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Case Report

Inhaled nitric oxide and sildenafil therapy for a pediatric patient with multiple pulmonary arteriovenous malformations

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Abstract. Pulmonary arteriovenous malformations may result in intrapulmonary shunting and hypoxemia, and often are treated by embolization or surgical resection. Previous reports have demonstrated effective treatment of hypoxia with inhaled nitric oxide in the acute setting. In this report, we describe a child with severe hypoxemia secondary to an inoperable pulmonary arteriovenous malformation that was initially managed with the use of nitric oxide followed by long term management with the phosphodiesterase-5 inhibitor, sildenafil.

Keywords: Arteriovenous malformations, nitric oxide, phosphodiesterase-5 inhibitors

1. Introduction

Pulmonary arteriovenous malformations (PAVM) may result in intrapulmonary shunting and hypoxemia, and often are treated by embolization or surgical resection. Previous reports have demonstrated effective treatment of hypoxia with inhaled nitric oxide (iNO) in the acute setting [1,2].

In this report, we describe a child with severe hypoxemia secondary to an inoperable PAVM that was initially managed with the use of iNO followed by long term management with the phosphodiesterase (PDE)-5 inhibitor, sildenafil.

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2. Case report

The patient was a 6-year-old Peruvian boy who fell while playing, sustaining an injury to his upper lip. Despite adequate hemostasis, the injured site became progressively more swollen over the next 6 mo. He was subsequently diagnosed with a hemangioma of the upper lip and maxilla; however, he did not receive treatment while in Peru.

The family immigrated to the United States approximately 2 yr after the injury, and the patient was evaluated at the University of California Davis Children's

Hospital. Physical examination was significant for a noticeable deformity of the upper lip, left of midline, causing marked protrusion of the lip and narrowing of the left nostril. Cardiac examination revealed a grade II/VI systolic ejection murmur heard best at the left sternal border, radiating to the left chest. Extremities were notable for bilateral clubbing in all digits of both the upper and lower limbs with intraoperative oxygen saturation (SaO_2) in the low to mid 90s while awake and sitting upright. Computed tomography (CT) of the neck and magnetic resonance imaging of the orbit, face, and neck revealed a soft tissue mass extending from the upper left to the anterior portion of the maxilla, measuring $3 \times 2.8 \times 3$ cm. There were no large feeding vessels visible on the imaging studies. A biopsy was obtained, which was consistent with arteriovenous malformation.

While receiving sclerotherapy of the mass, the patient suffered an episode of hypoxia. His SaO_2 fell to 85%, and a postoperative arterial blood gas had a pH of 7.39, pO_2 of 61 mmHg, pCO_2 of 36 mmHg, and an SaO_2 of 92% while receiving 15 L per minute (Lpm) of oxygen via face mask. Ventilation/perfusion scintigraphy revealed normal symmetric ventilation of both lungs without significant segmental perfusion defects. A CT scan of the chest demonstrated numerous soft tissue densities of varying sizes scattered throughout the lungs bilaterally. Two particularly large masses (18×22 mm in the right middle lobe and 16×13 mm in the superior segment of the left lower lobe) were consistent with PAVMs.

To treat his hypoxemia, coil embolization of the right middle lobe PAVM was performed. During the catheterization procedure, the left lower lobe mass was found to be a collection of small vessels, and was left uncoiled. His post-procedure oxygen saturation was consistently in the upper 80s to low 90s while awake and in the high 70s while sleeping. One week later, he was seen as an outpatient in the University of California Davis Children's Hospital pediatric pulmonology clinic for routine follow-up. At that visit, he was tachycardic (heart rate 123 bpm) with SaO_2 of 80% on room air. Spirometry values were within normal limits, with SaO_2 of 95% on 10 Lpm of inspired oxygen. The hypoxia was felt to be secondary to significant intrapulmonary shunting. Based on these findings, the residual maxillary mass was excised. Estimated blood loss during surgery was 500 mL resulting in a post-operative hematocrit of 28% (compare with 43% pre-operatively). Throughout surgery, the SaO_2 was above 95%, however following extubation the saturations fell to 90% on 6 Lpm oxygen, and several intermittent desaturation episodes to the high 70% range were noted. The patient was admitted to the pediatric intensive care unit (PICU) for further treatment and continuous monitoring.

Upon transfer to the PICU, the heart rate was 156 bpm, respiratory rate was 24, blood pressure was 101/50 mmHg, oral temperature was 38.0 ºC, and SaO_2 was 98% on 4 Lpm oxygen by nasal cannulae. The patient was awake, alert, and in no respiratory distress. The precordium was hyperactive, and distal pulses were bounding. Overnight, after two fluid boluses (lactated ringers 20 mL/kg), his heart rate returned to approximately 120 bpm with SaO_2 in the low 90% range on 6 Lpm oxygen via nasal trumpet. During the first 24 h after transfer to the PICU, his SaO_2 decreased to the 50% to 60% range in spite of increasing oxygen therapy to 15 Lpm via non-rebreather facemask. Arterial blood gas revealed a pH of 7.39, pO_2 of 30 mmHg, pCO_2 of 38 mmHg, and SaO_2 of 55%.

SaO_2 remained in the 50% to 60% range with occasional desaturations into the high 30s. The desaturations were not associated with a change in mental status and all resolved spontaneously. Despite transfusion of packed red blood cells to a hematocrit of 41%, there was no improvement of the SaO_2. A CT angiogram of the chest demonstrated no change in the existing PAVMs and coils, and showed no evidence of pulmonary embolism. Chest X-rays were unchanged from prior, and echocardiogram demonstrated no intracardiac shunting and no evidence of pulmonary hypertension.

On the 2^{nd} PICU day, iNO was initiated at 5 parts per million (ppm), and within a few minutes his saturation increased to approximately 90% and stabilized. On PICU day three, sildenafil therapy was added (2 mg/kg/d divided into 9 mg/dose every 6 h), the oxygen therapy was weaned as tolerated to maintain SaO_2 above 88%, and the iNO was decreased by 1 ppm every 6 h. By the 4^{th} d, the iNO was discontinued, and the SaO_2 ranged from 86% to 93% on 2 Lpm oxygen therapy. The patient was weaned to room air with an SaO_2 of 92% on day five, and was transferred to the general pediatric ward. He remained stable on room air, and was discharged after 3 d on sildenafil 9 mg by mouth four times daily.

3. Discussion

PAVMs are a recognized cause of hypoxemia secondary to intrapulmonary shunting and their treatment involves embolization or resection. iNO has been described to treat hypoxemia in previous reports of such

cases. Although the use of sildenafil in cases of hypoxemia due to pulmonary hypertension and PAVMs have been previously reported to our knowledge [3,4], this is the first case report that utilizes sildenafil for chronic management of hypoxia after iNO therapy in a case of hypoxemia caused by PAVMs and unrelated to pulmonary hypertension.

PAVMs are abnormal communications between pulmonary arteries and pulmonary veins without an intervening pulmonary capillary bed. Such malformations result in a right-to-left intrapulmonary shunt. The degree of systemic desaturation depends on multiple factors including the percentage of the total pulmonary blood flow that flows through the PAVMs, the hematocrit, the cardiac output, and the mixed venous oxygen saturation. Clinical characteristics of a patient with a PAVM may include hypoxia, cyanosis, clubbing and polycythemia. Finally, cardiac catheterization of patients with PAVMs reveal normal right heart pressures, indicating that pulmonary hypertension is not a part of the pulmonary pathophysiology [5].

In 1897, Churton first reported a patient with a PAVM, and as of a 2002 review more than 500 cases of PAVMs have been reported [6]. Eighty percent of these malformations are congenital, and it is estimated that 70% of the congenital lesions are associated with hereditary hemorrhagic telangiectasia [7]. The remaining 20% of PAVMs are acquired, and may be caused by trauma, cardiothoracic surgery, hepatic cirrhosis, mitral valve stenosis, pulmonary schistosomiasis, thyroid carcinoma metastases, or systemic amyloidosis [6].

Current treatment for PAVMs consists of either percutaneous embolization or surgical resection; however, iNO therapy used specifically for PAVMs has been described in five reports. The first report, published in 1996, outlines the case of an adult with post-operative hypoxemia (leading to the new diagnosis of PAVM) successfully reversed with iNO therapy [8]. A case report from 1998 demonstrates a pediatric patient with an undiagnosed PAVM, who presented with hypoxemia and was also treated successfully with iNO in the acute setting. However, subsequent attempts to wean iNO in this patient were unsuccessful until two embolization procedures were performed [9]. The final three reports describe the use of iNO in acquired PAVMs, formed as complications after cavopulmonary shunt operations. In all cases, post-operative hypoxemia was successfully reversed with iNO [10–12].

Endogenous nitric oxide (NO) is a key regulator of pulmonary vascular resistance [13]. NO is synthesized and released from the endothelial cell in response to vascular stimuli [14]. Once released, NO diffuses into vascular smooth muscle cells, activating a guanosine-3', 5'-cyclic monophosphate (cGMP)-mediated cascade, which induces vascular smooth muscle relaxation and vasodilation. Endothelium-derived NO has been shown to be an important mediator of resting pulmonary vascular tone [15] and a modulator of hypoxic pulmonary vasoconstriction [16]. With the elucidation of NO physiology, free inhalation NO gas emerged as a selective pulmonary vasodilator. Currently, however, the only US Food and Drug Administration (FDA) approved use of iNO is in newborns with hypoxemic respiratory failure and persistent pulmonary hypertension.

Sildenafil is a phosphodiesterase inhibitor specific to PDE-5, the predominant isoenzyme present in pulmonary vascular smooth muscle. Vascular smooth muscle relaxation is moderated by PDEs; enzymes which catalyze the breakdown of cGMP to an inactive form. Therefore, sildenafil acts on the same iNO-induced cGMP cascade, but operates downstream, inhibiting the breakdown of Cgmp [17]. Previous reports outline the use of sildenafil to augment therapy with iNO for severe pulmonary hypertension [18], in the case of pulmonary hypertension associated with PAVMs [3,4], and to attenuate rebound post-operative pulmonary hypertension after iNO withdrawal [19], however no reports document the use of sildenafil for PAVMs without associated pulmonary hypertension in pediatric or adult patients.

In August 2012, citing a recent publication [20], the FDA issued a warning on the long-term use of sildenafil in pediatric patients with pulmonary hypertension [21]. In their warning, the FDA noted that: "This recommendation against use is based on a recent long-term clinical pediatric trial showing that: (1) children taking a high dose of Revatio [sildenafil] had a higher risk of death than children taking a low dose and (2) the low doses of Revatio are not effective in improving exercise ability. Most deaths were caused by pulmonary hypertension and heart failure, which are the most common causes of death in children with PAH." The case reported here occurred prior to the 2012 warning. Further, it is unclear the extent to which the FDA warning applies to our patient because our patient demonstrated clinically significant response to a dose of sildenafil that was well below the "high" dose range (based on our patient's weight, 9 mg four times daily would fall into the low

to medium dose range reported by Barst et al. [20]. Clinicians should be cautious, however, in using sildenafil long-term in any pediatric patient.

In the current case, the patient developed acute on chronic hypoxia immediately after operative excision of a maxillary arteriovenous malformation and coil embolization. It is unclear what precipitated this change in cardiopulmonary physiology. Possible explanations for his decreased systemic saturation include: (1) an increase in shunt fraction, (2) systemic changes such as increased oxygen consumption, decreased cardiac output, decreased hemoglobin and/or decreased oxygen delivery, or (3) a combination of these changes. An increase in shunt fraction could have occurred by a disruption in the balance of pulmonary vasoconstriction of normal pulmonary vasculature relative to the PAVM or from other postoperative changes (e.g., prolonged supine position postoperatively). However, other post-operative changes, such as increased systemic oxygen consumption, decreased cardiac output, decreased hemoglobin concentration or decreased oxygen delivery could also lead to a decline in systemic saturation, regardless of the shunt fraction. Any of the above post-operative changes could have led to acute hypoxia and therefore hypoxic vasoconstriction of the normal pulmonary vasculature, decreasing the mixed venous oxygen saturation and increasing the shunt fraction, respectively, and ultimately diminishing systemic saturation.

We suspect that the initiation of iNO induced selective vasodilation of the normal pulmonary vasculature, thereby decreasing its sum total resistance relative to the PAVM, and promoted flow through the gas-exchange units with an improvement in oxygen saturation. The addition of sildenafil to our therapeutic regimen sustained pulmonary vasodilation and provided the opportunity to wean iNO therapy and discharge from the hospital. Although the exact physiological mechanism at play in this case remains unclear, we suspect that because the PAVMs had extremely low resistance at baseline, the addition of sildenafil lead to a significantly greater percentage reduction in pulmonary vascular resistance in the normal vasculature when compared to the percentage reduction in the PAVMs. As such, while the reduction in pulmonary vascular resistance caused by the sildenafil was non-selective, because the percentage reduction was significantly greater in the normal, ventilated, lung segments, the overall ventilation/perfusion match improved. Finally, while iNO has been reported for use in hypoxemia due to PAVMs, we report the additional use of sildenafil for the chronic management of inoperable PAVMs.

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