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Ectopic Cushing's syndrome in light of modern diagnostic techniques and treatment options

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Abstract

Ectopic adrenocorticotropic hormone secretion (EAS) is responsible for approximately 10–15% cases of Cushing's syndrome. EAS is associated with various tumors such as small cell lung cancer and well-differentiated bronchial or gastrointestinal neuroendocrine tumors. Hormonal diagnostics include assessments in basic conditions as well as dynamic tests, such as the high-dose dexamethasone suppression test and corticotrophin releasing hormone (CRH) stimulation test. Treatment selection depends on the type of tumor and its extent. In the case of neuroendocrine tumors, the main treatments are surgery and administration of somatostatin analogs that may be additionally radiolabeled for targeted radiotherapy. The tumor histology and the presence and control of hypercortisolemia and metastases are of major importance in prognosis. In this article we presented the principles of modern hormonal and imaging diagnostics techniques as well as the key issues associated with treatment of ACTH-dependent Cushing's syndrome due to EAS.

REVIEW ARTICLE

1. INTRODUCTION

Diagnosis and treatment of adrenocorticotropic hormone (ACTH, corticotrophin)-dependent Cushing's syndrome (CS) are among the greatest challenges of modern endocrinology. The most common cause of Cushing's syndrome is corticotropin-secreting pituitary adenoma that leads to Cushing's disease. However, approximately 10–15% of Cushing's syndrome cases are due to extrapituitary tumors of various histological grades, which are responsible for ectopic ACTH production and lead to hypercortisolemia with all its manifestations. Ectopic ACTH syndrome (EAS) can be defined as hypercortisolemia with prevalent hypokalemia, metabolic alkalosis and skin hyperpigmentation, originating from extrapituitary tumors secreting ACTH (Ilias *et al.* 2005; Isidori *et al.* 2006; Biller *et al.* 2008; Nieman *et al.* 2008; Alexandraki & Grossman 2010; Guignat & Bertherat 2010; Kolesnikowa *et al.* 2013; Zada 2013; Maragliano *et al.* 2015).

In Europe and the United States EAS is equally common in both sexes. This differentiates it

from Cushing's disease greatly, where incidence levels in females range between 4–8 : 1, when compared to males.

2. ETIOLOGY

Ectopic corticotropin-secreting tumors are most commonly located in the lungs. Over 50% of all ACTH-secreting tumors causing Cushing's syndrome are found in the bronchi and lungs. Up to 50% of small cell lung cancers (SCLCs), common in populations with high rates of smokers, secrete immunoreactive precursors and fragments of ACTH molecules. However, biologically active ACTH molecules lead to CS clinical manifestation in 2–5% of those individuals. In Europe and the U.S. the most common causes of EAS are ACTH-secreting neuroendocrine tumors (NETs) of the lung (Ilias *et al.* 2005; Isidori *et al.* 2006; More *et al.* 2011).

Neuroendocrine tumors of the gastroenteropancreatic tract (GEP/NET) are a less common cause of extrapituitary Cushing's syndrome. These tumors can be found in the pancreas, stomach, thymus, intestines or the vermiform appendix (Ilias *et al.* 2005; Isidori *et al.* 2006; More *et al.* 2011; Alexandraki & Grossman 2010; Karageorgiadis *et al.* 2015; Maragliano *et al.* 2015). There have been reports of gastrinoma or pheochromocytoma additionally secreting ACTH (O'Brien *et al.* 1992; Ilias *et al.* 2005; Isidori *et al.* 2006). There are cases of ACTH-secreting medullary thyroid carcinoma (Ilias *et al.* 2005; Isidori *et al.* 2006). It is only very rarely that corticotropin-releasing hormone (CRH) is secreted by NETs (O'Brien *et al.* 1992; Karageorgiadis *et al.* 2015).

Additionally the challenge in diagnosis and treatment of extrapituitary Cushing's syndrome is hampered by not locating the source of ectopic ACTH secretion in 15–20% of cases, even with state-of-the-art diagnostic and imaging techniques (occult EAS) (Alexandraki & Grossman 2010).

3. CLINICAL PRESENTATION

The clinical presentation of EAS depends on tumor grade and stage, including the presence of metastases. The specific manifestations may be modified by secretion of other biologically active substances, apart from ACTH, such as catecholamines in the case of pheochromocytoma (concomitant severe, refractory, or paroxysmal hypertension), gastrin in the case of gastrinoma (refractory peptic ulcer disease, gastric ulceration, including post-gastrectomy scar involvement), or serotonin (carcinoid syndrome, occurring in the case of hepatic metastases) (O'Brien *et al.* 1992; Ilias *et al.* 2005; Isidori *et al.* 2006).

Neoplasms characterized by rapid progression and early dissemination, such as high-grade neuroendocrine carcinoma or SCLC do not typically present as fully manifested Cushing's syndrome. Such patients typically develop rapidly increasing hypercortisolemia, predominantly with muscle weakness, hypertension, significant hypokalemia (potassium levels often below 2.5 mmol/L), as well as metabolic alkalosis and impaired glucose tolerance. Hypokalemia is caused by the effect of excess cortisol on mineralocorticoid receptors as well as overproduction of deoxycorticosterone (DOC) characterized by mineralocorticoid activity. Impaired glucose tolerance, developed by over 50% of patients, results from increased gluconeogenesis, hypokalemia-induced impairment in insulin secretion, and higher insulin resistance. Skin hyperpigmentation is relatively common and results from the effect of high levels of ACTH on melanotropin receptors. Although some patients may initially gain weight, high-grade carcinomas are more typically associated with progressive emaciation (characteristic for neoplastic disease) and normocytic anemia (Ilias *et al.* 2005; Isidori *et al.* 2006).

Low-grade neuroendocrine tumors or carcinomas in patients with potentially low malignancy usually experience slower progression of the disease and the clinical presentation. This resembles Cushing's syndrome due to ACTH-dependent pituitary adenoma: weight gain; skin atrophy; bruising; purple striae on the abdomen, thighs, buttocks; myopathy. Low bone mineral density and a higher risk of fractures affect 75% of patients. Over 70% of women develop menstrual disorders and hirsutism (adrenal androgen overproduction). Men, on the other hand, experience decreased libido and erectile dysfunction. Hypertension is observed in over 70% of patients, while over 50% develop carbohydrate metabolism disorders that may lead to clinically overt diabetes mellitus (Ilias *et al.* 2005; Isidori *et al.* 2006; Nieman *et al.* 2008, Witek *et al.* 2012).

Carcinoid syndrome is a relatively rare manifestation of tumors with ectopic ACTH-secretion. It is observed when the tumor (usually a midgut GEP/NET) secretes large quantities of serotonin. Fully symptomatic carcinoid syndrome does not develop until after the appearance of hepatic metastases, i.e. in the cases of tumors with malignant potential. Only then can serotonin be released into the inferior vena cava system and affect systemic circulation. Typical manifestations include flushing, palpitations, and diarrhea. A physical examination may reveal systolic heart murmurs associated with tricuspid regurgitation or pulmonary stenosis. Long-term sequelae are: chronic valvular heart disease with the associated symptomatic right ventricular insufficiency, and less commonly, gastrointestinal complications, including intestinal obstruction or infarction.

4. DIAGNOSIS

Ectopic ACTH secretion should be considered in every patient with rapidly increasing somatic evidence of Cushing's syndrome, with severe hypokalemia and metabolic alkalosis, accompanied by elevated serum ACTH and cortisol levels. The greatest challenge lies in differentiating EAS from the much more prevalent

Cushing's disease. In each case, diagnostic assessments should include highly specific blood and urine hormonal tests as well as complex imaging studies. The latter help determine the extent of the disease and select the optimal therapeutic strategy.

4.1. Blood and urine hormonal tests

Hormonal assessments typically show high plasma ACTH and high serum cortisol levels, with abnormal circadian rhythm as well as high levels of urine free cortisol (UFC) (Biller *et al.* 2008; Nieman *et al.* 2008; Guignat & Bertherat 2010; Zada 2013). Blood ACTH and cortisol levels are particularly high in patients with SCLC that produces biologically active ACTH molecules. In these patients ACTH levels significantly exceeding 1,000 pg/mL are not uncommon. In other patients, i.e. those with Cushing's syndrome due to NETs of the bronchi or GEP/NET, ACTH levels usually do not exceed 700–800 pg/mL. However, establishing a precise cut-off point seems to be impossible (Ilias *et al.* 2005; Isidori *et al.* 2006).

Out of all diagnostic tests two are the most important. These are: high-dose (8 mg over 2 days) dexamethasone suppression test (HDDST) and CRH stimulation test. Patients with EAS do not suppress cortisol levels, as evidenced by high serum cortisol and UFC after two days of 8 mg dexamethasone administration. The usually adopted cut-off point is failure to reduce serum cortisol or UFC levels (obtained in 24-hour urine collection) by at least 50% versus their respective baseline values. Such lack of cortisol suppression is observed in 80–90% of EAS patients (Ilias *et al.* 2005; Isidori *et al.* 2006; Alexandraki & Grossman 2010; Karageorgiadis *et al.* 2015). Some authors propose a stricter criterion of suppression (i.e. more than 80%) to distinguish between Cushing`s disease and EAS. In such cases the specificity of HDDST increases in terms of CD confirmation but at the expense of lower sensitivity.

The CRH stimulation test (100-μg fixed dose of intravenous CRH, or the weight-based 1 μg/kg) in EAS patients typically shows no significant ACTH or cortisol elevation, i.e. their elevation by <30% and <20%, respectively. Sometimes the criterion of <50% elevation for ACTH is proposed but at the expense of lower sensitivity. The CRH stimulation test has a high potential to differentiate between extrapituitary (ectopic) and pituitary ACTH secretion. The difference in response to the test due to the presence of CRH receptors in pituitary corticotropin-secreting adenomas and the absence of CRH receptors in the vast majority of extrapituitary tumors. Literature reports and our own observations indicate that the lack of ACTH elevation following CRH administration characterizes 90–95% of ectopic corticotropin-producing tumors. The use of these two tests in the differential diagnosis of ACTH-dependent Cushing's syndrome, with the results showing both unsuppressed cortisol secretion and/or elimination in the dexamethasone test and a lack of ACTH elevation in the CRH test. Definitively implicating an ectopic (extrapituitary) source of ACTH, even if the precise location of the tumor is unknown (Ilias *et al.* 2005; Isidori *et al.* 2006; Karageorgiadis *et al.* 2015).

However, despite the diagnostic importance of these tests, differentiating between causes of ACTH-dependent Cushing's syndrome in atypical situations continues to pose a serious challenge. Differentiation becomes more difficult due to the corticotroph pituitary tumors that do not respond to CRH compared to NETs of the bronchi that yield positive results in the CRH test (Isidori *et al.* 2006).

Another tool in diagnostically difficult cases of ACTH-dependent hypercortisolemia is inferior petrosal sinus sampling (IPSS). This method involves simultaneous measurement of ACTH levels in samples obtained from catheterized inferior petrosal sinuses and peripheral venous blood (superior or inferior vena cava system), prior to and after CRH administration. The ACTHcentral/ACTHperipheral ratio of over 3 following CRH stimulation is typical for Cushing's disease, while the ratio less than 1.8 is seen in EAS. If CRH stimulation is not used, the ACTHcentral/ACTHperipheral ratio of over 2 suggests a pituitary tumor (Ilias *et al.* 2005; Isidori *et al.* 2006; Nieman *et al.* 2008).

Additionally, depending on their grade and stage, ectopic ACTH-producing tumors can also secrete other peptides. One NET marker, 5-hydroxyindoleacetic acid (5-HIAA), is measured in 24-hour urine collection. Positive results are observed in NETs of the *midgut* and *hindgut*, and rarely in lung cancer (often, there is no DOPA decarboxylase expression in bronchial NET cells, which more often leads to the secretion of 5-OH-tryptofan than serotonin). One non-specific marker released by neuroendocrine cells is chromogranin A (CgA). Calcitonin levels are increased in approximately 20–30% of cases, especially in ACTH-producing medullary thyroid carcinoma, but also in some cases of SCLC, pheochromocytoma, and GEP/NETs including gastrinoma. Other markers include: gastrin (pancreatic insulinomas), somatostatin (medullary carcinoma, SCLC), or glucagon. Human chorionic gonadotropin (HCG) levels may also increase; this happens in NETs and ectopic ACTH-producing teratomas (Ilias *et al.* 2005; Isidori *et al.* 2006).

4.2. Imaging studies (radiographic and functional)

If hormonal assessments suggest ectopic ACTH production, imaging studies should be scheduled. In SCLC, chest X-ray films reveal pulmonary hilum involvement or a coin lesion, and the subsequent computed tomography scan help determine precise stage of the disease.

Determining the location of other ectopic ACTH-producing tumors is much more difficult. Plain, routine chest X-rays help detect only about a third of bronchial NETs, which is due to the fact that the diameter of these tumors does not typically exceed 1–2 cm. High-resolution computed tomography (CT) is a routine evalua-

tion. It should be conducted using the multi-detector row CT technique with 2–3-mm slice thickness and span the area from pulmonary apices to iliac spines. Bronchial lesions can be detected with bronchofiberoscopy. Patients with increased levels of calcitonin as well as elevated ACTH require thyroid ultrasound, and fine-needle aspiration biopsy, if necessary. Eighty percent of pulmonary carcinoids are located centrally in the parahilar area of the lung, 20% of them are solid peripheral pulmonary nodules (Jeung *et al.* 2002; Ilias *et al.* 2005; Isidori *et al.* 2006).

A suspected gastrointestinal NET requires abdominal CT scanning with careful evaluation of the pancreas and adrenal glands. According to data from the literature, CT sensitivity and specificity ranges are 61–100% and 71–80% for abdominal/thoracic tumors, 63–82% and 83–100% for pancreatic NETs, and 63–90% and 98–100% for NET metastases to the liver (Ilias *et al.* 2005; Isidori *et al.* 2006; Sundin *et al.* 2009; Aleksandraki & Grossman 2010).

The diagnosis of lesions located in the stomach or duodenum may require gastroduondenoscopy. Due to its high-sensitivity and the opportunity to additionally obtain fine-needle aspiration biopsy, endosonography plays an important role especially in GEP/NETs derived from the foregut (stomach, proximal duodenum, and pancreas). The sensitivity of endoscopic ultrasound-guided biopsy in the diagnostics of pancreatic NETs is approximately 80% (Ardengh *et al.* 2004). Also, intraoperative ultrasound diagnostics decidedly improves treatment outcomes in small pancreatic tumors. In suspected lesions of the large intestine, apart from a CT scan, the patient should undergo colonoscopy. These methods are used in detecting tumors of the colon that may secrete ACTH and lead to Cushing's syndrome (Ardengh *et al.* 2004; Ilias *et al.* 2005; Isidori *et al.* 2006; Sundin *et al.* 2009).

Magnetic resonance imaging (MRI) is not typically superior to a CT scan as a means of assessing the primary lesion and metastases; however, it may be used in cases of diagnostic ambiguity, especially involving abdominal tumors. MRI sensitivity and specificity in diagnosing pancreatic NETs are 85–100% and 75–100%, respectively, and the rate of hepatic metastasis detection via MRI is up to 95% (Ilias *et al.* 2005; Isidori *et al.* 2006; Sundin *et al.* 2009). Moreover, MRI of the hypothalamic-pituitary system helps in the differential diagnosis of ACTH-dependent hypercortisolemia (Biller *et al.* 2008; Guingnat *et al.* 2010). However, the possibility of pituitary lesions, or the so-called incidentalomas, should be considered in the analysis of the resulting images. These lesions may occur in up to 10% of the healthy population, with the odds increasing with age.

Radioisotope function studies, such as somatostatin receptor scintigraphy (SRS), have been widely used in locating the source of EAS. SRS helps detect and precisely locate tumors that express somatostatin receptors, especially receptors 2 and 5 (SSTR2, SSTR5). SSTR2 and SSTR5 overexpression can be found in 70–90% of NETs (Papotti *et al.* 2002). Most NETs of the respiratory and digestive systems are characterized by high density of these receptors. Indium-111 (^{111}In, OctreoScan) and technetium-99m (Tc, Tektrotyd)-labeled somatostatin analogs have been used in locating these tumors. Apart from locating neoplastic lesions, SRS helps qualify patients for treatment with somatostatin analogs, evaluate treatment response, or detect recurrence after radical surgery. The sensitivity of this method in detecting the primary lesion is 60%, hepatic metastases – 90%, and bone metastases – approximately 70% (Chiti *et al.* 1998; Meijer *et al.* 2003). The use of single-photon emission computed tomography (SPECT) as well as hybrid canning systems such as SPECT/CT and SPECT/MRI enhances the sensitivity of this technique. The most common cause of the sometimes false-positive results are inflammatory diseases of the lungs and blood vessels, the presence of reactive lymph nodes, collection of radioisotope markers in the digestive tract and gallbladder, and neoplastic diseases, e.g. lymphomas or meningiomas. False-negative results are most commonly found in the case of lesions measuring less than 1 cm, insulinomas, and neuroendocrine carcinomas.

Iodine-123- or Iodine-131 (^{123}I or ^{131}I)-labeled meta-iodobenzylguanidine (MIBG) is a marker less commonly used in the diagnostics of particular cases of ectopic ACTH-producing tumors. MIBG is an analog of noradrenalin and guanethidine, which makes it useful in locating pheochromocytomas that may secrete ACTH and result in Cushing's syndrome. Although scintigraphy with the use of MIBG is less sensitive than that with oktreoscan, it may be useful in locating and staging the NETs exhibiting no somatostatin receptor expression (Cwikla *et al.* 2006; Isidori *et al.* 2006; Rufini *et al.* 2006).

Positron emission tomography (PET) plays an important role in locating ectopic ACTH-producing tumors (Scanga *et al.* 2004; Balogova *et al.* 2013). Gallium-(^{68}Ga)-labeled somatostatin analogs, such as ^{68}Ga-DOTA-TATE, ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA are especially common in EAS diagnostics. This modality is characterized by higher resolution (0.5 cm) in comparison with SPECT. One additional benefit of ^{68}Ga is the fact that it is generator-produced, which makes it independent from a cyclotron. This means that the isotope can be obtained and used for labeling somatostatin analogs at a PET lab. PET with the ^{18}F-fluorodeoxyglucose (^{18}F-FDG) marker is less common in the diagnostics of ectopic ACTH-producing NETs. The use of ^{18}F-FDG may be helpful in tumors with a high proliferation index, which is typical for poorly differentiated NETs, de-differentiated NETs, or SCLC with ectopic ACTH-production (Srirajaskanthan *et al.* 2010; Balogova *et al.* 2013). The examples of the results of imaging ACTH-secreting tumors using PET are shown in Figures 1 and 2.

Another phenomenon sometimes used in NET imaging is the ability of NET cells to take up and decarboxylate amine precursors (amine precursor uptake and decarboxylation, APUD). For instance, 5-hydroksy-L-tryptofan (5-HTP) and L-DOPA can be taken up by tumor cells and decarboxylated to serotonin and dopamine, respectively. This is why amide precursors labeled with ^{11}C and ^{18}F isotopes (11C-5-HTP and 11C-L-DOPA, 18F-L-DOPA) may be used in PET for imaging of those NETs that secrete ACTH in addition to amines.

Despite the great progress in radiological and functional diagnostics of tumors, ectopic ACTH-producing tumors may be very difficult. In these cases, the established practice calls for periodic repetition of tumor-locating examinations, e.g. CT scans of the chest, abdomen, and pelvis, for example every 6–12 months. In some cases this eventually leads to locating the neoplastic lesion. However, even in the best centers and with the use of state-of-the-art imaging modalities there are still approximately 10–20% of cases where finding the source of ACTH secretion remains impossible, even with the strategy of periodic repetition of imaging studies. Such cases are called occult EAS.

One way to definitively confirm the diagnosis established on the basis of hormonal assessments and imaging studies are the results of histopathological and immunohistochemical examinations of primary tumor or metastatic tissues. The necessary tissue samples are obtained through surgical treatment or through the use of diagnostic biopsy. Figure 3 presents an example of immunohistochemical report confirming the presence of ACTH in secretory granules. Also, a postoperative decrease in plasma ACTH and serum cortisol levels to subnormal, which may require periodic hydrocortisone replacement therapy, is a clinical confirmation of the diagnosis (and treatment effectiveness) of ectopic ACTH-producing tumors.

5. EAS TREATMENT

5.1. Surgical treatment

Surgical treatment is the management of choice in all types of ectopic ACTH-producing tumors, except SCLC. After the lesion has been visualized via imaging studies, the optimal strategy is radical surgery, i.e. surgery undertaken with curative intention. Cytoreductive surgery, i.e. surgery that reduces tumor mass by >95%, may be performed in the case of generalized, diffuse and poorly differentiated neuroendocrine carcinomas. Finally, surgical treatment may be used to improve the quality of life, i.e. as palliative treatment, such as metastasis resection, bile duct prosthesis, or the treatment of bleeding or intestinal obstruction. In the case of SCLC surgical treatment is undertaken only in limited-stage disease as part of more complex strategy

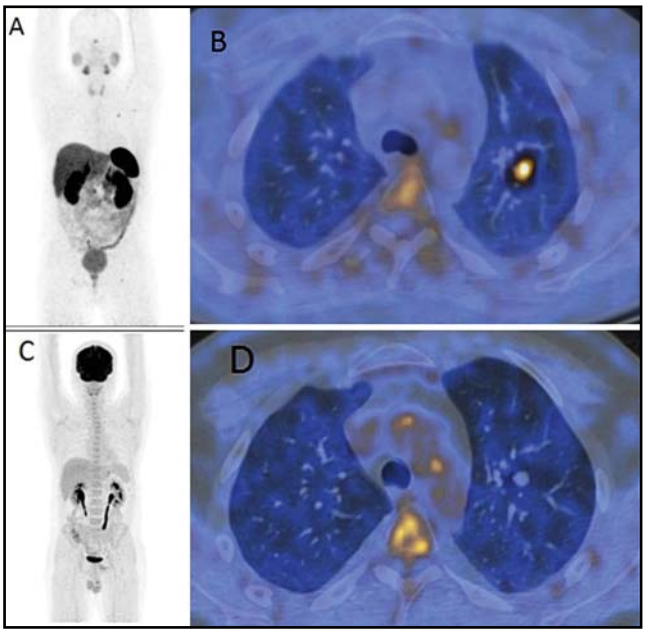

Figure 1. ACTH-dependent Cushing's syndrome in a 23-year-old male with the neuroendocrine tumor of the upper left lobe (histopathology: a typical ACTH-secreting carcinoid lung tumor (G1). **A,B)**. A PET-CT scan with the gallium-68-labeled somatostatin analog DOTA-TATE (^{68}Ga-DOTA-TATE), showing somatostatin receptor overexpression in the left lung tumor. **C,D).** A fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET-CT; tumor of the upper left lobe without increased ^{18}F-FDG uptake.

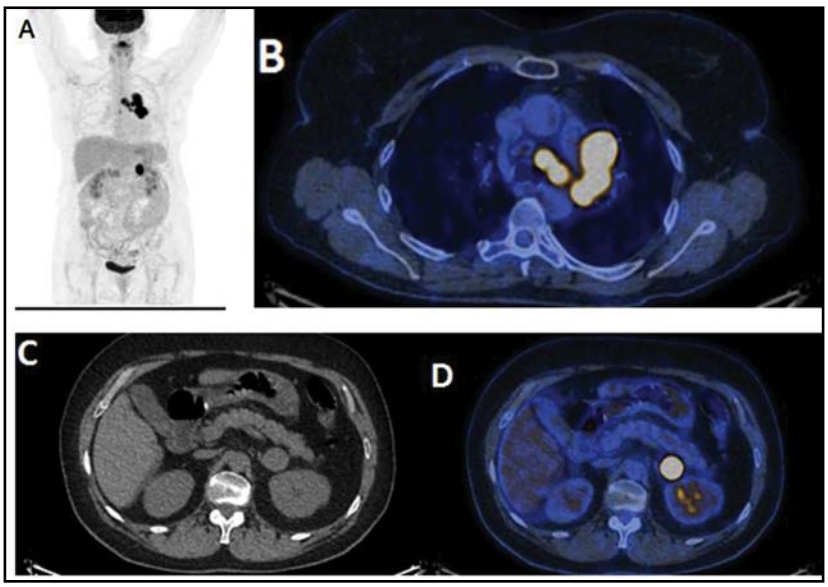

Figure 2. A fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET-CT scan in a 56-year-old female with small cell lung cancer of the left hilum and ipsilateral mediastinal node involvement **(A, B)** as well as a metastatic lesion in the left adrenal gland (**C, D**). Increased ^{18}F-FDG uptake within both the pulmonary lesions and the adrenal metastasis.

including also chemotherapy and radiotherapy (Ilias *et al.* 2005; Isidori *et al.* 2006; Nieman *et al.* 2008; Alexandraki & Grossman 2010).

Due to the fact that hypercortisolemia – regardless of its cause – increases mortality and worsens prognosis, total bilateral adrenalectomy may be used as a life-saving procedure in all tumors with ectopic ACTH production, including occult EAS. It is a definitive cure for hypercortisolemia, uncontrollable with causative therapy. One advantage of total bilateral adrenalectomy is a rapid and effective elimination of life-shortening hypercortisolemia, while one disadvantage of the method is its invasive nature, possible perioperative complications, and permanent and complete adrenal cortical insufficiency requiring life-long gluco- and mineralocorticosteroid replacement therapy (Ilias *et al.* 2005; Isidori *et al.* 2006; Nieman *et al.* 2008).

5.2. Medical treatment

Treatment of EAS involves drugs affecting neoplastic tissue (somatostatin analogs, interferons), adrenal steroidogenesis inhibitors (ketoconazole, metyrapone, mitotane), and, in selected cases of neuroendocrine carcinoma and small cell lung cancer, chemotherapy (anticancer drugs used in combination therapy).

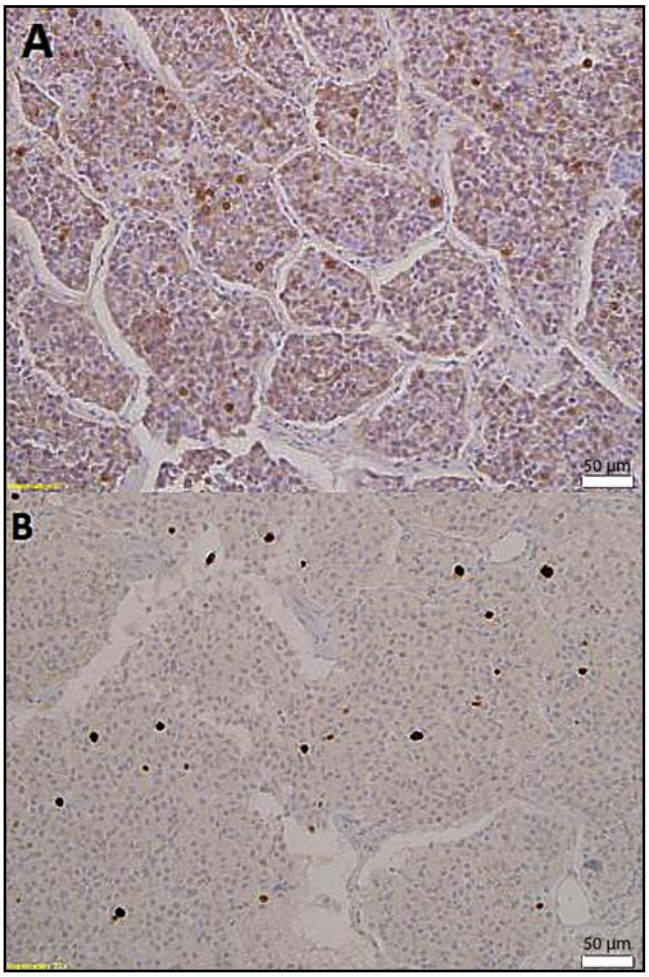

Figure 3. Immunohistochemistry of ACTH-secreting, well differentiated NET of the lung (patient from Figure 1). **A).** ACTH-staining, **B).** MIB-1; (original magnification 20x)

5.2.1.Somatostatin analogs

Somatostatin analogs – ooctreotide and lanreotide – are the main group of drugs used in long-term treatment of NETs associated with Cushing's syndrome. They are ineffective against SCLC. Somatostatin analogs show affinity mainly to somatostatin receptors 2 and 5 (SSTR2 and SSTR5). These drugs inhibit disease progression by stabilizing, or – less commonly – reducing primary and metastatic growths. The resulting improvement is associated with antiproliferative, cytostatic, and immunomodulatory effects of the drugs, as well as their ability to induce apoptosis and inhibit angiogenesis in the tumor. Somatostatin analogs block ACTH secretion (and may block the secretion of other tumor-derived hormones), which leads to reduction, or sometimes complete elimination, of the manifestations associated with hypercortisolemia or other hormone secretion-related abnormalities. The use of somatostatin analogs in carcinoid syndrome reduces the frequency of paroxysmal facial flushing in nearly 60% of patients, with the frequency and severity of these episodes reduced by over 50% in more than 85% of patients. Moreover, these drugs normalize gastrointestinal motility in 30% of patients, with the majority reporting significant reduction in stool frequency (Arnold *et al.* 1996; Werder *et al.* 1996; Öberg *et al.* 2004; Pivonello *et al.* 2005; Nieman *et al.* 2008).

Long-term use of somatostatin analogs may alter expression of surface receptors on tumor cells, consequently leading to developing resistance to the given treatment. This often requires increasing the dose or changing the management strategy. Tumor progression may occur even when disease manifestations resulting from tumor-related hormone production seem to be well controlled. In the case of developing resistance to treatment, somatostatin analogs are usually not discontinued despite disease progression; instead, they are added to chemotherapy regimen or radioisotope therapy (Werder *et al.* 1996; Öberg *et al.* 2004).

5.2.2. Interferons

They may be sometimes used in the treatment of NETs, either in monotherapy or combination therapy. Interferon monotherapy is used in lower-grade, more benign neoplasms. Conversely, in the case of poorly-differentiated (high-grade) neuroendocrine carcinomas some centers use interferons in combination with somatostatin analogs and conventional chemotherapy. Interferons have immunomodulatory effects by increasing the body's natural NK cell- and T-cell-mediated antitumor activity. There have been reports of the effect of interferons on tumor angiogenesis, as well as their tendency to induce tumor apoptosis and stimulate fibrosis within metastases (Plöckinger *et al.* 2004).

5.2.3. Chemotherapy

Chemotherapy involves various treatment regimens, with drug selection dictated mostly by tumor histology. Cisplatin and etoposide are used in chemotherapy of gastrointestinal neuroendocrine carcinomas, especially in high-stage disease, where radical surgical treatment is impossible and somatostatin analogs are no longer effective. The combination of cisplatin and etoposide may be complemented with paclitaxel. Pancreatic NETs sometimes require monotherapy with streptozocin, doxorubicin, or 5-fluorouracil. In low-grade NETs various chemotherapy regimens can be used, typically involving streptozocin, 5-fluorouracil, doxorubicin, epirubicin, decarbazine, irinotecan, or gemcitabine (Sun *et al.* 2005; Biller *et al.* 2008; Nieman *et al.* 2008; Karageorgiadis *et al.* 2015).

5.2.4. Adrenal steroidogenesis inhibitors

These inhibitors are a group of drugs used in order to reduce the severity of hypercortisolemia as, uncontrolled, it may lead to cardiovascular, metabolic, or electrolyte disorders. Adrenal steroidogenesis inhibitors neither affect neoplastic tissue nor inhibit ACTH secretion. These drugs may be used in long-term treatment of hypercortisolemia, in cases where radical surgical treatment is impossible, or in preparation for surgical treatment – either radical therapy or possible bilateral adrenalectomy. This preoperative use of adrenal steroidogenesis inhibitors may limit surgical complication rates and accelerate healing of damaged tissues, the latter being especially difficult in hypercortisolemic patients. The most commonly used drugs are ketoconazole, metyrapone, and mitotane (Winquist *et al.* 1995; Ilias *et al.* 2005; Isidori *et al.* 2006; Biller *et al.* 2008).

5.2.5. Radiation and radioisotope therapy

Teleradiotherapy is used as part of combined-modality treatment in limited-stage SCLC (involving lungs and the mediastinum) as well as palliative treatment in bone and central nervous system metastases. This modality may be used in NETs in the form of neuroendocrine carcinomas of the bronchi and thymus. Gastrointestinal NETs are typically less sensitive to irradiation, and abdominal radiotherapy has been associated with multiple complications that warrant reduced radiation dosing.

Radiolabeled somatostatin analogs may be used for peptide receptor radionuclide therapy (PRRT) of neuroendocrine carcinomas. However, this treatment requires a confirmed high expression of somatostatin receptors in tumor tissues by SRS. The aim of radioisotope therapy is to reduce the size of the primary and metastatic growths, thus reducing disease progression. Patients with ectopic ACTH-secreting tumors typically demonstrate reduced ACTH secretion and the resulting low cortisol secretion. Historically, high-activity ^{111}In-octreotide was used in treatment. Indium-111 emits low-energy Auger electrons characterized by low tissue penetration; therefore, its practical use is limited. Currently, somatostatin analogs labeled with beta-emitters, such as the high-energy beta-emitter yttrium (^{90}Y) and/or medium-energy beta-emitter lutetium (^{177}Lu) are used. In the case of ^{90}Y-DOTA-octreotide (^{90}Y-DOTA-TOC), the complete and partial response (CR and PR) rates are 7–29%, with stable disease (SD) found in 52–88% of patients. If ^{90}Y-DOTA-octreotate is used, these rates are 37% and 52% respectively. Similar results are achieved in patients receiving ^{177}Lu-DOTA-octreotide, with CR/PR achieved in 27% and SD in 34% of patients (Winquist *et al.* 1995; Werder *et al.* 1996; Witek *et al.* 2012). The use of PRRT requires patient monitoring for side effects, especially myelotoxicities (transient lymphocytopenia and thrombocytopenia). However, myelodysplastic syndrome (MDS) may also develop in isolated cases. In order to avoid impairment of renal excretory function, the absorbed dose to the kidney should not exceed 27 Gy and arginine- and lysine-rich solutions should be used for nephroprotection (Kwekkeboom *et al.* 2009; Imhof *et al.* 2011; Filice *et al.* 2012).

In patients with ACTH-producing pheochromocytoma and other NETs with no somatostatin receptor expression and with MIBG uptake, treatment with ^{131}I-MIBG may be administered following thyroid blockade.

6. PROGNOSIS

The prognosis in ectopic ACTH-secreting tumors correlates closely with their histological type. The poorest prognosis involves patients with extrapituitary ACTH-secreting SCLC or high-grade neuroendocrine carcinoma. Concomitant hypercortisolemia is an additional negative prognostic factor as it may lead to cardiovascular risk, thromboembolic complications, carbohydrate metabolism disorders, or increased risk of severe and/or opportunistic infections. Medullary thyroid carcinoma, gastrinoma, and thymic ACTH-producing NETs are associated with poor prognosis, while NETs of the bronchi, pancreas, and vermiform appendix are associated with fair prognosis. Tumors, where the source of ectopic ACTH production is occult are associated with good prognosis, provided that hypercortisolemia is effectively controlled.

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Conflict of interests

The authors have nothing to disclose.

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