MANAGEMENT OF ENDOCRINE DISEASE

Cushing's syndrome due to ectopic ACTH secretion: an expert operational opinion

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Abstract

Ectopic ACTH syndrome (EAS) is rare but is frequently a severe condition because of the intensity of the hypercortisolism that may be dissociated from the tumoral condition. EAS should often be considered as an endocrine emergency requiring an emergency response both in terms of diagnostic procedures and therapeutic interventions. Patient management is complex and necessitates dual skills, in the diagnosis and treatment of CS and in the specific management of neuroendocrine tumors (NET). Therefore, initial management should be performed ideally by experienced endocrinology teams in collaboration with specialized hormonal laboratory, modern imaging platforms and intensive care units. Diagnostic procedures vary according to the endocrine and tumoral contexts but should be reduced to a minimum in intense hypercortisolism. Preventive and curative treatments of cortisol-induced comorbidities, non-specific management of hypercortisolism and etiological treatments should be considered simultaneously. Therapeutic strategies vary according to (1.) the intensity of hypercortisolism, the general condition of the patient and associated comorbidities and (2.) the tumoral status, ranging from resectable ACTH secreting tumors to non-resectable metastatic endocrine tumors or occult tumors. The ideal treatment is complete excision of the ACTH-secreting tumor that can be performed rapidly or after preoperative preparation using cortisol-lowering drugs. When this is not possible, the therapeutic strategy should be discussed by a multidisciplinary experienced team in a personalized perspective and include variable combinations of pharmacological agents, bilateral adrenalectomy and non-specific tumoral interventions. Here we discuss the diagnosis and therapeutic strategies including the modern, currently available tools and emphasize on the operational effectiveness of care.

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Invited Author's profile

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Introduction

Cushing's syndrome (CS) due to ectopic ACTH secretion (EAS), also called paraneoplastic Cushing's syndrome, is an infrequent form of ACTH-dependent Cushing's syndrome (1, 3) that is usually associated with intense hypercortisolism. EAS results from unregulated ACTH expression and secretion by neuroendocrine tumors (NETs) of various locations and various degrees of histological differentiation and aggressiveness which usually cause massive cortisol secretion by the adrenal cortex (4, 5, 6, 7, 8, 9, 10, 11, 12, 13). Some ectopic ACTH-secreting tumors (EAT), for example, localized, indolent and well-differentiated typical bronchial (previously called 'carcinoid') tumors, carry an excellent tumor prognosis, in which case the main threat is intense hypercortisolism which is responsible for life-threatening comorbidities. At the other end of the spectrum from EAT are neuroendocrine carcinomas (NEC), in which an additional prognostic factor is the aggressiveness of the tumor and its locoregional or distant spread (14). Obviously, these situations require different diagnostic and therapeutic approaches, adapted to the prognosis in order to anticipate and prevent complications and death. In most cases, however, a rapid response is specifically required owing to the intensity of hypercortisolism. Due to the rarity and heterogeneity of the disease, there are no established evidence-based recommendations. We propose herein an expert opinion review of the modes of presentation, current diagnostic procedures and the different treatments in EAS with the ultimate ambition to propose up-to-date operational and pragmatic diagnostic and therapeutic procedures for the clinician.

Epidemiology

The true incidence and prevalence of EAS are very difficult to establish. It is unlikely that all cases are recorded, and most epidemiological data come from tertiary referral centers in which patient recruitment is biased (4, 5, 6, 7, 8, 9, 10, 11, 12, 13). Despite these limitations, the literature suggests that EAS represents between 9% and 18% of cases of ACTH-dependent Cushing's syndrome (1, 3), which in turn represents between 80% and 85% of all cases of endogenous Cushing's syndrome (1, 3). The vast majority of EAS cases are sporadic and occur in adulthood (4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14). Pediatric and adolescent cases remain exceptional but have been increasingly reported in recent years (15, 16).

Some exceptional inherited familial cases are described, with ACTH-secreting thymic NETs, in the context of multiple endocrine neoplasia type 1 (MEN 1) (17, 18, 19, 20). However, EAS is rare in MEN1 patients, and most cases of ACTH-dependent CS in this setting are associated with pituitary ACTH secretion (17). Similarly, the prevalence of EAS is very low in familial MEN 2 and in medullary thyroid cancer (MTC) (21, 22, 23). Exceptional cases of EAS related to pancreatic NETs have also been reported in patients with the Von Hippel–Lindau syndrome (24, 25, 26).

Location, nature and differentiation status of ACTH-secreting neuroendocrine tumors

EAT have a variety of locations, histological types and prognoses (4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14). Their respective frequencies vary among series possibly because of recruitment bias. The period of recruitment of patients also has an influence on this variability: in the 1970s, EAT were mainly represented by small-cell lung carcinomas (SMLC) (4, 5, 6, 7, 8, 9, 10, 11, 14). However, due to changes in referral patterns (e.g. cancer vs endocrinology departments), improvements in diagnostic tools and improved knowledge and awareness in the field of NETs, the spectrum of EAS seen in recruited endocrine patients has broadened in the past 30 years (4, 5, 6, 7, 8, 9, 10, 11, 12, 13). Overall EATs derive mainly (but not exclusively) from the foregut (larynx, thymus, lungs, stomach, duodenum and pancreas) (27). By definition, EATs express and secrete bioactive mature ACTH. However, the quality of the processing of POMC is variable and correlates with the degree of differentiation of the EAT (28, 29). Well-differentiated NETs may secrete mature and bioactive 1–39 ACTH and other peptides, similar to the processing that occurs in pituitary corticotrophs. Conversely, less-differentiated NETs and neuroendocrine carcinomas (NEC) may secrete variable amounts of mature ACTH with other POMC-derived peptides or unprocessed POMC reflecting altered post-translational processing of POMC as compared to pituitary corticotrophs (29, 30). In very rare cases, secretion of CRH and co-secretion of CRH and ACTH has also been described in the subsequent section. The main anatomical sites of EAS-causing NETs are listed in Table 1.

(A) NETs in the cervical spine region

EATs from the cervical region are mainly represented by medullary thyroid cancer (MTC), although fewer than a hundred cases have been reported in the literature,

Review	J Young and others	Ectopic ACTH syndrome	182:4	R31
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Table 1 Causes of Cushing's syndrome secondary to ectopic ACTH secreting tumors in previously published case series.

Tumor type	Liddle 1969 (2)	Aniszewski <i>et al.</i> (4)	Ilias <i>et al.</i> (6)	Isodori <i>et al.</i> (7)	Salgado <i>et al.</i> (8)	Ejaz <i>et al.</i> (10)
Number of patients	104	106	90	40	25	23
Bronchial carcinoid	5%	24.5%	38.9%	30%	40%	21%
SCLC	50%	11.3%	3.3%	17.5%	0%	21%
Gut NET	14%	17%	8.9%	12.5%	12%	14%
MTC	2%	8.5%	2.2%	7.5%	0%	11.6%
Thymic carcinoid	11%	4.7%	5.6%	5%	16%	6.9%
Pheochromocytoma/ paraganglioma	4%	2.8%	5.6%	2.5%	16%	0%
Occult	6.7%	16%	18.9%	12.5%	8%	9.3%
Others	9%	17%	13.50%	Z96	1%	1.60%

Gut-NET: gut neuroendocrine tumors; MTC: medullary thyroid carcinoma; SCLC: small-cell lung carcinoma.

accounting for less than 1% of EATs (22, 31). In some cases, EAS onset occurs several years after initial diagnosis of MCT. Almost all cases of EAS due to MCTs are associated with aggressive NETs with cervical lymphadenopathies that are readily detected by classic imaging methods and increased serum calcitonin (CT) levels (23, 31, 32). Absence of detectable thyroid tumor in the presence of increased plasma CT concentrations indicate a gut ACTH and CT co-secreting tumor (33, 34).

Rare thyroid EATs, distinct from MCTs, have been reported as intrathyroid metastases from cervical or lung NETs or cervical paragangliomas and chemodectomas (33, 35).

(B) Thoracic neuroendocrine tumors and carcinomas

Most primary endocrine tumors responsible for EAS are located in the chest (36, 37, 38, 39, 40) (Table 1). Among all ACTH-secreting thoracic tumors, the most common, in a modern endocrine patient recruitment, are well-differentiated NETs located in the bronchi (formerly called 'carcinoids') and these account for 20% to 40% of all cases of EAS in recent series (4, 5, 6, 7, 8, 9, 10, 11, 12, 13). Despite being localized and slowly growing, well-differentiated NETs may be responsible for local node metastasis which may or may not be visible on imaging studies. They can recur, especially after initial resection without systematic lymphadenectomy (4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 31, 33, 34, 35). Well-differentiated bronchial NETs account for the vast majority of 'occult' (radiologically invisible) forms, but their apparent frequency may decline as imaging techniques improve (see subsequent section).

'Tumorlets' or diffuse idiopathic pulmonary neuroendocrine cell hyperplasia, a precursor to carcinoid tumors and tumorlets, represent a particular bronchial NET type, being small (<5 mm) multiple well-differentiated NETs (41, 42, 43, 44, 45, 46). These are mainly located

in the chest and can mimic lung metastases. This rare diagnosis should be raised in a patient with obstructive lung disease and bronchiectasis on imaging studies (36, 37, 38, 39, 40, 41).

Thymic NETs are also an important cause of EAS due to thoracic tumors accounting for 5% to 10% of EATs, depending on the series (47, 48, 49, 50, 51). They are usually aggressive, poorly differentiated NEC, frequently accompanied by locoregional invasion and metastases (42, 43, 44, 45, 46). More rarely, EAS can be due to a thoracomedial paraganglioma (52, 53, 54).

Small-cell or large-cell bronchial NEC (4, 5, 6, 7, 8, 9, 10, 14) are usually aggressive EATs. These may produce massive ACTH secretion which often causes excessive skin pigmentation. The short-term prognosis in this case is bleak, because of rapid tumor spread associated with intense hypercortisolism (4, 5, 6, 7, 8, 9, 10, 14).

(C) Abdominal and retroperitoneal NETs

Pancreatic NETs account for fewer than 15% of all cases of EAS (55). Most of these are overt tumors that are readily visible on imaging studies. Pancreatic NETs are sometimes amenable to surgical resection, but they are often accompanied by node involvement and liver metastases (50).

Pheochromocytoma/paraganglioma: These catecholamine-secreting endocrine tumors are a rare cause of EAS, and are responsible for less than 5% of all reported EAS cases (56, 57, 58, 59). They are mostly unilateral, localized and retroperitoneal (18, 51, 52, 53, 54). In rare cases, EAS can be due to a bilateral pheochromocytoma associated with MEN2A (18, 51, 52, 53, 54).

ACTH-secreting pheochromocytomas and paragangliomas generally also secrete catecholamines and metanephrines. From a diagnostic perspective, it is therefore crucial to assay methoxyamines, in addition to urinary cortisol, in EAS associated with adrenal/

Review	J Young and others	Ectopic ACTH syndrome	182:4	R32
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abdominal mass especially in cases of severe hypertension. Pheochromocytomas responsible for EAS also raise specific issues for management of blood pressure (21, 54, 55, 56, 57). The potentiation of catecholamines-induced hypertension by cortisol-induced stimulation of the phenol-etholamine-N-methyl-transferase enzyme, which is responsible for the transformation of noradrenaline to adrenaline, has been described in the rare instance of catecholamine and ACTH co-secreting pheochromocytomas (60).

(D) Very rare locations

Exceptional causes of EAS include a myriad of tumors with neuroendocrine differentiation of almost all organs (61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79). There are reports of EAS secondary to small gut NETs (72, 75), breast (61, 62), ovarian (67) and prostate cancers (68, 69), uterine tumors (76, 77), parotid tumors (65, 66), olfactory bulb neuroblastomas (63, 78), sarcomas, pleural mesothelioma (70) and peritoneal mesothelioma (74). Similarly, there are exceptional reports of abdominal NETs located in the ileum, the rest of the mesentery (64) or in the liver (78). Another exceptional location reported is a tumor of the sphenoid sinus near the pituitary, raising the problem of differential diagnosis with Cushing's disease due to an ectopic pituitary corticotroph adenoma (73, 79).

(E) Ectopic CRH secretion

These tumors are very rare, with only around two dozen reported cases (16, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93).

Most cases involve concomitant secretion of CRH and ACTH, although rarer forms of exclusive CRH secretion have been described (80). These NETs can be pancreatic (83, 92), thymic (84, 89) or bronchial, pheochromocytomas (93) or MTC (87), but may also arise in other locations (16, 18, 40). They occur in both adults and children/adolescents (16, 90). Clinically, ectopic CRH-secreting NETs resemble typical EAS, and the diagnosis is usually based on immunohistochemistry, which shows CRH expression in the tumor. It should, however, be noted that these NETs can sometimes create a formidable diagnostic pitfall. Indeed, due to stimulation of corticotroph pituitary cells by tumor-derived CRH, an ACTH gradient may be found on bilateral inferior petrosal sinus sampling (BIPSS), mimicking Cushing's disease (16, 83, 93, 94).

Clinical presentation

The clinical presentation of EAS depends on the characteristics of the tumor (differentiation and spread),

age of the patient and the intensity and duration of hypercortisolism that are responsible for various comorbidities and complications (13, 95, 96). It should be emphasized that the clinical phenotype of EAS is highly variable and that Cushing's disease is sometimes associated with intense hypercortisolism and severe clinical phenotype. Aside from relatively rare forms of florid CS that resemble typical Cushing's disease, the progression of Cushing's syndrome is usually accelerated, and some patients with a very rapid onset of intense hypercortisolism may present with predominantly catabolic symptoms (purple striae, bedsores, osteoporosis, profound hypokalemia and severe hypertension with oedema) with less apparent facial rounding, absence of weight gain or even loss of weight (95, 96). Frank melanoderma at presentation is rare (<20% of patients with EAS) due to the rapidity of the onset of the disease and is observed only when large secretion of POMC-derived peptides is sustained (95, 96). Difficulty and delay in diagnosis can occur when patients are hospitalized in non-endocrine units for widespread tumoral disease or for predominant complications (see subsequent section). In these settings, the physicians' attention is often captured either by these complications or by the neoplastic presentation and the signs of Cushing's syndrome are overlooked, leading to a delay or misdiagnosis. In such instances, the presence of hypokalemia is a clue that should evoke the diagnosis.

Complications of severe hypercortisolism

Although the definition of intense hypercortisolism is debatable and arbitrary, complications are very common and can arise unexpectedly throughout the course of the disease when UFC is increased 5-fold above the upper limit of normal. Severe Cushing's syndrome significantly worsens the prognosis and can be fatal, even in the absence of tumor progression. Therefore, severe EAS should be considered as an endocrine emergency requiring an 'emergency response'. This includes a rapid and systematic evaluation of comorbidities using a check-list (Fig. 1A and B) as soon as the diagnosis is evoked. At the end of this rapid evaluation, the endocrinologist should decide whether patients should be directed toward the ICU. Preventive and curative treatments of comorbidities should be started immediately (see subsequent section). Lastly, the endocrinologist must rapidly assess, based on the severity of the clinical presentation, the time to initiation of specific treatments including cortisol-lowering

Figure 1

(A) General algorithm of the emergency attitude in the context of intense hypercortisolism responsible for severe Cushing's syndrome. (B) Symptomatic evaluation and treatment of comorbidities induced by cortisol excess. (C) Proposed algorithm for the etiological evaluation and treatment of intense hypercortisolism.

Review	J Young and others	Ectopic ACTH syndrome	182:4	R34
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therapy (Fig. 1C). Therefore, and contrary to the usual attitude in the evaluation of a patient with other etiologies of Cushing's syndrome, the time devoted to biochemical etiological investigations might be dramatically shortened (13, 97).

(A) Hypokalemia

In historical papers, authors have suggested that hypokalemia could be a consequence of increased adrenal DOC secretion stimulated by excessive ACTH levels. However, serum aldosterone and DOC levels are found to be low in patients with severe hypercortisolism when measured with specific methods such as liquid chromatography-mass spectrometry (98, 99). The degree of hypokalemia is closely related to the severity of hypercortisolism and, whatever its etiology and although frequent (approximately seen in 70% of cases), is not specific to EAS (13, 95, 96, 97, 98, 99). Hypokalemia is due to urinary losses induced by the mineralocorticoid effect of cortisol since, in intense hypercortisolism, the renal enzyme system that inactivates cortisol (11 β -hydroxysteroid dehydrogenase) is saturated by excess substrate (99). Cortisol therefore exerts its mineralocorticoid effect on the convoluted/collecting distal tubules, creating a state of apparent mineralocorticoid excess with suppression of renin and aldosterone secretion (98, 99). Thus, from a pathophysiological standpoint, the most effective management of hypokalemia is to effectively treat the hypercortisolism itself (97, 98, 99), combined with an anti-mineralocorticoid therapy and potassium supplementation (see subsequent section). These cases of severe hypokalemia can lead to cardiac arrhythmias, ranging from T wave inversion to fatal 'torsade de pointes'.

(B) Hyperglycemia and diabetes

Hyperglycemia is also a frequent acute complication of EAS (95, 96), sometimes leading to ketoacidosis. Hyperglycemia is due to cortisol-induced insulin resistance, increased hepatic glucose production secondary to runaway gluconeogenesis and impaired insulin secretion (100, 101). Increased blood glucose may also increase the risk of infections. Depending on the severity of hyperglycemia, various medications can be used, but continuous insulin infusion associated with frequent monitoring of blood glucose is often necessary in acute situations. It should be emphasized that the most effective treatment for hyperglycemia in this setting is very rapid correction of the hypercortisolism and that its improvement is an 'intermediate' marker of the effectiveness in the control of cortisol secretion (see subsequent section) (13, 97, 100).

(C) Cardiovascular complications

Cardiovascular complications are common in patients with Cushing's syndrome, regardless of its etiology, but they are more often acute in patients with EAS (102, 103, 104, 105).

Hypertension is a common complication of EAS, affecting more than 80% of patients in some series (4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 104). Malignant or accelerated hypertension, the most severe form of hypertension (106) can be a complication of intense hypercortisolism (95, 96). Multiple mechanisms are involved, including fluid retention secondary to the mineralocorticoid effect of cortisol (99, 102) and a direct cardiac effect of cortisol via mineralocorticoid receptors (107). Hypertension can also contribute in synergy with cortisol-induced cardiomyopathy to the left ventricular failure (104, 105). In addition, hypertension, combined with a prothrombotic state, can lead to myocardial infarction, which is more common and dangerous in patients with intense hypercortisolism (108, 109, 110). Stroke has also been described in EAS patients (110).

Cushing's syndrome induces a prothrombotic state that is aggravated by altered fibrinolysis and is therefore a major risk factor for thromboembolic disease (109, 110, 111, 112). The risk is even higher in severe Cushing's syndrome as the patient is frequently bedridden because of muscle atrophy (4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14). Although systematic prospective studies are lacking, leading to underestimation, pulmonary thrombosis has been described in up to 14% of patients with EAS (10, 13, 95, 96, 98, 112). Systematic evaluation for thrombophlebitis and pulmonary thrombosis should be performed and preventive anticoagulation treatment is essential in intense Cushing's syndrome (13, 97, 112).

(D) Acute respiratory distress

Without rapid and effective treatment, acute respiratory distress can lead to death (113, 114, 115). The mechanisms of respiratory failure are multiple and sometimes entangled: they include undiagnosed pulmonary embolism (that must be actively looked for), acute pulmonary edema, pneumonia of any type (95, 96, 113, 115), a restrictive syndrome secondary to costal and/or vertebral fractures and diaphragmatic myopathy (see subsequent section) (114). Ventilatory capacity in patients with severe EAS must therefore be evaluated daily to detect dyspnea.

(E) Infectious complications

These are particularly frequent during intense hypercortisolism of any etiology (13, 96, 97, 113, 116,

117, 118, 119). The definition of intense hypercortisolism is debated. They result from the immunosuppression caused by the massive increase in cortisol, and the risk is closely linked to cortisol concentrations (115, 116). Cushing's syndrome associated infections have four main characteristics: (1.) These infections include all kinds of opportunistic infections due to bacteria and related organisms as viruses and fungi, including *Pneumocystis carinii* or *jirovecii* (115, 116, 117, 118, 119). All organs may be affected (skin, hollow organs and brain), but the lungs are the site of the most frequent and severe infections (116); (2.) the classical symptoms of infection such as fever and increased levels of C-Reactive Protein may be lacking (115, 116, 117, 118, 119); (3.) infections will often result in delay of invasive diagnostic procedures such as inferior petrosal sinus sampling (IPSS) and any surgery such as excision of the ACTH-secreting tumor or bilateral adrenalectomy (BLA); (4.) their occurrence may be favored by diabetes mellitus and also by antineoplastic chemotherapy that should be ideally deferred until hypercortisolism is controlled and (5.) *Pneumocystis jirovecii* pneumonia can emerge rapidly once hypercortisolism is brought under control (115, 116, 117, 118, 119). Prophylaxis of *Pneumocystis jirovecii* pneumonia with sulfamethoxazole-trimethoprim is recommended for all patients with intense hypercortisolism (120).

In a recent survey issued from the European Register on Cushing's Syndrome (ERCUSYN) registry, infections were the most common cause of death during the 3 months following diagnosis, emphasizing the need for clinical vigilance at that time, especially in patients with intense hypercortisolism and diabetes mellitus (119).

In the presence of an unexplained septic state, physicians should also be aware of cortisol-induced gut perforation responsible for peritonitis that can occur without 'contracture' and prescribe abdominal imaging (121, 122, 123).

(F) Muscular complications, wasting, and complications of decubitus

Cortisolic myopathy may be severe during intense hypercortisolism; it is particularly frequent in EAS (95, 96). It can affect all muscles, including the heart (105, 113). It is particularly noteworthy in the quadriceps, preventing the patient from standing up unassisted and thus confining the patient to bed. Prolonged recumbence, by damaging the skin barrier, can quickly lead to pressure ulcers which, because of immunosuppression and diabetes, can easily become infected (100). Therefore, prevention and daily evaluation of cutaneous status is of importance.

(G) Bone fractures

Osteoporosis, bone fragility and fractures are well-known complications of Cushing's syndrome (124, 125, 126, 127, 128). Data obtained from studies with exogenous corticoids have shown that the prevalence of fractures is correlated with their dosage. Although poorly studied in EAS, osteoporosis resulting from altered bone quality appears to be more frequent than in florid Cushing's Syndrome (95, 96). Fractures can affect the entire skeleton, with a high risk of vertebral fractures that will result in pain and the patient being bedridden (118, 119, 120, 121). Aseptic necrosis of the femoral head is a painful complication that reduces mobility (127) and again confines the patient to bed. These fractures can affect even a very young patient (127). We therefore recommend performing systematic vertebral X-rays in intense Cushing's Syndrome.

(H) Psychiatric complications

Psychiatric complications can be observed in all forms of Cushing's syndrome (103, 119, 129, 130, 131) but seem to correlate with the intensity of hypercortisolism. Their prevalence is particularly high in patients with EAS (up to 50%, or even higher) (95, 96, 131). Various symptoms including depressive symptoms are very frequent in Cushing's syndrome, but intense hypercortisolism may also result in steroid psychosis. The clinical picture often associates agitation or paranoid symptoms, with or without delusional episodes (129, 130, 131, 132, 133). True melancholic syndromes, refractory to standard therapy, may also occur. Similarly to other complications, the most effective treatment is rapid control of hypercortisolism (125, 126, 127). Psychiatric complications can also prevent the patient's adherence to oral therapy and render parenteral administration of steroidogenic inhibitors necessary.

Diagnostic approach

General considerations

The diagnostic workup must pursue four objectives simultaneously (Fig. 1C): (1.) to confirm ACTH-dependent Cushing's syndrome and obtain evidence favoring EAS and not Cushing's disease; (2.) to identify and locate the NET responsible for ACTH secretion and to evaluate tumor extension; (3.) to determine/assess histoprognosis factors in the presence of large and/or metastatic tumours. The endocrinologist should first be aware that the tumoral aggressiveness and intensity of cortisol secretion may be dissociated. This is illustrated by occult EAT that are invisible despite intense hypercortisolism emphasizing

Review	J Young and others	Ectopic ACTH syndrome	182:4	R36
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the specific deleterious role of hormonal overproduction in this presentation. Elsewhere, it must be noted that well-differentiated NET can exhibit a slow progression despite being evidently metastatic at the time of presentation (132). It is therefore mandatory to obtain tumoral tissue, by biopsy or surgery, to determine the differentiation status and proliferation index in this situation and (4.) to search very actively for the previously mentioned complications of severe hypercortisolism.

(A) Diagnosis of Cushing's syndrome

In patients with EAS, positive diagnosis of ACTH-dependent Cushing's syndrome usually poses no major difficulties given the severity of hypercortisolism (4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14). It is based on a 24-h urinary free cortisol assay and/or measurement of cortisol and ACTH concentrations in several samples drawn during the day and at midnight. Aside from exceptional cases of cyclic EAS (12, 133), urinary free cortisol, serum cortisol and ACTH concentrations are usually dramatically increased (13, 96), and are associated with loss of circadian rhythm (4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14). However, it should be mentioned that, in a life-threatening condition justifying an urgent initiation of specific treatments of hypercortisolism, the biochemical investigation should be reduced to a minimal evaluation including only one or two blood samples for cortisol and ACTH measurements.

(B) Etiological diagnosis

(1) General considerations

Algorithms used for the differentiation between EAS and CD are usually based on results of both imaging studies and biochemical tests (1, 13). Classically, imaging studies are primarily directed at the pituitary gland in view of the prevalence of Cushing's disease (1, 52), while several biochemical tests, such as the CRH and high-dose dexamethasone test, are carried out to show differences in molecular equipment of EATs compared to pituitary corticotroph adenomas (134, 135, 136). However, pituitary MRI is associated with numerous false negative and positive results, and well-differentiated NETs may share molecular similarities with corticotrophic pituitary adenomas, explaining overlapping responses to biochemical tests (see subsequent section). Accordingly, published algorithms recommend performing BIPSS when this first set of imaging and biological investigations prove inconclusive. When the results of BIPSS suggest an ectopic source of ACTH, complementary imaging studies looking for an ectopic ACTH-secreting tumor are then performed (137). Although we agree with the effectiveness

of this ideal and time-consuming exploratory algorithm in most cases of ACTH-dependent Cushing's syndrome, it may not be compatible with the urgency to treat intense hypercortisolism that itself imposes a reduction in biochemical investigations. Similarly, in our opinion, BIPSS, an invasive procedure, may not be compatible with both the urgency to treat and the general condition of the patient. Obviously, dynamic biochemical tests and MRI might be useless in the presence of evident EAT at CT scanning. Thus, in our opinion, it may be more appropriate to rapidly perform a whole-body thin-slice CT-scan, a radiological examination that can be quickly done, in patients with intense ACTH-dependent hypercortisolism, as the probability of EAS is dramatically increased (13, 97) and postpones time-consuming biological tests (Fig. 1C). Finally, and from a practical perspective, the main priority in a context of severe EAS is to ascertain the absence of an obvious and aggressive tumor that may require urgent surgical excision and/or antineoplastic medical treatment (120). As recommended by the Endocrine Society (120), physicians should prioritize symptomatic over etiological treatments. In other words, treatment of hypercortisolism must be engaged in devastating ACTH-dependent Cushing's syndrome even if the primary tumor responsible (pituitary adenoma or ectopic) is invisible at presentation but may be later identified during patient follow-up when the patient's condition has improved (Fig. 2).

(2) First-line imaging procedures

The detection of a pituitary lesion compatible with a microadenoma and ≥ 5 –6 mm at MRI is very suggestive of Cushing's disease (138). However, up to 40% of patients with Cushing's disease have occult corticotroph microadenomas that are not visible on properly conducted pituitary MRI in experienced centers (139, 140). The choice of the MRI technique and the experience of the radiologist are both key factors (141, 142, 143), and corticotroph microadenomas are best detected by MRI in an expert center. The additional diagnostic value of 3.0 T field strength over 1.5 T MRI has not been firmly established to date (144). New technologies such as $c^{11}C$ -methionine PET have been proposed to visualize occult pituitary microadenomas, but these are still part of clinical research (145) and are not compatible in this context of emergency. Additionally, it should be mentioned that small pituitary images, mimicking a pituitary adenoma, can be observed in control subjects and in patients with EAS (133, 140).

Spiral thin-slice CT of the cervical-thoracic-abdominal and pelvic regions is essential (146, 147), together with pituitary MRI (148), in severe ACTH-dependent Cushing's

Figure 2

CT-scan follow-up during 2 years of an ACTH-secreting bronchial well-differentiated neuroendocrine tumor that was occult at initial evaluation.

syndrome. CT must be performed quickly because these results will orient subsequent etiological explorations and patient management, as visualization of a large cerebral, thoracic or abdominal tumor or distant metastases (13, 146, 149, 150) is suggestive of EAS.

The performance of CT depends on the type and localisation of the EAT. CT can readily detect most thymic tumors and small-cell pulmonary neuroendocrine carcinomas (7, 146, 150) showing their extension (151). Abdominal CT also detects most pancreatic NETs (152, 153) and rare ACTH-secreting pheochromocytomas and paragangliomas (11). ACTH-secreting medullary thyroid cancers are readily detectable by neck or thyroid imaging combined with plasma calcitonin measurements (22). One of the main diagnostic issues is bronchial carcinoids which represent one of the main causes of EAS (Table 1). Indeed these richly vascularized tumors are notoriously difficult to detect due to their small size and their location being close to pulmonary vessels (150). However, the frequency of 'occult' EAS has declined over time with the improvement of CT technology, the use of thin-slice CT with early and late arterial phases (154), and increasing awareness among radiologists. Consequently, the frequency of occult EAS appears to have decreased by 10–30% in recent years (146, 149, 150). Elsewhere, a metanalysis published in 2015 suggests that, overall, approximatively 53% of EAT NET will be clearly revealed by CT, making this imaging method a valuable tool for diagnosis and patient management (140, 144). Apart from improvements in CT technology, we would like to emphasize the importance of a dedicated radiologist with considerable experience and involvement in the field of EAS and NETs. When imaging shows no culprit NET, special attention should then be paid to sites such as the bronchi (149), small intestine (152, 153) and other much rarer sites involved in ectopic ACTH secretion (61, 79). Before prescribing additional imaging procedures, we strongly suggest a second careful examination of the thoracic CT-scan, which is the main source of occult EATs, ideally by several radiologists, to limit the risk of false negatives. Elsewhere, false positives on CT have been described in 3.6% of cases (149, 155), a finding that emphasizes the importance of using an appropriate CT protocol and the experience of the radiologist to limit the frequency of thoracic lures. Additionally, it should be emphasized that imaging of the thorax in the search for an EAT may be particularly complex in patients with a pulmonary embolism or infection (see previous section). In any case, this data demonstrates that the sensitivity and specificity of CT scans is suboptimal and reinforces the need for other imaging tools.

Review	J Young and others	Ectopic ACTH syndrome	182:4	R38
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(3) Biochemical investigations

Among biochemical diagnostic tools, serum assays of POMC (29), and its peptide derivatives such as lipotropin (LPH) (156), have been developed as markers of EAT, since EAT may inadequately process POMC. These assays, which are often inaccessible locally, only point to EAS if the concentrations are markedly increased, which is usually observed in patients with aggressive tumors that are also easy to diagnose by morphological examinations (29, 156).

Dynamic endocrine tests are only interpretable in patients with active hypercortisolism, to be able to confirm suppression of pituitary corticotroph activity, and must therefore be carried out before the initiation of specific treatments (134, 135, 136). As mentioned previously, no dynamic test has perfect sensitivity and specificity, and thus the possibility of false positives and false negatives must be kept in mind and dogmatic attitude should be avoided (97, 136, 157). Additional caution is necessary in the analysis of the cut-offs mentioned in the literature, since these depend on the ACTH and cortisol assays used, the limited number of EAS cases in the series from which the analysis of the performance of tests has been established and the degree of differentiation of EATs (see subsequent section).

The rationale of the CRH test is that corticotroph pituitary adenomas strongly express CRH receptors and associated molecules of the cell signaling pathway downstream, and therefore respond to this peptide by releasing excessive amounts of ACTH, as opposed to EATs (135, 136, 158, 159, 160).

Various criteria of response (cortisol vs ACTH) and thresholds have been proposed in the literature resulting in sensitivities ranging from 59 to 93% and specificities ranging from 70 to 100%, respectively (135, 136, 158, 159, 160).

In clinical practice, the more intense the response to CRH, the less likely is the diagnosis of EAT (161). However, definitive positive response to CRH test have been described in well-differentiated NETs, a finding that may be due to the expression of CRH receptors and downstream signaling in these tumors (136, 162, 163).

In our opinion, the excellent tolerance and short duration of the CRH test, associated with its good diagnostic performance, make it compatible with use in severe CS.

Desmopressin is a vasopressin analogue, selective for the type 2 vasopressin receptor (V2R) that is absent in normal pituitary corticotrophs but may be expressed in corticotroph adenomas (164). Consequently, an aberrant increase in plasma ACTH and cortisol can be observed after injection of desmopressin in patients with

CD (165). Conversely, an absence of both ACTH and cortisol response is expected in patients with EAS. The duration and tolerance of the test is compatible with its use in severe CS. However, a limited number of studies, using variable and sometimes arbitrary criteria, makes it difficult to assess its performance in distinguishing EAS from Cushing's disease (165). False negatives have been described in up to 19% of patients in the least optimistic series of patients with Cushing's disease, while the number of patients with EAS studied is too small to evaluate the specificity of the test. That said, false-positive ACTH responses in EAS have been described and (166) these may be related to tumoral expression of the V3 receptor (149). It remains to be seen whether ACTH stimulation by desmopressin, when combined with the CRH test, can help to better distinguish Cushing's disease from EAS (158, 167, 168, 169).

The rationale of high-dose dexamethasone suppression test (HDDST) is that corticotroph pituitary adenomatous cells in Cushing's disease retain partial sensitivity to glucocorticoids, whereas NETs responsible for EAS are fully resistant to exogenous glucocorticoid suppression (157). Various thresholds have been proposed in the literature, with a percentage of urinary or serum cortisol suppression varying from 50% to 90% (170, 171). However, some authors have shown an almost complete overlap between the response of EAT and corticotrophic adenomas and have insisted on the impossibility of finding a discriminating threshold, especially in the case of well-differentiated NETs (172, 172). This lack of specificity may be due to the expression of functional GR in well differentiated, often occult, NETs (157). Some authors have claimed that the diagnostic performance of the HDDST for the differentiation between Cushing's disease and EAS is not better than that of the low-dose dexamethasone (173). Others authors consider the HDDST useful in association with the CRH test (145), while in some studies the combination of both tests gave a correct diagnosis in a lower percentage of cases than the CRH test alone (166). Therefore, HDDST is controversial (136, 172) and is even considered to be outdated by some experts (157). In our opinion, the usefulness of this test is particularly questionable in the context of an intense hypercortisolism.

(4) Bilateral inferior petrosal sinus sampling (BIPSS)

BIPSS combined with CRH and/or desmopressin administration is considered the 'gold standard' for distinguishing EAS from Cushing's disease (137, 174, 175).

Review	J Young and others	Ectopic ACTH syndrome	182:4	R39
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The proposed diagnostic thresholds for EAS are a basal concentration of ACTH, in the IPS, not exceeding two times than that observed in peripheral blood and a stimulated ACTH level in the IPS not exceeding twice of that in peripheral blood (137, 174, 175). It must be stressed that false negatives (no central-to-peripheral gradient) can occur in patients with Cushing's disease (176), leading to false diagnosis of EAS. Venous angiograms and prolactin assay of the same samples may be useful for avoiding such false negatives (175, 176, 177, 178). BIPSS should be performed in a situation of active hypercortisolism, since cyclical EAS can result in false positives if BIPSS is performed in a phase of spontaneous remission. Consequently, the presence of hypercortisolism should be checked just before BIPSS. Combined pituitary stimulation with CRH and desmopressin during BIPSS has also been proposed to avoid those false negatives (179). Conversely, rare false positives have been reported in patients with EAS due to NETs that secrete CRH alone or both ACTH and CRH (83, 92, 93, 94). This is an almost unavoidable pitfall if no extra-pituitary mass is apparent (83, 92, 93, 94). Unexplained false positives have also been described (177). It is, however, important to be reminded first that IPSS should be performed in a situation of active hypercortisolism, and therefore before normalisation of cortisol levels, to ensure the prerequisite of suppression of the activity of non-adenomatous pituitary corticotrophs, and secondly that, due to variations in venous anatomy, successful catheterization is more likely when carried out by trained hands (176). A meta-analysis published in 2005 showed that IPSS had a sensitivity and specificity of about 94% (159). Safety and efficacy are adequate with experienced neuroradiologists, and the reported rate of significant adverse effects, such as venous thrombosis, cranial nerve paralysis and so on, is low (168, 169). Jugular venous sampling for ACTH measurement, a technically simpler procedure than IPSS, has also been proposed but has not gained wide acceptance due to its lower diagnostic performance (159).

In current algorithms, BIPSS is proposed as a third-line test, when pituitary MRI is negative/inconclusive or discordant with the results of dynamic endocrine tests (1, 13). According to the results of IPSS, second-line imaging investigations including whole-body thin-slice CT scanning are recommended. Although not evaluated to date, we think that, owing to the improvements in CT technology, CT-scanning should be performed prior to IPSS in inconclusive cases in order to reduce the number of patients in whom the invasive procedure of IPSS will be absolutely required. As mentioned previously,

IPSS may not be appropriate in a patient with intense hypercortisolism responsible for severe comorbidities and in bad general condition.

(5) Functional imaging

The first goal of performing functional imaging (FI) in a context of EAS is to identify an occult EAT after initial morphological examination. FI can also be useful to assess the neuroendocrine phenotype of a tumor identified at morphological examination and may contribute to the staging of a malignant tumor (170, 171). Here, we will focus mainly on the first diagnostic aspect. Analysis of the performance of imaging studies from the literature is particularly complex for several reasons, including the rarity of the EAS and the evolution of imaging technology over time. More importantly, in the specific situation of occult tumors, (1.) the type and number of first-line imaging investigations used to define this status is variable across studies (149); (2.) the definition of occult EAT varies considerably among studies and the type of imaging performed. We have also noted some confusion between occult EAT and metastatic EAT of unknown origin which is clearly a different diagnostic situation (146) and (3.) no prospective head-to-head comparison between imaging studies nor standardized follow-up protocols have been used in this rare condition. Indeed, secondary and third-line imaging studies were performed in different and random orders among studies, making it impossible to know specifically which technique led to the discovery of the EAT and preventing an accurate evaluation of their respective performances. A particular word of caution is necessary for the latest FI procedures because of the small number of cases published to date and the probable under-reporting of false-negative cases that could lead to an overestimation of their diagnostic performance.

Octreoscan

Due to the frequent expression of SSTR type 2 in NETs, scintigraphy imaging using 111-indium pentetreotide as SSTR receptor ligand (namely octreoscan) has been used over almost 3 decades to visualise EAT. However, since the beginning of its implementation, we and others have shown that, in truly occult EAT at CT, octreoscan was of limited help in detecting the tumoral source of ACTH (98, 171). In a meta-analysis published in 2015, Isidori *et al.* (146) identified 32 EATs in 50 patients reported as having covert EAS and who were explored with octreoscan, with a global sensitivity of 64%. However, sensitivity was lower for EATs localized in the abdomen and pelvis due to the

physiological tracer uptake of the liver, spleen, urinary tract, bowel and gallbladder that increases the risk of false negatives (180). Some *in vitro* studies and case reports have suggested that hypercortisolism may downregulate SSTR2 and SSTR5 expression and that cortisol-lowering treatments could help to reveal some initially occult EATs by increasing tumoral somatostatin receptor expression (181, 182). However, these observations have been challenged by others (183), and an alternative hypothesis is that the delayed identification of the tumor after hypercortisolism therapy might be merely the consequence of spontaneous growth of the tumor with time. Despite this, and in view of our current knowledge (154), repeating imaging, including functional imaging, after the initial diagnosis is recommended in occult EAS (184).

In EAT, octreoscan may also be useful to reinforce the hypothesis of the neuroendocrine nature of a tumor identified at CT (146), a situation that is of particular importance for the chest, given the high prevalence of non-endocrine incidental pulmonary nodules. Also noteworthy is the fact that false positives with octreoscan may occur in various situations such as pulmonary infections or related to physiological uptake in the uncinate process of the pancreas where the density of SSTR2 receptors is greater (185) (Fig. 3).

PET/CT using Gallium-68 labeled somatostatin receptor ligands

Gallium-68 labeled somatostatin receptor PET/CT (^{68}Ga -SSTR PET/CT) is a shared term to designate combined PET/CT imaging using various SSTR-radiolabeled ligands with variable affinities for SSTRs (186), including ^{68}Ga -DOTATATE, DOTATOC and DOTANOC. These more recently used radiolabeled ligands have, as a whole, higher affinity for the SSTR2 receptor than ^{111}I pentetreotide used in octreoscan imaging (187). In addition, published data indicates that ^{68}Ga -SSTR PET/CT offers better spatial resolution and anatomical detail than octreoscan and could therefore help to detect smaller tumors. In the general context of NETs, several studies suggest that ^{68}Ga -SSTR PET/CT is superior to octreoscan in detecting small NETs (188, 189) and staging metastatic NETs (170). In the specific context of EAS, to our knowledge only one small head-to-head study (involving only five patients with EAS) directly compared the diagnostic performances of octreoscan and ^{68}Ga -SSTR PET/CT (188) (Fig. 4). Moreover, to date there is no published study comparing the specific relative diagnostic efficiencies of ^{68}Ga -DOTATOC,

Figure 3

False-positive imaging of the chest after 1 year of follow-up in a patient with an occult ectopic ACTH-secreting tumor. CT scanning of the chest identified a left pulmonary tumor (A) that is also visible using Octreoscan (B) but invisible using ^{18}F -DOPA PET/CT (C). Cytological analysis of the tumor after biopsy revealed a sequellar granulomatous focus of a pulmonary *Pneumocystis jiroveci* infection that occurred few days after presentation.

Figure 4

Somatostatin-receptor imaging of an ACTH-secreting bronchial well-differentiated neuroendocrine tumor. The tumor is visible using PET-TDM ^{68}Ga -DOTATOC (A) but invisible using Octreoscan (TEMP-TDM ^{111}In -pentetreotide) performed at the same period (B).

^{68}Ga -DOTATATE and ^{68}Ga -DOTANOC PET/CT in EAS. A single report has suggested that ^{68}Ga -DONANOC PET/CT might be slightly more sensitive than ^{68}Ga -DOTATOC PET/CT and ^{68}Ga -DOTATATE PET/CT (183).

A recently published meta-analysis (146), suggests that the performance of ^{68}Ga – SSTR PET/CT was superior to all other imaging modalities in identifying EATs, with 100% sensitivity in covert cases, but only 23 patients and nine covert cases were analysed. A recent report, having included six new EAS cases, suggested that the sensitivity of ^{68}Ga – SSTR PET/CT for identifying ectopic ACTH-secreting lesions (including multiple metastases) was lower than previously reported, with a sensitivity of 64% as compared to 69% for CT (183). Our literature search, on the performance of ^{68}Ga – SSTR-PET/CT, identified 51 patients with possible occult and covert EAS at initial morphological imaging, assuming that the diagnosis of occult/covert EAS was based on variable imaging procedures across the studies (149, 183, 187, 188, 189, 190): ^{68}Ga – SSTR PET/CT led to the discovery of the source of EAS in 29 out of 51 patients, indicating a sensitivity of only 57%. Despite its limitations, we consider that ^{68}Ga – SSTR PET/CT may be a useful complementary tool in the difficult context of occult EAS, but evaluation of its performance deserves additional studies, including a significantly larger number of unselected EAS patients.

False-positive findings have been described particularly due to the physiological uptake by the adrenal medulla (183), the pancreatic uncinate process (191) and inflammatory lesions, emphasizing on the importance of expertise in the analysis of imaging (170, 192).

^{18}F FDG-PET/CT scan

^{18}F FDG-PET PET/CT is a powerful imaging tool for the detection and the staging of various cancers and sometimes to distinguish between benign and malignant tumors, based on the high consumption of glucose by cancer cells, which leads to an increased uptake of ^{18}F FDG. In the context of NETs, ^{18}F FDG -PET PET/CT is usually associated with a relatively active cellular proliferation rate (193) (Fig. 5). Contrary to patients with evident SCLC or widespread metastatic disease (194), in the context of occult EATs some experts recommend performing the ^{18}F FDG PET/CT scan after Octreoscan or ^{68}Ga – SSTR PET/CT (146). The claimed rationale for justification of this attitude is that occult tumors are often non-metastatic and that well-differentiated NETs are characterized by their slow growth rate, factors that theoretically could result in negative ^{18}F FDG -PET imaging (195). However, meta-analysis of Isidori *et al.* (146) reported that ^{18}F FDG PET/CT, performed in fewer than a hundred EAS patients, identified

Figure 5

Poorly differentiated ACTH-secreting metastatic rectal carcinoma. As expected in poorly differentiated neuroendocrine tumors, ^{18}F -FDG-PET demonstrates multiple metastatic foci (A) while somatostatin-receptor imaging using Octreoscan is negative (B).

the responsible NET in nearly 52% of cases. ^{18}F -FDG-PET has also been proposed for further characterizing the biological behavior of tumors detected at CT (146), since a significant FDG uptake is preferentially associated with atypical 'carcinoids' or with NETs having a worse prognosis (196). This point has not been validated to date in the context of EATs. Thus, the exact place for ^{18}F -FDG PET/CT, as compared to ^{68}Ga – SSTR PET/CT, for the detection of occult EATs is still debated even if expression of SSTR2 in NETs suggest to preferentially use ^{68}Ga – SSTR PET/CT for occult EAS. Lastly, both techniques may be equally useful for the characterization and staging of metastatic tumors.

Other functional imaging

MIBG scintigraphy and FDOPA PET are usually performed in third intention after a negative CT, octreoscan or ^{68}Ga - SSTR PET/CT and ^{18}F -FDG-PET-CT, or when the clinical context or biochemical data points toward pheochromocytoma/ paraganglioma or a specific mid-gut EAT.

In a context of EAS, MIBG (iodine 123 or 131 meta-iodobenzylguanidine) is used with CT to localise and characterize rare ACTH-secreting pheochromocytomas and paragangliomas (59, 197) that are diagnosed with serum and/or urine metoxyamine assays. MIBG scintigraphy can detect multiple tumour locations,

though its reduced sensitivity for multiple or metastatic pheochromocytomas/paragangliomas responsible for EAS has been highlighted in a recent literature review (59, 149, 197). Apart from the context of pheochromocytoma, MIBG scintigraphy has poor sensitivity in identifying other NETs (6, 149).

Finally, the number of published cases of occult EATs explored using ^{18}F -DOPA PET/CT is too low to allow accurate assessment of its diagnostic performance. A prospective study identified six among 11 overt EATs using F-DOPA PET/CT (five lung NET and one thymoma) (150), while it was not informative in three patients with occult EATs. In the meta-analysis of Isidori *et al.* (11), the sensitivity of F-DOPA PET/CT, evaluated in few patients, was 54% in overt EATs ($n=13$) and 85% in covert EATs ($n=7$). The sensitivity of F-DOPA was variable depending on the tumor site and was reported to be around 71% for lung EATs ($n=14$) and 33% for mediastinal EAT ($n=3$). Thus, ^{18}F -DOPA PET/CT could represent a third-line FI when ^{68}Ga -PET/CT and ^{18}F -FDG PET/CT are negative. As suggested recently, in metastatic NETs of unknown origin, ^{18}F -DOPA PET/CT seems to be useful for identifying small well-differentiated NETs with serotonin secretion that are located in the ileum, duodenum or pancreas (198). Thus, ^{18}F -DOPA PET/CT use could be of interest in finding a primary NET where findings in the pancreas or ileum on CT/MRI are equivocal, but this speculation remains to be demonstrated for EATs.

On the basis of the available literature and our personal experience, we propose that in the context of severe EAS, the search for an EAT should begin with good-quality whole-body thin-slice CT performed by a dedicated expert radiologist aware of the difficulty in identifying these tumors. Functional imaging such as ^{68}Ga -PET/CT or ^{18}F -FDG PET/CT should be considered in second line to detect occult tumors on CT or to reinforce the hypothesis of the neuroendocrine nature of small tumors detected by CT and also to contribute to the workup of a metastatic tumor. The respective place and order of prescription of ^{18}F -FDG PET/CT and ^{68}Ga -PET/CT in the diagnostic algorithm are debatable and vary according to the specific situation and local possibilities. Published studies point toward ^{68}Ga -PET/CT and ^{18}F -FDG-PET/CT as complementary rather than alternative techniques. Low-grade evidence suggests performing ^{68}Ga -PET/CT first in occult EAS. Thoracic and pancreatic MRI, ^{18}F -DOPA PET or, rarely, MIBG can be considered in third intention depending on the clinical context, the positivity of tumor markers, the results of CT and ^{68}Ga -PET/CT, the availability of imaging in the center and by following a multidisciplinary discussion by an expert

Review	J Young and others	Ectopic ACTH syndrome	182:4	R43
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team. Finally, in occult EAT still present after an initial comprehensive imaging check-up, repeated imaging should be performed during follow-up after 6 months and then at yearly intervals. For reasons of availability, performance and cost, thin-slice CT could be the examination of choice with specific attention being paid to the chest. This proposition could be reconsidered after the acquisition of more clinical experience with ^{68}Ga -PET/CT.

Initial management, in brief

From a therapeutic standpoint, physicians face three main scenarios: (1.) the hormonal risk predominates, since the tumor is small and localized, or occult – it is then likely to be a well-differentiated NET with an excellent prognosis, and the objective is then to control hypercortisolism, followed by surgical excision of a visible NET; (2.) the tumoral risk predominates, especially in the case of a metastatic and aggressive/progressive NEC. In this case, chemotherapy (usually with etoposide and cisplatin) must be started urgently, either coupled with medical therapy of hypercortisolism or after BLA and (3.) the hormonal risk is high and the tumoral risk is uncertain – this is the case for well- and relatively well-differentiated metastatic NETs associated with severe Cushing's syndrome. In this situation, medical control of the hypercortisolism is mandatory, associated to either further imaging evaluation at 3 months to assess the spontaneous progression of the tumour and/or rapid implementation of various antineoplastic therapies (locoregional antitumor therapy, biotherapies) (151, 199).

As emphasized, symptomatic treatments and prevention of complications should be started immediately together with diagnostic investigations.

(A) Non-specific treatment: one size fits all

It should be emphasized that the best preventive treatment of cortisol-induced comorbidities is effective treatment of hypercortisolism that results in rapid improvement of hypertension, hypokalemia and hyperglycemia. While waiting for control of hypercortisolism, preventive and curative treatment of comorbidities should be started immediately after the systematic rapid assessment of comorbidities (Fig. 1A, B and C). Elsewhere it should be emphasized that the follow-up of some comorbidities can serve as efficient intermediate markers of hypercortisolism to guide the titration of pharmacological treatments of hypercortisolism. Indeed, monitoring of plasma potassium, glycemia and blood pressure can provide a

quicker indication of the efficiency of these treatments compared to the results of biochemical analysis of plasma or urinary cortisol that may take several days obtain.

Hypokalemia is very common (13, 97) and, depending on its severity, is treated with oral potassium or parenteral administration via a syringe pump. Because of the mechanism underlying this hypokalemia (apparent mineralocorticoid excess (99)), spironolactone can be highly effective, provided it is used at a sufficient dose (100–300 mg/d). Indeed, in the absence of impaired renal function or concomitant use of other potassium-sparing drugs, the risk of hyperkalemia induced by anti-mineralocorticoid drugs is low. Spironolactone and potassium requirements may decline rapidly on the introduction of fast-acting cortisol-lowering drugs, and the close monitoring of serum potassium is necessary to avoid hyperkalemia.

Physicians should be aware that treatment of severe Cushing's syndrome with the anti-glucocorticoid drug mifepristone (see subsequent section), which is rarely used in EAS, may aggravate pre-existing hypokalemia (200) due to the decreased expression of $11\beta\text{-HSD2}$, which protects the mineralocorticoid receptor (99).

Several drugs may be used to treat hyperglycemia, but continuous insulin therapy via an IV or SC pump is often necessary and very useful in this context, because of its flexibility for dosage titration and avoiding the occurrence of hypoglycemia during effective treatment of hypercortisolism (100, 101). Given the very high risk of venous thromboembolism (109), preventive heparin anticoagulation therapy must be systematically prescribed, keeping in mind that a number of patients will already have pulmonary thromboembolism at presentation and thus require therapeutic heparin anticoagulation treatment. Arterial hypertension should also be treated first using easy-to-use and well-tolerated drugs, such as calcium channel blockers associated, if necessary, with permanent continuous monitoring of blood pressure. Combination treatment with spironolactone significantly improves the blood pressure profile (201). For acute pulmonary edema, a loop diuretic, such as furosemide, often yields a significant improvement. Background therapy to prevent recurrence should be discussed with the relevant specialists, bearing in mind that correction of severe hypercortisolism dramatically improves left ventricular contractile capacity and reduces fluid retention.

Infections are another common threat faced by patients with EAS. The frequency and severity of *P. jirovecii* pneumonia in patients with EAS warrants systematic prophylaxis with trimethoprim-sulfamethoxazole (120).

Review	J Young and others	Ectopic ACTH syndrome	182:4	R44
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In the presence of an infection, the choice of antibiotics should be discussed with an infectious disease specialist who has a good knowledge of infections associated with immunosuppression. Skin condition, which is often markedly deteriorated in these patients, must be carefully monitored. Active nursing care is necessary to prevent pressure ulcers and bedsores, especially if the patient is bedridden.

(B) Specific treatments: personalized medicine

In patients with severe CS and multiple complications, reducing the intensity of hypercortisolism is an emergency, and the choice between surgical excision of a non-metastatic tumor, pharmacotherapy of hypercortisolism and BLA (BLA) should be discussed by an experienced multidisciplinary team (endocrinologist, surgeon and anesthetist) according to the patient's condition. We insist on the fact that, in severe EAS, the absolute and immediate priority is to control excessive cortisol secretion and that the etiological diagnosis, if not immediately done, can always be corrected later using second-line imaging investigations when the patient's clinical condition has improved.

(1) Pharmacological treatments of hypercortisolism

Pharmacological treatments of hypercortisolism include a variety of drugs acting at different levels involved in the genesis of Cushing's syndrome. Although these agents have variable efficacy, endocrinologists should remember that adrenal insufficiency is a 'desired' side effect of all drugs used in the treatment of EAS.

(a) Immediate-acting steroidogenesis inhibitors

Steroidogenesis inhibitors (202), used alone or in combination, are a first-line treatment option for intense hypercortisolism secondary to EAT due to their efficacy and rapidity of action (97, 113, 201). Ideally these treatments should be managed by endocrinologists accustomed to their use in single-, dual- or triple-agent therapy (113, 201) and who are able to master drug titration, adequately interpret follow-up endocrine investigations and detect adverse effects, particularly adrenal insufficiency, as well as drug-drug interactions. Efficacy can be monitored by repeated urinary or serum cortisol assays. In severe cases, the endocrinology laboratory must deliver cortisol results quickly (24–48 h), to titrate drug dosage. As mentioned previously, the improvement of cortisol-induced hyperglycemia, hypertension and hypokalemia may serve as intermediate markers of efficacy.

Metyrapone is a specific inhibitor of 11-hydroxylase (202). Its efficacy in EAS has been known for almost 5 decades (203, 204, 205, 206) and has been confirmed in more recent studies (113, 201, 202). Given its short half-life and pharmacokinetics, metyrapone needs to be administered in three of four daily fractions. The dosage depends on the degree of hypercortisolism and may range from 1500 to 6000 mg/d (202, 203, 205, 206). When used at adequate doses, it is a very effective drug in the short term, leading to a drastic fall in urinary cortisol within 24 to 72 h (113, 201, 202). Onset of adrenal insufficiency (201) should lead to a dose reduction or to the addition of glucocorticoid replacement therapy ('block and replace' approach). The main adverse effects, when given at high doses, are gastrointestinal (nausea and sometimes vomiting), which can undermine treatment adherence in the mid-term (202, 207). Metyrapone monotherapy at high dosage can occasionally favor high blood pressure and hypokalemia secondary to the accumulation of the mineralocorticoid precursor DOC (204). One specific medium-term adverse effect in women is hyperandrogenism secondary to androstenedione accumulation, resulting in increased testosterone concentrations (202, 206). Many adverse effects are attenuated by association with other steroidogenesis inhibitors such as ketoconazole (see subsequent section).

Importantly, monitoring of metyrapone efficacy is more reliable when cortisol is measured with analytical methods such as highly specific immunoassays or techniques with high specificity for cortisol, such as LCMS and GCMS. These methods avoid interference from the dramatic increase in the concentration of the immediate precursor of cortisol (11-deoxycortisol) which can lead to overestimation of cortisol levels (208).

Ketoconazole is a steroid synthesis inhibitor acting on several cytochrome P450 steroidogenic enzymes that has been implemented in clinical practice since more than 3 decades (209, 210, 211). This compound is used orally (200-mg capsules), at increasing doses ranging between 600 and 1200 mg/day (212, 213, 214, 215, 216, 217), according to the degree of hypercortisolism. It is a fast-acting drug, inducing a decline in the cortisol level within a few days (214, 217), even if the rapidity of its action is less well-documented than that of metyrapone. In intense hypercortisolism, high doses (1000–1200 mg) are usually required (214). Endocrinologists are often wary of the hepatic toxicity of ketoconazole, including a rare risk of fulminant hepatitis (218, 219). This idiosyncratic risk, that is not correlated to ketoconazole dosage, necessitates close monitoring of liver function during the first days and weeks

Review	J Young and others	Ectopic ACTH syndrome	182:4	R45
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after the initiation of treatment. However, a recent French retrospective multicenter study of ketoconazole in 200 patients with Cushing's disease showed that transaminase elevation occurred in only 2.5% of cases and that it regressed on drug withdrawal, with no reported cases of severe drug-induced hepatitis (217). Moreover, in a small cohort of patients with EAS, severe hypercortisolism and increased baseline transaminase levels may have been due to cortisol-induced hepatic steatosis. The improvement in cortisol levels during ketoconazole therapy, was associated with a decline in transaminase levels (219, 220). Therefore, in our view, in a life-threatening situation, such as intense hypercortisolism, increased liver enzymes should not contraindicate the use of ketoconazole.

Metyrapone and ketoconazole combination therapy: Metyrapone and ketoconazole are fast-acting, orally administered drugs that inhibit distinct enzymes involved in adrenal steroidogenesis. Their association thereby reduces cortisol production synergistically and can be used to curb intense hypercortisolism and/or reduce side-effects induced by high dosage of one drug without decreasing cortisol-lowering effectiveness. In a personal series of fourteen patients with intense EAS, and using a strategy of immediate administration of high doses of the two drugs (median starting doses of 2500 mg/d of metyrapone and of 1000 mg/d ketoconazole), we observed a decrease in the median UFC from 40 ULN to 3 ULN after 1 week of treatment (201). UFC values were normal for 50% of patients, while UFC was normal in 73% of patients after 1 month, without major side-effects.

A new 11-hydroxylase inhibitor with improved potency and a longer half-life than metyrapone, called Osilodrostat[®] or LCI 699, is currently being developed for use in Cushing's disease (221, 222, 223). This compound is remarkably effective in Cushing's disease, including forms with severe hypercortisolism (222, 223). Recently reported preliminary data of its specific use in EAS also suggests a promising efficacy but must be confirmed in clinical trials including significant number of patients with EAS.

Etomidate is a hypnotic drug, commonly used in anesthesia, that efficiently inhibits 11- β hydroxylase (205). At subhypnotic doses, etomidate induces a drastic reduction in cortisol levels within 48–72 h (224, 225, 226). Several treatment protocols involving drug titration or a 'block and replace' regimen have been published (218, 219, 220). Given intravenously, this drug can be particularly useful if the oral route is unavailable (gastrointestinal intolerance or complications, steroid psychosis, etc.). The difficulty in its use lies in its sedative properties that may necessitate ICU hospitalisation.

(b) Slow-acting cortisol-lowering drugs

Mitotane, also called op'DDD, is an isomer of the insecticide pp'DDD. This adrenolytic drug was first used decades ago for the treatment of adrenocortical cancer (ACC) and later for other causes of Cushing's syndrome (227, 228). Mitotane exerts cytotoxic effects on the adrenal cortex and inhibits enzymes in the steroidogenic pathway, thus suppressing cortisol production (228, 229, 230). Indeed, a number of studies have demonstrated mitotane inhibition of adrenocortical steroid synthesis by inhibition of cholesterol side-chain cleavage (also called human cytochrome P450 (CYP), cholesterol desmolase or 20, 22 desmolase, encoded by *CYP11A1*) and 11 β -hydroxylase (i.e. P450 11 β or *CYP11b1*) (228, 229). Mitotane also affects extra-adrenal cortisol bioavailability by inducing its hepatic clearance and increasing secretion of cortisol-binding protein (CBG), thus reducing hormone availability (231). At present, despite being rarely used in this indication outside of France, mitotane has been shown by different teams to be an effective drug in ACTH-dependent Cushing's syndrome, either in CD or in EAS, when used either alone or in combination (227, 232, 233, 234, 235).

The main mitotane drawback in severe Cushing's syndrome is its delayed effect that ranges from 3 to more than 6 months (234, 235). This pharmacodynamic property means that mitotane, as monotherapy, is unsuited to acute situations requiring rapid control of cortisol hypersecretion. However, once adrenal blockade has been obtained after a few months, mitotane has some advantages over reversible competitive steroidogenesis inhibitors. Its main advantage is the stability and inertia of its antisecretory effect, possibly related in part to its adrenolytic properties that can be achieved and maintained long term with relatively low doses (between two and six 500-mg capsules per day) (113). Mitotane treatment often results in adrenal insufficiency and the need to add hydrocortisone supplementation (113, 234). Since mitotane is a potent enzyme inducer (CYP3A4), the required doses of hydrocortisone supplementation may have to be increased by approximately one-third in some patients (231).

Apart from its therapeutic effects, mitotane is responsible for many side-effects. Frequently reported side-effects include gastrointestinal symptoms, with anorexia, nausea, and sometimes vomiting and diarrhea (203). Other side-effects are hypogonadism, gynecomastia, ovarian macrocysts, hepatotoxicity and hypercholesterolemia (113, 230, 234, 235). Severe neurological side-effects (dizziness/lethargy, confusion, headache, dysarthria,

Review	J Young and others	Ectopic ACTH syndrome	182:4	R46
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ataxia and paraesthesia) reflecting cerebral toxicity occur more frequently at higher plasma concentrations than those allowing the control of hypercortisolism in patients with non-cancerous adrenal glands (236, 237). Indeed, control of hypercortisolism in EAS can be obtained with mitotane blood concentrations below 10 mg/L (113, 234, 235) that are associated with better tolerance than the 14 mg/L threshold recommended in adrenal cortical cancer. It should be also noted In Cushing's syndrome, blood assays for mitotane can also be useful for checking treatment adherence and for avoiding and limiting risk of overdose. Mitotane efficacy can be monitored by measuring urinary cortisol. Serum cortisol monitoring is also useful, but the elevation of the carrier protein (cortisol-binding globulin, CBG) that is induced by mitotane (237) could lead to an underestimation of the efficacy of mitotane therapy.

To compensate for its delayed action, mitotane can be combined with fast-acting inhibitors (metyrapone and ketoconazole) (113). This helps to cover the initial period of 3–6 months necessary for the antisecretory effect of mitotane to kick in. Mitotane efficacy is confirmed when gradual, complete withdrawal of fast-acting inhibitors does not lead to recurrent hypercortisolism (109). Crucially, mitotane is a potent enzyme inducer, thus altering the metabolism of many other drugs, including antineoplastic agents. Mitotane should thus be avoided if such treatments are necessary.

(c) Mifepristone

Mifepristone has been used in the treatment of EAS for many years but evidence is based mainly on scarce isolated case reports (238, 239). Apart from a few retrospective series (240), the published data are limited (188). In theory, mifepristone has certain advantages in the treatment of hypercortisolism related to EAS, including its rapid action and blockade of glucocorticoid receptor activation that is responsible for the clinical manifestations and, particularly, psychiatric symptoms of hypercortisolism (200, 240). However, mifepristone only antagonizes the binding of cortisol to its nuclear receptor, without inhibiting cortisol biosynthesis. Consequently the urinary, serum and salivary cortisol levels remain high and may even rise (241, 242), rendering these useless for monitoring efficacy. Efficacy can therefore only be evaluated based on non-specific clinical parameters and surrogate biomarkers such as blood sugar levels, with the potential danger of misdiagnosis of adrenal insufficiency. Moreover, as noted previously, mifepristone can aggravate or sometimes cause severe hypokalemia (200, 240, 241, 242).

(d) Drugs inhibiting ACTH secretion by NETs

Kinase inhibitors

Several reports of highly effective therapy using kinase inhibitors in EAS secondary to medullary thyroid cancer (MTC) have been published (243, 244, 245, 246). Vandetanib, sorafenib or sunitinib produced a dramatic inhibition of ACTH secretion, enabling a sustained control of hypercortisolism that could be observed in the absence of antitumoral effect. These preliminary but promising results suggest that first-line kinase inhibitor therapy may be worth considering for patients with EAS due to an unresectable MCT (243, 244, 245, 246).

Somatostatin analogues

Theoretically, this type of medication could be a treatment choice given the frequent expression of SST2 somatostatin receptors by NETs. Octreotide and lanreotide have shown short- and medium-term efficacy in a few EAS patients (247, 248, 249, 250, 251, 252). However, failures have also been reported, and they may also be underestimated because of publication bias. Apart from a few interesting cases, the effect of these analogs on ACTH secretion is often partial and transient, necessitating the use of other, more effective treatments (247, 248, 249, 250, 251, 253). Given the usual severity of Cushing's syndrome in EAS, we disagree with a first-line trial approach with these drugs as monotherapy, even when somatostatin receptor imaging is positive. Somatostatin analogs may be used in combination with other agents or as antitumoral therapy in non-excisable metastatic well-differentiated NETs.

Dopamine agonists

Cabergoline has been used successfully, though this is anecdotal usually in combination with a somatostatin analog or with steroidogenesis inhibitors (250, 252). Given its variable therapeutic effect, reported in only a handful of patients, it is difficult to recommend first-line use of this dopamine agonist.

Additionally, efficient antitumoral chemotherapy may be able to reduce the intensity of hypercortisolism as was reported in a patient with EAS secondary to a pancreatic NET, in whom, following chemotherapy with streptozocin, 5-fluorouracil and doxorubicin, metyrapone could be withdrawn (254).

(2) Surgery

(a) Excision of ACTH-secreting NETs

Surgical excision is the ideal curative treatment for EAS (4, 5, 6, 7, 8, 9, 10, 11, 12, 13). If successful, surgery has the major advantage of halting hypercortisolism while maintaining adrenal function in the long-term despite

Review	J Young and others	Ectopic ACTH syndrome	182:4	R47
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transient post-operative corticotropic insufficiency. However, before considering surgical resection, three conditions must be met: (1.) unambiguous identification and precise localization of the NET; (2.) an excisable, locoregional NET without distant metastases and (3.) general condition of the patient allowing anesthesia and surgery with an acceptable risk that may be compromised by cortisol-induced complications. The ideal candidates are radiologically visible, well-differentiated bronchial NETs that can be readily excised or removed after days to weeks of preparation with pharmacological treatment in patients with bad general condition at presentation. When NETs are unresectable, because of local invasion and/or multiple metastases, determination of the histoprognosis on tissue samples obtained by biopsy will guide the choice of chemotherapy while therapies to control hypercortisolism such as medical agents or BLA are employed. BLA (see subsequent section) may also be warranted in such cases. This solution, in the absence of acute complications that contraindicate surgery, has the advantage of its rapid action and high efficacy. Moreover, it allows antitumoral drug therapy to be conducted without undesirable interactions with pharmacological treatment of hypercortisolism that can affect the efficacy and tolerability of both treatments.

(b) Bilateral adrenalectomy

BLA in EAS has been used for many years (255) and is currently performed mostly by the laparoscopic route in order to reduce its morbidity (256, 257, 258, 259). BLA is highly effective on hypercortisolism, with an immediate effect (247, 248, 249, 250). Rare failures are responsible for detectable post-operative cortisol but rarely for persistence of hypercortisolism (260). These failures are related to poor tissue quality in patients with severe Cushing's syndrome, which may promote bleeding and make the adrenals difficult to identify (258). More rarely, failure is due to the existence of ectopic adrenocortical tissue (accessory adrenals) that are missed by the surgeon and therefore left in place. However, BLA in patients with severe Cushing's syndrome carries significant risk of surgical mortality, and intraoperative complications are more frequent in EAS than in other forms of Cushing's syndrome (258). These complications include myocardial infarction, internal bleeding and surgical lesions of adjacent organs (liver, spleen, pancreas and colon) (256, 257, 258, 259), as well as poor abdominal wall healing, superficial and deep infections, hematomas and post-operative thromboembolic events (256, 257, 258, 259). It should also be mentioned that, in a recent metanalysis,

the perioperative mortality of BLA has not changed with the advent of laparoscopic surgery (258). In our opinion, BLA has two main indications in EAS: the first one is BLA as rescue treatment (256, 257, 259, 260) in very severe cases, when steroidogenesis inhibitors are unavailable, ineffective or poorly tolerated and the second one is to prevent drug-drug interactions in patients with well-differentiated metastatic NETs (and relatively long life expectancy), in whom the efficacy and/or safety antineoplastic drugs such as tyrosine kinase inhibitors could be affected by cortisol-lowering drugs. Indeed, the ideal indication is an unresectable NET responsible for ectopic Cushing's syndrome, where pharmacological therapy of hypercortisolism is ineffective (see previous section) or locally unavailable. It should be borne in mind that, in the long term, primary adrenal insufficiency may decompensate with fatal consequences (261, 262) in nearly 6% of cases. This can be particularly concerning in a patient with an occult EAT that corresponds in most cases to a non-metastatic well-differentiated and indolent NET that will be discovered after several months or years of follow-up (Fig. 2). Excision of the EAT at that time will allow a full and life-long recovery of HPA axis function. In such cases, and in responsive patients, the control of hypercortisolism for months by steroidogenesis inhibitors should be therefore considered as a first-line option (113). This strategy is also useful for elderly patients with multiple severe complications preventing even rescue BLA. The only recourse in these extreme situations is supportive high-dose drug therapy associated with intensive care. Some patients have thus been 'resurrected' and then had their NET excised later, with a return to normal adrenocortical function (109).

(3) Antineoplastic treatments

Antineoplastic treatments either general or localized (such as radiofrequency ablation and chemoembolization (263, 264) are used in non-resectable ACTH-secreting NETs and carcinomas. The indication of these treatments must be discussed in each case by a multidisciplinary team.

Conclusions

EAS is a rare, often severe disease. Its management is complex and requires expertise in two distinct areas: diagnosis and treatment of Cushing's syndrome and treatment of neuroendocrine tumors. These patients often represent an endocrine emergency due to the intensity of their hypercortisolism. The frequency and severity of

complications are such that initial treatments must be conducted by expert teams and sometimes in collaboration with an intensive care unit. Diagnostic procedures, including specialized hormonal tests and modern imaging methods, must be deployed very quickly in these unstable patients, at the same time as preventive and curative treatments of comorbidities and complications, to avoid rapid death of the patient. Although, the ideal treatment is excision of the ACTH-secreting endocrine tumor, it may be impossible to perform initially in patients with occult or, conversely, metastatic tumors; or when the intensity of hypercortisolism and its associated complications prevent surgery. Apart from symptomatic treatments, hypercortisolism must be controlled without delay. Frontline treatment should consist of high-dose, fast-acting steroidogenesis inhibitors or adrenalectomy. We believe that adrenalectomy should be used mainly when medical treatment fails, is poorly tolerated or is unavailable or when the neoplastic context requires the use of antitumoral drugs. Adrenal sparing is a priority for patients with less aggressive tumors that are compatible with a long life expectancy (6). In the future, advances in imaging techniques will improve the identification of small occult NETs and thus allow their removal, thereby further limiting recourse to BLA.

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Author contribution statement

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Review	J Young and others	Ectopic ACTH syndrome	182:4	R50
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