Noncardiogenic Pulmonary Edema as the Sole Manifestation of Pheochromocytoma

PETER W. DE LEEUW, FRANS L. WALTMAN, AND WILLEM H. BIRKENHÄGER

SUMMARY A 40-year-old man was admitted to the hospital with pulmonary edema without signs of left ventricular failure. Noncardiogenic pulmonary edema was diagnosed, and a subsequent workup identified a pheochromocytoma as the cause of this condition. The clinical picture could be mimicked by infusion of exogenous norepinephrine. It is concluded that surges of catecholamines from a pheochromocytoma may provoke pulmonary edema in a manner similar to that by which neurogenic pulmonary edema related to cerebral disorders occurs. (Hypertension 8: 810–812, 1986)

KEY WORDS • catecholamines • heart failure • hypertension

PRESSOR crises, excessive sweating, and headache are among the most frequent symptoms of pheochromocytoma. Furthermore, pulmonary edema may develop as a result of cardiac failure. The latter usually is due to a sudden or sustained rise in arterial pressure or the result of catecholamine-induced cardiomyopathy. We report on a patient with pheochromocytoma in whom several episodes of pulmonary edema occurred in the absence of hypertension and without signs of left ventricular dysfunction.

Case Report

A 40-year-old man was admitted to the coronary care unit because of acute, severe dyspnea and production of blood-stained sputum. He had been well until 8 years earlier when he was involved in a car accident and remained comatose for 24 hours. Since that time he had had several bouts of mild dyspnea accompanied by feelings of unease and restlessness. Although such episodes were short-lived, the patient had noticed an increased frequency over the previous 2 or 3 months.

On examination he appeared tachypneic, cyanotic, and clammy. Systolic blood pressure was 80/60 mm Hg, and the heart rate was 115 beats/min. The heart was normal, and no ventricular gallop was heard, but numerous rales were audible in both lungs. No other abnormalities were evident. Laboratory investigation disclosed slightly elevated hemoglobin levels (12 mmol/L), hematocrit (59%), and creatinine levels (135 μmol/L). The levels of serum glutamic-oxalacetic-transaminase, serum glutamic-pyruvate transaminase, and lactic dehydrogenase were modestly increased, but the creatinine kinase level was normal. A chest roentgenogram showed massive pulmonary edema but a normal-sized heart; an electrocardiogram revealed sinus tachycardia and signs of right ventricular strain with no evidence of myocardial infarction.

After a Swan-Ganz thermodilution catheter had been introduced, the following hemodynamic data were obtained: pulmonary artery pressure, 21/3 mm Hg (mean, 12 mm Hg); pulmonary capillary wedge pressure, 2 mm Hg; right atrial pressure, 0 mm Hg. Cardiac output was 3.45 L/min, while intra-arterial pressure was still low: 75/55 mm Hg. All measurements were done while the patient was still recumbent. Calculated systemic vascular resistance was normal, but pulmonary vascular resistance was increased. Treatment consisted of oxygen by mask and infusion of plasma and the patient recovered within a few hours. Cardiac output then stabilized at 7 L/min, and blood pressure increased to 110/70 mm Hg. The next day, results of physical examination and chest roentgenogram were unremarkable. All biochemical values returned to normal, and no signs of myocardial infarction were found.

The patient was discharged with a diagnosis of noncardiogenic pulmonary edema, and after thorough investigation by both a neurologist and a chest physician, neither of whom found a specific cause for this patient’s ailment, he was referred to the department of medicine for further evaluation. A provisional diagnosis of neurogenic pulmonary edema was made, possi-
bly related to the previous head trauma. However, since neurological examination failed to reveal focal cerebral abnormalities and since there were no signs of an intracranial infectious process, we reasoned that instead of enhanced sympathetic discharge, a surge in plasma catecholamines could have been responsible. Therefore, the workup focused on suspected pheochromocytoma. Excretion of vanillylmandelic acid into the urine was found to be 2.7 mmol/mmol creatinine on 1 day but remained below the upper normal limit of 2.5 mmol/mmol creatinine on two other occasions. Plasma levels of catecholamines (measured radioenzymatically) appeared to be only mildly elevated (norepinephrine, 3.2 nmol/L; epinephrine, 1.0 nmol/L; normal levels, 2.5 and 0.8 nmol/L, respectively).

The patient was scheduled to undergo caval venous sampling, but before this investigation could be done, he was again acutely admitted to the hospital with pulmonary edema. The same picture emerged as during the first hospitalization; however, this time peripheral venous blood for determination of catecholamines was sampled on admission. Both norepinephrine (20.2 nmol/L) and epinephrine (3.80 nmol/L) far exceeded normal levels, thus providing support for the hypothesis that release of catecholamines from a pheochromocytoma was causing the pulmonary edema. Subsequent localization studies revealed a tumor in the left adrenal gland.

To make sure that the adrenal tumor was not a chance finding unrelated to the pulmonary complications, we assessed the response to infused norepinephrine (after informed consent had been obtained from the patient) to evaluate whether the clinical picture could be mimicked by exogenous norepinephrine. Results from this experiment are depicted in Figure 1. During stepwise increasing doses, the plasma norepinephrine level rose from 6.83 to 69.4 nmol/L. At doses below 3 /μg/kg/min, no changes in systemic arterial pressure or pulmonary capillary wedge pressure occurred. Mean pulmonary artery pressure initially exhibited transient rises but eventually increased from 11 to 16 mm Hg. At an infusion rate of 3 μg/kg/min, systemic pressure also rose substantially but wedge pressure remained stable. At this point, the patient began to experience shortness of breath and he tended to feel the same as during previous crises. A chest roentgenogram was obtained, which demonstrated incipient pulmonary edema without cardiac enlargement. Blood gas analysis revealed a drop in partial oxygen tension. The infusion was stopped, and all symptoms disappeared within a few minutes.

Shortly before operation, and just after pretreatment with prazosin had begun, one more attack of pulmonary edema occurred, during which norepinephrine and epinephrine reached levels of 1470 and 340 nmol/L, respectively. All symptoms subsided within a few minutes after intravenous administration of phenolamine. The patient subsequently underwent operation, and a pheochromocytoma with a diameter of 8 cm was removed from the left adrenal gland. The postoperative course was uneventful, and 2 years after the operation, the patient is still free of symptoms.

Discussion

This case exemplifies the protean manifestations of pheochromocytoma. The patient under discussion did not present with hypertension or palpitations but rather with low blood pressure and pulmonary edema. In view of the normal values of pulmonary artery and right atrial pressure and considering the fact that pulmonary capillary wedge pressure was low, the edema could not be attributed to cardiac failure or overhydration. Thus, we concluded that either increased microvascular permeability or transient rises in capillary hydrostatic pressure as a result of local factors were causing the extravasation.

Noncardiogenic pulmonary edema may develop from a variety of disorders, 3,4 most of which could be dismissed as a cause of this patient’s illness. In fact, the sudden onset of edema without any signs of an underlying disease suggested a similar pathogenesis to that of neurogenic pulmonary edema. Although the latter usually develops in association with acute and often fatal injuries to the central nervous system, it may also be related to seizures. 3 Since it is assumed
that massive α-adrenergic stimulation caused by enhanced sympathetic discharge plays an important role in the initial phase of neurogenic pulmonary edema, we speculated that a similar mechanism might be operative when the level of circulating catecholamines is increased suddenly. Thus, we focused on the possibility of a pheochromocytoma and indeed were able to demonstrate such a tumor in the left adrenal gland.

To the best of our knowledge, an unequivocal association between pheochromocytoma and noncardiac pulmonary edema had not been described before; hence, we wondered whether this association in our patient was really causal or merely incidental. This prompted us to study the effects of exogenous norepinephrine. As indicated in Figure 1, norepinephrine administration caused transient rises in pulmonary artery pressure, and although systemic arterial pressure also rose when the highest dose was infused, no changes in pulmonary capillary wedge pressure occurred. At the same time the patient experienced the prodromal signs (e.g., tachypnea and uneasiness) with which he had become so familiar during previous attacks. Although we did not allow frank pulmonary edema to develop, we still thought this investigation provided sufficient evidence to reject left ventricular failure as a significant mechanism in this patient’s illness. The reason that the norepinephrine infusion was associated with a rise in vascular resistance (as inferred from the increase in blood pressure), while vascular resistance was normal when spontaneous pulmonary edema developed, may be related to the fact that the adrenal tumor also released large amounts of epinephrine. The latter may have counterbalanced norepinephrine’s effect on the vasculature.

Several other features in this case report support a causal relation between the pheochromocytoma and the development of pulmonary edema. First, when catecholamine levels were sampled during the acute episodes, they invariably appeared to be grossly elevated, far more than could be explained by stress alone. Second, during the last attack, intravenous administration of the α-adrenergic receptor blocking agent phentolamine resulted in prompt and sustained relief of all symptoms. Third, removal of the tumor led to complete cure of the patient.

Our patient bears some resemblance to at least two other patients who have been described in the literature. The first was presented in a case record several years ago. In this patient, severe pulmonary edema was found while pulmonary capillary wedge pressure was only 5 mm Hg; a pheochromocytoma was detected at autopsy. However, this patient had been clearly hypertensive, and left ventricular enlargement and dilatation of the ascending aorta had been found on admission. Because numerous other abnormalities were present, we cannot be certain that alternative mechanisms were not contributing to the pulmonary edema.

A second case report that is of interest was described by Naeije et al. These authors found a pheochromocytoma in a young woman who was admitted with diffuse parenchymal infiltrates in both lungs that lasted only several hours. Although it was claimed that this patient had noncardiogenic pulmonary edema, no measurements of pulmonary artery wedge pressures were done. Therefore, it is impossible to prove that the patient did not suffer from pulmonary edema due to other causes.

The mechanisms that were responsible for the development of pulmonary edema in our patient remain obscure. Nevertheless, our observations nicely fit the hypothetical sequence of events put forward by Theodore and Robin. The immediate cause of the edema may have been a transient increase in pulmonary capillary pressure, possibly related to vasoconstriction of the pulmonary venous system. Altered capillary permeability, either as a result of mechanical injury or caused directly by catecholamines, could explain the persistence of pulmonary edema in the face of normal vascular pressures. The massive shift of fluid may also underlie the low systemic pressure and hemococoncentration.

In conclusion, we found a pheochromocytoma to be the cause of repeated bouts of pulmonary edema. The absence of raised pulmonary capillary pressures and the results of norepinephrine infusion ruled out conventional left ventricular failure and suggested a direct effect of catecholamines on the pulmonary vascular bed.

References
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