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Cushing's Syndrome in Multiple Endocrine Neoplasia Type 1

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Summary

Objective—In patients with multiple endocrine neoplasia type 1 (MEN1), Cushing's syndrome (CS) from endogenous hypercortisolism can result from pituitary, adrenal, or other endocrine tumors. The purpose of this study was to characterize the range of presentations of CS in a large series of MEN1 patients.

Design—Retrospective review of NIH Clinical Center inpatient records over an approximately 40 year period.

Patients—19 patients (8 males, 11 females) with CS and MEN1.

Measurements—Biochemical, imaging, surgical, and pathological findings.

Results—An etiology was determined for 14 of the 19 patients with CS and MEN1: 11 (79%) had Cushing's disease (CD) and three (21%) had ACTH-independent CS due to adrenal tumors, frequencies indistinguishable from sporadic CS. Three of 11 MEN1 patients with CD (27%) had additional non-ACTH secreting pituitary microadenomas identified at surgery, an incidence 10-fold higher than in sporadic CD. Ninety-one percent of MEN1 patients with CD were cured after surgery. Two of three MEN1 patients with ACTH-independent CS (67%) had adrenocortical carcinoma. One patient with adrenal cancer and another with adrenal adenoma were cured by unilateral adrenalectomy. No case of ectopic ACTH secretion was identified in our patient cohort. The etiology of CS could not be defined in five patients; in three of these, hypercortisolism appeared to resolve spontaneously.

Conclusions—The tumor multiplicity of MEN1 can be reflected in the anterior pituitary, MEN1-associated ACTH-independent CS may be associated with aggressive adrenocortical disease, and an etiology for CS in MEN1 may be elusive in a substantial minority of patients.

Keywords (MeSH terms)

ACTH-Secreting Pituitary Adenoma; Adrenal Gland Neoplasms; Cushing Syndrome; Hypophysectomy; Genes; Tumor Suppressor

Introduction

Cushing's syndrome (CS) from endogenous hypercortisolism can occur sporadically or in the context of familial disease as a result of pituitary or nonpituitary neuroendocrine tumors [1]. Among familial endocrine tumor syndromes, multiple endocrine neoplasia type 1

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(MEN1) is unique because CS in this setting can result from both ACTH-dependent (Cushing's disease [CD] and ectopic tumoral ACTH secretion [EAS]) and ACTH-independent causes.

MEN1 is a familial cancer syndrome whose prominent expressions include primary hyperparathyroidism, anterior pituitary tumors, foregut carcinoid tumors, and enteropancreatic endocrine tumors [2]. Pituitary tumors are present in about 40% of adult MEN1 patients; 5–10% of such tumors secrete ACTH [3, 4]. Functional and particularly non-functional adrenocortical tumors occur frequently, and include benign and malignant tumors causing CS [5]. EAS from thymic carcinoids [6, 7] has also been reported in MEN1. MEN1 can include non-endocrine tumors in several tissues [2].

No large series has described the range of presentation and etiologies of CS in MEN1. We report here a retrospective review of 19 patients with CS and MEN1 admitted over four decades to the inpatient wards of the NIH Clinical Center.

Patients and methods

Patients

By iterative screening of medical records we retrospectively identified patients with CS and MEN1 admitted to the NIH Clinical Center between 1966 and 2009. MEN1 patients were admitted for periodic monitoring or for management of expressions of MEN1. Patients were not specifically recruited or rejected for evaluation of CS. Approximately 120 patients were identified initially by a computer search of discharge diagnoses. Their medical records were individually reviewed to confirm documentation of hypercortisolism and signs and symptoms of CS and MEN1, resulting in the identification of the 19 patients described here. All patients participated in protocols approved by the Investigational Review Boards of the National Institute of Diabetes and Digestive and Kidney Diseases or the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and each gave written consent.

Diagnostic evaluation

For MEN1 patients initially diagnosed and/or treated for CS outside the NIH Clinical Center, and who then subsequently came to the NIH, all available pertinent outside results were reviewed. For patients evaluated at the NIH, morning electrolytes, glucose, serum cortisol, plasma ACTH, 24-hr urinary excretion of free cortisol (UFC) and/or 17-hydroxycorticosteroid (17OHCS) were measured. The normal range for UFC was 70–300 nmol/d, and the normal range for 17OHCS was 6–28 μmol/d. Additional studies included high-dose dexamethasone suppression testing (HDDST) [8, 9], ovine CRH stimulation test [10], and/or bilateral inferior petrosal sinus sampling (IPSS) before and after administration of CRH [11]. A positive result for HDDST was defined as suppression by greater than 90% of UFC or greater than 64% of urinary 17OHCS [8], a positive ovine CRH stimulation test was defined as an ACTH response greater than 35% above baseline at 15 or 30 minutes after CRH injection [10], and a positive central-to-peripheral gradient in bilateral IPSS testing was defined as a ratio of ≥ 3:1 following CRH administration [11]. Additional imaging studies for the differential diagnosis of CS, as appropriate for selected patients, included computed tomography (CT) and/or magnetic resonance imaging (MRI), and [^{131}I]-19-iodocholesterol scintigraphy. Some tests were not available or used in the earlier years. Patients received a provisional diagnosis of CD, EAS, or ACTH-independent CS based on the results of dynamic testing. The final diagnosis was based on surgical cure and/or pathological and immunohistochemical examination of tumor obtained at surgery or autopsy.

Analysis

Continuous data are presented as mean ± S.E.M. Categorical data were analyzed by Fisher's exact test using two-tailed P values, with statistical analyses performed utilizing Prism software (version 5.0c, GraphPad Software, Inc., La Jolla, CA).

Results

Patients

Among approximately 400 MEN1 patients seen at the NIH Clinical Center between 1966 and 2009, nineteen had documented hypercortisolism and/or signs and symptoms of CS (Table 1). Their mean age at diagnosis of CS (36 ± 15.9 yr) was similar to that of unselected CS patients [12]. Nevertheless, the presence of three adolescents with CS in our series is striking (Table 1). Fourteen patients (74%) had MEN1 on a familial basis, while 5 (26%) had sporadic disease (Table 1). Germline *MEN1* mutational testing results were available on 11 of 19 patients and showed a distribution of truncation and missense mutations across the *MEN1* gene similar to those previously reported in MEN1 patients (Table 1, Supplementary Figure 1) [13]. Based on biochemical findings, response to surgery and/or pathological and immunohistochemical examination of tumor, the causes of CS were CD (CD group, n = 11) or ACTH-independent CS due to adrenal tumors (CA group, n = 3). In five patients, no clear etiology (CX group) could be determined (Table 1, and below). No patient was proven to have EAS. Among the 14 patients with CS for whom an etiology could be identified, the frequencies of CD (11 cases; 79%) and ACTH-independent CS (3 cases; 21%) resembled those reported in non-familial CS [12, 14].

Biochemical and dynamic testing results

Eighteen of 19 patients had elevated UFC or 17-OHCS at the time of initial presentation (Table 2).

Sixteen of the 19 patients had one or more dynamic test results available (Table 2). Among the CD group with testing results, all had positive CRH-stimulation tests [10] (n=8), suppressed their serum cortisol and/or UFC or urinary 17OHCS in response to high-dose dexamethasone administration [8, 9] (n=8), and showed central-to-peripheral gradients of ACTH during IPSS testing (n=9) (Table 2). Within the CA group, one patient failed to respond to either CRH or HDDST, and another did not respond to HDDST but responded to CRH test and had a central-to-peripheral ACTH gradient during IPSS testing (Table 2). Interestingly this latter patient (no. 13), who did not appear to have cyclic CS, underwent unsuccessful transsphenoidal pituitary surgery (TSS) before she was cured by recognition and removal of an adrenal adenoma (see below). All five of the patients in the CX group underwent at least one dynamic test (Table 2).

Imaging results

Sixteen of the 19 patients with MEN1 and CS had pituitary and/or adrenal imaging results (Table 3). Among 10 patients in the CD group for whom preoperative pituitary imaging was available, six had pituitary micro- or macroadenomas or pituitary enlargement documented, while four had normal studies. Two CA patients had normal pituitary imaging and large unilateral adrenal masses. Four of the five patients in the CX group had one or more relevant imaging result available (Table 3).

Surgical and pathological findings and clinical course

Ten of 11 patients in the CD group had TSS (Table 4). One or more pituitary adenoma was identified at surgery in eight patients. In two cases no tumor was found, but these patients

had biochemical and clinical remission after TSS and hemi-hypophysectomy (patients 2 and 8). Three patients of the 11 with CD (27%) had two separate pituitary microadenomas identified at surgery (patients 1, 3, and 10). This incidence of multiple pituitary adenomas is significantly higher than both that reported previously in a large series of CD cases (11 out of 658 total, excluding two patients with MEN1; ~2%) [15] ($P < 0.001$) and that found in a series of unselected sporadic pituitary adenomas (3 out of 116; 2.6%) [16] ($P < 0.01$). Of note, four of the CD patients had macroadenomas or invasive tumors at surgery and another developed Nelson's syndrome after adrenalectomy.

Seven of the nine patients in the CD group for whom surgical pathology reports were available had at least one immunoreactive microadenoma identified (Table 4). An ACTH-positive tumor was documented in four. Among the three patients with two adenomas, one had two distinct prolactin (PRL)-staining tumors (patient 3), while two had an ACTH-positive tumor and a second distinct PRL or PRL/growth hormone immunoreactive tumor (patients 1 and 10 respectively). Nine of the 10 patients with CD were cured after TSS (Table 4).

The three CA patients had adrenal cortical tumors identified by surgery or autopsy. Two (67%) had adrenocortical carcinoma (ACC) based on pathologic identification of vascular invasion (patient 12) or pulmonary metastases (patient 14). The incidences of ACC among the 14 MEN1 patients with an identifiable etiology and among the subset with ACTH-independent CS were similar to those reported in large series of unselected CS patients [12, 14].

Three patients among five in the CX group underwent surgery directed at CS (Table 4). Two patients had failed TSS (patients 16 and 19) without tumor visualization at surgery. Although patient 19 had a hemi-hypophysectomy with a 1 mm ACTH-immunoreactive microadenoma subsequently reported in the excised tissue, hypercortisolism persisted during 24 months of follow-up. By contrast, patient 16 had spontaneous resolution of hypercortisolism between four and 14 months after surgery (Supplemental Table 1). Patient 15 had bilateral ADX at which time an adrenocortical tumor and contralateral pheochromocytoma were removed. Although this patient was cured after ADX it is unclear whether the hypercortisolism was ACTH-independent and resulting from the adrenocortical tumor, or due to ectopic release of ACTH from the pheochromocytoma. ACTH staining of the pheochromocytoma was not performed at the time of surgery (1971) and the archival specimen was not retrievable.

The remaining two patients in the CX group had spontaneous resolution of hypercortisolism without any surgical intervention.

Discussion

CS is an uncommon manifestation of MEN-1 that can be caused by both ACTH-dependent and independent disorders. Although none of the 19 patients reported here had clear-cut ectopic ACTH secretion, the proportion of CD and adrenal etiologies was similar to that reported in non-familial cases, underscoring the need to consider all etiologies of CS in patients with MEN1.

The high incidence of multiple pituitary adenomas discovered at surgery in MEN1 patients with CD reported here must be seen in the context of other "multiplicities" that characterize this familial tumor syndrome. Not only are multiple endocrine organs affected by the tendency to neoplasia, but also within susceptible tissues the tumors are frequently multiple. Thus it perhaps is not surprising that pituitary tumor multifocality would be observed, since the anterior pituitary is frequently affected in MEN1 [3].

Why then, was the frequent multifocality of pituitary tumors in MEN1 not recognized in a large series of pituitary adenomas in MEN1 patients by Vergès *et al* [3]? These authors studied a cohort of 324 MEN1 patients including 136 with pituitary disease and reported no multiple pituitary tumors [3]. In contrast to the microadenomas found in the majority of MEN1 patients with CD described here, 85% of pituitary tumors in the series reported by Vergès *et al* were macroadenomas [3, 17]. The presence of large macroadenomas in the Vergès series may have obscured detection of coexisting microadenomas during neurosurgery [3].

The frequency of ACC among the MEN1 patients described here, though striking, did not reach statistical significance compared to surveys of largely sporadic CS [12, 14], due in part to the small numbers in our series. ACC has been previously reported in MEN1 patients with CS [5, 18–20].

Our inability to determine the etiology of CS in five of the 19 MEN1 patients in our series is puzzling, since such a large category of diagnostic unknowns was not similarly recognized in two large contemporary series of sporadic CS [12, 14]. One possibility is that not all patients underwent IPSS, which is the best test for the differential diagnosis (11). Patient 15 underwent bilateral adrenalectomy in 1971 prior to the development of IPSS testing, whereas the hypercortisolism of patients 16 and 17 resolved prior to scheduled IPSS. Since patient 16 had resolution of hypercortisolism between four and 14 months after TSS (Supplemental Table 1), and delayed remission of Cushing's disease following TSS has been reported in a subset of cases [21, 22], it is possible that patient 16 had CD. Even though EAS as a cause of CS has been reported rarely in MEN1 [6, 7], our failure to identify EAS as the cause of CS in any of our 19 patients is consistent with the absence of any MEN1 patient among the 90 cases of EAS reported from our institution in a 20-year retrospective review [23]. Spontaneous resolution of CS may have contributed to our inability to identify the cause of CS in at least two of the five patients in our CX group (Table 4). Since periodic or cyclic CS occurs with all etiologies of CS [24], the spontaneous resolution of CS does not in itself offer any diagnostic clue.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Signs and symptoms and demographic information at presentation of Cushing's syndrome in patients with multiple endocrine neoplasia type 1.

Patient ID	Presenting Signs/ Symptoms	Age at Diagnosis of CS (years)	Sex (M/F)	Year of CS Diagnosis	MEN1 (Sporadic/ Familial)	Germline *MEN1* mutation (location)	Other manifestations of MEN1
Cushing's Disease Group							
1	Wt gain, irritability, insomnia, poor growth	10	M	2004	Familial	NA [a]	Angiofibromas
2	Wt gain, headaches	14	M	1989	Familial	NA [b]	HPT
3	Wt gain, bone aches, easy bruisability, acne	15	M	2005	Familial	NA [a]	HPT
4	Wt gain, violaceous striae, acneiform rash, easy bruisability	22	M	1978	Familial	NA [b]	HPT
5	Wt gain, fatigue, muscle weakness	29	F	1957	Sporadic	NA [b]	HPT
6	Amenorrhea	30	F	1987	Sporadic	Q258X (exon 4)	HPT, ZES, prolactinoma
7	Wt gain, weakness, depression, fatigue	30	F	1993	Familial	512delC (exon 2)	HPT, insulinoma, lipomas
8	Prospective screen	38	M	1980	Familial	K119Del (exon 2)	HPT, ZES
9	Not available	41	M	1999	Familial	N [a]	HPT, ZES
10	Wt gain, truncal obesity, insomnia, easy bruisability	47	F	1980	Sporadic	894-9 G->A (intron 4)	HPT, ZES, lipomas
11	Wt gain, facial plethora, fatigue, hypokalemia, HTN	58	F	2004	Familial	mut not found	HPT
ACTH-independent Cushing's, Adrenal Tumor Group							
12	Wt gain, decreased concentration, fatigue, round facies, buffalo hump, HTN	25	M	1997	Familial	L22R (exon 2)	HPT, ZES, pancreatic NE tumor
13	Wt gain, menorrahgia, proximal muscle weakness, easy bruisability	38	F	1990	Familial	735del4 (exon 3)	HPT
14	Proximal muscle weakness, DM, HTN, confusion, easy bruisability	66	F	1965	Familial	C431Y (exon 9)	HPT, pituitary microadenoma
Cushing's Syndrome from Unknown Etiology Group							
15	Wt gain, truncal obesity, HTN, hirsutism	30	F	1970	Familial	1132delG (exon 7)	HPT, ZES, prolactinoma, bronchial carcinoid,esophageal leiomyoma, angiofibroma
16	Wt gain, weakness, easy bruisability, buffalo hump, decreased concentration	37	F	1988	Familial	713delG (exon 3)	HPT, ZES, lipomas
17	Wt gain, fatigue	44	F	2000	Familial	1650delC (exon 10)	HPT, ZES, angifibromas, lipomas
18	Wt gain, fatigue, muscle weakness, decreased concentration	46	M	1994	Sporadic	F447S (exon 9)	HPT, ZES, bronchial carcinoids

Patient ID	Presenting Signs/ Symptoms	Age at Diagnosis of CS (years)	Sex (M/F)	Year of CS Diagnosis	MEN1 (Sporadic/ Familial)	Germline *MEN1* mutation (location)	Other manifestations of MEN1
19	Wt gain, fatigue, hirsutism, HTN	64	F	1990	Sporadic	NA [(b)]	HPT

[(a)] genetic testing not performed at time of NIH Clinical Center evaluation, and patient lost to follow-up.

[(b)] genetic testing not available at time of NIH Clinical Center evaluation, and patient lost to follow-up.

Abbreviations: CS, Cushing's syndrome; M, male; F, female; MEN1, multiple endocrine neoplasia type 1; wt, weight; HPT, hyperparathyroidism; ZES, Zollinger-Ellison syndrome; HTN, hypertension; DM, diabetes mellitus, NA, result not available; mut not found, mutation testing performed but no germline *MEN1* mutation found.

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Table 2

Biochemical and dynamic testing results of multiple endocrine neoplasia type 1 patients with Cushing's syndrome.

Patient ID	UFC (nmol/d) or [17OHCS (µmol/d)] *(a)*	Plasma ACTH (pmol/l) *(b)*	CRH Stim Test *(c)*	HD Dex Suppr Test *(d)*	IPSS Result *(e)*
Cushing's Disease Group					
1	381, 488	5	Pos	ND	Pos
2	361,604	8	Pos	Pos	Pos
3	596, 579	13, 11	Pos	Pos	Pos
4	1020, 1098	NA	NA	NA	NA
5	NA	NA	NA	NA	NA
6	1076, 1214	4	Pos	Pos	Pos
7	1145, 1424	2,3	Pos	Pos	Pos
8	544, 999	5	Pos	Pos	Pos
9	836	<1	Pos	Pos	Pos
10	731, 1244	4, 10	Pos	Pos	Pos
11	1021	15	ND	Pos	Pos
ACTH-independent Cushing's, Adrenal Tumor Group					
12	552, 720	2	Neg	Neg	ND
13	684, 781	2	Pos	Neg	Pos
14	5518	ND	ND	ND	ND
Cushing's Syndrome from Unknown Etiology Group					
15	[52]	ND	ND	Neg	ND
16	546, 646	ND	ND	Neg	ND
17	4701	2	Pos	Pos	ND
18	7035, 7932	29	Neg	Neg	Pos
19	883	3	Pos	ND	Pos

(a) baseline urinary free cortisol or 17-hydroxy corticosteroid excretion at the time of initial presentation with Cushing's syndrome; two representative values are provided when available, otherwise a single value is shown; normal range for urinary free cortisol 70–300 nmol/d; normal range for urinary 17-hydroxy corticosteroid 6–28 µmol/d.

[b] baseline plasma ACTH at the time of initial presentation with Cushing's syndrome; two representative values are provided when available, otherwise a single value is shown; normal range for ACTH 2–11 pmol/l.

[c] CRH Stim Test positive result (Pos)= >35% increase in ACTH (measured at 15' and 30') above baseline; Neg = negative.

[d] High dose dexamethasone suppression test result positive (Pos) if UFCs suppressed > 90% or urinary 17OHCS suppressed > 64%; Neg= negative.

[e] Positive (Pos) indicates central-to-peripheral ACTH gradient of ≥ 3:1 observed with CRH stimulation during inferior petrosal sinus sampling.

Abbreviations: UFC, urinary free cortisol; 17OHCS, 17-hydroxy corticosteroids; HD, high dose; NA, result or data not available; ND, not determined.

Table 3

Imaging results of multiple endocrine neoplasia type 1 patients with Cushing's syndrome.

Patient ID	Pituitary Imaging	Adrenal Imaging	Other
Cushing's Disease Group			
1	Heterogeneous enlarged pituitary 12 X 12 X 15 mm	Normal	ND
2	Neg	ND	ND
3	Neg	6 mm nodule; left adrenal	ND
4	Neg	Bilateral adrenal hyperplasia; possible nodular hyperplasia of right adrenal	ND
5	NA	NA	ND
6	Pituitary macroadenoma, with central necrosis, growing into left sphenoid sinus	Normal	Mass in pancreatic head
7	Multiple hypo-enhancing lesions on left, largest 4 mm; stalk deviation to right	2 cm left adrenal nodule	2 hepatic masses *(a)*
8	Neg	Bilateral adrenal hyperplasia	Right renal mass *(b)*
9	2–3 mm hypo-enhancing lesion on left	Right adrenal nodule left adrenal thickening	None
10	Fullness on right, no focal lesion.	ND	3 cm pancreatic mass
11	5–6 mm hypointense lesion on left	3 cm left adrenal nodule	None
ACTH-independent Cushing's, Adrenal Tumor Group			
12	Neg	4 X 6 cm right adrenal mass	None
13	Neg	5 cm right adrenal mass	None
14	ND	ND	ND
Cushing's Syndrome from Unknown Etiology Group			
15	Neg *(c)*	NA *(d)*	NA *(d)*
16	6 mm lesion on right	NA *(d)*	NA *(d)*
17	Poorly defined lesion on right	Enlarged, nodular left adrenal	Neg chest CT
18	2–3 mm asymmetry on left	Slight bilateral hyperplasia	Multiple pulmonary nodules; small lesion in pancreatic tail
19	Neg	Diffuse bilateral nodular enlargement	Left pulm nodule vs. granuloma

(a) masses were surgically confirmed hepatic adenomas.

(b) renal mass was confirmed surgically to be an angiomyolipoma.

(c) sella turcica imaging studies (c. 1971) normal at an outside institution.

(d) imaging studies while patient with Cushing's syndrome performed prior to NIH evaluation and results not available.

Abbreviations: Neg, negative; NA, result or data not available; ND, not determined.

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Table 4

Surgical and pathological findings and follow-up of patients with multiple endocrine neoplasia type 1 and Cushing's syndrome.

	Surgery or Autopsy Findings			Response to surgery and/or follow-up		
Patient ID	**Type of Operation/ Intervention**	**Operative Findings or Gross Pathology**	**Pathology Results**	**Earliest time UFCs or 17OHCS documented returned to normal post-op (days)**	**Follow-up (months)**	**Post-surgical or post-evaluation clinical course**
Cushing's Disease Group						
1	TSS	2 separate adenomas: 11 mm left sided adenoma; 9 mm right adenoma. The right one invaded the cavernous sinus.	Left-sided tumor pos. PRL Right-sided tumor pos. ACTH	4	4	Clincally cured post-TSS.
2	TSS	No tumor found	No tumor found	4	85	Clinically cured post-TSS with blind left hemi-hypophysectomy; pt grew 12 cm and proceeded into puberty within 1 year.
3	TSS	2 separate adenomas: Tumor 1= 3mm left superior adenoma; Tumor 2= 2 mm midline inferior adenoma	Tumor 1 pos. PRL, neg. ACTH Tumor 2 pos. PRL, neg. ACTH	4	1	Clincally cured post-TSS.
4	TSS	3 mm right inferior adenoma	NA	7	8	Developed recurrent hypercortisolism within 5 months post-TSS at an outside institution; declined pituitary XRT and instead had bilat ADX
5	Bilat ADX, then transfrontal hypophys. and XRT	NA	NA	NA	192	Six years after bilat ADX, developed Nelson's syndrome, requiring transfrontal hypophys. and XRT; large residual pituitary mass evident up to 16 years later
6	TSS	Cystic/ necrotic adenoma invading left cavernous sinus	Tumor pos. for PRL, neg. for ACTH; probable nematode, toxoplasma cyst seen	5	144	Clincally cured post-TSS.
7	TSS	3 mm left paramedial microadenoma	Pituitary microadenoma, Pos. PRL, neg. ACTH	11	192	Clincally cured post-TSS.
8	TSS	No tumor found	No tumor found	11	264	Clinically cured post-TSS with left hemi-hypophysectomy.

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9	TSS	5 mm right adenoma	Positive for ACTH	5	48	Clincally cured post-TSS.
10	TSS	2 separate adenomas: Tumor 1= 3mm left inferior adenoma; Tumor 2= 5 mm right lateral adenoma, invading right cavernous sinus	Tumor 1 pos. PRL, GH Tumor 2 pos. ACTH Invading right cavernous sinus.	4	96	Clincally cured post-TSS.
11	TSS	Left microadenoma	Positive for ACTH	NA	72	Clinically cured post-TSS; lost 70 lbs. post-op
ACTH-independent Cushing's, Adrenal Tumor Group						
12	Right ADX	Right adrenal tumor, 6 X 5 cm	adrenal cortical carcinoma, low-grade, with unequivocal vascular invasion	120	108	Post-op UFCs, serum cortisol nml within 4 months
13	TSS; later right ADX	no tumor found on TSS; 4 X 4 X 3 cm right adrenal adenoma	no tumor found on TSS; right adrenal adenoma found on ADX	8 (following ADX)	216	Had failed TSS; became eucortisolemic after right adrenal tumor excised
14	Autopsy	13 X 9.5 X 9 cm left adrenal mass pulmonary metasases	left adrenal cortical carcinoma pulmonary metasases of adrenocortical cancer	NA	NA	Died from complications of Cushings prior to surgical intervention; autopsy showed large left adrenal carcinoma metastatic to lung
Cushing's Syndrome from Unknown Etiology Group						
15	Bilat ADX	Left adrenocortical tumor Right pheochromocytoma	NA *(a)*	NA *(b)*	336	Cured after bilat ADX and removal of left adrenal tumor and right pheochromocytoma; did not develop Nelson's syndrome over next 25 years
16	TSS	no tumor found	no tumor found	420	228	Persistent hypercortisolism for >4 months post-TSS; then spontaneous resolution sometime during next 10 months
17	NA *(c)*	NA *(c)*	NA *(c)*	NA *(c)*	NA *(c)*	Hypercortisolism resolved spontaneously; never had required surgery.

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18	NA *(c)*	NA *(c)*	NA *(c)*	NA *(c)*	132 (since spont. resolution of CS)	Spontaneous resolution of hypercortisolism prior to scheduled TSS.
19	TSS	No tumor visualized; blind right hemi-hypophys.	1 mm microadenoma; positive for ACTH	NA	24	Persistent hypercortisolism for at least 2 years post-TSS

(a) surgical pathology analysis performed at outside institution in 1971, prior to NIH evaluation, and not available.

(b) postoperative biochemical data collected at outside institution in 1971, prior to NIH evaluation, and not available.

(c) surgery to treat Cushing's syndrome not performed.

Abbreviations: TSS, transsphenoidal pituitary surgery; PRL, prolactin; ACTH, adrenocorticotropic hormone; GH, growth hormone; CS, Cushing's syndrome; UFC, urinary free cortisol; ADX, adrenalectomy; hypophys., hypophysectomy; Bilat., bilateral; NA, result or data not available.

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