CASE REPORT

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Noncardiogenic pulmonary edema induced by a molecular adsorbent recirculating system: case report

Abstract Noncardiogenic pulmonary edema is a well-recognized manifestation of acute lung injury which has been related, among others, to blood or blood-product transfusion, intravenous contrast injection, air embolism, and drug ingestion. We describe two cases of noncardiogenic pulmonary edema after use of a molecular adsorbent recirculating system, a cell-free dialysis technique. Patients in this series presented at our institution to be evaluated for liver transplantation. Subsequently, they developed an indication for the molecular adsorbent recirculating system. Two patients of 30 (6.6%) treated with the molecular adsorbent recirculating system for acute-on-chronic liver failure and intractable pruritus had normal chest X-rays before treatment and developed severe pulmonary edema, in the absence of cardiogenic causes, following use of the molecular adsorbent recirculating system. For each patient we reviewed the history of blood or blood-product transfusion, echocardiograms if available, daily chest X-rays, and when available pre- and postmolecular adsorbent recirculating systemic blood pressure, central venous pressure, pulmonary arterial pressures, cardiac output, cardiac index, systemic vascular resistance index, and arterial blood gas. Our data suggest that the molecular adsorbent recirculating system may cause noncardiogenic pulmonary edema, possibly by an immune-mediated mechanism.

Key words Albumin · Dialysis · Artificial liver · Cytokine · Lung edema · Hepatitis

Introduction

The molecular adsorbent recirculating system (MARS) (Teraklin, Aktiengesellschaft, Rostok, Germany) is an artificial liver support system first introduced into clinical practice in 1993. MARS aims only at clearing the blood of metabolic waste products normally metabolized by the liver. It is, essentially, a modified dialysis system, employing an albumin-containing dialysate that is recirculated and perfused in-line through charcoal and anion exchanger columns. This effects the removal of albumin-bound toxins together with free solutes that are removed by standard dialysis.

Noncardiogenic pulmonary edema is a well-known immunologically mediated complication of blood or blood-component transfusion. Noncardiogenic pulmonary edema has also been reported as a consequence of intravenous administration of contrast media, drug ingestion, recurrent venous air embolism, and postextubation.

Many extracorporeal blood circulation devices have also been reported to be able to activate an immune-mediated reaction, secondary to the contact of the patient’s blood with filters, membranes, and/or charcoal, which can cause activation of the complement cascade with cytokine release, subsequent increase in the pulmonary capillary permeability, and development of pulmonary edema.

Our protocol includes 7 MARS sessions, on consecutive days, for each treatment. A single MARS session is 6 h in duration. A second MARS treatment is started in cases of partial response to the first treatment.

MARS treatment was performed through a hemodialysis double-lumen catheter. A flush of the extracorporeal circuit...
with 11 of heparinized saline solution (1000 U heparin sulphate/l) was carried out before commencement of MARS treatment. Therefore, no systemic heparinization was obtained and heparin allergy could not be advocated as a reason for the development of pulmonary edema. The extracorporeal blood circuit was driven by a standard dialysis machine (D-85716, Baxter, Unterschleibheim, Germany) at a flow rate of 100 ml/min initially, increasing to 200 ml/min if the patient remained hemodynamically stable.

**Case 1**

A 49-year-old white male affected by HBV/HDV-related cirrhosis presented at The Mediterranean Institute for Transplantation and Advanced Specialized Therapies to be evaluated as a potential candidate for liver transplantation (LTx). After completing the pretransplant work-up the patient was excluded from the LTx waiting list because he was found to have portal vein thrombosis. His course was complicated by recurrent upper gastrointestinal bleeding secondary to rupture of esophageal varices resistant to numerous sessions of banding ligation. In the process, he required multiple hospital admissions during which 2-3 units of packed red blood cells were transfused every week. Following an episode of uncontrollable upper gastrointestinal bleeding, after obtaining informed consent, the patient underwent a successful mesocaval shunt. Three months following surgery he developed acute-on-chronic hepatic failure, presenting with rapid development of worsening encephalopathy, rising bilirubin, and worsening coagulopathy despite intensive medical management. After obtaining informed consent, the patient was treated with MARS. Throughout MARS treatment the patient had negative blood cultures with no sign of infection or sepsis (i.e., fever, hypothermia, increase white blood cell count, and positive culture); was hemodynamically stable (no vasopressor requirement, mean arterial pressure ≥60 mmHg); and a normal chest X-ray (Fig. 1a). A pre-MARS echocardiogram showed an ejection fraction of 55%. His Child and MELD scores were C11 and 13, respectively. Blood analysis results were: total bilirubin 10.66 mg/dl, aspartate aminotransferase (AST) 86 IU/l, alanine aminotransferase (ALT) 33 IU/l, gamma-glutamyl transpeptidase (γGT) 13 IU/l, prothrombin time (PT) 21.5 s, ammonia 103 mg/dl, creatinine 0.7 mg/dl, creatinine clearance 140.5 ml/min, urine output 1.5 ml/kg/h, and central venous pressure (CVP) 14 mmHg.

Because of a partial response following the first full MARS treatment, a second course was started. During the 4th session of the second treatment course, the patient developed pulmonary edema (Fig. 1b) requiring orotracheal intubation. An even fluid balance was maintained throughout the entire MARS treatment. No blood/blood products were transfused in the 48 h prior to the development of severe pulmonary edema, nor could we identify other known causes of noncardiogenic pulmonary edema.5–8 MARS treatment was stopped and aggressive medical management of the pulmonary edema was initiated. The pulmonary edema was believed to be of noncardiogenic origin. Table 1 shows stable hemodynamic and arterial blood gas values before and after the development of pulmonary edema. Following the discontinuation of MARS treatment and the appearance of pulmonary edema, Child and MELD scores were C11 and 18, respectively. Blood analysis results were: total bilirubin 15.48 mg/dl, AST 55 IU/l, ALT 34 IU/l, γGT 13 IU/l, PT 19 s, ammonia 61 mg/dl, creatinine 0.6 mg/dl, creatinine clearance 176.75 ml/min, urine output 1.1 ml/kg/h, and CVP 4 mmHg. Twenty-four hours after cessation of MARS treatment and the application of aggressive medical management, the pulmonary edema resolved. Subsequently the patient became hemodynamically unstable requiring increased dosages of vasopressors without sign of infection/sepsis. Nine days after the last MARS session, the patient died of terminal end-stage liver disease and multiple organ failure; autopsy was declined.

**Case 2**

A 70-year-old white male presented at the Institute to be evaluated as a potential candidate for LTx. During the pretransplant work-up, after obtaining informed consent,