

The patient was found to have three hypercoagulable states: essential thrombocythemia, protein C deficiency, and hyperhomocysteinemia. Hyperhomocysteinemia might have been attributable to possible nutritional folate deficiency. The patient's neurologic deficit improved with physiotherapy. At discharge, the patient was maintained on low-molecular-weight heparin, vitamin B₁₂, folic acid, and pyridoxine supplements in addition to hydroxyurea.²

Six months later, the patient was asymptomatic and had minimal residual neurological deficit. The hypercoagulability work-up was repeated, confirming the presence of protein C deficiency, but the homocysteine level had decreased to the normal range (Table 1), presumably because the folate deficiency had been corrected (red cell folate level was normal after 6 months of supplements). Heparin cofactor II level, plasminogen activator level, and individual factor assays 6 months after the acute event were normal.

Discussion

Hypercoagulable states are underrecognized causes of ischemic stroke, and "dual" hypercoagulability as a cause of ischemic stroke is extremely rare.³ To the best of our knowledge, coexistent protein C deficiency, hyperhomocysteinemia, and essential thrombocythemia has not been reported previously. It is important to realize, however, that various combinations of inherited or acquired hypercoagulable states exist and will be increasingly recognized.

Recent reviews on thrombophilia have discussed the concept of gene-gene interactions and gene-environment interactions in the genesis of mixed hypercoagulable states.⁴ The possibility of synergism of risk factors in multiple coexistent prothrombotic states has also been noted.⁴ Hence it is imperative that a complete evaluation for hypercoagulability be done at initial presentation in previously asymptomatic young individuals (with no known risk factors) presenting with acute cerebrovascular ischemic events.⁵ This case emphasizes the fact that hyperhomocysteinemia is a modifiable risk factor that can be treated easily with pyridoxine or folate and vitamin B₁₂ supplements. Our case also exemplifies the recent concept that ischemic stroke can be the first manifestation of essential thrombocythemia.⁶ Although myeloproliferative disorders may be associated with protein C deficiency as a part of the syndrome complex, essential thrombocythemia, even when appropriately treated with hydroxyurea therapy, may lead to acquired protein C deficiency.^{7,8} This consideration tends to support the therapeutic use of anagrelide (recently approved by the US Food and Drug Administration) in essential thrombocythemia. It was also interesting to note that contrary to expectation, our patient did not have factor V resistance to activated protein C, and had normal levels of plasminogen activator inhibitor-1 and antithrombin III.^{7,9}

Acknowledgment

The authors are grateful to Dr. Martin F. Heyworth for helpful discussions and for reviewing the manuscript.

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Acquired Sulfhemoglobinemia An Underreported Diagnosis?

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SULFHEMOGLOBINEMIA IS A disorder of hemoglobin characterized by cyanosis in the absence of cardiopulmonary pathology. Cyanosis is intense and becomes clinically apparent even at very low concentrations of sulfhemoglobin (SHb). A mean capillary concentration of only 0.5 g/dl SHb is sufficient for detectable cyanosis. This level is about 10 times less than the detectable level with deoxygenated hemoglobin.¹ SHb shares a similar peak spectral absorbance with methemoglobin (MetHb) at approximately 626 nm. Therefore, automated blood gas analysis using spectrophotometers does not accurately differentiate between MetHb and SHb. The clinical picture can be further confusing because many agents known to cause methemoglobinemia also have been reported to cause sulfhemoglobinemia. In most patients, sulfhemoglobinemia, unlike methemoglobinemia, has few adverse clinical consequences and will resolve spontaneously with the physiologic turnover of red blood cells. The clinician that may erroneously treat sulfhemoglobinemia as methemoglobinemia under the false impression from automated blood

(Noor M, Beutler E. Acquired sulfhemoglobinemia—an underreported diagnosis? *West J Med* 1998; 169:386-389)

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ABBREVIATIONS USED IN TEXT

Hb = hemoglobin
MetHb = methemoglobin
Shb = sulfhemoglobin

gas analyzers could potentially harm the patient. We report a case of drug-induced sulfhemoglobinemia initially misdiagnosed as methemoglobinemia based on blood gas analysis.

Report of a Case

A 69-year-old woman was admitted to the hospital with severe cyanosis. Approximately 1 week before admission, she had an uncomplicated lower urinary tract infection. She was initially treated with a regimen of 400 mg norfloxacin twice a day for 3 days. When symptoms persisted, the regimen was changed to trimethoprim/sulfamethoxazole (TMP/SMX), and 100 mg phenazopyridine three times a day was added for urinary analgesia. Two days before admission, she noted "bluish stains on finger tips" that "would not wash away." On the day of admission, she was exercising on a treadmill when she noted onset of anterior chest tightness lasting 3 minutes followed by dizziness and marked exertional intolerance. At initial outpatient evaluation, she was noted to have severe acral cyanosis but did not appear to be in respiratory distress. An electrocardiogram showed no acute ischemia, and she was transferred for admission.

Her medical history included hypertension, hypercholesterolemia, and fibromyalgia. She also suffered from irritable bowel syndrome with chronic constipation. Besides TMP/SMX and phenazopyridine, her medications included simvastatin, lisinopril, trazodone, estrogen, and progesterone.

On examination she was alert and in no acute respiratory distress. Her blood pressure was 138/70 mmHg, pulse 70, respiratory rate 20, and temperature 36.5°C. A slate-gray color to her skin with accentuation at fingers and toes was noted. Mucous membranes had a violaceous hue with dark conjunctival vessels. Cardiorespiratory examination was normal. Extremities were warm and well perfused.

Pulse oximetry on room air revealed a hemoglobin oxygen saturation of 78%, which improved to only 80% with 100% O₂ delivered by face mask. Arterial blood gas analysis on 100% oxygen was performed using a cooximeter (Model IL482, Instrumentation Laboratory, Lexington, Massachusetts) and revealed a pH of 7.43, partial pressure of oxygen 337 mmHg, partial pressure of carbon dioxide 32 mmHg, and Hb oxygen saturation 82%. The MetHb level was 24%. Hb level was 11.3 g/dl and hematocrit 33.6%; all indices were normal. The white cell count was 6500/mm³ with a normal differential. Electrolytes were normal. Blood urea nitrogen was 20 mg/dl and creatinine 1.5 mg/dl. CK was 88 U/liter and lactate dehydrogenase 166 U/liter.

An initial diagnosis of toxic methemoglobinemia was made. TMP/SMX and phenazopyridine were stopped and vitamin C was added to the patient's regimen. She was given two doses of methylene blue at 2 mg/kg, which failed to resolve cyanosis. Further studies revealed that Hb electrophoresis was normal, with 97.1% HbA and 2.9% HbA₂. Erythrocyte glutathione level was 6.9 mmol/g Hb (normal range 4.5–8.7 mmol/g Hb). MetHb level by spectrophotometric assay was 0.7 g/dl (normal <1.5 g/dl) and SHb 0.754 g/dl (normal <0.037 g/dl). Her hospital course was uncomplicated and gradual spontaneous resolution of cyanosis was noted. SHb level over the next 3 weeks revealed a gradual decline at the rate of the normal physiologic turnover of the red blood cells (Figure 1).

Discussion

Although uncommon, SHb and MetHb are important causes of cyanosis. They must be differentiated early to avoid possible harm to the patient with the treatment rendered. Sulfhemoglobin derives its name from the fact that it can be produced *in vitro* from the action of hydrogen sulfide on hemoglobin. The histidine imidazole group of the porphyrin ring is protonated at the sixth position with sulfur atom attached to the β carbon on the porphyrin ring. The incorporation of the sulfur into hemoglobin results in oxidative denaturation of the molecule. This severe disturbance of tertiary protein structures explains the considerable departure of the absorption spectrum of SHb from that of Hb. The final product of this reaction is an irreversible hemichrome that cannot be reconverted to normal hemoglobin.

The sulfamethoxazole molecule contains a sulfanilimide group, SO₂NH₂, that can react with ferryl hemoglobin (HbFe⁴⁺) in the presence of hydrogen peroxide (H₂O₂). Sulfonamides, the class of antibiotics to which sulfamethoxazole belongs, were developed from aniline dye as the earliest antibacterial agents.² The anilines are well known to cause sulfhemoglobinemia and methemoglobinemia.^{3,4} Other concurrent physiologic factors might enhance this reaction. There have been reports that chronic constipation may predispose to SHb formation. Theoretically, the increased colonic transit time leads to increased bacterial breakdown of amino acids with resultant release of hydrogen sulfide.⁵

Dyspnea and other signs of end organ damage are uncommon in sulfhemoglobinemia because cyanosis becomes clinically apparent at extremely low concentrations. A SHb concentration of only 0.5 g/dl is sufficient to cause severe cyanosis; this concentration is 10 times less than that of deoxyhemoglobin needed to cause clinically detectable cyanosis. In addition, the apparent oxygen delivery to the tissue is actually facilitated by the changes in hemoglobin conformation.⁶ At low levels of abnormal pigment, only one or two of the hemoglobin tetramers are sulfurated. The unsulfurated tetramers shift toward the unliganded conformation, which in turn reduces the oxygen affinity of their unmodified subunits.

Figure 1: Sulfhemoglobin Levels

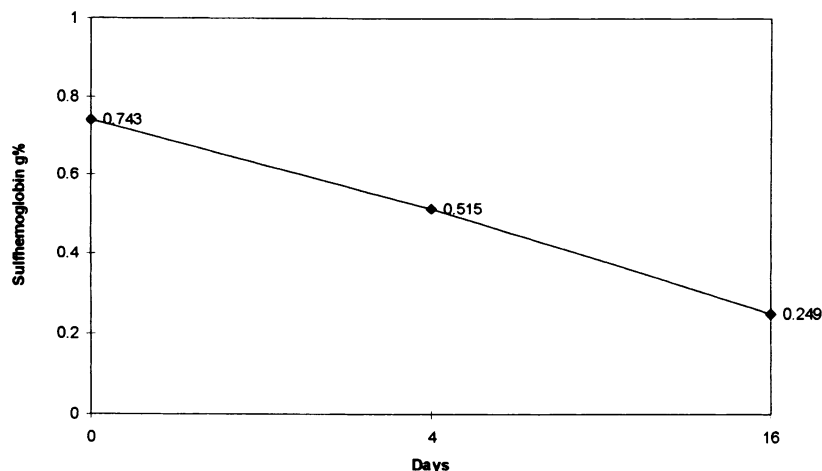


Figure 1.—Sulfhemoglobin levels during the patient's medical course.

This shift to the right of the oxygen dissociation curve actually ameliorates the effects of the reduced oxygen binding capacity and facilitates oxygen delivery to the tissue. Dyspnea is uncommon unless the level of SHb is extremely high. In the majority of patients, despite intense cyanosis, little more than careful clinical observation is needed. The abnormal hemoglobin disappears with the physiologic turnover of red blood cells.

Methemoglobin, on the other hand, is an oxidation product of hemoglobin. The resultant ferric hemoglobin (HbFe^{3+}) cannot reversibly bind oxygen. In the physiologic state, hemoglobin is oxidized at a very slow rate to MetHb. This steady state is maintained by the cell's endogenous mechanisms, which can transfer an electron back to the heme moiety, thereby regenerating reduced ferrous hemoglobin (HbFe^{2+}).⁷ There are several known cellular mechanisms for preventing oxidation of hemoglobin. These include glutathione peroxidase, cytochrome b5 reductase, and catalase.⁸ Damage will occur to red blood cells if an abnormally increased oxidant stress exceeds the normal source of reducing power; if there is a deficiency of reducing power; or if there are structural abnormalities of the hemoglobin that will render it more susceptible to the oxidative stresses. In the oxidized ferric state, the hemoglobin molecule itself also undergoes conformational changes that increase the oxygen affinity of the remaining three ferrous heme groups. The loss of oxygen-carrying capacity is thus further augmented, and this combination of effects may present a serious medical emergency when the MetHb levels rise to comprise 25% or more of the total pigment.

Clinically acute toxic methemoglobinemia is treated by administration of methylene blue. The NADPH formed in hexose monophosphate pathway can rapidly reduce MetHb to hemoglobin.⁹ The onset of action is very rapid, with immediate resolution of cyanosis. The regeneration of NADPH requires an intact pentose phosphate

pathway. If administered to those patients who are glucose-6-phosphate dehydrogenase (G6PD) deficient, methylene blue has no effect and can induce acute hemolysis.¹⁰ Hemolysis has also been reported after administration of repeated doses of methylene blue even in those patients with normal G6PD.¹¹ The clinical consequences of such adverse reactions are serious and can include dyspnea, precordial pain, restlessness, apprehension, and persisting cyanosis.

The error in this case arose from reliance on blood gas values obtained using automated blood gas analyzers. The automated blood gas analyzers such as the IL482 Co-Oximeter System are equipped with a program for calculating total hemoglobin, percent oxyhemoglobin, percent carboxyhemoglobin, percent methemoglobin, and percent reduced hemoglobin. An anticoagulated whole blood sample is aspirated into the instrument, mixed with diluent, hemolyzed, and brought to a constant temperature in the cuvette. Monochromatic light at four specific wavelengths (535, 582.2, 594.5, and 626.6 nm) passes through the cuvette to a photodetector, which measures the absorbance and computes the percentages of different forms of hemoglobin.¹² The presence of other abnormal forms of hemoglobin with a different spectral absorbance can introduce errors in this measurement. These include presence of SHb, high MetHb levels, interfering dyes such as indocyanine, lipemic samples, and high bilirubin levels. These species can significantly absorb light at these wavelengths and introduce errors in the results. Of note, SHb has a peak spectral absorbance similar to that of MetHb, explaining a limitation of the system. The presence of this type of hemoglobin with an oxygen affinity different from that of oxygenated Hb is a rare but important source of error.¹³ The presence of SHb has also been found to be an established source of error in the spectrophotometric determination of carboxy Hb.¹⁴ In the case reported here, presence of SHb with a similar

set of maximum absorptive spectrum at 626 nm was erroneously calculated by the cooximeter as MetHb. The correct diagnosis was made from the results of an assay based on the difference in absorbance between MetHb and cyanomethemoglobin.^{15,16} With the addition of cyanide, methemoglobin forms cyanomethemoglobin, thus losing its peak absorbance at 626 nm. Sulfhemoglobin, on the other hand, is an irreversible hemichrome, and unaffected by the cyanide, it retains its peak absorbance at 626 nm.

Conclusion

Sulfhemoglobinemia is a relatively benign clinical presentation of hemoglobin pigment. The diagnosis is frequently missed because automated spectrophotometers generally report this abnormal form of hemoglobin (with the peak absorbance at 626 nm) as MetHb, not differentiating it from SHb. When faced with cases of acute toxic methemoglobinemia as reported by blood gas analysis, the clinician should be aware of this error, since treatment can have potential for adverse outcomes. In the future it would be of interest to know the prevalence of such errors reported in routine blood gas analysis using automated blood gas analyzers.

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