Dyspnea in a Lung Transplant Recipient

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Introduction

Lung transplantation is the last resort for treatment of advanced lung disease or irreversible lung failure. The different types of acquired or genetic lung diseases that should be considered for lung transplantation include chronic obstructive pulmonary disease, emphysema, alpha-1 antitrypsin deficiency, cystic fibrosis and other causes of bronchiectasis, idiopathic pulmonary fibrosis, non-specific interstitial pneumonia, pulmonary fibrosis associated with collagen vascular disease, pulmonary arterial hypertension, sarcoidosis, lymphangioleiomyomatosis, and pulmonary Langerhans cell histiocytosis.[1] Despite improvements in surgical techniques, lung preservation, immunosuppression, and management of ischemia/reperfusion injury and infections, acute and chronic allograft dysfunction and rejection remain major obstacles. The incidence and severity of acute rejection in lung transplantation exceeds all other solid-organ transplantations.[2-4] Chronic allograft rejection, also called bronchiolitis obliterans syndrome, is the clinical counterpart of obliterative bronchiolitis, a fibrotic process that progressively narrows bronchiolar lumens and obstructs air flow.[5] Chronic rejection or bronchiolitis obliterans syndrome affects up to 60% of patients who survive 5 years after transplantation and accounts for > 30% of all deaths occurring after the third postoperative year.[5] In the early era of lung transplantation, airway dehiscence was a common cause of early death.[6] Systemic arterial blood supply is not restored during transplantation, so anastomotic complications are primarily attributed to ischemia of the donor bronchus.[7] Additional factors that can compromise airway healing include inadequate organ preservation,[7] invasive infections,[8] intense immunosuppressive therapy,[9] and rejection.[10] Severe reperfusion edema and early rejection are independent predictors of bronchial complications.[11] Standardized surgical techniques for the anastomosis help avoid bronchial complications after lung transplantation.[12]

Post-lung-transplantation immunosuppression therapy involves 3 classes of drugs: a calcineurin inhibitor (tacrolimus or cyclosporine), an antimetabolite (mycophenolate or azathioprine), and a glucocorticoid (prednisone). Because of the immunosuppressant therapy, prophylactic antimicrobial therapy is required to prevent opportunistic infections, including fungi, cytomegalovirus, and *Pneumocystis jiroveci*. Substantial post-lung-transplantation morbidity is common from medication adverse effects, because of the number of medications required and their interactions with other drugs. These adverse effects can include drug-induced methemoglobinemia, which can be identified quickly by the presence of clinical cyanosis, with normal arterial oxygen saturation measured by an arterial blood sample (S_{aO_2}).

Case Summary

A 65-year-old female who underwent left single lung transplantation 92 days earlier for emphysema and end-stage chronic obstructive pulmonary disease, presented with dyspnea and mild cyanosis. The lung transplantation had been uneventful and she was extubated on the fourth postoperative day and discharged on the 15th postoperative day. Her postoperative course was complicated by leucopenia (nadir white-blood-cell count 2,000/μL), so resulting in the need for alteration of her immunosuppressive and prophylactic regimen. The mycophenolate was reduced to 500 mg twice daily, valganciclovir was reduced to 450 mg once daily, and *Pneumocystis jiroveci* prophylaxis was changed from trimethoprim/sulfamethoxazole to dapsone. Mycophenolate, valganciclovir, and trimethoprim/sulfamethoxazole can cause myelosuppression, with potential additive effects.[13-15] Clinic follow-up appointments on the 21st, 32nd, 45th, 60th, and 80th postoperative days were uneventful; she reported mild dyspnea, but her pulmonary function was improving and her S_{aO_2} was in the range 93–95% during those visits.

On the 91st postoperative day she was evaluated urgently by her primary care physician due to worsening

acute dyspnea, but with no other complaints. On her own accord, she started supplemental oxygen at 2 L/min at home the day prior to seeing her primary care physician, but there was no improvement in symptoms. She was referred to the lung transplant center for further evaluation and was seen on the 92nd postoperative day.

Her medical history included prednisone-induced hyperglycemia, gastroesophageal reflux, and chronic obstructive pulmonary disease. She had 2 surveillance bronchoscopies at 2 weeks and 2 months postoperatively, which identified a well healing allograft anastomosis with no evidence of infection by bronchoalveolar lavage fluid culture, cytology, and histopathological analysis of transbronchial biopsies. Her medications included tacrolimus 2.5 mg twice daily, mycophenolate 500 mg twice daily, prednisone 20 mg daily, dapsone 100 mg daily, itraconazole 200 mg daily, valganciclovir 450 mg daily, and omeprazole 20 mg twice daily, and sliding-scale regular insulin. At her evaluation in the lung transplant center her physical examination revealed an elderly female in no distress, with a respiratory rate of 18 breaths/min and S_{aO_2} of 85% despite the supplemental oxygen. She was mildly cyanotic, with blue nail beds. Her pulmonary examination revealed no retractions, clear breath sounds in the left allograft, and substantial reduction of air entry and sporadic wheeze in the native right lung. Cardiac examination identified tachycardia (104 beats/min), without a hyperdynamic precordium. Her remaining physical examination was unremarkable.

Spirometry revealed a forced vital capacity of 2.11 L (72% of predicted) and a forced expiratory volume in the first second of 1.58 L (67% of predicted), compared to a forced vital capacity of 1.90 L (64% of predicted) and forced expiratory volume in the first second of 0.54 L (23% of predicted) prior to the lung transplant. Chest radiograph showed the allograft was clear, and the chronic changes in the native right lung were stable. The patient refused arterial blood sampling due to severe anxiety from a poor previous experience. She underwent bronchoscopy to determine the cause of the refractory dyspnea, and an arterial blood sample was obtained while she was under conscience sedation. During the bronchoscopy her oxygen saturation (measured via by pulse oximetry) was 88–89% on room air prior to administration of lidocaine, and the arterial blood gas (ABG) analysis revealed pH 7.47, P_{aCO_2} 31 mm Hg, P_{aO_2} 215 mm Hg, and oxygen saturation 98%.

The arterial blood sample also showed that the methemoglobin level was elevated (15.6%), so the patient was hospitalized and the dapsone was stopped. A total of 10 mL of 2% lidocaine solution was applied to the upper airway, and a total of 10 mL of 1% lidocaine solution was applied to the lower airways during the bronchoscopy. The methemoglobin level peaked at 21.7% on the 94th postoperative day. The bronchoscopy identified an intact, well healing anastomosis, while bronchoalveolar lavage fluid cultures and transbronchial biopsy histopathological analysis found no infection or acute rejection, respectively. The continued methemoglobin rise in the hospital was thought to be due to the lidocaine during bronchoscopy. A qualitative glucose-6-phosphate dehydrogenase analysis was normal, but the quantitative level was 30.8 U/g hemoglobin (normal range 7.0–20.5 U/g hemoglobin).

After stopping the dapsone, the patient was treated with a one-time dose of pentamidine via nebulization for prophylaxis and then re-started on trimethoprim/sulfamethoxazole. She was discharged on the 94th postoperative day after resolution of the dyspnea, and her methemoglobin level returned to normal over the next 2 weeks.

Discussion

Methemoglobinemia is a rare but potentially fatal disorder that can be either acquired or congenital. Patients with methemoglobinemia typically present with cyanosis and dyspnea that is unrelated to a cardiopulmonary etiology. For both hereditary and acquired etiologies, methemoglobinemia is clinically defined as > 1% of hemoglobin being oxidized to methemoglobin.[16] Methemoglobin is an altered state of hemoglobin in which the iron in the heme group is oxidized to the ferric (Fe^{3+}) state and not the ferrous (Fe^{2+}) state of normal hemoglobin. In the oxidized state, hemoglobin is unable to bind oxygen. The oxygen affinity of any accompanying heme in the ferrous state within the hemoglobin tetramer is increased,[17] so the oxygen-dissociation curve is shifted left. Methemoglobinemia results in a functional anemia in which circulating methemoglobin molecules are unable to both carry oxygen and deliver it to the tissues, which causes cyanosis and dyspnea.

The constant exposure of erythrocytes to oxidative stress occurs from normal metabolism, which converts hemoglobin to methemoglobin that binds a water molecule rather than oxygen. This spontaneous formation of methemoglobin is counteracted by the enzyme systems, cytochrome b5 reductase (major pathway) and nicotine adenine dinucleotide phosphate (NADPH) methemoglobin reductase (minor pathway)[18] (Fig. 1). These 2 pathways maintain methemoglobin at < 1% of the total hemoglobin in healthy individuals.[16] The NADPH methemoglobin reductase pathway uses NADPH that is generated by glucose-6-phosphate dehydrogenase in the hexose monophosphate shunt as a source of electrons.

An important constituent of the endothelium that is produced there is nitric oxide, which diffuses from the endothelial cell into the vessel lumen and enters the erythrocyte. Once inside the red blood cell, nitric oxide reacts differently with oxyhemoglobin and deoxyhemoglobin.[19] The interaction with oxyhemoglobin leads to the production of nitrate (NO_3^-) and methemoglobin.[19] This yields an endogenous methemoglobin level, and hemoglobin functions as a nitrite reductase.[19]
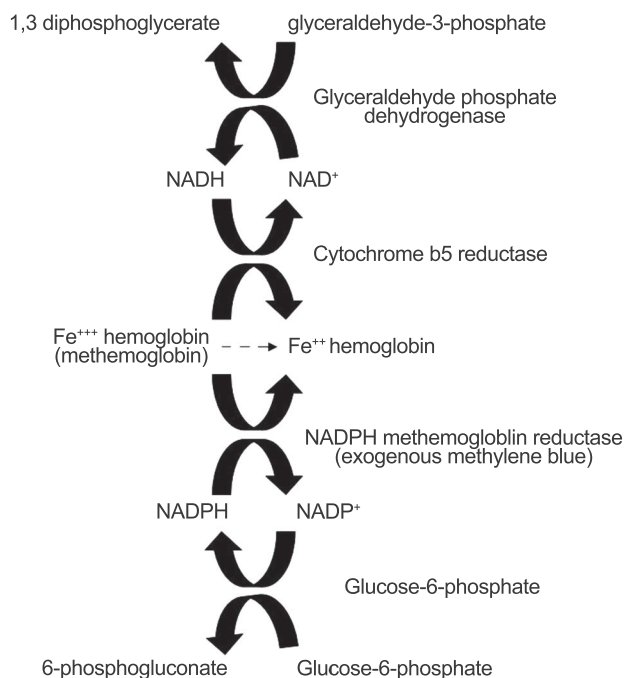
Fig. 1. Metabolic pathways for the reduction of methemoglobin. The major pathway for methemoglobin reduction is cytochrome b5 reductase. An alternative pathway that requires an exogenous electron acceptor (ie, methylene blue) is nicotinamide adenine dinucleotide phosphate (NADPH) methemoglobin reductase. A small amount of methemoglobin is reduced through a nonenzymatic pathway (dashed line).

The percent oxygen saturation of hemoglobin in the blood can be measured either directly via ABG analysis, or indirectly via pulse oximetry. The percent actually refers to the proportion of hemoglobin that is oxygenated to the total amount of hemoglobin. When 2 compounds with different absorption spectra are together in solution, the ratio of their concentrations can be determined from the ratio of the light absorbed at 2 different wavelengths. Deoxygenated hemoglobin preferentially reflects light at 940 nm (infrared), while oxygenated hemoglobin reflects at 660 nm (red). Figure 2 illustrates the extinction curves of different hemoglobin species. The extinction coefficient of methemoglobin at 660 nm is similar to that at 940 nm, resulting in a red-to-infrared ratio of 1:1 (see Fig. 2), so the corresponding S_{aO_2} value for this ratio is approximately 85%. As the methemoglobin level increases, the S_{aO_2} will tend toward 85%; and when the methemoglobin level exceeds 30%, the S_{aO_2} will plateau at 85% and will thus be unaffected by the oxygenation status.

To develop clinically relevant methemoglobinemia, one of the following factors must be present:

- Increased production of methemoglobin

- Abnormal hemoglobin resistant to reduction after oxidation

- Decreased enzymatic activity, primarily erythrocytic NADH-cytochrome b5 reductase
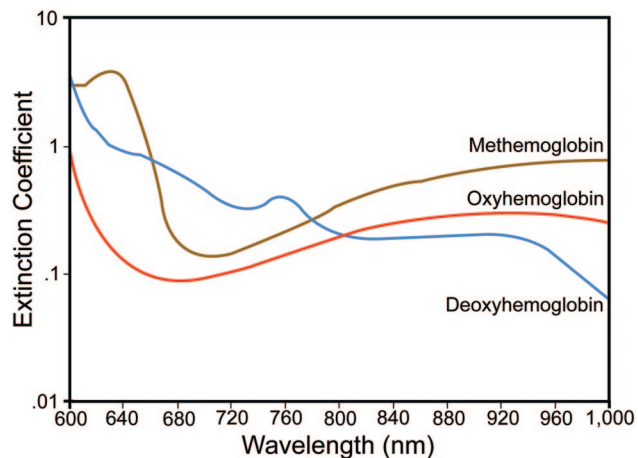

Fig. 2. Extinction curves of 3 hemoglobin species. Oxyhemoglobin and reduced hemoglobin have different absorptions of 660-nm and 940-nm light waves. Methemoglobin has a similar absorption at the 2 wavelengths. The extinction coefficient is shown with a logarithmic scale.

Congenital methemoglobinemia due to an enzyme effect is classified into 4 types.[20] Type 1 is a deficiency in cytochrome b5 reductase with few symptoms other than visible cyanosis and occasional headache, fatigue, and exertional dyspnea.[21] Type 2 is more pervasive with a generalized systemic deficiency due to alterations of lipid metabolism, which affects numerous tissues, including the central nervous system, and results in progressive neurological deterioration.[22,23] Type 3 is no longer considered a separate entity since it was shown to be identical to Type 1.[24] Type 4 has been described in only one case and is manifested by attenuated concentration of cytochrome b5 reductase.[25]

Congenital methemoglobinemia is extremely rare. Acquired methemoglobinemia is much more common. Table 1 outlines the most common agents that cause methemoglobinemia. In a retrospective case series of 138 cases over 28 months at 2 tertiary-care hospitals, Ash-Bernal and colleagues found that dapsone was the most common etiology of acquired methemoglobinemia (42% of all cases). There was one fatality and 3 near-fatalities directly attributable to methemoglobinemia.[18]

Teaching Points

Pulse oximetry cannot accurately measure S_{aO_2} in the presence of methemoglobinemia and cannot be used to confirm the diagnosis. However, the presence of methemoglobin should be suspected when the blood oxygen saturation measured via pulse oximetry is significantly less than the saturation calculated from ABG analysis (an "oxygen-saturation gap"). If the gap is greater than 5%, the hemoglobin may be abnormal, which can indicate carbon monoxide poisoning, methemoglobinemia, or sulfhemoglobinemia.[26] Acquired methemoglobinemia should be

Table 1.   Substances That Can Cause Methemoglobinemia

Inorganic agents
   Nitrates: fertilizers, contaminated well water, preservatives,
     industrial products
   Chlorates
   Copper sulfate: fungicides
Organic nitrites/nitrates
   Amyl nitrite
   Isobutyl nitrite
   Nitroglycerin
   Nitroprusside
   Nitric oxide
   Nitrogen dioxide
   Sodium nitrite
   Trinitrotoluene (TNT), combustion products
Analgesics/antipyretics: acetaminophen, acetanilid, phenacetin,
   celecoxib
Antiemetic: metoclopramide
Antimalarials: primaquine, chloroquine
Antimicrobials: sulfonamides, nitrofurans, p-amino-salicylic acid,
   dapsone, clofazimine
Antineoplastic agents: cyclophosphamide, ifosfamide, flutamide
Benzene derivatives
Herbicides: paraquat (dipyridylium)
Indigo carmine (indigotindisulfonate)
Industrial/household agents: aniline dyes, nitrobenzene, naphthalene
   (moth balls), aminophenol, nitroethane (nail polish remover)
Local anesthetics: benzocaine, lidocaine, prilocaine, phenazopyridine
   (pyridium)
Methylene blue (high dose or in glucose-6-phosphate dehydrogenase
   deficient patients)
Rasburicase
Resorcinol
Vitamin components: menadione, naphthoquinone
Zopiclone

strongly suspected in the setting of clinical cyanosis with a normal P_{aO_2} on ABG analysis. Numerous agents can cause methemoglobinemia, and some post-lung-transplant patients require certain of these agents in their treatment course, so clinicians need to be aware of this risk.

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