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Original Article

ECTOPIC CUSHING SYNDROME: A 10-YEAR EXPERIENCE FROM A TERTIARY CARE CENTER IN SOUTHERN INDIA

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ABSTRACT

Objective: Ectopic adrenocorticotropic hormone (ACTH) secretion is a less common cause of Cushing syndrome and is seen in 5 to 10% of cases with endogenous hypercortisolemia. We hereby describe our experience of patients with ectopic ACTH syndrome, who have been managed over the past 10 years at a tertiary care center in Southern India.

Methods: The inpatient and outpatient records of patients from 2006 to 2015 were retrospectively reviewed. The clinical features, clinical history, biochemical values, imaging features, including radiologic findings and positron emission tomography scans, management, details of follow-up, and outcomes, were documented. We compared the biochemical findings in these patients with 20 consecutive patients with Cushing disease (Cushing syndrome of pituitary origin).

Results: A total of 21 patients were studied. The median age at presentation was 34 years (range, 19 to 55 years). Seven patients had thymic carcinoid, 7 had bronchial carcinoid, 3 had lung malignancies, 2 had medullary carcinoma thyroid, 1 patient had a pancreatic neuroendocrine tumor, and 1 patient had an occult source of ACTH. The most common clinical features at presentation were muscle weakness (95%), hyperpigmentation (90%), facial puffiness (76%), easy bruising (61%), edema (57%), and striae (52%). Extensive acne was seen in a large number of patients (43%). Only 3 patients (14%) had central obesity. The median 8 AM cortisol was 55.5 μg/dL (3.8 to 131 μg/dL), median 8 AM ACTH was 207 pg/mL (range, 31.1 to 703 pg/mL), and the median 24-hour urinary free cortisol was 2,484 μg (range, 248 to 25,438 μg). Basal cortisol and ACTH, as well as midnight cortisol and ACTH level, were markedly higher in patients with ectopic Cushing syndrome as compared to patients with Cushing disease. Twelve of 21 patients had developed life-threatening infections by follow-up. Nine patients had undergone surgical intervention to address the primary tumor. However, only 1 patient exhibited a complete cure on follow-up.

Conclusion: In our series, ectopic Cushing syndrome was most commonly seen in association with intrathoracic tumors such as bronchial or thymic carcinoid. Hyperpigmentation and proximal myopathy were frequent, while central obesity was uncommon. Early and rapid control of hypercortisolemia was important in order to prevent life-threatening infections and metabolic complications. **(Endocr Pract. 2017;23:xxx-xxx)**

Abbreviations:
ACTH = adrenocorticotropic hormone; **CT** = computed tomography; **DOTATATE** = ^{68}Ga-DOTA-Tyr^{3}-octreotate; **ECS** = ectopic Cushing syndrome; **FDG** = fluorodeoxyglucose; **MTC** = medullary thyroid cancer; **NET** = neuroendocrine tumor; **PET** = positron emission tomography

INTRODUCTION

Cushing syndrome caused by ectopic adrenocorticotropic hormone (ACTH) secretion was first described by Brown in 1928 (1). Subsequently, this entity was found to be associated with a wide variety of tumors. Based on available literature, ectopic ACTH-dependent Cushing syndrome (ECS) constitutes 5 to 10% of all cases of ACTH-

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dependent Cushing syndrome (2). Small cell carcinoma of the lung was described as the most common cause of ECS in older series (3). More recently, ECS has been frequently reported with a number of less-aggressive neuroendocrine tumors (NETs) (4)but the more prevalent tumours are bronchial carcinoids, small cell lung carcinomas, pancreatic carcinoids, thymic carcinoids, medullary carcinomas of the thyroid, and phaeochromocytomas. Occult tumours are highly represented in all the series (12-38%.

As compared to patients with pituitary-dependent Cushing syndrome, patients with ECS present with a rapid progression of symptoms. It is also associated with typical features of proximal muscle weakness, severe hypokalemic metabolic alkalosis, hyperpigmentation, edema, hypertension, and glucose intolerance. Early diagnosis and localization of the ectopic source of ACTH is crucial, because the treatment of choice in most of these patients is complete excision of the tumor. Localizing the source of excess ACTH continues to be a challenge in most patients.

In our study from a tertiary care center in Southern India, we describe our experience with ECS over the past 10 years. We describe the challenges faced during diagnosis, treatment, and postoperative follow-up of these patients. We also compare the clinical and biochemical features of these patients with 20 consecutive patients with Cushing disease and discuss the differences observed.

METHODS

This was a retrospective review of patients diagnosed over a period of 10 years (2005- 2015). ECS was diagnosed in 21 patients on the basis of biochemical findings, imaging, and histopathologic examination.

Diagnosis of Cushing Syndrome

Patients with clinical features of endogenous hypercortisolism were evaluated in stepwise manner. Endogenous hypercortisolism was confirmed by elevated basal urinary free cortisol, nonsuppressed serum cortisol following a 1-mg dexamethasone dose, and loss of the circadian rhythm of cortisol secretion. A diagnosis of ACTH-dependent Cushing was made if the basal plasma ACTH level was elevated (>20 pg/mL) and there was no response to the low-dose dexamethasone suppression test. Imaging modalities included computed tomography (CT), magnetic resonance imaging and positron emission tomography–CT (PET-CT). Thirteen patients underwent diagnostic biopsies. In patients in whom the tumor was not identified, imaging was repeated at an interval of 1 to 2 years.

Biochemical Methods

Plasma cortisol was measured using a solid-phase competitive chemiluminescent immunoassay manufactured by Siemens Advia Centaur, with inter- and intra-assay coefficients of variability (CVs) of 7 and 6.7%, respectively. ACTH was measured using a solid-phase two-site chemiluminescent immunoassay (Siemens Immulite 2000, with a CV of 5.6%).

The overnight dexamethasone suppression test (ONDST) was done by administering 1 mg of dexamethasone at midnight and measuring serum cortisol at 8 am. Serum cortisol of more than 1.8 μg/dL was used to define nonsuppressibility. This was followed by the high-dose dexamethasone suppression test using 8 mg of dexamethasone. The failure of 8 AM cortisol and a 24-hour urinary free cortisol to suppress by 50% of the basal values was considered as a positive test.

RESULTS

A diagnosis of ECS was made in 21 patients. Fourteen patients were male and 7 were female. The median age at presentation was 34 years (range, 19 to 55 years). The mean duration of symptoms at presentation was 11.5 months. Of the 21 patients, 7 had bronchial carcinoid, 7 had thymic carcinoid, 3 had carcinoma of the lung, 2 had medullary thyroid cancer (MTC), and 1 had a pancreatic NET. The source of ectopic ACTH secretion could not be localized in 1 patient.

Clinical and Biochemical Features

The clinical manifestations are summarized in Table 1. Classical clinical manifestations of Cushing syndrome, such as proximal muscle weakness, hyperpigmentation, facial puffiness, and easy bruising were seen in 95, 90.5, 76%, and 62% of patients, respectively. Extensive acne was seen in 9 patients (43%). Central obesity was noted only in 3 patients (14%). One patient presented with psychosis. Twelve patients (57%) had diabetes mellitus, and 16 patients (76%) had hypertension.

Serious pre-operative and postoperative infections were common. Three patients had pulmonary tuberculosis, 3 patients needed treatment for lower respiratory tract infections. One patient developed nocardial pneumonia in the immediate postoperative period. One patient had a gluteal abscess with methicillin-resistant Staphylococcus aureus, and 1 patient developed *Salmonella* gastroenteritis.

In subjects with pituitary-dependent Cushing syndrome, there was a greater prevalence of central obesity (18 of 20 patients), as compared to 3 of 21 patients with ECS. Peripheral edema was less common in patients with pituitary-dependent Cushing syndrome (25% versus 57.1%). Serious pre-operative and postoperative infections were distinctively uncommon. One patient was diagnosed with a breast abscess, and 1 patient had developed a perianal abscess.

Biochemical values recorded in our patients are summarized in Table 2. Hypokalemia was seen in a majority of patients with ECS (85.7%). The median potassium was 2.6 mEq/L (range, 1.2 to 3.9 mEq/L). Hypokalemia

Table 1
Clinical Features in Patients With ECS and Cushing Disease

Clinical features	ECS (n = 21) n (%)	Cushing disease (n = 20) n (%)
Facial puffiness	16 (76.1)	17 (85)
Central obesity	3 (14.2)	18 (90)
Muscle weakness	20 (95.2)	16 (80)
Easy bruising	13 (61.9)	2 (10)
Hyperpigmentation	19 (90.47)	14 (70)
Acne	9 (42.8)	7 (35)
Edema	12 (57.1)	5 (25)
Psychosis	1 (4.7)	-
Striae	11 (52.3)	10 (50)
Hirsutism	4/6 females	9/13 females
Amenorrhea	4/6 females	-
Diabetes mellitus	12 (57.1)	10 (50)
Hypertension	16 (76.1)	14 (70)
Infections	9 (42)	-
Deep vein thrombosis	2 (9)	-

Abbreviation: ECS = ectopic Cushing syndrome.

was difficult to correct, with a median of 5 days (range, 1 to 20 days) required for correction. Parenteral potassium was used in all of these patients, in addition to oral potassium and spironolactone. Hypokalemia was uncommon in patients with pituitary-dependent Cushing syndrome. Metabolic alkalosis was seen in 17 of 21 (80%) patients. A 1-mg ONDST was done in 13 patients, and all had failed to suppress 8 AM cortisol to <1.8 μg/dL. An overnight 8-mg high-dose dexamethasone suppression test was done in 6 patients. Two of these showed suppression of 24-hour urinary free cortisol and 8 AM cortisol to <50% of basal levels. Both these patients were diagnosed with bronchial carcinoid. All ECS patients had elevated midnight cortisol and ACTH levels. Median midnight cortisol was 16.9 μg/dL in the patients with Cushing disease and 31 μg/dL in the ECS group (P<.0001). Median midnight ACTH was 62.5 pg/mL in patients with Cushing disease and 161 pg/mL in the ECS patients (P = .03). Median 24-hour urinary free cortisol was 923 μg/24 hours in patients with Cushing disease and 2,482 μg/24 hours in the ECS group (P = .009).

Localization

Contrast CT of the chest was done in 17 patients, and this had localized the lesion in 12 patients. In 1 patient with thymic carcinoid, a ^{68}Ga-DOTA-NaI^{3}- octreotide scan had been performed at initial evaluation and had detected the lesion. Four patients with bronchial carcinoid underwent a ^{68}Ga-DOTA -Tyr^{3}-octreotate (^{68}Ga DOTATATE) PET-CT. One patient had a fluorodeoxyglucose (FDG) PET-CT.

One patient on follow-up for a period of 9 years had initially undergone an inferior petrosal sinus sampling, which localized ACTH secretion to a peripheral source. However ^{68}Ga DOTATATE PET-CT, repeated on two occasions, had failed to localize the lesion.

With regard to the time taken for localization of the ACTH source, all 7 patients with thymic carcinoid had been diagnosed at initial evaluation. Four of 7 patients with bronchial carcinoid had been diagnosed at initial evaluation. All 3 patients with carcinoma lung, 2 patients with MTC, and 1 patient with pancreatic NET were diagnosed without a lag period.

Management and Outcomes

Medical and surgical options for our patients were individualized according to the source of ACTH and the condition of the patient at presentation. The mean duration of follow-up was 20.1 months. Details of the treatment modality used and outcomes observed are summarized in Table 3. A total of 8 patients (4 with thymic carcinoid and 4 with bronchial carcinoid) underwent surgery to address the primary lesion.

All 7 patients with thymic carcinoid had metastatic disease at presentation. Four of the 7 patients underwent debulking surgery. All 4 patients remained uncured after surgery. Two patients had thrombotic complications in the postoperative period. One patient succumbed to pulmonary thromboembolism. The postoperative course was complicated by lower respiratory tract infection in 2 patients. Three patients subsequently underwent bilateral endoscopic adrenalectomy for control of hypercortisolemia. Hypertension, which was present in 2 of these patients, diabetes mellitus diagnosed in 1 patient, and refractory hypokalemia encountered in 2 of these patients, all resolved after adrenalectomy. One patient had a hospital admission for hypocortisolemic crisis 2 years after surgery. One of these patients died after 5 years of follow-up. Death was attributed to extensive pulmonary metastasis. The other 2 patients are stable at 24 and 36 months of follow-up.

Two patients with thymic carcinoid did not undergo surgery, as they had extensive metastatic disease at presentation. One patient with thymic carcinoid also had pulmonary tuberculosis at diagnosis. He was started on antituberculous treatment but was lost to follow-up.

Five patients with bronchial carcinoid were on bridge therapy with ketoconazole prior to surgery. The median duration of ketoconazole treatment prior to surgery was 4 months. Four of them underwent lobectomy. One of them, cured following surgery, remains asymptomatic at 57 months of follow-up. Histopathology for this patient showed a well-differentiated NET with no lymphovascular invasion and lymph nodes free of tumor. Two patients were cured following surgery but had disease recurrence after

Table-2
Biochemical Features of Patients With ECS and Cushing Disease

Biochemical parameters	ECS (n = 21)		Cushing disease (n = 20)		*P* value (independent *t* test)
	Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)	
8 AM cortisol (μg/dL)	54.78 (26.18)	50.78 (13.8-131)	23.59 (5.36)	22.70 (12.4-33.2)	<.0001[a]
8 AM ACTH (pg/mL)	226.69 (210.45)	188 (53.4-703)	94.61 (45.47)	86.60 (32.4-196)	.007[a]
Midnight cortisol (μg/dL)	38.29 (19.23)	31 (7.1-75)	16.7 (5.41)	16.1 (6.8-25.9)	<.0001[a]
Midnight ACTH (pg/mL)	196.64 (166.23)	162 (31.1-657)	55.52 (39.49)	60 (5-142)	.003[a]
24-hour UFC (μg/24 hours)	5,429.78 (6,710.44)	2,482 (248-25,438)	947.57 (574.06)	873 (395-2,671)	.009[a]
Serum potassium (mmol/L)	2.63 (0.65)	2.6 (1.2-3.9)	4.27 (0.51)	4.15 (3.3-5.1)	<.0001[a]
Serum bicarbonate (mmol/L)	28.89 (3.29)	28.5 (23.9-35)	26.73 (5.3-26)	26 (20-41)	.140
Serum albumin (g/dL)	3.7 (0.52)	3.55 (2.8-4.9)	4.31 (0.37)	4.3 (3.7-5.1)	<.0001[a]

Abbreviations: ACTH = adrenocorticotropic hormone; ECS = ectopic Cushing syndrome; UFC = urinary free cortisol.
[a]Statistically significant difference.

Table 3
Treatment Modality and Outcome

Diagnosis	Number of patients	Definitive surgery	Metastasis	Second-line management	Final outcome
Bronchial carcinoid	7	Lobectomy–4 Planned surgery–1 Lost to follow-up–2	3	Ketoconazole–5 (pre-operative) Chemotherapy–1	Cured–1 Uncured–3 Planned surgery–1 Lost to follow-up–2
Thymic carcinoid	7	Debulking–4	7	Chemotherapy/RT–3 Lutetium–2 Adrenalectomy–3	Death 1 month postop (PE)–1 Death at 66 months follow-up–1 Stable 18 months follow-up–1 Stable 48 months follow-up–1 Extensive metastasis at diagnosis–2; lost to follow-up Pulmonary TB at diagnosis; lost to follow-up–1
Carcinoma lung	3	-	3	-	Chemotherapy/RT-follow-up for 12 months–1 Deaths–2
Medullary thyroid cancer	2	1	2	-	Deaths–2
Pancreatic NET	1	planned	-	-	Lost to follow-up
Occult source	1	-	-	-	Controlled with mitotane at 96 months

Abbreviations: NET = neuroendocrine tumor; PE = pulmonary embolism; RT = radiotherapy; TB = tuberculosis.

17 and 24 months. Histopathology for these patients had shown well-differentiated NET with lymphovascular invasion and nodal disease. They had not received any adjuvant therapy postoperatively. One patient underwent bilateral adrenalectomy prior to lobectomy, in view of his poor general condition. Manifestations of hypercortisolemia in the form of diabetes, hypertension, and muscle weakness improved postoperatively. He subsequently underwent lobectomy, and as the lung lesion showed evidence of metastatic disease, he was started on adjuvant chemotherapy. One patient with bronchial carcinoid is awaiting surgery, while 2 have been lost to follow-up.

Two patients with MTC had metastatic disease at presentation. Both of them presented with rapid progression of hypercortisolemia over a 1- to 2-month period. Both patients developed lower respiratory tract infection and succumbed to complications of sepsis.

Three patients in our series with ECS had underlying carcinoma of the lung. All 3 patients were started on ketoconazole for control of hypercortisolemia. One patient was on palliative chemotherapy and was on follow-up for a period of 1 year. One patient also had pulmonary tuberculosis at diagnosis and was started on antitubercular therapy; he was subsequently lost to follow-up. One patient died of complications related to sepsis at the initial admission.

One patient with an occult source of ACTH secretion has been on medical management with mitotane for a period of 9 years.

Details of individual cases included in our series are summarized in Table 4.

DISCUSSION

This is a retrospective review of the clinical, biochemical and radiological features of 21 patients with ECS seen at our center over a period of 10 years. Intrathoracic tumors—bronchial carcinoid, thymic carcinoid, and carcinoma lung—were the most common causes of ECS in our center. This was similar to previously reported series of ECS patients (2,5-7)life-threatening hypercortisolemia. This retrospective follow-up study describes the clinical characteristics and course of EA in a large referral center. Computer-based cross-index codes for EA, CS, and bilateral adrenalectomy were used to identify patients treated at the Mayo Clinic between 1956 and 1998. EA was confirmed in 106 patients. Gender distribution showed a slight female predominance (61:45.

ECS was more common in male patients (66%). The most common clinical features were proximal muscle weakness, hyperpigmentation, facial puffiness, and easy bruising. Extensive acne was seen in a significant proportion of our patients (42.8%). Secondary diabetes and hypertension were commonly observed in our cohort, similar to previously reported data (6,8)contributing to 10 per cent cases of endogenous Cushing's syndrome. We describe our experience of about two decades of patients with ectopic Cushing's syndrome (ECS. Specific clinical features, seen with a higher frequency in the group of patients with ECS as compared to Cushing disease, included peripheral edema and an absence of central obesity. The severity of illness and the rapidity of onset of symptoms in patients with ECS could account for this finding.

A high index of suspicion is necessary for early diagnosis of ECS in patients with Cushing syndrome. Biochemical parameters conventionally thought to point towards a diagnosis of ECS include the degree of hypokalemia and alkalosis as well as the absolute levels of plasma ACTH. Prevalence of hypokalemia was much higher in ECS patients (90% vs. 0%), with a majority of patients requiring hospitalization and intravenous potassium. This could probably be explained by the action of the higher levels of cortisol on mineralocorticoid receptors (9). With regard to ACTH, 57% (n = 12) of our patients had ACTH levels >200 pg/mL, and 43% (n = 9) had ACTH <200 pg/mL. However all patients with Cushing disease had an 8 AM ACTH level of <200 pg/mL. Therefore, even though there is some overlap in the absolute ACTH levels, especially with larger pituitary tumors, a level of >200 pg/mL could be an indicator of an ECS (9,10). Twenty-four-hour urinary free cortisol levels were also found to be higher in the group of patients with ECS, with 13 patients having values of >2,000 μg/24 hours. Refractory hypokalemia and an ACTH level of >200 pg/mL could be indicators of ECS, especially in the absence of clinical features like weight gain and obesity.

In terms of localization, CT had revealed the lesion in 12 of 17 (70%) patients, similar to that reported in the literature (11)131I/123I-metaiodobenzylguanidine, 18Ffluoro-2-deoxyglucose-positron emission tomography (FDG-PET. Four patients underwent a ^{68}Ga DOTATATE PET. DOTATATE PET-CT was the initial imaging modality, and the lung lesion was identified on CT in 3 patients. DOTATATE PET-CT localized the lesion in 1 patient with bronchial carcinoid. FDG PET is not thought to help in localization in patients with ECS, as most NETs have a low metabolic rate (12). However, 2 patients had undergone FDG PET scans in our series, with bronchial carcinoid being identified in both.

ECS was associated with a high rate of infectious complications. This increased predisposition to infection has been previously documented in the literature (13). Pulmonary tuberculosis was seen in 3 patients, probably in part reflecting the higher prevalence of tuberculosis in our environment. A high prevalence of tuberculosis, with 29% involvement, was noted in another series as well (8). Other bacterial and fungal lung infections were common and were seen in 7 patients. Two patients with metastatic MTC and 1 patient with lung cancer succumbed to pneumonia. Pulmonary infections in the postoperative period were seen in 2 patients, with 1 patient developing nocar-

Table 4
Details of Diagnosis and Management in 21 Patients With Ectopic Cushing Syndrome

Serial no.	Age/sex	Primary site	Time to diagnosis (from symptom onset)	Method of localization	Metastasis	Management	Second-line management	Outcome
1	29/Male	Thymic carcinoid	36 months	CECT thorax	Yes	Debulking surgery	Chemotherapy Radiotherapy Lutetium therapy BLA	Death 66 months after diagnosis-metastatic disease
2	21/Male	Thymic carcinoid	2 months	CECT thorax	Yes	Thymectomy Excision of metastatic nodes	Chemotherapy Radiotherapy BLA	48 months of follow-up–bone metastasis
3	19/Male	Thymic carcinoid	2 months	CECT thorax	Yes	Thymectomy	Chemotherapy Lutetium therapy	Stable at 18 months of follow-up
4	40/Female	Thymic carcinoid	12 months	CECT thorax	Yes	-	-	Lost to follow-up
5	34/Male	Thymic carcinoid	5 months	CECT thorax	Yes	Debulking surgery	-	Death– postoperative pulmonary embolism
6	33/Male	Thymic carcinoid	24 months	CECT thorax	Yes	-	-	Lost to follow-up
7	48/Male	Thymic carcinoid	6 months	CECT thorax	Yes	-	-	Lost to follow-up
8	36/Male	Bronchial carcinoid	24 months	CECT thorax	Yes	-	-	Lost to follow-up
9	29/male	Bronchial carcinoid	39 months	^{68}Ga-DOTATATE PET	Yes	Lobectomy	Ketoconazole	Relapse at 18 months after surgery
10	30/Male	Bronchial carcinoid	14 months	FDG PET CT	Yes	Lobectomy	Ketoconazole	Relapse at 15 months after surgery
11	24/Male	Bronchial carcinoid	4 months	^{68}Ga-DOTATATE PET	Yes	Lobectomy	Chemotherapy adrenalectomy	On follow-up –5 months postoperative
12	32/Female	Bronchial carcinoid	6 months	CECT thorax	-	-	-	Lost to follow-up
13	34/Male	Bronchial carcinoid	12 months	CECT thorax/FDG PET	No	Lobectomy	-	Cured after surgery
14	35/Female	Bronchial carcinoid	12 months	^{68}Ga-DOTATATE PET	No	-	Ketoconazole	Planned for surgery
15	44/Female	Carcinoma lung	12 months	CECT thorax	Yes	Chemotherapy Radiotherapy	Ketoconazole	On follow-up for 12 months
16	20/Male	Carcinoma lung	3 months	CECT thorax	Yes	-	-	Lost to follow-up
17	48/Female	Carcinoma lung	6 months	CECT thorax	Yes	-	-	Died of sepsis-related complications at initial admission
18	42/Female	Medullary thyroid cancer	2 months	-	Yes	-	-	Died of sepsis-related complications at initial admission
19	18/Male	Medullary thyroid cancer	12 months	-	Yes	-	-	Died of sepsis-related complications at initial admission
20	55/Male	Occult EAS	3 months	IPSS-peripheral source	-	Mitotane	-	Controlled with mitotane at 96 months
21	52/Male	Pancreatic NET	6 months	CECT thorax	-	-	Ketoconazole	Lost to follow-up

Abbreviations: BLA = bilateral adrenalectomy; CECT = contrast-enhanced computed tomography; CT = computed tomography; EAS = ectopic adrenocorticotropic hormone syndrome; FDG = fluorodeoxyglucose; ^{68}Ga-DOTATATE = ^{68}Ga-DOTA-Tyr^{3}-octreotate; IPSS = inferior petrosal sinus sampling; NET = neuroendocrine tumor; PET = positron emission tomography.

dial pneumonia. Infections in the postoperative period could be manifestations of a syndrome of immune reconstitution. An inflammatory response syndrome triggered during recovery of the immune system could lead to paradoxical clinical deterioration. This syndrome, though most frequently seen in the setting of antiretroviral therapy, is also observed in HIV-negative patients who have recovered from immunosupression. This complication could occur in endogenous Cushing syndrome after successful medical or surgical therapy (14). One of our patients developed *Nocardia* pneumonia 8 days after bilateral adrenalectomy. This corresponds to the literature, with re-activation of fungal and mycobacterial infection being reported between days 8 and 11 after recovery of immunosuppression; and viral infection, including worsening of pre-existing hepatitis B infection, at days 21 to 42 (14). Paradoxical worsening of clinical features during treatment therefore needs careful investigation. Appropriate antibiotic therapy forms the mainstay of management. The role of steroid therapy with gradual dose reduction needs to be evaluated in this situation. A thorough evaluation for possible subclinical infection, before initiation of treatment could be considered, especially in situations where there is a high background prevalence of infections. In the postoperative period, thrombotic complications in the form of deep vein thrombosis affecting the large veins of the neck and thorax occurred in 2 patients with thymic carcinoid. One of these patients succumbed to pulmonary embolism.

Prognosis and cure rates depended on the tumor type. All patients with thymic carcinoid had overt tumors and metastatic disease at presentation. These tumors were aggressive and were not cured by surgery. Poor prognosis in patients with thymic carcinoid has been noted previously (8,15). Total thymectomy is the preferred treatment for thymic carcinoid. However, metastatic disease at diagnosis or disease recurrence after thymectomy are common and affect a majority of patients (5). The role of adjuvant chemotherapy and radiotherapy are less clear, in view of the rarity of the disease (16). Postoperative radiotherapy has been associated with lower rates of local recurrence in certain series (17). However, a recently reported large clinical series did not show an advantage with either chemotherapy or radiotherapy (18). Four patients with bronchial carcinoid underwent surgery in our series. Surgery was successful in 3 patients, which led to clinical and biochemical remission. However, 2 of these patients had disease recurrence. Bronchial neuroendocrine tumors have a malignant potential, as they share some histologic features with small cell lung cancer and represent part of the tumor spectrum (19). Patients with positive lymph nodes on histopathology could therefore be considered as candidates for adjuvant therapy in the form of chemotherapy or radiotherapy (20). There is no current consensus on adjuvant therapy in patients who undergo complete resection, and treatment needs to be planned on an individual patient basis. Overall cure rate in patients with ECS has varied from 12 to 30% in a number of clinical series (5-7,21).

Three patients with thymic carcinoid and 1 patient with bronchial carcinoid underwent bilateral adrenalectomy. Two of these patients with thymic carcinoid and the patient with bronchial carcinoid were doing well at the last follow-up. The optimal timing and the role of bilateral adrenalectomy or medical therapy for Cushing syndrome are less clear. Indications for bilateral adrenalectomy in patients with thymic or bronchial carcinoid are primary or recurrent tumor which cannot be surgically resected, and as an emergency procedure in patients with severe Cushing syndrome (22)BADx is mainly used as an ultima ratio after transsphenoidal surgery and medical therapies have failed. In these cases, the time span between the first diagnosis of CD and treatment with BADx is relatively long (median 44 months. Our patient with bronchial carcinoid showed rapid clinical improvement following adrenalectomy and could subsequently undergo a major surgery in the form of lobectomy. Surgical morbidity is higher in patients with ECS because of severe hypercortisolism, inducing immunosuppression, muscle weakness, and metabolic disorders, and additionally the presence of an underlying malignant tumor with our without metastases. Bilateral adrenalectomy may help in reducing morbidity in these patients by rapidly controlling severe hypercortisolism. This could decrease morbidity and mortality associated with infectious, metabolic disorders, and thromboembolic disease. Early bilateral adrenalectomy could potentially be lifesaving, especially in our setting, where a large proportion of patients present with advanced disease and severe hypercortisolemia. A systematic review by Ritzel et al (23) reported a surgical mortality rate of 4%, as compared to 1% in patients with pituitary-dependant Cushing. The probable life expectancy needs to be weighed against the risks of procedure-related complications in this group of patients, and a timely decision regarding adrenalectomy could significantly increase quality of life and overall survival. An early decision regarding bilateral adrenalectomy could also benefit patients with ECS related to MTC and carcinoma lung, who have persistent hypercortisolism in spite of medical management.

A poorer prognosis was seen in patients with ECS due to MTC and lung cancer. Both patients with MTC presented with florid features of Cushing syndrome. A delay in diagnosis may be due to inadequate awareness of the previous treating physicians of the potential of MTC developing ECS.

CONCLUSION

Ectopic ACTH secretion is an uncommon cause of Cushing syndrome. In our series, patients with ECS had more profound hypokalemia and hypercortisolemia, with higher levels of ACTH. ECS due to conditions like thymic

carcinoid, MTC, and carcinoma lung presented with rapid progression. Nearly half the patients in this series had life-threatening infections inclusive of bacterial, mycobacterial, and fungal etiology. Infections in the postoperative period, probably due to immune reconstitution, were also observed, highlighting the importance of both pre-operative screening and postoperative management.

The prognosis in patients with ECS was dependent on tumor histology. The prognosis was guarded in patients with thymic carcinoids, lung cancers, and MTC. Radical excision was curative in some patients with bronchial carcinoid. However, the role of adjuvant therapy in bronchial and thymic carcinoid needed to be evaluated on a case by case basis in patients with a high risk of recurrence, rather than by a set algorithm. The role of a timely adrenalectomy needs to be considered in patients with hypercortisolemia unresponsive to medical management and in patient with metastatic or recurrent disease.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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