Chapter 3
Abrupt Weight Gain, Hypertension, and Severe Hypokalemia in a Young Male

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Objectives
- To recognize clinical presentation of Cushing's syndrome (CS).
- To appropriately work up and diagnose CS.
- To select optimal treatment of CS.
- To manage comorbidities/risks associated with CS.

Case Presentation

A 29-year-old male presented to a hospital clinic with weakness, edema, and weight gain. Past medical history was significant for recently developed hypertension and diabetes. Weight gain of 70 pounds over 6 months was noted. Recently developed painful purple stretch marks on the abdomen and chest and easy bruising were reported by the patient. The patient also reported that he had an active job and had experienced recent difficulty with lifting boxes and going up stairs. The patient denied use of alcohol or glucocorticoids.

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Physical examination (Fig. 3.1) was remarkable for hypertension (blood pressure; BP 146/107 mm Hg), obesity (body mass index; BMI 35), moon facies, facial plethora, mild acne, dorsocervical and supraclavicular fat pads, decreased skin fold thickness, abdominal bruising, and purple striae. Based on clinical presentation, it was suspected that this patient had excess cortisol production or Cushing's syndrome (CS).

Fig. 3.1 Physical exam (photographs). Moon facies and facial plethora (**a**). Dorsocervical and supraclavicular fat pads (**b**). Abdominal bruising and purple striae (**c**). Finger decreased skin fold thickness; patient compared with examiner (**d**). Obtained with patient consent/permission. (Provided by Andre Mansoor, M.D., Department of Medicine, Division of Hospital Medicine, Oregon Health & Science University)

Does This Patient Have Cushing's Syndrome?

Cushing's syndrome (CS) can be difficult to differentiate from metabolic syndrome and obesity. Fatigue, weight gain, obesity, hypertension, decreased libido, menstrual abnormalities, hirsutism, dorsocervical fat pad, supraclavicular fullness, and peripheral edema are features of CS that are also common in the general population [1]. Signs and symptoms that have a higher specificity for diagnosing CS include easy bruising, facial plethora, proximal myopathy or muscle weakness, reddish purple striae >1 cm, osteoporosis, and decreased skinfold thickness (measured over the proximal phalanx of the middle finger of the non-dominant hand; Fig. 3.1) [1, 2]. These more specific signs are a result of increased protein breakdown caused by the underlying catabolic state in hypercortisolism [3].

Other laboratory findings in CS include hypokalemia (due to action of excess cortisol on mineralocorticoid receptor) [4], hyperglycemia [5], leukocytosis with higher percentage of polymorphonuclear cells [6], elevated liver enzymes [7], and secondary hyperparathyroidism [8]. A summary of pertinent patient laboratory results is provided in Table 3.1. Based on the laboratory results, it was determined that this patient had hypokalemia, hyperglycemia, mildly elevated liver function tests, and leukocytosis.

It is possible for patients to present with alterations in other endocrine hormone levels. Patients with pituitary CS (Cushing's disease, CD) may have hypopituitarism from a pituitary adenoma, mostly resulting in growth hormone (GH) deficiency and/or hypothyroidism [8–10]. Patients with both pituitary and non-pituitary CS often have functional central hypogonadism and hypothyroidism [8]. In the case of this patient, there was central hypogonadism and a slightly suppressed thyroid-stimulating hormone (TSH) level with normal free T4 level. Insulin-like growth factor 1 (IGF-1) and prolactin levels were in the normal range.

Once CS is suspected, exogenous corticosteroid exposure (the most common etiology) should be excluded through history and medication review. If endogenous CS is suspected, the patient should undergo several tests to confirm the presence of

Table 3.1 Patient laboratory results

Laboratory	Units	Normal range	Patient result	Patient range result
Potassium	mmol/L	4.5–5.0	3.1	Low
Hemoglobin A1c	%	<5.7	6.1	High
Alanine transaminase	U/L	<60	103	High
White blood cell count	K/mm^3	3.5–10.80	12	High
Testosterone (total)	ng/dL	>250	172	Low
Follicle-stimulating hormone	mIU/L	1.3–19.3	0.2	Low
Luteinizing hormone	mIU/L	1.2–8.6	<0.2	Low
Thyroid-stimulating hormone	mIU/L	0.4–3.98	0.32	Low
Free T4	ng/dL	0.6–1.2	0.7	In range
Insulin-like growth factor 1	ng/mL	84–250	233	In range
Prolactin	ng/mL	2.1–17.7	14.4	In range

cortisol excess. The three main tests used are 24-hour urinary free cortisol (UFC), late night salivary cortisol (LNSC), and dexamethasone suppression testing. These tests have a high sensitivity but not high specificity in diagnosing CS [1]. Urinary free cortisol measures cortisol not bound to cortisol-binding globulin (CBG) and therefore is not affected by conditions or medications that alter CBG, such as pregnancy and oral estrogen-containing contraceptive use [1]. Urinary free cortisol may be falsely high in patients with high fluid intake or falsely low in those with chronic renal insufficiency [3]. Late night salivary cortisol is reported to have high sensitivity (92–100%) and specificity (85–100%); however, this varies by assay characteristics and technique. False positives may occur due to smoking, oral bleeding, oral infections, and depression or shift work. It is recommended to collect at least two samples because of test variability [3]. Low-dose dexamethasone suppression test (LDT) is conducted by the patient taking a bed time dose of 1 mg dexamethasone with blood collection the following morning for cortisol (>1.8 μg/dL is consistent with CS) and dexamethasone serum levels. False positives can occur in women on oral contraceptives or medications that increase metabolism of dexamethasone (e.g., carbamazepine, phenytoin). Inaccurate results may also occur in patients with renal or liver insufficiency who have reduced dexamethasone clearance [3, 11]. It is not recommended to use random serum cortisol, adrenocorticotropic hormone (ACTH) levels, and/or urine 17 ketosteroids to diagnose CS [1]. Pseudo-Cushing's states, caused by physiological activation of the hypothalamic-pituitary adrenal axis, should be ruled out. Common causes of this include obesity, eating disorders, poorly controlled diabetes, chronic alcoholism, and depression [12]. Clinicians should use the results of several screening tests and clinical judgment to determine if any given patient has CS.

In the case presented, 24-hour UFC was significantly elevated as determined by repeated measures (7950 μg/24 h; a normal value is <60 μg/24 h). This information, along with the details of clinical presentation, confirmed a diagnosis of CS.

The next step was to determine if CS was ACTH dependent (ACTH >20 pg/mL) or independent (ACTH <5 pg/mL) [13]. The patient's ACTH was elevated at 480 pg/mL, confirming ACTH-dependent CS.

How to Determine an ACTH Source?

This step should not precede confirmation of cortisol excess as patients may have pituitary or adrenal incidentalomas that can lead to unnecessary treatment [1]. If the patient has ACTH-independent CS (15–20% of CS patients), the next step would be to perform adrenal imaging to determine if there is an adrenal adenoma, which commonly requires surgical therapy [8, 14]. Since this patient had ACTH-dependent CS, the differential was an ACTH-producing pituitary adenoma (80% of cases) or ectopic ACTH secretion (EAS; approximately 20% of cases) [14, 15]. Tumors that cause EAS include most commonly carcinoid tumors of the lung, islet cell tumors
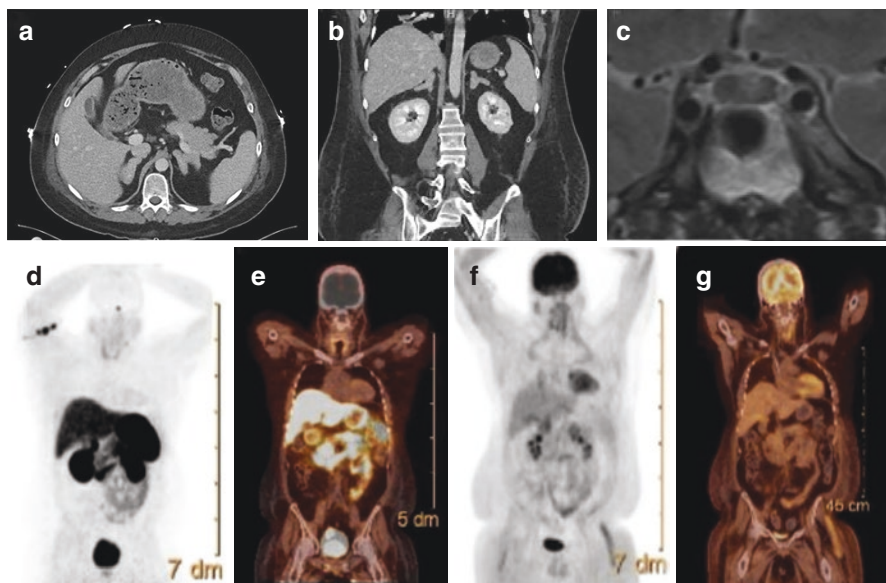
Fig. 3.2 Imaging. Abdominal axial (**a**) and coronal (**b**) computed tomography (CT), showing bilaterally enlarged adrenal glands. Pituitary coronal T2 magnetic resonance imaging without contrast (**c**), showing a 3 × 4 mm T2 hyperintense mass in the posterior superior aspect of the pituitary gland. Functional positron emission tomography; PET imaging gallium-68 somatostatin receptor (^{68}Ga-SSTR) PET/CT (**d** and **e**) and 2-deoxy-2-fluorine-18-fluoro-D-glucose (^{18}F-FDG)-PET (**f** and **g**), only physiologic uptake is observed

of the pancreas, medullary carcinoma of the thyroid, small cell tumors of the lung, and tumors of the thymus [16]. In the case presented, pituitary magnetic resonance imaging (MRI) revealed a 3 × 4 mm pituitary lesion (Fig. 3.2).

However, this did not confirm pituitary CS (CD) since 10% of healthy adults have pituitary lesions <6 mm. Additionally, 12% of patients with EAS have abnormal pituitary imaging [8]. Given that this patient's tumor was <6 mm, inferior petrosal sinus sampling (IPSS) to localize the ACTH source was performed. Inferior petrosal sinus sampling is the gold standard for ACTH source localization (sensitivity 82–100%; specificity 100%), and serious complications are rare [14]. However, IPSS is a technically challenging procedure, one that should be conducted at specialty centers by an experienced interventional radiologist [8, 14]. Asymmetric venous drainage, improper catheter placement, or treatment with cortisol-lowering therapies may result in false-negative results [17]. It is important to note that this procedure has poor accuracy in lateralizing ACTH source to one side of the pituitary gland, nor can it distinguish normal or pseudo-Cushing's patients from those patients with CS [8, 15, 18]. In the case presented, IPSS results (Table 3.2) [19] were consistent with EAS, and venography confirmed appropriate catheter placement and normal venous anatomy. If the patient had a pituitary ACTH source, they would have been referred for transsphenoidal resection.

Table 3.2 Patient inferior petrosal sinus sampling (IPSS) results

	Adrenocorticotropic hormone (pg/mL)			Cortisol (μg/dL)	ACTH petrosal sinus: peripheral
	Peripheral	Left petrosal sinus	Right petrosal sinus	Peripheral	Ratio[a]
Pre-CRH	451	480	499	95.2	1.11
Post CRH	1303	1514	1496	–	1.15

[a]Ratio ≥ 2 pre-CRH and ≥ 3 post-CRH indicates a pituitary source; *ACTH* adrenocorticotropic hormone; *CRH* corticotropin-releasing hormone

Once EAS is confirmed, the next step is to localize the ectopic ACTH-producing tumor, evaluate tumor extension, and determine surgical candidacy. Degree of hypercortisolism does not correlate with tumor aggressiveness [16]. Spiral thin slice computed tomography (CT) of cervical, thoracic, abdominal, and pelvic regions is recommended initially and may be performed in conjunction with pituitary MRI if the patient is deteriorating rapidly. Most thymic tumors, small cell pulmonary neuroendocrine carcinomas, pancreatic neuroendocrine tumors (NETs), ACTH-secreting medullary thyroid cancers and ACTH-secreting pheochromocytomas, and paragangliomas are detected by this imaging. However, bronchial carcinoids, one of the main causes of EAS, may be overlooked due to small size and proximity to pulmonary vessels. If the tumor remains occult, then it is recommended to proceed with functional imaging. Octreoscan detects tumors based on expression of somatostatin receptor 2 (SSTR2). However, sensitivity is low (64%), and hypercortisolism may cause downregulation of SSTR2 and SSTR5, resulting in false negatives. False positives may occur with pulmonary infections or physiologically higher uptake in the pancreatic uncinate process [16]. Positron emission tomography (PET)-CT using gallium-68 (^{68}Ga)-labeled SSTR ligands can also be used. Gallium-68-radiolabeled ligands have a higher affinity for the SSTR2 than those used in the octreoscan. Additionally, this imaging may offer better spatial resolution and anatomical detail than an octreoscan. The sensitivity of ^{68}Ga-SSTR PET/CT is not well established (64-100%); EAS is rare and statistics are based on case reports and small case series [20]. False positives may occur due to physiological uptake in the adrenal medulla, pancreatic uncinate process, and inflammatory lesions. False negatives may occur due to downregulation of receptors in response to high cortisol; medical treatment may lower cortisol levels and result in positive imaging [16, 20]. ^{18}F-labeled fluoro-2-deoxyglucose (^{18}FDG) and CT (^{18}FDG-PET/CT) utilize the high consumption of glucose by cancer cells and therefore higher uptake of ^{18}FDG to detect tumors. However, NETs may be slow growing, and thus ^{18}FDG-PET imaging may not aid in revealing such tumors [16]. If a small, localized tumor is found, then it is likely to be a well-differentiated NET with an excellent prognosis after surgical resection. If metastatic disease is found, then chemotherapy should be started urgently along with treatment of hypercortisolism. Radiofrequency ablation and chemoembolization have been used in patients with non-resectable tumors [16].

The patient underwent CT of the abdomen and chest, which did not identify an ectopic ACTH-secreting tumor but showed bilaterally enlarged adrenal glands consistent with ACTH-dependent bilateral adrenal hyperplasia in the setting of intense ACTH stimulation (Fig. 3.2). ^{68}Ga-DOTATATE PET/CT and ^{18}F-DG-PET/CT imaging was also unrevealing (Fig. 3.2).

Treatment in Severe Cases with Rapid Clinical Deterioration

In severe cases with rapid clinical deterioration, treatment should be prioritized over etiologic workup [16]. Thus, the patient was prescribed ketoconazole (US Food and Drug Administration; FDA off-label use), which was up titrated to a dose of 600 mg/ twice daily. Ketoconazole is an imidazole anti-fungal drug that inhibits steroidogenesis by blocking CYP11 and CYP17. Other adrenal steroidogenesis inhibitors that are used to treat CS are detailed in Table 3.3 [8, 21–23]. Of note, etomidate is the only adrenal steroidogenesis inhibitor available intravenously.

Ketoconazole, etomidate, metyrapone, mitotane, and levoketoconazole (in clinical trials) are not FDA approved for use in treating CS but, however, are often used off-label [22]. Levoketoconazole is an enantiomer of ketoconazole that has greater potency compared to ketoconazole in vitro. In the SONICS clinical trial, levoketoconazole was shown to be efficacious and appears to have a lower risk of severe transaminitis as compared with ketoconazole (though no direct comparison was made) [23].

While taking ketoconazole, the patient's UFC reduced to 73.3 μg/24 h, but unfortunately he developed transaminitis (5 times the upper limit of normal; ULN) and ketoconazole was discontinued.

Metyrapone, a potent inhibitor of CYP11B1, can also be used to treat CS and has rapid action. Side effects include hypertension and hypokalemia (due to aldosterone precursors), hirsutism, and adrenal insufficiency.

Mitotane, an insecticide derivative, inhibits steroidogenic acute regulatory protein (StAR) and CYP11 enzymes and is approved for use in adrenal carcinoma [22]. Mitotane has a slow onset of action and is not useful to quickly control hypercortisolism [16]. Side effects include dizziness, altered cognition, gastrointestinal distress, and adrenal insufficiency [22].

Osilodrostat is an US FDA- and European Medicines Agency (EMA)-approved treatment for CD and inhibits CYP11B1 and aldosterone synthase. Efficacy is high, and in a phase III trial, more patients maintained a complete response with osilodrostat versus placebo at 34 weeks (31 [86%] vs 10 [29%]; odds ratio 13:7, $p < 0.0001$) [21]. Though not FDA approved for this indication, osilodrostat has been used more recently to treat other forms of CS, including severe EAS and adrenal carcinoma. In one case series, patients who could not tolerate other CS medications were started on high dose of osilodrostat and achieved rapid control of hypercortisolism (<2 weeks) without significant adverse events [24]. Potential side effects include nausea, diarrhea, hypertension, hypokalemia, hirsutism, and adrenal insufficiency [21].

Table 3.3 Medical treatment of Cushing's syndrome

Medication	Dosing	Mechanism of action	Side effects	US FDA approved for CD or hyperglycemia associated with CS
Adrenal steroidogenesis inhibitors				
Osilodrostat	4–60 mg (2× daily)	Inhibits CYP11B1 and aldosterone synthase	Nausea, diarrhea, asthenia, hypertension, hypokalemia, hirsutism, hyperkalemia, adrenal insufficiency	Yes
Ketoconazole	400–1200 mg (2× daily)	Inhibits steroidogenic acute regulatory protein (StAR), CYP11A1, CYP11B1, CYP17	Transaminitis, gastrointestinal distress, hypogonadism, adrenal insufficiency	No
Fluconazole	200 mg (1× daily)	Inhibits CYP17	Transaminitis	No
Etomidate	Bolus 5 mg (one time) followed by intravenous 0.02–0.3 mg/kg/h	Inhibits StAR, CYP11A1, CYP11B1, CYP17	Sedation, propylene glycol toxicity, adrenal insufficiency	No
Metyrapone	0.5–4.5 g (3× or 4× daily)	Inhibits mainly CYP11B1, Inhibits also CYP17, CYP11B2, CYP19	Hypertension, hypokalemia, hirsutism, gastrointestinal distress, adrenal insufficiency	No
Mitotane	2–5 g (1× daily)	Inhibits StAR, CYP11A1, CYP11B1, CYP11B2, 3β-HSD adrenolytic	Dizziness, altered cognition, gastrointestinal distress, teratogenic, cytopenia, low T4, hyperglycemia, adrenal insufficiency	No

Table 3.3   (continued)

Medication	Dosing	Mechanism of action	Side effects	US FDA approved for CD or hyperglycemia associated with CS
Levoketoconazole (in phase 3 clinical trials)	150–1200 mg (2× daily)	Inhibits StAR, CYP11A1, CYP11B1, CYP17 Inhibits also CYP21A2	Nausea, headache, edema, transaminitis, adrenal insufficiency	No
Pituitary directed drugs				
Pasireotide	600–900 μg (2× daily)	Somatostatin receptor agonist	Nausea, gallstones, transient diarrhea, prolonged QT_c, hyperglycemia is very frequent	Yes
Pasireotide long-acting release; LAR	10–30 mg (monthly)	Somatostatin receptor agonist	Nausea, gallstones, transient diarrhea, prolonged QT_c, hyperglycemia is very frequent	Yes
Cabergoline	0.5–7 mg (weekly)	Dopamine receptor agonist	Nausea, dizziness, psychological symptoms, valvular disease at higher doses	No
Temozolomide (aggressive pituitary tumors and carcinomas)	150–200 mg/m²/day (for 5 days) Repeat at 28-day cycles	DNA alkylation	Fatigue, hearing loss, urinary tract infection, transaminitis, cytopenias	No
Glucocorticoid receptor blocker				
Mifepristone	300–1200 mg (daily)	Glucocorticoid receptor antagonist	Hypertension, hypokalemia, adrenal insufficiency, vaginal bleeding, endometrial hyperplasia, nausea, fatigue, edema, arthralgias	Yes

Mifepristone is approved for treatment of hyperglycemia associated with CS and if used in high doses has glucocorticoid receptor (GR) and progesterone receptor antagonist properties. There is no biochemical marker to follow efficacy of mifepristone; therefore, clinical evaluation is key. Adrenocorticotropic hormone and cortisol levels may increase, and excess cortisol can activate mineralocorticoid

receptors, resulting in hypokalemia and hypertension. Vaginal bleeding and endometrial hyperplasia in women can also occur. If adrenal insufficiency occurs, high doses of dexamethasone are needed to overcome the GR blockade [22].

In severe CS, combination therapy is frequently used to lower cortisol to allow more time for diagnostic workup and optimize surgical candidacy. A combination of metyrapone and ketoconazole has been used in patients with EAS and adrenal cortical carcinoma (ACC). The result was a dramatic UFC reduction within 1 week [25]. Another study using mitotane, metyrapone, and ketoconazole combination drastically reduced patients' UFCs within 24–48 hours [26]. The principle behind this approach was to use two fast-acting steroidogenesis inhibitors (ketoconazole and metyrapone) to rapidly control hypercortisolism in the lag period before mitotane exerted its action. A block and replace regimen with oral hydrocortisone was used in those patients to prevent adrenal insufficiency [26]. In both cases, reduction in cortisol resulted in localization of previously occult EAS-producing tumors in some patients and optimized surgical conditions in other patients, while some patients were also able to avoid bilateral adrenalectomy (BLA) [25, 26].

If the patient had CD, then medical treatment options would have also included pasireotide, cabergoline, and temozolomide (very rarely used in ACTH-secreting carcinoma).

Pasireotide is a SSTR ligand that works to decrease ACTH secretion and cell proliferation. Side effects include nausea, gallstones, transient diarrhea, hyperglycemia, and prolonged QTc.

Cabergoline is a dopamine receptor agonist that can sometimes, but not in all cases, decrease ACTH secretion. Side effects include nausea, dizziness, and impulse control disorders.

Temozolomide causes DNA methylation and tumor regression. Side effects include fatigue, hearing loss, urinary tract infections, transaminitis, and cytopenias [22].

In cases of occult, metastatic EAS, or life-threatening and severe ACTH-dependent disease unable to be controlled by medical therapy, guidelines recommend removal of the adrenal glands [8].

The patient presented here was deteriorating rapidly, and treatment options were limited by side effects and pharmacy availability. Thus, he underwent a bilateral laparoscopic adrenalectomy (BLA), which is highly effective in treating hypercortisolism with an immediate effect. Surgical failure is rare but can occur due to difficulty identifying the adrenals or ectopic adrenocortical tissue (accessory adrenals) that are missed by the surgeon [16]. The patient's serum cortisol dropped to 0.7 µg/dL post-operatively, indicating a good surgical outcome.

Patients with EAS have higher rates of complications (myocardial infarction, internal bleeding, poor wound healing, infections, hematomas, and post-operative thromboembolic events) after BLA than those with less severe CS [16]. Patients with CD who undergo BLA are at risk of Nelson's syndrome (NS), corticotroph adenoma progression associated with increasing ACTH levels. Treatment options for NS include surgery, radiotherapy, chemotherapy, pasireotide, or temozolomide [27].

Evaluation and Treatment of Complications

Complications of severe hypercortisolism include hypertension, hypokalemia, hyperglycemia, thombosis/thromboembolism, infection, *Pneumocystis* pneumonia, and steroid psychosis [16]. The patient presented here was treated with insulin and oral antihypertensives. Cushing's syndrome results in hypercoagulability and increased risk of thromboembolic events; therefore, the patient was prescribed enoxaparin 40 mg/day for prophylaxis. The risk of thromboembolism remains elevated even after surgery, and the patient continued to take enoxaparin for 28 days post-discharge; guidelines do not provide recommendations on duration, and an individualized approach is needed [28]. The patient also developed respiratory distress requiring supplemental oxygen. Infectious workup was negative, except for elevated serum 1,3-β-d-glucan (188 pg/mL; normal range <80 pg/mL), which was concerning for a fungal infection. Chest CT (Fig. 3.3) showed bilateral ground glass opacities highly suspicious for *Pneumocystis jiroveci* pneumonia (PJP).

The patient declined bronchoscopy to confirm diagnosis and was empirically treated with trimethoprim-sulfamethoxazole and prednisone with rapid improvement in respiratory status [29]. Patients with CS are at high risk of opportunistic infection. Cortisol excess results in depressed immune function, allowing PJP to colonize the lungs. Treatment of CS leads to recovery of T cells, which can result in an inflammatory reaction to PJP, analogous to immune reconstitution syndrome in human immunodeficiency virus patients [30]. The risk of PJP is associated with EAS and high cortisol levels, and thus these patients should be considered for PJP prophylaxis prior to initiation of cortisol-lowering therapy [16, 30].

At 2 months follow-up, the patient had lost 30 pounds, hypertension had resolved, and he was no longer taking insulin. He was transitioned from prednisone to replacement hydrocortisone and fludrocortisone. He was provided with sick day instructions and emergency injectable steroids for use in the event of an adrenal crisis.
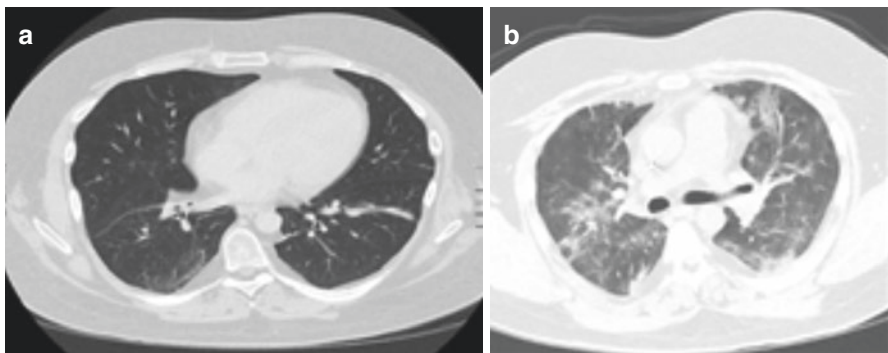

Fig. 3.3 Chest axial computed tomography. Images (**a**) and (**b**) showing bilateral ground glass opacities concerning for *Pneumocystis jiroveci* pneumonia

Later in recovery, hypogonadism and hypothyroidism resolved. The patient is scheduled to undergo repeat imaging for localization of the ACTH-secreting neuro-endocrine tumor.

Conclusions

Cushing's syndrome can be a difficult diagnosis to ascertain. Clinicians must have a high index of suspicion and be able to identify more specific features of CS to distinguish from more common metabolic syndrome. Even when a patient presents with classic symptoms, confirmation of CS takes time and multiple tests (e.g., 24-hour UFC, LDT, and salivary free cortisol). It is important to confirm diagnosis before attempting to localize a source; skipping ahead in disease workup can lead to unnecessary treatment and surgery. Once cortisol excess is confirmed, it is important to determine whether the disease is ACTH-dependent or ACTH-independent. Computed tomography adrenal imaging is used to locate an ACTH-independent tumor source. Inferior petrosal sampling is used to determine an ACTH-dependent tumor source. Magnetic resonance imaging is used to locate pituitary adenomas. A combination of CT and functional imaging can locate ectopic tumors. While this diagnostic workup is ongoing, it is important to keep in mind the patient's clinical picture and progression. In rapidly deteriorating patients, it is more important to treat the high cortisol with either medication or BLA than to delay treatment while looking for a source. It is also important to be aware of and manage the complications associated with CS, including PJP and cardiovascular and deep vein thrombosis risks.

Lessons Learned
- Diagnosis of CS remains difficult in most situations and could be more challenging in a severely ill patient; it is important to screen and confirm the diagnosis in a timely manner. Cortisol is usually high in all patients with severe illness. A next step should be determining ACTH dependence or independence.
- Once ACTH dependence is confirmed, in patients where IPSS has ruled out a pituitary source, functional imaging plays an important role in identifying an ectopic ACTH-producing tumor. However, a tumor will not be found in some patients, and treatment should be started while looking for a cause.
- Medications for treating hypercortisolemia have different targets and mechanism of action, and combination therapy is sometimes used in patients with severe CS; side effects could be occasionally a limiting factor in properly up-titrating doses to maximum efficacy. Bilateral laparoscopic adrenalectomy remains the treatment of choice in severe CS with no definite source and clinical deterioration, while on medical therapy.
- Cushing's syndrome has many complications in general, but patients with severe CS have risk of *Pneumocystis jiroveci* pneumonia and deep vein thrombosis, and prophylaxis should be started immediately after diagnosis.

Multiple-Choice Question

A 50-year-old male presents with a 30 pound weight gain in 8 months, easy bruising, and new stretch marks and fatigue.

Physical Exam

The patient appears to be well and is friendly, however, they have difficulty rising from the chair to greet you. Upon examination, they have central abdominal obesity with multiple bruises on their abdomen >1 cm, violaceous abdomen and chest stretch marks, and increased dorsocervical fat pad deposition.

Other Details

Vital signs	Patient result
Blood pressure (mm Hg)	152/85 bilaterally
Heart rate (beats per minute)	70
Temperature (°F)	98.2
Respiration (breaths per minute)	16
Body mass index (kg/m²)	33

Laboratory	Normal range	Patient result
Sodium (mmol/L)	136–145	143
Potassium (mmol/L)	3.4–5.0	3.4
Glucose (mg/dL)	97–108	120
Hemoglobin A1c (%)	5.7	6
Creatinine (mg/dL)	0.6–1.1	1.2
Urinary free cortisol (µg/24 h)	≤ 45.0	225 and 300
Cortisol (µg/dL) [after overnight 1 mg dexamethasone suppression test]	1.8	4.0
Adrenocorticotropic hormone (pg/mL)	6–50	2

Imaging	Patient result
Pituitary magnetic resonance	4 mm pituitary adenoma
Chest computed tomography	2 mm left lung nodule 3 mm right lung nodule and 3 cm right adrenal adenoma

Given the collective laboratory results, this patient has been diagnosed with Cushing's syndrome.

1. What is the best next step in the management of this patient?

    (a) Obtain functional imaging (^{68}Ga-SSTR PET/CT)
    (b) Refer for pituitary surgery
    (c) Refer for inferior petrosal sinus sampling

(d) Refer for adrenal vein sampling
(e) Refer for right adrenalectomy

2. What is the most important pre-operative consideration in this patient?

(a) Toxoplasmosis gondii prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX)
(b) Diabetes management with metformin
(c) Deep vein thrombosis prophylaxis with enoxaparin
(d) Prophylactic radiation to prevent Nelson's syndrome

Answers

1. (e)
2. (c)

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