Acute pulmonary capillary leak syndrome during elective surgery under general anesthesia

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Abstract

A 75-year-old previously healthy man presented for elective resection of rectal cancer under general anesthesia. Six days before the operation, he had a high-grade fever, and elevated leukocyte count and C-reactive protein concentration, but this was resolved by an intravenous antibiotic. His condition was well controlled before the operation. Soon after the operation started, severe hypoxemia emerged, with low arterial pressure. Fiberoptic bronchoscopy demonstrated a massive amount of plasma-like edema fluid; the total amount of suctioned fluid was approximately 800 ml at the end of the surgery. This acute pulmonary edema appeared to be due to increased permeability rather than pulmonary congestion as indicated by chest radiography, pulmonary artery occlusion pressure, echocardiogram, and the protein-rich edema fluid. Elevated concentrations of the proinflammatory cytokines, interleukin (IL)-6 and IL-8, in both plasma and the pulmonary edema fluid, suggested a possible role of systemic and pulmonary inflammation in the development of this acute pulmonary capillary leak. According to the "two-hit" hypothesis, the bacterial infection preceding the operation may have primed the immune cells, and the following surgical stress may have then triggered rapid progression of acute respiratory distress syndrome. We should keep in mind that, especially following sepsis, sudden massive pulmonary capillary leak can occur during elective surgery, even though the patient's condition is well controlled.

Key words Acute respiratory distress syndrome (ARDS) · Proinflammatory cytokine · Capillary leak · Two-hit hypothesis

Introduction

The essential pathophysiology of acute respiratory distress syndrome (ARDS) is considered to be the increased vascular permeability caused by systemic and pulmonary inflammation [1]. Humoral mediators such as proinflammatory cytokines play an important role in the initiation and the progression of this syndrome [1–6]. Systemic inflammation can occur during major abdominal surgery; however, the development of ARDS during a well-controlled operation is quite rare. We describe a case of ARDS that occurred and rapidly progressed during elective rectal surgery in a patient under general anesthesia. Concentrations of proinflammatory cytokines in this patient are also described.

Case report

A 75-year-old previously healthy man (150 cm, 32 kg) presented for elective removal of rectal cancer. Six days before the surgery, the patient's temperature had increased to 38.7°C, with white blood cell count, 17 900·μl^{-1} and C-reactive protein, 8.8 mg·dl^{-1}. Urinalysis was positive for white blood cells, and urine sediments showed 30 to 50 white blood cells per high-power field. Sepsis from urinary tract infection was suspected, and the patient was treated with intravenous fosfomycin for 5 days, and then became afebrile. Two days before the operation, urinalysis was negative for white blood cells, and the number of white blood cells in urine sediments had dropped to 5 to 10 per high-power field. Arterial blood pressure, pulse rate, and body temperature were 132/68 mmHg, 60 bpm, 36.0°C, respectively, and a chest radiograph presented no significant findings (Fig. 1A) the day before the surgery.

Before anesthesia induction, an epidural catheter was inserted via the L2–3 interspace. A lumbar puncture was also made, between L3–4, and 2.5 ml of 0.5% isobaric bupivacaine was administered intrathecally to obtain muscle relaxation in the lumbo-sacral region. The upper level of neural blockade to cold and light touch sensation was Th4 bilaterally 5 min after the intrathecal drug

Fig. 1A,B. Chest radiographs showing **A** no significant findings preoperatively and **B** revealing diffuse bilateral infiltrates without cardiomegaly just after the operation

administration. Propofol and vecuronium were administered to facilitate tracheal intubation, and anesthesia was maintained with nitrous oxide (66%) and sevoflurane (0.5%–1.0%) in oxygen. Prior to skin incision, 5 ml of 1% lidocaine was administered via the epidural catheter, and cefazolin sodium was infused intravenously as a prophylactic antibiotic. At this point, arterial blood pressure was 140/84 mmHg; heart rate, 62 bpm; central venous pressure (CVP), 5 mmHg; and the finger oximetric saturation, 99%.

Thirty minutes after the operation started, arterial pressure, CVP, and oxyhemoglobin saturation decreased, to 74/38 mmHg, 0 mmHg, and 87%, respectively, and the diameter of the pupils was 3 mm bilaterally. Fiberoptic bronchoscopy revealed massive yellowish plasma-like fluid flowing out of the bilateral bronchi to the trachea. Pa_{O_2} was 49.5 mmHg; Pa_{CO_2}, 58.3 mmHg; and pH, 7.234 while the patient was inspiring 100% oxygen. Frequent tracheal suctioning, with recruitment maneuver, continuous dopamine infusion, and massive colloid and crystalloid resuscitation, was required during the surgery. The amount of suctioned pulmonary edema fluid was approximately 800 ml at the end of the operation. A chest radiograph just after the operation revealed diffuse bilateral infiltrates, without cardiomegaly (Fig. 1B).

The patient was taken to the intensive care unit, where a pulmonary artery catheter was inserted. The pulmonary artery occlusion pressure (PAOP) was 16 mmHg and the cardiac index was $2.5 \text{l} \cdot \text{min}^{-1} \cdot \text{m}^{2-1}$. Transthoracic echocardiography demonstrated a small pericardial effusion, but showed no signs of left ven-

Table 1. Concentrations of total protein and proinflammatory cytokines in plasma and in the pulmonary edema fluid

	Plasma	Pulmonary edema fluid
Total protein ($g \cdot l^{-1}$)	4.1	3.1
IL-6 ($pg \cdot l^{-3}$)	881.8	894.5
IL-8 ($pg \cdot l^{-3}$)	381.9	389.8

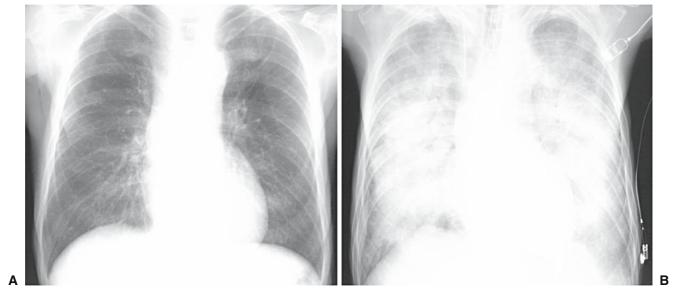Normal ranges, plasma IL-6, $<25 \text{pg} \cdot l^{-3}$; plasma IL-8, $<15 \text{pg} \cdot l^{-3}$
IL-6, interleukin-6; IL-8, interleukin-8

tricular asynergy and volume overload. Therefore the patient was diagnosed as having ARDS.

Table 1 shows the concentrations of total protein, interleukin-6 (IL-6), and interleukin-8 (IL-8) in the patient's plasma and alveolar edema fluid collected just after the operation. Concentrations of the cytokines were measured with a human IL-6 and IL-8 enzyme-linked immunosorbent assay kit (TFB, Tokyo, Japan). The patient was treated with mechanical ventilation with positive end-expiratory pressure, infusion of hydrocortisone (1000 mg·day^{-1} for 3 days), and continuous catecholamines. Continuous hemodiafiltration was needed temporarily because of acute renal failure. The patient was extubated on the eighth postoperative day, and he was finally discharged from the hospital on the twenty-third postoperative day.

Discussion

The current case was characterized by the sudden onset of massive pulmonary edema soon after the patient's

operation started. The pulmonary edema progressed rapidly, and the amount of edema fluid during the surgery was 800ml. The protein level in the fluid was 75% more than that in serum protein, indicating that it was exudative. The patient's extremely poor oxygenation, bilateral infiltrates, no cardiomegaly on the chest radiograph, and no signs of left atrial hypertension (indicated by PAOP and echocardiography) all supported the idea that the acute pulmonary edema was permeability edema rather than static edema.

Several drugs have been demonstrated to cause acute permeability lung edema. Luis et al. [7] reported the development of ARDS during an operation in a patient previously exposed to bleomycin, and they suggested that oxygen toxicity and bleomycin exposure were the possible cause of the ARDS. Although other drugs, such as intrathecal methotrexate [8] and intravenous aprotinin [9], have been reported to be possible causes of ARDS, no reports, as far as we investigated, have described the development of ARDS induced by the drugs that we used during the anesthesia. Furthermore, a multicenter analysis of adverse allergic reactions during anesthesia has indicated that acute pulmonary capillary leak was an unlikely clinical feature of drug allergy [10].

Aspiration of the gastric contents should be considered in patients with ARDS during anesthesia. Massive gastric fluid retention, emergency surgery, and multiple intubation attempts can be related to the aspiration of gastric contents during the induction of anesthesia [11]. However, our patient showed no signs of digestive tract obstruction before the operation, he had fasted for more than 10h, and was intubated easily at the first attempt, without evident regurgitation.

Therefore, the reason why ARDS progressed so rapidly during the patient's elective surgery remains a mystery. It is considered that the "two-hit" hypothesis can explain at least some categories of ARDS and acute lung injury, induced both experimentally [12,13] and clinically [7,14]. One possible explanation for the ARDS in our patient could be that sepsis from the urinary tract infection before the operation had first triggered systemic inflammation and primed neutrophils that accumulated in the lung. The following second event, i.e., the surgical invasion itself, then resulted in exaggerated systemic inflammation and acute pulmonary capillary leak.

The increased concentrations of the proinflammatory cytokines IL-6 and IL-8 in our patient's plasma and alveolar fluid also suggest that systemic and pulmonary inflammation played some role in his development of ARDS. Though major surgery itself can induce systemic inflammation, the IL-6 and IL-8 concentrations in plasma in our patient were apparently higher than those measured by the same enzyme-linked immunosorbent assay kit in patients who underwent esophageal cancer resection [15] and higher than those in patients with septic ARDS [16]. However, other studies [3–6] have shown that IL-6 and IL-8 concentrations in bronchoalveolar lavage or alveolar edema fluid were much higher, regardless of the cause of ARDS, than those in plasma. Unlike the findings in these studies, in our patient, the concentrations of IL-6 and IL-8 in plasma and in the pulmonary edema fluid were similar. It is possible that, in patients with ARDS, proinflammatory cytokines are produced mainly in the lung and then spill into the systemic circulation. In the present patient, the amount of capillary leak was so large that the extravascular fluid was immediately diluted by leaked plasma. The relatively higher cytokine/total protein ratios in the pulmonary edema fluid than those in plasma (Table 1) may indicate that the lung was the major source of the IL-6 and IL-8 production.

In summary, sudden and profound pulmonary capillary leak syndrome occurred during elective rectal surgery. The increased concentrations of the proinflammatory cytokines, IL-6 and IL-8, in the patient's plasma and in the lung, suggest the possible role of systemic and pulmonary inflammation in the development of this capillary leak. The combination of two insults, sepsis before the operation and the following surgical stress, may have triggered the rapid progression of ARDS. We should be aware that acute pulmonary capillary leak syndrome can occur during elective surgery even though the patient's condition is well controlled.

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