Protein C Deficiency as a Cause of Pulmonary Embolism in the Perioperative Period

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Pulmonary embolism in the perioperative period is associated with significant morbidity and mortality. Although air, fat, and amniotic fluid can embolize to the pulmonary vasculature, a thromboembolic event is the most common etiology. Deficiency of protein C, a vitamin K-dependent anticoagulant that inhibits activated factors V and VIII, is a rare cause of thromboembolic phenomena. We report a case of perioperative pulmonary embolism secondary to undiagnosed protein C deficiency and resulting in nonresuscitable cardiac arrest in a pediatric patient.

**CASE REPORT**

An 8-yr-old girl was referred to our hospital with abdominal discomfort, pain of the left hip, and mild respiratory distress. Physical examination on admission was significant for tachypnea: she presented diffuse rales, multiple skin lesions of her lower extremities, and a tender, swollen left hip. Blood gas tensions while she was breathing room air were PaO₂ 59 mmHg and PaCO₂ 31 mmHg, pH 7.48. The initial chest radiograph showed prominent right peribular markings without infiltrates. She was admitted with a diagnosis of lower respiratory illness, an acute left hip infection, and probable sepsis.

Subsequent chest radiographs taken the day of admission showed alveolar densities consistent with right lower lobe (RLL) pneumonia, and antibiotic treatment was begun. An orthopedic surgery consultation indicated that at least part of the clinical presentation was due to a left thigh abscess, and the patient was taken to the operating room for an incision and drainage. The anesthetic course and surgery were brief and uneventful. Her oxyhemoglobin saturations (SpO₂) by pulse oximetry remained 99–100% at an inspired oxygen concentration (FiO₂) of 50%. Surgically, no suppuration could be elicited from the operative incision. Postoperatively, her condition did not improve and she continued to have leukocytosis, abdominal tenderness and distention, and a general appearance of sepsis despite multiple antibiotics.

An abdominal computed tomography (CT) scan revealed possible peripendependent inflammatory changes.

The patient returned to the operating room on the second night for an emergency exploratory laparotomy and appendectomy. Upon arrival in the operating room, the patient's SpO₂, while breathing room air was noted to be 81%. This was believed to be due to shunting induced by the RLL pneumonia or the septic state. A rapid-sequence induction with ketamine and succinylcholine was uneventful. The patient's anesthesia and muscle paralysis were maintained with isoflurane and vecuronium, respectively. Her SpO₂ remained 100% at an inspired oxygen concentration of 50% with controlled ventilation, and her anesthetic course was uncomplicated. Surgically, no acute processes were found in her abdomen.

In the recovery room, the patient developed progressively worsening respiratory distress, and her trachea was electrolytically reintubated after atropine, ketamine, and succinylcholine. She soon developed hypotension that was unresponsive to fluid therapy, and a dopamine infusion was begun. She had several periods of bradycardia, which required increasing dosages of dopamine, atropine, and calcium, and a brief period of closed-chest compressions. Her condition remained critical; blood pressure decreased to less than 80/40 mmHg despite fluid resuscitation and inotropic support.

The patient was transferred to the pediatric intensive care unit in critical condition. Approximately 3 h after arrival to the unit, she again developed bradycardia. Despite maximal advanced cardiac life support, the cardiac rhythm degenerated to electromechanical dissociation, from which the patient could not be resuscitated.

A postmortem exam revealed multiple thromboemboli, in various stages of organization in the pulmonary, femoral, and pelvic venous systems. A massive saddle pulmonary embolism was determined to be the proximate cause of death. An enzyme-linked immunosorbent assay (ELISA) revealed a protein C antigen concentration of 18 units · dl⁻¹ and a protein S antigen concentration of 64 units · dl⁻¹ (normal for both proteins C and S is 85–145 units · dl⁻¹). Subsequent testing of the patient's five siblings revealed one to have a protein C activity level of 33 units · dl⁻¹ but all to have protein S activity levels above 65 units · dl⁻¹.

**Discussion**

Pulmonary embolism is one of the most serious causes of hypoxemia during the perioperative period. Possible causes of emboli include hematologic thrombi, air, fat, amniotic fluid, foreign bodies, neoplastic cells, and methyl methacrylate. The majority of pulmonary emboli are secondary to thromboembolic phenomena, usually arising from thrombi of the deep venous system of the lower extremities. Other common sites of thrombi formation are the pelvic veins, and in patients with atrial fibrillation, the right atrium. Primary etiologic factors in this form of thromboembolism are venous stasis, abnormalities of the vessel wall, and alterations in blood coagulation. Numerous conditions common in the surgical pa-
tient population are associated with one or more of the above etiologic factors: advanced age, immobilization, underlying systemic disease, trauma, cardiac failure, oral contraceptive use, pregnancy and the puerperium, blood group A, and a recent history of other surgery.

Protein C deficiency is a rare cause of hypercoagulability and so can lead to pulmonary embolism. An endogenous anticoagulant, protein C is a vitamin K-dependent protease zymogen synthesized in the liver. Protein C has no intrinsic anticoagulant activity and exerts its physiologic anticoagulant properties only once it is activated. It is activated by thrombin in combination with the endothelial cell membrane bound cofactor thrombomodulin. Because thrombomodulin is present on the intact endothelial cell membrane, protein C will not be active at the vessel injury, and therefore, a thrombus can form unhindered at this site. Thrombomodulin interacts with thrombin only at the perimeter of the vessel disruption, to prevent the thrombus from uncontrolled propagation. Once activated, protein C proteolytically cleaves activated factors V and VIII and indirectly stimulates fibrinolysis.

Protein C deficiencies can be either acquired or inherited. Some disease states and medications that cause an acquired protein C deficiency are listed in table 1. Hereditary protein C deficiency is a disorder that has been described as autosomal dominant, autosomal recessive, and autosomal dominant with incomplete penetrance. Most likely, based on clinical manifestations, there are two distinct phenotypes of protein C deficiency—an autosomal recessive and an autosomal dominant. The dominant form of heterozygous protein C deficiency has an estimated prevalence of 1 in 15,000, whereas the recessive form has a prevalence of 1 in 250. Because our patient had a markedly depressed protein C concentration and a normal protein S concentration, we conclude that a protein C deficiency was the etiology of her hypercoagulable state. Given the age of our patient and an isolated decreased protein C concentration in an asymptomatic sibling, a hereditary disorder most likely was the basis for her deficiency state.

Homozygous-deficient patients have protein C levels of less than 1% of normal. They are critically affected with a hypercoagulable state in the neonatal or early childhood period. The homozygous disease is characterized by purpura fulminans, an acute hemorrhagic necrosis of the skin secondary to thrombosis of the cutaneous vasculature. They usually die in the neonatal period with purpura fulminans, disseminated intravascular coagulation, or massive thrombosis.

Those heterozygous for protein C deficiency typically have protein C levels of between 5 and 55% of normal. Either the protein C antigen or the protein C activity levels can be reduced. The protein C-deficient heterozygous patients can range from having severe thromboembolic disease to being totally asymptomatic. We conclude, based on her protein C level, that our patient’s deficiency was heterozygous deficiency.

The most common clinical manifestation of either the acquired or heterozygous hereditary form of protein C deficiency is recurrent thromboembolic disease. The thrombosis usually develops in the superficial or deep iliofemoral veins and progresses to pulmonary embolism, as it did in our patient. With the systemic hypercoagulability characteristic of this deficiency disease, thromboses also can develop at unusual sites such as the axillary, mesenteric, and cerebral veins. These may present as pneumonia secondary to massive mesenteric vein thrombosis, thrombosis of the cavernous sinus, renal vein thrombosis, or priapism. With this deficiency, the thromboembolic phenomena usually appear in adolescence or early adulthood. The protein C-deficient patient may show the initial episode only with some other predisposing factor, such as infection, surgery, bed rest, oral contraception, or pregnancy. Several of these factors were present in our patient, and probably exacerbated her inherited protein C deficiency and thereby precipitated the thromboembolic event. Because of the location of this patient’s thromboemboli, as determined by autopsy, as well as the negative operative findings, we hypothesize that her multiple symptoms at presentation were due probably to these various emboli.

The treatment of symptomatic protein C deficiency is long-term anticoagulant therapy with oral Coumadin (Du Pont, Wilmington, DE). In the future, genetically engineered protein C produced through recombinant DNA technology may become available. Current perioperative recommendations for protein C-deficient patients already receiving Coumadin include: continuation of oral anticoagulant therapy until the day of surgery, anticoagulant reversal with vitamin K or fresh frozen plasma on the morning of surgery, and institution of minidose

<table>
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<tr>
<th>Table 1. Causes of Acquired Protein C Deficiency</th>
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<tr>
<td>Coumarin³ Disseminated intravascular coagulation²⁹</td>
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<tr>
<td>Liver disease¹⁵ Adult respiratory distress syndrome¹⁵</td>
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<tr>
<td>Postpartum state¹⁵ some acute Leukemias³</td>
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<td>Multiple Myelomas¹⁴ Circulating lupuslike anticoagulant immunoglobulins²⁸</td>
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<td>L-asparaginase¹⁴ Antibiotic with N-methyl thiotetrazole ring (i.e., Cefmetazole, Cefamandol, Cefotan, Cefoperazone, Moxalactam)</td>
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<tr>
<td>Cyclophosphamide, methotrexate, and 5-flourouracil combination¹² Hemodialysis⁴</td>
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<td>Nephrotic syndrome¹³ Systemic lupus erythematosus¹³</td>
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heparin postoperatively until Coumadin therapy can be reinstituted.

In summary, we report a case of a perioperative pulmonary embolism secondary to undiagnosed protein C deficiency and resulting in cardiac arrest. Because protein C deficiency does not cause abnormalities in the routine screening coagulation tests (e.g., prothrombin time, partial thromboplastin time, and bleeding time) the anesthesiologist must maintain a high index of suspicion for patients who report either a personal or family history of thromboembolic disease at a young age.

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REFERENCES

Complication from a Nasopharyngeal Airway in a Patient with a Basilar Skull Fracture

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Airway management in patients with craniofacial trauma presents the anesthesiologist with several complex problems. Not only are these patients often in acute respiratory distress, but also disruption of normal anatomic relationships in the head and neck can make placement of artificial airways, laryngoscopy, and tracheal intubation both technically difficult and hazardous. Because these patients may be at risk for increased intracranial pressure, increased arterial carbon dioxide or decreased arterial oxygen tensions may prove devastating. Despite the urgency of the situation, time must be taken to assess injury to the soft tissues and skeletal structures of the head and neck in order to avoid further injury. We present a case in which insertion of a nasopharyngeal airway in a patient with head and neck injury may have contributed to further damage to the central nervous system.

CASE REPORT

A 46-yr-old woman was involved in a motor vehicle accident. The patient sustained multiple injuries, which included a depressed frontal parietal skull fracture with exposure and herniation of the underlying cerebral cortex, bilateral LeFort III fractures of the facial skeleton, a basilar skull fracture, and suspected fracture of the spinous processes of C5 and C6. The patient also presented with multiple scalp and facial lacerations, marked facial edema, and contusions of the right frontal and temporal lobes.

The patient was transported to the local medical facility, where she was found to be unresponsive to commands but spontaneously moving all four extremities. Shortly after arrival, she developed respiratory distress, and a no. 50 Bardex nasopharyngeal airway was inserted. The patient then was transferred to our medical facility, where she was noted to be in severe respiratory distress. After rapid-sequence induc-