Cushing's disease is caused by a benign tumor of the anterior pituitary gland that produces excessive amounts of adrenocorticotropic hormone (ACTH), resulting in excess cortisol release from the adrenal glands. It has an incidence of 1.2–2.4 patients per million every year. Patients typically present with generalized weakness, high blood pressure, weight gain, easy bruising, moon facies, facial plethora, purple thick striae, and menstrual abnormalities in females. Biochemical diagnostic tests include midnight salivary cortisol levels, 24-hour free urinary cortisol, and low-dose and high-dose dexamethasone suppression tests. Treatment of Cushing's disease includes pharmacologic, surgical, and/or radiation therapy. The classic surgical procedure performed is transsphenoidal pituitary adenoma resection. Postsurgical recurrence is not uncommon, with rates reaching up to 12%–45% with macroadenomas. Biochemical remission rate is only 65% postsurgical resection in cases of macroadenomas. When surgery is not curative, radiotherapy is considered, and medical treatment is also employed to control hypercortisolism. Pharmacologic therapy for Cushing's disease can be classified based on the site of action. Mifepristone is a glucocorticoid receptor antagonist that targets cortisol-related hyperglycemia. It exhibits its effect by blocking cortisol action at the level of its receptors. Cabergoline, a long-acting dopamine receptor agonist, and pasireotide, a somatostatin analog, are pituitary-directed drugs. They both suppress ACTH secretion, with pasireotide being more potent. Ketoconazole and metyrapone are adrenal-directed drugs that aim to decrease the secretion of cortisol. Ketoconazole is an oral agent whose effects appear to be mediated by the inhibition of 17,20-lyase and 11β-hydroxylase, enzymes in the corticosteroid synthesis pathway. In fact, ketoconazole improves clinical signs and symptoms in 40% of patients with Cushing's disease. Metyrapone inhibits cortisol production by inhibiting 11β-hydroxylase and therefore blocks the conversion of 11-deoxycortisol to cortisol. It has been shown to normalize cortisol levels in approximately 50% of treated patients. Medical therapy shows variable effects on cortisol levels, and generally, multiple agents are used to achieve a higher percentage of cortisol normalization.
adverse effects are associated with the above medications, and therefore, novel drugs have been studied and introduced to the market.

Osilodrostat, a steroidogenesis inhibitor recently FDA-approved in 2020, is an oral agent that blocks the adrenal 11β-hydroxylase enzymes, causing decrease in aldosterone and cortisol production. In a trial consisting of 137 patients with Cushing’s disease, 86% of patients achieved a biochemical and clinical response at Week 34 with osilodrostat versus 29% with placebo; the effect was consistent throughout the study duration.11 Osilodrostat has a rapid absorption, a half-life of approximately 4 h and a steady state achieved in 2 days.12 The main side effect is hypocortisolism associated with nausea, vomiting, and fatigue. Other side effects include hypokalemia, hypertension, and adrenal insufficiency.11 The latter can be avoided by slowly increasing the dose at ≥2-week interval. The recommended initial dose is 2 mg twice daily. Medication is particularly indicated in patients with incomplete adenoma resection or recurrent disease, in addition to patients who are ineligible for pituitary surgery.13 We present a case of iatrogenic adrenal insufficiency in the setting of osilodrostat treatment for recurrent macroadenoma-induced Cushing’s disease.

2 | CASE REPORT

A 41-year-old nurse presented with worsening fatigue and dyspnea on exertion. Her symptoms started about a month prior to presentation and progressed 2 weeks prior to admission. She was experiencing extreme fatigue, nausea, vomiting, dizziness, and shortness of breath on exertion. She was referred to the emergency department by her primary care provider as her oxygen saturation dropped to 80% on ambulation at his office. She had been diagnosed with Cushing’s disease about 10 years earlier and underwent transsphenoidal pituitary macroadenoma resection. Two years later, her signs and symptoms of Cushing’s disease recurred, and she had a second transsphenoidal surgical resection. The latter was however incomplete because the pituitary macroadenoma was invading the cavernous sinus. She then received 25 sessions of radiation/proton therapy. She has been on ketoconazole 200 mg 2 tablets twice daily and aldactone 100 mg twice daily regularly since the surgery. Multiple additional agents were then attempted to achieve eucortisolism including metyrapone, which she opted to stop as she did not prefer the frequent dosing required daily. Pasireotide injections were then administered, but the patient could not tolerate the side effects and medication was stopped. The patient was started on Osilodrostat a year prior to presenting to our hospital and the dose was titrated incrementally up to 15 mg twice daily to target normal 24-hour urine-free cortisol levels. Her surgery also resulted in central hypothyroidism, and she had since been on levothyroxine 112 mcg daily.

On admission, her blood pressure was 96/85 mm Hg, her oxygen saturation was 99% on room air, her temperature was 96.8 F, and her pulse was 99 beats per minute. Her BMI was 25.2 kg/m². On physical examination, she appeared to be her stated age. She was resting comfortably with no acute distress. She had good bilateral air entry and regular heart rate with no murmurs noted. She had no abdominal striae or skin bruises, and she had no hyperpigmentation of creases or pressure areas. Her laboratories were pertinent for a sodium level of 129 mmol/L (Reference Range: 135–145 mmol/L), potassium of 5.0 mmol/L (Reference range: 3.5–4.9 mmol/L), urea 32 mg/dl (Reference range: 6–20 mg/dl), and creatinine of 1.9 mg/dl (Reference range: 0.5–1.1 mg/dl). A random cortisol level on admission was 5.7 mcg/dl (Morning reference range: 6.7–22.6 mcg/dl) with an albumin level of 3.6 g/dl (Reference range: 3.2–5.5 g/dl), free T4 was 0.8 ng/dl (Reference Range: 0.6–1.7 ng/dl), and free T3 was 3.8 pg/ml (Reference range: 2.5–3.9 pg/ml).

She was admitted to the general medical floor, and the endocrinology team was consulted. A few hours after admission, her blood pressure dropped to 88/53 mm Hg; she was given two liters of normal saline with minimal response and later given a one-time dose of intravenous hydrocortisone 100 mg with adequate blood pressure response. Twenty-four hours after her corticosteroid dose, her morning cortisol was 7.9 mcg/dl with ACTH of 62 pg/ml (Reference range: 6–50 pg/ml). Her outpatient neuro-endocrinologist was then contacted. He confirmed her osilodrostat dose was titrated up to 10 mg twice daily.

Our patient had inappropriately increased her dose to 15 mg twice daily. In fact, a 24-hour urine collection was done while inpatient that resulted in a 24-hour urine volume of 2940 ml and urine-free cortisol of <1.0 mcg/L, which could suggest adrenal insufficiency; however, the value of the test is limited since the patient received IV hydrocortisone. Patient did not have any imaging of the adrenals during this admission.

Over the next 48 h, the patient’s blood pressure normalized and her osilodrostat was resumed at a dose of 10 mg twice daily. Her aldactone was initially held in the setting of hyperkalemia, and her ketoconazole was resumed at 200 mg twice daily. She did not require another dose of corticosteroids. Her fatigue, nausea, and dizziness had also improved significantly. Her potassium normalized, and aldactone was resumed on discharge. The patient had an appointment to follow up with her endocrinologist with close monitoring of her clinical status. She was instructed that she may require oral hydrocortisone at times of stress due to the state of chronic drug-induced adrenal insufficiency.
3  |  DISCUSSION

Optimal treatment for Cushing’s disease remains surgical resection; however, patients who have macroadenomas have low rates of cure. This patient had two transsphenoidal surgical resections and received radiation therapy. She was being treated with ketoconazole and osilodrostat in an attempt to achieve eucortisolism and decrease her risk for hyperglycemia, obesity, osteoporosis, and cardiovascular disease. She was also being managed with aldaclone to address potential osilodrostat-induced hypokalemia. She presented with symptoms of fatigue, nausea, and dizziness for 1 month following an increase in her osilodrostat dose from 10 mg twice daily to 15 mg twice daily.

To date, there has not been a head-to-head clinical trial comparing the above-described pharmacologic therapies. Moreover, using two steroidogenesis inhibitors at lower dose to achieve eucortisolism can help avoid major side effects of these drugs if used as monotherapy. The combination of ketoconazole and osilodrostat has been recently reported in literature with limited data on dosages.

Simultaneously, monitoring for side effects and biochemical and clinical efficacy of therapy is incredibly challenging for both physicians and patients. Evaluation of clinical signs of hypercortisolism or signs of adrenal insufficiency can guide management and indicate under- or overdosing, respectively. Measuring urinary free cortisol, salivary, and blood total cortisol levels is essential for monitoring therapy. However, several issues can affect the value of measured cortisol levels. Factors include the assay type and the patient’s ability to collect urine appropriately. For example, osilodrostat can cause high 11-deoxycortisol levels that can cross-react with the cortisol immunoassay. This may cause falsely elevated serum or salivary total cortisol levels. At present, 24-hour urinary free cortisol measurement remains the assay utilized in most studies to determine the efficacy of treatment. Nevertheless, variability can reach up to 50% in different urine samples from the same patient, and thus, a normal urine-free cortisol cannot completely rule out cases of mild hyper/hypocortisolism. Serum cortisol is also routinely measured, with suggested approaches such as measuring up to eight serum cortisol samples throughout the day with the goal mean value of 5.5–11 μg/dl or measuring morning serum cortisol with a target of 8–10 μg/dl. Cortisol levels can be confounded and falsely elevated when cortisol-binding globulin levels are elevated, such as in women on oral contraceptives. This patient had a morning cortisol level of 7.9 mcg/dl; however, her 24-hour urine-free cortisol was below 1.0 mcg/L. This reflects the variability in testing and reiterates the challenge in assessing adequacy of therapy, biochemical hypercortisolism, hypocortisolism, or eucortisolism.

Monitoring treatment efficacy in Cushing’s disease is essential, as patients undergoing treatment are at an increased risk of having a complete block of adrenal steroidogenesis. In mild-to-moderate hypercortisolism, 24-hour urine-free cortisol is measured 1–2 weeks after treatment is initiated. The same applies when the drug dose is adjusted and then in 2–3 weeks interval until a normal 24-hour urine-free cortisol level is achieved. Monthly monitoring occurs thereafter when the dose is found to be optimal. In cases of very severe hypercortisolism, daily serum cortisol levels can be checked while the patient is hospitalized to assess the need to up titrate the dose within 5 days. In addition to monitoring biological markers, it is of paramount importance that physicians educate patients about the symptoms of adrenal insufficiency (fatigue, nausea, weight loss, abdominal pain, diarrhea, and dizziness upon standing) and inform patients when it is necessary to present to the emergency department and/or contact their endocrinologist. Patients should be informed that adrenal insufficiency can occur any time after treatment initiation or dose adjustment, or even at a stable dose. In fact, patients during the COVID-19 pandemic have reduced the frequency of seeking care in an emergency department setting. A survey of 5412 people revealed that 41% of US adults have delayed or avoided care because of concerns related to COVID-19 with 12% avoiding urgent care. Thus, physicians must always consider the benefit of rapidly controlling the symptoms and biochemical abnormalities of Cushing’s disease versus inducing the risk of adrenal insufficiency, especially if patients will defer seeking hospitalization for a prolonged time.

4  |  CONCLUSION

In conclusion, ketoconazole–osilodrostat combination therapy usually is a well-tolerated strategy to decrease cortisol levels in Cushing’s disease and prevent hypercortisolism-associated comorbidities such as infection, diabetes, obesity, osteoporosis, and cardiovascular disease. However, close monitoring is crucial to avoid adrenal insufficiency, the life-threatening potential complication of therapy. Laboratory studies such as morning serum cortisol, late-night salivary cortisol, and 24-hour urine-free cortisol are essential to ensure eucortisolism despite test-to-test and same-test variability. This patient recognized impeding signs and symptoms of adrenal insufficiency and presented to the hospital appropriately, and her medication dose was adjusted before a life-threatening event occurred. Further research is needed to develop evidence-based protocols for biochemical and symptomatic monitoring and treatment guidelines to provide to physicians treating this disease and patients under their care.
AUTHOR CONTRIBUTIONS
Catherine Ekladios, MD, designed and wrote the manuscript. Jessica Khoury, MD, wrote the manuscript. Shahzad Mehr, MD, and Krystel Feghali, MD, contributed to the critical revision and editing for intellectual content.

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CONFLICT OF INTEREST
The authors whose names are listed immediately below certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers’ bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript. Osilodrostat is approved by the Food and Drug Administration for use in the United States, where our case above is reported.

DATA AVAILABILITY STATEMENT
None.

ETHICAL APPROVAL
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CONSENT
Written consent was obtained from the patient to publish this report in accordance with the journal consent policy.

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