

Paraganglioma with acute hyperamylasaemia masquerading as acute pancreatitis

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ABSTRACT

Phaeochromocytomas are rare catecholamine-producing tumours. Although classically described to present with headache, diaphoresis and palpitations, they also present in unusual ways; hyperamylasaemia is one such rare presentation. We describe a man with an extra-adrenal phaeochromocytoma (paraganglioma) presenting with diaphoresis, abdominal pain and multi-organ failure. He had hyperamylasaemia of 1,087 (normal range [NR] 44–161) U/L, which mimicked acute severe pancreatitis. Serum lipase and radiographic imaging of the pancreas appeared normal, and the serial amylase levels normalised over six days upon stabilisation of his condition. 24-hour urinary metanephrines of 10,406 (NR 400–1,500) nmol/day suggested a catecholamine-secreting tumour, and metaiodobenzylguanidine scintigraphy confirmed this. We postulate that amylase (of the salivary isotype) is released by hypoxic tissues when high catecholamine levels cause vasoconstriction and that fluctuating hypotension decreases organ perfusion. This case highlights the need for awareness of rare presentations of phaeochromocytomas and encourages physicians to rethink the diagnosis when investigations are inconsistent.

Keywords: hyperamylasaemia, pancreatitis, phaeochromocytoma

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INTRODUCTION

Catecholamine-secreting tumours that arise from chromaffin cells of the adrenal medulla and sympathetic ganglia are referred to as phaeochromocytomas and catecholamine-secreting paragangliomas (or extra-adrenal phaeochromocytomas), respectively. These catecholamine-secreting tumours are rare. The classic triad of presenting symptoms consists of episodic

headache, diaphoresis and palpitations. However, they can present occasionally in highly unusual ways. Hyperamylasaemia is one of the rarer reported presentations of phaeochromocytomas. Here, we describe a case of an extra-adrenal phaeochromocytoma (paraganglioma) presenting with diaphoresis, abdominal pain, hyperamylasaemia and multi-organ failure mimicking acute severe pancreatitis.

CASE REPORT

A 64-year-old man presented to the emergency department with a one-day history of intermittent episodes of diaphoresis, nausea and cold sweats. His medical history included poorly controlled hypertension of ten years, three myocardial infarctions in the past two years, and a recently diagnosed large retroperitoneal leiomyosarcoma. He had presented several months earlier to another institution for workup of a palpable abdominal mass. Computed tomography (CT) revealed a 7.0 cm × 6.0 cm × 5.0 cm lesion, and diagnostic fine-needle aspiration of the lesion revealed findings of an epithelioid leiomyosarcoma. This elective procedure unfortunately had precipitated a non-ST elevation myocardial infarction, which resulted in a subsequent long and complicated hospital stay in the intensive care unit. In view of the patient's high cardiovascular risk for surgery, surgical resection was held off and neo-adjuvant radiotherapy was scheduled in the interim.

On presentation to our institution, the patient was diaphoretic and clammy. Blood pressure (BP) was elevated at 234/117 mmHg, heart rate was 75 beats per minute (on beta blockers) and oxygen saturation was 99% on room air. Cardiovascular, respiratory and neurological examinations were unremarkable. There was a large, firm, non-tender central abdominal mass, but the abdomen was soft with no guarding and the bowel sounds were normal. Systolic BP remained persistently elevated above 220 mmHg despite oral anti-hypertensives; hence, intravenous infusion of labetalol was started. There was improvement in the BP to 139/87 mmHg, and the patient felt symptomatically

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better. Cardiac enzymes were unremarkable and electrocardiogram (ECG) showed no acute changes. Full blood count (FBC), renal panel and liver function tests (LFTs) were all normal.

On the second day of admission, the patient again became diaphoretic, but this time, it was associated with vomiting, severe central abdominal pain and a fever of 38.5°C. He deteriorated rapidly and became hypotensive (BP 70/40 mmHg) and drowsy. Abdominal examination revealed a soft abdomen with present bowel sounds. Investigations showed compensated metabolic acidosis (pH 7.36, PCO₂ 20 mmHg, HCO₃ 14.2 [19.0–31.0] mmol/L, PO₂ 80.6 mmHg), acute renal failure (creatinine increased from 101 to 314 [63–101] µmol/L within a day) and very high amylase levels (1,087 [44–161] U/L). FBC, LFTs and cardiac enzymes remained normal. Chest radiograph showed normal cardiopulmonary silhouette and clear lung fields, and ECG was unremarkable. Given the abdominal pain and high amylase levels, a diagnosis of acute pancreatitis with associated sepsis was made. However, subsequent CT of the abdomen showed no radiological evidence of pancreatitis (Fig. 1a). The retroperitoneal tumour had remained stable in size and appearance (Fig. 1b). Serum lipase tests performed showed normal levels at 32 and 29 (14–40) U/L.

Retrospectively, the patient had previously presented with similar spells of diaphoresis, nausea and uncontrolled systolic BP > 200 mmHg on three occasions. All these episodes resulted in prolonged hospital admissions, during which he had acute coronary events with multiple complications. Serum amylase test performed during one of these episodes showed an elevated level (1,307 U/L). Imaging of the pancreas then did not reveal any pathology. Similarly, these symptoms had resolved within five days.

On this occasion, the patient proceeded to have a stormy course in the intensive care unit, with labile BP (ranging from 70/40 mmHg to 180/60 mmHg) and intermittent runs of supraventricular tachycardia (heart rate up to 160 beats per minute). There was worsening renal impairment as well as evidence of ischaemic hepatitis over the next three days. He was treated for acute pancreatitis (inhibition of oral intake, intravenous hydration and broad-spectrum antibiotics) and responded well to fluids during hypotensive episodes. Serum amylase levels dropped gradually to 114 (44–161) U/L after six days. During this period, serial ECGs showed new T wave inversions in the anterior leads, together with a significant rise in troponin-T, implying another myocardial infarction.

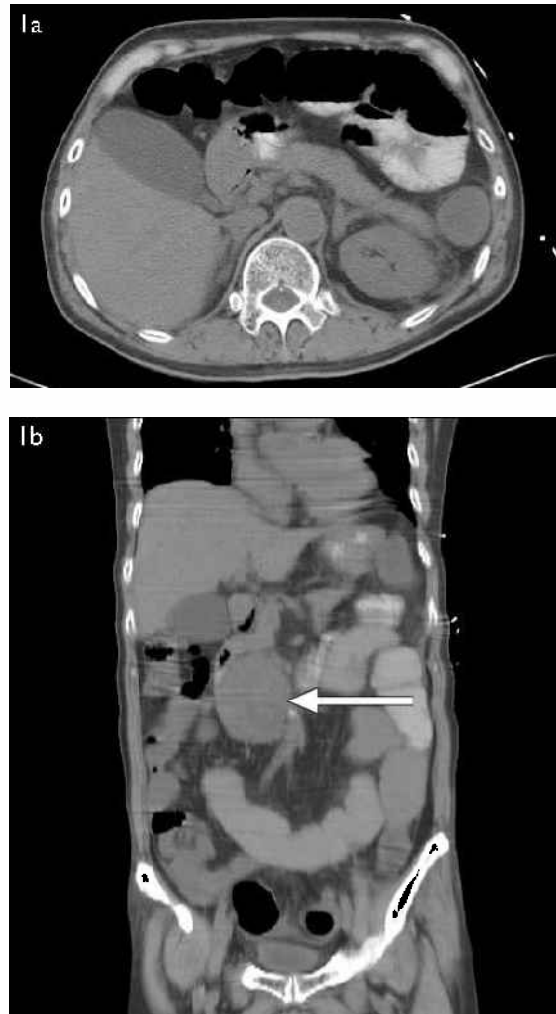


Fig. 1 a) Axial CT image of the abdomen shows the pancreas with a normal appearance. (b) Coronal CT image shows the large heterogeneous retroperitoneal tumour (white arrow).

Table I. 24-hour urinary catecholamine and metanephrine levels.

24-hr collection	3 wks later	4 wks later	Normal range
Epinephrine (nmol/d)	63	69	3–109
Norepinephrine (nmol/d)	3,473	2,534	89–473
Dopamine (nmol/d)	1,074	1,211	425–2,612
Metanephrine (nmol/d)	3,643	2,373	400–1,500
Normetanephrine (nmol/d)	50,241	36,802	600–1,900
Urine volume (ml)	3,000	3,300	700–2,000

Note: Marked elevation of up to 26 times the upper limit of normal is observed. Data in bold strongly suggest the presence of a pheochromocytoma.

In view of the suspicious history of labile blood pressure, recurrent spells of diaphoresis and multiple myocardial events, the patient's urinary metanephrines and catecholamines were analysed. The former showed a ten-fold increase to a level of 10,406

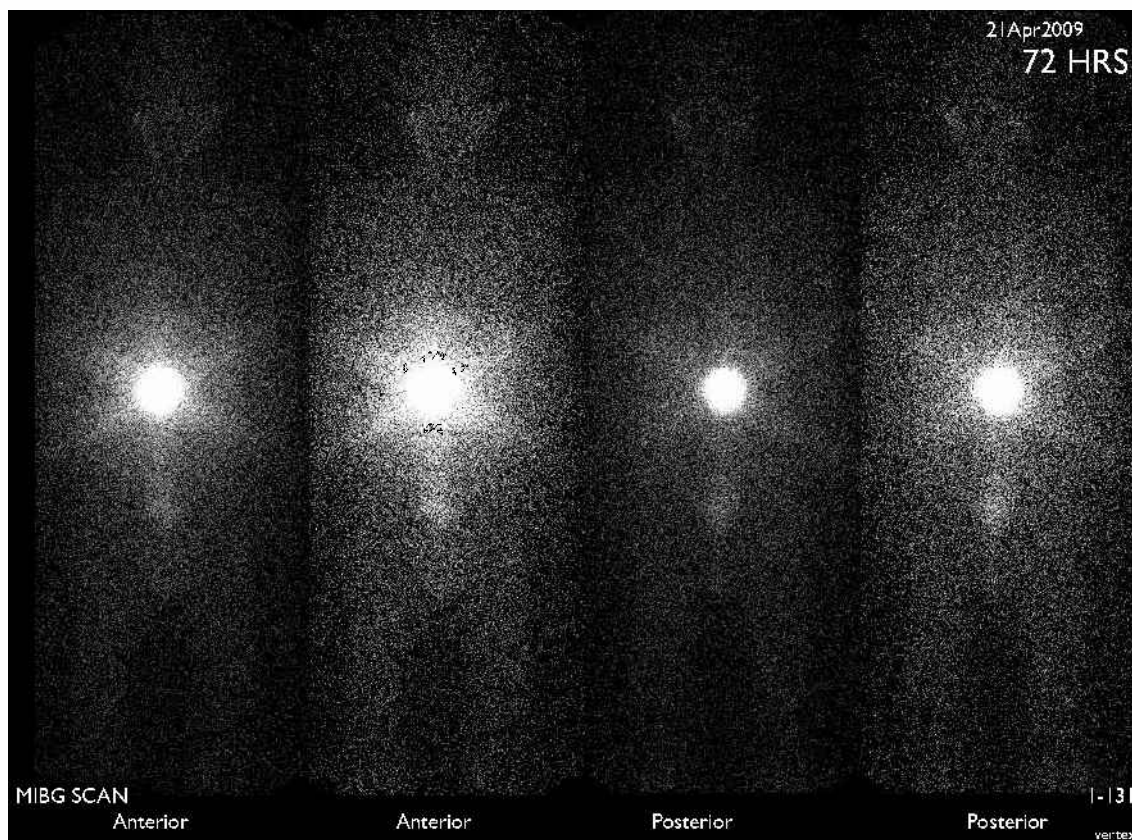


Fig. 2 Iodine-131-MIBG images show discrete intense uptake localised to the region of the retroperitoneal tumour.

(400–1500) nmol/day and urinary normetanephrines were high beyond detection limit (no dilution to absolute value was performed). Two further repeat collections in the outpatient setting showed similarly high levels (Table I). These markedly elevated urinary levels of norepinephrine and normetanephrine raised more suspicion that the retroperitoneal mass was likely an extra-adrenal pheochromocytoma or paraganglioma rather than a leiomyosarcoma. Subsequent iodine-131-meta-iodobenzylguanidine (MIBG) imaging (Fig. 2) with intense uptake seen in the aorta-caval region corresponding to the tumour confirmed our suspicion.

The patient underwent an uncomplicated laparotomy and successful tumour removal after three weeks of alpha-blockade and optimisation with phenoxybenzamine. Histopathology confirmed a paraganglioma, which stained positive for chromogranin and S100. At nine months post surgery, the patient's BP was under control with a single low-dose antihypertensive. There have been no further episodes of diaphoresis, myocardial events or 'pancreatitis', and his 24-hour urinary metanephrines and catecholamines remained normal.

DISCUSSION

The clinical picture of severe abdominal pain with significant hyperamylasaemia > 1,000 IU/L

mimicked severe acute pancreatitis in our patient. However, neither the clinical course nor investigations were entirely supportive of this diagnosis. The repeated diaphoretic spells, labile BP and myocardial infarctions eventually led to the investigation and diagnosis of a pheochromocytoma.

As a diagnostic marker for pancreatitis, total serum amylase lacks specificity (85%–95%).⁽¹⁾ Its production is not isolated to the pancreas and salivary glands, but may also be found in other organs (lung, fallopian tubes, liver)⁽²⁾ and in certain malignancies (breast, gastric, oesophageal, chorioepithelioma).^(3–5) Two isoforms of amylase may be identified by electrophoresis: the P-form specifically from the pancreas and the S-form from the salivary glands and various glandular epithelia.⁽²⁾ Pheochromocytoma-associated hyperamylasaemia has been predominantly reported as the S-isoform.^(6,7)

Perrier et al⁽⁶⁾ who described hyperamylasaemia in a patient with pheochromocytoma, catecholamine-induced cardiomyopathy and pulmonary oedema, postulated that amylase was released from hypoxic lung tissue damage. After all, S-form amylase has been found to be present in both normal and diseased lung tissue.⁽⁸⁾ In addition, acute hypoxaemia ($PO_2 < 75$ mmHg) has been shown to cause an increase in amylase levels even in the absence of pancreatic or salivary disease, a finding related

to pulmonary disease itself, hypoxia, or a combination of the two.⁽⁹⁾ It is plausible that hyperamylasaemia in this case could be due to hypoxic injury to the pulmonary epithelial cells during vasoconstriction from circulating catecholamines. In the literature, reported cases of phaeochromocytoma with hyperamylasaemia typically have pulmonary oedema. Although our patient was critically ill and had myocardial injury, there was no evidence of acute pulmonary oedema or hypoxia, and he had never required assisted ventilation. Alternatively, the paraganglioma itself may be the source for amylase. Paraneoplastic or ectopic production of s-type amylase has been described in multiple myeloma, lung, liver and ovarian cancers.^(3,5,10,11) Amylase has been found within the phaeochromocytoma of a patient who also had hyperamylasaemia,⁽⁶⁾ but this finding is not consistent.⁽¹²⁾ In our patient, the paraganglioma itself was not assessed for the presence of amylase.

Another possible cause is that of macroamylasaemia. Amylase may form large complexes through binding with macromolecules like immunoglobulins and polysaccharides.⁽¹³⁾ This may be seen in autoimmune diseases and cancers where humoral immunity is disturbed. Large complexes undergo delayed renal clearance, resulting in a low amylase-to-creatinine clearance ratio^(14,15) and consequently, high amylase levels. This may be confirmed by determining the molecular weight of the amylase present. Macroamylasaemia has been reported in one case of phaeochromocytoma associated with acute pulmonary oedema, abdominal discomfort and hyperamylasaemia.⁽¹²⁾ However, amylase remained elevated despite surgical resection of the phaeochromocytoma with normalisation of catecholamines.⁽¹²⁾ Hence, this was likely a phenomenon independent of the diagnosis of phaeochromocytoma. In our patient, significant hyperamylasaemia was transient, with a maximum duration of six days and normalisation of levels between crises. Therefore, it is unlikely to be due to macroamylasaemia.

The cause of hyperamylasaemia in our patient is not entirely clear. Transient hyperamylasaemia was noted only during hypertensive crises. This is likely to have been caused by the S-isoform amylase, as the pancreas was morphologically normal on imaging and the serum lipase (specific pancreatic inflammatory marker) was normal. An iso-enzyme analysis would have been useful to confirm this. Alternatively, amylase could have been released from ischaemic injury of other organs, as this patient had extremely labile BP with episodes of

hypotension, resulting in ischaemic hepatitis and pre-renal acute renal failure.

In conclusion, phaeochromocytomas and paragangliomas have varied presentations. Hyperamylasaemia associated with pancreatitis is rare. Our patient had an abdominal paraganglioma presenting with abdominal pain, hyperamylasaemia and multi-organ failure, mimicking acute severe pancreatitis. The absence of pancreatic abnormality on imaging and a normal lipase level were inconsistent with this diagnosis. The combination of extremely labile BP, diaphoretic spells and multiple myocardial events triggered the search for a catecholamine-secreting tumour, leading to its successful removal subsequently. This case highlights the need for an awareness of rare presentations of phaeochromocytomas, and encourages physicians to rethink the diagnosis when investigations are inconsistent, in order that a potentially fatal condition may be treated.

REFERENCES

1. Matull WR, Pereira SP, O'Donohue JW. Biochemical markers of acute pancreatitis. *J Clin Pathol* 2006; 59:340-4.
2. Pieper-Bigelow C, Strocchi A, Levitt MD. Where does serum amylase come from and where does it go? *Gastroenterol Clin North Am* 1990; 19:793-810.
3. Calvo-Villas JM, Alvarez I, Carretera E, Espinosa J, Sicilia F. Paraneoplastic hyperamylasaemia in association with multiple myeloma. *Acta Haematol* 2007; 117:242-5.
4. Moriyama T. Sialyl salivary-type amylase associated with ovarian cancer. *Clin Chim Acta* 2008; 391:106-11.
5. Tsukawaki M, Izawa M, Yoshida M, et al. A case of amylase-producing lung cancer. *Intern Med* 1992; 31:60-3.
6. Perrier NA, van Heerden JA, Wilson DJ, Warner MA. Malignant pheochromocytoma masquerading as acute pancreatitis--a rare but potentially lethal occurrence. *Mayo Clin Proc* 1994; 69:366-70.
7. Yamanishi J, Nishikawa M, Ohomori Y, Furuta Y, Fukuzaki H. Phaeochromocytoma with transient hyperamylasaemia during hypertensive crisis. *Br Med J (Clin Res Ed)* 1985; 291:1171.
8. Otsuki M, Yuu H, Maeda M, Saeki S, Yamasaki T. Amylase in the lung. *Cancer* 1977; 39:1656-63.
9. Jam I, Shoham M, Wolf RO, Mishkin S. Elevated serum amylase activity in the absence of clinical pancreatic or salivary gland disease: possible role of acute hypoxemia. *Am J Gastroenterol* 1978; 70:480-8.
10. Galus M, Schiffman R, Olkowska D. Massive liver necrosis associated with hyperamylasaemia. *Liver* 1998; 18:205-7.
11. Shigemura M, Moriyama T, Shibuya H, et al. Multiple myeloma associated with sialyl salivary-type amylase. *Clin Chim Acta* 2007; 376:121-5.
12. Munk Z, Tolis G, Jones W, Fallen E, McLean P. Pheochromocytoma presenting with pulmonary edema and hyperamylasaemia. *Can Med Assoc J* 1977; 116:357-9.
13. Berk JE, Kizu H, Wilding P, Searcy RL. Macroamylasaemia: a newly recognized cause for elevated serum amylase activity. *N Engl J Med* 1967; 277:941-6.
14. Levitt MD. Clinical use of amylase clearance and isoamylase measurements. *Mayo Clin Proc* 1979; 54:428-31.
15. Klonoff DC. Macroamylasaemia and other immunoglobulin-complexed enzyme disorders. *West J Med* 1980; 133:392-407.