Case Report

Anti-thymocyte globulin induced non-cardiogenic pulmonary edema during renal transplantation

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Abstract

Non-cardiogenic pulmonary edema (NCPE) is a clinical syndrome characterized by simultaneous presence of severe hypoxemia, bilateral alveolar infiltrates on chest radiograph, without evidence of left atrial hypertension/congestive heart failure/fluid overload. The diagnosis of drugrelated NCPE relies upon documented exclusion of other causes of NCPE like gastric aspiration, sepsis, trauma, negative pressure pulmonary edema. We describe a 28year-old, 50 kg male with ASA risk III posted for laparoscopic renal transplantation, who developed NCPE after 4 hours of administration of rabbit anti-human thymocyte immunoglobulin (ATG). He was successfully treated with mechanical ventilatory support and adjuvant therapy. This report emphasizes that this fatal complication may occur with use of ATG.

Keywords: Anti-human thymocyte immunoglobulin, non-cardiogenic pulmonary edema, renal transplantation

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Introduction

Thymoglobulin, rabbit anti-human thymocyte immunoglobulin (ATG), is an immunosuppressive drug used as an anti-rejection therapy in solid organ transplantation and in hematological diseases. An association between ATG and acute lung injury was first described in an experimental model in 1975. Since then, few cases have been reported from which it is believed that in rare cases, ATG is responsible for a spectrum of lung injuries varying from transient infiltrate to full-blown acute respiratory distress syndrome (ARDS).

We report a case of ATG-induced non-cardiogenic pulmonary edema (NCPE), its diagnosis and management under general anesthesia.

Case Report

A 28-year-old, 50 kg man with ASA risk III was posted for laparoscopic renal transplantation. He was diagnosed to have hypertension since 2 years and chronic interstitial nephritis leading to chronic renal failure (CRF) since 6 months and was on maintenance hemodialysis twice a week. He had undergone laparoscopic cholecystectomy and bilateral nephrectomy 2 months back without any complications. In preoperative examination, his blood pressure was controlled with Nifedipine 20 mg, Metoprolol 50 mg, and Clonidine 0.1 mg. Preoperative electrocardiogram (ECG) was normal nd 2-Dimensionl Echocardiography showed 60% ejection fraction with no wall motion abnormality. There was no history of allergic drug reactions.

Preoperative dialysis was done on the previous evening of the surgery. Morning ECG, serum electrolytes and coagulation profile were normal. He received morning dose of all antihypertensives. His morning blood pressure was 110/70 mm Hg in the preoperative room. There were no signs of overload on auscultation. Test dose of Inj. ATG was given half an hour before induction.

After premedication with Inj. Glycopyrrolate 0.2 mg and Inj. Fentanyl 150 µg, the patient was given balanced general anesthesia. Induction was done with thiopentone

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sodium 350 mg, and suxamethonium 75 mg was given to facilitate endotracheal intubation. Nitrous oxide, isoflurane and atracurium were used for maintenance anesthesia. Right-sided internal jugular vein was cannulated by Seldinger's technique for central venous pressure (CVP) monitoring. Continuous monitoring of ECG, Pulse oxymetry, Capnography , invasive blood pressure , CVP, airway pressure and temperature was done.

For surgical procedure, pneumoperitonium was created, keeping the CO_2 pressure between 12 and 15 mm Hg. Patient was placed at 25° head low position for vascular anastomosis and ureteric reimplant. Airway pressure was 21 cm H_2O after induction of anesthesia, which increased to 25 cm H_2O after pneumoperitonium and stabilized at 28 cm H_2O in head down position.

After confirming negative reaction to test dose of ATG and prophylactic administration of 100 mg IV Hydrocortisone and 45.5 mg of IV chlorpheniramine maleate, 75 mg of ATG diluted in 100 ml normal saline was started in central line which was to be given over a period of 4 hours.

Inj. Methyl prednisolone 500 mg in 500 ml of normal saline was also started as an anti-rejection therapy. Intraoperatively, 3 l of normal saline and 100 ml albumin 20% was given to keep the CVP between 15 and 20 mm Hg. No blood products were used during surgery. Inj. Mannitol 100 ml 20% was given during anastomosis. Inj. Furosemide 100 mg was given IV just before clamp release. Vascular anastomosis time was 45 min. Urine output was established immediately after clamp release. After achieving adequate hemostasis, ureteric reimplant was done. At the end of surgery, which lasted for 4.5 hours, the urine output was around 2 l.

Throughout the procedure, all parameters remained normal, but at the time of port closure, suddenly airway pressures were elevated up to 35–40 cm of H_2O. On manual ventilation, resistance was felt. All the causes of mechanical obstruction were ruled out. At that time, BP, temperature, $ETCO_2$ and CVP were normal. There was tachycardia (~120/min). Gradually, oxygen saturation started falling to less than 90% even with 8 l/min of oxygen, with persistent high airway pressures. On auscultation, coarse crepitations were present bilaterally. Arterial blood gas analysiswas normal except for decreased PaO_2 (54 mm Hg). Soon, copious pink frothy secretions started pouring from the tube. CVP line was changed to PA catheter and pulmonary capillary wedge pressure (PCWP) of 15 mm Hg was noted. Diagnosis of NCPE was confirmed. When surgery was completed, the patient was given Inj. Morphine 10 mg, Inj. Diazepam 5 mg, Furosemide 100 mg IV and shifted to ICU.

In ICU, the patient was kept on ventilator on Synchronized intermittent mandatory ventilation (pressure control)+ pressure support mode with 10 cm of Positive end-expiratory pressure and 100% FiO_2) Chest X-ray was done which showed diffuse infiltrates consistent with pulmonary edema. Gradually, as the patient's oxygenation and X-ray chest improved, he was weaned off the ventilator and extubated by next day morning. Postoperative urine output was 6 l with satisfactory creatinine clearance. The patient was kept in the ICU for 3 days for observation.

Discussion

Pulmonary edema can be cardiogenic due to increase in the net hydrostatic pressure across the pulmonary capillaries or fluid overload or non-cardiogenic due to increase in the permeability of alveolar capillary membrane.[1] NCPE is characterized by simultaneous presence of severe hypoxemia, bilateral alveolar infiltrates on chest radiograph and no evidence of left atrial hypertension/congestive heart failure/fluid overload. The common causes are gastric aspiration, sepsis, trauma, and respiratory obstruction leading to negative pressure pulmonary edema.[2] Less appreciated is the fact that various drugs, either taken as standard therapy or as an overdose, may precipitate NCPE.[1]

The first extensive review[3] on agents causing pulmonary insult was published in 1972 which included 20 medications. Since that time, the number of agents implicated has risen to more than 350. Bauman *et al*.[3] published a paper on drug-induced lung diseases in which ATG is mentioned as a causal agent for drug-induced NCPE. Dean *et al*.[4] and Murdock[5] reported ATG-induced ARDS. Like the other case reports, it was impossible for us to definitely prove that pulmonary edema was secondary to ATG. However, several factors suggest this as an etiological factor.

In our case, cardiogenic pulmonary edema and fluid overload were ruled out by the absence of preexisting heart disease, good left ventricular systolic function and normal PCWP. The other causes of NCPE are less likely as it was an elective surgery, there was no respiratory obstruction and pulmonary edema developed at the end of surgery with endotracheal tube *in situ*. The only possibility seems to be ATG. Pulmonary edema developed at the time of completion of ATG infusion probably due to administration of antihistaminics and steroids during surgery. Although rechallenging can

definitely establish the causal link, we did not believe it safe for purely diagnostic purposes.

Diagnosing drug-induced NCPE is actually an exercise of exclusion as there is no diagnostic test available. It is related to the time proximity of administration of drugs, and pathogenesis involves direct cytotoxic insults to the lung epithelial cells and induction of cytokine triggered inflammatory responses. NCPE can be reversed by prompt recognition following immediate discontinuation of the offensive drug.

Little is known about the mechanism of ATG-induced lung injury. Various postulates are as follows: (1) ATG contains antibodies of animal origin which are active against human T lymphocyte antigen, with cellular activation, degranulation and respiratory burst response damaging pulmonary endothelium. (2) Other possible mechanism is cytokine releasing syndrome. Pulmonary capillary endothelial permeability increases in response to tumor necrosis factor and alpha interleukin 1 and 8 released from damaged or activated lymphocytes similar to the pathogenesis of ARDS in sepsis.[6]

Our purpose of reporting this case is to alert anesthesiologists involved in transplantation program of this acute complication related to ATG infusion so that they are prepared to treat it promptly.

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