An Unexpected Cause of Hypoxemia in an Immunosuppressed Patient

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Introduction

Methemoglobinemia:
- An altered state of the hemoglobin molecule such that the iron cations are oxidized to the ferric (Fe3+) state. This both decreases the hemoglobin’s oxygen binding capacity and increases its oxygen affinity.
- The result is decreased oxygen delivery to tissues and functional anemia.
- Methemoglobinemia is associated with hypoxia:
  - Properties of the methemoglobin molecule make pulse oximetry read inaccurately low and hypoxemia does not correct appropriately with oxygen.
  - Blood gas analysis overestimates oxygen saturation since the arterial oxygen partial pressure remains normal in methemoglobinemia.

Learning Objectives
1. Describe the diagnosis of an unusual cause of asymptomatic hypoxemia.
2. Review the treatment of acquired methemoglobinemia.

The Case

History and Physical:
A 71-year-old man with history of end stage systolic heart failure secondary to nonischemic cardiomyopathy and atrial fibrillation rate controlled previously with Amiodarone, now status post orthotropic heart transplant 3 months prior admitted from cardiology clinic with persistent, new hypoxemia.

The patient's post transplant course had been complicated by leukopenia with a WBC nadir of 1.57 one month prior to presentation, presumed to be secondary to a medication effect with subsequent discontinuation of Myfortic, Bactrim and Valcyte and the addition of Dapsone for PJP prophylaxis. One week prior to presentation he had been diagnosed with mild acute cellular rejection by right heart biopsy and his prednisone had been increased to 15mg daily and low dose Myfortic had been resumed. Mild exertional hypoxemia had been noted a few days previously at cardiac rehab leading to early termination of that day’s exercise session.

On presentation the patient reported about 2 days of a frequent, dry cough. He denied fevers, chills, night sweats or dyspnea and felt generally quite well. Vital signs were notable for a resting oxygen saturation of 88% on room air only improving to 92-94% with 2L oxygen.

Physical exam revealed an alert, well appearing elderly Asian male with an unremarkable cardiopulmonary exam and no evidence of volume overload. Labs were notable for a WBC of 11 and hemoglobin of 12.7.

Initial Differential Diagnosis and Work Up:
Given recent history the major concern was for PJP though consideration was given to pulmonary embolism or Amiodarone induced pulmonary toxicity.
- Chest CT with pulmonary angiography was completely unremarkable.

Additional Work Up and Treatment:
Given history of Dapsone use, the possibility of acquired methemoglobinemia was considered.
- Blood gas analysis revealed a methemoglobin level elevated to 4.1%.
- 24 hours after discontinuation of Dapsone the patient’s methemoglobin had decreased to 3.3% and he was able to maintain an ambulatory oxygen saturation of 90% on room air.
- He was switched to a monthly dose inhaled Pentamidine for PJP prophylaxis.

At clinic follow up 2 weeks later the patient’s oxygenation had improved to 96% on room air.

Discussion

The diagnosis of methemoglobinemia often starts with a high degree of clinical suspicion in the setting of known exposure to a commonly implicated medication or chemical. The findings of sudden onset cyanosis or hypoxia and abnormally colored blood (dark red, chocolate or brownish blue) with phlebotomy in the right clinical setting should raise concern for acquired methemoglobinemia. Direct measurement of methemoglobin in an arterial or venous sample is the preferred method of testing.

Acquired methemoglobinemia secondary to Dapsone use is generally dose dependent though the presence of underlying risk factors can make some patients more sensitive to the effect even at a relatively low dose. In our patient’s case his underlying anemia likely placed him at higher risk for developing significant methemoglobinemia. Other risk factors include G6PD deficiency, partial cytochrome b5 reductase deficiencies and underlying heart or lung disease.

Treatment of acquired methemoglobinemia generally consists only of the discontinuation of the offending agent. If patients are symptomatic or if the level of methemoglobin is over 20% treatment with either methylene blue or ascorbic acid should be considered. In the case presented here, the patient rapidly responded to discontinuation of Dapsone.

References