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Probable allergic reaction to cyclosporin and early formation of thrombi on a pulmonary artery catheter: two unusual complications during bilateral lung transplantation

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We describe a patient who had two rare complications (a probable allergic reaction to cyclosporin and the early formation of a right atrial thrombus) during bilateral sequential single lung transplantation performed under the one anaesthetic. The thrombus, discovered at the end of the procedure, was then removed under cardiopulmonary bypass. Peroperative transoesophageal echocardiography was useful in providing critical diagnostic and therapeutic information.

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Bilateral sequential single lung transplantation during one anaesthetic is an option for patients who require double lung replacement.[1] It does not require routine use of cardiopulmonary bypass because each graft is performed while ventilation and circulation are supported by the contralateral lung; the native lung during the first part of the procedure, and the first transplanted lung during the second. However, in case the haemodynamic condition of the patient deteriorates, cardiopulmonary bypass should always be made ready for use.[1]

We describe two rare complications occurring in a patient during bilateral sequential single lung transplantation: a

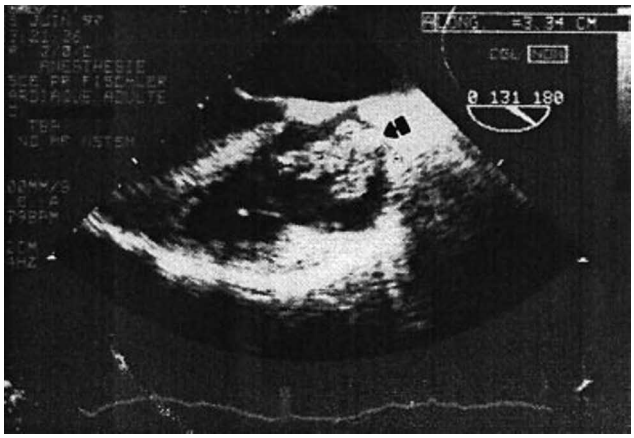

Fig 1 TOE examination using a multiplan probe revealed an echo-dense mass (arrow) bound to the pulmonary artery catheter in the right atrium on a 131° axis of the four-chamber view.

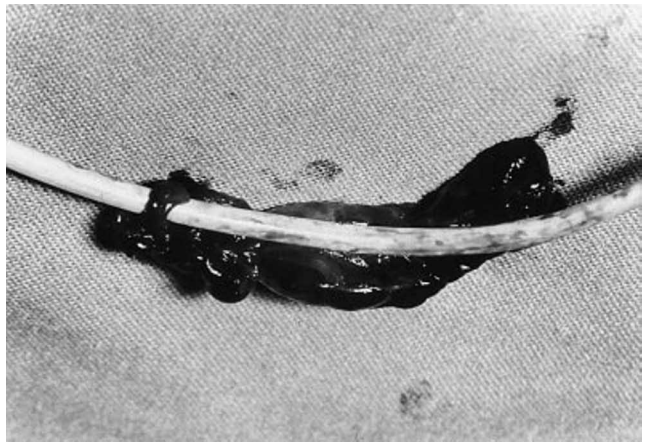

Fig 2 Thrombus bound to the distal end of the pulmonary artery catheter.

probable allergic reaction to cyclosporin, and the formation of a right atrial thrombus discovered at the end of the procedure.

Case report

A 38-yr-old man with cystic fibrosis was scheduled for double lung transplantation. Immunosuppressive agents (cyclosporin 2 mg kg^{-1} and azathioprine 2 mg kg^{-1}) given over 30 min by i.v. infusion were started according to the hospital procedure, immediately before induction of anaesthetic. Simultaneously, a right femoral artery catheter was inserted under local anaesthesia. Suddenly, the patient complained of severe respiratory distress and pulse oximetry showed a rapid decrease in arterial oxygen saturation. The first recorded systolic arterial pressure was 35 mm Hg. Initial management included i.v. injection of epinephrine 1 mg and cessation of the infusion of immunosuppressants. Face mask ventilation with 100% oxygen was quickly followed by tracheal intubation with a double-lumen tracheal tube after bolus administration of etomidate 20 mg and rocuronium 100 mg. Stable haemodynamics were achieved 20 min later, the patient having received two more boluses of epinephrine 1 mg followed by an epinephrine infusion 2 mg h^{-1}. Transoesophageal echocardiography (TOE) showed vigorous, homogeneous contraction of small right and left ventricles without segmental wall motion abnormalities. It ruled out other possible causes of sudden cardiopulmonary distress, especially pneumothorax (there was no right atrial or right ventricle compression), and acute pulmonary embolism (no right ventricular dilatation). The possibility of an anaphylactic reaction either to the latex gloves worn by the anaesthetic team or to the immunosuppressive agents was raised, despite the lack of associated signs such as wheezing or urticaria. We changed to latex-free gloves, and other latex-based products were removed from contact with the patient. As the clinical situation was under control, we decided to reintroduce the i.v. cyclosporin and to complete anaesthesia with the infusion of a large dose of sufentanil (10 μg kg^{-1} over 20 min). Arterial pressure fell within a few seconds of administrating both these drugs to 55/30 mm Hg and required three epinephrine 0.5 mg boluses to correct it. The medical staff discussed the likelihood of an anaphylactic reaction to cyclosporin. We changed the immunosuppressive procedure to high-dose steroids. As usual during lung transplantation, a 8.5-Fr introducer catheter was then placed into the right internal jugular vein, followed by a 7.5-Fr thermodilution, heparin-coated pulmonary artery catheter. The remainder of the anaesthetic procedure was uneventful.

Surgery consisted of bilateral sequential single lung transplantation performed through an anterior bithoracosternotomy incision, as described previously.[1] TOE monitoring continued throughout the surgical procedure to assess haemodynamic status and the arterial and venous vascular anastomoses.[2] At the final perioperative TOE examination, performed before skin closure, an echo-dense mass, 34 mm wide, was detected, attached to the pulmonary artery catheter in the right atrium (Fig. 1). The mass was mobile, entering the right ventricle through the tricuspid orifice during diastole, and returning to the right atrium during systole. It was decided to remove this thrombus. The patient was given heparin 300 IU kg^{-1}. Ascending aortic and right atrial cannulation was employed for cardiopulmonary bypass. The right atrium was opened, and the surgeon cut the extremity of the Swan–Ganz catheter and removed it with the thrombus attached (Fig. 2). The right atrium was closed, the cannulae were removed and the heparin effect was reversed with an infusion of protamine sulphate 300 units over 20 min. At the end of the procedure, we withdrew the proximal part of the Swan–Ganz catheter and replaced it by a triple-lumen central venous catheter.

Postoperative recovery was uneventful. Blood loss in to the chest drains was 980 ml during the first postoperative 24 h. The patient is alive and healthy 24 months after transplantation.

Discussion

Two major complications occurred during this double lung transplantation: a probable allergic reaction to cyclosporin before induction of anaesthesia, and the formation within a few hours of a large right atrial thrombus. TOE ruled out other possible causes of the cardiopulmonary collapse, and facilitated its treatment. It then revealed the atrial thrombus.

The differential diagnoses of the acute cardiopulmonary deterioration before induction of anaesthesia included a tension pneumothorax, massive pulmonary embolism (both complications this patient was at risk of), and anaphylactic shock or another type of adverse drug reaction. The first two diagnoses were ruled out as TOE did not show compression or dilatation of the right cardiac chambers. Moreover, the timing of events suggested that this was a probable allergic reaction to cyclosporin, with immediate hypotension following its administration, and recurrence after reintroduction of the immunosuppressive agent. Proof of the anaphylactic aetiology of the cardiopulmonary collapse is not available, as we did not take blood for histamine, serum tryptase, or complement analyses. Moreover, after recovery, skin prick-tests would not necessarily have led to the diagnosis as immunosuppressive therapy decreases skin reactivity and consequently could have given a false negative result.

Several case reports of life-threatening anaphylactic reactions to i.v. cyclosporin have been reported, one of which resulted in cardiopulmonary arrest.[3] Allergic reactions to i.v. cyclosporin are uncommon (0.1%) and are usually a result of the solvent Cremophor EL (polyoxyethylated castor oil base),[4] which is known to cause anaphylactoid shock. Inappropriate mixing of the solution can lead to a large plasma concentration of Cremophor EL during the initial phase of the infusion; the heavier solvent may fall to the bottom of the mixture and pass through the infusion set first. A recent study reported that cyclosporin and Cremophor EL concentrations could be up to 9-fold higher than intended during the first 10 min of the infusion. This high concentration can be a predisposing factor for anaphylactoid shock.[5] Such a complication requires a change in the immunosuppressive procedure, as in our patient, or the administration of cyclosporin capsules which have been demonstrated to be well tolerated in a patient allergic to standard oral and i.v. solutions of cyclosporin.[4]

The atrial thrombus was attached to the Swan–Ganz catheter. Thrombus formation on a pulmonary artery catheter has been described by several authors.[6 7] In their original description of the double-lumen flow-directed balloon-tipped catheter, Swan and colleagues[8] detailed two patients who had evidence of thrombosis related to the pulmonary artery catheter. In an autopsy study, mural thrombi were found in the right cardiac chambers in approximately one-third of patients.[9] The main mechanism of thrombus formation is dependent on the thrombogenicity of the catheter surface. Thrombus formation starts when a fibrin sleeve forms around an indwelling catheter, exerting a procoagulant effect. Moreover, a hypercoagulable state created by high-dose aprotinin,[10] or administration of epsilon aminocaproic acid,[11] may lead to the formation of thrombi around the catheter within the first hour after insertion. Heparin-coated catheters may prevent or reduce the incidence or severity of such complications. Hoar[12] examined 20 consecutive pulmonary artery catheters in cardiac surgical patients and found adherent thrombi formation on all non-heparin-bonded catheters but none on heparin-bonded catheters. In our case, thrombus formation was diagnosed 10 h after pulmonary artery catheter insertion, in the absence of any precipitating factor (atrial fibrillation, aprotinin administration, blood transfusion, or removal of the introducer sheath).

Any link between an allergic reaction and early thrombus formation is speculative. However, it is well-known that anaphylaxis can trigger a systemic inflammatory reaction in which platelet activating factor and thromboxan A2 are released and induce platelet aggregation and clotting.[13] Moreover, if the reaction to cyclosporin is a result of complement activation by Cremophor EL, this can lead to the release of anaphylatoxin C5a. Again, the end result is platelet aggregation.[14] Another hypothesis might be that clotting is activated during lung transplantation itself. Indeed, a significant rise in concentrations of thrombin/antithrombin III complex and tissue-type plasminogen activator have been reported during the early phase of such surgery.[15]

Perioperative or postoperative diagnosis of an atrial thrombus attached to a central venous catheter or a pulmonary artery catheter using TOE has seldom been reported.[16 17] As the thrombus was discovered during surgery and because of its potential for tricuspid entrapment or pulmonary embolism, we decided to remove it under cardiopulmonary bypass despite the haemorrhagic risk.

This case highlights the importance of simple precautions: monitoring lines and venous access should be established before any drugs are administered. Administration of immunosuppression therapy, or of any drug with potential allergic complications such as aprotinin, must not be concomitant with administration of an anaesthetic drug. This case illustrates how TOE can provide critical diagnostic information and help to manage unstable patients. TOE was useful in two respects: it ruled out right sided atrial and ventricular compression, right ventricular dilatation, right or left ventricular failure, and hypovolaemia when the patient experienced acute cardiorespiratory distress; and it also identified a right atrial thrombus.

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