Pituitary (2019) 22:561–568
https://doi.org/10.1007/s11102-019-00965-9

Ectopic cushing's syndrome due to corticotropin releasing hormone

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Published online: 30 April 2019

Abstract
Cushing's syndrome (CS) secondary to corticotropin releasing hormone (CRH) producing tumors is rare. In this paper we present an Iranian patient who was admitted to our hospital with classic signs and symptoms of CS. Laboratory evaluation revealed high serum and urine cortisol which could not be suppressed with dexamethasone. Abdominal CT scan revealed a mass in abdominal cavity. A percutaneous needle biopsy was performed and histopathologic evaluation revealed that the mass was a neuroendocrine tumor. A multi-disciplinary approach including resection of the mass, bilateral adrenalectomy somatostatin analogue and chemotherapy was applied for management of the disease. Extensive review of English literature focusing on the topic from 1971 to 2018 revealed that there have been only 75 similar cases. Clinical, laboratory, imaging, histopathologic characteristics and managements of these patients will also be discussed in this paper.

Keywords Cushing's syndrome · Ectopic · Corticotropin-releasing hormone producing tumor · CRH producing tumor

Introduction

Endogenous Cushing's syndrome results from exposure of the body to increased amounts of cortisol secreted by the adrenal cortex. The disease results from hypersecretion of adrenocorticotropic hormone (ACTH) from a pituitary adenoma (PA) in the majority of cases [1, 2]. In approximately 10% of the cases, CS develops from hypersecretion of ACTH from non-pituitary tumors with different histopathologic characteristics. In rare circumstances, non-pituitary tumors gain the ability to secrete corticotropin-releasing hormone (CRH). The ectopically secreted CRH stimulates the pituitary gland, leading to hypersecretion of ACTH from pituitary gland with resultant stimulation of adrenal cortex and development of CS [3–5]. Ectopic Cushing's syndrome (ECS) secondary to CRH producing tumors are the least prevalent form of CS. CRH producing tumors may be pure CRH secreting tumors or they may secrete ACTH as well. As will be discussed later, they have different etiologies, course and prognosis that are important in diagnosis and management of patients.

In 1971, Upton and Amatruda for the first time found evidences for the existence of peptides with corticotropin-releasing factor-like (CRF) activity in two patients, one with a pancreatic neuroendocrine tumor and the other with an oat cell carcinoma of lung [6] and suggested a new

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pathophysiological mechanism for development of ectopic ACTH syndrome [7].

Here we present briefly our case and then review the clinical characteristics, laboratory and pathologic findings and therapeutic management and prognosis of patients with Cushing's syndrome from all the published cases in whom the CS was secondary to either CRH or mixed ACTH-CRH-producing neoplasms [3–68].

Case presentation

A 62-year-old Iranian woman was admitted to hospital in 2009 because of high blood glucose, hypertension and proximal muscle weakness that had developed during last few months. Physical examination was positive for central obesity, moon face and easy bruising. She had a history of rheumatoid arthritis which was treated with prednisolone and hydroxychloroquine from 10 years ago. She claimed that the RA symptoms had resolved and she ceased taking her medications last year.

Morning serum cortisol was 15.5 µg/dl (normal range: 10–21) at basal state and 14.2 µg/dl (normal range < 1.8) after overnight dexamethasone suppression test (ODST). Twenty four-hour urine free cortisol was 2000 µg (normal range: < 100 µg/day) and plasma ACTH was 68 pg/ml (normal range: 10–50 pg/ml). Serum cortisol and plasma ACTH were measured using commercial kits by Chemiluminescence Immunoassay method and urine free cortisol was determined by ELISA (enzyme-linked immunosorbent assay) method. Magnetic resonance imaging (MRI) of pituitary gland was normal. Based on clinical and laboratory findings, possibility of ectopic CS was proposed. A whole body Octreotide scan indicated the presence of lesions with increased uptake, one in the abdominal cavity and four within the right lobe of the liver. A multi-slice abdominal CT scan revealed a 40 mm mesenteric mass in the mid-portion of the abdomen with metastatic lesions in right lobe of the liver (Fig. 1).

A CT-guided percutaneous needle biopsy of the metastatic lesions of the liver revealed a neuroendocrine carcinoma. Immunohistochemical analysis of the tissue revealed that the tissue was positive for chromogranin and synaptophysin but negative for ACTH. Treatment with ketoconazole and somatostatin analogue was started and surgical removal of the abdominal tumor was advised but declined by the patient.

The patient returned to hospital after 10 months with recurring signs and symptoms of CS and clinical symptoms of acute cholecystitis. UFC was more than 1000 µg/day. Due to critical condition of the patient, we advised bilateral adrenalectomy, resection of mesenteric tumor and biopsy of the hepatic metastases.

Surgery was uneventful and symptoms of CS ameliorated significantly. Both tumor and metastases sections were investigated histologically and revealed that the mesenteric tumor was the same as the liver metastases. Immunohistochemical analysis of the specimen was also undertaken. Methods have been previously described [69]. Immunostaining of the mesenteric tumor for CRH (Peninsula Laboratories, San Carlos, CA; polyclonal; 1:1000; Cat#ABIN573959) showed strong positivity throughout the tumor cells while ACTH (Biocompare, San Francisco, CA; monoclonal; 1:100; orb88609) was sparsely positive (Fig. 2). To ensure the specificity of the antibodies, both positive and negative formalin-fixed, paraffin embedded tissues were included in the immunostaining. For CRH, human placenta was used for the positive control while for ACTH, human pituitary tissue was used. For negative controls, slides containing the same tissue specimen were run in tandem with the other specimen except the antibody was eliminated for the negative controls as previously described [69].

Post-surgical serum cortisol was < 1 µg/dl and UFC while on hydrocortisone was 6.8 µg/24 h. Sandostatin LAR was

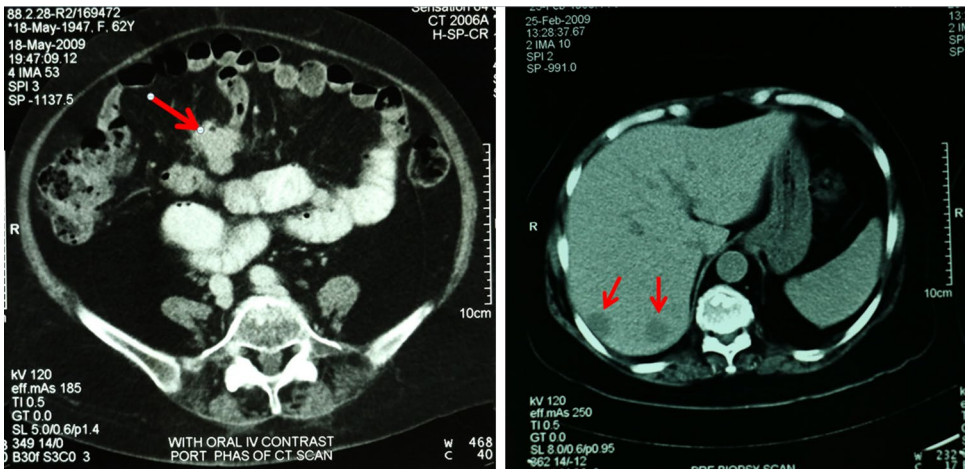

Fig. 1 A multi-slice abdominal CT scan revealed a 40 mm mesenteric mass in the mid-portion of the abdomen with metastatic lesions in right lobe of the liver

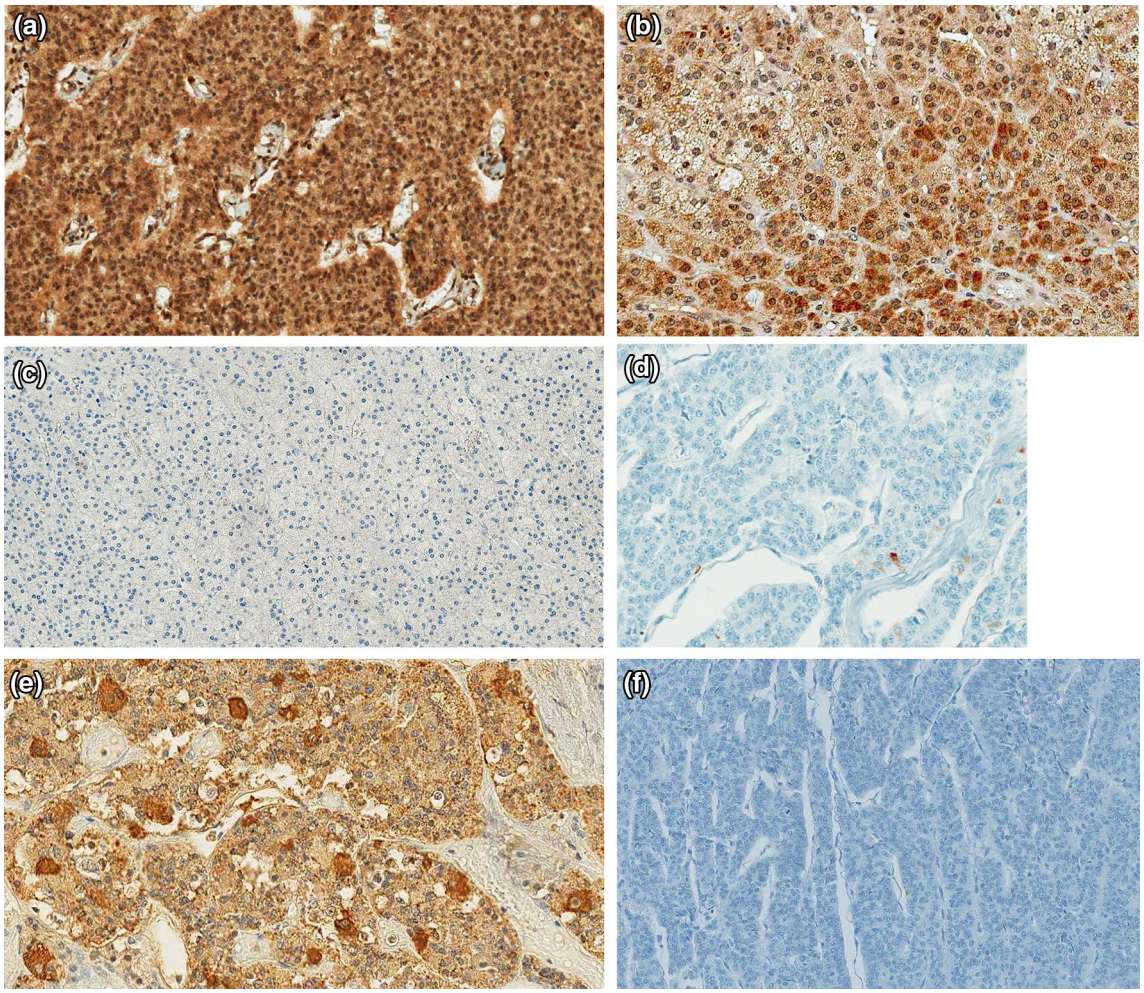

Fig. 2 **a** Immunostaining of the mesenteric tumor for CRH showed strong positivity throughout the tumor cells. **b** CRH positive control. **c** CRH negative control. **d** Immunostaining of the mesenteric tumor for ACTH showed sparse positivity throughout the tumor cells. **e** ACTH positive control. **f** ACTH negative control

continued and the oncologist advised a course of chemoembolization. After second round of chemoembolization, the patient developed fever, retroperitoneal hemorrhage and peritonitis. She was transferred to ICU but her condition deteriorated gradually and died at hospital.

Literature review

Clinical characteristics

As mentioned earlier, CS secondary to CRH producing tumors is exceedingly rare. Literature review dating back to 1971 revealed that 75 cases including our case are reported from 1971 to 2018. The disease is seen with almost equal frequency among men and women (38 males and 37 females). It presents in all age groups (2 to 75 years (41.6 ± 20.8 years) but diagnosis has been made in fifth to seventh decades in majority of cases.

Clinical presentation was typical CS in 49 patients. In 12 patients [6, 7, 9, 13, 15, 19, 26, 34, 38, 48, 59, 67] presentation was quite nonspecific and diagnosis was confirmed after work up of diverse scenarios such as hypokalemia, metabolic alkalosis, hyperglycemia, resistant hypertension, hyperpigmentation, behavioural disturbances and proximal muscle weakness.

Origin of the tumors

It was found that tumors leading to this form of CS originated in various organs and most of them had neuroendocrine features. As outlined in Table 1, most frequent tumor type as the source of CRH secretion was bronchial carcinoid tumor, followed by thymic carcinoid tumor, pancreatic tumors, pheochromocytoma and medullary thyroid carcinoma [3, 6, 7, 9, 11, 12, 14–17, 20–23, 25, 27, 28, 31–36, 38–41, 43, 47, 50–53, 57, 58, 60, 61, 68]. As a result, in

Table 1 Origin of tumors in 75 patients with Cushing's syndrome secondary to ectopic CRH producing tumors

Origin of Tumor	n	%
Lung	13	17.3
Thymus	11	14.7
Pancreas	10	13.3
Adrenal	8	12
Thyroid (MTC)	8	10.7
Sella turcica	6	8
Prostate	4	5.3
Unidentified	4	5.3
Colon	2	2.7
Kidney	2	2.7
Other sites	7	8

approximately 1/3 of the cases, the tumors leading to the disease were localized in lung and mediastinum. It is important to note that these data are from tumors that secret both CRH and ACTH. If we consider only the tumors with pure CRH secreting characteristic, the most prevalent tumors would be medullary thyroid carcinoma (MTC) and pheochromocytoma (PCC). This is in accordance with findings of Shahani et al. on their study on 21 patients with pure CRH secreting tumors [4]. No primary tumor could be identified in four cases [3, 4, 8, 42]. In three patients, diagnosis was based on positive immunostaining for CRH in the tissue specimens obtained from liver metastases [3, 4, 8] and in the fourth case, no definitive site was established and the diagnosis was based solely on an elevated serum CRH level [42].

Laboratory findings and diagnostic evaluations

Laboratory values of reported cases (Table 2) revealed that the median of cortisol excretion is higher than the values obtained from cases with Cushing's disease or ectopic ACTH syndrome although it should be noted that there is considerable overlap between the values [70–72]. Median of 24 h urinary free cortisol excretion values was 14.5 times the upper limit of normal. Base-line serum cortisol was 38 µg/dl and the values did not show suppression after overnight dexamethasone suppression test (ODST) or low dose dexamethasone suppression tests (LDDSD). Serum cortisol after the low dose dexamethasone suppression test was 35.6 µg/dl (median). Median values for plasma ACTH and CRH were 217 pg/ml (normal values 10-50 pg/ml) and 30 pg/ml (normal values < 10 pg/ml), respectively.

Approximately 80% of the cases had overt diabetes mellitus. Serum potassium was less than 4 mEq/L in all patients and 80% were hypokalemic (K < 3.5 mEq/L). Metabolic alkalosis was found in all patients who had undergone blood gas analysis. These values clearly demonstrate the high secretory capabilities of these tumors.

Criteria used for diagnosis of the disease included increase in plasma CRH (22 cases), positive CRH immunoreactivity (62 cases), in vitro study of tumor for CRF-like activity (11 cases) and CRH concentration gradient across the tumor bed (4 cases) (Table 3). CRH was measured in 32 patients but only 22 patients had elevated serum CRH levels. This may be due to cyclic secretion of CRH from the tumor or resulted from different methods used for laboratory measurement of CRH [3, 39, 42, 47]. In earlier studies when IHC staining for CRH or measurement of CRH were not available, demonstration of CRF-like bioactivity was performed by exposing extracts of the tumors to monolayer of rat anterior pituitary cell cultures and evaluation of ACTH synthesis from the cells.

Table 2 Laboratory findings of 75 patients with Cushing's syndrome due to ectopic CRH production

Lab test (patients with available data)	Mean ± SD (median)	Range (quartiles)
ACTH (pg/mL) (60)	345 ± 608 (217)	12–4425 (90–351)
UFC (µg/d) (44)	4165 ± 7143 (999)	64–38,200 (526–4395)
UFC/ULN (27)	63 ± 116.2 (14.5)	0.8–424 (4–37.3)
CRH (pg/mL) (29)	159.5 ± 447.4 (30)	2–2417 (5.2–107.9)
Serum Cortisol (µg/dL) (59)	54.1 ± 35.8 (38)	11.8–139.7 (26.9–74.6)
Serum Cortisol (µg/dL) after ODST/LDDST (25)	40 ± 29 (35.6)	4.7–116.7 (14.4–53.7)
Potassium (mEq/L) (38)	2.9 ± 0.7 (2.9)	1.5–4 (2.3–3.3)
Sodium (mEq/L) (21)	142.8 ± 5.4 (143)	128–150 (142–147)
FBS (mg/dL) (24)	184 ± 82 (165)	74–400 (127–224)
DM	29/36	80
Hypokalemia (K < 3.5 mEq/L)	33/42	80
Metabolic Alkalosis	18/18	100

ACTH Adrenocorticotropic hormone, *CRH* Corticotropin releasing hormone, *DDST* Dexamethasone suppression test, *DM* Diabetes mellitus, *ODST* Overnight dexamethasone suppression test, *UFC* Urinary free cortisol, *ULN* Upper limit of normal

Table 3 Criteria of diagnosis in patients with CS secondary to ectopic CRH production

	n	%
IHC Positive for CRH & ACTH	31	41
IHC Positive for CRH & negative for ACTH	31	41
CRF-like activity but no ACTH-like activity in tumor extracts	6	8
CRF-like activity and ACTH-like activity in tumor extracts	5	7
Elevated serum CRH levels	22	29
CRH concentration gradient across the tumor bed	4	5

Management and prognosis

Surgical removal of the tumor was the primary therapeutic option. In cases in which total resection of the tumor could not be achieved, other modalities such as chemotherapy and radiotherapy were used. Inhibitors of glucocorticoid synthesis such as ketoconazole, metyrapone and mitotane were used in patients with florid CS and uncontrollable hypercortisolism. In cases in which hypercortisolism could not be controlled, as in our case, bilateral adrenalectomy was performed to save patient's life. It is important to note that in 11 patients [3, 8, 11, 23, 41, 42, 53, 66, 68], erroneous diagnosis of pituitary dependent CS had been made and the patients had undergone unnecessary pituitary surgery. It seems that similarities of clinical presentations in patients with milder forms of ectopic CRH syndrome with patients with Cushing's disease and similarities of laboratory values have been important factors in the wrong diagnosis.

Inferior petrosal sinus sampling (IPSS) has been done in 17 patients with CRH producing tumors. The test was helpful in establishing the diagnosis of ECS in only 6 cases [3, 14, 40]. In the remaining 11 cases, [3, 11, 23, 27, 34, 35, 39, 42, 46, 55, 66] the result was in favor of pituitary dependent CS (central/peripheral gradient of ACTH levels > 2 before and > 3 after CRH stimulation). In one patient [46] central/peripheral gradient of ACTH has been measured during surgery of Sellar choristoma.

Prognosis was generally poor and approximately 30% of patients died within six month after diagnosis despite treatment. It seems that prognosis in CS caused by ectopic secretion of CRH is worse than pituitary adenoma or adrenal adenoma and ectopic ACTH syndrome [70–72] with the exception of patients with pheochromocytoma in whom adrenalectomy led to complete resolution of CS. Poor prognosis seems to be secondary to invasive nature of the underlying tumors and also to the fact that most patients have been diagnosed when the disease had been in advanced stages with local and distant metastases.

Conclusion

We have presented in this paper an unusual form of CS secondary to hypersecretion of CRH from a mesenteric neuroendocrine tumor and reviewed the clinical and laboratory characteristics of this rare form of CS. In reviewing our case along with the published data on cases of CS secondary to CRH producing tumors, many challenges in diagnosis and management of the disease still remain. Future studies should focus on the molecular and genetic components of these tumors to better understand the pathophysiology of this rare cause of CS.

Acknowledgement Authors are grateful to the Jarislowsky and Lloyd Carr-Harris foundations for their support.

Compliance with ethical standards

Conflict of interest Authors have no conflicts of interest to declare.

Ethical approval This work has been conducted with the consent of the patient and in accordance to the standards of institutional/national Ethics Committee. All work also conforms to the provisions of the Declaration of Helsinki and Tokyo.

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