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Diffuse alveolar hemorrhage associated with low molecular weight heparin

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Abstract

Diffuse alveolar hemorrhage (DAH) has a varied etiology, including anticoagulation drugs. There is conflicting evidence whether low molecular weight heparin (LMWH) has a low risk of bleeding complications compared to unfractionated heparin. We report here a case of DAH in a 74-year-old woman who was administered enoxaparin, a LMWH, after bilateral total knee arthroplasty. Although congestive heart failure after blood transfusion and fluid infusion could in part be associated with the bleeding, LMWH may be a major cause of DAH since the patient quickly recovered after its cessation. DAH should be of concern when acute respiratory failure with ground-glass shadow develops in both lungs during anticoagulation therapy with LMWH.

Introduction

A hemorrhagic event concomitant with pulmonary diseases can be life threatening. Diffuse alveolar hemorrhage (DAH) should be considered when the bleeding area is diffusely distributed in both lungs. Severe damage to pulmonary capillary vessels associated with collagen diseases or anti-neutrophil cytoplasmic antibody (ANCA)-related vasculitis often cause DAH. Medications, such as penicillamine and amiodarone, also cause DAH by injuring the endothelium of lung capillaries [1]. In addition, several cases of anticoagulation associated with DAH have been reported, even without vascular damage [1, 2].

Low-molecular-weight heparin (LMWH) was developed to minimize the risk of bleeding compared to unfractionated heparin (UFH). Previous reports suggest that bleeding complications from LMWH, when used for prophylaxis of postoperative venous thromboembolism, are fewer than those from UFH [3]. In contrast, a few clinical studies have demonstrated similar bleeding risk between LWMH and UFH [4]. Thus, there is conflicting evidence whether LMWH is associated with the risk of a severe hemorrhagic event in the lung.

Case Report

A 74-year-old woman, non-smoker, who underwent bilateral TKA for the treatment of osteoarthritis, presented with mild dyspnea and a small amount of hemosputum 2 days after surgery. She was given 2,000 IU of enoxaparin twice daily to prevent deep vein thrombosis from 24 hour after surgery. Her respiratory failure developed on day 4. We suspected that she might have congestive heart failure because 1250 ml of fluids were given during surgery, then followed by 1000 ml in the next 12 hours, and 400 ml of autologous blood was given on day 3. In addition, a chest radiograph (Figure 1 A) and computed tomography (Figure 2 A, B) scans showed not only ground-glass opacity, but also pleural effusion, in both lungs. The patient's N-terminal prohormone of brain natriuretic peptide (NT-proBNP) level was 1,212 pg/ml on day 5 after surgery. At that time, we presumed that her hemosputum and respiratory failure were associated with heart failure. Prothrombin time and international normalized ratio (PT-INR) was 0.95 and activated partial thromboplastin time (APTT) was 32.4 second at that time.

Six days after surgery, respiratory failure developed despite treatment of heart failure with a diuretic. We performed bronchofiberoscopy to identify the cause of her respiratory failure. We presumed the patient might have DAH, because her bronchoalveolar lavage fluid (BALF) was red in color and thickened during 3 sequential lavages. Approximately 12% of hemosiderin phagocytic macrophages were found in the BALF. No bleeding focus was remarkable in the upper airway, or bronchus.

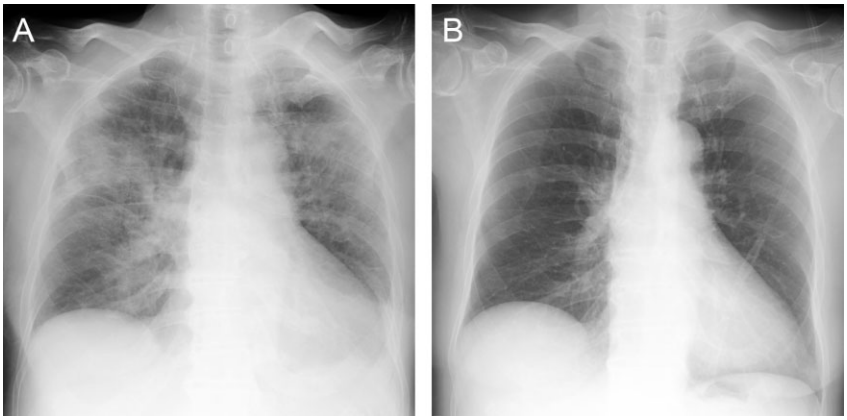

Figure 1. Chest radiograph on day 5 after surgery (A) showed disseminated ground-glass opacity in the upper and lower parts of both lungs. These findings quickly disappeared on day 13 (B).

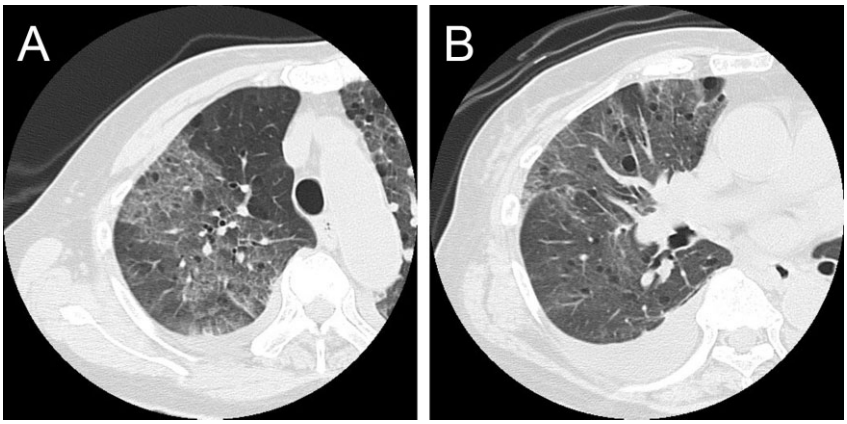

Figure 2. Chest computed tomography scan on day 5 after surgery showed disseminated non-segmental ground-glass opacity in the upper (A) and lower (B) lungs. A small amount of pleural effusion was detectable.

DAH is caused by a high incidence of infection, autoimmune vasculitis, or malignant neoplasm in the lung or airway. However, no autoantibody, including ANCA, was detectable in the blood; no pathogen was detectable in the cultured BALF; and no new medication was started other than enoxaparin. Therefore, we assumed enoxaparin might be a major cause of DAH and discontinued it.

The chest radiograph abnormalities and respiration improved by the next day after stopping enoxaparin. At that point, a slightly ground-glass opacity remained on the chest radiograph, but gradually became clear after 2 weeks from surgery and after a week from stopping enoxaparin (Figure 1 B). Echocardiography performed before and after surgery showed normal left ventricular function.

Discussion

LMWH was expected to have less bleeding risk, because of its high specific anti-Xa activity and less anti-IIa activity compared to UFH. However, many clinical studies demonstrated a similar risk of bleeding between UFH and LWMH, and rarely severe bleeding in either medication group [4].

DAH associated with anticoagulants, such as tissue plasminogen activator, urokinase, warfarin, and UFH [2] has been reported. Many patients show hemosputum, but it is absent in patients with occult DAH, making diagnosis without bronchoalveolar lavage difficult. There is conflicting evidence whether the use of LMWH is associated with the risk of a severe hemorrhagic event in the lung, including DAH. Thus, no case of DAH caused by LMWH has so far been reported.

Although, respiratory failure and radiographic abnormalities improved by the next day after stopping enoxaparin, it is difficult to assume enoxaparin alone caused DAH. We speculated that DAH developed via a synergy between LMWH and elevated capillary pressure, which was associated with congestive heart failure after blood and fluid transfusion under general anesthesia. In our patient,

TKA was performed on both knees on the same day. Her elevated NT-proBNP level suggested stress on the cardiovascular system after surgery. Previous reports suggest that elevated left atrial pressure, which is associated with mitral valve disorder, may be the cause of DAH [5]. However, her heart failure was unlikely a major cause of DAH, but just a co-factor, because treatments for congestive heart failure did not improve her condition.

Unlike UFH, frequent monitoring of LMWH is not necessary, because variability in the dosage requirement of LMWH is much lower than that in UFH. Active prothrombin time (APTT) is a standard monitoring method for UFH, but is not available for LMWH. The anti-Xa assay is the most common monitoring method for LMWH. Since the effect of LMWH depends on weight and renal function, dosage adjustment is recommended in patients with renal dysfunction to minimize bleeding risk. In our patient, anti-Xa levels were not determined before and after surgery. However, her renal function was normal and APTT was within the normal range.

Although LMWH is presumed to have a low risk of hemorrhagic complications, it could contribute to the progression of DAH, sometimes synergistically with other risk factors such as congestive heart failure.

Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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