Pulmonary Edema After Resection of a Fourth Ventricle Tumor: Possible Evidence for a Medulla-Mediated Mechanism

MARK T. KEEGAN, M.B., M.R.C.P.I., AND WILLIAM L. LANIER, M.D.

A well-recognized fact is that some patients may have development of pulmonary edema in association with disorders of the central nervous system. The origin of this phenomenon, known as neurogenic pulmonary edema, is unclear but may result, in part, from select pulmonary venaconstriction modulated by autonomic outflow from the medulla oblongata. We describe a 21-year-old man who had development of pulmonary edema in association with surgical resection of a brain tumor that was close to the medulla. Other than the possibility of medullary dysfunction, which could have occurred after surgical manipulation, no other risk factor for pulmonary edema was identified. Of note, the patient's blood pressure remained normal throughout the perioperative period, and no fluid overload or primary cardiac dysfunction was evident. This case supports the theory that the medulla is an important anatomic site of origin for neurogenic pulmonary edema and that alterations in medullary function can induce pulmonary edema in humans, independent of systemic hypertension.

REPORT OF CASE
A 21-year-old man who weighed 90 kg underwent elective suboccipital craniectomy and cervical laminectomy to facilitate resection of a tumor in the fourth ventricle and spinal canal. Three months before hospital admission, he first began experiencing symptoms related to the tumor: retro-orbital and frontal headaches, dysphagia, dysarthria, and "mood swings." Subsequent evaluation with magnetic resonance imaging demonstrated a large midline tumor centered in the inferior aspect of the fourth ventricle and extending through the foramina of Magendie and Luschka, into the upper cervical spinal canal. No obstruction of the fourth ventricle or intraspinal metastatic disease was evident.

Previously, the patient had been in good health and had led an active lifestyle. Specifically, he had no history of cardiac or pulmonary disease. He had had a 3-pack-year history of cigarette use but had quit smoking 2 years earlier. Preoperative electrocardiography (ECG) revealed normal sinus rhythm at a rate of 60 beats/min, and findings on chest roentgenography were normal except for a small area of fibrosis at the right costophrenic angle. His baseline blood pressure was 130/75 mm Hg. Preoperative medications for the tumor-related headaches were oral dexamethasone, 2 mg three times a day for 10 days, and acetaminophen, 1,000 mg four times a day as needed.

Anesthesia was induced with intravenous (IV) administration of fentanyl, 100 µg, and sodium thiopental, 450 mg. Controlled ventilation through a mask was provided without difficulty. After IV administration of 10 mg of vecuronium to induce paralysis and administration of an additional 50 mg of sodium thiopental, the patient was given esmolol, 70 mg, to blunt the sympathetic response to instrumentation. Intubation of the trachea with a wire-
spiral reinforced tracheal tube was performed with no complications. Thereafter, anesthesia was maintained with 1 to 2% inspired isoflurane in 50% N₂O and O₂, and supplemental doses of vecuronium were administered as needed. Monitors included ECG leads II and V₅, pulse oximetry, direct measurement of radial artery blood pressure, esophageal stethoscope and temperature probe, transesophageal echocardiography (TEE), right atrial catheter, precordial Doppler ultrasonography, and quantification of inspired and expired gases by using mass spectrometry.

The patient was placed in the sitting position, and the surgical procedure proceeded. With use of a midline approach, the floor of the fourth ventricle was exposed, and the tumor was removed from around the striae medullares and obex. Throughout the surgical resection, no cardiac dysfunction was evident. Systolic blood pressure (transducer was at ear level) ranged from 90 to 140 mm Hg. During the course of the 7-hour anesthetic, blood loss was approximately 300 mL. The patient was given 3,200 mL of lactated Ringer’s solution and 250 mL of 5% albumin; however, no blood products were administered. Urine output was 1,200 mL. No diuretics were administered. No change in cardiac contractility or wall motion abnormality was evident on TEE, and no changes occurred on ECG that suggested myocardial dysfunction. The surgeon noted no sign of increased intracranial pressure.

Of importance, however, arterial blood gas studies revealed an increased alveolar-to-arterial oxygen difference. Intraoperatively, partial arterial pressure of oxygen (PaO₂) ranged from 114 to 134 mm Hg, despite the fact that this young man was breathing 50% O₂. In addition, a mild tachycardia (90 beats/min) was noted during the course of the operation. Intraoperatively, partial arterial pressure of carbon dioxide (PaCO₂) was 30 mm Hg.

At completion of the operation, central venous pressure was 10 mm Hg, a mere 1 mm Hg greater than when the patient was originally placed in the sitting position. No apparent change was noted on TEE. The patient was then returned to the supine position, and neuromuscular block was reversed with IV administration of neostigmine, 5 mg, and glycopyrrolate, 1 mg. Subsequently, adequate reversal was confirmed by return of a normal train-of-four in the adductor pollicis muscle in response to supramaximal electrical stimulation of the ulnar nerve. On discontinuation of the anesthetic and cessation of mechanical ventilation, the patient began producing frothy pink sputum. The trachea was reintubated by using a blind nasal technique. The roentgenogram showed bilateral pulmonary infiltrates consistent with diffuse pulmonary edema.

IV therapy was initiated with furosemide, 40 mg, and morphine, 8 mg. The patient was transported to the postanesthetic care unit, and 10 cm H₂O of continuous positive airway pressure was added to a T-piece supplying 100% O₂. Tachypnea persisted. Repeated blood gas analysis revealed a PaO₂ of 63 mm Hg and a PaCO₂ of 50 mm Hg. Mechanical ventilation was initiated with 100% O₂ by using an assist/control mode at 30 breaths/min, a 30-L minute volume, and 10 cm H₂O positive end-expiratory pressure. With these settings, blood gas results improved to a PaO₂ of 136 mm Hg and a PaCO₂ of 41 mm Hg. The pharmacologic interventions resulted in brisk diuresis (2,100 mL in 1 hour). After stabilization of the patient’s clinical condition, he was transferred to a neurosurgical intensive-care unit, where both clinical and radiologic improvement were dramatic during the next few hours. With hemoglobin oxygen saturations consistently greater than 97%, the trachea was extubated while the patient was in the intensive-care unit, 3 hours after the initiation of mechanical ventilation in the postanesthetic care unit.

The next day, the patient’s respiratory function was almost normal, although he still required oxygen, 2 L/min through a nasal cannula, for 24 hours to maintain a hemoglobin oxygen saturation of greater than 97%. Neurologic status remained normal throughout the postoperative period, and the patient was dismissed from the hospital on the third postoperative day, with normal respiratory function.

Microscopic examination of the surgical specimen revealed a choroid plexus papilloma. Follow-up care with an oncologist was arranged.

DISCUSSION
The causes of pulmonary edema include myocardial dysfunction, fluid overload, aspiration, negative intrathoracic...
pressure, hypoproteinemia, and transfusion-associated acute lung injury. Our patient had no ECG or echocardiographic evidence of myocardial dysfunction, and fluid administration during the 7-hour anesthetic was not excessive. No blood products were given. That the patient experienced negative pressure pulmonary edema is also improbable. He had no evidence of difficulty with airway management, either at anesthesia induction or after tracheal extubation; intubation was uneventful, and the wire-spiral endotracheal tube was not obstructed at any time. Thus, these factors also can be ruled out as an origin of edema. We believe that our patient experienced NPE.

Pulmonary edema in association with central nervous system insults has been described since the early part of the century. Initial descriptions were in patients with epilepsy who died of postictal respiratory distress. Other descriptions have included series of patients with head trauma, both civilian and military. In addition, the phenomenon of NPE has been described in association with subarachnoid hemorrhage, intracerebral hemorrhage, cerebral tumors, venous air embolism, multiple sclerosis, and intracranial operation, as well as various other conditions.

The diagnosis of NPE is primarily one of exclusion. Because of this limitation, the incidence of NPE is difficult to establish and—especially in late-onset, milder variants—this condition may be underdiagnosed.

The pathophysiology of NPE has not been fully elucidated. The condition has been broadly divided into "cardiogenic" and "permeability" lesions, and both mechanisms probably have a role. Investigators have described NPE in association with systemic and left atrial hypertension; in this association, the presence of increased pulmonary capillary pressures is presumed to cause an imbalance of the Starling forces in the lung and shifts fluid (with a low protein concentration) from the pulmonary capillaries into the interstitium and, later, into the alveoli. Other cases have been reported in which the edema fluid serum protein content is greater than 0.7, a reflection of an apparent permeability defect in the capillaries.

Previous reports, mainly involving research in animal models, have described a sympathetic nervous system overactivity phenomenon resulting in acute hemodynamic derangements, acute left ventricular failure, and pulmonary edema. α-Adrenergic antagonists have been shown to prevent NPE in animals. The "blast injury" theory postulates that the sympathetic surge leads to a direct injury to the pulmonary capillaries and hence a high protein content in the edema fluid. This may be due to a "stress failure" of the pulmonary capillaries, similar to the alveolar hemorrhage seen in galloping racehorses. Sympathetic nerve fibers innervate contractile elements in the endothelial cells; thus, sympathetic activity may lead to physical opening of the tight junctions in the capillaries and allow protein flux.

Reports in humans, however, fail to demonstrate conclusively a hypertensive surge, and investigators have advocated that supraspinally induced isolated pulmonary vasoconstriction may be responsible for the efflux of fluid from the pulmonary capillaries into the interstitium and the alveoli. Consistent with this viewpoint, our patient had no evidence of meaningful hypertension during either the intraoperative or the postoperative period.

The specific neurologic pathway or pathways for the production of NPE have not definitively been identified. Various "effectors" or "edemagenic" sites have been postulated, and, based primarily on animal data, hypothalamic derangements as well as lesions in the medulla oblongata (specifically, areas 1 and 5, the nucleus of the solitary tract, and the area postrema) have been cited as the origin of the pathophysiologic process. A supraspinal origin is widely accepted because NPE is extremely rare in patients with cervical cord lesions.

Human evidence for an anatomic site has been limited to case reports; however, with the advent of newer imaging techniques, evidence for a derangement of the medulla (the accepted human vasomotor center) is increasing. Simon and associates described a woman with multiple sclerosis whose recurrent pulmonary edema was attributed to a lesion in the posterior aspect of the rostral medulla involving the floor of the fourth ventricle. Other cases involving multiple sclerosis lesions have been described, and NPE has been attributed to trauma and edema, as well as various other lesions of the medulla and perimedullary structures.

The inferior aspect of the floor of the fourth ventricle, the site of microsurgery in our patient, is formed by the posterior medulla, in which lie the adrenergic areas 1 and 5 and the nucleus of the solitary tract. Nerve fibers pass from area 5 to the intermediolateral cell column of the thoracolumbar spinal cord (the site of sympathetic outflow) and from area 1 to the hypothalamus. Stimulation of these areas in animals has been shown to cause pulmonary edema. In our patient, derangement of these structures during surgical resection, either by alterations in peri- medullary pressures or by direct force on the medulla, may have resulted in triggering of the neurogenic stimulus for pulmonary edema formation. Dysfunction within the nearby medullospontine respiratory fibers may also have occurred, as manifested by the patient's erratic respiratory pattern on awakening from anesthesia.
are limitations in concluding that the pulmonary edema resulted from medullary hyperactivity. First, we did not quantify medullary activity. Nevertheless, increased or aberrant electrical activity in the central nervous system is a well-appreciated problem after a neurologic operation. The most common manifestation of this phenomenon is postoperative seizures.26 Thus, surgical manipulation close to the medulla may be sufficient to expose the patient to a high risk for medullary hyperactivity. The anesthetic agents may have decreased or masked a hyperactivity phenomenon. Although our patient had evidence of respiratory dysfunction during the operation (tachycardia with an increased alveolar-arterial gradient indicating a pathologic shunt of 12 to 15%),27 the full-blown syndrome was not noticed until he emerged from anesthesia at the completion of the operation. Second, we did not analyze the content of the edema fluid. If the pulmonary edema in our patient was truly the result of a permeability defect, an edema fluid/plasma protein ratio greater than 0.7 would be expected. Third, the possible influence of an alteration in cerebrospinal fluid dynamics and intraventricular pressure on the development of pulmonary edema cannot be ignored.

In our patient, the absence of pronounced systemic hypertension correlates with the theory that NPE is caused by pulmonary venoconstriction resulting in an imbalance of Starling forces within the lung,27,28 rather than an acute left ventricular dysfunction resulting from sympathetically mediated systemic hypertension. Pulmonary venoconstriction can synergistically increase fluid movement across the pulmonary endothelium in the presence of a permeability defect.39 The temporal relationship of florid pulmonary edema with the patient's recovery from anesthesia may have been influenced by factors that suddenly altered the pulmonary vasculature-to-alveoli pressure gradients. At the end of the operation, our patient was moved from a sitting to a supine position, a situation that may have increased central venous and pulmonary artery pressures. In addition, the mode of ventilation was changed from mechanical to spontaneous, a change that would tend to diminish intra-alveolar pressure and promote edema formation.

The differential diagnosis of pulmonary edema after a neurosurgical procedure includes a host of factors.1,3,12 Most cases can be explained on the basis of common etiologic factors such as cardiac dysfunction or fluid overload. Nevertheless, based on theoretical physiology, experimental work in animals, and case reports of humans—including our patient—we believe that NPE as a result of medullary manipulation should be included in the list of possibilities, although it currently remains a diagnosis of exclusion.

**SUMMARY**

Our patient had sudden onset of pulmonary edema after surgical resection of a brain tumor in the fourth ventricle. We assume that the edema was of neurogenic origin. Standard therapy with diuretics, venodilators, and mechanical ventilation with positive end-expiratory pressure was successful, and neurologic outcome was excellent. Although not proved by our report, our observations are consistent with research in animals that suggests that derangement of medullary structures may be a factor in the pathogenesis of NPE and that this phenomenon may occur independent of systemic hypertension.

**REFERENCES**


