CASE REPORT

Sevoflurane-Induced Diffuse Alveolar Hemorrhage

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ABSTRACT

Diffuse alveolar hemorrhage (DAH) is a potentially life-threatening pulmonary pathology which results in intra-alveolar hemorrhage secondary to disruption of the alveolar capillary basement membrane. Most commonly, these patients present with hemoptysis, hypoxemia and pulmonary infiltrates. Although rare, sevoflurane, an inhalational anesthetic used as a rapid induction agent for anesthesia may be implicated in the etiology of DAH. We report a case of a 21-year-old otherwise healthy male found to have postoperative diffuse alveolar hemorrhage secondary to sevoflurane inhalation. Thus far, only five documented cases describing sevoflurane induced diffuse alveolar hemorrhage have been described in the literature, with prior cases also showing a clear temporal association between sevoflurane administration and symptom onset. Although uncommon, we must take sevoflurane into consideration as a possible etiology of diffuse alveolar hemorrhage when encountering signs of respiratory distress and hemoptysis in postoperative patients.

KEYWORDS: Sevoflurane; Anesthesia; Diffuse Alveolar Hemorrhage; Respiratory Distress; Critical Care

INTRODUCTION

Diffuse alveolar hemorrhage (DAH) is a pulmonary pathology that can be life-threatening. It is defined as bleeding into the alveoli secondary to disruption in the capillary-alveolar basement membrane, disc disruption is commonly caused by inflammation of the vasculature of the alveoli and the most common presenting symptom is hemoptysis although it may not always present in this manner [1]. Our case details a 21-year-old otherwise healthy male found to have postoperative diffuse alveolar hemorrhage secondary to sevoflurane inhalation in the absence of other risk factors or other causes during an uncomplicated orthopedic procedure.

CASE PRESENTATION:

An otherwise healthy 21-year-old male with a height of 181 cm, weight of 90 kg, and a body mass index of 27.47 with no significant past medical history or known drug allergies or history of recreation substance abuse, presented to the emergency room due to intractable left hip pain secondary to a partial tear of the iliopsoas muscle diagnosed after a gym injury three weeks prior. He presented with an inability to bear weight on the extremity and was experiencing spasms in the left groin, however the remainder of his physical examination and vital signs were within normal limits. Despite minimal activity, bedrest, and analgesia, the patient's left hip and groin pain continued to worsen. Patient denied any fever, chills, nausea, vomiting, or diarrhea. He denied shortness of breath, chest pain or palpitations.

Laboratory results revealed leukocytosis with a left shift, normocytic anemia, thrombocythemia, elevated erythrocyte sedimentation rate, C-reactive protein, and procalcitonin (Table 1). Magnetic Resonance Imaging (MRI) of the left hip revealed septic arthritis and osteomyelitis requiring an emergency incision and drainage, the fluid from the incision and drainage confirmed the MRI findings after lab analysis. The patient was given 2mg/2mL midazolam, 350 mcg fentanyl, 250 mg propofol, 2 g cefazolin, 4 mg ondansetron, and sevoflurane titrated for general anesthesia. End-tidal carbon dioxide ($ETCO_2$) during the procedure ranged between 21-69 mmHg, The patient was also afebrile during the procedure with a temperature of 36.8°C. Surgery was completed within 1 hour and 10 minutes and cultures were obtained. An hour following the surgery, the patient became tachycardic with a heart rate of 100-110 beats per minute, hypertensive with a systolic blood pressure between 140-150 mmHg, and tachypneic with 30 breaths per minute, but improved with oxygen supplementation.

However, the morning following the procedure, the patient complained of chest tightness, shortness of breath, and blood-tinged sputum. Patient was hypoxic and diaphoretic. He was placed on 3 L/min of oxygen via nasal cannula which improved saturation and was given one

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Table 1. Laboratory results on admission.

Laboratory Test	Patient's Laboratory Values	Normal Laboratory Value Range
White Blood Cell Count	16.0×10^9/L	3.0-10.0 $\times 10^9$/L
Hemoglobin	10.6 g/dL	13.5-17.0 g/dL
Platelet count	446×10^9/L	150-400 $\times 10^9$/L
Erythrocyte Sedimentation Rate	80 mm/hour	0-14 mm/hour
C-Reactive Protein	234.2 mg/L	0-8 mg/L
Procalcitonin	0.81 ng/mL	< 0.08 ng/mL
MCV	82.4 fL	80.0-99.0 fL
PT	14.3 Seconds	12.2-14.5 Seconds
INR	1.10 Ratio	0.91-1.40 Ratio
Neutrophil Absolute	11.99×10^9/L	2.00-7.50 $\times 10^9$/L
Lymph Absolute	2.03×10^9/L	1.00-4.00 $\times 10^9$/L
Monocyte Absolute	1.19×10^9/L	0.00-1.00 $\times 10^9$/L
Eosinophil Absolute	0.02×10^9/L	0.00-0.50 $\times 10^9$/L
Basophil Absolute	0.03×10^9/L	0.00-0.20 $\times 10^9$/L
IG Absolute	0.12×10^9/L	0.00-0.10 $\times 10^9$/L

0.3mg dose of sublingual nitroglycerin without improvement of chest pain. Arterial blood gases were taken and revealed severe alkalosis (pH 7.66) with a low $PaCO_2$ (19 mmHg) and bicarbonate (21 mmol/L), suggesting the patient was in acute respiratory alkalosis, calculated alveolar arterial oxygen gradient (A-a gradient) was 111.9 mmHg and the estimated normal gradient in the patient was 9.3 mm Hg showing an elevated A-a gradient, a base excess was calculated showing 0.1 mmol/L with a calculated bicarbonate of 20.7 mmol/L calculated.

Further investigative tests and imaging were performed given the patient's hypoxic state. 12-lead electrocardiogram showed sinus tachycardia without significant ST segment abnormalities. Chest x-ray revealed extensive perihilar opacities with more confluent left lower lobe consolidation without evidence of pleural effusions or pneumothorax. Computed Tomography Angiogram (CTA) was obtained and revealed numerous nodular opacities and areas of more confluent consolidation involving the bilateral upper lobes, right middle lobe, lingula and bilateral lower lobes which were more central in location (Figure 1). Pulmonology recommended a bronchoscopy which was revealing for DAH, thought to be secondary to sevoflurane exposure. Alternative diagnoses were worked up as his presentation was concerning for possible vasculitis as well, the patient underwent testing for hepatitis serologies which were negative active infection however consistent with previous vaccination history. Patient was also tested for antinuclear antibodies (ANA), anti-glomerular basement membrane (Anti-GBM) antibodies, anti-phospholipid antibodies, human immunodeficiency virus (HIV), perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), antineutrophil cytoplasmic antibodies (c-ANCA), complement levels, and cryoglobulins, which came back negative, further cementing our diagnosis. Urinalysis was also negative for any macroscopic or microscopic abnormalities both at time of admission and follow up. Therefore, further invasive workup for vasculitides was not indicated.

During bronchoscopy, serial samples could not be taken due to hypoxic events (desaturated to 65%), necessitating an immediate termination of the procedure.

Oxygen supplementation at 4-5 L/min was continued after bronchoscopy along with the antibiotics for the infection with ceftriaxone (2000mg) and vancomycin (1000mg). The patient also received three days of high dose of IV methylprednisolone (250mg). Chest pain and hemoptysis resolved; however, the patient was slowly weaned off supplemental oxygen over the 3 days. Following completion of methylprednisolone, the patient received five days of Prednisone 40 mg. Chest x-ray was repeated and showed improved bilateral perihilar infiltrates. Patient was able to be weaned completely off the supplemental oxygen and pulmonology advised adding sevoflurane to his allergy list.

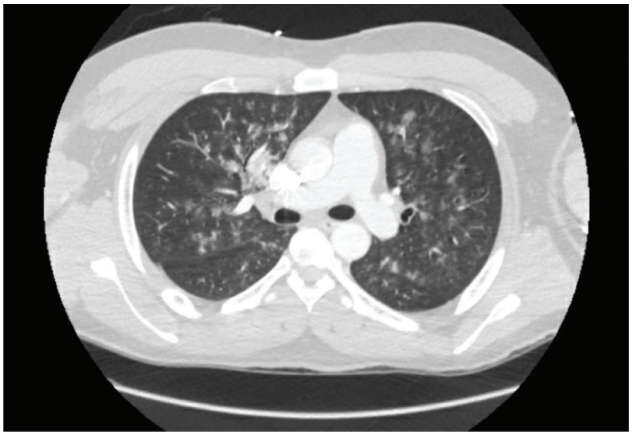

Fig. 1. Chest CT axial section - Extensive bilateral abnormal lung opacities, which are more prominent in the perihilar regions of the lungs, but are scattered within all lobes of the lungs.

DISCUSSION

Sevoflurane is a colorless, volatile, non-flammable liquid that has been used as an inhalation anesthetic for the past 30 years [2]. Sevoflurane has an oil/gas partition coefficient of 47.2 and a minimum alveolar concentration (MAC) of 2.05%, making it three times more potent than its predecessor, desflurane [3]. Sevoflurane also has a low blood/gas partition coefficient of 0.69, making it an ideal choice for rapid induction and maintenance in the operating room [2]. The mechanism of action of sevoflurane and other volatile inhalation anesthetics is largely unknown at this time, but it is thought to amplify signals to GABA receptors and cause favored central nervous system (CNS) depression [3].

Sevoflurane is metabolized directly by alkaline carbon dioxide absorbents in the circuits of anesthesia machines,

resulting in the production of toxic metabolites. Among these metabolites, fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether, also referred to as Compound A, has been shown through studies to cause direct renal toxicity [4,5]. The connection between Compound A and pulmonary toxicity has not been studied at this time; However, other volatile gases have been known to elicit inflammation and pulmonary endothelial damage through the activation of the arachidonic cascade [6]. Sevoflurane, in theory, may have similar mechanisms and may lead to increased alveolar permeability and oxidant-induced pulmonary vasoconstriction, and thus potential DAH [6].

A few case studies in prior literature have described thermal airway injuries secondary to exothermic reactions with sevoflurane and carbon dioxide absorbers in the anesthesia circuits, evident by necrosis, hemorrhage, and ulceration on bronchoscopy [7,8]. However, the bronchoscopy performed on our patient showed only erythema and inflammation and no signs of thermal airway injury. Infection, infiltrative diseases, rheumatic, vasculitides, and malignancy were ruled out for our patient and he also responded well to IV glucocorticoid therapy, making the connection between sevoflurane and the onset of DAH more likely. Thus far, there have been five documented cases describing sevoflurane-induced DAH in the absence of thermal airway injury [1,9-12]. Some similarities that are observed between most of these cases and our patient is that they were all of a similar age demographic and the time of onset of respiratory symptoms was approximately 1 hour after the surgery/procedure.

CONCLUSION

DAH is a syndrome that can abruptly present with cough, hemoptysis, hypoxemia, and pulmonary infiltrates and can be life-threatening. Although there have only been 5 reported cases making a connection between sevoflurane use and DAH, we must take sevoflurane into consideration as a possible etiology of this syndrome when encountering signs of respiratory distress and hemoptysis shortly after anesthesia. We conclude that the underlying mechanism is related to the activation of the arachidonic cascade, leading to oxidant-induced pulmonary vasoconstriction and resulting DAH. If patients are exposed to volatile inhaled anesthetics in the absence of other risk factors and present with this symptomatology, DAH should be on any clinician's differential when working up this kind of presentation.

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