Endocrine Journal 2010, **57** (12), 1061-1069

ORIGINAL

Clinical features and management of ectopic ACTH syndrome at a single institute in Japan

Masaru Doi, Toru Sugiyama, Hajime Izumiyama, Takanobu Yoshimoto and Yukio Hirata

Department of Clinical and Molecular Endocrinology, Tokyo Medical and Dental University Graduate School, Tokyo 113-8519, Japan

Abstract. Ectopic ACTH syndrome (EAS) is a diagnostic challenge because it is often indistinguishable from Cushing's disease. We describe our series of EAS patients referred to us during 1992-2009. Among 16 cases (9 females / 7 males), with mean age of 58.4 ± 19.0yr, the ectopic source was identified in ten (proven EAS), whereas unidentified in six (occult/unknown EAS). Their salient clinical manifestations included Cushingoid feature (88%), skin pigmentation (88%), profound hypokalemia (88%), hypertension (75%), diabetes/impaired glucose tolerance (75%), hyperlipidemia (69%), and severe infection (44%). Dynamic endocrine tests revealed markedly elevated plasma ACTH levels (211 ± 116pg/mL) and cortisol levels (60.9 ± 30.1μg/dL) which showed resistance to overnight high-dose (8mg) dexamethasone suppression test in 15 (94%) and unresponsiveness to CRH stimulation in 12 (75%). No ACTH gradient during inferior petrosal sampling was noted in 13 of 15 (87%). Imaging tests by CT/MRI identified the tumors in 8 of 16 (50%), in 4 of 11 (36%) and 4 of 6 (66.7%) octreotide-responders by somatostatin receptor scintigraphy, but in only one of 9 (11.1%) by FDG-PET scan. Six cases deceased, including small cell carcinoma (2) and adenocarcinoma (1) of lung, neuroendocrine carcinoma of pancreas (1) and stomach (1), and olfactory neuroblastoma (1), whereas 4 cases survived after removal of the tumors, including bronchial carcinoid tumor (3) and thymic hyperplasia (1). Six occult/unknown EAS patients survived for 67.5 months after medical treatment with metyrapone to control hypercortisolism. Thus, various endocrine tests combined with imaging studies are required to correctly localize the tumors. Control of hypercortisolemia by metyrapone, even if tumor is unrecognized, is critical for better prognosis, and the long-term follow-up by repeated endocrine and imaging tests is mandatory.

Key words: Ectopic ACTH syndrome (EAS), Octreotide suppression test, Somatostatin receptor scintigraphy (SRS), Metyrapone

ECTOPIC secretion of ACTH from non-pituitary tumors, referred to as ectopic ACTH syndrome (EAS), accounts for about 10-20% of Cushing's syndrome (CS) [1]. About half of EAS patients have lung cancer, such as small cell lung carcinoma (SCLC) and bronchial carcinoid tumor, but about 8-19% of EAS patients have unidentified source of ACTH by any diagnostic means [2-4].

Correct diagnosis by indentifying and localizing the ectopic ACTH source is crucial because treatment of choice for EAS is complete resection of the tumors. Despite the recent advances in diagnostic imaging and endocrine tests to differentiate EAS from Cushing's disease (CD), it is often difficult to localize occult and/or indolent tumors by the conventional imaging procedures, such as computed tomography (CT) and magnetic resonance imaging (MRI), and even the functional imaging procedures, such as somatostatin receptor scintigraphy (SRS) and [^{18}F]fluorodeoxyglucose-positron emission tomography (FDG-PET).

Since the prevalence of EAS is so rare, only a small number of EAS patients have been reported from different institutions with variable investigational protocols, assays, diagnostic techniques as well as different treatments and follow-up periods. Therefore, it is important to analyze all EAS patients who are diagnosed on the basis of an established investigational protocol, updated novel diagnostic modalities, treated and followed up at the same institute to minimize such differences. Recently, there have been three large series published in detail on clinical features, and clinical outcome of EAS patients at a single institute in USA and

Received Sep. 10, 2010; Accepted Oct. 13, 2010 as K10E-265
Released online in J-STAGE as advance publication Nov. 9, 2010

Correspondence to: Yukio Hirata, M.D., Ph.D., Department of Clinical and Molecular Endocrinology, Tokyo Medical and Dental University Graduate School, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8519, Japan. E-mail: yhirata.cme@tmd.ac.jp

Europe [2-4]. Therefore, the present study was aimed to evaluate the clinical, endocrinological, and imaging features, the management and the prognosis of 16 EAS patients encountered at a single institute in Japan.

Methods

Patients

Sixteen patients with ACTH-dependent CS who had been referred, diagnosed as EAS, treated and followed-up at Tokyo Medical and Dental University (TMDU) Hospital during 1992 to 2009, were studied. Diagnostic imaging test by SRS not available in Japan yet was approved by the Ethics Committee of TMDU Hospital; written informed consent was obtained from each patient. Some cases have been reported elsewhere [5-10].

Diagnostic endocrine tests

For differential diagnosis of ACTH-dependent CS, dynamic endocrine tests were performed according to the clinical guideline for the diagnosis of CD proposed by the working group of the Ministry of Health, Welfare and Labor of Japan [11]. A probable diagnosis of EAS was made based on the following criteria, 1) morning serum cortisol level more than a half the basal level after overnight high-dose (8mg) dexamethasone suppression test (HDDST); 2) plasma ACTH response less than 1.5-fold increase over the basal level after stimulation with human corticotropin-releasing hormone (hCRH, 100μg iv bolus:Mitsubishi-Tanabe Pharma, Osaka, Japan) [12], 3) ACTH gradient as estimated by central to peripheral (C/P) ratios less than 2.0 and 3.0 before and after hCRH stimulation, respectively, during inferior petrosal sinus (IPS) / cavernous sinus (CS) sampling [13], and 4) absence of pituitary tumor by MRI scan. Suppression of octreotide (OCT) test was defined as a fall in plasma ACTH levels more than a half the basal level 4-6 hours after sc injection of octreotide (Sandostatin ®, 100μg).

Diagnostic imaging tests

For localization of the tumors, all 16 cases with probable EAS had anatomical imaging tests including CT and MRI scans. As for functional imaging tests, 11 had SRS using [^{111}In-DTPA-D-Phe] pentetreotide [14] and 9 had [^{18} F] FDG-PET scan [15].

A confirmed diagnosis of EAS (proven EAS) was made in 10 cases by demonstration of the presence of ACTH in the tumor tissue specimens obtained from primary or metastatic lesions by surgery or biopsy. ACTH was measured by immunoassays, immunohistochemistry or RT-PCR for POMC, as well as other neuroendocrine makers (chromogranin A, synaptophysin and neuron-specific enolase) by immunohistochemical study. The remaining 6 cases (occult/unkonwn EAS) had negative results of various imaging tests. In those cases with unidentified EAS by any imaging tests, repeated diagnostic imaging tests (CT and/or MRI) were performed every 6–12 months.

Assays

Plasma ACTH and serum cortisol levels were measured by an immunoradiometric assay (Mitsubishi IRMA kit, Mitsubishi Kagaku Medience, Tokyo, Japan), and an enzyme immunoassay (EIA:TOSOH, Tokyo, Japan), respectively.

Statistical analysis

Results are presented as the *mean* ± *SD*. The *t*-test was used for continuous variables, and χ square test for qualitative variables. Survival was analyzed using the Kaplan-Meier method.

Results

Clinical characteristics

Clinical characteristics of sixteen EAS patients (7 males, 9 females) with mean age of 58.4 ± 19.0 (range 21-75), are shown in Table 1. The source of ectopic ACTH secretion was identified (proven EAS) in 10 cases, including small cell lung carcinoma (SCLC) (2), adenocarcinoma of the lung (1), olfactory neuroblastoma (1), gastric malignant carcinoid tumor (or neuroendocrine carcinoma) (1), islet cell carcinoma (or pancreatic neuroendocrine carcinoma) (1), bronchial carcinoid tumor (3), and thymic hyperplasia (1), whereas it was unidentified (occult/unknown EAS) in 6 cases.

Duration of symptoms was 0-46 (11.5 ± 13.2) months. Cushingoid features (moon face, central obesity, easy bruising, hirsutism, muscle weakness) and skin pigmentation were noted in 14 (88%), hypertension in 14 (88%), diabetes mellitus / impaired glucose tolerance(IGT) in 12 (75%), dyslipidemia in 11 (69%), hypokalemia (<3.5mEq/L) in 14 (88%), with mean serum potassium levels (2.58 ± 0.53mEq/L), and severe infection in 7 (44%), including pneumocys-

tis carinii pneumonia (3), septic shock (2), meningitis (1) and pulmonary empyema (1). Two SCLC patients presented concomitantly with syndrome of inappropriate ADH secretion (Case 1) and Eaton-Lambert myasthenic syndrome (Case 2), respectively.

Dynamic Endocrine and imaging tests

Basal plasma ACTH levels (211 ± 116 pg/mL) and serum cortisol levels (60.9 ± 30.1 μg/dL) were markedly elevated (Table 2). There was a significant inverse correlation between serum cortisol and potassium levels (p=0.0044, R^2=0.451). 15 cases (94%) showed no cortisol suppression after overnight HDDST, while 12 cases (75%) had no ACTH response after hCRH stimulation. Among 15 cases who had OCT test, six (40%) showed suppression of ACTH after octreotide administration.

Among 10 cases who underwent IPS/CS sampling, 8 (80%) showed no ACTH gradient before and after CRH stimulation except for two; Case 4 (olfactory neuroblastoma) with C/P ratio (2.8) under the basal state [5] and Case 8 (pulmonary carcinoid tumor) with C/P ratio (3.5) after CRH stimulation [9].

Primary and/or metastatic tumors were identified with CT/MRI scans in 8 of 16 cases (50%): Cases 1, 2, 3 (lung cancer), Case 10 (thymic hyperplasia) and Case 7 (bronchial carcinoid tumor) by chest CT/MRI scan, Case 4 (olfactory neuroblastoma) by head CT/MRI scan, Case 5 (gastric neuroendocrine carcinoma) and Case 6 (pancreatic neuroendocrine carcinoma) by abdominal CT/MRI scan. Case 9 (bronchial carcinoid tumor) and Case 15 (occult/unknown) showed an equivocal pituitary lesion by brain MRI.

Among 11 cases who underwent SRS, 4 (36%) showed positive results; 4 of 6 cases (66.7%) who showed suppression of ACTH after octreotide administration were SRS-positive. Only one (Case 1) of 9 cases (11.1%) showed positive FDG-PET scan.

Management

To control severe hypercortisolemia (>30μg/dL), 15 cases were initially treated with metyrapone (0.75g - 3g/day), in combination with mitotane in two (Cases 2, 15), and later with bilateral adrenalectomy in one (Case 10) [8].

In 10 cases with proven EAS, curative surgery, tumor debulking and/or chemotherapy were performed (Table 3). Four cases had complete remission after surgery, including bronchial carcinoid tumor (Cases 7, 8, 9) and thymic hyperplasia (Case 10). Two cases underwent tumor debulking of advanced neuroendocrine carcinoma with multiple liver metastases, originated from the stomach (Case 5) [6], and the pancreas (Case 6) [7]. Multidisciplinary therapy, including transhepatic arterial embolization, systemic chemotherapy (adriamaycin, dacarbadine, streptozotocin, and fluorouracil), α-interferon, and finally liver transplantation was performed in Case 6 [7]. All 3 cases with lung cancer, 2 SCLC (Cases 1, 2) and one adenocarcinoma (Case 3), had repeated systemic chemotherapy and radiation.

All 6 cases with occult/unknown EAS were treated medically by block-and-replacement therapy with metyrapone (0.75-2.25g/day) with or without dexamethasone (0.5mg/day) to control hypercortisolemia (Table 3). In all cases, serum cortisol levels were suppressed less than 10μg/dL after metyrapone administration without any adverse effects even after long-term treatment, and Cushignoid features, metabolic abnormalities (hypokalemia, hypertension, and diabetes) and severe infection subsided.

Prognosis

Four of ten cases (40%) with confirmed EAS, including 3 bronchial carcinoid tumors (Cases 7, 8, 9) and one thymic hyperplasia (Case 10) are all alive. In contrast, 3 with lung cancer (Cases 1, 2, 3), 2 with neuroendocrine carcinoma (Cases 5, 6) and one with olfactory neuroblastoma (Case 4), all deceased due to the progression of the primary lesions and/or the widespread metastatic lesions. As shown in Fig. 1, the median duration of follow-up was 57.2 months (range 6-238) with 10 proven EAS; 6 cases had no remission by surgical and/or medical treatment (range 7-89), whereas 4 cases had complete remission (range 38-238). Six cases with occult/unknown EAS are all alive for the median duration of follow-up of 67.5 months (range 36 -127).

Discussion

Despite the intensive search for the culprit tumors by dynamic endocrine tests and imaging tests, it is often difficult to localize and confirm the source of occult ectopic ACTH secretion. Thus, it is a diagnostic challenge for endocrinologist to differentiate ACTH-dependent CS because EAS and CD share many clinical and endocrinological features in common. This study evaluated the clinical, endocrinological, and radiological features of 16 EAS patients diagnosed and treated as well as the management and prognosis at a

Table 1 Clinical characteristics of 16 EAS patients at TMDU Hospital

Case #	Age/ gender	Tumor type	Cushingoid feature	Skin pigmentation	Hypertension	Diabetes/ IGT	Dys-lipidemia	Serum potassium (mEq/L)	Severe infection
1	58 M	Small-cell lung cancer	-	-	-	-	-	3.8	-
2	69 M	Small-cell lung cancer	-	-	+	+	+	2.6	-
3	74 M	Lung adenocarcinoma	+	+	+	+	-	2.5	-
4	39 F	Olfactory neuroblastoma	+	+	+	-	-	1.2	+
5	49 M	Gastric carcinoid	+	+	+	+	+	2.5	-
6	21 F	Islet cell carcinoma	+	+	+	+	+	2.0	+
7	69 F	Pulmonary carcinoid	+	+	+	+	-	2.2	-
8	75 F	Pulmonary carcinoid	+	+	+	+	+	3.7	-
9	70 F	Pulmonary carcinoid	+	+	+	+	+	2.2	-
10	25 M	Thymic hyperplasia	+	+	-	IGT	+	3.1	+
11	32 M	Occult/unknown	+	+	+	-	+	3.3	-
12	61 F	Occult/unknown	+	+	-	IGT	+	2.6	+
13	63 F	Occult/unknown	+	+	-	-	+	1.8	+
14	74 F	Occult/unknown	+	+	-	+	-	2.0	-
15	75 M	Occult/unknown	+	+	+	+	+	2.8	+
16	81 F	Occult/unknown	+	+	+	+	+	2.9	+
Mean±SD	58.4±19.0 / 7M, 9F		14/16 (88%)	14/16 (88%)	12/16 (75%)	12/16 (75%)	11/16 (69%)	14/16* (88%)	7/16 (44%)

IGT: impaired glucose tolerance, * frequency of hypokalemia (<3.5mEq/L), Case 1 and Case 2 were concomitantly associated with syndrome of inappropriate ADH secretion and Eaton-Lambert myasthenic syndrome, respectively.

Table 2 Dynamic endocrine and imaging tests in 16 EAS patients at TMDU Hospital

	Endocrine test						Imaging test				
Case #	ACTH (pg/mL)	Cortisol (μg/dL)	DST (8mg)	CRH	OCT	IPSS C/P ratio	Pituitary MRI	CT	MRI	SRS	FDG-PET
1	284	18.7	-	-	-	ND	-	+	+	ND	+
2	40.2	70.2	-	-	-	ND	-	+	+	ND	ND
3	297	57.1	-	-	+	ND	ND	+	+	+	ND
4	150	80.1	-	+	-	2.8*	-	+	+	ND	ND
5	220	50	-	-	-	ND	-	+	+	ND	ND
6	735	145	-	-	+	ND	-	+	+	+	ND
7	205	47	-	-	-	1.0	-	+	+	-	-
8	158	31.6	-	+	+	3.5	-	-	-	+	-
9	142	43.2	-	-	+	1.1	+	-	-	+	-
10	45	30.3	-	+	ND	ND	-	+	+	ND	ND
11	90	41.4	+	+	-	1.0	-	-	-	-	ND
12	130	76.3	-	-	-	1.1	-	-	-	-	-
13	490	77.4	-	-	+	1.3	-	-	-	-	-
14	173.2	102.2	-	-	-	1.5	-	-	-	-	-
15	153	48	-	-	-	1.3	+	-	-	-	-
16	157	56.9	-	+	+	1.2	-	-	-	-	-
Mean±SD	216.8±175	61.0±31.1	15/16 (94%)	12/16 (75%)	6/15 (40%)	8/10 (80%)	2/15 (13%)	8/16 (50%)	8/16 (50%)	4/11 (36%)	1/9 (11%)

DST: dexamethasone suppression test , IPSS; Inferior petrosal sinus sampling, CT; computed tomography, MRI; magnetic resonance imaging, SRS; somatostatin receptor scintigraphy, FDG-PET; [^{18}F] fluorodeoxyglucose-positron emission tomography, ND: not determined, * sampling without CRH stimulation

Table 3 Multidisciplinary treatment and clinical outcome in 16 EAS patients at TMDU Hospital

Proven EAS (n=10)

Case #	Tumor type	Meta-stasis	Multidisciplinary therapy	Follow-up (month)	Outcome
1	Small-cell lung cancer	-	ChT	7	deceased
2	Small-cell lung cancer	+	Met, Mit, ChT	6	deceased
3	Lung adenocarcinoma	-	Met, Rad	7	deceased
4	Olfactory neuroblastoma	+	Met, Tx, Rad	89	deceased
5	Gastric carcinoid	+	Met, INFα	10	deceased
6	Islet cell carcinoma	+	Met, Oct, Tx, TAE, TAI, CT, LTx, INFα	61	deceased
7	Pulmonary carcinoid	-	Met, Tx	50	alive
8	Pulmonary carcinoid	-	Met, Oct, Tx	38	alive
9	Pulmonary carcinoid	-	Met, Oct, Tx	66	alive
10	Thymic hyperplasia	-	Hypox, Met, Adx, Thymex	238	alive

Occult/unknown EAS (n=6)

Case #	Medical therapy	Cortisol (μg/dL)	Follow-up (month)	Outcome
11	Met (0.75g/day)	0.2	92	alive
12	Met (2.25g/day)	0.44	42	alive
13	Met (0.75g/day)	11.1	127	alive
14	Met (0.75g/day)	5.4	36	alive
15	Met (1.5g/day), Mit (2g/day)	5.9	65	alive
16	Met (1.25g/day)	0.51	43	alive
		3.9±4.4	67.5±28	

ChT:chemotherapy, Met:metyrapone, Mit:mitotane, Oct:octreotide, Tx:tumor resection, Rad:radiation, TAE: transcatheter arterial embolization, TAI: transcatheter arterial infusion LTx; liver transplantation, Hypox: hypophysectomy, Adx: adrenalectomy, Thymex: thymectomy

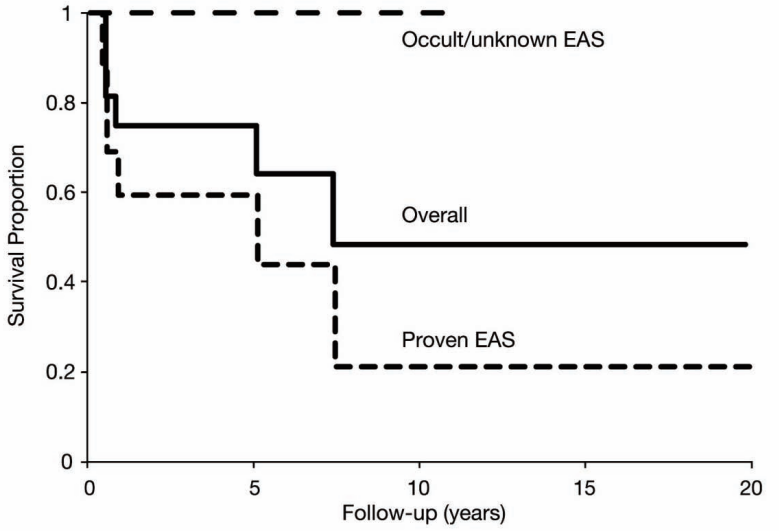

Fig. 1 Survival curves for 16 EAS patients at TMDU Hospital

Kaplan-Meier survival curves for 16 EAS patients. Overall EAS (*n*=16), proven EAS (*n*=10), and occult/unknown EAS (*n*=6), A 5/10-year survival rate in overall, proven, and occult/unknown EAS was 75%/48%, 60%/23% and 100%/100%, respectively.

single institution in Japan.

In our series, the lung is the major organ (37.5%) harboring an ectopic source of ACTH secretion, including slowly-growing bronchial carcinoid tumors (3) and rapidly-growing lung cancers (3), such as SCLCs (2) and adenocarcinoma (1). These data are consistent with those of other series [16], as well as those in Japan [17, 18] in which nearly 50% ectopic ACTH-secreting tumors are localized in the lung, including SCLC and bronchial carcinoid tumors.

A majority of our EAS patients (88%) presented with skin pigmentation and Cushingoid features due to chronic excess of ACTH and cortisol, respectively, except for 2 SCLC cases who had too short duration and rapid progression of tumors to develop Csushignoid features and skin pigmentation [19]. Recently, EAS patients with lung cancer, especially SCLC, a predominant tumor causing EAS, documented in the previous series in Japan [17], have been often diagnosed and managed by nonendocrinologists. Instead, patients with slowly-growing tumors, especially carcinoid tumors presenting with clinical and endocrinological features indistinguishable from CD, usually consult endocrinologists. The incidence of Cushingoid features in our series (88%) appears to be consistent with those of recent other series (61-100%) [1] and very similar to those of CD [20]. In contrast, the incidence of skin pigmentation in our series (88%) seems somewhat higher than those of other studies (19-76%) [1-3, 20]. This may be partly accounted for by the increased sensitivity of skin melanocytes to chronic exposure of the MSH-like activity of excess ACTH and/or the careful and thorough physical examination to detect not only diffuse skin pigmentation, but also local pigmentation, such as in oral mucosa and nail bed.

Our EAS patients had various metabolic complications due to hypercortisolemia, such as hypertension (75%), diabetes (75%), and dyslipidemia (69%), whose frequencies appear comparable to those of other type of CS [21]. It should also be noted that most EAS patients (81%) in our series presented a profound hypokalemia, which is in accordance with previous studies [1, 2]. Since the mineralocorticoid receptor (MR) in the renal tubule is protected from the excess of cortisol by the action of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) to convert cortisol to inactive cortisone, saturation of renal 11β-HSD2 by excess circulating cortisol such as in EAS allow it to reach MR to induce hypokalemia [22]. In fact, hypokalemia was inversely related to hypercortisolemia in our series. Thus, a salient hypokalemia could be a biochemical marker more suggestive of EAS rather than CD.

In our series, severe infection (pneumocystis carinii pneumonia, septic shock, meningitis and pulmonary empyema) occurred in 44%, due to increased susceptibility to opportunistic infection by hypercortisolemia. Since severe infection caused by hypercortisolemia is a major cause of mortality in EAS patients [23], rigorous evaluation of causative microorganisms and appropriate selection of antibiotics as well as prophylaxis for opportunistic infections, such as pneumocystis carinii, should be done.

All cases except one had extremely elevated ACTH and cortisol levels in our series, but there were no major differences of ACTH and cortisol levels between the proven and the occult/unknown EAS patients. Thus it is suggested that occult tumors have increased secretory activity to induce florid clinical manifestations comparable to those of the proved tumors, irrespective of recognizable tumor size.

Various dynamic endocrine tests have been established and widely used for the differential diagnosis of ACTH-dependent CS. For example, HDDST had sensitivity (65-100%) and specificity (60-100%), and CRH stimulation test had sensitivity (86%) and specificity (95%), respectively [24]. Only one patient (6.3%) showed suppression by HDDST, but 25% responded to hCRH stimulation in our series. It has been reported that 6-40% EAS patients showed suppression of serum cortisol, urinary cortisol or 17-OHCS by HDDST [16], and that 8-10% of CD patients do not respond to CRH stimulation, whereas about 20% EAS patients respond to CRH stimulation [12]. Although each test on its own may be of relatively limited diagnostic accuracy, lack of responses to both tests has a very high, albeit not perfect, sensitivity for the diagnosis of EAS.

IPS/CS sampling with CRH stimulation has been regarded as the most accurate and reliable method to differentiate CD from EAS with high sensitivity (88-100 %) and specificity (90-100 %) [13, 25]. Although there are several possible causes of false-negative findings mainly due to anatomical abnormalities of venous drainage, false-positive cases have been rarely reported [26, 27]. In our series, two cases showed positive result of IPS sampling (Case 4) and normal response to CRH stimulation (Case 8), which may be partly explained by tumor venous drainage closest to the cavernous sinus [5] and the possible trough period of cyclic hormono-

genesis by the tumor [9], respectively.

Despite extensive evaluation by various imaging tests, tumor was unidentified in 6 of 16 (37.5%) in our series, which seem higher than those (8-19%) reported by other institutes [2-4]. This is possibly reflecting referral bias and/or limited follow-up periods. In fact, 2 of 6 cases with occult/unknown tumor were referred to us from other institutes in search for the unidentified tumor(s) by diagnostic imaging tests including SRS. Thus, this study has a limitation of accrual bias. Since EAS patients with overt tumor were referred less frequently than those with occult/unknown tumor, the frequency of its localization may be estimated to be low.

The correct localization and confirmation of the ectopic ACTH source by indolent tumor, essentially bronchial carcinoid tumor, is often difficult by the conventional imaging tests, because such tumors are often too small and occult to be detected by the conventional imaging modalities; up to 50% EAS patients are undetectable by CT and MRI scans [2, 28]. In our series, tumors were detected by CT and/or MRI in 8 of 16 cases (50%), thus complimenting those of other institutes [2-4].

SRS has been widely used as a useful tool for the visualization of a wide variety of neuroendocrine tumors (NET) to localize the primary tumor as well as the recurrent and/or the metastatic tumors[29]. Because of the predominant expression of somatostatin receptor subtype 2 and 3 in NET [30], the sensitivities of SRS for detection of EAS varied from 25% [4] to 73% [31]. In our series, 4 of 11 cases (36%) showed positive results by SRS which appear to be comparable to those of other studies [2, 14]. It should be noted that 4 of 6 cases (67%) with ACTH suppression by octreotide showed positive result on SRS. Thus, OCT test could be used in occult/unknown EAS patients as a screening for selection of SRS, because SRS is not available in Japan yet.

Only one (SCLC) out of 9 cases (11.1%) in our series had positive FDG-PET scan. FDG-PET has been reported for detection of EAS with sensitivity of 64% [14]. Since FDG-PET is known to identify tumors with high proliferative activities [15], this modality seems limited to localize malignant tumors with highly aggressive and invasive nature, like SCLC. Since a single positive finding may represent a false-positive result, combination of anatomical and functional imaging tests should be taken into account in such cases with a questionable, but equivocal tumor [14, 31].

All 15 cases in our series were initially and successfully treated medically with steroid synthesis inhibitor, metyrapone, except for one (Case 10) who had bilateral adrenalectomy later [8]. The control of the excess cortisol burden represents an important part of the management [23, 32]. There are many options for adrenal–directed medical therapies, such as steroid synthesis inhibitors (metyrapone, mitotane, trilostane, ketoconazole, aminoglutethimide) and glucocorticoid receptor antagonists (mifepristone) [33, 34]. However, only three drugs (metyrapone, mitotane, trilostane) are available in Japan, among which metyrapone has been only approved as a drug for metyrapone test. Thus, metyrapone, a selective inhibitor of adrenal 11β-hydroxylase, due to its potent and reversible blockade on cortisol synthesis without major adverse effects during long-term use, should be approved as a drug for medical treatment of choice for intractable CS including EAS in Japan.

The prognosis of EAS patients depends on the tumor type. All 6 cases with malignant tumors, including SCLC and gastroenteropancreatic NET (GEP-NET), deceased within 30 months on average, irrespective of multidisciplinary treatment. By WHO classification of ‘endocrine tumors 2004’, SCLC and GEP-NET which belong to poorly-differentiated and well-differentiated endocrine carcinoma with high-grade and low-grade malignant behavior, respectively [35], had the worst prognosis, especially SCLC. On the other hand, all 3 cases with bronchial carcinoid tumor, as classified as well-differentiated endocrine tumors with benign or uncertain behavior, could survive, should the tumor correctly localized and removed. All 6 occult/unknown EAS patients, even if a tumor unrecognized, are alive under medical management of hypercortisolism. For example, Case 7 with occult/unknown EAS had been medically treated with metyrapone for 3 years until it was found to be ACTH-secreting bronchial carcinoid tumor successfully localized by selective pulmonary artery sampling (covert EAS) [10]. Thus, a long-term follow-up of such patients with unrecognized tumor are required by repeated endocrine and imaging tests.

In summary, the clinical spectrum of EAS is broad. To localize the tumors responsible for ectopic ACTH secretion, combination of dynamic endocrine tests and imaging tests, including anatomical modalities (CT, MRI) and functional modalities (SRS, FDG-PET) is required. SRS could be more useful for localization of tumors in EAS patients who show ACTH suppression

by octreotide administration. The prognosis of EAS patients depends on the tumor histology. Even patients with unrecognized tumor could have a favorable prognosis, if hypercortisolism is managed until the tumor may develop to allow its localization.

Acknowledgments

We are indebted to the follows and the nurses of endocrine/metabolism ward at TMDU Hospital for taking care of the patients and the house staff of the affiliated hospitals for referring them included in this study. This study was supported in part by Grants-in-Aid for Scientfic Research from the Ministry of Health, Welfare and Labor and the Ministry of Education, Science, Sports and Culture of Japan.

References

1. Wajchenberg BL, Mendonca BB, Liberman B, Pereira MA, Carneiro PC, Wakamatsu A, Kirschner MA (1994) Ectopic adrenocorticotropic hormone syndrome. *Endocr Rev* 15: 752-787.
2. Ilias I, Torpy DJ, Pacak K, Mullen N, Wesley RA, Nieman LK (2005) Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. *J Clin Endocrinol Metab* 90: 4955-4962.
3. Salgado LR, Fragoso MC, Knoepfelmacher M, Machado MC, Domenice S, Pereira MA, de Mendonca BB (2006) Ectopic ACTH syndrome: our experience with 25 cases. *Eur J Endocrinol* 155: 725-733.
4. Isidori AM, Kaltsas GA, Pozza C, Frajese V, Newell-Price J, Reznek RH, Jenkins PJ, Monson JP, Grossman AB, Besser GM (2006) The ectopic adrenocorticotropin syndrome: clinical features, diagnosis, management, and long-term follow-up. *J Clin Endocrinol Metab* 91: 371-377.
5. Kanno K, Morokuma Y, Tateno T, Hirono Y, Taki K, Osamura RY, Hirata Y (2005) Olfactory neuroblastoma causing ectopic ACTH syndrome. *Endocr J* 52: 675-681.
6. Tsuchiya K, Minami I, Tateno T, Izumiyama H, Doi M, Nemoto T, Mae S, Kasuga T, Osamura RY, Oki Y, Hirata Y (2005) Malignant gastric carcinoid causing ectopic ACTH syndrome: discrepancy of plasma ACTH levels measured by different immunoradiometric assays. *Endocr J* 52: 743-750.
7. Doi M, Imai T, Shichiri M, Tateno T, Fukai N, Ozawa N, Sato R, Teramoto K, Hirata Y (2003) Octreotide-sensitive ectopic ACTH production by islet cell carcinoma with multiple liver metastases. *Endocr J* 50: 135-143.
8. Ohta K, Shichiri M, Kameya T, Matsubara O, Imai T, Marumo F, Hirata Y (2000) Thymic hyperplasia as a source of ectopic ACTH production. *Endocr J* 47: 487-492.
9. Tani Y, Sugiyama T, Hirooka S, Izumiyama H, Hirata Y (2010) Ectopic ACTH syndrome caused by bronchial carcinoid tumor indistinguishable from Cushing's disease. *Endocr J* 57: 679-686.
10. Sugiyama M, SugiyamaT, Yamaguchi M, Izumiyama H, Yoshimoto T, Kishino M, Akashi T, Hirata Y (2010) Successful localization of ectopic ACTH-secreting bronchial carcinoid by selective pulmonary arterial sampling. *Endocr J* 57: 959-964.
11. Suda T, Kageyama K, Nigawara T, Sakihara S (2009) Evaluation of diagnostic tests for ACTH-dependent Cushing's syndrome. *Endocr J* 56: 469-476.
12. Newell-Price J, Morris DG, Drake WM, Korbonits M, Monson JP, Besser GM, Grossman AB (2002) Optimal response criteria for the human CRH test in the differential diagnosis of ACTH-dependent Cushing's syndrome. *J Clin Endocrinol Metab* 87: 1640-1645.
13. Kaltsas GA, Giannulis MG, Newell-Price JD, Dacie JE, Thakkar C, Afshar F, Monson JP, Grossman AB, Besser GM, Trainer PJ (1999) A critical analysis of the value of simultaneous inferior petrosal sinus sampling in Cushing's disease and the occult ectopic adrenocorticotropin syndrome. *J Clin Endocrinol Metab* 84: 487-492.
14. Zemskova MS, Gundabolu B, Sinaii N, Chen CC, Carrasquillo JA, Whatley M, Chowdhury I, Gharib AM, Nieman LK (2010) Utility of various functional and anatomic imaging modalities for detection of ectopic adrenocorticotropin-secreting tumors. *J Clin Endocrinol Metab* 95: 1207-1219.
15. Pacak K, Ilias I, Chen CC, Carrasquillo JA, Whatley M, Nieman LK (2004) The role of [(18)F]fluorodeoxyglucose positron emission tomography and [(111)In]-diethylenetriaminepentaacetate-D-Phe-pentetreotide scintigraphy in the localization of ectopic adrenocorticotropin-secreting tumors causing Cushing's syndrome. *J Clin Endocrinol Metab* 89: 2214-2221.
16. Alexandraki KI, Grossman AB (2010) The ectopic ACTH syndrome. *Rev Endocr Metab Disord*. 11: (online first).
17. Imura H (1980) Ectopic hormone syndrome. *Clin Endocrinol* 9: 235-260.

18. Hirata Y, Matsukura S, Fujita T (1983) ACTH and related peptide in normal and abnormal tissue. In: Fotherby K and Pal SB (ed) Hormones in Normal and Abnormal Human Tissues Vol.3 Walter de Gruyter, Berlin / New York: 169-193.
19. Collichio FA, Woolf PD, Brower M (1994) Management of patients with small cell carcinoma and the syndrome of ectopic corticotropin secretion. Cancer 73: 1361-1367.
20. Beuschlein F, Hammer GD (2002) Ectopic pro-opiomelanocortin syndrome. *Endocrinol Metab Clin North Am* 31: 191-234.
21. Boscaro M, Arnaldi G (2009) Approach to the patient with possible Cushing's syndrome. *J Clin Endocrinol Metab* 94: 3121-3131.
22. Torpy DJ, Mullen N, Ilias I, Nieman LK (2002) Association of hypertension and hypokalemia with Cushing's syndrome caused by ectopic ACTH secretion: a series of 58 cases. *Ann N Y Acad Sci* 970: 134-144.
23. Sarlis NJ, Chanock SJ, Nieman LK (2000) Cortisolemic indices predict severe infections in Cushing syndrome due to ectopic production of adrenocorticotropin. *J Clin Endocrinol Metab* 85: 42-47.
24. Newell-Price J, Trainer P, Besser M, Grossman A (1998) The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. *Endocr Rev* 19: 647-672.
25. Oldfield EH, Doppman JL, Nieman LK, Chrousos GP, Miller DL, Katz DA, Cutler GB Jr, Loriaux DL (1991) Petrosal sinus sampling with and without corticotropin-releasing hormone for the differential diagnosis of Cushing's syndrome. *N Engl J Med* 325: 897-905.
26. Swearingen B, Katznelson L, Miller K, Grinspoon S, Waltman A, Dorer DJ, Klibanski A, Biller BM (2004) Diagnostic errors after inferior petrosal sinus sampling. *J Clin Endocrinol Metab* 89: 3752-3763.
27. Vilar L, Freitas Mda C, Faria M, Montenegro R, Casulari LA, Naves L, Bruno OD (2007) Pitfalls in the diagnosis of Cushing's syndrome. *Arq Bras Endocrinol Metabol* 51: 1207-1216.
28. Doppman JL, Nieman L, Miller DL, Pass HI, Chang R, Cutler GB Jr, Schaaf M, Chrousos GP, Norton JA, Ziessman HA, et al. (1989) Ectopic adrenocorticotropic hormone syndrome: localization studies in 28 patients. *Radiology* 172: 115-124.
29. Ramage JK, Davies AH, Ardill J, Bax N, Caplin M, Grossman A, Hawkins R, McNicol AM, Reed N, Sutton R, Thakker R, Aylwin S, Breen D, Britton K, Buchanan K, Corrie P, Gillams A, Lewington V, McCance D, Meeran K, Watkinson A (2005) Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. *Gut* 54 Suppl 4: iv1-i16.
30. Cimitan M, Buonadonna A, Cannizzaro R, Canzonieri V, Borsatti E, Ruffo R, De Apollonia L (2003) Somatostatin receptor scintigraphy versus chromogranin A assay in the management of patients with neuroendocrine tumors of different types: clinical role. *Ann Oncol* 14: 1135-1141.
31. Tsagarakis S, Christoforaki M, Giannopoulou H, Rondogianni F, Housianakou I, Malagari C, Rontogianni D, Bellenis I, Thalassinos N (2003) A reappraisal of the utility of somatostatin receptor scintigraphy in patients with ectopic adrenocorticotropin Cushing's syndrome. *J Clin Endocrinol Metab* 88: 4754-4758.
32. Graham, B.S., Tucker, W.S. Jr (1984) Opportunistic infections in endogenous Cushing's syndrome. *Ann. Intern. Med.* 101: 334-338.
33. Biller BM, Grossman AB, Stewart PM, Melmed S, Bertagna X, Bertherat J, Buchfelder M, Colao A, Hermus AR, Hofland LJ, Klibanski A, Lacroix A, Lindsay JR, Newell-Price J, Nieman LK, Petersenn S, Sonino N, Stalla GK, Swearingen B, Vance ML, Wass JA, Boscaro M (2008) Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 93: 2454-2462.
34. Sonino N, Boscaro M, Fallo F (2005) Pharmacologic management of Cushing syndrome : new targets for therapy. *Treat Endocrinol* 4: 87-94.
35. Kloppel G, Perren A, Heitz PU (2004) The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. *Ann N Y Acad Sci* 1014: 13-27.