Chapter 10
Cushing's Disease: Preconception Management

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Case Presentation

A 34-year-old woman returns to you for evaluation of recurrent Cushing's disease. Four years earlier, she presented with weight gain, hypertension, amenorrhea, "brain fog," fatigue, and difficulty getting through the day as an elementary school teacher. Screening tests were consistent with Cushing's syndrome, with bedtime salivary cortisol values 50% above normal and 24-hour urine free cortisol (UFC) values two- to fourfold above the upper limit of normal. Pituitary MRI showed a right-sided 6.5 by 7.7 mm lesion (Fig. 10.1), and cortisol and ACTH both increased by more than

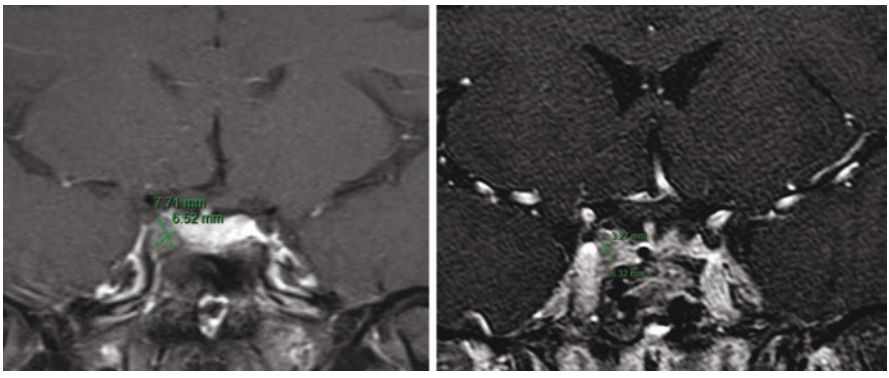

Fig. 10.1 Coronal T1 spin echo MRI sequences after gadolinium demonstrate a hypo-intense right-sided lesion before surgery (left panel) and at the time of recurrence (right panel)

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50% above baseline after corticotropin-releasing hormone (CRH) administration. She had an uncomplicated resection of an ACTH-producing pituitary adenoma that was adjacent to the right cavernous sinus, without obvious invasion, and postoperative cortisol values were less than 3 μg/dL (83 nmol/L). She required hydrocortisone replacement for about 9 months, with resolution of her symptoms by 1 year after surgery. An MRI done at that time showed postoperative changes without any obvious lesion.

In the last 6 months, some of her earlier symptoms returned, beginning with a five-pound weight gain, "brain fog," and fatigue, some of which she attributed to the COVID-19 pandemic and related difficulties in teaching young children via video conference. However, over time, her blood pressure rose from its usual 110/75 to 125/80 mmHg. She continues to have menses, but her cycles are not as regular as they were 2 years ago.

Repeat evaluation shows UFC at the upper limit of normal, with two high normal bedtime cortisols and four that are 20–40% increased. Pituitary MRI shows a lateral 6.3 by 3.3 mm right-sided lesion (Fig. 10.1). Over the next few months, more UFC are elevated and her blood pressure remains between 125 and 135/75 and 85 mmHg. She becomes impatient with the testing and says that she wants to "do something" because she and her husband want to have a child and she is worried about getting too old, as she is about to turn 35.

Pathophysiology

In contrast to ACTH-dependent causes of CS, benign adrenal causes of CS rarely recur. This chapter focuses primarily on recurrent Cushing's disease in women desiring fertility but will provide additional information on patients with recurrent ectopic ACTH secretion, which usually occurs because of metastasis.

Up to 65% of patients with Cushing's disease recur [1], always at the same site [2]. Several factors are associated with recurrence, including large tumor size, particularly macroadenomas, piecemeal tumor removal (vs. pseudocapsule technique), dural invasion, postoperative eucortisolemia, and early recovery (less than 6 months) of cortisol secretion [3–5]. Taken together, these data suggest that the tissue was left behind at the time of initial surgery, possibly in the dura, allowing for higher postoperative hormone levels and subsequent growth of residual tissue leading to early recovery of the axis.

A persistent positive ACTH response to the desmopressin stimulation test after surgery predicts recurrence [6]. However, as up to 30% of CD patients do not respond to this test before surgery, it does not have universal applicability [7].

Salivary cortisol is the first screening test that becomes abnormal when recurrence occurs [8]. This makes sense, as a small increase in bedtime cortisol will be interpreted as abnormal; by contrast, UFC does not become abnormal until many cortisol pulses exceed cortisol-binding globulin (CBG) capacity and are excreted in the urine.

Even mild increases in circulating cortisol can affect cognitive functioning, leading to "brain fog" and difficulties in performing normal tasks [9]. Anecdotally, endocrinologists have noted that the return of preoperative cognitive and emotional deficits often accompanies a true recurrence.

Diagnostic Considerations

Patients should be evaluated for recurrent CS with the screening tests recommended by the Endocrine Society [10]. In contrast to the recommendation for at least two abnormal screening tests for the initial diagnosis, there is no explicit guidance on the number of abnormal tests needed to establish recurrence. However, given that mild elevations in salivary cortisol can occur in patients without CS, it seems prudent to require at least two abnormal tests or sets of tests (recognizing that both salivary and urine cortisol should be measured at least twice because of inherent variability).

As with de novo CS, the screening tests should be individualized to each patient. Because it is the first test to become abnormal, consideration should be given to prioritizing a late-night salivary cortisol measurement. This test is more appropriately termed a bedtime salivary cortisol, as the nadir of the diurnal cortisol rhythm is tightly entrained to the onset of sleep [11]. However, even if collected at the appropriate time, a salivary cortisol result may be falsely abnormal in older patients and those with hypertension or diabetes [12] and those experiencing excitement or stress shortly before bedtime [13] or who have inconsistent bedtimes (e.g., shift workers) [14].

Urine free cortisol may be normal in the earliest stage of recurrence. When recurrence seems likely based on clinical features, repeated measurement of UFC will eventually lead to an abnormal result, as our patient demonstrated. Urine free cortisol is not a good test for patients with very high (>4 L) fluid intake or low urine output due to renal failure (eGFR<30 ml/min), and as noted above, it may be falsely normal in patients with mild (or cyclic) hypercortisolism [15]. Urine must be collected in a way that includes one post-sleeping void and not the other. If this is not followed, erroneous results will reflect under- or over-collection. Some of these problems can be assessed by noting the volume of the specimen and obtaining a creatinine measurement. Urine creatinine should not vary by more than 15% or so from day to day.

The final recommended first-line screening test is the dexamethasone suppression test. Here, cortisol is measured around 8 am after oral intake of dexamethasone, 1 mg, between 2300 h and 0000 h the previous night. Cortisol-binding globulin (CBG) levels increase in high estrogen states so that cortisol levels may be falsely elevated; thus, this test may not be ideal in women taking oral contraception with daily ethinyl estradiol doses of 20 mcg or more [16]. Because dexamethasone is metabolized by CYP3A4, it is susceptible to impaired or enhanced clearance (and

hence an increased or decreased effect), in patients taking medications that interact with that enzyme complex [17]. This potential pitfall can be addressed by measuring dexamethasone at the time of the cortisol blood draw, as normal ranges for the 1 mg dose are available.

Pituitary MRI is not a recommended screening test for CS. However, when patients with CS recur, they recur with the same type of CS as before. Hence, in this case, it was reasonable to obtain a pituitary MRI. A new lesion would help to confirm recurrence and assist in management, as it would represent a possible target for repeat surgery. The postoperative pituitary MRI is often heterogeneous and difficult to interpret, and it is possible that the 6 mm "lesion" in this case is not a true lesion. Because its location matches what is expected (recurrence in the same place as the original tumor), if it has a round shape, with hypo-enhancement on T1SE or SPGR sequences after administration of contrast [18], it would be a good candidate for resection.

The desmopressin stimulation would be another helpful diagnostic test if it had been done before surgery and had been positive.

When patients present with few symptoms that might be explained in other ways (such as mild weight gain during the COVID-19 epidemic), a dexamethasone–corticotropin-releasing hormone (Dex-CRH) test with measurement of cortisol and dexamethasone levels might be useful. However, patients with mild CS might not respond, and this test has not been studied extensively in patients with early recurrence.

Other tests are not necessary, as their risk–benefit ratio makes them inappropriate for use in this setting. These include a peripheral corticotropin-releasing hormone (CRH) test, which is expensive, and inferior petrosal sinus sampling (IPSS), which carries risk. Because the etiology of CS does not change with recurrence, tests for the differential diagnosis are not needed if the initial etiology was confirmed by pathology.

Management in the Context of Future Pregnancy

All patients with CS should be managed in as expeditious a way as possible to reduce the number, severity, and duration of comorbidities [19]. In this case, there is an additional pressure of time because of the couple's wish to conceive and the patients "older" maternal age, recognizing that her somewhat irregular menstrual periods may take some time to resolve after eucortisolism is restored. In addition to the specific treatments of the cause of Cushing's syndrome, any associated comorbidities should be optimized in the context of a potential future pregnancy, especially obesity, hypertension, and diabetes. Consideration should be given to physical therapy so that the patient will be able to meet the physical challenges of pregnancy and life with an infant.

Table 10.1 Factors influencing the choice of treatment for recurrent Cushing's disease in a woman desiring pregnancy

Factor	Repeat pituitary surgery	Bilateral adrenalectomy	Radiation therapy	Medical therapy
Probability of endocrine remission	43–72%, depending on whether there is a surgical target or dural invasion	100% unless cells are left behind	22–84%	50–100% depending on tolerated dose, level of UFC, agent used
Time to remission	Immediate if successful	Immediate	Mean 15–24 months (but up to 10 years)	Weeks to months
Effects on fertility	Little effect unless extensive exploration of the gland	No effect	50% have hypogonadism by 10 years	Mifepristone prevents ovulation; mitotane is abortifacient
Effects on pregnancy/fetus	No effect	Lifelong glucocorticoid and mineralocorticoid replacement; may be difficult if emesis occurs	No effect once pregnancy is established; may need adjustment of hypopituitary replacement drugs (e.g., levothyroxine)	Many drugs are not approved or recommended for pregnancy

While surgery to remove the causal tumor(s) is the optimal initial treatment, the choice is not so clear-cut with a recurrence. Because of this, the values and preferences of the patient/the couple should be taken into consideration after discussion of the advantages and disadvantages of the various options (Table 10.1), which are described below.

Repeat Transsphenoidal Surgery

The success rate of repeat surgery ranges from 42% if a tumor is not found and subtotal or total hypophysectomy is performed to 73% when a tumor is located and resected. Factors that predict success include the presence of a surgical target on MRI, knowledge of the site of the previous tumor (when there is no lesion on MRI), and lack of dural involvement at the first surgery [20]. The advantage of repeat transsphenoidal surgery is the possibility of immediate cure and the high likelihood that the adrenal axis will recover, given the low rate of hypopituitarism after selective adenomectomy [20]. The disadvantage of pituitary surgery is the high rates of panhypopituitarism including hypogonadism when larger amounts of the gland are removed.

Bilateral Adrenalectomy

Like successful transsphenoidal surgery (TSS), bilateral adrenalectomy immediately cures Cushing's syndrome. However, unlike TSS, this procedure has a 100% success rate. Its disadvantages include a lifelong need for glucocorticoid and mineralocorticoid replacement therapy and the concomitant risk of acute adrenal insufficiency. Of additional concern in our patient's situation are the possible difficulties of hormone replacement if pregnancy is complicated by hyperemesis. The possibility of Nelson's syndrome (corticotrope tumor progression) also is a concern, although the risk is probably less than 20% [21] and one small study suggested that pregnancy per se does not accelerate tumor enlargement [22].

Radiation Therapy

Radiation therapy has a similar success rate as transsphenoidal surgery, up to 84%, regardless of the way in which it is given. The mean rate of initial endocrine control in a recent comprehensive review was 65.8% for stereotactic radiosurgery and 67.5% for conventional radiotherapy [23]. While some reports suggest that focused radiosurgery may achieve remission slightly quicker than fractionated radiotherapy, the same literature review reported similar times to remission, with a median of 15–24 months, but a range of up to 10–12 years. As might be expected, hypopituitarism may occur more quickly when the large dose is given over one to three sessions, with up to 50% rates of hypopituitarism at 5 years. Eventually it seems that both approaches lead to hypopituitarism in up to 80% at 10 years [24, 25].

Medical Therapy

Patients who receive radiation therapy must also receive adjunctive medical therapy to normalize cortisol levels until radiation takes effect. In general, medical therapy is not recommended for women who wish to attempt pregnancy, for a variety of reasons. Mitotane and mifepristone are abortifacients; mifepristone blocks ovulation, so pregnancy would not occur. Ketoconazole may feminize a male fetus. The safety of pasireotide in pregnancy is not known as few fetuses have been exposed; the FDA places it in category C: animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Cabergoline has been used in a larger group of women with prolactinomas, without an obvious increase in congenital anomalies [26], and it carries FDA category C. However, cabergoline is not very effective when UFC levels are more than 3 times normal [27]. Although metyrapone may aggravate hypertension if it develops, there are limited data on its off-label use in pregnancy, and it appears to

be effective and safe [28]. However, because of the risk of fetal mortality and maternal morbidity, medical treatment is not recommended as the sole treatment of Cushing's syndrome, with the intention of normalizing ovulation and becoming pregnant [29]. Instead, medical treatment is reserved for the unfortunate situations when Cushing's syndrome is recognized during an established pregnancy.

Elements Leading to Our Patient's Management Decisions

Regarding the case, the patient is almost 35 years old and wishes to become pregnant soon. She now has mild, progressive, recurrent Cushing's disease, presumably caused by re-growth of tumor in the right lateral portion of the pituitary gland. Issues driving the management decision include:

1. *Probability of remission with each treatment option*

She has about a 75% chance of remission with repeat transsphenoidal surgery, based on the MRI target and known location of the initial tumor. However, given the position of the tumor, it is possible that she has dural invasion. She has a 100% probability of remission after a bilateral adrenalectomy, if no tissue is left behind, with a similar probability of short duration to return of menses and discontinuation of replacement therapy. The probability of remission with radiation therapy is close to that of repeat surgery, 80% at best.

2. *Length of time to remission*

If remission occurs with either surgery, it will be immediate. It may take up to 10 years to achieve remission after radiation therapy, making this a less attractive option [23–25].

3. *Length of time to discontinuation of replacement glucocorticoid*

Because the hypercortisolism is mild, it is possible that the length of time of requiring replacement therapy will be short after either surgery. She will need to take medical treatment (possibly with replacement glucocorticoid) until radiation is effective. It is possible that she will subsequently require replacement glucocorticoids.

4. *Potential effects on return of regular menses and fertility*

Radiation therapy carries a risk of hypogonadism; she may have a return to normal menses before hypogonadism occurs if adjunctive medical therapy achieves eucortisolism. Because the hypercortisolism is mild, it is likely that menses will become regular within a few months of either surgery. Extensive pituitary surgery also carries a risk of loss of gonadal function, but in her case, the location of the tumor is known so that this risk is extremely small. Bilateral adrenalectomy does not affect fertility.

5. *Potential effects on the pregnancy/fetus*

The need to take medication during and after radiation therapy until remission is achieved will present additional difficulties in terms of the choice of an agent and its

efficacy, which cannot be known a priori. Repeat pituitary surgery should not affect a subsequent pregnancy. Bilateral adrenalectomy complicates pregnancy management if there is hyperemesis, and the dose of replacement glucocorticoid will need to be increased in the second or third trimester.

Final Synthesis and Outcome

The patient felt that repeat pituitary surgery provided the optimal mix of risk and benefit for her and her husband. The neurosurgeon, chosen because of extensive experience and high remission rates, planned to resect the lesion using a pseudocapsular technique and to biopsy and possibly remove the dura and wall of the cavernous sinus if the tumor was directly adjacent to it. A desmopressin test was done before surgery and was positive. At surgery, the tumor was adjacent to the dura and the resected tumor and dural specimen contained ACTH-positive cells. Postoperative cortisol levels were less than 2 μg/dL, but the desmopressin test was still positive, though to a lesser extent. Additional discussion of the possibility of cells in the remaining tissues led to a decision to undergo stereotactic radiation therapy to the right cavernous sinus and to then attempt pregnancy as soon as menses became regular, even if she was on replacement glucocorticoid. The rationale was that this might prevent further growth of any remaining tumor cells and allow them to have more children. The long-term plan was to have bilateral adrenalectomy if CD recurred after this.

What if our patient had ectopic ACTH secretion? Recurrence of ectopic ACTH secretion usually occurs due to metastatic disease, often one or two enlarged lymph nodes in the context of pulmonary neuroendocrine tumors. Here, the evaluation is directed to the possibility of remission after nodal resection, which may provide long-term remission and, if not, a window of opportunity for pregnancy. Other possibilities include bilateral adrenalectomy, particularly if metastases are multiple and small (or microscopic, if not seen on imaging). This approach may or may not be coupled with chemotherapy or oncologic treatment, depending on the tumor burden and type, which might also reduce fecundity. Clearly, there are additional issues of survival time and the implications of delaying additional tumor-directed treatments during a pregnancy that must be explored with a multidisciplinary team.

Conclusion

Consideration of short- and long-term risk goals is important when prioritizing individualized choices for the treatment of recurrent Cushing's syndrome. The hope for childbearing is just one of the many considerations for these patients, but all patients

of childbearing age should be asked if preservation of this option is important to them. Our goals are not just to reverse hypercortisolism and address morbidity but also to allow patients to consider all the options in life that they had before CS.

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