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Characterization of Persistent and Recurrent Cushing's Disease

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Clinical Case

A 38 year-old woman presented in 2005 with classic signs and symptoms of Cushing's disease (CD) and was found to have an elevated 24-hour urinary free cortisol (UFC) of 146 $\mu\text{g}/24 \text{ hr}$ ($<50\mu\text{g}/24 \text{ hr}$), midnight salivary free cortisol (MSC) of 7.2 nmol/L ($<4.3 \text{ nmol/L}$) and inappropriate suppression to 1 mg overnight dexamethasone suppression test (ODST) with serum cortisol of 5.9 $\mu\text{g}/\text{dl}$ ($<1.8 \mu\text{g}/\text{dl}$). Plasma ACTH was 58 pg/ml ($<52 \text{ pg/mL}$) and pituitary MRI showed a microadenoma. She underwent transsphenoidal adenomectomy (TSA) in December of 2005, with surgical pathology confirming the presence of a corticotroph tumor by immunohistochemistry, and achieved clinical and biochemical remission, with an initial postoperative serum cortisol of 1.5 $\mu\text{g}/\text{dl}$. However, four years later she developed new recurrence of her presenting symptoms, in particular weight gain and insomnia, in addition to a gradual return of hypertension and diabetes mellitus. While her UFCs have been normal, ranging from 9.7–23.7 $\mu\text{g}/24 \text{ hr}$ ($<50\mu\text{g}/24 \text{ hr}$), biochemical testing has also shown the following: elevation of one of eight MSCs, with results ranging from 2.8–6.1 nmol/L ($<4.3 \text{ nmol/L}$), partial suppression to ODST with serum cortisol of 3.4 $\mu\text{g}/\text{dl}$ ($<1.8 \mu\text{g}/\text{dl}$), and dramatic elevation of plasma ACTH, with values ranging from 110–132 pg/ml. (Table 1). This case highlights the complexities of defining CD recurrence in the setting of discordant biochemical results and suggestive but not definitive clinical features. The present review therefore aims to summarize the current literature surrounding existing definitions of CD remission, persistence, and recurrence. In order to understand what constitutes CD recurrence, a review of the concepts underlying remission is first required, which is therefore the main focus of this review. In the final section and in Table 2, we then summarize current definitions of recurrence. We will also highlight treatment options and potential areas of future investigation.

Background

Initially described by Harvey Cushing in 1932, Cushing's syndrome is defined as a condition of chronic glucocorticoid excess. Eighty percent of cases of endogenous Cushing's syndrome are due to elevated adrenocorticotrophic hormone (ACTH) secretion, of which the vast majority results from a pituitary corticotroph adenoma, an entity known as Cushing's disease. While this is an uncommon disease with an incidence of only 0.7 to 2.4

million cases per year, left untreated it is associated with significant morbidity and a mortality rate of 50% at 5 years [1–3]. Therefore, prompt diagnosis and successful therapy are paramount.

Diagnosis and management of CD is based upon clinical and biochemical markers. Classic phenotypic changes of glucocorticoid excess include the development of dorsocervical and supraclavicular fat, truncal obesity, thinning of the skin, violaceous striae, and proximal muscle weakness [4–7]. Neuropsychiatric symptoms are common and include depression, sleep disturbances, cognitive deficits and emotional lability [8,9]. Objectively, hypertension, glucose intolerance or diabetes, and osteoporosis are concerning co-morbidities [4–7].

ACTH-secreting adenomas cause excess adrenal cortisol secretion, resulting in elevated urine cortisol concentrations as assessed by UFC measurements [5,7]. An abnormal set point for cortisol feedback occurs, resulting in insufficient serum cortisol suppression after low dose or overnight dexamethasone suppression testing (LDDST and ODST, respectively) [5]. Finally, loss of physiologic circadian rhythm of cortisol secretion is demonstrated by elevated MSC concentrations [7]. Hence, these physiologic disturbances in the hypothalamic-pituitary-adrenal (HPA) axis serve as the basis for the biochemical markers employed to diagnose CD.

TSA has been widely accepted as first-line therapy for CD. First performed in the early 1960's by Jules Hardy, remission rates with this procedure for microadenomas (<10 mm) have been reported to vary between 65–90% [4]. Multiple factors may account for this wide range including the skill and experience of the surgeon, and the size and location of the adenoma. Furthermore, the criteria by which initial and sustained remission have been defined in studies lack uniformity [10–17].

Consensus Statement

The 2008 Endocrine Society Consensus Statement recommends the use of serum cortisol during the first postoperative week for defining initial remission and predicting sustained remission. Serum cortisol concentrations less than 5µg/dl, measured while withholding glucocorticoid treatment or while using low doses of dexamethasone (below the standard low-dose test amount), predict a long-term remission rate of approximately 90% at 10 years [4,10–12,18–23]. Serum cortisol concentrations greater than 5µg/dl within the first 6 weeks postoperatively require further evaluation [4]. Patients with serum cortisol concentrations between 2 and 5µg/dl can be observed and have similar recurrence rates to those with a serum cortisol below 2 µg/dl [4,10–12,18–23]. If serum cortisol levels are equivocal, the Consensus Statement recommends measuring UFC, with a value below 20µg/24h consistent with remission, a value in the normal range (20–100 µg/24h) being equivocal, and a value above the normal range (>100µg/24h) signifying persistent disease [4]. Despite these recommendations, there is debate as to which methods and thresholds best define CD remission and predict successful outcomes, including both the degree and timing of postoperative serum hypocortisolism, as well as the use of other biochemical markers.

Postoperative hypocortisolism

Postoperative serum hypocortisolism has been suggested as an index for remission based on the pathophysiology of this disease process. In CD, long-standing hypercortisolism results in suppression of normal corticotroph cells. Therefore, surgical resection of the ACTH-secreting adenoma should lead to transient ACTH and cortisol deficiency. For this reason, many argue that the best predictor for initial and sustained remission is an undetectable postoperative serum cortisol [22,24–26]. This concept first gained acceptance after a study by Trainer et al. in 1993 in which none of the patients with postoperative serum cortisol less than 1.8 µg/dl had disease recurrence at median follow up of 40 months [12]. Postoperative serum cortisol ultimately was equated to a tumor marker for residual disease, and the authors advocated for early repeat intervention in patients with any level of detectable postoperative serum cortisol [25,27].

Yet, by using such a stringent criterion, we may fail to identify patients who have achieved initial remission, leading to unnecessary interventions. This was well-illustrated by Patil et al. who found that when using a serum cortisol level below 2µg/dl, only 45.5% of the total cohort of 215 patients would be classified as achieving remission, as compared to 85.6% who achieved remission when defined by the need for glucocorticoid replacement or a normal UFC, 70% of whom were reported to be in sustained remission at mean length of follow up of 45 months. However, those with initial postoperative serum cortisol levels above 2 µg/dl were 2.5 times more likely to recur [28]. This highlights the major critique of using such a strict measure to define initial remission in that it results in good sensitivity but poorer specificity. Therefore, it may better serve as a predictor of sustained remission rather than as a method to define initial remission.

It should be noted that even this narrow index for defining remission is imperfect [12,23,29]. In 2002, Yap et al. evaluated patients who had achieved initial remission following TSA, as defined by a serum cortisol below 50 nmol/L (1.8 µg/dl) on postoperative day 3 and 4. At median follow up of 36.3 months, 7 out of 61 (11.5%) of these patients had developed recurrence, all of whom initially had undetectable postoperative serum cortisol levels [23]. Similarly, Pereira et al. in 2003 found that of the 37 patients who achieved initial remission with serum cortisol values below 50 nmol/L (1.8 µg/dl) in the second postoperative week, 14% developed recurrence at 7.2 years. Yet, there were no instances of recurrence during this same length of follow up in patients with initial postoperative serum cortisol levels greater than 50 nmol/L (1.8 µg/dl) [12]. Thus, even such a strict criterion is not an infallible measure for predicting sustained remission.

Accordingly, the use of a higher serum cortisol threshold to define initial remission has been advocated. In 2006, Esposito et al. used a serum cortisol value of less than 5µg/dl to define initial remission. Ninety-seven percent of patients who achieved initial remission by this criterion had sustained remission at median follow up of 32 months. Of note, less than half of these patients would have been defined as having achieved remission according to the more stringent criterion of less than 1.8µg/dl. Thus, postoperative serum cortisol cutoff value below 5 µg/dl maintained sensitivity and increased the specificity of this test for predicting sustained remission [21].

Similarly, Pereira et al. in 2003 demonstrated that there were no differences in 6-month remission rates when comparing those with postoperative serum cortisol levels of less than 1.8 µg/dl versus less than 5 µg/dl. They did note, however, that 20% of patients with serum cortisol levels above 5 µg/dl 2 weeks postoperatively later went on to have a delayed nadir below 1.8 µg/dl 3 months postoperatively. They concluded that serum cortisol measurements between 6–12 weeks postoperatively better predict sustained remission than values obtained 2 weeks postoperatively [13].

Several studies have also noted this phenomenon of delayed remission, in which postsurgical serum hypocortisolism is not achieved in the immediate postoperative period but rather weeks to months later [10,30–32]. The mechanism behind this remains unclear. It has been proposed that chronic exposure to elevated ACTH concentrations may lead to adrenal hypertrophy with partial autonomy that gradually resolves over time [30]. However, there is no direct evidence to support this hypothesis, as adrenal imaging is not routinely performed in patients with CD. In fact, Valassi et al. found that patients with hypercortisolism after surgery who went on to have a delayed nadir had higher levels of ACTH in the postoperative period, arguing against adrenal autonomy. However, this finding does support another potential mechanism for delayed remission, which is late necrosis of residual corticotroph adenoma cells. Adenomatous cells, particularly from macroadenomas, may either be damaged during surgery or incompletely resected, providing a potential source of ACTH secretion until their eventual necrosis [30]. Interestingly, 5 out of 6 subjects in the Pereira study who achieved sustained remission after a delayed nadir initially had macroadenomas [13].

It is also important to note that patients with minimal preoperative hypercortisolism, either due to mild disease or preoperative medical therapy with a cortisol biosynthesis inhibitor such as ketoconazole, may be eucortisolemic after surgery, and this may not represent persistent disease or an increased risk of recurrence [4]. Overall, with a lack of consensus in the literature on both the optimal degree and timing of postoperative cortisol levels to define initial remission, the use of additional biochemical markers has been examined for measuring successful postoperative outcomes.

Restitution of cortisol suppression after dexamethasone

The LDDST (0.5mg every 6 hours for eight doses) and ODST (1mg once) have been used to evaluate the functional status of the HPA axis and to define initial remission. Chen et al. found sustained remission rates as high as 93% at 5 years when using a morning serum cortisol level of less than 3 µg/dl after ODST, and Hammer et al. demonstrated rates as high as 91% at median follow up of 11.3 years with a serum cortisol threshold below 5 µg/dl after ODST [12,20]. However, dexamethasone suppression testing may not be as specific for predicting long-term remission as undetectable postoperative serum cortisol. A large retrospective study of 668 patients performed by the European Cushing's Disease Survey group found recurrence rates of 12.7% when defining initial remission by LDDST, compared to 4.3% when using undetectable postoperative serum cortisol as the criterion [33].

Restoration of physiologic diurnal cortisol rhythm

As mentioned previously, one of the hallmarks of CD is the alteration of the diurnal cortisol circadian rhythm and as such, midnight serum cortisol concentrations have been used to detect CD, with sensitivity as high as 100% [34]. Therefore, the recovery of normal midnight serum cortisol concentrations has been proposed as a method to define initial remission [10,11,14]. In 2001, Estrada et al. demonstrated that in patients with the same degree of postoperative serum hypocortisolism, those with recuperation of the diurnal circadian rhythm (defined by 2300h serum cortisol levels less than 40% of 0800h serum cortisol levels) had significantly lower recurrence rates than those with abnormalities in circadian rhythm (3.4% vs. 50%, respectively). In fact, despite being hypocortisolemic postoperatively, patients with persistent elevations in midnight serum cortisol behaved similarly to those who never achieved hypocortisolism, with recurrence rates of 50% and 64%, respectively. These findings suggest that resumption of the normal cortisol circadian rhythm may be the most sensitive measure for detecting residual corticotroph cells and defining initial remission [11].

More recently, the use of MSC, an easier method of assessing cortisol circadian rhythm compared to midnight serum cortisol measurements, has gained acceptance as an important tool in the diagnosis of CD [35–37]. MSC has therefore been considered as another index of defining and predicting CD remission. In 2008, Carrasco et al. measured MSC in 68 patients with CD 6–12 months after surgical resection and compared the sensitivity and specificity of this test to define initial remission with both UFC and postoperative serum cortisol. Of the patients with sustained remission at 45+/- 31 months postoperatively, all had MSC levels below 2 ng/ml (normal range 0.4–2.1 ng/ml, using radioimmunoassay), and this test was shown to have 100% sensitivity and 98% specificity for defining initial remission. Conversely, UFC levels below the upper limit of normal (90µg/24h, also using radioimmunoassay) had only 70% sensitivity and 93% specificity, and postoperative morning serum cortisol of less than 1.8µg/dl had 93% sensitivity and 74% specificity for defining initial remission. MSC was therefore concluded to be a valid marker for remission with better sensitivity and specificity than UFC or postoperative morning serum cortisol [13]. This may be due to the ability of MSC to detect subtle changes in the dynamics of cortisol secretion that are not evident in a more global evaluation of hypercortisolism, such as provided by UFC measurements. For example, MSC has been shown to be a better diagnostic tool than UFC in cases of mild CD [35]. Ultimately, further data are needed to assess the accuracy of MSC in defining CD remission.

Treatment of persistent and recurrent disease

In the setting of persistent or recurrent CD, repeat adenomectomy remains the first line intervention. Since most cases are due to persistence or recurrence of adenoma cells in the original tumor bed, the first step of repeat surgery is a thorough reexploration of the original resection site [38–40]. Although remission rates are lower than with the initial surgery, they are still reported to be 50–70% [41–44]. The higher incidence of postoperative complications after repeat transsphenoidal surgery is likely due to the increased frequency of more aggressive surgical approaches performed, such as hemihypophysectomy and total

hypophysectomy. For example, rates of postoperative panhypopituitarism are reported to be as high as 45% following hypophysectomy, whereas rates of panhypopituitarism after repeat selective adenomectomy are reported to be 0–5% [38,44–46]. This reasonably low complication rate of repeat selective adenomectomy, a surgical approach which is typically possible, coupled with relatively good success rates, rapid improvement of symptoms with successful surgery, and the fact that an unsuccessful operation will not interfere with the use of other treatment modalities makes repeat transsphenoidal surgery the preferred first treatment option for recurrent and persistent CD.

If repeat surgery cannot be performed or is unsuccessful, particularly in cases where recurrent or residual tumor is in the cavernous sinus, radiotherapy is another option that can be offered to control hypercortisolism. Conventionally, fractionated radiation therapy has been used with remission rates ranging from 56–83%, occurring within an average of 2 years [47,48]. The most common complication is hypopituitarism, with an incidence ranging from 50–100%, in addition to less frequent complications including radiation necrosis, cerebral vasculopathy, and damage to sellar and parasellar structures [48]. Single-treatment stereotactic radiosurgery with photon beams (gamma knife) has now replaced conventional fractionated radiation therapy as the primary radiation modality due to its larger radiobiological effect [48]. Eucortisolemia has been demonstrated in 43–63% of patients at 12.1–22 months, with rates of hypopituitarism reported to vary from 16–55% [49–51]. More recently, two groups have reported proton beam radiosurgery to have similar rates of remission and hypopituitarism, with slightly lower rates of toxicity to cranial nerves as compared with gamma knife [52,53]. Long-term sequelae of this newer technology have not yet been assessed.

For patients who fail the aforementioned treatment modalities, bilateral adrenalectomy provides an immediate reversal of hypercortisolism in 88–100% of cases [54]. This procedure carries a higher morbidity than TSA or radiotherapy, although surgical risks have been minimized with the advent of laparoscopic approaches [55,56]. Bilateral adrenalectomy additionally results in lifelong glucocorticoid and mineralocorticoid replacement. Furthermore, 8–29% of patients may develop Nelson's syndrome, which is characterized by rapid enlargement of adenomatous corticotroph cells in the pituitary after negative feedback inhibition is removed [57]. This aggressive syndrome may lead to cranial nerve palsies and visual field deficits from tumor compression, necessitating further surgical intervention [58–60]. Thus, bilateral adrenalectomy is usually reserved for patients who have failed or have contraindications to other treatment options [4].

Medical therapies

Current available medical therapies for CD have been recently extensively reviewed elsewhere [4,60–64] and therefore will only be addressed in brief here. Traditionally, definitive therapy with surgery or radiotherapy has been considered first, with medical therapy used in adjunct. The targets of medical therapy are divided into three groups: adrenal-directed therapy, pituitary-directed therapy, and glucocorticoid receptor antagonism.

Adrenal-directed therapy consists of the steroidogenesis inhibitors, most commonly ketoconazole (which inhibits several enzymes of steroidogenesis) and metyrapone (which inhibits 11 β -hydroxylase). Clinical and biochemical improvements are typically seen rapidly in a dose-dependent manner, with titration aimed at normalization of UFC. The diurnal circadian rhythm may not necessarily be restored, however, and the clinical implication of this has not yet been determined [4]. Normalization of UFC has been reported to occur in 45–81% of patients treated with ketoconazole [60,61].

Pituitary-directed therapy consists of the use of dopamine receptor agonists and somatostatin analogues. Although bromocriptine has been shown to only have modest success rates of 4–23% [65,66], cabergoline has been reported in small studies to normalize UFC in 30–40% of patients with good long-term efficacy and tolerance at doses ranging from 1–6 mg/weekly [67–69]. The advent of the somatostatin analogue pasireotide, which was recently approved by the FDA to treat CD, has provided a more promising treatment option. This multi-receptor ligand somatostatin analog targets four of the five somatostatin receptor subtypes and possesses strongest affinity for sst5, at a magnitude 40-fold higher than octreotide, in addition to a high affinity for sst1 and sst2 [64,70]. A recent study demonstrated normalization of UFC in 15% of CD patients receiving 600 μ g twice daily and 26% of those receiving 900 μ g twice daily. However, 73% of patients were reported to have a hyperglycemia-related adverse event, with 46% requiring a new glucose-lowering medication [71]. This raises an important reminder that although the improvement of biochemical markers of hypercortisolism are often prioritized, the primary goal of treatment should be to decrease the morbidity and mortality associated with its resultant clinical and metabolic abnormalities.

Finally, mifepristone, a glucocorticoid receptor antagonist that was also recently FDA approved for the treatment of Cushing's syndrome, provides another medical option for patients. In a multicenter open label 6-month trial of 50 adults, mifepristone in doses of 300–1200mg daily was shown to significantly decrease mean HbA1c from $7.43 \pm 1.52\%$ to $6.29 \pm 0.99\%$ [72]. Adverse effects included hypertension, hypokalemia, and increased endometrial thickness in some women. Since biochemical markers cannot gauge treatment response, symptoms, clinical features, and metabolic parameters must be used, once again emphasizing their importance in assessing successful outcomes [79].

Areas of uncertainty and potential for future research surrounding the post-hypercortisolemic state: differentiating CD recurrence versus remission subtypes

Returning to the clinical dilemma presented by our case, which is whether or not this patient has CD recurrence (and if so, how best to treat her), we now address the definitions of recurrence and surrounding areas of uncertainty. While the 2008 Endocrine Society Consensus Statement defines CD recurrence as UFC levels above the normal range for the assay used ($>100 \mu\text{g}/24 \text{ h}$ per these guidelines) [4], many studies have utilized other biochemical and phenotypic markers to determine recurrence. In addition to the reemergence of signs and symptoms of CD, insufficient suppression of plasma cortisol to

LDDST or ODSST [10–13,15–19,31,57,73–75], loss of diurnal circadian rhythm [10,13,14,20], elevations in serum cortisol [14,16,21,22,25,76,77], and plasma ACTH [14,16,76,77], have all been used, with a lack of standardization of what values constitute an abnormal result (Table 2). To complicate matters further, some studies require only one abnormal marker to define recurrence, while others require more than one. The determination of which biochemical test has more significance in defining recurrence when there are discrepancies between markers is inconsistent among studies, as well [11,13]. Finally, the question arises regarding how elevated a test result must be to meet the definition of recurrence, and thus necessitate treatment, which itself introduces potential risks and adverse events.

Without uniformity on the biochemical definition of recurrence, making this determination becomes increasingly subjective, which can be problematic from both a research and clinical perspective. For example, in the clinical case previously discussed, it is reasonable to suspect recurrence since disruption of diurnal variation may be present well before overt hypercortisolism is evidenced by an elevated UFC [13]. However, a neurosurgeon may be hesitant to reoperate without “classic or definitive” evidence of recurrence in the form of a UFC value above the normal range.

Excitingly, we are now in an age of expanding use of medical treatment for CD. Previously, indications for medical therapy typically included correction of severe complications of hypercortisolemia prior to surgery, treatment of persistent disease while awaiting a response to radiation therapy, palliative improvement of symptoms in severe refractory cases, or treatment of persistence or recurrence if the tumor is in an inoperable location such as the cavernous sinus. Now, we have the opportunity to decide if a patient such as the one described with recurrent CD symptoms and some abnormalities on HPA axis testing would benefit from the initiation of medical therapy. One reasonable approach would be to start medical treatment, with improvement of symptoms serving as further evidence of recurrence. The decision regarding repeat transsphenoidal surgery can then be revisited or the patient can continue on medical therapy for recurrent CD. Ultimately, the ability to make the determination of CD recurrence and to decide whether further treatment is appropriate would be more consistent if standardization of the biochemical definition of recurrence was established. Notably, special attention should be paid to the fact that UFC is not as sensitive a marker as MSC, and therefore it may no longer be the most appropriate test to provide “classic or definitive” evidence of CD recurrence [7].

On the other hand, what if these subtle abnormalities in the HPA axis were not used to redefine CD recurrence but rather to identify different remission subtypes. These remission subtypes, for example, may be associated with an increased risk of recurrence and could help alert clinicians to the need for closer monitoring. Castinetti et al. in 2009 demonstrated that in 80% of patients the combined dexamethasone desmopressin test became and remained positive 6–60 months prior to classic biochemical markers, with this test becoming positive at the same time as the other biochemical markers in the remaining 20% of patients [78]. Ultimately, the study suggested that a positive test result should not be used as a new method to diagnose recurrence and initiate further treatment, but rather as a way to identify

patients at increased risk of recurrence, so that they can then be monitored more closely with classic markers of hypercortisolism.

Different remission subtypes could also be associated with increased morbidity. It has been observed that the correction of hypercortisolism in CD patients may not lead to complete remission of clinical and metabolic abnormalities [79]. For example, persistence in alterations of body composition, such as visceral adiposity and altered adipokine secretory pattern has been demonstrated [80–82]. These alterations in body composition are likely the contributing factors to the elevated cardiovascular risk that may persist in CD patients, even 5 years after resolution of hypercortisolism [83]. In addition, sustained neuropsychiatric abnormalities such as impairments of memory and language performance, as well as persistence of depression, anxiety, and mania is well documented in patients after resolution of hypercortisolism [84–87]. Persistence of impaired quality of life despite sustained remission is also widely known and is likely partially attributable to the continuance of altered physical and psychological features as just discussed [79,88–91]. Finally, normalization of bone density is known to occur only after a prolonged recovery from hypercortisolism, up to 72 months [92]. Yet, some patients have shown persistent impairment of bone density well beyond this time point [93]. It has never been fully understood why some patients have persistent morbidity despite biochemical remission, while others have resolution of their symptoms, although many factors have been examined, including presence of postoperative hypopituitarism and the degree and duration of hypercortisolism [87,90,92]. Duration of hypercortisolism has not only been associated with persistent morbidity, but has been shown to be a predictor of mortality [94].

Further studies are warranted to examine if patients in apparent CD remission who have subtle HPA axis abnormalities represent distinctive remission subtypes versus mild or early recurrence. Additional investigations could also explore the degree to which specific mild HPA axis abnormalities, such as alterations in circadian rhythm or partial resistance to dexamethasone, are associated with persistence of specific CD morbidities. A final area of interest is the use of medical therapies in patients with different remission subtypes who suffer from persistent CD morbidities to determine if treatment improves important clinical outcomes, such as neuropsychiatric impairments, alterations in body composition, and increased cardiovascular risk. Given the overall lack of consensus of biochemical criteria to define CD recurrence and persistence at this time, assessment of clinical parameters by an experienced endocrinologist remains a critical aspect of evaluating CD outcomes.

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Table 1

Summary of biochemical testing and clinical features since recurrence of presenting symptoms, which began 4 years after TSA.

Date	UFC (4–50 µg/24 hr)	Plasma ACTH (0–46 pg/ml)	Serum Cortisol (6.7–22.6 µg/dl)	MSC (<0.03–4.3 nmol/L)	ODST	Blood Pressure (mmHg)	Hemoglobin A1C (%)
3/2010	9.7			3.7, 3.6, 3.4, 6.1		124/90	
3/2011	10.9			2.8, 4.0		128/88	
8/2011	17.4	132	14.1				6.2
6/2012	23.7	110	13.8			140/84	7.0
7/2012					ACTH 39 Cortisol 4.8	140/90	
8/2012						156/99	

Abbreviations:
UFC: 24-hour urinary free cortisol
ACTH: adrenocorticotrophic hormone
MSC: midnight salivary free cortisol
ODST: 1 mg overnight dexamethasone suppression test

Table 2

Biochemical criteria used to define CD recurrence

Author, year	Biochemical Test	Criteria for recurrence
Boggan, 1983	Plasma ACTH	Elevated
	Serum cortisol	Elevated
	LDDST	Elevated
Schrell, 1987	AM plasma ACTH	>50pg/ml
	AM serum cortisol	>21µg/dl
	LDDST	Serum cortisol >2µg/dl
Trainer, 1993	AM serum cortisol	>1.8µg/dl
Bochicchio, 1995	LDDST	Inappropriate suppression
Sonino, 1996	UFC	Elevated
	LDDST	Inappropriate suppression
Blevins, 1998	UFC	>120µg/24h
	LDDST	Inappropriate suppression
Invitti, 1999	AM serum cortisol	Elevated
	AM plasma ACTH	Elevated
	UFC	Elevated
Barbetta, 2001	UFC	Elevated
	ODST	Inappropriate suppression
Chee, 2001	AM and midnight serum cortisol	Elevated
	UFC	Elevated
	1.5mg ODST	Serum cortisol >3.6µg/dl
Estrada, 2001	UFC	Elevated
	ODST	Serum cortisol >5µg/dl
Rees, 2002	AM serum cortisol	>1.8µg/dl
Shimon, 2002	UFC	Elevated
	LDDST	>5µg/dl
Yap, 2002	UFC	Elevated
	LDDST	Inappropriate suppression
Chen, 2003	UFC	Elevated
	8AM and 4PM serum cortisol	Elevated values and lack of diurnal variation
Pereira, 2003	ODST (on more than one occasion)	Serum cortisol >3.6µg/dl
	UFC × 2 consecutive samples	Elevated

Author, year	Biochemical Test	Criteria for recurrence
Hammer, 2004	ODST	Serum cortisol $5\mu\text{g/dl}$
	UFC	Elevated
Valero, 2004	UFC	Elevated
	Plasma ACTH	High or normal
	Serum cortisol	High
	Midnight serum cortisol	$>1.8\mu\text{g/dl}$
	ODST	Serum cortisol $>1.8\mu\text{g/dl}$
Rollin, 2004	ODST	Serum cortisol $>3\mu\text{g/dl}$
Atkinson, 2005	UFC	Elevated
	LDDST	Inappropriate suppression
Esposito, 2006	Serum cortisol	$>25\mu\text{g/dl}$
Carrasco, 2008	UFC	$>90\mu\text{g}/24\text{h}$
	ODST	$>1.8\mu\text{g/dl}$
	Midnight serum cortisol	$>7.5\mu\text{g/dl}$
Salem, 2010	LDDST	Serum cortisol $>1.8\mu\text{g/dl}$

Units were converted to $\mu\text{g}/24\text{h}$ for UFC and $\mu\text{g/dl}$ for serum cortisol

Abbreviations:

UFC: 24-hour urinary free cortisol

ACTH: adrenocorticotropic hormone

LDDST: low dose dexamethasone suppression test

ODST: 1 mg overnight dexamethasone suppression test