Endokrynologia Polska
DOI: 10.5603/EP.2015.0002
Tom/Volume 66; Numer/Number 1/2015
ISSN 0423–104X

Ectopic Cushing's syndrome secondary to lung and mediastinal tumours — report from a tertiary care centre in Iran

Ektopowy zespół Cushinga u pacjentów z nowotworem śródpiersia lub płuc — doniesienie z ośrodka trzeciego stopnia referencyjności w Iranie

Ali A. Ghazi[1], Azizollah Abbasi Dezfooli[2], Alireza Amirbaigloo[1, 3], Abolghasem Daneshvar Kakhki[2], Farzaneh Mohammadi[4], Farrokh Tirgari[5] and Marina Pourafkari[6]

[1]Endocrine Research Centre, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Thoracic Surgery, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Endocrine Research Centre, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran
[4]Department of Pathology, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
5Department of Pathology, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran
[6]Department of Radiology, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Introduction: Ectopic Cushing`s syndrome (ECS) secondary to neuroendocrine tumours (NETs) of the lung and mediastinum are rarely encountered. In this study, we present our experience in Iran on 15 patients with ECS secondary to lung and mediastinal tumours over a period of 27 years.

Material and methods: Since 1985, 15 patients with ECS secondary to lung and mediastinal tumours have been diagnosed and prospectively followed by the endocrinology team of Taleghani Hospital, Tehran, Iran. The clinical signs and symptoms, laboratory findings, radiological features, immunohistochemical characteristics, management strategies and outcome data are here presented.

Results: There were six women and nine men, aged 26–70 years, all presenting with typical features of Cushing's syndrome. Based on histopathologic evaluations, four patients had small cell lung cancer (SCLC) and seven patients had pulmonary NETs, one patient had a thymic NET, and one case was diagnosed as a lung tumourlet. The mean ± SD serum cortisol, 24h urine free cortisol and plasma ACTH were 47.2 ± 20.5 μg/dL, 2,702 ± 5,439 μg/day, and 220 ± 147 pg/mL, respectively. Pulmonary lesions ranged in diameter from 1.1 to 4 cm (mean 1.9 ± 1.1 cm). One patient had a 10 cm mediastinal mass. The duration of follow up in these cases was between one month and seven years (mean 29.9 ± 27.5 months). The four patients with SCLC died within three months of diagnosis.

Conclusion: Our data demonstrates the protean clinical and laboratory manifestations of ECS secondary to lung and mediastinal tumours, the problems encountered in diagnosis, and the need for a multidisciplinary approach. This study confirms other series from Western Europe and North America that, unlike the SCLC patients who show a poor outlook, ECS secondary to lung carcinoids has a more favourable prognosis. **(Endokrynol Pol 2015; 66 (1): 2–9)**

Key words: *ectopic Cushing's syndrome; mediastinum; lung; carcinoid; carcinoma*

Streszczenie

Wstep: Ektopowy zespół Cushinga (ectopic Cushing`s syndrome, ECS), który rozwija się u pacjentów mających nowotwory neuroendokrynne (neuroendocrine tumours, NET) śródpiersia lub płuc, jest zaburzeniem rzadko spotykanym. Niniejsza publikacja przedstawia doświadczenia autorów z ośrodka w Iranie, którzy w okresie 27 lat prowadzili 15 pacjentów z zespołem Cushinga wtórnym do nowotworów śródpiersia lub płuc.

Materiał i metody: W okresie od 1985 zespół endokrynologów ze szpitala Taleghani Hospital w Teheranie zidentyfikował i prowadził w sposób prospektywny 15 pacjentów z objawami ECS uwarunkowanymi obecnością nowotworów śródpiersia lub płuc. Niniejsza publikacja przedstawia obraz kliniczny i objawy podmiotowe, wyniki badań laboratoryjnych i radiologicznych oraz badań immunohistochemicznych materiału tkankowegoz guzów nowotworowych, a także informacje na temat wdrożonego leczenia i jego wyników.

Wyniki: W badanej grupie znalazło się 6 kobiet i 9 mężczyzn, w wieku 26–70 lat. U wszystkich pacjentów stwierdzono typowe cechy kliniczne zespołu Cushinga. Na podstawie badań histopatologicznych wycinków z guzów nowotworowych postawiono rozpoznanie drobnokomórkowego raka płuca (SCLC, small cell lung cancer) u 4 pacjentów, neuroendokrynnego nowotworu płuca (NET) bliżej nieokreślonego typu u 7 pacjentów, NET grasicy u jednej osoby oraz rozpoznanie zmiany typu tumorlet w płucu u jednej osoby. Średnie stężenie kortyzolu w surowicy (± odchylenie standardowe) wyniosło 47,2 ± 20,5 μg/dl, stężenie wolnego kortyzolu w moczu ze zbiórki dobowej 2.702 ± 5.439 μg/dobę, a stężenie ACTH w osoczu 220 ± 147 pg/ml. Zmiany nowotworowe w płucach miały wielkość od 1,1 do 4 cm (średni wymiar guza 1,9 ± 1,1 cm). Guz śródpiersia (u jednej osoby) miał średnicę 10 cm. Czas obserwacji wyniósł od 1 miesiąca do 7 lat (średnia 29,9 ± 27,5 miesięcy). Czterech chorych na SCLC zmarło w okresie do 3 miesięcy od postawienia rozpoznania.

Alireza Amirbaigloo, MD., Endocrine Research Centre, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran; Endocrine Research Centre, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran, P. O. Box: 15937-48711, tel.: +98 21 889 451 72, fax: +98 21 889 451 73, e-mail: amirbaigloo@alumnus.tums.ac.ir

Wnioski: Przedstawione dane wskazują na różnorodność obrazu klinicznego i danych laboratoryjnych u pacjentów z objawami ECS w przebiegu choroby nowotworowej śródpiersia lub płuc. Konstelacja ta wymaga więc wielospecjalistycznej opieki już od momentu wdrożenia postępowania diagnostycznego. Przedstawione wyniki są zbieżne z danymi z publikacji pochodzących z Europy Zachodniej i Stanów Zjednoczonych i wskazują na stosunkowo korzystne rokowanie u pacjentów mających objawy ECS w związku z rakowiakiem płuca, w przeciwieństwie do pacjentów mających zmiany typu SCLC. **(Endokrynol Pol 2015; 66 (1): 2–9)**

Słowa kluczowe: *ektopowy zespół Cushinga; śródpiersie; płuco; rakowiak; rak*

This study was supported by a grant from the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran. There is no relationship with industry.

Introduction

Ectopic Cushing`s syndrome (ECS) is defined as endogenous hypersecretion of cortisol secondary to excess secretion of ACTH from a non-pituitary origin. The syndrome was first described by Brown in 1928 [1]. In 1963, Liddle et al. defined the condition in more detail and suggested possible mechanisms for the pathogenesis of the syndrome [2].

ECS constitutes approximately 10% of patients with endogenous Cushing's syndrome (CS) [3-5]. The lung is the most prevalent site of tumours leading to ECS. Earlier reports indicated that small cell lung carcinoma (SCLC) was the main cause of the syndrome, but according to more recent studies neuroendocrine tumours (NETs) or carcinoids have overtaken SCLC as the most frequent tumours causing the syndrome [5–7].

The main concern in the diagnosis and management of ECS secondary to lung and mediastinal tumours is the heterogeneous clinical presentation, ranging from a typical picture of CS to a non-specific picture of muscle weakness, electrolyte abnormalities, psychiatric manifestations, weight loss, infections and osteoporosis. As a result, physicians from different disciplines may encounter the syndrome [8, 9].

Due to the rarity of the syndrome, most clinical reports in the medical literature present a single case or a limited number of cases, and there are few papers specifically reviewing clinical and laboratory data in a large number of patients suffering from ECS secondary to lung tumours [10–14].

In this study, we present our experience in 15 patients with ECS secondary to lung and mediastinal tumours who were diagnosed, treated and followed up over 27 years at Taleghani and Masih Daneshvari University Hospitals affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran. This is the first study in a Middle Eastern country addressing protean manifestations of ECS secondary to lung and mediastinal tumours in a substantial number of patients.

Material and methods

From 1985, of 110 patients with a diagnosis of Cushing's syndrome, 15 patients with ECS secondary to lung and mediastinal tumours were studied and followed. The patients included six women and nine men. All patients were examined by the authors and admitted for endocrinological evaluation at either the Department of Endocrinology of Taleghani General Hospital or Kasra Hospital. The surgery and histopathologic evaluations were carried out at Taleghani General Hospital, Masih Daneshvari and Kasra Hospital.

All patients underwent routine laboratory evaluation and measurement of serum and 24 hour urinary free cortisol (UFC) and basal plasma ACTH concentrations. Dexamethasone suppression tests were performed according to Liddle's classic protocols of low-dose (2 mg daily for two days) and high-dose (8 mg daily for two days) suppression tests, except that instead of measuring urinary ketosteroids, UFC was measured [15–17]. All the UFC measurements were carried out by commercial kits using the RIA (radioimmunoassay) method.

Pituitary CT scanning or MRI, abdominal CT scanning, chest radiology and chest CT scanning were performed in all cases. CT scans were performed with conventional or spiral single slice CT scanners. In all of the scans, IV contrast was used. A more sophisticated CT scanner was not available to us. Radionuclide octreotide scanning with ^{111}-indium octreotide was carried out in only two cases. Inferior petrosal sinus sampling (IPSS) was not available to us and, due to unavailability of corticotrophin releasing hormone (CRH), we could not perform CRH stimulation test for our patients. Histopathologic evaluations including immunohistochemistry (IHC) studies were interpreted by three expert academic pathologists. One patient had MEN1 syndrome and has been reported earlier [18]. The protocol was approved by the ethics committee of the Research Institute for Endocrine Sciences affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Results

Clinical characteristics (Tables I and II)

The patients were six women and nine men, aged 26–70 years (47.7 ± 14.7 mean ± SD). The duration of symptoms was less than one month to 48 months (mean

Table I. *Clinical data of 15 patients with ectopic Cushing's syndrome*
Tabela I. *Dane demograficzne 15 pacjentów z objawami ektopowego zespołu Cushinga*

Case no.	Sex	Age (years)	Presenting symptoms	Duration (months)	Aetiology	Follow up (months)	Outcome
1	F	62	Fatigability, muscle weakness	3	SCLC	1	Died after two weeks from sepsis
2	M	32	Muscle weakness, hyperpigmentation, impotence	24	NET?	24	Died two years after adrenalectomy due to a huge mediastinal mass
3	F	58	Moon face, striae, muscle weakness, hypertension	48	Atypical carcinoid	60	Died after five years
4	F	68	Moon face, fatigability, muscle weakness, fever, sepsis	2	NET?	1	Died the night before surgery because of cardiac arrhythmias
5	M	37	Weight gain, striae, moon face, muscle weakness	48	Typical carcinoid	48	Alive without recurrence
6	M	35	Moon face, fatigue, headache, striae, weight gain	10	Typical carcinoid	24	Alive without recurrence
7	M	34	Truncal obesity, muscle weakness, hypertension	12	Typical carcinoid	60	Alive without recurrence
8	M	43	Moon face, fatigability, muscle weakness	2	Typical carcinoid	84	Alive without recurrence
9	F	70	Moon face, fatigability, muscle weakness, fever, sepsis	3	NET, tumourlet?	3	Died after three months
10	F	65	Muscle weakness, cough, hemoptysis	2	SCLC	2	Died after two months
11	M	40	Fatigability, muscle weakness, facial puffiness, anxiety, polyuria, polydypsia	1	SCLC	2	died after three months
12	M	41	Typical Cushing's facies, renal stone, jaw tumour, striae	4	Moderately differentiated NET, MEN 1	36	Died three years after diagnosis
13	F	43	Weight gain, striae, moon face, muscle weakness	1	Moderately differentiated NET	1	alive without recurrence
14	M	61	Jaundice, hypokalaemia, muscle weakness	1	SCLC	1	Died after one month
15	M	26	Moon face, fatigability, muscle weakness, striae	24	Typical carcinoid	12	Alive with complete recovery

12.3 ± 16.4). Based on histopathologic evaluations, four patients (cases 1, 10, 11 and 14) had SCLC, and seven patients (cases 3, 5–8, 13 and 15) had pulmonary NETs (carcinoid tumours). One patient (case 12) had a thymic NET. Case 9 was diagnosed as a lung tumourlet. In cases 2 and 4, we have no tissue diagnosis. In these cases, diagnoses were based on clinical grounds, laboratory and radiologic data and also follow-up. Patient 2 presented with mild Cushing's syndrome in 1986; he was a 32-year-old man presenting with muscle weakness and a UFC of 220 μg/24 h that was suppressed in Liddle's low dose suppression test to 143 μg/24 h and in Liddle's high dose suppression test to 202 μg/24 h. Plasma ACTH was 187 pg/mL, and pituitary MRI was normal. Evaluations at that time were suggestive of pituitary-dependent CS, and the patient underwent bilateral adrenalectomy (the only available treatment modality at that time). The bilateral adrenalectomy showed no evidence of adenoma or carcinoma. After surgery, he continued to feel unwell but refused regular follow-up. He was seen after two years with dyspnoea, and chest radiology revealed a large mediastinal mass. Based on the low level of UFC suppression in Liddle's high dose suppression test, and finding no macroadenoma in pituitary MRI and that high level of plasma ACTH and that mediastinal mass in follow-up, we assumed the Cushing's syndrome could have been caused by an ectopic ACTH source. The patient was also severely hyperpigmented. He refused surgery and died after two months because of respiratory failure. Patient 4 was a 68-year-old woman presenting with moon face, muscle weakness, HTN, severe hypokalaemia (K= 2.1 mEq/L)

Table II. *Clinical features of 15 patients with ectopic Cushing's syndrome*

Tabela II. *Obraz kliniczny 15 pacjentów z objawami ektopowego zespołu Cushinga*

Gender	n	%
Female	6	40
Male	9	60
	Mean ± SD	range
Age (years)	47.7 ± 14.7	26–70
Duration (months)	12.3 ± 16.4	1–48
Length of follow-up (months)	29.9 ± 27.5	1–84
Clinical findings	n	%
Muscle weakness	13	86.7
Moon face	10	66.7
Truncal obesity	9	60
Weight gain/Loss	9/6	60/40
Striae	5	33.3
HTN (SBP ≥ 140 and/or DBP ≥ 90 mm Hg)	11	73.3
Blood pressure	Mean ± SD	range
SBP [mm Hg]	152.7 ± 21.9	120–190
DBP [mm Hg]	91.3 ± 8.1	80–100

and metabolic alkalosis of two months' duration. UFC was 1,390 μg/24 h that was increased in Liddle's low dose suppression test to 1,540 μg/24 h and in Liddle's high dose suppression test was suppressed to 890 μg/24 h. Plasma ACTH was 210 pg/mL. Pituitary MRI was normal and abdominal CT scan showed bilateral adrenal hyperplasia; chest CT scan showed a 2 cm solitary pulmonary nodule. Given these figures, we assumed Cushing's syndrome in this patient could not be of pituitary origin and that there was an ectopic source for ACTH. She was referred for surgery but unfortunately died the day before it was to be carried out.

SCLC patients (patients 1, 10, 11, 14)

Two of the patients were female (patients 1 and 10). Patient 1 was admitted to CCU because of severe hypokalaemia and a refractory arrhythmia. She died within two weeks due to sepsis, intractable tachyarrhythmias, and heart failure. Tissue diagnosis was made post mortem by sampling by a *Tru-Cut* needle. Patient 10 presented with severe muscle weakness, weight loss and anorexia, and was admitted for evaluation of a possible occult carcinoma. Patient 11 was hospitalised because of muscle weakness, fatigability, the sudden appearance of severe hyperglycaemia, and acute mania. She was found to have a mediastinal mass producing superior vena caval obstruction. A diagnosis of SCLC was obtained following surgical thoracotomy. Patient 14 presented with jaundice and severe muscle weakness and was hospitalised by a gastroenterologist with the assumption of liver cirrhosis or metastatic liver disease; he also had severe hypokalaemia, diabetes mellitus and metabolic alkalosis. He was finally diagnosed as a case of ECS secondary to SCLC.

NET patients (patients 3, 5, 6, 7, 8, 9, 12, 13, and 15)

Three patients were female (patients 3, 9, and 13) and six patients were male. All patients with ECS due to NET had a typical clinical picture of CS with a 'moon face', truncal obesity, weight gain, muscle weakness, fatigability and purple striae, while patients with SCLC did not show these classic manifestations of Cushing's syndrome. Patient 12 was a non-classic case of MEN I syndrome with Cushing's syndrome due to a thymic neuroendocrine tumour and hyperparathyroidism who underwent thoracotomy twice because of tumour recurrence, as reported earlier [18]. All patients except four (cases 6, 11, 13 and 14) had hypertension, with systolic blood pressures ranging from 120 to 190 mm Hg and diastolic blood pressures ranging from 80 to 100 mmHg. Clinical data of the patients is presented in Tables I and II.

Laboratory characteristics of patients (Tables III and IV)

Basal SC and UFC were high and were unresponsive to dexamethasone in all cases. In case 13, basal UFC was more than 20 times the normal values. These high values are sometimes seen in patients with ECS due to elaboration of a significant amount of ACTH from the tumours. In seven cases, due to high levels of basal UFC and the poor condition of the patients, low-dose dexamethasone suppression testing (LDDST) was not performed. In response to dexamethasone, only one case, number 6, showed 90% suppression during the HDDST. This suppression after dexamethasone has been reported in 21% of patients and has resulted in an erroneous diagnosis of pituitary-dependent CS and incorrect therapeutic strategies such as TSS [6]. In seven cases, a paradoxical increase in UFC was observed. Mean and SD for morning serum cortisol was 47.2 ± 20.5 μg/dL. The value for UFC at basal state and after low dose (LD) and high dose (HD) DST were 2,702 ± 5,439, 1,687 ± 1,960 and 2,182 ± 4,552 μg/24 h respectively.

Plasma ACTH was elevated in all cases, ranging from 110 to 579 pg/mL (220 ± 147 pg/mL). Serum potassium was low in all cases, ranging from 1.8 to 3.4 mmol/L (2.5 ± 0.6). Fasting blood glucose was 119–370 mg/dL (206 ± 80). Indeed, seven patients had overt diabetes and were under treatment with oral agents or insulin. The frequency of overt diabetes was higher in our patients

Table III. *Laboratory findings of 15 patients with ectopic Cushing's syndrome*

Tabela III. *Wyniki badań laboratoryjnych u 15 pacjentów z objawami ektopowego zespołu Cushinga*

	Mean ± SD	Range
FBS [mg/dL]	206 ± 80	119–370
Potassium [mmol/L]	2.5 ± 0.6	1.8–3.4
Serum cortisol [μg/dL]	47.2 ± 20.5	21.6–106
UFC [μg/24 h]	2,702 ± 5,439	220–22,105
ACTH [pg/mL]	225 ± 141	61–579
	n	%
DM	14	93.3
IFG	1	6.7
Hypokalaemia [K < 3.5 mmol/L]	15	100
Hypokalaemia [K < 3 mmol/L]	11	73.3
Metabolic alkalosis	13/13	100
Suppression of UFC after HDDST		
> 80%	3	20
< 50%	10	66.7

compared to the NIH report, which may be due to longer duration of the disease. Diabetes disappeared in all patients with NET who were successfully treated.

Arterial blood gases were evaluated in 13 patients, showing metabolic alkalosis in all cases. The laboratory data is summarised in Table III. The differences in laboratory findings between SCLC patients and NET patients are shown in Table IV.

Imaging characteristics

Plain chest radiology was positive in all cases except cases 2, 14 and 15. The pulmonary lesions ranged in size from 1.1 to 4 cm (1.9 ± 1.1 cm). In ten cases, the diameter was 2 cm or less. Patient 12 had a 10 cm mediastinal mass. Lesions were interpreted as non-significant in three patients. In one patient, the lesion was misinterpreted as fibrosis, because he worked in a mine.

CT scanning of the chest defined the lesions in more detail and the surgical decision was based on the findings of the chest CT. In cases 3, 10, 11 and 14, mediastinal lymph nodes were apparent.

Pituitary CT scanning or MRI was carried out in all cases except 1, 11 and 14 because the pulmonary lesion was prominent and the patient's general condition was so poor that the procedure was contra-indicated. In all cases, pituitary gland was reported as normal except in case 13 that showed a 5mm pituitary lesion.

Abdominal CT scanning for the evaluation of adrenal glands was carried out in 12 cases, demonstrating bilateral hyperplasia in seven cases and being reported as normal in five cases.

Table IV. *Comparison of laboratory findings in patients with SCLC and NET*

Tabela IV. *Porównanie wyników badań laboratoryjnych u pacjentów mających nowotwory typu SCLC i pacjentów z rozpoznaniem NET*

	NET	SCLC
Serum cortisol	39.30 ± 8.84	52.75 ± 14.02
UFC	1,739 ± 898	723 ± 228
Plasma ACTH	148 ± 50	300 ± 129
Serum potassium	2.51 ± 0.58	2.25 ± 0.11
Fasting blood glucose	182 ± 55	299 ± 55

A radionuclide octreotide scan was performed in cases 12 and 13: it was positive in the first and negative in the second.

Histopathologic characteristics (Tables I and V)

Tissue for histopathologic evaluation was available in 13 cases. In case 1, the tissue was obtained through a closed needle biopsy after the patient's death. In patient 14, the tissue was obtained through a bone marrow biopsy. In the remaining cases, the tissue was obtained through a standard thoracotomy. The size of the tumours varied between 1 and 2.5 cm in all cases except case 9, who had a tumourlet, and case 12 who had a 10 cm mediastinal mass.

Four cases were diagnosed as SCLC, six cases were diagnosed as NETG1 (typical carcinoid) of the lung, one case was diagnosed as a tumourlet, and three cases as NETG2 (atypical carcinoids). In patients with NETG1 (typical carcinoids), microscopic evaluation revealed no necrosis with mitotic features less than 2 per high power field; the Ki-67 index was less than 4% in these cases. In cases 3, 12 and 13, whose diagnoses were NETG2 (atypical carcinoids), the Ki-67 was 20%, 30% and 7% respectively. It is worth noting that in case 12 the resected tumour at first surgery showed less aggressive behaviour with a Ki-67 of 7%, but showed more aggressive behaviour at second surgery with a Ki-67 of 30%. IHC staining was performed in eight cases: all cases showed positivity for chromogranin and ACTH. The interesting finding was that the number of cells which were positive for ACTH was considerably lower in cases with NETG2 (atypical carcinoids). Tables 1 and 4 show the histopathologic and IHC characteristics of the patients.

Medical therapy

In eight cases, ketoconazole was advised either before surgery to ameliorate the severe hypercortisolic state or to control Cushing's syndrome after surgery. The dose of ketoconazole was between 200 and 600 mg/day. No

Table V. *Immunohistochemical characteristics of the patients*
Tabela V. *Wyniki badań immunohistochemicznych nowotworów*

Case no.	Diagnosis	Chromogranin	Synaptophysin	Cytokeratin	ACTH		Ki-67
					frequency	intensity	
3	NETG2 (atypical carcinoid)	+	+	+	+	+++	20%
5	NETG1 (typical carcinoid)	+	+	+	+	+++	4%
6	NETG1 (typical carcinoid)	+	+	+	+++	++	3%
7	NETG1 (typical carcinoid)	+	+	+	+++	++	4%
8	NETG1 (typical carcinoid)	+	+	+	+	+++	4%
12	NETG2 (atypical carcinoid)	+	+	+	++	++	30%
13	NETG2 (atypical carcinoid)	+	+	+	++	++	7%
15	NETG1 (typical carcinoid)	+	+	+	+++	+++	4%

special adverse effect necessitating discontinuation of treatment was observed.

Surgical therapy

Two patients with SCLC and nine patients with NET underwent surgery, which was uneventful. The surgical technique was a postero-lateral thoracotomy under general anaesthesia with a double-lumen endotracheal tube. Cases 11 and 12 underwent surgery for mediastinal mass. Extensive lymph node dissection was not performed, and in all cases lymph nodes that were larger than normal in the surgeon's opinion were removed.

Outcome and follow up

SCLC patients

The four cases with SCLC died 1–3 months after diagnosis despite treatment with ketoconazole and other supportive measures.

NET patients

Case 3 who was diagnosed as NETG2 (atypical carcinoid) was alive for five years despite the recurrence of CS. She relapsed one year after surgery, but was fairly well-controlled on ketoconazole after her second surgery. Case 4 died the night before surgery, presumably due to electrolyte imbalance and a cardiac arrhythmia. Patient 9, who had a tumourlet, died three months after surgery because of pulmonary tuberculosis and non-compliance on follow-up; the patient was an Afghan immigrant in a poor condition due to the severity of hypercortisolism, infection and malnutrition. Case 12 had a thymic NET and MEN1 and died after three years despite two mediastinal operations because of the relapse of his CS and reappearance of the tumour. The other patients (cases 5–8, 13 and 15) with NETG1 (typical carcinoids) are all still alive without any symptoms or signs of CS or recurrence of the tumour, and are in complete remission.

The criterion for remission was two UFC measurements within normal limits after surgery, and then a UFC measurement every six months. The duration of follow up in these cases was between one month and seven years (29.9 ± 27.5 months).

Discussion

The data presented here clearly demonstrates the protean clinical and laboratory manifestations of ECS secondary to lung and mediastinal tumours. The problems encountered in diagnosis, the need for a multidisciplinary approach, and the different outcomes of the patients are also highlighted.

As mentioned earlier, ECS secondary to lung and mediastinal tumours is rare and there are only a limited number of papers reviewing the full spectrum of disease. Of the papers focusing on lung and mediastinal tumours leading to CS, Pass et al. from the NIH reported on 14 cases [14], the paper from Amer et al. from the UK on 19 cases [12], Sharger et al. from the Massachusetts General Hospital reported on seven cases [13], and Deb et al. [11] from Mayo Clinic discussed the clinical and laboratory data of 23 patients.

The recognition of different lung tumours leading to ECS has changed substantially in recent decades. In 1969, Liddle et al. reported that 52 out of 57 patients with lung tumour and ECS had SCLC [2, 9], while recent studies have shown that NETs or carcinoids of the lungs and mediastinum are the most common tumours leading to ECS and comprise around one-third of the cases. SCLC is the causative tumour in 20% of cases. As a result, more than half of the cases of ECS originate from tumours within the thorax [5, 6, 19].

The clinical symptoms of patients with SCLC differed substantially from those with a carcinoid tumour. Patients with SCLC presented with non-specific symptoms, such as weight loss, muscle weakness and electrolyte abnormalities, and presented to physicians from different specialties. This paraneoplastic or acute EAS contrasts with classic EAS that is present *ab initio* with a classic presentation of Cushing's syndrome [4, 20]. The duration of the disease was less than one month in our patients. Symptoms of pulmonary problems were seen only in case 11, who presented with superior vena cava (SVC) obstruction. In other patients, severe hypokalaemia and muscle weakness were the most important symptoms which led to diagnosis.

Clearly, ECS should be kept in mind in the differential diagnosis of severe hypokalaemia and muscle weakness. All patients died within three months after diagnosis. It seems that both severe hypercortisolism and its direct consequences including hypokalaemia and its related cardiac arrhythmias, hyperglycaemia and severe infection (sepsis), and rapid progression of the tumour and its complications such as SVC or hepatic metastases, contribute to this poor prognosis.

Patients with ECS secondary to NETs were symptomatically similar to patients with pituitary-dependent CS and diagnosed much earlier. The diagnoses in these cases were due to prominent symptoms of CS, clinical suspicion of ECS, and also positive radiological findings of the lung in the majority of cases. The unavailability of IPSS was a main problem in differentiating pituitary-dependent CS from ECS. Thus, as mentioned earlier, case 2 underwent bilateral adrenalectomy and the mediastinal tumour that was not seen at first evaluation became apparent after two years, a phenomenon referred to as 'covert Cushing's syndrome' [4, 5]. However, the diagnosis is not easy in all cases and in many patients the underlying neoplasm may be so small that it escapes detection for a long time; hence, there may be a substantial delay in terms of years in establishing the correct diagnosis [21, 22].

The duration of the disease in patients with SCLC was 1–3 months, which underlines the rapid course and severity of the disease. In contrast, the duration of the disease for patients with NET was much longer; between one month and four years, which is in accordance with a more favourable course of the disease.

It seems that thymic carcinoids secreting ACTH show a more aggressive course and present at a younger age, and it has been proposed to call them 'neuroendocrine carcinomas' instead of carcinoids. Thymic NETs may be associated with MEN-I and this possibility should be considered [18, 23].

Plain chest radiology was positive in all cases except 2, 14 and 15. In the study by Deb et al. [11], 13 of 23 patients (57%) had positive radiology. In the study by Pass et al. [14], and the study by Limper et al. [24], plain radiology revealed a tumour only in 33% (five of 15 patients in each study). In the St. Bartholomew's Hospital series, positive plain radiology findings were reported in five of 12 patients with bronchial carcinoids and five of seven patients with SCLC [5] hence, it seems that our patients might have had larger tumours or it might have been because of the larger number of patients with SCLC in our series. Chest CT scanning was positive in all cases except case 2. The lesions were better illustrated on chest CT scans. In three patients with tumours of less than 2 cm, plain radiology findings were interpreted as fibrosis or a non-significant finding. Radiologic misinterpretation which resulted from the small size of the tumours led to delays in chest surgery.

Our impression is that any pulmonary lesion should be interpreted as significant in patients suspected of ECS. Contrary to the findings of Sharger et al. and Pass et al. [13, 14] that reported almost 50% lymph node metastases in their patients with pulmonary carcinoid, we could find lymph node metastasis in only four cases. These four cases had either SCLC or NETG2 (atypical carcinoids). This is in accordance with the benign course of NETG1 (typical carcinoids). The 5 mm lesion in the pituitary MRI of the patient 13 was apparently an incidentaloma. Incidental findings in pituitary imaging have led to erroneous diagnoses of pituitary-dependent CS and implementation of untoward treatment strategies such as transsphenoidal surgery (TSS) [22]. Indeed, a significant percentage of patients with EAS (up to 50%) have undergone inappropriate TSS before the correct diagnosis [6, 11, 12, 14, 20, 24–27]. Some patients have even undergone a second TSS [25, 26] or received pituitary radiotherapy with the assumption of persistent Cushing's disease [6, 11, 20, 26]. A few patients have been reported to have undergone unilateral adrenalectomy, either as the first treatment of Cushing's syndrome with the assumption of adrenal origin of hypercortisolism, or after an unsuccessful TSS [6, 20]. One patient has been reported to have undergone TSS twice, pituitary radiotherapy, and eventually adrenalectomy [26]. This points to difficulties in diagnosing the true source of the Cushing's syndrome.

Bilateral adrenal hyperplasia was seen in seven cases. This could be either due to duration of the disease or sensitivity of the imaging machines used.

The major limitation in this study was the unavailability of IPSS and also CRH for a more accurate differentiation between EAS and pituitary-dependent CS. However, while IPSS and CRH testing was not available to us, the diagnosis was based on strong clinical grounds, firm laboratory findings of hypercortisolism,

the exclusion of other causes of CS, histopathologic findings, IHC of tumours showing positivity for ACTH and chromogranin, and clinical and biochemical improvement after resection of the tumour.

Thus, while these more sophisticated techniques can accelerate the diagnosis of such patients, their absence does not preclude accurate diagnosis and effective therapy, and this point is especially relevant in the delivery of medical care in the developing world.

Conclusion

We have presented the clinical and laboratory picture and also the management strategy of ECS secondary to lung and thymic tumours from a tertiary centre in Iran. According to the data provided, it is obvious that the disease is rare and if not properly managed can be lethal. When ECS develops in patients with SCLC, the clinical picture of CS does not develop, and muscle weakness and hypokalaemia can be the most prominent features. In cases due to pulmonary NET, the clinical picture of CS in usually present. The responsible tumour is usually small and can easily be missed.

Our study confirms other series from Western Europe and North America showing that, unlike ECS secondary to SCLC which is highly lethal, the prognosis in ECS secondary to NET is more favourable provided that the patients are diagnosed and surgically managed early in their course. In the case of a relapse, medical treatment can be effective for many years.

Acknowledgements

The authors express their deepest appreciations to Professor Ashley Grossman for his comments on the manuscript. The authors thank Drs S. Habibi Moeini, N. Saadat, S. Ghazi, F. Sarvghadi, F. Hosseinpanah, A. Amouzegar, F. Hadaegh, F. Azizi and M. Sharifzadeh for referring their patients and helping us in the diagnosis and management of the patients. We also thank the fellows and residents of the Endocrinology Department of Taleghani Teaching Hospital.

References

1. Brown WH. A case of pluriglandular syndrome: "diabetes of bearded women". The Lancet 1928; 212: 1022–1023.
2. Liddle GW, Island DP, Ney RL et al. Nonpituitary neoplasms and Cushing's syndrome. Ectopic "adrenocorticotropin" produced by nonpituitary neoplasms as a cause of Cushing's syndrome. Arch Intern Med 1963; 111: 471–475.
3. Aniszewski JP, Young WF Jr., Thompson GB et al. Cushing syndrome due to ectopic adrenocorticotropic hormone secretion. World J Surg 2001; 25: 934–940.
4. Alexandraki KI,Grossman AB. The ectopic ACTH syndrome. Rev Endocr Metab Disord 2010; 11: 117–126.
5. Isidori AM, Kaltsas GA, Pozza C et al. The ectopic adrenocorticotropin syndrome: clinical features, diagnosis, management, and long-term follow-up. J Clin Endocrinol Metab 2006; 91: 371–377.
6. Ilias I, Torpy DJ, Pacak K et al. Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. J Clin Endocrinol Metab 2005; 90: 4955–4962.
7. Bhansali A, Walia R, Rana SS et al. Ectopic Cushing's syndrome: experience from a tertiary care centre. Indian J Med Res 2009; 129: 33–41.
8. Doi M, Sugiyama T, Izumiyama H et al. Clinical features and management of ectopic ACTH syndrome at a single institute in Japan. Endocr J 2010; 57: 1061–1069.
9. Ejaz S, Vassilopoulou-Sellin R, Busaidy NL et al. Cushing syndrome secondary to ectopic adrenocorticotropic hormone secretion: the University of Texas MD Anderson Cancer Center Experience. Cancer 2011; 117: 4381–4389.
10. de Matos LL, Trufelli DC, das Neves-Pereira JC et al. Cushing's syndrome secondary to bronchopulmonary carcinoid tumor: report of two cases and literature review. Lung Cancer 2006; 53: 381–386.
11. Deb SJ, Nichols FC, Allen MS et al. Pulmonary carcinoid tumors with Cushing's syndrome: an aggressive variant or not? Ann Thorac Surg 2005; 79: 1132–1136; discussion 1132–1136.
12. Amer KM, Ibrahim NB, Forrester-Wood CP et al. Lung carcinoid related Cushing's syndrome: report of three cases and review of the literature. Postgrad Med J 2001; 77: 464–467.
13. Shrager JB, Wright CD, Wain JC et al. Bronchopulmonary carcinoid tumors associated with Cushing's syndrome: a more aggressive variant of typical carcinoid. J Thorac Cardiovasc Surg 1997; 114: 367–375.
14. Pass HI, Doppman JL, Nieman L et al. Management of the ectopic ACTH syndrome due to thoracic carcinoids. Ann Thorac Surg 1990; 50: 52–57.
15. Nieman LK, Biller BM, Findling JW et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2008; 93: 1526–1540.
16. Liddle GW. Tests of pituitary-adrenal suppressibility in the diagnosis of Cushing's syndrome. J Clin Endocrinol Metab 1960; 20: 1539–1560.
17. Dichek HL, Nieman LK, Oldfield EH et al. A comparison of the standard high dose dexamethasone suppression test and the overnight 8-mg dexamethasone suppression test for the differential diagnosis of adrenocorticotropin-dependent Cushing's syndrome. J Clin Endocrinol Metab 1994; 78: 418–422.
18. Ghazi AA, Dezfooli AA, Mohamadi F et al. Cushing syndrome secondary to a thymic carcinoid tumor due to multiple endocrine neoplasia type 1. Endocr Pract 2011; 17: e92–96.
19. Isidori AM,Lenzi A. Ectopic ACTH syndrome. Arq Bras Endocrinol Metabol 2007; 51: 1217–1225.
20. Hernandez I, Espinosa-de-los-Monteros AL, Mendoza V et al. Ectopic ACTH-secreting syndrome: a single center experience report with a high prevalence of occult tumor. Arch Med Res 2006; 37: 976–980.
21. Wajchenberg BL, Mendonca B, Liberman B et al. Ectopic ACTH syndrome. J Steroid Biochem Mol Biol 1995; 53: 139–151.
22. Rashid F, Riccio SA, Munk PL et al. Vertebroplasty for vertebral compression fractures secondary to Cushing's syndrome induced by an ACTH-producing bronchial carcinoid tumour. Singapore Med J 2009; 50: e147–150.
23. Neary NM, Lopez-Chavez A, Abel BS et al. Neuroendocrine ACTH-producing tumor of the thymus — experience with 12 patients over 25 years. J Clin Endocrinol Metab 2012; 97: 2223–2230.
24. Limper AH, Carpenter PC, Scheithauer B et al. The Cushing syndrome induced by bronchial carcinoid tumors. Ann Intern Med 1992; 117: 209–214.
25. Jex RK, van Heerden JA, Carpenter PC et al. Ectopic ACTH syndrome. Diagnostic and therapeutic aspects. Am J Surg 1985; 149: 276–282.
26. Findling JW,Tyrrell JB. Occult ectopic secretion of corticotropin. Arch Intern Med 1986; 146: 929–933.
27. Loli P, Vignati F, Grossrubatscher E et al. Management of occult adrenocorticotropin-secreting bronchial carcinoids: limits of endocrine testing and imaging techniques. J Clin Endocrinol Metab 2003; 88: 1029–1035.