thetic. The expected time for nerve regeneration has passed, suggesting that the injury is permanent.

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References

1. Farrar MD, Scheybani M, Nolte H: Upper extremity block effectiveness and complications. Reg Anesth 6:133–134, 1981
2. Winnie AP: Interscalene brachial plexus block. Anesth Analg 49:455–466, 1970
3. McCredie M, Lovejoy FW, Kaltreider ML: Pulmonary function in diaphragmatic paralysis. Thorax 17:213–217, 1962
4. Knoblanche GE: The incidence and aetiology of phrenic nerve blockade associated with supraclavicular brachial plexus block. Anaesth Intens Care 7:346–349, 1979
5. Moore DC: Regional Block, fourth edition. Springfield, Charles C Thomas, 1965
6. Stock MC, Downs JB: Transient phrenic nerve blockade during internal jugular vein cannulation using the anteriolateral approach. ANESTHESIOLOGY 57:230–233, 1982
7. Obel IWP: Transient phrenic-nerve paralysis following subclavian venipuncture. ANESTHESIOLOGY 33:369–370, 1970
8. Vest JV, Pereira M, Senior RM: Phrenic nerve injury associated with venipuncture of the internal jugular vein. Chest 78: 777–779, 1980
9. Drachler DH, Koepke GH, Weg JG: Phrenic nerve injury from subclavian vein catheterization. JAMA 236:2880–2881, 1976
10. Epstein EJ, Quereshi MSA, Wright JS: Diaphragmatic paralysis after supraclavicular puncture of subclavian vein. Br Med J 1:693–694, 1976
11. Alexander J: Temporary phrenic nerve paralysis. JAMA 102: 1552–1553, 1934
12. Mitchell RS: Phrenic nerve interruption in the treatment of pulmonary tuberculosis. Am Rev Tuberculosis 58:619–645, 1948

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Respiratory Failure Secondary to Homologous Blood Transfusion

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The appearance of alveolar flooding in the perioperative period is often unheralded and usually unwelcome. Accurate diagnosis and prompt treatment are imperative. An example of a severe form of acute pulmonary edema with an uncommon etiology will be described, followed by a differential diagnosis and a review of the available information on this phenomenon.

Report of a Case

A 32-year-old man with progressive, juvenile rheumatoid arthritis was scheduled to undergo total hip arthroplasty. Preoperative evaluation also revealed a history of paroxysmal atrial tachycardia controlled with digoxin, inflammatory iritis—improved through the use of flurometholone ophthalmic drops—and iron deficiency anemia. Aspirin and steroid therapy had resulted in upper gastrointestinal bleeding several years earlier, necessitating a partial gastrectomy and vagotomy. Previous anesthetics were historically uncomplicated; the family anesthetic history was negative; and he neither smoked cigarettes nor used alcohol. Chronic medications included, in addition to those mentioned above, naproxen, aspirin, and prednisone, and he denied medication allergy. He was small in stature, at 167 cm tall, weighing 52 kg. In addition to the joint deformities associated with rheumatoid arthritis, the patient exhibited considerable restriction of temporomandibular and cervical motion, and anisocoria, with the diameter of the right pupil being approximately 3 mm larger than the left pupil. The preoperative chest roentgenogram showed evidence of early interstitial fibrous changes consistent with rheumatoid arthritis, and the EKG indicated digoxin effect. His hemoglobin concentration was 11.5 $g \cdot dl^{-1}$ and the hematocrit was 35%; however, the remainder of laboratory data, including quantitative serum immunoglobulins and immunoelectrophoresis, were normal.

Anesthesia was induced with thiopental 300 mg iv, followed by succinylcholine chloride 70 mg iv to facilitate laryngoscopy. Using a conventional technique, only the tip of the epiglottis could be visualized; however, an 8-mm ID cuffed endotracheal tube was inserted successfully. Anesthesia was maintained with an initial fentanyl dose of 10 $\mu g \cdot kg^{-1}$ iv, along with isoflurane and oxygen. Following induction, radial arterial and central venous cannulae were inserted for monitoring. With an FI_{O_2} of 1.0 pH_a was 7.47, Pa_{CO_2} 33 mmHg, and Pa_{O_2} 379 mmHg. His gas exchange and acid–base status did not change significantly during this 2-h operation. A central venous pressure of approximately 10 mmHg was maintained through an infusion of 1,800 ml lactated Ringer's solution, two units of whole blood were transfused to replace blood loss, and nitroglycerin was administered to reduce the arterial blood pressure by 30% from his baseline. Paralysis was induced by an atracurium infusion titrated to 90% thenar twitch and electromyogram (EMG) depression; the effects later were antagonized with edrophonium and glycopyrrolate, and the trachea was extubated.

One hour after arrival in the recovery room, with an FI_{O_2} of 0.4, the pH_a was 7.42, Pa_{CO_2} 39 mmHg, and Pa_{O_2} 86 mmHg. His central venous pressure and arterial blood pressure were 8 and 136/74 mmHg, respectively. With a hematocrit of 26% and a heart rate of

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113 bpm, two units of blood were ordered for transfusion. Twenty minutes following completion of the transfusion of the third unit, the patient complained of shortness of breath and was producing large amounts of sputum. He was tachypneic, tachycardic at 155 bpm, and his central venous pressure and arterial pressure were 7 and 150/63 mmHg, respectively. On an $F_{I_{O_2}}$ of 0.4, the pH_a was 7.35, Pa_{CO_2} 49 mmHg, and Pa_{O_2} 35 mmHg. The hematocrit had increased to 40%. At this point, a nasotracheal tube was inserted with the use of a flexible fiberoptic bronchoscope. Pulmonary ventilation was initiated with an intermittent mandatory ventilation (IMV) rate of 15 per minute, an $F_{I_{O_2}}$ of 1.0 and positive end-expiratory pressure (PEEP) of 10 cm H_2O pressure. Blood and urine samples were collected and sent to the blood bank, and the director of the blood bank was informed. Samples were also obtained for serum electrolytes and blood cultures. Five hundred milliliters of edema fluid emanated from the endotracheal tube during the first 30 min of this episode. The colloid osmotic pressure of this fluid was compared with the colloid osmotic pressure in the serum on two different occasions, one-half hour apart, revealing ratios of 0.72 (15.4 mmHg/21.4 mmHg) and 0.92 (19.0 mmHg/20.5 mmHg), respectively. The chest roentgenogram depicted alveolar flooding. A pulmonary arterial catheter was inserted through the left internal jugular vein, revealing a cardiac index of 4.74 $l \cdot min^{-1} \cdot m^{-2}$, pulmonary artery pressure (PAP), pulmonary artery occlusion pressure (PAOP), and right atrial pressure (RAP) of 40/12, 10, and 7 mmHg, respectively. The $P\bar{v}_{O_2}$ was 23 mmHg and the Q_s/Q_t was 0.61. With an arterial blood pressure of 109/38 mmHg and a heart rate of 148 bpm, his systemic vascular resistance was low (499 $dyne \cdot s \cdot cm^{-5}$). The core temperature was now 39.5° C.

The provisional diagnosis was pulmonary edema caused by increased permeability, and therefore the therapeutic goal was, initially, to improve oxygenation through expansion of the functional residual capacity (FRC) with PEEP and, secondly, to decrease the gradient for the transudation of fluid toward the alveolus through reduction of the pulmonary hydrostatic pressure. Furosemide was administered iv during the first hour in doses totaling 100 mg until the PAOP was 2 mmHg; however, the cardiac index and arterial blood pressure decreased to 2.8 $l \cdot m^{-1} \cdot m^{-2}$ and 90/47 mmHg, respectively. Methylprednisolone was administered in a dose of 30 $mg \cdot kg^{-1}$ iv, to be repeated every 6 h for 2 days, and PEEP gradually was increased to 18 cm H_2O pressure, at which point there was a significant decrease in cardiac index without improvement of oxygenation. The cardiac output was temporarily increased with a dopamine infusion of 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$; however, the gas exchange did not improve. For the next 20 h, the Pa_{O_2} ranged from 36 to 44 mmHg, while the Pa_{CO_2} and pH were normal, and the $P\bar{v}_{O_2}$ remained in the midtwenties. The IMV rate was decreased progressively from 15 to 8 per min, without change in the Pa_{CO_2} or pH.

Twenty-one hours after the onset of pulmonary dysfunction, the Pa_{O_2} increased to 78 mmHg, with an $F_{I_{O_2}}$ of 1.0 and PEEP of 15 cm H_2O, indicating a turning point in the disease process. By this time, the ratio of colloid osmotic pressure in the pulmonary edema fluid to the plasma had decreased to 0.3, and the serum albumin had also decreased from a preoperative value of 3.9 $g \cdot dl^{-1}$ to 2.2 $g \cdot dl^{-1}$. The shunt fraction decreased to 0.35, and the Pa_{O_2} steadily increased, despite gradual reduction in the $F_{I_{O_2}}$. By the second postoperative day, a specific human leukocyte antigen (HLA) antibody had been isolated in the donor plasma from the second unit of blood that had been transfused in the operating room. HLA and leukocyte antibody screening tests were negative in the other two units of blood, as well as in the recipient's plasma. Blood cultures showed no growth, and evidence for a hemolytic transfusion reaction was absent. At this time, the hematocrit had decreased to 26%, and two units of washed red blood cells were transfused without incident. By the third postoperative day, the roentgenogram showed considerable improvement. The weaning process was completed, and the trachea was extubated. On an $F_{I_{O_2}}$ of 0.4, the pH_a was 7.43, Pa_{CO_2} 34 mmHg, and Pa_{O_2} 83 mmHg. From this time onward, the recovery process was uncomplicated, and the patient was discharged from the hospital on the eighth postoperative day. Three months later, the same operative procedure was completed on the opposite side without complication. Washed red blood cells were transfused to replace the operative loss.

Discussion

This case depicted a profound and apparently abrupt onset of acute pulmonary edema that was temporally and erroneously associated with the transfusion of the third unit of blood, administered postoperatively in the recovery room. This life-threatening deterioration demanded immediate and effective therapy, supported by data that elucidated the physiologic disturbance, followed by determination of the precise cause through a process of elimination. The appearance of alveolar flooding with fluid of a high relative oncotic pressure in the presence of a high cardiac index and normal ventricular filling pressures indicated pulmonary edema of increased permeability, or noncardiac origin.[1] The treatment centered around the improvement of oxygenation through expansion of the FRC with PEEP, increasing the $F_{I_{O_2}}$ and aggressive lowering of the pulmonary vascular hydrostatic pressures with furosemide and vasoactive drugs.[2]

Foremost on the list of potential causes was a pulmonary vascular insult associated with insertion of the hip prosthesis and a transfusion reaction; however, by necessity, shock, hypoxia, toxic inhalants, drug reactions, aspiration of gastric contents, neurogenic phenomena, and sepsis[3] also were included. The diagnosis was made by exclusion.

Vigilance combined with online invasive monitoring modalities and timing made shock, hypoxia, and toxic inhalants remote possibilities. There was no history of penicillin allergy, so a drug reaction to nafcillin was unlikely. Allergic responses to thiopental and succinylcholine,[4,5] have been described, however a delayed response of this magnitude would have been unusual. Aspiration as well as a neurogenic origin in a conscious and reflexic individual would have been paradoxic, while negative blood cultures eliminated sepsis. The only other possible causes were a pulmonary complication associated with the operation and an immunologically mediated transfusion reaction.

Pulmonary capillary leak associated with total hip arthroplasty has been reported[6]; however, in this account, the phenomenon transpired intraoperatively; only right ventricular filling pressures were measured prior to treatment, pulmonary edema fluid oncotic pressure was not determined, and the pathologic signs dissipated rapidly. These problems make identification of the etiology of this occurrence obscure. The pulmonary and

circulatory reactions to total hip arthroplasty have been well described.[7,8] Their etiology rests in the increased femoral intramedullary pressure and resulting pulmonary embolism of medullary contents during the insertion of the bone cement and prosthesis.[9] These alterations vary in intensity and consist of increased venous admixture ($\dot{Q}_s/\dot{Q}_t$), dead space (V_D/V_T), Pa_{CO_2}, pulmonary artery pressure and pulmonary vascular resistance, and decreased Pa_{O_2}, thoracic compliance, and, occasionally, arterial blood pressure. Experimentally, these occur maximally within 5 min of the impaction of the prosthesis and return toward normal in the early postoperative period. If this embolization had contributed significantly to the pulmonary compromise in this patient, an earlier deterioration corresponding to prosthetic impaction would have been expected.

Pulmonary edema associated with blood transfusion in the absence of hypervolemia was first described in 1951,[10] and since then several reports of leukoagglutinin-induced noncardiogenic pulmonary edema have appeared.[11,12] While leukoagglutinins in the recipient's plasma directed against donor granulocytes can result in a reaction, it is commonly febrile and minor in nature. The pulmonary compromise in this patient was caused by the passive transfer from the donor to the recipient of agglutinating antibodies directed against human leukocyte antigens (HLA), granulocyte-specific antigens, or both. This transfer usually leads to prompt neutropenia—typical signs of a transfusion reaction including fever, chills, and pain—and, finally, overt pulmonary dysfunction and pulmonary edema.

The postulated pathophysiology of this pulmonary dysfunction is a complement C_5a-mediated pulmonary leukocyte aggregation and leukostasis.[13,14] While leukostasis by itself is not a trivial event, the pulmonary endothelial damage and subsequent alveolar flooding result from the increased adhesiveness of these complement-activated granulocytes and their production of oxygen radicles, which increase endothelial permeability. The addition of platelets to this reaction leads to further amplification of the endothelial damage wrought by the stimulated granulocytes.

The treatment of this type of pulmonary edema should include both supportive measures as well as inhibition of the ongoing pathophysiologic process. In this case, it consisted of previously mentioned measures that optimized gas exchange and ventilation–perfusion relationships and interventions that simultaneously reduced pulmonary intravascular hydrostatic pressure and thereby decreased the gradient influencing the movement of fluid into the alveoli. Additionally, large doses of corticosteroids were administered in hopes of interrupting this pathophysiologic process, for recent evidence indicates that pharmacologic doses of these drugs can prevent aggregation of granulocytes exposed to C_5a *in vitro* and can also inhibit granulocyte production of superoxide.[15,16]

This case of severe pulmonary edema and respiratory failure caused by a leukocyte agglutinin reaction associated with transfusion represents the most severe example of this phenomenon in a surviving patient. Early diagnosis, aided by availability of technical facilities and thoughtful treatment, resulted in a satisfactory outcome.

References

1. Staub NC: The pathogenesis of pulmonary edema. Prog Cardiovasc Dis 23:53–80, 1980
2. Staub NC: Pulmonary edema due to increased microvascular permeability to fluid and protein. Circ Res 43:143–151, 1978
3. Staub NC: "State of the Art" Review. Pathogenesis of pulmonary edema. Am Rev Respir Dis 109:358–372, 1974
4. Lilly JK, Hoy RH: Thiopental anaphylaxis and reagin involvement. ANESTHESIOLOGY 53:335–337, 1980
5. Ravindran RS, Klemm JE: Anaphylaxis to succinylcholine in a patient allergic to penicillin. Anesth Analg 59:944–945, 1980
6. Safwat AM, Dror A: Pulmonary capillary leak associated with methylmethacrylate during general anesthesia. A case report. Clin Orthop 168:59–63, 1982
7. Modig J, Malmberg P: Pulmonary and circulatory reactions during total hip replacement surgery. Acta Anaesth Scand 19:219–237, 1975
8. Mebius C, Hedenstierna G: Gas exchange and respiratory mechanics during hip arthroplasty. Acta Anaesth Scand 26:15–21, 1982
9. Kallos T, Enis JE, Gollan F, Davis JH: Intramedullary pressure and pulmonary embolism of femoral medullary contents in dogs during insertion of bone cement and a prosthesis. J Bone Joint Surg 56A:1363–1367, 1974
10. Barnard RD: Indiscriminate transfusion: A critique of case reports illustrating hypertensitivity reactions. NY State J Med 51:2399–2402, 1951
11. Dubois M, Lotze MT, Diamond WJ, Kim YD, Flye MW, Macnamara TE: Pulmonary shunting during leukoagglutinin-induced noncardiac pulmonary edema. JAMA 244:2186–2189, 1980
12. Popovsky MA, Abel MD, Moore SB: Transfusion-related acute lung injury associated with passive transfer of antileukocyte antibodies. Am Rev Respir Dis 128:185–189, 1983
13. Jacob HS, Craddock PR, Hammerschmidt DE, Moldow CF: Complement-induced granulocyte aggregation. N Engl J Med 302:789–794, 1980
14. Hammerschmidt DE, Jacob HS: Adverse pulmonary reactions to transfusion. Adv Intern Med 27:511–530, 1982
15. Goldstein IM, Roos D, Weissmann G, Kaplan HB: Influence of corticosteroids on human polymorphonuclear leukocyte function in vitro: Reduction of lysosomal enzyme release and superoxide production. Inflammation 1:305–315, 1976
16. Hammerschmidt DE, White JG, Craddock PR, Jacob HS: Corticosteroids inhibit complement-induced granulocyte aggregation: A possible mechanism for their efficacy in shock states. J Clin Invest 63:798–803, 1979