Pheochromocytoma presenting with pulmonary edema and hyperamylasemia

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A 28-year-old woman was admitted to hospital with acute pulmonary edema, mild abdominal discomfort and hyperamylasemia. From the 2nd hospital day hypertensive episodes occurred daily. The furosemide screening test for renovascular hypertension revealed elevated plasma renin activity (PRA) but an intravenous pyelogram revealed a right suprarenal mass and no evidence of renovascular compression. Elevated values of plasma and urinary catecholamines indicated a pheochromocytoma, and a single chromaffin tumour was resected. It is important to monitor left ventricular filling pressure during operative removal of a pheochromocytoma. Postoperatively the patient had normal blood pressure and PRA. Decreased urinary amylase clearance and abnormal pancreatic and salivary amylase isoenzymes were found.

Une femme de 28 ans a été hospitalisée souffrant d'oedème pulmonaire aigu, de légers malaises abdominaux et d'hyperamylasémie. A partir du 2e jour d'hospitalisation des épisodes hypertensifs sont survenus quotidiennement. Le test de dépistage à la furosémide pour l'hypertension rénovasculaire a révélé une activité rénine plasmatique (ARP) augmentée, mais un pyélogramme intraveineux a mis en évidence une masse surrénale droite sans signe de compression rénovasculaire. Une augmentation des taux de catécholamines plasmatiques et urinaires indiquait un phéochromocytome, et une seule tumeur chromaffine a été enlevée. Il est important de surveiller la pression de remplissage du ventricule gauche durant l'ablation chirurgicale d'un phéochromocytome. Dans la période postopératoire la patiente a présenté une tension artérielle et une ARP normales. Une diminution de l'épuration urinaire de l'amylase et des anomalies des isoenzymes amylasiques pancréatiques et salivaires ont été observées.

Pheochromocytoma is a rare disease, often associated with hypertensive episodes. Among the unusual presentations of this disease is a diffusely hypermetabolic state simulating hyperthyroidism. It has also been confused with carcinoid syndrome, arteriovenous fistula, gram-negative septic shock, pulmonary embolism, diabetic lactic acidosis and acute psychosis.[1] This report concerns a patient with pheochromocytoma who presented with pulmonary edema and symptoms suggesting acute pancreatitis.

Case report

Clinical history and findings

A 28-year-old woman was admitted to hospital Sept. 14, 1974 with a 6-hour history of progressive dyspnea and mild cough productive of frothy pink sputum, associated with mild nausea and abdominal discomfort.

The patient had had four brief episodes of weakness, nausea, headaches and palpitations during the 12 months prior to admission. She was normotensive on each occasion and no firm diagnosis was established. She was nulliparous. There was no history of exposure to industrial toxins, alcohol intake or gallbladder disease. Her father had been hypertensive for many years and had died at age 58 years.

She was extremely anxious and in acute respiratory distress. The recumbent blood pressure was 125/75 mm Hg in both arms. The pulse rate was 100 beats/min and the rhythm was regular. The respiratory rate was 50/min. Respiratory rales were heard diffusely in both lungs. There was no cardiomegaly, gallop rhythm, jugular venous distension or ankle swelling. A grade 2/6 systolic ejection murmur was heard at the apex; there was no radiation to the carotids or left axilla. Examination of the abdomen, rectum and flanks revealed no abnormalities.

Laboratory, electrocardiographic and radiologic findings

Hematocrit was 52% and leukocyte count, 11 x $10^9/l$ with a normal differential. Serum amylase value was 525 IU (normal, 300 IU). Serum total protein value was 8.3 g/dl (normal, 5.2 to 8.7 g/dl). Cellulose acetate protein electrophoresis revealed a slightly elevated α_1-globulin value of 0.27 g/dl (normal, 0.06 to 0.22 g/dl). Serum IgA concentration was increased, at 430 mg/dl (normal, 100 to 350 mg/dl). Serum concentrations of total hemolytic complement and the β_1C component of complement were normal, and tests for rheumatoid factor and antinuclear antibody gave negative results. Values of other serum constituents, including lactic dehydrogenase, glutamic oxaloacetic transaminase, creatine phosphokinase and calcium, were within normal limits. Arterial blood gas values while the patient was breathing room air were as follows: P_{O_2}, 30 mm Hg; P_{CO_2}, 40 mm Hg; oxygen saturation, 69%; pH, 7.31; and bicarbonate, 19.5 mmol/*l*. Urinalysis

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results and creatinine clearance were normal, and sputum and blood cultures yielded negative results.

The electrocardiogram (ECG) showed T-wave inversion in leads II, III and AVF, with diffusely peaked P waves.

Diffuse alveolar edema without cardiomegaly was seen on the chest radiograph (Fig. 1, left). Abdominal radiographs gave normal results.

A second chest radiograph, made 1 hour after intravenous administration of 20 mg of furosemide, revealed clearing of the previous radiologic abnormalities (Fig. 1, right). Arterial blood gas values and ECG returned to normal. The serum amylase value increased to 1012 IU although the abdominal symptoms disappeared.

Clinical course and results of subsequent investigation

On the 2nd hospital day hypertensive episodes began; blood pressure was as high as 280/160 mm Hg for 10 to 15 minutes. The episodes occurred daily (Fig. 2) and were accompanied by nausea, occasional vomiting and sinus tachycardia. Values of urinary vanillylmandelic acid (VMA) and plasma and urinary catecholamines were distinctly elevated (Table I). Intravenous pyelography revealed a large right suprarenal mass with some compression of the upper pole of the kidney; during the procedure the blood pressure increased to 205/150 mm Hg and was controlled with an intravenous infusion of phentolamine. The patient was then treated orally with phenoxybenzamine and propranolol for 1 week prior to operation with no recurrence of hypertension or the associated symptoms (Fig. 2).

Preoperative serum amylase values ranged from 260 to 1012 IU, seven of nine being elevated (Fig. 3). Urinary amylase concentrations remained very low and the admission diagnosis of acute pancreatitis was not substantiated. Plasma volume and red blood cell mass were slightly decreased; administration of intravenous fluids expanded the plasma volume. Peripheral plasma renin activity (PRA), measured 4 hours after 60 mg of furosemide was taken orally, was greatly elevated, at 13.6 ng/ml•h (normal, 1.0 to 3.0 ng/ml•h). (This test has recently been recommended in screening for renovascular hypertension.[2])

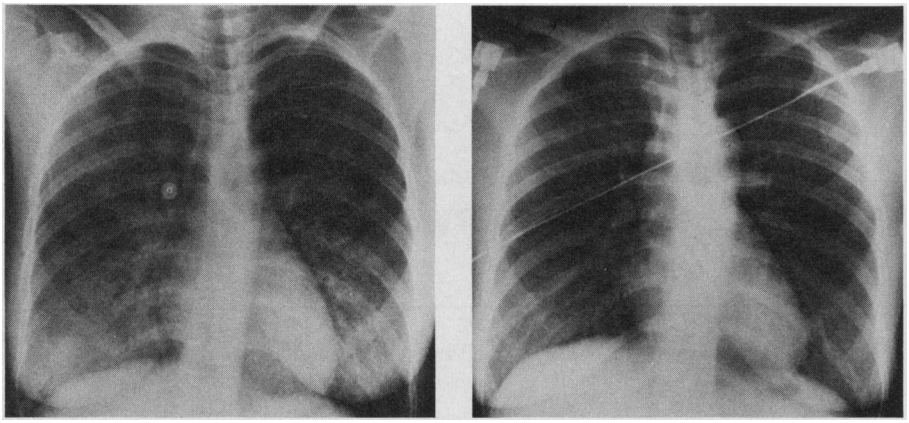

FIG. 1—Left: Diffuse pulmonary edema without cardiomegaly on admission. Right: Clearing within 24 hours. Both radiographs taken during inspiration with patient erect.

Table I—Values of vanillylmandelic acid and catecholamines and plasma renin activity before and after excision of pheochromocytoma

Variable	Values		
	Normal	Preoperative	Postoperative
Urine			
Vanillylmandelic acid (mg/g of creatinine)	0 — 7.0	30.6 — 116.0	0.2
Epinephrine (μg/d)	0 — 15.0	61.2 — 82.2	0 — 0.33
Norepinephrine (μg/d)	0 — 50.0	126.0 — 210.6	0 — 0.61
Plasma			
Epinephrine (μg/l)	0 — 0.5	1.0 — 1.9	0.38
Norepinephrine (μg/l)	0 — 1.0	1.16 — 2.85	0.54
Renin activity (ng/mg·h)	1.0 — 3.0	13.6	1.2

Results of laparotomy

A 317-g right-sided adrenal pheochromocytoma was removed at laparotomy on Oct. 3, 1974. There was no compression of renovascular structures. During the operation blood pressure, central venous pressure and pulmonary wedge pressure (PWP) were monitored. The initial blood pressure was 120/80 mm Hg and the PWP was 11 to 13 mm Hg. During manipulation of the tumour the blood pressure increased to 260/150 mm Hg and the PWP to 25 mm Hg. Intravenous administration of phentolamine was required to restore the pressures to normal. Abdominal exploration revealed no other abnormalities.

The tumour contained 3.04 mg of norepinephrine and 0.64 mg of epinephrine per gram of tissue (normal concentrations of catecholamines in the adrenal medulla:

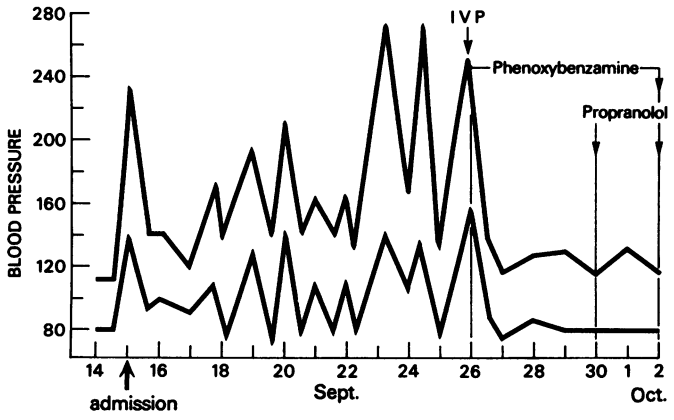

FIG. 2—Fluctuations in blood pressure (mm Hg) prior to operation. Hypertensive episode during intravenous pyelography (IVP). Blood pressure controlled with phenoxybenzamine and propranolol for 1 week before operation.

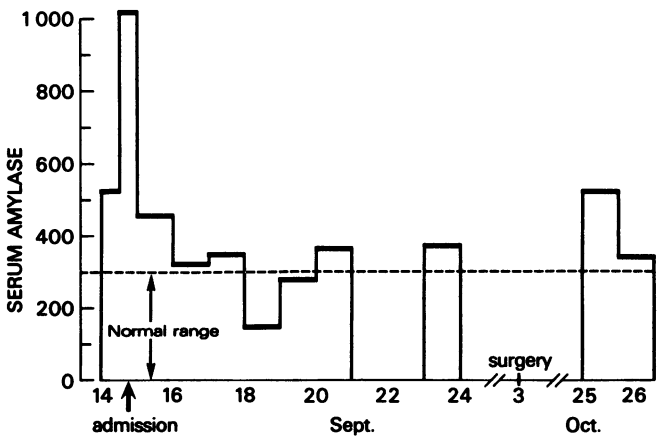

FIG. 3—Variations in serum amylase values (IU) before and after operation.

epinephrine, 0.5 mg/g of tissue; and norepinephrine, 0.1 mg/g). The tumour contained no amylase.

Postoperative course

Three months postoperatively the patient had normal blood pressure and values of urinary VMA and plasma catecholamines. Glucagon stimulation did not produce elevation of blood pressure or plasma catecholamine concentrations. Peripheral PRA had returned to normal (1.2 ng/ml•h).

The patient's serum amylase values remained elevated, at 520 and 335 IU on two occasions. Amylase clearance had decreased with respect to creatinine clearance (amylase clearance ÷ creatinine clearance × 100 = 1.7%), a finding suggestive of macroamylasemia.[3] Serum amylase isoenzymes were studied by polyacrylamide gel electrophoresis.[4] The patient's serum demonstrated two amylase bands in the "pancreatic" region; the "salivary" region also appeared abnormal (Fig. 4).

Discussion

The admission diagnosis in this case was pancreatitis with pulmonary edema. However, the clinical course was that of an unanticipated condition.

The clinical presentation suggested "normal-pressure pulmonary edema". The acute dyspnea and the radiographic evidence of diffuse alveolar edema (without cardiomegaly) subsided promptly with bed rest and administration of a diuretic. Although this response effectively ruled out inflammation or infection, it did not exclude a neurogenic cause of pulmonary edema.

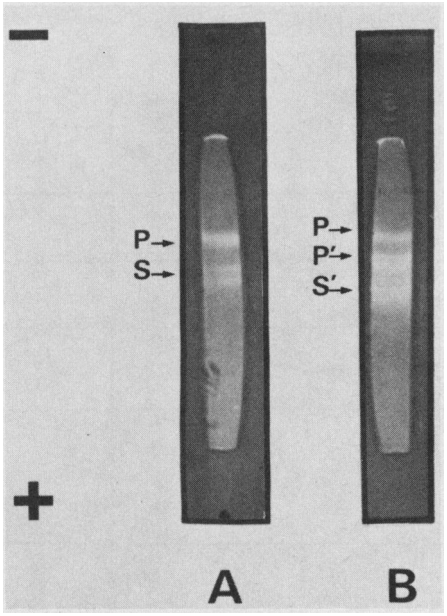

FIG. 4—Separation of amylase isoenzymes by polyacrylamide gel electrophoresis. A: Normal human serum contains amylase of salivary origin, yielding double S band, and amylase of pancreatic origin, yielding single P band. B: Patient's serum yielded extra band in pancreatic region (P') with some trailing into salivary region, which also seems altered (S').

It was not until the severe hypertensive episodes occurred later in the hospital course that left ventricular decompensation was again considered as a possible cause of the pulmonary congestion. As the tumour mass was manipulated at operation the PWP increased to 25 mm Hg and the blood pressure to 260/150 mm Hg. The left heart was thus implicated in the disease process.

Intermittent acute hypertensive episodes by themselves would seem to be insufficient to induce pulmonary edema in an otherwise healthy young patient. This raised the possibility that our patient had underlying myocardial disease. The electrocardiographic T-wave inversion and the normal heart size in the presence of elevated left ventricular diastolic pressure suggested a cardiomyopathy characterized by reduced left ventricular compliance.

Epinephrine-secreting pheochromocytomas have been associated with congestive heart failure in normotensive patients,[5] and in animals catecholamine-induced lesions often produce focal necrosis and interstitial infiltration of the myocardium.[6] It is unresolved whether this form of ischemic myopathy is a direct effect of the catecholamines or the result of energy demand exceeding myocardial nutrient supply. Our case illustrates that the function of the left ventricle can become seriously impaired in the presence of a pheochromocytoma. It is recommended that the filling pressure of the left ventricle be carefully monitored during surgical removal of these tumours.

The elevated serum amylase and low urinary amylase values suggested macroamylasemia.[3] This patient's serum was analysed by polyacrylamide gel electrophoresis for macroamylase and to exclude salivary-type hyperamylasemia, which is also associated with high serum and low urinary amylase values.[7] The serum exhibited two bands in the pancreatic region and an abnormal salivary region. It is unclear whether this represents the existence of amylase molecules of various sizes or molecules that are altered or bound by abnormal serum factors such as globulins or other proteins. The α_1-globulin and IgA serum values were also increased. The relation of these abnormalities to the tumour is not known.

The increased PRA reflects another interesting aspect of pheochromocytoma. Cases of pheochromocytoma with coexisting renal artery stenosis and increased PRA have been well documented.[8,9] Increased PRA without associated renal vascular lesions has also been reported in some cases of pheochromocytoma.[10,11] Catecholamines are known to stimulate renin release,[12,13] and the blood volume contraction often observed with pheochromocytoma is a potent stimulus to renin production. Harrison, Birbari and Beaton[10] have postulated that the renin secreted from the kidneys in response to circulating catecholamines in patients with pheochromocytoma may be involved in the production of hypertension. Our patient's PRA returned to normal after removal of the tumour and her blood pressure remained normal without medication.

The clinician should be aware of the various presentations of pheochromocytoma, including acute pulmonary edema. Further studies may reveal serum amylase abnormalities in other patients with pheochromocytoma.

Increased PRA in a hypertensive patient screened with the furosemide test may result from causes other than renovascular hypertension. Patients with a positive furosemide test should also be screened for pheochromocytoma before intravenous pyelography and renal angiography are performed. Unanticipated hypertensive crises can thus be avoided.

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