Donor-acquired fat embolism syndrome after lung transplantation

Samuel Jacob¹, Andrew Courtwright¹, Souheil El-Chemaly⁴, Emilian Racila¹, Miguel Divo⁴, Patrick Burkett⁴, Anne Fuhlbrigg⁴, Hilary J. Goldberg⁴, Ivan O. Rosas⁴,* and Phillip Camp⁴

¹ Division of Thoracic Surgery, Brigham and Women’s Hospital, Boston, MA, USA
² Division of Pulmonary and Critical Care, Brigham and Women’s Hospital, Boston, MA, USA
³ Department of Pathology, Brigham and Women’s Hospital, Boston, MA, USA
⁴ Corresponding author. Division of Pulmonary and Critical Care, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, 75 Francis Street, Thorn 9, Boston, MA 02115, USA. Tel: +1-617-2780434; fax:+1-617-2645133; e-mail: irosas@rics.bwh.harvard.edu (I.O. Rosas).

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Abstract

OBJECTIVES: Fat embolism is a known complication of severe trauma and closed chest cardiac resuscitation both of which are more common in the lung transplant donor population and can lead to donor-acquired fat embolism syndrome (DAFES). The objective was to review the diagnosis and management of DAFES in the lung transplantation literature and at our centre.

METHODS: We performed a literature review on DAFES using the Medline database. We then reviewed the transplant record of Brigham and Women’s Hospital, a large academic hospital with an active lung transplant programme, for cases of DAFES.

RESULTS: We identified 2 cases of DAFES in our centre, one of which required extracorporeal membrane oxygenation (ECMO) for successful management. In contrast to the broader literature on DAFES, which emphasizes unsuccessfully treated cases, both patients survived.

CONCLUSION: DAFES is a rare but likely underappreciated early complication of lung transplant as it can mimic primary graft dysfunction. Aggressive interventions, including ECMO, may be necessary to achieve a good clinical outcome following DAFES.

Keywords: Extracorporeal membrane oxygenation • Fat embolism • Lung transplantation • Graft dysfunction • Survival

INTRODUCTION

Fat embolism occurs when fat particles from soft tissues and bones are released into the circulation causing macro- and microvascular obstruction followed by a delayed inflammatory reaction to low-density lipoproteins and chylomicrons [1–3]. This leads to acute lung injury, encephalopathy and a petechial rash from thrombocytopenia and disseminated intravascular coagulation (DIC), a constellation of findings collectively known as fat embolism syndrome (FES). The incidence of clinically significant FES ranges from <1 to 29% depending on the patient population [4]. Unsurprisingly, FES is more common in trauma and orthopaedic injuries, although it has been reported in severe burns, liver injury and closed chest cardiopulmonary resuscitation (CPR) [5, 6]. Because the organ donor pool is enriched for individuals who have suffered trauma or CPR and because manifestations of FES can be delayed, it is possible to transplant seemingly healthy organs, including lungs, into recipients who subsequently develop donor-acquired fat embolism syndrome (DAFES). We reviewed the published literature on DAFES and our transplant centre’s experience to emphasize the possibility for better clinical outcome after this potentially devastating event.

MATERIALS AND METHODS

We performed a literature review on DAFES using the Medline database and search terms such as ‘lung transplantation AND fat embolism’, ‘donor AND fat embolism’ and ‘fat embolism AND graft dysfunction’. We reviewed the references of identified articles to locate additional publications not found in our initial search. We then reviewed all cases of known or suspected DAFES at Brigham and Women’s Hospital, a large academic hospital whose lung transplant programme performs ~30 transplants a year. Over the last 3 years, 37.3% of our donors have had trauma preceding organ procurement. Our incidence of primary graft dysfunction (PGD) is in keeping with national averages, from 10 to 15%.

RESULTS

Literature review

A review of the existing literature on DAFES demonstrated a small number of case reports totalling 5 patients [7–11]. We excluded a sixth case reporting on recipient-acquired FES in a post-transplant...
patient with a vertebral body fracture [12]. The included cases are summarized in detail in Table 1.

Case 1

A 54-year old man with a history of familial interstitial pneumonia related to short telomere syndrome was admitted for right single-lung transplant. The donor was a 31-year old man who had been in motor vehicle collision and suffered multiple facial and rib fractures without pelvic or long-bone fractures. He had, however, had a cardiac arrest and closed chest CPR. He was considered a donor of increased risk per Center for Disease Control guidelines because of multiple transfusions, including more than 10 units of packed red blood cells (PRBCs) as well as platelets and fresh frozen plasma.Bronchoscopy showed blood-tinged mucosa with minimal secretions. Chest CT showed a consolidative opacity in the left lower lobe consistent with a pulmonary contusion. On 100% fraction of inspired oxygen (FiO2) and positive end-expiratory pressure (PEEP) of 8 cmH2O, his partial pressure of arterial oxygen (PaO2) was 287 mmHg. His right lung was procured for transplant after 7 total days of mechanical ventilation. His left lung, which was not appropriate for transplant due to contusion, was procured en bloc and kept for research purposes.

Both anterograde and retrograde flushings were performed prior to transplant without producing significant clots. The recipient underwent right single-lung transplant without technical difficulty using cardiopulmonary bypass. He initially did well upon reperfusion of the lungs but within 12 h he developed significant hypoxaemic respiratory failure and required increased ventilatory support. PA pressures became markedly elevated requiring the initiation of inhaled epoprostenol. Chest CT showed interval development of consolidations in the donor lung, particularly in the middle and lower lobes (Fig. 1). Additional evaluation, including transoesophageal echocardiogram (TOE), showed no evidence of intracardiac shunting or impairment of the pulmonary vein (PV) or PA anastomoses. Bronchoscopy showed an intact anastomosis with minimal secretions. The patient was diagnosed with PGD based on his clinical presentation.

On postoperative day 2, histological evaluation of the unused left donor lung revealed global fat emboli, suggesting DAFES as the primary aetiology of the recipient's respiratory decompensation (Fig. 2). In addition to epoprostenol, he was managed with low tidal volume ventilation and a conservative fluid strategy. He was also started on 1000 mg intravenous methylprednisolone for 3 days followed by a long prednisone taper. Serial CT scans showed progressive improvement in donor lung consolidations (Fig. 1). He eventually underwent tracheostomy for prolonged respiratory failure but was discharged to an acute rehabilitation facility on postoperative day 31. He was decannulated 6 weeks later and discharged home without supplemental oxygen. He continues to do well with no evidence of acute or chronic rejection 28 weeks after transplant.

Case 2

A 28-year old man with a history of cystic fibrosis was admitted for sequential bilateral lung transplant. The donor was a 26-year old male who had suffered blunt head trauma including comminuted fracture of the anterior arch of C1 but no known pelvic or long-bone fracture. Bronchoscopy showed minimal secretions and initial chest X-ray showed no acute cardiopulmonary abnormalities.

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Table 1: Summary of case reports of donor-acquired fat embolism syndrome
He had received five units of PRBC during his hospital course and had been mechanically ventilated for almost 24 h before donation. Prior to procurement on 100% FiO₂ and PEEP of 5 cmH₂O, his PaO₂ was 352 mmHg.

The recipient underwent sequential bilateral lung transplant on cardiopulmonary bypass. Detailed inspection of the donor pulmonary artery prior to anastomosis revealed yellow, opaque material consistent with fat embolism. Retrograde flushing was performed to clear this material. The surgery was completed without technical difficulty. The patient weaned easily from bypass onto low inspired oxygen provided through endotracheal intubation. Prior to leaving the operating room, however, marked hypoaxaemia and copious frothy secretions developed. Because of worsening oxygenation and concern for DAFES as the precipitating event, the decision was made to transition to extracorporeal membrane oxygenation (ECMO) before transporting the patient to the intensive care unit (ICU).

Postoperative chest CT demonstrated multifocal patchy opacities concerning for acute respiratory distress syndrome (ARDS). TOE indicated that the PA and PV anastomoses were intact and bronchoscopy showed intact bronchial anastomoses along with copious non-bloody secretions. Together with the intraoperative findings, these results were most consistent with DAFES. The patient required veno-venous ECMO support for 17 days postoperatively and eventually underwent tracheostomy for prolonged respiratory failure. He was weaned from ECMO and mechanical ventilatory support and was discharged to an acute rehabilitation facility on postoperative day 39. He was weaned off oxygen shortly thereafter but developed severe antibody-mediated rejection and died 81 weeks after transplant.

**DISCUSSION**

DAFES occurs when donor pulmonary fat emboli are transplanted into a recipient resulting in a significant pulmonary injury. In contrast to FES, in which pulmonary manifestations are part of a broader systemic reaction, including encephalopathy and DIC, both patients in this report and the reviewed literature had exclusively pulmonary manifestations. It is likely that a reaction to free fatty acids and other biochemical products of neutral fat hydrolysis led to a post-transplant inflammatory response and subsequent respiratory distress [3]. Because the manifestations of DAFES occur rapidly after transplant, it can mimic a more well-described early post-transplant complication, PGD. PGD refers to the clinical syndrome of a reduction in the ratio of PaO₂ to FiO₂ that occurs within 72 h of transplant in association with radiographic opacities on chest imaging without other identifiable causes. PGD occurs in 10–25% of lung transplants and is associated with significant short- and long-term mortality [13, 14].

It is unknown what percent of PGD cases are actually DAFES. In almost every previously reported case, DAFES was identified on autopsy after unsuccessful management, suggesting a reporting bias towards dramatic cases with unanticipated outcomes and clinically interesting findings on pathological examination. It is likely that the true incidence of DAFES masquerading as PGD is underappreciated, particularly given the difficulty establishing the diagnosis [15]. In our cases, we were able to make the diagnosis on the basis of visualizing fat emboli, microscopically in an unused donor lung in the first case and macroscopically at the time of transplant in the second case. Because routine histopathological review of untransplanted organs is not standard practice, transplant centres may underestimate the true incidence of DAFES.
Supporting the hypothesis that DAFES is an underappreciated early transplant complication, Oto et al. performed retrograde flushes of 74 consecutive donor PA prior to implantation and found 7 cases of macroscopic fat emboli (9.4%) [16]. The presence of fat embolism was associated with significant risk for prolonged intubation and ICU stay compared with patients without any donor-associated embolism and compared with patients with donor-associated pulmonary venous thromboembolism, suggesting that fat embolism was not merely an incidental finding.

Once the diagnosis of DAFES is made, management strategies are similar to those used to support patients with ARDS. We employed low tidal volumes, optimized PEEP and minimized FiO2. We used a conservative fluid management strategy and relied on inhaled epoprostenol to improve ventilation-perfusion matching. In the second case, we successfully used veno-venous ECMO as a supportive measure until the resolution of allograft dysfunction [17]. High-dose steroid therapy was used in the first case, although data on its effectiveness in FES are mixed [18]. We did not use other potential therapies derived from the orthopaedic literature on FES including high-dose statin therapy, captopril and antithrombin III and metalloproteinase inhibitors because of their experimental nature [19].

Given the limited therapeutic options for DAFES and the associated poor outcomes, it is important to identify pretransplant strategies for minimizing or avoiding this complication. Because between 20 and 40% of potential donors have suffered major trauma, it would be impractical to decline offers from all patients with long-bone fractures [12]. Unfortunately, the early optimism that the presence of fat droplets in alveolar macrophages on bronchoalveolar lavage would be sensitive enough to diagnose fat embolism has not been borne out in subsequent studies [20]. Similarly, the analysis of complement activation, lipiduria and phospholipase A2 levels has not been sufficient to identify trauma patients with and without fat embolism. Clinical predictors of FES such as an Injury Severity Score over 16 in combination with a femoral fracture and clinical instability at the time of admission can help identify patients at higher risk for FES and could be considered at the time of donor evaluation although neither donor in our cases had a femoral fracture [21].

Some authors have hypothesized that routine preimplantation retrograde flushing to remove embolized material, including fat, may help prevent early graft failure [22]. Preliminary animal and human studies have supported the idea that retrograde flushing may improve early graft function. Whether this is through removal of embolized fat, venous thromboembolic material or another mechanism is unknown and remains understudied [23, 24]. We routinely perform both anterograde flushing of the PA and retrograde flushing of the PV prior to transplant in our centre. Although retrograde flushing did not appear to prevent DAFES in our patients, we do not know in many other cases it might have occurred if we did not routinely perform this flushing. Finally, the introduction of ex vivo lung perfusion strategies may provide a mechanism to allow for a more definitive diagnosis through careful observation during the perfusion process. An ex vivo approach may also offer a therapeutic window to recondition lungs with suspected or known fat emboli prior to transplant, thereby preventing DAFES [25].

Conflict of interest: none declared.

REFERENCES


