



# Repeated Remissions of Cushing's Disease Due to Recurrent Infarctions of an ACTH-Producing Pituitary Macroadenoma

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**Abstract.** Infarction of prolactin-secreting or growth hormone-secreting pituitary adenomas is not unusual. However, infarction of ACTH-secreting adenomas has rarely been reported. Cyclical course of Cushing's syndrome alternating with adrenal insufficiency due to recurrent infarction of an ACTH-secreting pituitary adenoma has not been reported. We report here a 20-year-old lady who presented with florid signs of Cushing's syndrome but was found to have adrenal insufficiency on biochemical evaluation. Magnetic resonance imaging (MRI) of the pituitary gland showed that she had infarction of an ACTH-secreting macroadenoma. Over the next 6 years, her disease ran a cyclical course characterized by periods of hypercortisolism alternating with adrenal insufficiency due to repeated episodes of infarctions of the ACTH-secreting pituitary macroadenoma with corresponding changes in the pituitary adenoma on serial MRIs. The case alerts clinicians to this possibility when a patient presents with clinical picture of Cushing's syndrome but has adrenal insufficiency on biochemical testing. It also suggests that silent or subclinical infarction of pituitary adenomas is not uncommon and is probably under diagnosed.

**Key Words.** apoplexy, Cushing's disease, adrenal insufficiency

## Introduction

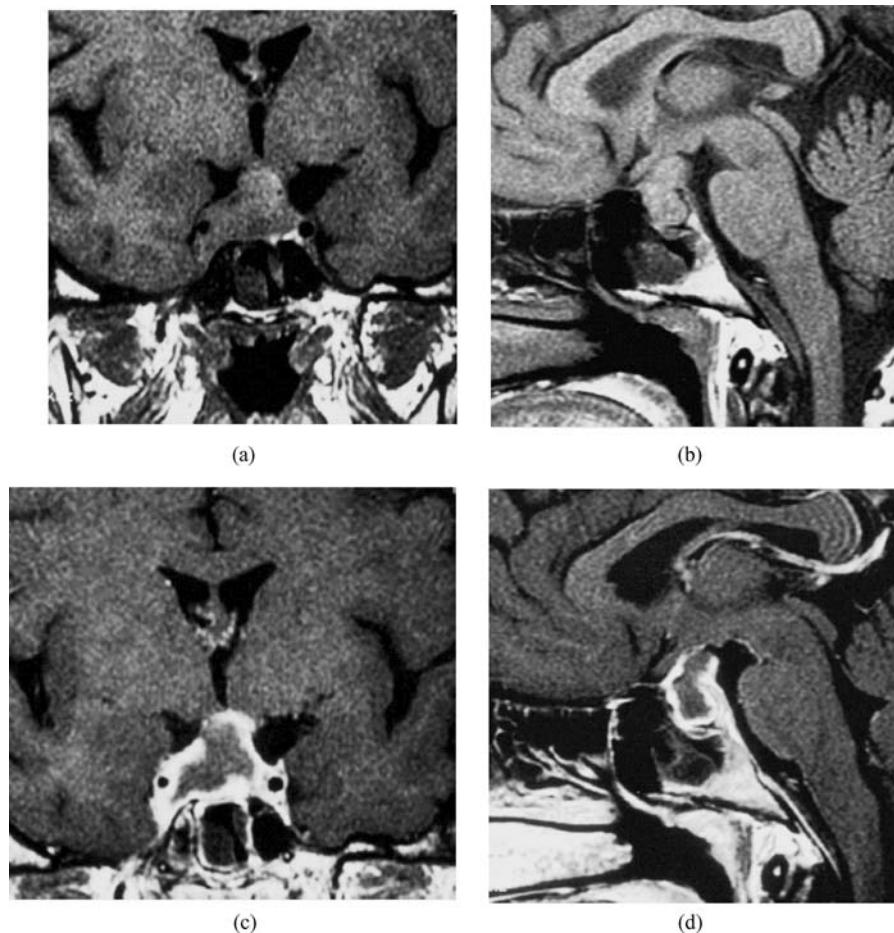
Pituitary infarction leading to the clinical syndrome of pituitary apoplexy may complicate pituitary tumors secreting growth hormone, prolactin or non-functioning tumors [1–4]. However, apoplexy has rarely been reported in patients with Cushing's disease. Recurrence of Cushing's disease after variable periods of remission following an episode of infarction is known to occur, but recurrent infarctions in Cushing's disease have rarely been documented [5]. We report a unique case of Cushing's disease running a cyclical course of hypercortisolism alternating with adrenal insufficiency due to repeated episodes of infarction of an ACTH-secreting pituitary macroadenoma. We also reviewed all previously reported cases of apoplexy of ACTH-secreting

adenomas. Our case alerts clinicians to this possibility when a patient presents with clinical signs of Cushing's syndrome but is found to have adrenal insufficiency on biochemical evaluation. It also suggests that silent infarction of pituitary tumors is probably common and frequently underdiagnosed.

## Case Report

A 20-year-old lady was referred to King Faisal Specialist Hospital and Research Centre (KFSHRC) in September 1997. She presented to a local hospital in August 1997 with one-year history of headache, progressive weight gain, acne, hirsutism, increased skin pigmentation, and frequent but scanty menses. She had no symptoms of muscle weakness, back pain, polyuria or polydipsia. She gave no history of exogenous steroid use and was not on any other medications. Her past medical history as well as family history were non-contributory. She had classical cushingoid features and her investigations at the referring hospital were suggestive of pituitary-dependent Cushing's syndrome with serum cortisol 625.5 nmol/L (normal range; 85–460), and ACTH 57 ng/L (normal range; 6–46). Magnetic resonance imaging (MRI) of the pituitary gland revealed a pituitary macroadenoma with a central area of mild hyperintensity suggestive of a recent silent infarction (Fig. 1).

On presentation to KFSHRC in September 1997, she was clinically cushingoid with central obesity, moon face, wide abdominal pink striae, proximal myopathy, supraclavicular fullness and dorsal fat pad. Her weight was 83 kg, height 156 cm, and blood pressure 110/70 mm Hg without postural changes. Surprisingly, on biochemical testing, she was found to have adrenal insufficiency; AM serum cortisol was 18 nmol/L



**Fig. 1.** Pituitary MRI T1 weighted image in a coronal (1A) and sagittal (1B) projections (August 1997, hypocortisolism): Intrasellar tumor with suprasellar extension and invasion into the right cavernous sinus. Mild hyperintense signal changes in the center represent possible infarction. Post gadolinium coronal (1C) and sagittal (1D) views reveal intrasellar tumor with peripheral contrast uptake and isointense center representing subacute infarction.

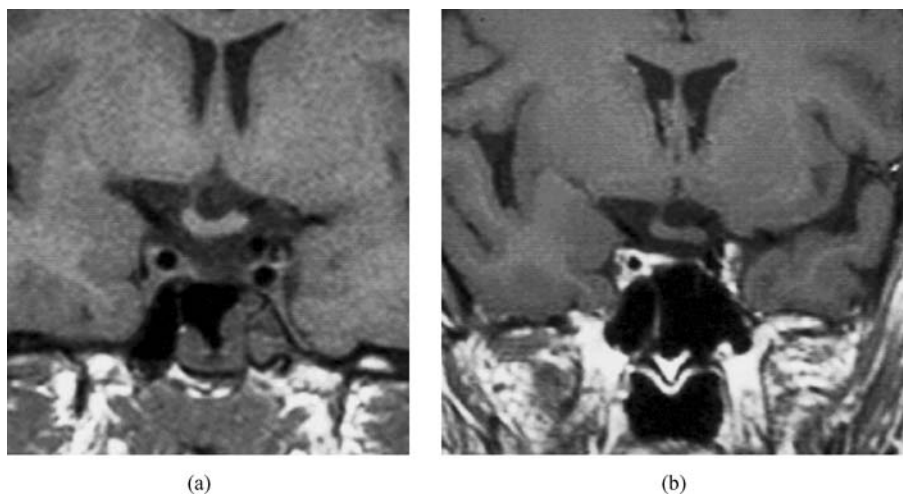
and ACTH 20 ng/L, 24 hr urine free cortisol (UFC) 12.9 nmol/day (normal range; 50–350), and ACTH stimulation test showed baseline cortisol of 67 nmol/L increasing to 471 nmol/L at 60 min after i.v injection of ACTH 250  $\mu$ g (Table 1). The other pituitary hormones were as follows: prolactin 10  $\mu$ g/L (normal range; 2.8–29.2), Estradiol was undetectable (normal range; 73–976 pmol/L), LH 3 u/L (normal range; 0.5–16.9), FSH 7 u/L (normal range; 1.5–9.1), FT4 13 pmol/L (normal range; 11–23), TSH 0.6 mU/L (normal range; 0.35–5.5), fasting growth hormone <0.5 mU/l (normal range; 0–13.5). She denied history of exogenous steroid use. She gave no history suggestive of pituitary apoplexy; no history of severe headache, visual disturbances, nausea, vomiting or orthostatic dizziness. Pituitary MRI showed a pituitary mass invading the right cavernous sinus. Computerized visual field study and ophthalmologic evaluation were normal. The possibility of silent pituitary infarction leading to hypopituitarism was consid-

ered and the patient was treated with hydrocortisone 25 mg daily. She did not receive estrogen/progestin or L-thyroxine replacement therapy. Over the next few months, pituitary adrenal axis recovered with a normal adrenal response to 250  $\mu$ g synthetic ACTH given i.v (cortisol post ACTH stimulation was 624 nmol/L). Hydrocortisone was discontinued. Menstrual period became regular and was of normal amount. Her hormonal evaluation in April 1998 revealed AM serum cortisol of 469 nmol/L, follicular phase estradiol 856 pmol/L, LH 5 u/L, FSH 9 u/L, prolactin 16  $\mu$ g/L, TSH 3.5 mU/L and FT4 17 pmol/L. Pituitary MRI at that time showed that the overall volume of the tumor decreased dramatically, showing a pituitary empty sella with a residual mass at right cavernous sinus (Fig. 2). On regular follow up, she remained in remission for about a year and half off glucocorticoids before a relapse of Cushing's disease was documented in August 1999 when she presented with frontal headache, increasing

**Table 1.** Summary of events from the time of presentation

Date (Month/year)	S. Cortisol (nmol/L) (N 85–460)	24 Hour UFC (nmol/day) (N 33–287)	ACTH ng/L (N 6–46)	MRI Pituitary
08/1997	625.5	–	57	
09/1997	18	–	20	Large pituitary tumor (Fig. 1)
02/1998	469*	–	–	Right cavernous sinus lesion and empty sella (Fig. 2)
08/1999	737	641	72	Right cavernous sinus lesions progressing in size
09/1999	–	–	–	Right cavernous sinus tumor bleeding (Fig. 3)
06/2000	402	174	66	Regressing right cavernous sinus lesion and empty sella (Fig. 4)
03/2001	559	234	104	Re growth of right cavernous sinus lesion (Fig. 5)
04/2003	551	760	108	Further progression of right cavernous lesion

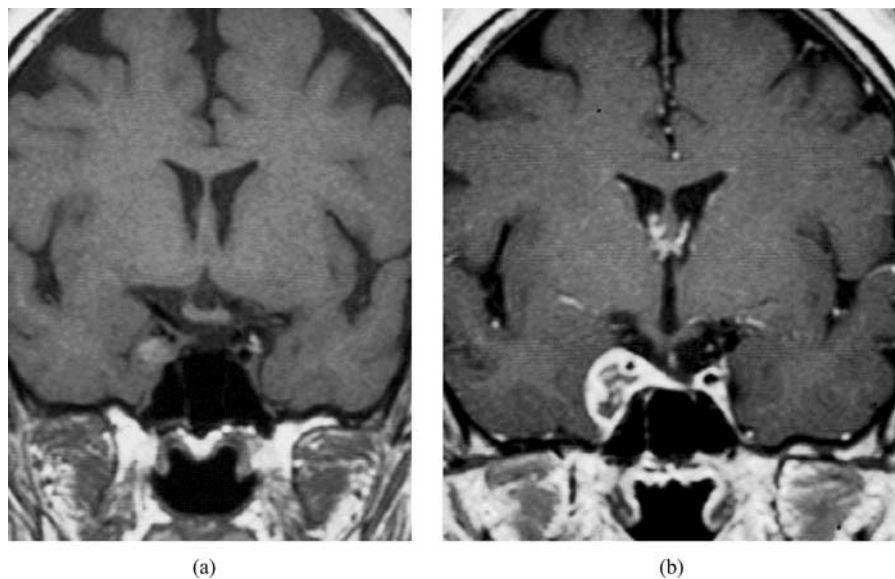
\*60 min post intravenous injection of 250 mcg synthetic ACTH.



**Fig. 2.** Pituitary MRI coronal views pre (2A) and post (2B) contrast injection (February 1998, recovering hypocortisolism): The overall volume of the tumor decreased dramatically showing a pituitary empty sella with a residual mass at right cavernous sinus.

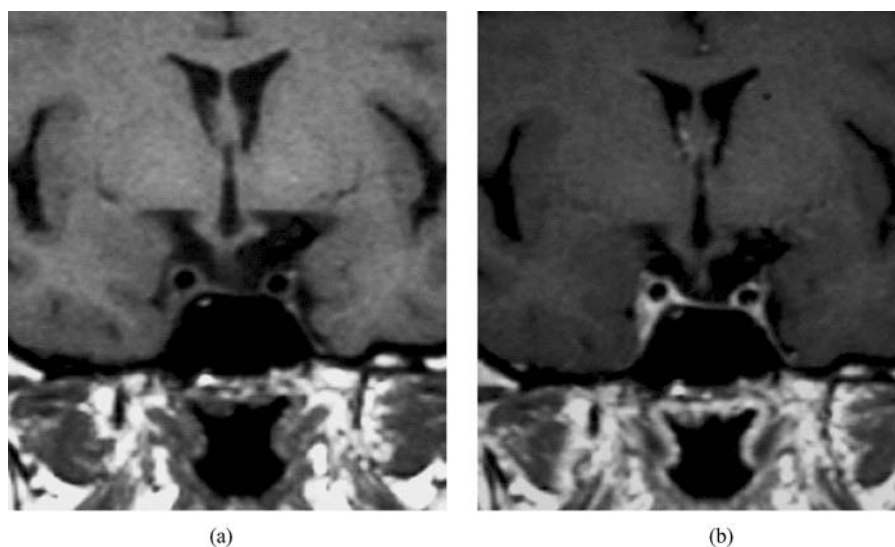
weight, and amenorrhea for 3 months. Clinically, she was clearly cushingoid and her UFC was elevated at 641 nmol/day, ACTH was 72 ng/L, and MRI pituitary showed progression of the right cavernous sinus lesion. Other hormonal profile at that time revealed FSH 7 u/L, LH 5 u/L, estradiol 228 pmol/L, prolactin 11 ug/L, FT4 12 pmol/L, TSH 0.9 mU/L, fasting growth hormone <0.4 mU/L and IGF-1 115 ug/L (normal range, 101–905). She was admitted a month later for possible transsphenoidal surgery. During hospitalization in September 1999, she had sudden severe headache,

nausea, vomiting and drowsiness. She also complained of diplopia and was found to have right third and sixth cranial nerve palsy. A repeated MRI of the pituitary gland at that time showed bleeding in the right cavernous sinus lesion (Fig. 3). She was treated conservatively with i.v hydrocortisone 100 mg 6 hourly and metoclopramide 10 mg three times per day for 4 days followed by hydrocortisone 30 mg daily for 5 months. She made a smooth recovery. This was followed by a second remission of Cushing's disease lasting for more than one year with an empty sella and regression of



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**Fig. 3.** Pituitary MRI coronal T1 weighted images pre (3A) and post (3B) contrast injection (September 1999, hypercortisolism): Hyper intense signal within the residual tumor inside the right cavernous sinus and peripheral uptake of contrast. Progression of the tumor is also appreciated.

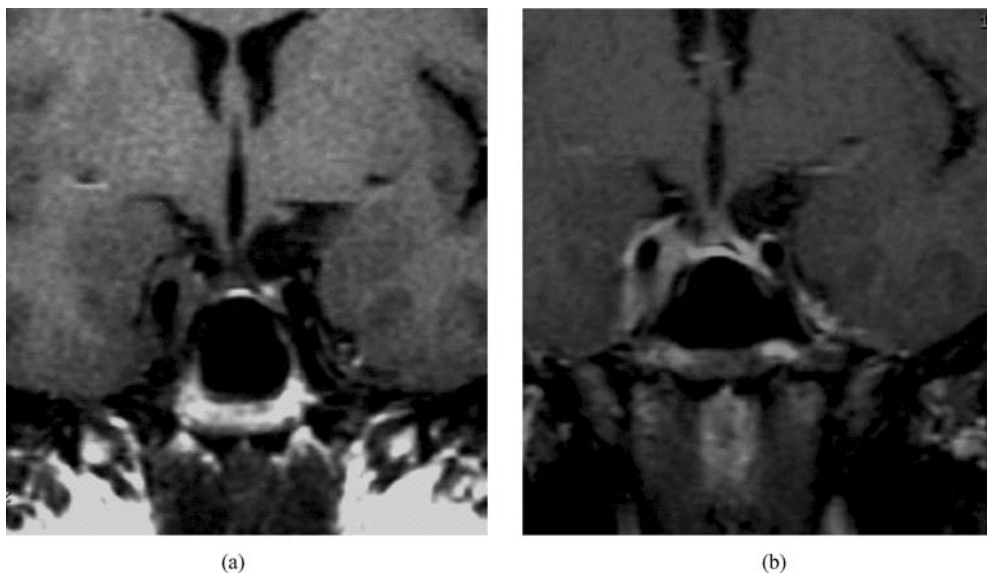


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**Fig. 4.** Pituitary MRI coronal T1 weighted images pre (4A) and post (4B) contrast (June 2000, Eucortisolism): Regression in tumor size occupying the right cavernous sinus and partial empty sella.

the previously seen right cavernous sinus lesion on MRI (Fig. 4). She had no symptoms except amenorrhoea and slow increase in her weight of about 4 kg but was otherwise stable without headache or visual disturbances, proximal weakness, back pain or psychological symptoms. In June 2000, UFC 174 nmol/day, serum AM cortisol 402 nmol/L, and ACTH 66 ng/L. A second recurrence of hypercortisolism on a repeated

24-hour UFC (760 nmol/day, ACTH 108 ng/L) accompanied by progressively enlarging right cavernous sinus lesion was documented on pituitary MRI done in March 2001 (Fig. 5). At that time she only complained of amenorrhoea for which she was taking oral contraceptive agents. She continued to have slowly increasing weight, hirsutism, and central obesity but was generally stable. In January 2003, UFC was 303 nmol/day, PM serum



**Fig. 5.** Pituitary MRI coronal sections in T1 weighted images pre (5A) and post (5B) contrast (March 2001, hypercortisolism): The tumor residue with moderate enhancement and slight progression of its size in the posterior part of the right cavernous sinus.

cortisol 551 nmol/L, ACTH 108 ng/L, prolactin 14.7 ug/L, FT4 14.1 pmol/L, IGF-1 77 ug/L, LH 6.2 u/L, FSH 7.9 u/L, estradiol 201 pmol/L. She was eventually treated with stereotactic fractionated radiotherapy (total 4500 cGy, 25 fractions) to the pituitary lesion given between July and August 2003. In December 2003, UFC was still elevated at 760 nmol/day with ACTH 74 ng/L. She was started on Ketoconazole 200 mg twice daily in January 2004. In May 2004, UFC decreased to 122 nmol/day and in October 2004 it was to 232 nmol/day. Both of these readings were while the patient was on ketoconazole 200 mg twice daily. Pituitary MRI done in October 2004 showed no change in the right cavernous sinus lesion and an empty sella. She was seen for the last time in February 2005. She had no symptoms of hypercortisolism. Her weight was stable for the last 1 year at around 80 kg. Blood pressure was 122/78 mm. She had amenorrhoea for which she was taking oral contraceptive pills. UFC was 155 nmol/L and FT4 13.8 pmol/L. She was maintained on ketoconazole.

## Discussion

We described a case of Cushing's disease due to an ACTH-secreting pituitary macroadenoma who developed multiple episodes of hypercortisolism alternating with adrenal insufficiency secondary to recurrent infarction of the pituitary macroadenoma. Pituitary infarction is a well-known complication of pituitary macroadenomas [1–4]. However, it is quite rare in pituitary microadenoma. In its classical form, it usually presents as a syndrome of one or more manifestations of sudden headache, nausea and vomiting, visual dis-

turbances and meningism [3,6]. While this classical picture is relatively rare, subclinical infarction might be more common [6]. Overall, pituitary apoplexy has been reported to occur in 9.5–16.6% of pituitary adenomas [1,2,4]. However, it is likely that these numbers underestimate the actual incidence of pituitary infarction; silent or subclinical infarction without the clinical syndrome of apoplexy may occur at a higher frequency but do not get diagnosed due to lack of symptoms [4,6].

Most previously described cases of pituitary apoplexy occurred in non-functioning, prolactin-secreting, or growth hormone-secreting adenomas [1,3,4,7]. Apoplexy in Cushing's disease is exceedingly rare [8–11]. This is probably due to the fact that most cases are secondary to pituitary microadenomas or corticotroph hyperplasia. The risk of infarction in pituitary tumors is increased by use of anticoagulation, oral contraceptive agents, clomiphene or gonadotrophin releasing hormone analogues, and thyrotropin releasing hormone. It has also been associated with pregnancy, thrombocytopenia, head trauma, cardiac surgery, and increased intracranial pressure [12]. It is also possible that the propensity for hemorrhagic infarction is related to some intrinsic features of the adenoma itself such as blood supply, rate of growth, or degree of stimulation by hypothalamic trophic hormones [4,13,14]. Eosinophilic adenomas have been reported to have a higher risk of infarction compared to basophilic adenomas. Hemorrhage and necrosis may result from rapid growth of adenomas, which may outgrow their blood supply leading to relative ischemia, hemorrhage and necrosis. Growth of tumors that are adjacent to the infundibulum or near the hypophyseal arteries

**Table 2.** Previously reported cases of infarction of ACTH-secreting pituitary adenomas

Reference	No. of cases	Adenoma	Clinical presentation	Management
Findling et al. 1981	1	Micro	Silent	Surgery
Le Nestour E. et al. 1994	1	Micro	Silent	Conservative
Mercado-Asis et al. 1995	2	Micro	One silent and 1 manifest	Surgery
Kamoi et al. 1998	1	Macro	Manifest	Surgery
Kamiya et al. 2000	1	–	Manifest	Conservative
Sasaki et al. 2003	1	Macro	Silent	Surgery

may lead to compression of these vessels resulting in compromise of the blood supply of these tumors. Infarction of pituitary tumors may also be induced by radiotherapy or medical therapy such as dopamine agonists in cases of prolactinomas. This is probably secondary to rapid shrinkage of the tumors or due to direct cellular effects of these therapies [12].

Recovery of pituitary function has been described after an apoplectic event. This may occur spontaneously [15,16]. However, early surgical decompression seems to improve the chances of both recovery of hormonal secretion and visual disturbances [6,17]. It is postulated that the sudden increase in the intrasellar contents following hemorrhage leads to vascular compromise and pressure on pituitary stalk which in turn causes ischemia and dysfunction of the residual normal pituitary tissue with consequent hypofunction [16]. In our patient, recovery of pituitary function was followed by relapse of Cushing's syndrome on 2 occasions. These relapses are probably a result of regrowth of residual minimal adenomatous tissue following infarction of most of the adenoma, which is suggested by the adrenal insufficiency that developed after each episode of infarction. Alternatively, the adenomatous tissue may have been only shocked by the sudden hemorrhage (did not undergo necrosis) and recovered later on.

When a patient presents with clear cushingoid features but his biochemical testing unexpectedly reveals adrenal insufficiency, a number of considerations have to be entertained. Obviously, pituitary infarction of an ACTH-producing adenoma, albeit rare, can explain such an apparent paradox. A much more common situation is the use of exogenous glucocorticoids, either factitiously or therapeutically for another medical condition such as bronchial asthma, rheumatoid arthritis, or post organ transplantations [18]. The latter is usually obvious by clinical history while in the former situation, measurement of urine glucocorticoids by high-pressure liquid chromatography may reveal glucocorticoids other than cortisol [19,20]. Other rare but important considerations in the differential diagnosis of clinically cushingoid but biochemically adrenal insufficient situations are food-induced Cushing's syndrome in which postprandial hypersecretion of gastric inhibitory peptide (GIP) leads to significant hypercortisolism in the postprandial period and may lead to

suppression of the endogenous ACTH secretion in between meals [21,22]. Similar situations may arise from ectopic expression on the adrenal cortical cells of other receptors leading to erratic cyclical hypercortisolism with periods of endogenous ACTH suppression [23]. Cyclical Cushing's syndrome has also been described in which the adrenal cortex secrete excess amounts of glucocorticoids episodically [24].

Only a handful of cases of apoplexy in Cushing's disease have been described in the literature (Table 2). Unlike our patients, none of these cases had more than one episode of hypoadrenalism following hypercortisolism. Findling et al. described a young woman who was found to have a pituitary infarction of a 5-mm ACTH-producing microadenoma removed several months following bilateral adrenalectomy for Cushing's disease [11]. Le Nestour et al. described a case of Cushing's disease that was spontaneously cured after a timely MRI-documented acute bleeding in a pituitary microadenoma [10]. Mercado-Asis et al. reported 2 cases who presented initially with cushingoid features but were found to have adrenal insufficiency on biochemical evaluation [25]. In both cases, Cushing's syndrome evolved 1–4 years later and surgical and histopathological examinations of the resected pituitary adenomas revealed evidence of infarction. Kamoi et al. described a case of Cushing's disease developing after 6 years of hypopituitarism due to Sheehan's syndrome [8]. Kamiya et al. described a patient who had a long-term remission after a silent infarction of a pituitary adenoma but had relapse of Cushing's disease 7 years later [26]. Sasaki et al. described an old woman who developed Cushing's disease 10 years after an episode of apoplexy [27]. They postulated that the patient probably had recurrence of Cushing's disease, which remitted initially after apoplexy. Rotman-Pikielny et al. described a case of Cushing's syndrome who developed an apoplexy of a pituitary macroadenoma 2 days after corticotrophin releasing hormone (CRH) stimulation test done during the work up for Cushing's syndrome [13]. She then developed hypopituitarism with resolution of clinical and biochemical manifestations of Cushing's syndrome. They postulated that the apoplexy was induced by CRH stimulation.

We conclude that a cyclical course of Cushing's disease with repeated relapses and remissions could be

caused by recurrent infarctions followed by re-growth of the remnant tissue of an ACTH-producing pituitary adenoma. The presentation of these infarctions is variable, from clinically silent to a more dramatic one with neurological manifestations and acute hormonal deficiency. This may lead to pitfalls in the diagnosis of Cushing's disease especially when the infarction is silent. Recurrence of Cushing's disease after an apparent cure following infarction of an ACTH-producing adenoma may occur; therefore long-term follow up is necessary.

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