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Use of a protease inhibitor, ulinastatin, for reexpansion pulmonary edema following evacuation of bilateral pleural effusion

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Introduction

Reexpansion pulmonary edema (RPE) following treatment of pneumothorax, pleural effusion, and atelectasis has been described, but the mechanism involved is poorly understood and the outcome was fatal in 20% of cases reported in the past 30 years [1]. Recent studies suggest that RPE is due to reoxygenation injury of the lung microvasculature, accompanying neutrophil infiltration [2,3]. We treated a patient with severe RPE following rapid evacuation of bilateral pleural effusion using a protease inhibitor.

Case Report

A 48-year-old woman who had undergone radical mastectomy for breast cancer 2 years previously was admitted with symptoms of abdominal distension. Physical examination revealed retention of ascites and computed tomography confirmed bilateral ovarian tumors with ascites. A chest roentgenogram showed signs of bilateral pleural effusion, more marked on the right. Hemoglobin and serum electrolyte concentrations were within normal limits. Arterial blood pressure was 160/100 mmHg and the heart rate 72 beats/min. A tentative diagnosis of Krukenberg tumor was made and excision of the ovarian tumors was scheduled.

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Anesthesia was induced with thiopental 150 mg and succinylcholine 60 mg. After endotracheal intubation, anesthesia was maintained with 0.4% halothane in 40% nitrous oxide with vecuronium and fentanyl. Clear yellowish ascites, 3700 ml, was aspirated at laparotomy and bilateral ovarian tumors were excised. Arterial blood pressure and heart rate were stable throughout the procedure. The duration of surgery was 40 min, then bilateral pleurocentesis was performed with a 16-gauge catheter attached to a 100-ml syringe. About 1400 ml of effusion was aspirated from the right and 400 ml from the left thorax, over 10 min. Hyperinflation was done to expand the collapsed lung fields. Following discontinuation of anesthesia and reversal of the muscle relaxant, the patient was immediately awakened and extubated after confirmation of full recovery from muscle relaxation and regular respiration.

The patient was transferred to the intensive care unit (ICU), where 40% O_2 was administered via a face mask. A chest radiograph taken 30 min after admission to the ICU showed both lungs fully expanded but there were patchy opacities in the primarily collapsed areas. The patient did not complain of dyspnea. Thereafter, respiration became shallow with sporadic coughing. However, the blood pressure was stable at 120/80 mmHg and the heart rate at 80 beats/min. One hour later, she suddenly coughed up copious amounts of clear yellowish fluid, became cyanotic and agitated. Tachypnea (40/min) developed and the arterial blood pressure fell to 80/70 mmHg with an increase in heart rate to 140 beats/min. Arterial blood gas analysis revealed a pH 7.394, Pao_2 30 mmHg, $Paco_2$ 46 mmHg, and HCO_3 28.3 mEq/L while the patient was inhaling 40% O_2 via a face mask.

The patient was immediately reintubated and mechanical ventilation with a pressure support of 10 cmH_2O, a positive end-expiratory pressure of 10 cmH_2O, and Fio_2 of 1.0 was initiated. Dopamine 6 μg/kg/min and 5% albumin solution 100 ml/h were administered by continuous infusion. An intravenous bolus

injection of the protease inhibitor, ulinastatin (Miraclid, Mochida Pharmaceutical, Tokyo, Japan), 100 000 U, every 8 h, was started. Arterial blood gas under mechanical ventilation with a Fio_2 of 1.0 showed a pH 7.414, Pao_2 68 mmHg, $Paco_2$ 32 mmHg, and HCO_3 22.6 mEq/L. The edema fluid contained a total protein 4.0 g/dl. Over the next 10 h, the hemodynamic and respiratory status did not improve and large amounts of plasma-like fluid were suctioned from the endotracheal tube. The hematocrit was 46% on admission to the ICU and it increased to 54% during the first 3 h. Ten hours after the onset of pulmonary edema, and 2 h after the second injection of ulinastatin, the amount of sputum decreased and was foamy and whitish. There was gradual improvement in blood pressure and heart rate. Thereafter, Fio_2 and pressure support of mechanical ventilation were gradually reduced. Sixteen hours after the initial event, the Pao_2 was 81 mmHg during pressure support ventilation with a Fio_2 of 0.4, the hematocrit was 40%, and the arterial blood pressure 120/80 mmHg with a heart rate of 78 beats/min. Forty hours after initiating the ventilatory support, pressure support ventilation changed to continuous positive airway pressure, and the patient was subsequently extubated. After 3 days in the ICU, she was returned to the ward. The remaining course was uneventful, and she was discharged on the 14th postoperative day.

Discussion

Pulmonary edema in this patient was caused by increased capillary permeability as shown by the high protein content of the edema fluid, an increase in hematocrit value during the episode and interstitial edema localized in the reexpanded lung fields on the chest X-ray film. It is recognized experimentally and clinically that reexpansion of a collapsed lung after treatment of pleural effusion, pneumothorax, or atelectasis may lead to ipsilateral pulmonary edema [4–6]. Reexpansion pulmonary edema (RPE) is characterized by a marked increase in pulmonary capillary permeability and an accumulation of large numbers of neutrophils in the alveolar spaces, both of which are phenomena common to the adult respiratory distress syndrome (ARDS) [2,7]. Pathogenesis of RPE was tentatively proposed to include decreased lung interstitial pressure [8], decreased surfactant production [9], and mechanical stretching of membranes [9]. Recent studies have focused on the hypothesis that RPE is related to reoxygenation injury. RPE may be initiated by excess production of superoxide and other toxic oxygen metabolites in the reexpanded lung, and this may contribute to the increase in capillary permeability [2]. There are at least two possibilities regarding the contribution of neutrophils to RPE: The first is that neutrophils are a major source of oxygen free radicals and are directly responsible for alveolar-capillary membrane damage; another theory holds that, though associated with RPE, neutrophils do not directly contribute to its etiology [3].

Clinical manifestations of RPE vary from asymptomatic with only radiographic evidence to severe RPE which resembles ARDS. Mortality from RPE may result from the development of irreversible ARDS and eventually multiple organ failure. Treatment of severe RPE includes mechanical ventilation with positive end-expiratory pressure, volume replacement, and inotropic support. Severe hypoxemia and shock do not always respond to therapy. The therapeutic effects of colloid in the clinical setting of capillary leakage are highly controversial [10]. We used a colloid rather than a crystalloid for fluid replacement to restrict volume. Since the hemodynamic state in severe RPE is comparable to that in anaphylactic shock or a severe burn, there is no simple way to replace fluid and thus restore normal hemodynamics and minimize pulmonary capillary leakage. If a Swan-Ganz catheter is used to follow filling pressure, great care must be taken to interpret the results, since the pulmonary capillary wedge pressure may reflect alveolar, not pulmonary venous pressure.

We used ulinastatin, a protease inhibitor, to deplete neutrophils and inhibit neutrophil-elastase activity. Ulinastatin is a urinary trypsin inhibitor purified from human urine [11]. A marked direct inhibition of neutrophil-elastase activity by ulinastatin is not inactivated by oxygen radicals, thus differing from findings with an α_1-protease inhibitor [12]. Although it is not clear whether participation of neutrophils is the cause or effect of RPE, there are experimental and clinical data to show that neutrophil depletion attenuates edema formation in RPE and ARDS [7,13]. Ulinastatin has been reported to be effective in the treatment of ARDS [14]. In our patient, oxygenation and circulation improved as the pulmonary edema subsided, following the second intravenous administration of ulinastatin. However, ulinastatin has not proven efficacious in this setting since the present case lacks clear evidence.

Our experience with this patient clearly shows that a large volume of pleural effusion cannot be easily removed. Until the exact mechanisms of RPE are known, prevention and proper management of severe cases will remain a problem for anesthesiologists.

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