Peptidergic phenotypes of pheochromocytoma

**Abstract**

Pheochromocytoma may present as either the classic catecholaminergic phenotype or as one of many kinds of peptidergic phenotypes, including’s Cushing syndrome, watery diarrhea, hypokalemia, and achlorhydria syndrome (WDHA), acromegaly, or humoral hypercalcemia, or a combination of both phenotypes. Cushing’s syndrome may be caused by a pheochromocytoma producing adrenocorticotropic hormone (ACTH) or one producing corticotropin-releasing hormone (CRH). WDHA can be caused by a pheochromocytoma producing vasoactive intestinal peptide (VIP). Acromegaly may be due to a pheochromocytoma producing growth hormone-releasing hormone (GHRH). Humoral hypercalcemia can be due to a pheochromocytoma producing parathyroid hormone-related peptide (PTHrP). -These findings strongly suggest that pheochromocytomas can produce and secrete many kinds of peptide hormones, reinforcing the multisecretory nature of chromaffin cells.

Knowledge of the clinical diversity of pheochromocytomas is important for both precise diagnosis and proper management. Complex clinical features among these cases may lead to the wrong diagnosis, such as an atypical overlap syndrome of multiple endocrine neoplasias. In the case of ectopic GHRH syndrome, unnecessary pituitary surgery may be performed because catecholaminergic features are scanty among patients with this syndrome.

**1. Introduction- /Background**

Pheochromocytomas are tumors derived from chromaffin cells of the adrenal gland. Generally they produce excess amounts of catecholamines causing the classical syndrome known as 5Hs (hypertension, headache, hyperglycemia, hyperhydrosis, and hypermetabolism). In addition to catecholamines, many neuropeptides are known to coexist in the chromaffin cells of both normal and pheochromocytoma tissues([Ivanova and Dashev, 1990](#_ENREF_28)). Diagnosis of a case of full-blown catecholaminesyndrome is not difficult, but an increasing number of these tumors are diagnosed in patients with syndromes caused by peptide hormones produced by the tumor.

These cases include 1. Cushing’s syndrome caused by the adrenocorticotropic hormone (ACTH) produced by the tumor, 2. Cushing’s syndrome caused by corticotropin-releasing hormone (CRH) produced by the tumor, 3. watery diarrhea, hypokalemia,and achlorhydria syndrome (WDHA) caused by vasoactive intestinal peptide (VIP) produced by the tumor, 4. acromegaly caused by growth hormone-releasing hormone produced by the tumor,and 5. humoral hypercalcemia caused by parathyroid hormone-related peptide (PTHrP) produced by the tumor.

This article has two purposes. The first is to review the wide variety of peptidergic phenotypes of pheochromocytoma. The second is to facilitate a thorough method for screening of these peptide hormones that may help in a precise diagnosis and individualized management of the patient with pheochromocytoma, which is liable to be overlooked due to the grave symptoms caused by catecholamines.

To fulfill the above-mentioned purposes, I reviewed case reports of adrenal pheochromocytoma that 1) presented with clinically apparent peptidergic syndrome with or without classical catecholaminergic syndrome, 2) were diagnosed by both histological and immunohistological evaluation of the surgical specimen,and 3) in which the production of the relevant peptide by the tumor itself was definitely substantiated by the complete reversal of the peptidergic syndrome after surgical resection and/or peptide hormone immunohistochemical staining in the tumor tissue or metastatic deposits, and/or complete/partial normalization of the peptide hormone after tumor removal/debulking.

**2. Ectopic Cushing’s syndrome due to ACTH production of adrenal pheochromocytoma**

Cushing’s syndrome comprises the signs and symptoms associated with prolonged exposure to inappropriately elevated levels of free plasma glucocorticoids. The classic features of Cushing’s syndrome include centripetal obesity, moon face, hirsutism, livid red-purple striae, and plethora. Skin pigmentation is common in ectopic ACTH syndrome (EAS), while it is rare in Cushing’s disease. Skin pigmentation arises because of overstimulation of melanocyte receptors by pro-opiomelanocortin (POMC) derived peptides.

Cushing’s syndrome is classified into ACTH-dependent and independent causes. ACTH-dependent Cushing’s syndrome is further subdivided into Cushing’s disease (pituitary dependent), ectopic ACTH syndrome (EAS), and ectopic CRH (corticotropin-releasing hormone)

syndrome.

EAS represents around 20% of ACTH-dependent and around 10-% of all types of Cushing’s syndrome (CS) ([Newell-Price et al., 2006](#_ENREF_44)). Tumoral sources associated with ectopic ACTH syndrome include small cell lung carcinoma, bronchial carcinoids, pancreatic carcinoids, thymic carcinoids, pheochromocytoma, and other neuroendocrine tumors Among these tumors, bronchial carcinoids are the most prevalent tumors associated with EAS ([Alexandraki and Grossman, 2010](#_ENREF_2)). About 5% of EAS cases were caused by pheochromocytoma ([Alexandraki and Grossman, 2010](#_ENREF_2), [Ilias et al., 2005](#_ENREF_26), [Isidori et al., 2006](#_ENREF_27), [Salgado et al., 2006](#_ENREF_61), [Bhansali et al., 2009](#_ENREF_7)), while fewer than 1% of pheochromocytomas are accompanied by Cushing’s syndrome([Chen et al., 1995](#_ENREF_13)).

The first step in the diagnosis of EAS is confirmation of endogenous hypercortisolism using an overnight dexamethasone test or a low-dose dexamethasone test (LDDST) and the demonstration of a detectable or high level of plasma ACTH. The second step of the diagnosis is confirmation of ACTH production by the tumor using CRH stimulation, high-dose dexamethasone inhibition, inferior petrosal sinus sampling, and/or confirmation of reversibility of clinical signs and symptoms after surgical resection of the tumor and/or reversibility of hypercortisolemia after tumor removal, and/or confirmation of ACTH production by the cultured tumor cells.

Most of the cases of pheochromocytoma associated with EAS showed a classic catecholaminergic phenotype, such as hypertension, hyperhidrosis, palpitation, and headache, and were associated with increased catecholamines in plasma and/or urine ([White et al., 2000](#_ENREF_76), [Bernardi et al., 2011](#_ENREF_6), [Chen et al., 1995](#_ENREF_13), [Fiebrich et al., 2009](#_ENREF_20), [Brenner et al., 2008](#_ENREF_9), [Danilovic et al., 2007](#_ENREF_17), [Otsuka et al., 2005](#_ENREF_49), [van Dam et al., 2002](#_ENREF_69)). However, some cases do not show this catecholaminergic phenotype ([Cohade et al., 2009](#_ENREF_14), [Nijhoff et al., 2009](#_ENREF_46), [Li et al., 2012](#_ENREF_34)).

In some cases, contralateral adrenal hyperplasia was detected but it was always resolved by unilateral tumor resection ([White et al., 2000](#_ENREF_76), [Bernardi et al., 2011](#_ENREF_6), [Chen et al., 1995](#_ENREF_13), [van Dam et al., 2002](#_ENREF_69)). Histological examination of the surgical specimen revealed diffuse hyperplasia of ipsilateral adrenocortical cells in two cases ([Cohade et al., 2009](#_ENREF_14), [Roux et al., 1955](#_ENREF_55)). Because unilateral surgical resection of the tumor was always successful, the adrenocortical hyperplasia seems to have been due to ACTH produced by a contra or ipsilateral tumor.

Pheochromocytoma usually shows high signal intensity on the T2-weighted MRI image and shows positive uptake on 123I-MIBG scans. However, some cases with EAS lacked these findings ([Cassarino et al., 2012](#_ENREF_12), [Ilias et al., 2005](#_ENREF_26), [van Dam et al., 2002](#_ENREF_69)).

No case of pheochromocytoma associated with EAS showing histological signs of malignancy was reported. In one case, the number of Ki67-positive cells was increased up to 20%, indicating malignant potential, but there were no overt malignant properties such as local invasion or metastasis ([Li et al., 2012](#_ENREF_34)). Multifunctional neuroendocrine tumors seldom seems to be malignant ([Wermers et al., 1996](#_ENREF_75)).

Knowledge of genetic changes in the tumorigenesis of pheochromosoma is growing very rapidly. Many germ line or somatic mutations or structural alterations affecting known PCC (pheochromocytoma)/PGL(paraganglioma) genes have been identified. In addition to these founder genetic events, intratumoral genetic heterogeneity was also identified using multi-region tissue samples ([Flynn et al., 2015](#_ENREF_22)). This kind of ongoing clonal evolution may cause additional peptide production among pheochromocytomas associated with EAS or other peptidergic phenotypes, although the relevant genes are not yet identified. In a case reported by van Dam et al. immunostaining for ACTH revealed not generalized but focal proliferation of 50-60 cells strongly positive for ACTH, also suggesting intratumoral heterogeneity ([van Dam et al., 2002](#_ENREF_69)).

**3. Cushing’s syndrome due to CRH produced by adrenal pheochromocytoma**

Corticotropin-releasing hormone (CRH) is known to be synthesized and secreted from non-hypothalamic tissues including the testis, gastrointestinal tract, adrenal medulla, and particularly the placenta ([Sasaki et al., 1987](#_ENREF_63)).

Ectopic production of CRH is a very rare cause of pituitary-dependent Cushing’s syndrome. Tumoral sources associated with ectopic CRH syndrome include bronchial carcinoids, medullary thyroid carcinoma ([Wajchenberg et al., 1995](#_ENREF_74)), prostate carcinoma ([Carey et al., 1984](#_ENREF_11)), Ewing’s sarcoma ([Preeyasombat et al., 1992](#_ENREF_52)), and pheochromocytoma. They secrete CRH alone ([Bayraktar et al., 2006](#_ENREF_5)) or in combination with ACTH ([Muller and von Werder, 1992](#_ENREF_40)), but in cases with dual production of ACTH and CRH, the role of CRH in patients’ with Cushing’s syndrome is ambiguous.

The first step in the diagnosis of ectopic CRH syndrome is confirmation of increased serum and urinary cortisol values, loss of diurnal serumcortisol rhythm, and an increased or unsuppressed ACTH value. The second step is confirmation of CRH production by the tumor using immunohistochemical examination ([Ruggeri et al., 2009](#_ENREF_56), [Eng et al., 1999](#_ENREF_19)), RNA analysis ([Liu et al., 1994](#_ENREF_35)), or measurement of the CRF-41 of the surgical specimens and/or measurement of CRF-41 of both pre-and postoperative plasma ([Jessop et al., 1987](#_ENREF_29)). Early morning serum cortisol and 24-hour urinary cortisol levels were unsuppressed after a high-dose dexamethasone suppression test, although simultaneous ACTH production by the tumor was excluded among these patients (single secretor) ([Ruggeri et al., 2009](#_ENREF_56), [Eng et al., 1999](#_ENREF_19), [Bayraktar et al., 2006](#_ENREF_5)). In contrast, cortisol levels were suppressed in a patient in whom concomitant ACTH production was confirmed (dual secretor). The opposite behavior of both single and dual secretors seems strange. because unresponsiveness to high-dose dexamethasone is usually observed among patients with ectopic ACTH syndrome and not observed in eutopic (pituitary) ACTH syndrome (Cushing’s disease). In a patient with a single CRH secretor, the production of ACTH should be eutopic (pituitary), while in a dual (ACTH and CRH) secretor, it should be at least partially ectopic in origin.

Most cases of pheochromocytoma associated with ectopic CRH syndrome did not show a classic catecholaminergic phenotype. As a result, an MIBG scan was seldom performed.

Although most cases showed an increased serum ACTH level , only one case showed contralateral adrenal hyperplasia ([Jessop et al., 1987](#_ENREF_29)). Histological examination of the surgical specimen revealed hyperplasia in the adjacent adrenal cortex ([Liu et al., 1994](#_ENREF_35), [Bayraktar et al., 2006](#_ENREF_5), [Eng et al., 1999](#_ENREF_19)).

No case of pheochromocytoma associated with ectopic CRH syndrome showing histological signs of malignancy was reported.

In three cases, rapid post-operative recovery of the hypothalamic-pituitary-adrenal (HPA) axis was observed ([Ruggeri et al., 2009](#_ENREF_56), [Bayraktar et al., 2006](#_ENREF_5), [O'Brien et al., 1992](#_ENREF_47)). In one of these cases, no hydrocortisone replacement therapy was necessary ([Ruggeri et al., 2009](#_ENREF_56)). This atypically rapid recovery of the HPA axis was supposed to be due to chronic CRH ‘priming’ of the anterior pituitary corticotrophs.

**4. WDHA caused by vasoactive intestinal peptide VIP produced by adrenal pheochromocytoma**

Watery diarrhea, hypokalemia, and achlorhydria (WDHA) syndrome is caused by excessive vasoactive intestinal peptide (VIP) secretion. This syndrome is usually associated with pancreatic neuroendocrine tumor, but rarely can be caused by nonpancreatic tumors, such as bronchogenic carcinoma, medullary thyroid carcinoma, retroperitoneal histiocytoma, and adrenal pheochromocytoma ([Said, 1976](#_ENREF_58)). VIP is a 28-amino acid peptide that activates adenylate cyclase in intestinal cells. Cyclic adenosine monophosphate (cAMP) causes excessive intestinal secretion of water, potassium, and chloride ions, leading to the clinical presentation of WDHA syndrome **(**[**Alam, 1994**](#_ENREF_1)**)**.

Since Loehry reported the first case of pheochromocytoma that caused WDHA syndrome ([Loehry et al., 1975](#_ENREF_36)), 21 cases of VIP-producing pheochromocytomas presenting with overt WDHA syndrome have been reported ([Jiang et al., 2014](#_ENREF_30), [Ende et al., 2012](#_ENREF_18), [Kikuchi et al., 2012](#_ENREF_32), [George et al., 2010](#_ENREF_24), [Ozbay et al., 2008](#_ENREF_50), [Ikuta et al., 2007](#_ENREF_25), [Onozawa et al., 2005](#_ENREF_48), [Smith et al., 2002](#_ENREF_65), [Van Eeckhout et al., 1999](#_ENREF_70), [Quarles Van Ufford-Mannesse et al., 1999](#_ENREF_53), [Contreras et al., 1991](#_ENREF_15), [Salmi et al., 1988](#_ENREF_62), [Nigawara et al., 1987](#_ENREF_45), [Fisher et al., 1987](#_ENREF_21), [Sackel et al., 1985](#_ENREF_57), [Viale et al., 1985](#_ENREF_72), [Cooperman et al., 1978](#_ENREF_16), [Matta et al., 1978](#_ENREF_37), [Pais, 1978](#_ENREF_51), [Trump et al., 1977](#_ENREF_68), [Loehry et al., 1975](#_ENREF_36)).

Most patients presented with protracted episodes of severe intractable watery diarrhea without blood or mucus. Severe hypokalemia sometimes caused skeletal muscle damage, such as generalized weakness, myalgia, or even rhabdomyolysis ([Ende et al., 2012](#_ENREF_18), [Onozawa et al., 2005](#_ENREF_48), [Nigawara et al., 1987](#_ENREF_45), [Viale et al., 1985](#_ENREF_72), [Trump et al., 1977](#_ENREF_68)) .

Among these cases, hypertension was seldom observed. Severe dehydration and vasodilator action ([Said and Mutt, 1970a](#_ENREF_59), [Said and Mutt, 1970b](#_ENREF_60)) caused by excessive VIP might have masked the vasospasmic symptoms of catecholamines. Similarly, glucose intolerance is seldom observed in these patients.

Histological examination of resected tumors frequently showed features consistent with composite pheochromocytoma-ganglioneuroma (in 8 out of the above-mentioned 21 cases). VIP expression in composite tumors is confined largely to the ganglioneuroma component ([Kikuchi et al., 2012](#_ENREF_32), [George et al., 2010](#_ENREF_24), [Onozawa et al., 2005](#_ENREF_48), [Schmid et al., 1993](#_ENREF_64), [Contreras et al., 1991](#_ENREF_15), [Salmi et al., 1988](#_ENREF_62), [Nigawara et al., 1987](#_ENREF_45)).

Two cases of malignant tumor were reported. Both cases initially presented with classic pheochromocytoma, but the recurrent malignant tumors were composite pheochromocytoma-ganglioneuromas that caused WDHA syndrome ([Kikuchi et al., 2012](#_ENREF_32), [Nigawara et al., 1987](#_ENREF_45)).

**5. Acromegaly to GHRH produced by adrenal pheochromocytoma**

Acromegaly is a rare disease caused by growth hormone (GH) hypersecretion, usually by a GH-producing pituitary adenoma derived from somatotroph cells of the adenohypophysis (classic acromegaly). Progressive acral changes are characterized by large fleshy lips and nose, spade-like hands, frontal skull bossing, and cranial ridges. Regardless of the etiology, the disease is characterized by elevated levels of GH and insulin-like growth factor 1 (IGF1) with resultant signs and symptoms of hypersomatotropism.

Growth hormone-releasing hormone (GHRH) is the most important stimulatory peptide for the somatotrophs. It is usually produced by hypophyseotropic neurons and is secreted into pituitary portal vessels at the median eminence. It stimulates GH secretion, upregulates GH gene expression, and stimulates somatotroph proliferation.

Acromegaly is classified into excess primary GH, excess extrapituitary GH, and excess GHRH causes. Excess GHRH syndrome is further subdivided as central (hypothalamic) and peripheral (ectopic GHRH syndrome)tumors. Tumor sources associated with ectopic GHRH syndrome include bronchial carcinoid, pancreatic islet cell tumor, small cell lung cancer, adrenal adenoma, medullary thyroid carcinoma, and pheochromocytoma ([Asa et al., 1985](#_ENREF_4), [Frohman et al., 1980](#_ENREF_23), [Mumby et al., 2014](#_ENREF_41), [Vieira Neto et al., 2007](#_ENREF_73), [Roth et al., 1986](#_ENREF_54)). Among these tumors, bronchial carcinoids are the most prevalent tumors associated with ectopic GHRH syndrome ([Borson-Chazot et al., 2012](#_ENREF_8), [Verrua et al., 2010](#_ENREF_71)).

The diagnosis of acromegaly requires demonstration of a growth hormone (GH) nadir during an oral glucose tolerance test. In patients with acromegaly, oral glucose fails to suppress GH. Serum IGF1 levels are invariably high. GHRH levels are invariably high in patients with peripheral GHRH-secreting tumors but normal or low in patients with pituitary adenomas. Because an enlarged pituitary is often present in patients with peripheral GHRH- secreting tumors, the diagnosis of the syndrome is challenging. Differential radiologic diagnosis of GHRH-induced somatotroph hyperplasia due to classic pituitary adenoma is difficult.

I have found three cases of GHRH-producing pheochromocytoma that presented with acromegaly in the literature. The causal relationship between ectopic GHRH secretion by adrenal pheochromocytoma and acromegaly was confirmed biochemically, histologically, and surgically. The association between acromegaly and pheochromocytoma had already been observed before these case reports ([Myers and Eversman, 1981](#_ENREF_43), [Anderson et al., 1981](#_ENREF_3), [Miller and Wynn, 1971](#_ENREF_38), [Kahn and Mullon, 1964](#_ENREF_31)). but the association had been attributed to overlapping multiple endocrine neoplasia syndromes in the majority of the cases, even if the probability was negligibly low. Because most of these cases were reported before the characterization of GHRH in 1980 by Frohman et al., the causal relationship between acromegaly in these patients and ectopic GHRH secretion by pheochromocytoma could not be confirmed ([Frohman et al., 1980](#_ENREF_23)).

Among these three cases, catecholaminergic symptoms were scant. All of them were normotensive, although increased serum and urinary catecholamines were confirmed. Histopathological examination of the adrenal tumor revealed the characteristic morphology of pheochromocytoma. Immunohistochemical staining for GHRH in the pheochromocytoma cells was positive.

In the first case reported by Roth et al. the diagnosis was confirmed by postmortem examination ([Roth et al., 1986](#_ENREF_54)). In the second case, transphenoidal surgery was initially done under the misdiagnosis of somatotropinoma. An adrenal pheochormocytoma was found after this surgery ([Vieira Neto et al., 2007](#_ENREF_73)). In the third case, the patient was treated by adrenalectomy alone ([Mumby et al., 2014](#_ENREF_41)).

**6. Humoral hypercalcemia caused by PTHrP produced by adrenal pheochromocytoma**

Humoral hypercalcemia is frequently seen among patients with advanced stage cancer. Humoral hypercalcemia of malignancy (HHM) is caused by systemic secretion of parathyroid hormone-related peptide (PTHrP) by malignant tumors. PTHrP enhances synthesis of a ligand for receptor activator of nuclear factor-κ B(RANKL), leading to activation of bone resorption. Elevated PTHrP also increases renal calcium reabsorption.

Clinical features of hypercalcemia are characterized by neurologic, gastrointestinal, cardiovascular, and renal disorders. Neurocognitive symptoms of hypercalcemia include anxiety, mood changes, and cognitive decline. In severe cases, altered states of consciousness or even coma may occur. Gastrointestinal symptoms include nausea, vomiting, anorexia, and constipation. Hypercalcemia may cause ECG abnormalities, such as a shortened QT interval and ST elevation. Renal manifestations include nephrogenic diabetes insipidus, distal renal tubular acidosis, and urolithiasis([Mirrakhimov, 2015](#_ENREF_39)).

Squamous-cell cancers, renal cancer, ovarian cancer, malignant lymphoma, and breast cancer account for the majority of malignancies leading to HHM ([Stewart, 2005](#_ENREF_66)). Humoral hypercalcemia caused by PTHrP secretion is infrequent in benign neoplasm. Only three cases of humoral hypercalcemia caused by PTHrP-producing pheochromocytoma have been reported so far ([Takeda et al., 2010](#_ENREF_67))-([Bridgewater et al., 1993](#_ENREF_10))-([Kimura et al., 1990](#_ENREF_33)). In these cases, PTHrP levels were increased, while the parathyroid hormone (PTH) concentration was either undetectable or within normal range. Two of the three were benign pheochromocytomas, and the PTHrP level was normalized after surgery ([Takeda et al., 2010](#_ENREF_67), [Kimura et al., 1990](#_ENREF_33)). The expression of PTHrP in tumor cells was confirmed by immunohistochemistry.

Two of the three were hypertensive, and elevated levels of urine catecholamines were confirmed. In Bridgewater’s case, the patient was normotensive and serum catecholamines were within normal limit([Bridgewater et al., 1993](#_ENREF_10)).

Mune et al. reported that the serum PTHrP of patients with pheochromocytoma is frequently elevated (seven out of ten cases) irrespective of pathological hypercalcemia, and that PTHrP became undetectable in all ten patients after surgery. Because α-adernoreceptor- blocking agents given as preoperative treatment decreased PTHrP, they supposed that PTHrP level was controlled via an α-adrenergic mechanism ([Mune et al., 1993](#_ENREF_42)).

**7. Conclusion**

Diagnosis of pheochromocytochoma presented with classic catecholaminergic phenotype is not so difficult. But it is sometimes become challenging among patients presented with above-mentioned peptidergic phenotypes because pheochromocytomas can produce and secrete many kinds of peptide hormones, reinforcing the multisecretory nature of chromaffin cells. Physicians should consider the clinical diversity of pheochromocytomas for both precise diagnosis and proper management. Screening of these peptide hormones may help in a precise diagnosis and individualized management of the patient with pheochromocytoma.

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