Case in Point

Amniotic Fluid Embolism

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Distinguishing this life threatening obstetric emergency from other possible causes of hypotension and cardiovascular collapse is crucial to maximizing patient survival. This case illustrates the key role of transesophageal echocardiography in rapid diagnosis.

Amniotic fluid embolism (AFE) is a rare, catastrophic complication of pregnancy that occurs when the barrier between the amniotic fluid and maternal circulation is disrupted (Figure 1).[1,2] Although AFE was first reported in 1926 and expanded upon in 1941,[3,4] few advances in its diagnosis and treatment have occurred since then. To this day, AFE retains a mortality rate of 60% to 80%, and 50% of AFE survivors have permanent neurologic sequelae.[2,5]

While the clinical presentation of AFE is similar to that of pulmonary thromboembolism and venous air embolism, the etiology and treatment options are distinctly different for each entity. In order to provide the appropriate treatment interventions quickly enough to maximize chances of recovery, therefore, prompt diagnosis of AFE in parturients with cardiovascular collapse is ideal—but problematic. The diagnosis of AFE is one of exclusion, and frequently it is not assigned until autopsy.[6]

In this article, we present a case of AFE in which transesophageal echocardiography (TEE) was used to arrive at a rapid and accurate diagnosis. While the patient in this case ultimately did not respond to resuscitative efforts, the ability of the team to rule out other entities in the differential diagnosis spared her from ineffectual treatment efforts that might have hastened her death or intensified her suffering.

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INITIAL EXAM

A 34-year-old, white, pregnant woman presented to the obstetric unit of a university medical center at 39.43 weeks of gestation with spontaneous onset of labor and pregnancy-induced hypertension (PIH). Her height was 114 cm (3 ft 9 in), her weight was 65 kg (143 lb), and she had severe skeletomuscular abnormalities. Her medical history was significant for spina bifida (resulting in paraplegia at the mid-thoracic level), seizure disorder, hydrocephalus, gastrointestinal reflux disorder (GERD), asthma, and tobacco use. She reported no alcohol or drug abuse. Her surgical history was significant for Harrington rod placement, meningomyelocele repair, ventricular-peritoneal (VP) shunt placement (multiple procedures), ureterostomy, ileostomy, colostomy, and knee arthroscopy.

Her obstetric history included one previous pregnancy, four years earlier, which culminated in a preterm delivery at 34 weeks gestation by cesarean section (due to cephalopelvic disproportion). This delivery was successful, with no complications. During the current pregnancy, the patient had received no prenatal care until she presented to the obstetric clinic at 35 weeks gestation. At that time, she was diagnosed with PIH, and she acknowledged her need for a repeat cesarean section due to cephalopelvic disproportion. The procedure was scheduled, but the patient presented to the obstetric unit in labor prior to that date.

At the current presentation, her medications consisted of prenatal vitamins, gentamicin for bacterial endocarditis prophylaxis (as recommended by her neurosurgeon following her VP shunt procedures), rabeprazole for her GERD, and labetalol for her PIH. (She had been prescribed the beta-blocker labetalol rather than magnesium sulfate because magnesium sulfate can interact with gentamicin to cause muscle weakness.) The patient reported allergies to intravenous pyelogram dye, povidone-iodine solution, and benzoin—but said that she had no latex allergy. There was no documentation of a latex allergy in her records. She had previously undergone radioallergosorbent testing.

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Ultrasound evaluation confirmed the gestational age of the fetus, a nonstress test was reactive, and amniocentesis revealed mature fetal lungs. The obstetrician elected to perform a repeat, low-transverse cesarean delivery due to the patient's worsening PIH and history of cephalopelvic disproportion. The patient also requested elective sterilization. She was not a candidate for regional anesthesia (spinal or epidural) due to her difficult anatomic configuration, spina bifida, Harrington rods, and her history of multiple VP shunt revisions. The decision was made, therefore, to proceed with general anesthesia.

HOSPITAL COURSE

The patient received standard aspiration prophylaxis medications (metoclopramide, famotidine, and sodium citrate). She was taken to the operating room, where standard American Society of Anesthesiologists monitors were applied and positioned with left uterine displacement. The fetal heart rate was determined to be 122 beats/min prior to anesthetic induction. Fetal exposure to the anesthetic agents was limited by abdominal preparation with chlorhexidine prior to rapid sequence induction of general anesthesia. Endotracheal intubation was accomplished without difficulty or complications. The patient received 100% oxygen with desflurane for maintenance anesthesia.

Uterine incision occurred six minutes after skin incision. Abdominal delivery of a viable female fetus by double, footling breech through the incision was accomplished three minutes later. The infant's one- and five-minute Apgar scores were both 6, while the one- and five-minute umbilical cord blood gas pH values were 7.24 and 7.30, respectively. The patient's vital signs had been stable to this point. The uterus was not exteriorized due to extensive adhesions in the abdominal cavity. This is important because, theoretically, exteriorizing the uterus could have entrapped air or amniotic fluid into the maternal circulation.

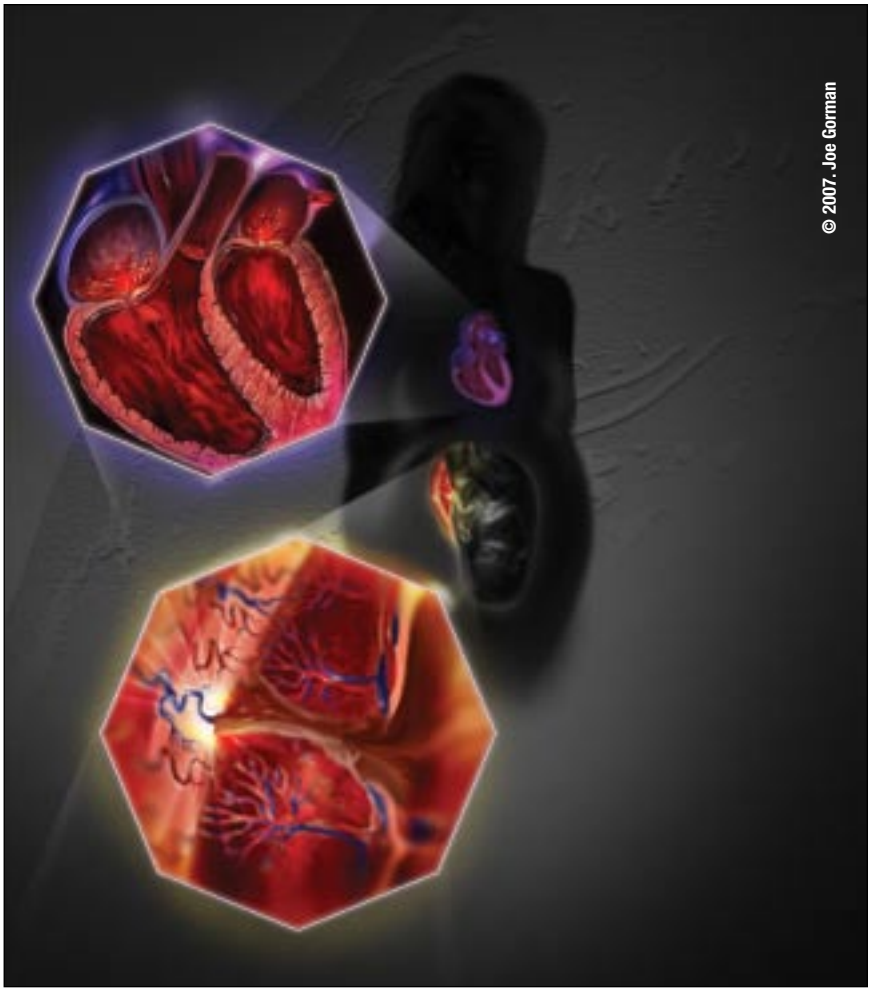

Figure 1. Amniotic fluid embolism, in which the introduction of amniotic fluid into the maternal circulation triggers a series of events that can include pulmonary hypertension, extreme hypoxia, heart failure, and disseminated intravascular coagulopathy. In up to 80% of cases, these events result in death.

A crisis develops

One minute following delivery of the fetus, the patient began to show signs of hypotension. Her blood pressure declined acutely to 66/20 mm Hg, with a mean arterial pressure of 26 mm Hg, and her pulse oximetry reading decreased from 100% to 92%. In addition, her end-tidal carbon dioxide level was noted to be acutely decreased. Her temperature declined from 36.2ºC to 35ºC over the ensuing five minutes.

Ephedrine and a fluid bolus were administered to reverse the hypotension, and these measures were effective initially. The patient was observed to have skin mottling and cyanosis. Sinus bradycardia was

noted seven minutes after the sentinel event, with a drop in heart rate from 90 to 42 beats/min. Pulseless electrical activity ensued 12 minutes after the inciting event and advanced cardiac life support resuscitative measures, consistent with the American Heart Association's 2005 guidelines on cardiopulmonary resuscitation and emergency cardiovascular care,[7] were instituted. Arterial and femoral central venous catheters were placed with difficulty. Initial resuscitative efforts resulted in restoration of an acceptable blood pressure (143/55 mm Hg) with sinus tachycardia (heart rate, 114 beats/min). The patient's core temperature continued to decline to a nadir of 32.2ºC.

A TEE probe was placed atraumatically 20 minutes after the inciting event to assist with the differential diagnosis. There was no evidence of pulmonary thromboembolism in the right atrium and ventricle (Figure 2) or in the pulmonary arteries (Figure 3). The pulmonary artery was visualized along the entire length of the main artery and into the proximal left and right branches. Right ventricular dilation, right ventricular contractile dysfunction, and severe tricuspid regurgitation were noted consistent with (acute) pulmonary hypertension and right ventricular failure (Figure 4). There was no evidence of venous air embolism. Moderate to severe centrally directed mitral regurgitation was noted and was consistent with acute left ventricular failure and papillary muscle dysfunction. The left ventricle was dilated and demonstrated acute, severe global hypokinesia, with an estimated left ventricle ejection fraction of 10% to 15% (Figure 5).

Resuscitative efforts were not successful in restoring viable hemodynamics. Arterial blood gas analysis during resuscitative efforts demonstrated metabolic acidosis and profound hypoxemia (pH, 7.16; partial pressure of carbon dioxide, 33 mm Hg; partial pressure of oxygen, 17 mm Hg; bicarbonate level, 12 mmol/L; base deficit, –15.8 mmol/L) despite adequate ventilation and a fraction of inspired oxygen level of 100%. Hematologic analysis was consistent with disseminated intravascular coagulation. The patient was pronounced dead 64 minutes after the initial episode of hypotension.

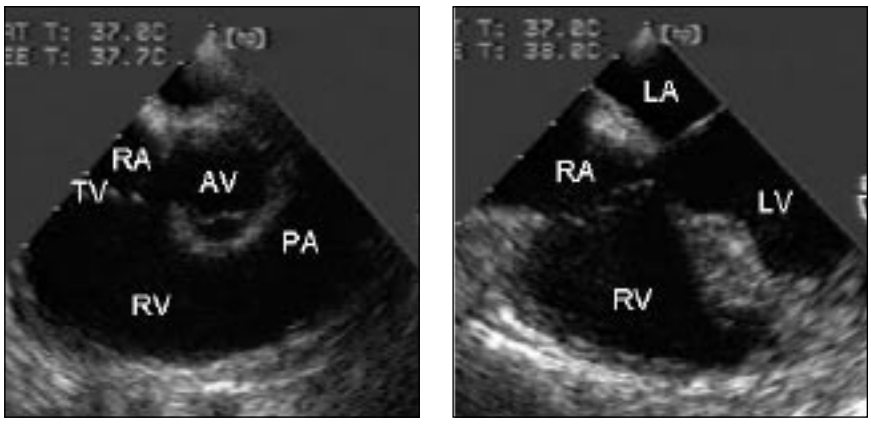

Figure 2. Transesophageal echocardiography (TEE) of the cardiac chambers, performed to evaluate for pulmonary or venous air embolism. TEE examination of the right heart (left) and a five-chamber view of the heart in a coronal plane (right) show no mobile masses or air within the cardiac chambers. Abbreviations: AV = aortic valve; LA = left atrium; LV = left ventricle; PA = pulmonary artery; RA = right atrium; RV = right ventricle; TV = tricuspid valve.

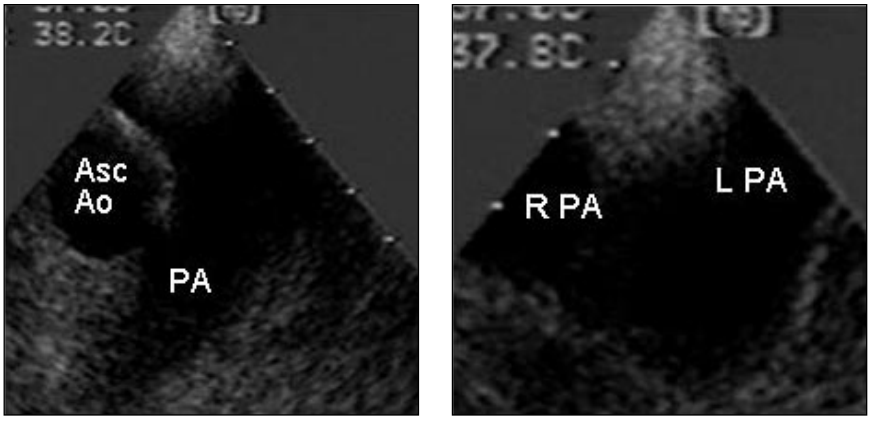

Figure 3. Transesophageal echocardiography (TEE) of the pulmonary artery bifurcation. Transverse plane TEE of the distal main pulmonary artery and bifurcation (left) demonstrates no saddle embolus. A close-up view of the bifurcation (right) is likewise devoid of any echogenic signal. Abbreviations: Asc Ao = ascending aorta; PA = pulmonary artery; L PA = left pulmonary artery; R PA = right pulmonary artery.

AUTOPSY FINDINGS

Autopsy examinations confirmed the patient's medical history and anatomic abnormalities. Gross examination noted significant scoliosis; a "barrel-shaped chest"; lower extremities that were abnormally short and externally

rotated; ileostomy, ureterostomy, and colostomy pouches; and a VP shunt extending from the left temporal lobe of the brain to the abdominal cavity, with clear cerebrospinal fluid. Chest radiographs confirmed the presence of Harrington rods. The skin was observed to be extremely pale, with no visual capillaries in the sclera (Figure 6), indicating profound blood loss.

Of the conditions initially included in the differential diagnosis, pulmonary thromboembolism and venous air embolism appeared unlikely based on intraoperative TEE. Findings of the chest radiographs supported the exclusion of venous air embolism (as there were no radiolucent areas in the ventricles) and ruled out pneumothorax. The internal examination revealed a patent pulmonary arterial tree, with no thrombi or emboli, thus excluding pulmonary thromboembolism as well.

The pericardium was smooth and intact. The coronary arteries were normal, without any stenosis or thrombosis. The pulmonary parenchyma exuded a marked amount of blood but only a minimal amount of frothy fluid, and it was without focal lesions. The abdominal cavity contained 1,300 mL of liquid blood, but no clotted blood was noted. This finding supported a terminal disseminated intravascular coagulopathy. The incision in the uterus was closed and without exudate. There was no retained placenta.

Microscopic examination of the lungs revealed squamous epithelial cells in the maternal circulation, the diagnostic feature of AFE (Figures 7 and 8). There was no gross or microscopic evidence of infection or inflammation. Microscopic examination of the liver demonstrated portal triads with normal hepatic cytoarchitecture and no evidence of fibrosis or inflammation, despite the diagnosis of PIH.

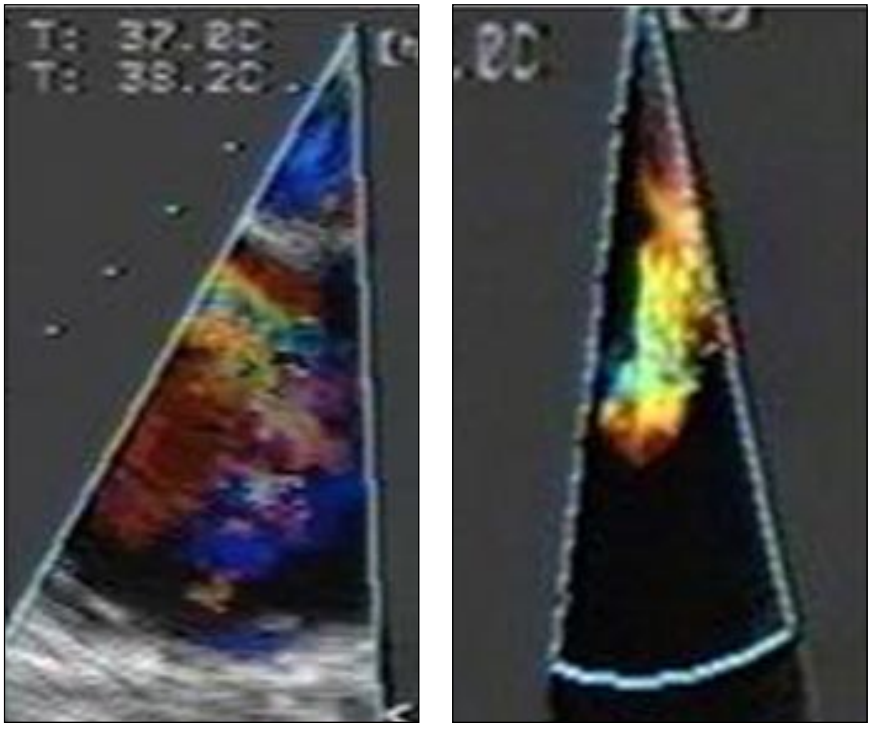

Figure 4. Color Doppler flow studies from transesophageal echocardiography of the cardiac valve structures, showing severe tricuspid regurgitation (left) and moderate mitral regurgitation (right). The patient's lack of murmur on preoperative physical examination suggests that these regurgitant lesions represent an acute change.

The cause of death was determined to be disseminated intravascular coagulation secondary to AFE in the immediate postpartum state.

ABOUT THE CONDITION

Admixture of amniotic fluid into the maternal circulation is thought to be commonplace following either vaginal or cesarean delivery, but typically it does not result in a physiologic problem. The clinical entity described as AFE, on the other hand, results in life threatening hypotension, hypoxia, and disseminated intravascular coagulation.

Acute occlusion of the pulmonary vasculature with concomitant pulmonary hypertension, decreased oxygen exchange, and acute right heart failure initially was ascribed as the pathogenesis of the AFE syndrome.[4] Both case reports and animal models, however, demonstrate that acute left ventricular dysfunction also occurs in the hemodynamic collapse that results from AFE. Specifically, case reports of AFE in humans have noted acute left ventricle failure, which was refractory to both inotropic and mechanical cardiac support.[8,9] Release of systemic cardiac inhibitory factors appears to be responsible, in part, for the left ventricle dysfunction. A dose-dependent reduction in coronary artery blood flow from human amniotic fluid resulting in depressed cardiac function has been observed in a rat model.[10]

The etiology of AFE and the physiologic disturbances responsible for the extreme hypoxia, depressed cardiac function, and coagulopathy are poorly understood. The entrain-

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ment of a foreign substance (fetal tissue) into the maternal circulation and release of endogenous mediators causes a profound myocardial depression with resultant hypotension and decreased cardiac output. The exact mechanism by which this occurs, however, has remained elusive.

Likewise, no established management strategy has been shown to improve fetal or maternal outcome. Supportive therapy is the primary method utilized to date. In this case, we directed our resuscitative efforts toward support of the acutely failing right and left heart and inadequate oxygenation.

The role of TEE in diagnosis

Although our resuscitative efforts did not succeed, they were directed appropriately because of a rapid, definitive diagnosis made possible largely by TEE. The differential diagnosis in this case, based on the clinical presentation, included anaphylaxis, primary cardiogenic shock (arising, for example, from acute myocardial infarction or massive hemorrhage), and mechanical etiologies (such as pneumothorax, venous air embolism, pulmonary thromboembolism, and AFE). TEE helped us to exclude all of these possibilities except AFE within 15 minutes of cardiovascular collapse.

Some potential causes of the patient's hypotension were excluded prior to TEE. Anaphylaxis, for instance, was ruled out because the clinical features of this case were not consistent with the diagnosis. Specifically, the care team avoided all known allergens (including latex, even though the patient had no history of latex allergy), the timing of the arrest was not associated with the administration of any medications, and the patient's rapid development of hypothermia is not a feature associated with anaphylaxis.

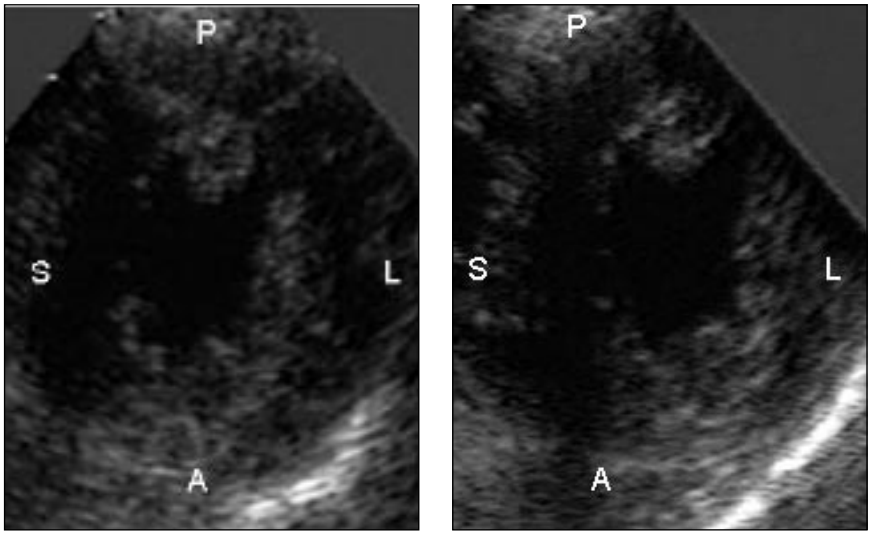

Figure 5. Transesophageal echocardiographic (TEE) evaluation of myocardial contractility. Transgastric TEE examination of the left ventricle (LV) at the mid-papillary muscle level demonstrates severe contractile dysfunction. The LV is shown in systole (left) and diastole (right); note that there is minimal change in the intraventricular cavity. The estimated LV ejection fraction is 10% to 15%, despite inotropic support with epinephrine. Abbreviations: A = anterior; L = lateral; P = posterior; S = septal.

Some types of primary cardiogenic shock also were determined to be inconsistent with the patient's presentation. The patient's age and lack of risk factors for coronary artery disease (such as familial dyslipidemia) made infarction unlikely. And while the physiologic stress of pregnancy usually results in decompensation of undiagnosed chronic heart failure, especially during the second trimester, the patient's physical examination findings and term intrauterine pregnancy argued against a primary cardiac cause.

Hypovolemic shock could have precipitated the initial hypotension, tachycardia, and decreased end-tidal carbon dioxide level, but the surgeons did not note any dramatic hemorrhage in the operative field. Occult hemorrhage was a distinct possibility, given the surgical challenges posed by this patient's adhesions and skeletomuscular abnormalities. If this were the case, however, TEE would have shown a hyperdynamic, empty heart—rather than an acutely failing heart with enlargement of all four chambers.

Of the potential mechanical causes of the patient's initial arrest, pneumo-

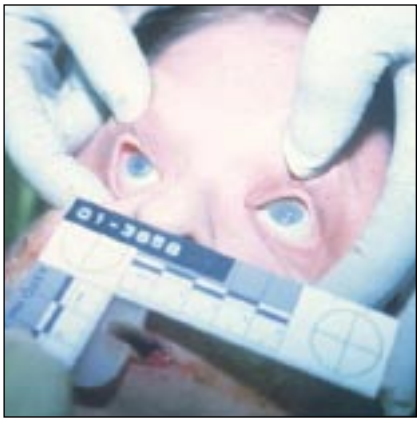

Figure 6. The patient's sclera at autopsy, showing a lack of vascular markings, which suggests massive hemorrhage. This is a rare finding in amniotic fluid embolism. In this case, it was most likely a result of disseminated intravascular coagulopathy.

thorax was excluded based on physical examination findings (bilateral breath sounds and a nondeviated trachea), observation of normal peak airway pressures during mechanical ventilation, and the absence of any significant risk factors (such as central line placement or attempts to place an epidural or spinal anesthetic) other than administration of positive pressure ventilation. Venous air embolism, pulmonary thromboembolism, and AFE, on the other hand, were all considered strong possibilities prior to TEE.

Venous air embolism can result when uterine venous structures are exposed to the atmosphere and negative pressure allows the entrainment of air into the vasculature. Cesarean delivery is known to increase the risk of venous air embolism. When a sufficient air bolus is delivered to the heart, an "air lock" can occur in the right ventricle, impeding the transit of blood from the great veins into the pulmonary system. Occasionally, the surgeon notes a sucking air sound in the field.

A sudden increase in the end-tidal nitrogen level is a sensitive and specific indicator of venous air embolism. On cardiac auscultation, a mill-wheel murmur is noted. Other signs and symptoms of venous air embolism are nonspecific and include hypoxia, cardiovascular collapse, a decreased end-tidal carbon dioxide level, and elevated cardiac filling pressures (central venous pressure) and pulmonary artery systolic and diastolic pressures, but not pulmonary capillary wedge pressure). TEE is exquisitely sensitive to the detection of intracardiac air, particularly as it enters the right side of the heart.[11] In this case, findings of TEE excluded venous air embolism.

The patient also was at very high risk for pulmonary thromboembolism. The hormones that support pregnancy result in a hypercoagulable state. And since this patient was bedridden due to her spina bifida, stasis of blood within the lower extremity veins was likely. Furthermore, her short stature and limitation of uterine mobility due to adhesions might have resulted in significant caval compression, which would be expected to increase blood return from the pelvic veins.

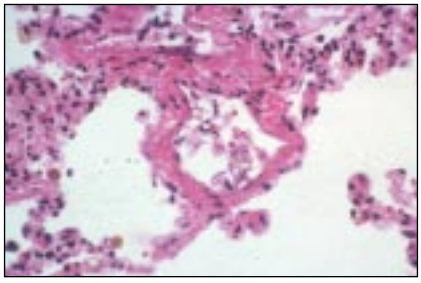

Figure 7. Histopathologic image showing fetal squamous epithelial cells in the maternal pulmonary tissue, which is highly suggestive of amniotic fluid embolism.

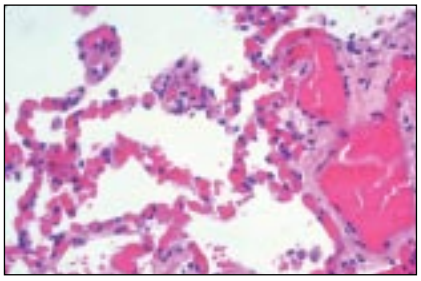

Figure 8. Histopathologic image of the maternal lung tissue, showing intravascular thrombosis, consistent with disseminated intravascular coagulation.

Acute right heart failure associated with acute pulmonary hypertension and hypoxia are the hallmarks of pulmonary thromboembolism. The left ventricle is hyperdynamic and underfilled (decreased preload) because the failing right heart is unable to deliver blood through the pulmonary vasculature. In our patient, however, TEE demonstrated that this was not the case, which effectively excluded pulmonary thromboembolism. This left only one option—AFE—to explain the patient's condition, and autopsy confirmed this diagnosis.

It is important to note that, while venous air embolism, pulmonary thromboembolism, and AFE are all embolic in nature, their presentation and treatment strategies differ significantly. Whenever the diagnosis of venous air embolism is suspected, the obstetrician should flood the surgical field immediately to prevent additional air entrainment. Once the diagnosis is made, venous air embolism is treated with central line placement for aspiration of air and with hyperbaric therapy. Pulmonary thromboembolism is treated by thrombolysis and, rarely, pulmonary artery embolectomy or mechanical cardiorespiratory support (extracorporeal membrane oxygenation). In our patient, all of these therapies would have been, at best, useless or, at worst, needlessly harmful. Thrombolytic therapy, in particular, carries a significant risk in surgical patients and might have had the effect of hastening death in this patient. Because TEE excluded venous air embolism and pulmonary thromboembolism, we were not forced to consider any of these options.

In summary, we believe that, despite the patient's death, this case shows TEE to be an important and potentially lifesaving tool in cases of acute hemodynamic instability.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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