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Diffuse Alveolar Hemorrhage Due to Drugs: Two Case Reports

İlaçlara Bağlı Olarak Gelişen Diffüz Alveoler Hemoraji: İki Olgu Sunumu

Sümeyra Kaplan, Ceyda Anar, Muzaffer Turan, Bunyamin Sertogullarindan

Abstract

We present here two cases who developed diffuse alveolar hemorrhage (DAH) after using inhaled anesthetic sevoflurane and warfarin as an anticoagulant. The first patient was a 32-year-old male who underwent general surgery for appendicitis, and who developed sudden hypoxemia and bleeding at the end of the operation. Bilateral diffuse alveolar infiltrates were identified on chest X-ray, and decreased serum hemoglobin in the postoperative period. The hypoxemia resolved on the fifth day, and alveolar infiltrates disappeared from the chest X-ray. The second case was prescribed Coumadin for the treatment of atrial fibrillation and was found to have an INR value of 12.6 upon presentation to the emergency department with a complaint of hemoptysis. The patient was administered intramuscular vitamin K, and the pulmonary infiltrates were noted to have regressed radiologically on the fifth day. Although DAH is rare with both drugs, early diagnosis and treatment can be lifesaving.

Keywords: *Alveolar hemorrhage, warfarin, sevoflurane.*

Öz

Antikoagülan olarak inhale anestezik sevofluran ve varfarin kullanımına bağlı yaygın alveoler kanama (DAH) gelişen iki olguyu sunmayı amaçladık. Hastanın ilki apandisit nedeniyle genel cerrahiye başvuran 32 yaşında bir erkekti. Ameliyat sonunda ani hipoksemi ve kanama tespit edildi. Akciğer grafisinde bilateral diffüz alveoler infiltratlar görüldü. Postoperatif dönemde serum hemoglobin seviyesinde düşüş gözlendi. Beşinci günde hipoksemi düzeldi ve akciğer grafisinde alveolar infiltratlar kayboldu. İkinci olgumuzda atriyal fibrilasyon nedeniyle coumadin kullanılmış olup, acil servise hemoptizi şikayeti ile başvuran hastanın INR değeri 12.6 idi. Hastaya intramusküler K vitamini verildi. Beşinci günde radyolojik olarak akciğer infiltratlarında gerileme gözlendi. Her iki ilaca bağlı DAH yaygın olmasa da erken tanı ve tedavi hayat kurtarıcı olabilir.

Anahtar Kelimeler: *Alveoler hemoraji, warfarin, sevofluran.*

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Diffuse alveolar hemorrhage (DAH) is a rare syndrome that presents with different symptoms that can lead to life-threatening hemoptysis. While immune-mediated systemic vasculitis, such as Wegener's granulomatosis, and some drugs may play a role in its etiology, its exact pathogenesis is as yet unknown (1). We present here two cases of DAH that developed following the use of inhaled anesthetic sevoflurane and warfarin for atrial fibrillation during appendectomy operations.

CASE

Case 1: A 32-year-old male patient was admitted to the general surgery outpatient clinic with a preliminary diagnosis of appendicitis. Preoperative clinical, physical examination and laboratory values were within normal limits, and there was no additional disease. Arterial blood pressure was 135/92 mmHg; oxygen saturation was 98%, and heart and respiratory rates were 84 and 15 per minute, respectively. Contrast-enhanced upper and lower abdomen computed tomography (CT) imaging during the preoperative evaluation revealed normal lung parenchyma areas (Figure 1). The patient was given midazolam 1mg and remifentanil 0.5mg/kg for procedural sedation, and was intubated, and anesthesia was achieved with sevoflurane (3%) and remifentanil 0.125 mg/kg/min. Post-surgery, the patient developed bronchospasm and hypoxemia during extubation, and the following values were recorded in room air blood gas, pH: 7.36 PCO_2: 41.3 mmHg, PO_2: 51.5 mmHg, HCO_3: 22.6 mEq/L and saturation: 80.4%. A postoperative thorax CT of the patient in the intensive care unit revealed central weighted alveolar ground-glass consolidated densities in the bilateral parenchyma (Figure 2). Hemoptysis was noted in the intubation tube, and the patient was given oxygen support with a double jack (with nasal + mask support) after extubation. The preoperative hemoglobin value of the patient was 14.7 g/dL, and the hemoglobin value was 13.8 g/dL on the postoperative 1st day, 13 g/dL on the 2nd day and 12g/dL on the 3rd day. The postoperative coagulation parameters were INR: 1.2, the partial thromboplastin time (a PTT) was 15 seconds, and a platelet count of 222 000/μl was recorded. The patient was treated postoperatively with antibiotherapy, and antitussive and tranexamic acid, and had no significant hemoptysis in the following days. Serological tests for vasculitis and connective tissue disease were within normal limits. Bronchoscopy was considered for the patient, however the patient's hypoxemia regressed on the fifth postoperative day, and a control Posterior-anterior chest X-ray showed regression of bilateral parenchyma infiltrates (Figure 3), and so no bronchoscopy was performed.

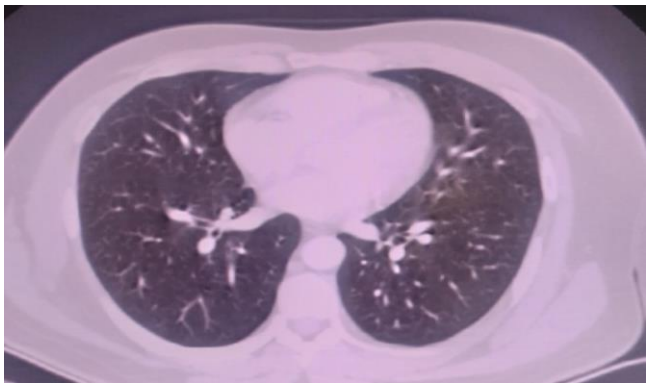

Figure 1: *Preoperative contrast-enhanced upper and lower abdomen computed tomography (CT) imaging, revealing the lung parenchyma in the examination area to be within normal limits*

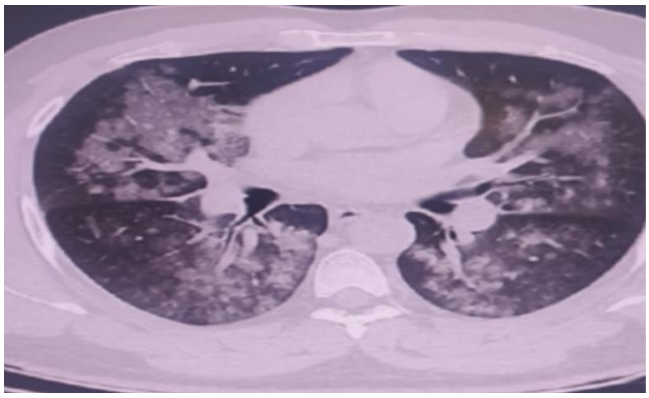

Figure 2: *Postoperative thorax CT revealing consolidated alveolar ground glass densities in the bilateral parenchyma*

Case 2: A 78-year-old female patient applied to the emergency department with cough and bruising in parts of the body with no hemoptysis or dyspnea. Around 5 days before applying to the emergency department the patient complained of 2–3 events of bleeding with sputum. The patient had atrial fibrillation, asthma and hypertension comorbidities, her arterial blood pressure was 153/82 mmHg, oxygen saturation was 93 with nasal support from 7L/min, heart rate was 73/min and respiratory rate was 16/min. A thorax CT revealed bilateral diffuse central and ground glass infiltrations (Figure 4). Laboratory values were INR 12.6, PTT 147.2, partial thromboplastin (a PTT) 88.5, hemoglobin 11.2 g/dL and platelet 242,000/μl. Due to the high INR and the present symptoms, the patient was given 1 ampoule of vitamin K administered intramuscularly in the emergency department, after which her INR was 3.03, PTT 36.2 and hemoglobin 11.6 g/dL. The patient started on antitussive treatment and the warfarin was stopped. On follow-up, the patient's hemoglobin values were recorded as 11.6 g/dL on day 1, 11.1 g/dL on day 2 and 12.1 g/dL on day 3. A PA chest X-ray taken on the 5th day revealed that the infiltrates in the bilateral parenchyma had regressed (Figure 5). Diffuse alveolar hemorrhage due to warfarin was thought to be due to the improvement of the

infiltrating areas radiologically and the regression of hemoptysis and bruising in the body in such a short time.

DISCUSSION

DAH has been described as bleeding originating from the microvascular structure of lung parenchyma (2). Although immune causes related to vasculitis are frequently, there are also non-immune causes such as heart disease, coagulation disorders, infections and drugs (1). In addition to asymptomatic radiological abnormalities, massive hemoptysis can also be seen in DAH. In most cases, a history of hemoptysis, low hemoglobin and bilateral diffuse patchy radiological infiltrates should alert physicians to the possibility of DAH. Bronchoscopy may rule out other causes of hemoptysis. The fact that BAL is hemorrhagic can contribute to a diagnosis of DAH (1). Both of the presented cases had low serum hemoglobin levels. The clinical and radiological evaluations of the patients supported the diagnosis of DAH and ruled out other causes in the etiology. At the same time, the rapid radiological improvement led us to consider drug-related etiology. Both cases had clinical dyspnea and hemoptysis. In our patient (case 2), who was dependent on warfarin, it was thought to be the lung involvement of COVID-19 pneumonia, given the ongoing pandemic, however, the rapid radiological regression in just 5 days, the low hemoglobin level and the high INR level at the time of admission also suggested DAH. Active pulmonary symptoms other than dyspnea were not observed in either of our cases. The oxygen needs of both patients, who were followed up with high oxygen support on the first day, continued to decrease.

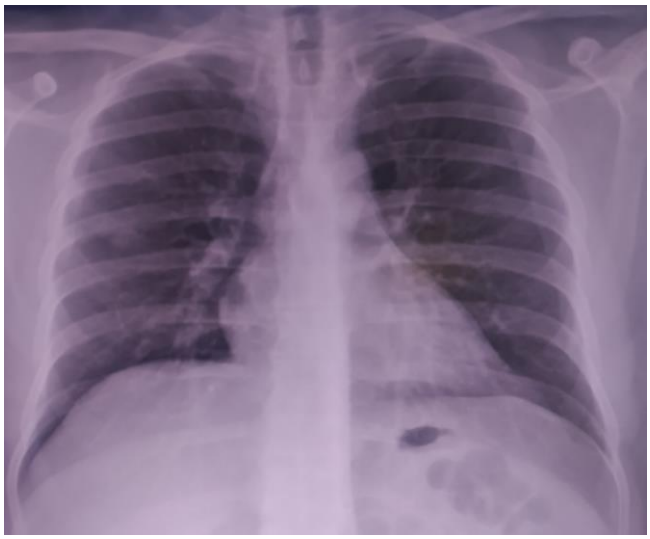

Figure 3: Posterior-anterior chest X-ray on the fifth postoperative day in which the bilateral parenchyma infiltrates can be seen to have almost completely regressed

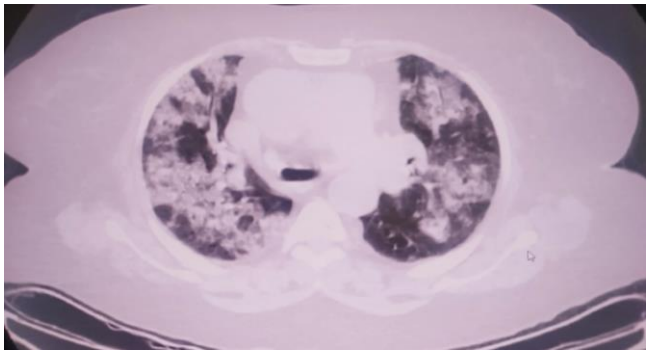

Figure 4: Bilateral diffuse central and ground glass density infiltrates on thorax CT imaging

Given the unexplained early onset of postoperative alveolar bleeding, we can conclude that the causative agent was sevoflurane, an inhaled anesthetic agent used for general anesthesia. Although sevoflurane has been associated with a number of respiratory side effects, including cough, apnea, laryngeal spasm and respiratory depression, alveolar hemorrhage occurs in only a small number of cases. Fat-soluble volatile gases may increase the inflammatory response by increasing the arachidonic cascade in the cell membrane, increasing alveolar permeability and oxidative stress (3,4), and previous studies have suggested that the mechanism causing DAH by sevoflurane may be related to this (5,6). It has also been shown that sevoflurane inhibits platelet function and decreases platelet aggregation rates (7,8).

Cases of DAH linked to sevoflurane have been reported in literature, although it has been suggested that cocaine and marijuana use accompanying sevoflurane may also lead to DAH in some cases (5,9,10,11), although the relationship between drug use and DAH in these studies remains speculative.

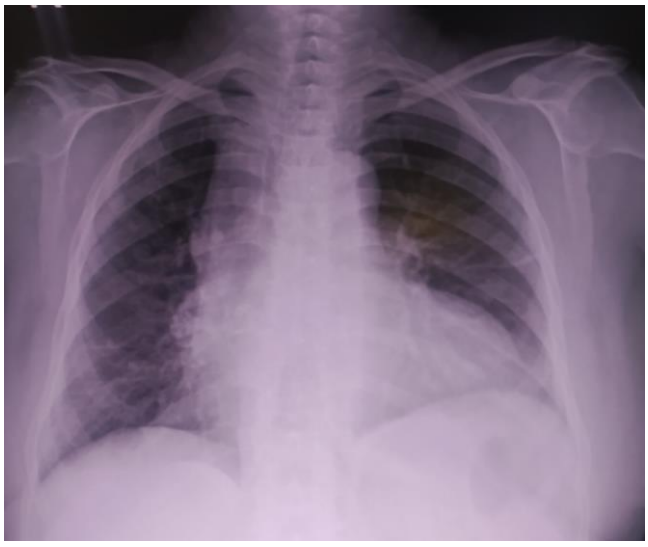

Figure 5: Regressed infiltrates observed in the bilateral parenchyma on PA chest X-ray

Mersh et al. (12) and Hao et al. (13) both suggested that alveolar hemorrhage may be associated with sevoflurane and negative pressure pulmonary edema. In two cases, none of the predisposing factors or causal causes were present as in our patient. Austin et al. (6) presented a case of a young male patient who underwent cystoscopy to widen the urethral stenosis, Cengiz et al. (14) reported on a young male patient who underwent orthopedic surgery and Yıldız et al. (15) reported on a 29-year-old male patient who applied for plastic surgery due to gynecomastia. All of these patients were males aged 20–40 years.

The drug in the second case presented here that caused DAH was Warfarin – an anticoagulant that is frequently prescribed all around the world. Warfarin-associated alveolar hemorrhage was first described by Brown et al. (16), and several warfarin-related cases of DAH have been reported since in literature (17,18).

The early diagnosis of DAH can be lifesaving, as the prognosis worsens over time. Treatment involves the destruction of the alveolar capillary membrane and the underlying cause, for which corticosteroids and immunosuppressives are used (1). Clinical and radiological regression was observed in both cases in the present study within a few days of drug discontinuation, since the underlying cause was drug related. In a patient with sevoflurane-induced DAH treated with daily methylprednisolone (1 g) administered intravenously for 3 days, the alveolar infiltrates disappeared on chest X-ray on the fourth day (15). In cases with bleeding due to oral anticoagulant use, the aim is to reverse any decreases in vitamin K-dependent coagulation factors. At this point, vitamin K antagonists should be stopped, oral or intravenous vitamin K supplementation should be provided, and clotting factors should be increased with Fresh Frozen Plasma. Prothrombin complex concentrates are used in cases with major bleeding (19). Intravenous vitamin K was administered to the patient in the present study who developed DAH due to warfarin. As supportive treatments, coagulation disorders should be corrected, and platelet replacement, careful fluid support and adequate oxygenation should be provided. In the event of hypoxemia, the NIMV support of patients is relatively contraindicated due to the risk of aspiration, and high-level oxygen support or high-flow oxygen support may be more appropriate. High oxygen support was provided to both of the presented cases due to the development of hypoxemia.

CONCLUSION

Since there was no underlying disease in either of our cases, we concluded that the responsible agents behind DAH were the inhaled anesthetic sevoflurane in the first case, and warfarin in the second case. The DAH development associated with either drug is uncommon, however, early diagnosis and treatment can be lifesaving. The possibility of DAH should be considered in patients receiving warfarin therapy and using sevoflurane as a general anesthetic agent in the presence of sudden onset respiratory failure and hemoptysis or low hemoglobin, as well as the identification of diffuse alveolar infiltrates in the bilateral lung parenchyma on radiological imaging.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - S.K., C.A., B.S., M.T.; Planning and Design - S.K., C.A., B.S., M.T.; Supervision - S.K., C.A., B.S., M.T.; Funding - S.K., M.T.; Materials - S.K., B.S.; Data Collection and/or Processing - S.K., C.A.; Analysis and/or Interpretation - S.K., C.A.; Literature Review - S.K., C.A.; Writing - S.K., C.A.; Critical Review - S.K., C.A.

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