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Ectopic Hormone-Secreting Pheochromocytoma: A Francophone Observational Study

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Abstract
Background Ectopic hormone-secreting pheochromocytomas are rare; only case reports exist in the literature. This condition has been linked with increased malignancy, familial syndromes, and ACTH secretion. We wanted to test these hypotheses and shed light on the nature of ectopic hormone-secreting pheochromocytomas.
Methods This is a multicenter (francophone) observational study. Inclusion was based upon abnormal preoperative hormone tests in patients with pheochromocytoma that normalized after removal of the tumor. Where possible, immunohistochemistry was performed to confirm that ectopic secretion came from the tumor.
Results Sixteen cases were found: nine female and seven male patients. Median age was 50.5 (range 31–89) years. Most presented with hypertension, diabetes, or cushingoid features. Ten patients had specific symptoms from the ectopic hormone secretion. Two had a familial syndrome. Of eight patients with excess cortisol secretion, three died as a result of the tumor resection: two had pheochromocytomas >15 cm and their associated cortisol hypersecretion complicated their postoperative course. The other died from a torn subhepatic vein. The 13 survivors did not develop any evidence of malignancy during follow-up (median 50 months). Symptoms from the ectopic secretion resolved after removal of the tumor. Immunohistochemistry was performed and was positive in eight tumors: five ACTH, three calcitonins, and one VIP.
Conclusions Most pheochromocytomas with ectopic secretion are neither malignant nor familial. Most ectopic hormone-secreting pheochromocytoma cause hypercortisolemia. Patients with a pheochromocytoma should be worked up for ectopic hormones, because removal of the pheochromocytoma resolves those symptoms. Associated cortisol secretion needs careful attention.

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Introduction

Ectopic hormone secretion from pheochromocytoma is rare. A PubMed search of the literature reveals many case reports but no multicase series that clearly state the problems and clinical features associated with these rare tumors [1–35]. Not every endocrine unit managing pheochromocytomas routinely screens for associated ectopic hormone secretion. We wanted to find out whether there are any

important lessons to be learnt from ectopic hormone secretion in pheochromocytoma, with particular reference to predominant ectopic hormone secretion, malignancy, associated familial genetic disease, and risk factors.

Methods

This was a retrospective observational study conducted in nine university hospital endocrine surgery departments in France and Belgium via the Francophone Association of Endocrine Surgeons, members were contacted and asked if they had any patients who had presented with ectopic hormone secretion from pheochromocytomas. All of the patients included needed biochemical evidence of a pheochromocytoma as well as biochemical evidence of another hormone being secreted in excessive quantity. The charts of these patients were searched for details of: the presenting symptoms, preoperative biochemical profile, intraoperative details, histopathology and postoperative biochemical profile, and follow-up. Return of catecholamine and ectopic hormone secretion to the normal range after adrenalectomy was considered proof of ectopic hormone secretion. However, where antibodies were available immunohistochemistry was used to correlate the biochemical findings. Malignant pheochromocytoma was defined as pheochromocytoma with metastases. These details were collected centrally through the organizing university site. Any extra details were individually requested from the participating university hospitals.

Results

Nine university hospitals contributed 16 patients during a 30 years period covering October 1978 to January 2009, corresponding to 1% of all pheochromocytoma operated on during this period. All had biochemical proof of pheochromocytoma either from urine catecholamine or plasma metanephrine levels. There were nine female and seven male patients. Median age was 50.5 (range 31–89) years; two were asymptomatic lesions discovered incidentally. Eight different ectopic hormones were secreted. Fourteen patients presented with symptoms attributable to their pheochromocytoma, and ten of these patients had additional symptoms specific to the ectopic hormone secretion. These hormones along with preoperative symptoms and catecholamine secretion are shown in Table 1. Table 2 shows number of ectopic hormone cases reported previously in the literature.

Ten of the tumors were right-sided and six were left-sided. Patient nine had bilateral pheochromocytoma and hypercalcitoninemia in the setting of neurofibromatosis type 1. Unilateral ectopic hormone secretion was established biochemically and on immunohistochemistry after the patient had undergone a bilateral adrenalectomy. The left gland had been removed first with no change in the calcitonin level, which fell into the normal range after the right adrenalectomy. The second patient with a familial syndrome (Von Hippel Lindau) also secreted calcitonin.

Laparoscopy was attempted in eight patients with one requiring open conversion. Of the other eight, six had incisions made in the lateral position, one had a thoracolaparotomy, and the other a bilateral subcostal incision. All patients had R0 resections. The median tumor size was 55 (range 25–150) mm. Patients had preoperative preparation with calcium channel inhibitors. Of eight patients with excess cortisol secretion, three died as a result of the tumor resection and none of these three had had normalization of their cortisol levels preoperatively. One of these three patients died from a torn subhepatic vein. The other two had

Table 1 Ectopic hormone and catecholamine secreted with symptom presentation

Ectopic hormone secreted	No. of cases	Symptomatology	Catecholamine secreted
Calcitonin	2	Pheochromocytoma symptoms (both familial syndromes)	Adrenaline and noradrenaline
Calcitonin and VIP	1	Diabetes and pheochromocytoma symptoms	Dopamine
VIP	1	Diarrhea and hypokalemia	Dopamine
Testosterone	1	Pheochromocytoma symptoms	Noradrenaline
Renin	1	Hypertension	Noradrenaline
Aldosterone	1	Diabetes and pheochromocytoma symptoms	Adrenaline
IL-6	1	Hyperthermia and inflammation	Noradrenaline
Cortisol only	2	Pheochromocytoma symptoms	Noradrenaline
ACTH	6	Cushing's (all cases)	Adrenaline and noradrenaline (all cases) + dopamine in one case

The familial syndromes were neurofibromatosis type 1 and von Hippel Lindau

VIP vasoactive intestinal peptide, *IL-6* interleukin-6, *ACTH* adrenocorticotrophic hormone

Table 2 Results of literature search for pheochromocytoma and ectopic hormone secretion

Ectopic hormone	No. of cases	Familial syndrome	Malignant	Reference number
CRH	11			[1]; [2]; [3]; [4] [5]; [6]
ACTH	13	1 MEN 2a [7]	1 [8]	[9]; [10]; [1]; [11]; [12]; [13]; [14]; [15]; [16]; [17]; [18]
IL-6	9			[19]; [20]; [21]; [22]; [23]; [24]; [25]; [26]; [27]
PTH	2			[28]; [29]
Calcitonin	1			[30]
VIP	1			[31]
GH	1			[32]
Calcitonin + VIP	2			[33]; [34]
ACTH + VIP	1			[35]

GH growth hormone, *ACTH* adrenocorticotrophic hormone, *VIP* vasoactive intestinal peptide, *PTH* parathyroid hormone, *IL-6* interleukin-6, *CRH* corticotrophin-releasing hormone

pheochromocytomas >15 cm and had complicated postoperative courses due to adrenal insufficiency, which may have been the result of hypercortisolism. One patient had profound hypotension from resection of the tumor that was not due to hemorrhage. Despite large doses of catecholamine and larger than normal doses of steroid replacement, she died on postoperative day 3 from the sequelae of hypotension. The second patient died 10 months after her operation, having never been discharged home and requiring multiple admissions to the intensive care unit with respiratory failure secondary to bronchoconstriction. For many years preoperatively, she had very brittle asthma that required multiple hospital admissions, but in the 18 months before surgery her asthma required no admissions. After adrenalectomy, her symptoms became increasingly hard to control with β adrenergic drugs and steroids and eventually she died from an exacerbation of her respiratory symptoms. There were no other deaths in this series. The 13 survivors did not develop any evidence of malignancy during follow-up (median 50 months). Symptoms from the ectopic secretion resolved after removal of the tumor.

In all cases, postoperative biochemical testing showed that both the catecholamine and ectopic hormone secretion had returned to the normal range. Eleven of 12 patients who underwent immunohistochemistry testing had positive staining (Table 3): five ACTH, three calcitonin, two vasoactive intestinal peptide (VIP), and one aldosterone-secreting tumor. The tumor associated with ectopic aldosterone secretion had negative immunohistochemistry and careful examination of the cortex failed to elucidate a coexisting Conns tumor. Immunohistochemistry stains were not available in France for renin or interleukin-6 (IL-6). There also were no immunohistochemistry results for the testosterone secreting tumor and a tumor with elevated cortisol but normal ACTH. One tumor was from a time (1978) when ACTH and immunohistochemistry measurements were not possible. These results suggest that excess catecholamine secretion may be responsible, in some cases, for causing excess production of other tumors, without actually secreting the ectopic tumor itself.

Discussion

Ectopic hormone secretion does not appear to be correlated with the malignant potential of pheochromocytoma or familial syndromes. Whereas 50% had excess cortisol secretion (largely as a result of ectopic ACTH production), a number of other hormones were secreted. Our series reflected the majority of previously described ectopic hormone secretion, but we are the first to report a renin-, aldosterone, and testosterone-secreting tumor from a pheochromocytoma, and others have found parathyroid hormone (PTH)-secreting [28, 29] and growth hormone-secreting [32] pheochromocytoma. Excessive renin secretion has been reported once before from an adrenal tumor [36] but not in combination with a pheochromocytoma, although there is a report of a paraganglionoma-secreting renin [37]. Calcitonin and VIP were secreted together as often as they were individually, and reasons for this are discussed later. Table 3 shows ectopic hormone secretion from this series, and Table 2 details previous case reports of ectopic hormone-secreting pheochromocytoma.

Although immunohistochemistry was not performed in all patients, in those that it was, it confirmed preoperative suspicions that the ectopic hormone was secreted from the pheochromocytoma. Exceptions were: the aldosterone-secreting tumor and one case where preoperative ACTH had been normal, but the patient had presented with Cushing's disease. The anti-ACTH antibodies were strongly positive on immunohistochemistry, suggesting that the preoperative test should have been repeated. Symptoms

Table 3 Details of ectopic hormone cases from this series

Patient	Ectopic hormone secreted	Preoperative results	Catecholamine secreted	Tumor size (mm)	Positive immunostaining	Outcome
1	Cortisol[a]	Urine cortisol >10,000	Adrenaline	55	N/A	Cured
2	ACTH	Urine cortisol >1000, serum cortisol 49 ACTH 153	Adrenaline and noradrenaline	60	ACTH	Died on table
3	ACTH[c]	Serum cortisol 221 ACTH 162	Adrenaline and noradrenaline	150	ACTH, dopamine, PS100, anti-synaptophysin, CGA	Died in ITU
4	ACTH	ACTH 554 pg/ml cortisol >500 ng/ml	Adrenaline and noradrenaline	25	ACTH, CGA, anti-vimentin, anti-synaptophysin	Cured
5	ACTH	ACTH 100 (8–55)	Adrenaline, noradrenaline, and dopamine	35	ACTH	Cured
6	ACTH	Low dose dex = 7.5/100 ml ACTH 7.7 pg/ml cortisol 20h00, 23.5 μg/100 ml, 24h00 14.8, 08h00 7.7. Synacthen test 08h30 = 7.4 μg/100 ml, 09h00 = 15.4, 09h30 = 7.5	Adrenaline and noradrenaline	N/A	ACTH, CGA, KL-1, anti-synaptophysin	Cured
7	Cortisol[b]	Free cortisol 74.9 ACTH suppressed Low dex test suppressed CgA = 118	Adrenaline and noradrenaline	150	N/A	Cured but died after 10 months
8	Aldosterone	Aldosterone 153, renin 5.6 ratio = 27.3	Adrenaline	30	PS100, CGA	Cured
9[d]	Calcitonin	Calcitonin 170	Adrenaline and noradrenaline	35-mm right 25-mm left	Calcitonin, CD56, CGA, PS100	Cured
10[d]	Calcitonin	Calcitonin 27 (<10) pentagastrin stim = 45 pg/ml/min	Noradrenaline	30	Calcitonin	Cured
11	Calcitonin and VIP	Calcitonin 48 VIP 95	Dopamine	70	Calcitonin, VIP, somatostatin	Cured
12	VIP	255 (23–63) CgA = 64	Dopamine	60	VIP	Cured
13	Testosterone	11-deoxycorticosterone = 578 (40–200) testosterone = 11.86 (3–8)	Adrenaline	25	N/A	Cured
14	Renin	626 μg/ml (<200)	Noradrenaline	N/A	N/A	Cured
15	Interleukin-6	71.7 ng/l (0–5)	Noradrenaline	75	N/A	Cured
16	ACTH	ACTH (8–55) = 105, cortisol = 2,673 (330–500) low dex supp = neg	Adrenaline and noradrenaline	20	ACTH	Cured

CGA chromogranin A, *ACTH* adrenocorticotrophic hormone, *VIP* vasoactive intestinal peptide

[a] ACTH not available at time

[b] The tumor secreting cortisol had a suppressed serum ACTH, but immunohistochemistry was not available

[c] Dopamine was not measured but anti-dopamine immunohistochemistry was positive so may have secreted dopamine as well. This is one of the patients who died postoperatively after removal of a 15-cm tumor

[d] Patient 9 had bilateral pheochromocytomas in the setting of neurofibromatosis 1 (NF1). Patient 10 had a unilateral pheochromocytoma in the setting of von Hippel Lindau syndrome (vHL)

attributable to ectopic hormones should be investigated to look for their presence as removal of the pheochromocytoma resolves the ectopic hormone symptoms too. The syndromes associated with the ectopic hormones isolated in this study correlate with those previously reported in the literature [1–35].

Another lesson to come from this observational study was that catecholamine secretion might be responsible for causing biochemical excess of other hormones, such as IL-6 or ACTH, as part of a physiological stress response, although positive receptor antibodies on IHC would argue against this in those cases where it was detected [24]. The renin-angiotensin aldosterone axis is affected by the sympathetic system with β_2 receptors found at the juxtaglomerular complex, and this could be an explanation for the aldosterone-secreting tumor [38, 39]. One patient who presented with cushingoid symptoms had normal preoperative ACTH levels but high urinary cortisol levels and a positive low-dose dexamethasone suppression test. Postoperatively immunohistochemistry did not show ACTH receptor antibodies in the pheochromocytoma tumor, but cortisol levels returned to normal. This patient may have had ectopic corticotrophin-releasing hormone (CRH) production, which has been described before and has been associated with normal ACTH levels [1, 3–6, 40]. This patient had surgery in the late 1970s when CRH staining was not available. Patient seven also had a suppressed ACTH and elevated cortisol, which may represent a physiological stress response. However, her past medical history and duration of hypercortisolism suggests that it was due to endogenous cortisol secretion.

In this study, we raise the danger associated with the combination of cortisol and catecholamine excess. Both hormone syndromes are associated with an increased risk of bleeding, thus complicating surgery: cortisol causes tissue fragility and catecholamine blockade leads to vasodilatation. Three patients died as a result of this combination of hormones, and they were the only deaths and complications of the whole series. In the two clearest cut cases, the tumors were unusually large, > 15 cm, and it maybe a combination of these factors—tumor size, catecholamine excretion, and cortisol—that are the most problematic. There is evidence that excess catecholamine secretion causes the catecholamine receptors to be downregulated at the end organ to minimize the damage that they cause. Steroids are responsible for their upregulation and increasing cell receptor density [41–43]. We know from Cushing's syndrome that normalization of the pituitary-adrenal axis takes several months after removal of the cortisol-secreting tumor. In pheochromocytoma with excess cortisol secretion, there may be a similar adaptation to cell response to cortisol; so that postoperatively cortisol levels become very low and there is no mechanism in place to reverse the cellular hyporesponsiveness to catecholamines. This would explain the unresponsive symptoms of the two patients with large tumors who died despite huge inotrope and cortisol replacement postoperatively. As a consequence of these findings, correcting cortisol excess preoperatively with metyrapone or ketoconazole and having an awareness of this potential problem is the safest strategy.

It is interesting to note that the two cases reported of secreting calcitonin occurred in the two familial syndrome cases, although correlation with the one pre-existing case report of ectopic calcitonin secretion did not add further evidence to this connection [30]. Calcitonin secretion in the presence of pheochromocytoma would normally make exclusion of multiple endocrine neoplasia type 2a (MEN 2a) mandatory to look for medullary thyroid cancer. Carcinoembryonic antigen (CEA) expression has been shown to be related to medullary thyroid cancer rather than pheochromocytoma when comparing MEN 2a patients with thyroid and adrenal disease to sporadic pheochromocytoma [44]. It is unfortunate that CEA estimation was not made in our two cases, although pentagastrin stimulation was, and it was negative. Both VIP secreting tumors were associated with dopamine-secreting pheochromocytomas and three of six (published case reports and cases from his series) cases of VIP secretion from pheochromocytomas also showed VIP secretion occurring in conjunction with calcitonin [33, 34] and another in conjunction with ACTH and somatostatin [35]. These peptides are linked by receptor type. Calcitonin, calcitonin-like receptor, calcitonin-related gene product (CRGP), VIP, and adrenomedullin [45–47]—with adrenomedullin shown to have effects at all levels of the hypothalamic–pituitary–adrenal axis [48]. Review of the literature on this and related subjects shows an overlapping of several of the ectopic peptides secreted here with adrenomedullin [45–49] and adrenomedullin with IL-6 [50, 51]. Adrenomedullin has been found in pheochromocytoma cells and adrenal cortex tumor cells in much higher quantities than normal cortex and medulla cells [46, 48]. The point of mutation in ectopic hormone pheochromocytomas may be instrumental to determine why an ectopic hormone is secreted and would make an interesting point for further study. The numbers, even in this study, were too small to make meaningful correlations but represent a point of interest for teams encountering these phenomena in the future. It is well known that a catecholamine-mediated stress response results in raised cortisol levels as part of that stress response. The cell receptors for these hormones are linked and catecholamine receptor activation downregulates the cell response to cortisol. Whether this means excessive secretion of catecholamines can lead to a kind of paraneoplastic elevation in cortisol is not known and may have occurred in our series. However, if a tumor stains

positive for ACTH antibodies, then it suggests that ectopic ACTH secretion from the adrenal medulla has occurred. Although not all of our cases had immunohistochemical staining performed, all the ACTH-secreting tumors that were stained were positive.

There are weaknesses to this study. It is retrospective and not everyone tests for the same things, which makes some comparisons difficult. The search method is almost certainly not exhaustive, because there is a bias toward more recent cases; these points would be overcome in a prospective study. We have not included the absolute values of biochemical results, because the study took place during a period of 30 years and in nine centers, making comparison between absolute values impossible. However, these tumors are exceptionally rare, and without an international, prospective database for centers to add cases to, a multicenter, retrospective, observational study, such as ours, is the best that can be achieved, so we should try to take meaningful conclusions from the results.

Ectopic hormone secretion in pheochromocytoma is rare (approximately 1% of all pheochromocytoma), nonmalignant, and nongenetic. The most frequent hormone expressed is ACTH. Ectopic hormone secretion often presents with unusual symptoms. Such patients should be tested for these rare associations, because removal of the adrenal tumor leads to symptom resolution. Patients presenting with pheochromocytoma also should have an ACTH test and low-dose dexamethasone suppression test to exclude excess cortisol secretion, which is both the most common and the most deadly. Patients who have cortisol excess should have this diagnosed and corrected preoperatively. Cortisol insufficiency must be considered postoperatively.

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Conflict of interest The authors have no conflicts of interest to declare.

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