CHEST

Selected Reports

Neurogenic Pulmonary Edema

Successful Treatment With IV Phentolamine

Danielle L. Davison, MD; Lakhmir S. Chawla, MD; Leelie Selassie, MD; Rahul Tevar, MD; Christopher Junker, MD; and Michael G. Seneff, MD, FCCP

Neurogenic pulmonary edema (NPE) is a clinical syndrome characterized by the acute onset of pulmonary edema following a significant CNS insult. The cause is believed to be a surge of catecholamines that results in cardiopulmonary dysfunction. Although there are myriad case reports describing CNS events that are associated with this syndrome, few studies have identified specific treatment modalities. We present a case of NPE caused by an intracranial hemorrhage from a ruptured arteriovenous malformation. We uniquely document a rise and fall of serum catecholamine levels correlating with disease activity and a dramatic clinical response to IV phentolamine.

CHEST 2012; 141(3):793–795

Abbreviations: AVM = arteriovenous malformation; HD = hospital day; NPE = neurogenic pulmonary edema

A 59-year-old man with history of hyperlipidemia and prostate adenocarcinoma presented to the ED with sudden onset of right hemiparesis and aphasia. The patient was initially alert and following commands with normal vital signs. Physical examination revealed bilateral brisk pupils with left deviation, right tongue deviation, facial droop, expressive aphasia and right hemiparesis. Cardiopulmonary examination was unremarkable. A noncontrast CT scan of the head showed an acute parenchymal hemorrhage (5.0 × 3.8 cm) in the left frontal lobe without evidence of herniation or ventricular involvement. While awaiting an MRI scan, the patient's mental status rapidly deteriorated, and he was subsequently intubated for airway protection. Postintubation arterial blood gas measurements showed pH of 7.37, P_{CO_2} of 41 mm Hg, and P_{aO_2} of 171 mm Hg while receiving 40% F_{IO_2}. The postintubation chest radiograph was clear with normal cardiac silhouette. Repeat head CT scan revealed an interval increase in the left frontal hemorrhage (6.7 × 3.9 × 5.5 cm) and migration of the hemorrhage into the ventricles. An external ventriculostomy was placed, and 2.4 mg IV recombinant factor VIIa was administered. Emergent cerebral angiography revealed an arteriovenous malformation (AVM), and the patient was taken to the operating room for AVM resection. Postoperatively, the patient remained intubated on aminocaproic acid, nicardipine, nitroprusside, and propofol infusions. An inferior vena cava filter was inserted on hospital day (HD) 2, given the patient's high risk for VTE.

On HD 3, the patient's respiratory status began to deteriorate. Bilateral diffuse alveolar infiltrates developed, hypoxemia worsened, and ventilatory support was increased. The patient's temperature rose to 38.7°C, and leukocytosis levels increased from 14,000 /μL to 21,800/μL. Broad-spectrum antibiotics, specifically piperacillin/tazobactam and linezolid, were started empirically for ventilator-associated pneumonia but were eventually discontinued after all cultures were confirmed negative. Despite aggressive diuresis of approximately 1.5 L net negative daily, hypoxia persisted, which was noted to temporally correlate with the fluctuation in ventriculostomy output and BP. A representative arterial blood gas measurement during this time revealed a pH of 7.28, P_{CO_2} of 75.6 mm Hg, P_{aO_2} of 68 mm Hg, oxygen saturation of 93% on pressure control ventilation while receiving an F_{IO_2} of 70% and partial end-expiratory pressure of 18 mm Hg. A two-dimensional echocardiogram showed normal left ventricular function and no evidence of left atrial hypertension. On HD 9, a pulmonary artery catheter was inserted; initial results were as follows: pulmonary artery pressure, 50/30 mm Hg (normal, 15-30/6-12 mm Hg); cardiac index, 5.4 L/min/m^2 (normal, 2.4-4.0 L/min/m^2); systemic vascular resistance, 523 dynes/s/m^2/cm^5; pulmonary capillary wedge pressure, 9 to 12 mm Hg (normal, 6-12 mm Hg); and pulmonary vascular resistance, 155 to 200 mm Hg (normal, 200-400 dynes/s/m^2/cm^5). Based on the acute development of hypoxemia and hypertension following a CNS insult, and further supported by a lack of an alternative cause, specifically heart failure, pneumonia, or pulmonary embolism, the diagnosis of neurogenic pulmonary edema (NPE) was made. Despite maximal infusion of nicardipine and multiple other antihypertensive agents including metoprolol,

Manuscript received March 29, 2011; revision accepted August 19, 2011.

Affiliations: From the Department of Critical Care Medicine and Anesthesiology, and the Division of Renal Diseases and Hypertension, Department of Medicine, George Washington University Medical Center, Washington, DC.

Funding/Support: Financial support was provided by the Department of Anesthesiology and Critical Care Medicine at the George Washington University Medical Center.

Correspondence to: Lakhmir S. Chawla, MD, Department of Anesthesiology and Critical Care Medicine, The George Washington University Medical Center, 900 23rd St NW, Rm G-105, Washington, DC, 20037; e-mail: lchawla@mfa.gwu.edu

DOI: 10.1378/chest.11-0789

hydralazine, and labetalol, BP remained labile and gas exchange deteriorated in an episodic fashion. Antibiotics and diuresis failed to alter the clinical trajectory. On HD 11, a phentolamine infusion was started at 0.17 mg/min and titrated for BP control. Over 6 h, the FIO_2 requirements dropped precipitously, gas exchange improved, and the chest radiograph showed improvement of pulmonary edema (Figs 1, 2). When the hospital supply of phentolamine was exhausted, the clinical status deteriorated rapidly. Within just 15 h of the discontinuation of phentolamine, the PaO_2 fell from 166 mm Hg to 66 mm Hg, and FIO_2 requirements rose from 60% to 100%. When the phentolamine supply was replenished and the infusion restarted, the same rapid improvement was observed and BP stabilized. Over the next 12 to 24 h, BP also stabilized, allowing for discontinuation of all other antihypertensive agents. The impressive improvement in respiratory parameters over the 3-day span of phentolamine infusion is illustrated in Figure 3. On HD 13, the patient was weaned off phentolamine. Catecholamine levels were measured on three separate occasions, and the results are shown in Table 1.

Discussion

NPE is characterized by the sudden development of hypoxemic respiratory failure following a catastrophic CNS event that cannot be attributed to other causes of ARDS. The pathophysiology is not completely understood but is believed to be linked to an intense activation of the sympathetic nervous system and the release of catecholamines following an abrupt increase in intracranial pressure (ICP).[1,2] The fundamental role of catecholamines is supported by the fact that the blockade of sympathetic activity in animal models via intrathecal lidocaine, phentolamine infusion, and pretreatment with phenoxybenzamine mitigate the pathologic neuro-pulmonary process.[3-5]

Although numerous case reports have described the various precipitating CNS insults and clinical scenarios associated with NPE, few studies have identified specific treatment modalities for this condition. The management of NPE to date has largely focused on treating the underlying neurologic condition and reducing ICP in order to quell the sympathetic discharge responsible for causing the lung injury. Although α-adrenergic blockade has shown promise in animal models, there are, to our knowledge, only a handful of reports of its use in humans, none of which measured concurrent catecholamine levels[3-5]

The patient developed severe NPE following an intracranial and subarachnoid hemorrhage secondary to a ruptured AVM. The clinical course was complicated by intermittent, severe deteriorations in gas exchange associated with surges in BP and ICP. A pulmonary artery catheter documented a high cardiac output, low-normal pulmonary capillary wedge pressure, and increased pulmonary artery pressures. Chest radiograph revealed bilateral airspace disease consistent with pulmonary edema. We documented extremely high catecholamine levels at the time of hemodynamic instability and respiratory failure. We also recorded the return to normal levels prior to discharge. To our knowledge, only one previous case report has documented elevations in catecholamine levels at the time of respiratory distress; however, the authors did not show resolution.[6]

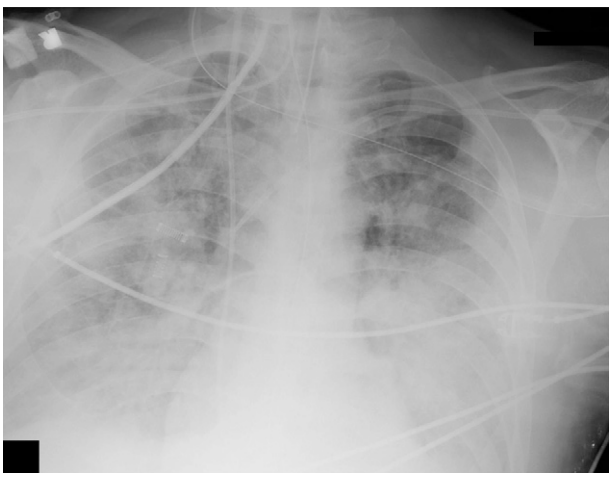

Figure 1. Chest radiograph revealing pulmonary edema prior to phentolamine infusion.

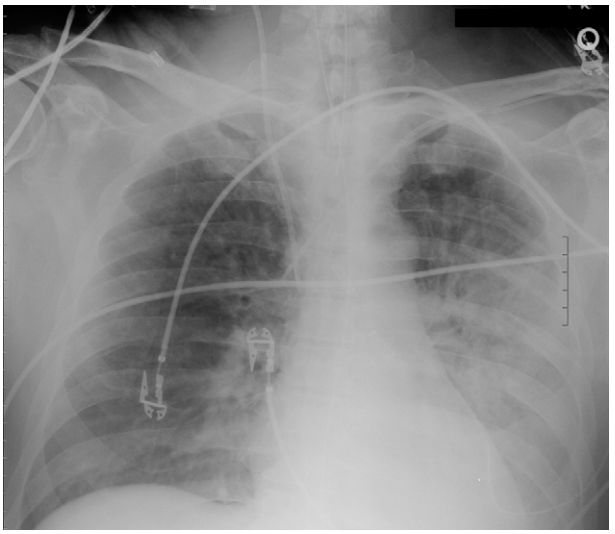

Figure 2. Chest radiograph 3 days after initiation of phentolamine infusion.

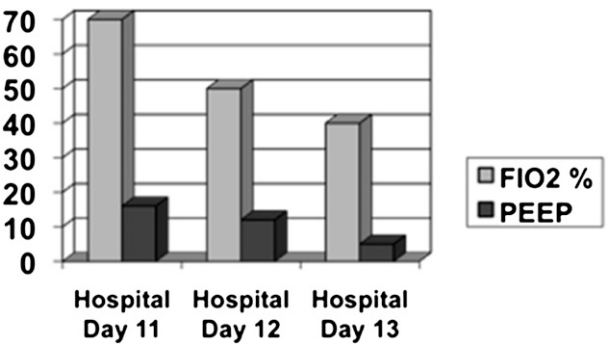

Figure 3. Bar graph of FIO_2 and PEEP values on hospital days 11, 12, and 13. PEEP = positive end-expiratory pressure.

Table 1—*Urine Catecholamine Levels (Metanephrine, Normetanephrine, and Vanillylmandelic Acid) and Serum Catecholamine Levels on Hospital Days 10, 21, and 65*

	Reference Ranges	Day 10	Day 21	Day 65
Urine (μg/24 h)				
Normetanephrine (24 h, fractionated)	44-540	2,582	1,647	243
Metanephrine (24 h, fractionated)	26-230	4,745	2,749	69
Total metanephrine (24 h)	90-690	7,327	4,396	312
Vanillylmandelic acid (24 h)	≤ 6.0	8.6	5.4	3.1
Plasma (pg/mL)				
Catecholamines (total, measured supine)	123-671	1,360	…	305

By blocking the adrenergic surge through the use of phentolamine, we believe we were able to interrupt the vicious cycle of hemodynamic instability and hypoxic respiratory failure. The clinical improvement following its initiation was profound. This case represents one of the few successful treatments of NPE with a pharmacologic agent and the only time, to our knowledge, that catecholamine levels were documented throughout the clinical course. Phentolamine competitively blocks α-adrenergic receptors and reduces hypertension by brief antagonism of the circulating catecholamines, epinephrine and norepinephrine. Whether phentolamine infusion is useful for all patients with NPE and whether continuous infusion vs intermittent dosing changes outcomes is not clear. Future studies of NPE should document the levels of serum and urine catecholamines. Further, we believe that phentolamine should be considered a candidate therapeutic agent for NPE and should undergo assessment in prospective clinical trials.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

References

1. Fontes RB, Aguiar PH, Zanetti MV, Andrade F, Mandel M, Teixeira MJ. Acute neurogenic pulmonary edema: case reports and literature review. *J Neurosurg Anesthesiol*. 2003; 15(2):144-150.
2. Rosner MJ, Newsome HH, Becker DP. Mechanical brain injury: the sympathoadrenal response. *J Neurosurg*. 1984; 61(1):76-86.
3. Wohns RN, Tamas L, Pierce KR, Howe JF. Chlorpromazine treatment for neurogenic pulmonary edema. *Crit Care Med*. 1985;13(3):210-211.
4. Baumann A, Audibert G, McDonnell J, Mertes PM. Neurogenic pulmonary edema. *Acta Anaesthesiol Scand*. 2007; 51(4):447-455.
5. Findler G, Cotev S. Neurogenic pulmonary edema associated with a colloid cyst in the third ventricle. Case report. *J Neurosurg*. 1980;52(3):395-398.
6. Yamamoto K, Anzai F, Kusajima K, Yamanishi N, Yamada M. Acute respiratory failure with gross hemoptysis in a patient with lymphangioleiomyomatosis as part of tuberous sclerosis complex. *Intern Med*. 2004;43(8):755-758.

Interstitial Pneumonia Associated With Bullous Pemphigoid

Daisuke Yoshioka, MD; Hiroshi Ishii, MD, PhD; Tomohisa Uchida, MD; Sakuhei Fujiwara, MD; Kenji Umeki, MD; Noriho Sakamoto, MD; and Jun-ichi Kadota, MD

Bullous pemphigoid, the most common autoimmune blistering disease, is characterized by an autoimmune response to a component of hemidesmosomes within the dermal-epidermal junction. Immunofluorescence examination of skin biopsies demonstrates linear deposition of IgG and C3 in the basement membrane zone. A 73-year-old woman was admitted to our institution because of interstitial lung disease with persistent dry cough, dyspnea on exertion, and bullous eruptions on the skin of her trunk and extremities. Chest CT scan, BAL fluid, and transbronchial lung biopsy findings indicated a likely nonspecific interstitial pneumonia pattern. Direct immunofluorescence showed linear deposition of IgG and C3 along the basement membranes of the lung and skin specimens. Lung disorders associated with bullous pemphigoid are extremely rare, and, to our knowledge, this is the first report of an immunologically confirmed case of interstitial pneumonia. ***CHEST 2012; 141(3):795–797***

Bullous pemphigoid is an acute or chronic autoimmune skin disease causing the formation of blisters (bullae) in the epidermal and dermal junction. The clinical manifestations include edematous erythema with pruritus and large tense blisters on the skin, which are characterized by an autoimmune response to a component of hemidesmosomes within the dermal-epidermal junction. Bullous pemphigoid most commonly occurs in

Manuscript received May 16, 2011; revision accepted July 1, 2011.

Affiliations: From the Department of Internal Medicine II (Drs Yoshioka, Ishii, Umeki, and Kadota), the Department of Molecular Pathology (Dr Uchida), and the Department of Dermatology (Dr Fujiwara), Oita University Faculty of Medicine, Oita; and The Second Department of Internal Medicine (Dr Sakamoto), Nagasaki University Hospital, Nagasaki, Japan.

Correspondence to: Hiroshi Ishii, MD, PhD, Internal Medicine II, Oita University Faculty of Medicine, 1-1 Idaigaoka, Yufu, Oita, Japan 879-5593; e-mail: hishii@oita-u.ac.jp

DOI: 10.1378/chest.11-1241