemoglobin levels and thus oxygen carrying capacity due to destruction of red blood cells.

Hemoglobin electrophoresis. Blood test that can identify variations of the hemoglobin protein including normal variants and abnormal types such as those found in sickle cell disease or thalassemia.

Hemolysis. The destruction (rupture) of red blood cells.

Heterozygous. An individual with two distinct alleles for a given gene.

Hypnozoite. A dormant form in a parasitic life cycle that can persist in human liver and cause delayed infection.

Presumptive antirelapse therapy (PART). Medication taken following prolonged exposure in malaria-endemic areas to prevent delayed-onset infection caused by the dormant liver stage of specific malaria strains (*Plasmodium vivax*, *Plasmodium ovale*).

Primaquine. An antimalarial medication used to eliminate dormant hypnozoites of *Plasmodium vivax* and *Plasmodium ovale*.

Disclaimer

The views expressed in this article are those of the authors and do not reflect the official policy or position of the US Army or Department of Defense.

Author Contributions

All authors were directly involved in the clinical care and diagnosis of this patient. RE conducted a review of relevant literature and wrote the initial draft, and all authors edited and approved the final manuscript.

Disclosure

The authors have indicated that they have no financial relationships relevant to this article to disclose.

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