CLINICAL VIGNETTE

COVID-19 Hypoxia Complicated by Methemoglobinemia

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Introduction

Acquired methemoglobinemia is a rare but dangerous condition causing hypoxia by rendering hemoglobin incapable of oxygen transport. Rapidly progressing hypoxia is also a hallmark finding of COVID-19, and co-morbidity with both conditions is not well described. We present a patient with severe hypoxia due to COVID-19 infection complicated by initially undiagnosed methemoglobinemia.

Case Presentation

A 65-year-old man with a history of Sweet's syndrome, diabetes mellitus, and monoclonal gammopathy of undetermined significance presented to the emergency department with oxygen saturation of 85-88% on a home pulse oximeter. He reported a one week history of subjective fevers, diarrhea, anosmia, ageusia, and shortness of breath. Travel history was significant for travel to New York City one month prior. On examination, he had clear breath sounds on auscultation and was not in respiratory distress, but had persistent oxygen saturations below 90% despite rapid titration of oxygen up to 15 liters per minute via a non-rebreather mask. Laboratory data was remarkable for leukopenia of 3900 cells/ul with a decreased absolute lymphocyte count of 950, an elevated d-dimer 841 ng/mL, a mildly elevated AST of 53 U/L, CRP of 11.6 mg/dL, and ferritin of 2,640 ng/mL. Chest x-ray was unremarkable without acute cardiopulmonary findings. The patient was transferred to the intensive care unit and subsequently tested positive on COVID-19 PCR.

Additional studies were obtained given his degree of hypoxia was disproportionately low when compared to the patient's clinical, laboratory, and imaging findings. Arterial blood gas showed pH 7.46, pCO2 36 mmHg, pO2 320 mmHg, SaO2 99%, and SpO2 89% revealed a saturation gap, with co-oximetry showing methemoglobin levels of 11.3% (reference 0.5-1.5%). Upon further interview, the patient revealed he has chronically taking dapsone for Sweet's syndrome. He received methylene blue treatment with resolution of methemoglobinemia and improvement in his hypoxia on 4 liters per minute via nasal cannula. His residual hypoxia was attributed to COVID-19 infection and improved with supportive care. He did not require intubation and was discharged after two weeks of hospitalization.

Discussion

Acquired methemoglobinemia has an oxidization of ferrous iron (Fe^{++}) to ferric iron (Fe^{+++}) within the hemoglobin molecule, rendering it incapable of oxygen transport and leading to tissue hypoxemia. Depending on the severity of disease, methemoglobinemia can present with a wide clinical spectrum, from no symptoms to seizures, respiratory failure, and death.[1] Oxidizing medications such as dapsone may overwhelm the body's innate mechanisms of methemoglobin reduction.[2,3]

Conventional pulse oximetry will report falsely low SpO2, and a difference between oxygen saturation detected on pulse oximetry and arterial blood gas should increase suspicion for methemoglobinemia. The diagnosis is made by documenting elevated blood methemoglobin levels measured on co-oximetry.[4] This important finding, along with the low pulse oximeter measurements out of proportion to clinical exam and imaging, encouraged us to broaden our differential on hypoxia in our patient.

Healthy patients may be asymptomatic with methemoglobin levels under 15%, but patients with co-morbidities affecting oxygen delivery or saturation can develop symptoms at significantly lower levels. When due to exposure, the offending agent should be discontinued. Medication treatment is recommended at approximately 20% methemoglobin levels in symptomatic patients and 30% methemoglobin levels in asymptomatic patients. Patients who are symptomatic or have significant concurrent heart disease, lung disease, carbon monoxide poisoning, or anemia should be treated at levels between 10% and 30%. The treatment of choice is methylene blue, which should reduce methemoglobin levels significantly in less than an hour. Complications of methylene blue treatment, include hemolysis, which can occur in those with G6PD deficiency.[5]

Conclusion

This case demonstrates the difficulty in diagnosing methemoglobinemia in patients with other pathologies causing hypoxia, in particular during the current COVID-19 pandemic where hypoxia and rapidly progressive respiratory failure are hallmarks of moderate to severe disease. Treatment with

methylene blue allowed us to better assess the degree of hypoxia due to COVID-19 alone. By keeping the differential diagnosis broad, we were also able to minimize confirmation diagnostic bias and a delay in diagnosis during a time where COVID-19 tops the differential in many cases with hypoxia.

REFERENCES

1. **Agarwal A, Prchal JT**. Methemoglobinemia and other causes of cyanosis. In: Kaushansky K, Litchtman MA, Prchal JT, et al (Eds). *Williams Hematology. 9th ed*. New York: McGraw Hill; 2015. p. 789.
2. **Ash-Bernal R, Wise R, Wright SM**. Acquired methemoglobinemia: a retrospective series of 138 cases at 2 teaching hospitals. *Medicine (Baltimore).* 2004 Sep;83(5):265-273. doi: 10.1097/01.md.0000141096. 00377.3f. PMID: 15342970.
3. **Cohen RJ, Sachs JR, Wicker DJ, Conrad ME**. Methemoglobinemia provoked by malarial chemoprophylaxis in Vietnam. *N Engl J Med*. 1968 Nov 21;279(21): 1127-31. doi: 10.1056/NEJM196811212792102. PMID: 5686480.
4. **Mengelkoch LJ, Martin D, Lawler J**. A review of the principles of pulse oximetry and accuracy of pulse oximeter estimates during exercise. *Phys Ther*. 1994 Jan;74(1):40-9. doi: 10.1093/ptj/74.1.40. PMID: 8265727.
5. **Wright RO, Lewander WJ, Woolf AD**. Methemoglobinemia: etiology, pharmacology, and clinical management. *Ann Emerg Med*. 1999 Nov;34(5):646-56. doi: 10.1016/s0196-0644(99)70167-8. PMID: 10533013.