

Twist of endocrine scenario: Approach of ectopic Cushing syndrome (review)

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ABSTRACT

Ectopic Cushing syndrome or ectopic ACTH (Adrenocorticotrophic Hormone) syndrome, a rare but severe condition, is due to a non-pituitary ACTH excess or exceptionally a non-hypothalamic CRH (Corticotropin - Releasing Hormone) hyper-production, usually due to a neoplasia which may be of endocrine or non-endocrine origin. Our objective is to introduce a brief literature regarding ectopic Cushing syndrome based on five micro-chapters: clinical evaluation, lab tests, imaging assays, therapy options and as discussions – the current limits of the topic. This actually comes with a twist in every aspect since a lot of data are yet to be clarify about this complex medical entity. Clinical presentation may be suggestive for Cushing syndrome but a few characteristics are more frequently seen as hyperpigmentation, rapid onset up even becoming an endocrine emergency, male preponderance, potential weight loss instead of weight gain, as oppose to Cushing disease or adrenal Cushing syndrome. Hypokalaemia is a hallmark of this particular situation. Additional tests are necessary to identify the source of ACTH excess and this twist is necessary in addition to traditional suppression tests for glucocorticoid axes. Some authors describe another twist in recognition of syndrome presentation: that actually there are two subtypes – one caused by a very aggressive tumour with rapid evolution and another with a lent slope of clinical features appearance caused by a occult neoplasm. Another twist is the fact that, in cases without a clear tumour origin, bilateral adrenal removal is actually necessary until adequate identification of source is done (if ever). Overall, a complex multidisciplinary team is necessary, the prompt recognition and therapy is life saving and numerous limits of both diagnosis and management are still a matter of debate.

Keywords: Cushing’s syndrome, cancer, adrenalectomy, adrenal tumour, cortisol

INTRODUCTION

Ectopic Cushing syndrome or ectopic ACTH (adrenocorticotrophic hormone) syndrome, a rare but severe condition, is due to a non-pituitary ACTH excess or exceptionally a non-hypothalamic CRH (corticotropin-

releasing hormone) hyper-production, usually due to a neoplasia which may be of endocrine or non-endocrine origin (1,2). This is considered a type of ACTH-dependent form, in addition to Cushing disease (3). Clinical presentation may be suggestive for Cushing syndrome but a few characteristics are more frequently seen as

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hyperpigmentation, rapid onset up even becoming an endocrine emergency, male preponderance, potential weight loss instead of weight gain, as oppose to Cushing disease or adrenal Cushing syndrome (4,5). Hypokalaemia is a hallmark of this particular situation (6). Additional tests are necessary to identify the source of ACTH excess and this twist is necessary in addition to traditional suppression tests for glucocorticoid axes (7,8). Some authors describe a twist in recognition of syndrome presentation: that actually there are two subtypes – one caused by a very aggressive tumour with rapid evolution and another with a lent slope of clinical features appearance caused by a occult neoplasm (7). Another twist is the fact that, in cases without a clear tumour origin, bilateral adrenal removal is actually necessary until adequate identification of source is done (if ever) (9). Overall, a complex multidisciplinary team is necessary, the prompt recognition and therapy is life saving and numerous limits of both diagnosis and management are still a matter of debate as Aimee R. Hayes and Ashley B. Grossman said “rarely easy, always challenging” (10).

AIM

Our objective is to introduce a brief literature regarding ectopic Cushing syndrome from evaluation to therapy. A priory unpublished case sample is introduced. The patient agreed to use her medical data. A number of 51 references are cited. The general data are organised in five micro-chapters: clinical evaluation, lab tests, imaging assays, therapy options and as discussions – the current limits of the topic. This actually comes with a twist in every aspect since a lot of data are yet to be clarify about this complex medical entity.

GENERAL DATA

Clinical evaluation

Ectopic Cushing syndrome represents 10-15% (varying from 5 to 20%) of all Cushing syndrome cases (11). Generally, the panel of Cushing syndrome is complex and severe associating a high risk of morbidity and mortality; among different aetiologies, ectopic Cushing syndrome has the most severe prognostic (12,13). Any age may be affected, usually adults, but cases is paediatric population are described (14,15). Ectopic ACTH production is part of paraneoplastic syndrome of endocrine or neuroendocrine pattern like tumour-related hypercalcemia, tumour-related hypoglycaemia, carcinoid syndrome etc. (16,17). The general presentation due to hypercortisolemia varies as severity and elements from issues with a higher prevalence in adult

general population like arterial hypertension, obesity, diabetes mellitus and osteoporosis to gonadal dysfunction (amenorrhea, impotence, infertility) in addition to hirsutism/hyperandrogenemia, plethora, red striae, ecchymosis, skin infections, poor wound healing, growth retard in children etc. (18,19).

However, in ectopic ACTH production myopathy, glucose anomalies, and weight loss are prominent in association to hyperpigmentation via skin effects of increased ACTH levels. (20) (Figure 1).



FIGURE 1. Recent skin hyperpigmentation at the level of scars and palmar interlines of a 52-year old female with ectopic Cushing syndrome. This is a non-smoking subject, admitted for marked asthenia, muscle weakness, polydipsia and polyuria progressively in addition to a two years history of high blood pressure. She has overweight (body mass index of 29.05 kg/m²), moon face, enlarged supra-clavicle fat pads, easy bruising, and minor bilateral leg oedema.

Lab tests

Laboratory tests may show high levels of morning cortisol, the loss of circadian rhythm, increased midnight and urinary free cortisol, lack of suppression to typical screening dexamethasone inhibition tests but these only confirms the endogenous Cushing syndrome (21,22). Elevated ACTH levels may allow the diagnosis of paraneoplastic Cushing syndrome to be established and the differentiation with Cushing disease comes from the results at 2 day of 8 mg dexamethasone which is less recommended these days (23,24). However, very high values of ACTH are mostly seen in ectopic ACTH production rather than ortho-topic excess (25). Potential use of hormonal assays like high androgens, suppressed gonadotropins are necessary in some situations (26). Biochemical anomalies as hypokalaemia, hyperglycaemia, high bone resorption markers, anaemia, etc. are expected (27,28,29). In Table 1 we introduce a sample case of a ectopic Cushing syndrome of unidentified primary cause at the moment of hypercorticism (Table 1). A large area of tumour markers as well as neuroendocrine markers like chromogranin A, calcitonin, serotonin, neuron specific enolase, etc. are

needed in some cases to identify the primary tumour (30,31).

TABLE 1. Biochemical and hormonal profile of a 52-year old female with paraneoplastic Cushing syndrome

Parameter	Patient's values	Normal limits	Units
Red blood cells	3.42	4-5	10 ¹² /l
Haemoglobin	10.2	12-15.5	g/dl
Haematocrit	29.2	37-47	%
Serum sodium	140	136-146	mmol/l
Serum potassium	2.39	3.5-5.1	mmol/l
Glycaemia	245	74-106	mg/dl
Total cholesterol	209	< 200	mg/dl
Triglycerides	147	< 150	mg/dl
Total calcium	8.8	8.8-10.6	mg/dl
Ionized calcium	4.4	4.4-5.4	mg/dl
Urea	45	17-43	mg/dl
Creatinine	0.62	0.51-0.95	mg/dl
Morning plasma cortisol	75.3	5-25	µg/dl
Plasma cortisol 8 p.m	66.8	2.5-13	µg/dl
Plasma cortisol 11 p.m.	66.2	< 7	µg/dl
ACTH	367	7.2-63.3	pg/ml
24-h free urinary cortisol	4728	50-190	µg/24 h
Morning plasma cortisol*	58.6	< 1.8	µg/dl
Morning plasma cortisol**	73.4**		µg/dl
Total serum testosterone	2.16	0.2-0.75	ng/ml
DHEA-S	2.52	0.9-3.6	µg/ml
FSH	0.16***		U/l
LH	0.11***		U/l
TSH	0.97	0.4-4	µIU/ml
FT4	1.04	0.61-1.35	ng/dl
Chromogranin A	39.87	< 76.3	ng/ml
Serotonin	50.74	40-200	µg/l
5 HIAA	1.92	2.00-9.00	mg/24 h
NSE	19.95	< 17	ng/ml
CEA	1.48	< 3	ng/ml

µg = microgram; ACTH = adrenocorticotropic hormone; * = after 1 mg dexamethasone overnight test; ** = after 2 days of 8 mg dexamethasone suppression test (suppression more than 50% from baseline values is suggestive for Cushing disease, while less than 50% is found in adrenal Cushing syndrome and ectopic Cushing syndrome); DHEA-S = dehydroepiandrosterone; FSH = follicle stimulating hormone; LH = luteinizing hormone; TSH = thyroid stimulating hormone; FT4 = free thyroxine; 5 HIAA = 5 hydroxyindoleacetic acid; NSE = enolase specific neuron; ACE = carcinoembryonic antigen; *** suppressed values as opposed to high testosterone levels.

Imaging assays

Imaging tools are essential in adequate management of ectopic Cushing syndrome but mostly in identifying and removal of primary cause of the syndrome, the ACTH producing neoplasia (32). Frequently, the source tumour is not identified and, in this unfortunate situation, if the severe hypercortisolemia is not controlled, a twist in case management is done by performing bilateral adrenalectomy until the underlying

tumour is found and eliminated (32,33). The most used methods are computed tomography and magnetic resonance imagery (especially with high resolution) but the approach depends on tumour location, size, type, the presence of metastasis etc. (34). High-resolution functional imagery is necessary like Gallium-DOTATE or whole body octreoscan for neuroendocrine tumours based on expression of somatostatin receptors (32,35).

Pulmonary carcinoid neoplasia that may cause ectopic Cushing syndrome are usually small lesions which may escape traditional assessment (2). Moreover, the onset is progressive and the clinical presentation may mimic Cushing disease (2). For small tumours like these, Gallium PET-CT scan (positron emission tomography and computed tomography) may be useful (36,37) For a clear differentiation of Cushing disease, the use of CRH receptor type 1 imaging at the level of a pituitary tumour using Gallium-68 PET-CT represents an important resource in ectopic Cushing syndrome approach (38). For the same differential diagnosis, inferior petrosal sinus sampling may help to confirm the Cushing disease (39).

Therapy options

Therapy options depend of clinical presentation severity including co-morbidities, ACTH excess – related tumour identification, presence of local and distant metastasis (40). Ideally the neoplasia complete removal and restauration of normal glucocorticoid axes function is seek (1,41). A part from medical approach of metabolic and cardiovascular complications, the ideal therapy is the ACTH secreting tumour removal (42). If the tumour is not removable or identified, the control of cortisol excess is still needed and this may be done through a medical and surgical approach (43,44). Steroidogenesis inhibitors like metyrapone are used for a limited period of time and a large area of side effects is expected (44). Postoperative bilateral adrenalectomy causes lifelong primary chronic adrenal insufficiency requiring permanent substitution but the clinical and paraclinical aspects of Cushing syndrome are mostly remitted (45,46). The surgical approach is preferably to be done laparoscopic during a one- time procedure (47,48). In Figure 2 we introduce the postoperative aspect on a patient with ectopic Cushing syndrome.



FIGURE 2. Postoperative aspect on a patient with ectopic Cushing syndrome

Current limits of the topic

The approach of ectopic ACTH syndrome is complex and it still represents a matter of discussion. The current twists of the topic may involve the difficulty of differentiation from Cushing disease in some cases requiring bilateral inferior petrosal sinus sampling which is not actually feasible in many centers (49). Also, cabergoline has been suggested as an adjuvant in occult cases (50). ACTH antagonists are still not applicable in every day practice (51).

CONCLUSIONS

Heterogeneous field of ectopic Cushing syndrome still has several twists in diagnosis and therapy due to various tumours that may cause it and different scenarios of evolution. Nevertheless adequate control of cortisol excess is needed even in case with unidentified primary tumour.

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