AACE Clinical Case Rep. 11 (2025) 53–57

Clinical Case Reports™
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Case Report

A Case of Severe Cushing Syndrome due to Metastatic Adrenocortical Carcinoma Treated With Osilodrostat

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ARTICLE INFO

Article history:
Received 11 June 2024
Received in revised form
4 October 2024
Accepted 15 October 2024
Available online 23 October 2024

Key words:
osilodrostat
block-and-replace
Cushing syndrome
hypercortisolism
adrenocortical carcinoma

ABSTRACT

Background/Objective: Osilodrostat used with block-and-replace dosing regimen is an off-label alternative to traditional management of Cushing syndrome due to adrenocortical carcinoma (ACC).
Case Report: A 70-year-old woman presented with abdominal pain and was found to have a large right adrenal mass and hypercortisolism. Right adrenalectomy was pursued with pathology consistent with diagnosis of ACC. Three months after surgery, hypercortisolemia recurred and bony metastatic disease was detected soon after. The patient received chemotherapy and mitotane; however, mitotane was stopped after development of hemolytic anemia. The patient's urinary free cortisol became severely elevated, and osilodrostat was subsequently initiated for steroidogenesis inhibition. As dosage was increased, the patient presented with fatigue and hypotension and was diagnosed with adrenal insufficiency. This was managed with hydrocortisone in a block-and-replace dosing strategy.
Discussion: ACC can cause severe hypercortisolism, which is associated with significant morbidity and mortality. Osilodrostat was an effective off-label option for steroidogenesis inhibition in our patient who developed severe hypercortisolism and did not tolerate first-line therapy. Our patient also experienced iatrogenic adrenal insufficiency during treatment with osilodrostat, which was successfully managed using a block-and-replace strategy. There are limited cases currently available that document use of osilodrostat under the above circumstances.
Conclusion: Although osilodrostat is currently only approved for use in pituitary Cushing disease, we found it effective in off-label use to treat Cushing syndrome due to ACC. Using a block-and-replace treatment strategy was a practical intervention after development of adrenal insufficiency.

Introduction

Adrenocortical carcinoma (ACC), a rare cause of hypercortisolism, is associated with significant morbidity and mortality. Between 20% and 30% of cases are detected incidentally on imaging, and nearly 50% of patients present with symptoms of hormonal excess—most commonly due to hypercortisolism, but also secondary to accumulation of cortisol precursors, which can cause symptoms of mineralocorticoid and androgen excess. Although older studies reported that nearly 50% of patients had metastatic disease at the time of presentation, more recent data show that only about 25% of patients present with stage 4 disease. Surgical resection remains the mainstay of initial management.[1] However, with more patients presenting with lower stage disease, there is a potential increased need for medical management after resection. Goals of therapy include reducing risk of disease recurrence, managing metastatic disease, and treating hormone excess. Management of hypercortisolism in ACC is an important factor for reduction of associated morbidity and mortality. The steroidogenesis inhibitor osilodrostat is a newer treatment approved for use in pituitary Cushing disease.[2]

Abbreviations: ACC, adrenocortical carcinoma; CT, computed tomography.

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https://doi.org/10.1016/j.aace.2024.10.005

We present a case in which osilodrostat was used off-label in a block-and-replace strategy to treat severe Cushing syndrome secondary to metastatic ACC.

Case Report

A 70-year-old woman presented for evaluation of abdominal pain in December 2021, and contrast computed tomography (CT) scan of the abdomen and pelvis showed a heterogeneously enhancing 5.6 × 3.5 × 5.1 cm right adrenal mass (Fig. 1). Her baseline morning cortisol of 31.8 μg/dL and adrenocorticotrophic hormone (ACTH) <1.5 pg/mL suggested hypercortisolism, and subsequent 1 mg dexamethasone suppression test indicated nonsuppressible cortisol of 29.0 μg/dL. Initial urinary free cortisol was 456 μg/24 hours (range, 6-42 μg/24 hours). No distant metastatic disease was identified on initial imaging or subsequent CT of the chest. The patient underwent open right adrenalectomy. Pathology was consistent with low-grade ACC measuring 8.4 × 4.5 × 3.5 cm, with negative microscopic margins, no capsular or lymphovascular invasion, focal necrosis <1%, Ki-67 index 5%, approximately 20% clear cells, and 10 mitoses in 50 high-power field with no atypical mitoses. Multidisciplinary tumor board reviewed the case, and due to stage 2 pathology with low Ki-67 index, initial management with serial biochemical and radiographic monitoring was planned.

Three months postoperatively, the patient's urinary free cortisol was persistently elevated at 94 μg/24 hours. Positron emission tomography/CT scan of the chest, abdomen, and pelvis at that time showed no evidence of metastatic disease. However, repeat urinary free cortisol 3 weeks later increased to 489 μg/24 hours, and subsequent positron emission tomography CT demonstrated new thoracic and lumbar osseous metastasis. Treatment with etoposide, doxorubicin, cisplatin, and mitotane was initiated. Mitotane therapy was complicated by hemolytic anemia and was replaced 1 month later with osilodrostat 2 mg twice daily to manage hypercortisolism. Her urinary free cortisol level increased to 1856 μg/24 hours after 1 month of treatment with osilodrostat 2 mg twice daily; thus, dosage was titrated up in 1 to 2 mg increments during the next 10 weeks. After dosage was increased from 5 to 7 mg twice daily, the patient presented with fatigue and hypotension. Morning serum cortisol level was 4.7 μg/dL, concerning for adrenal insufficiency. Stress dose hydrocortisone was initiated, 30 mg in the morning and 15 mg in the evening, with intention to transition to block-and-replace therapy.

Following 10 days of stress dose hydrocortisone, osilodrostat was titrated to 8 mg twice daily for complete steroidogenesis blockade, and hydrocortisone replacement decreased to 20 mg in the morning and 10 mg in the evening. After 3 weeks on this regimen, urinary free cortisol level was 59 μg/24 hour. Our patient remained on osilodrostat 8 mg twice daily and hydrocortisone replacement with good control of 24-hour urinary cortisol levels for the subsequent 8 months. She required between 25 and 50 mg spironolactone twice daily to control symptoms of mineralocorticoid excess (hypertension and hypokalemia) and androgen excess (alopecia) that occurred during treatment with osilodrostat. After 8 months with stable cortisol levels, her metastatic disease spread to her liver, with expanding hepatic masses noted on CT. Urinary free cortisol level increased to 305 μg/24 hour, and osilodrostat dosage was increased from 8 to 10 mg twice daily (see Fig. 2 for treatment timeline). Unfortunately, our patient's clinical status worsened over the following 6 months due to metastatic disease burden and adverse effects of chemotherapy, and she elected to transition to palliative care and passed away soon after.

Highlights

- Osilodrostat use in Cushing syndrome
- Block-and-replace approach in managing adrenal insufficiency secondary to steroidogenesis inhibition
- Alternative treatment of severe hypercortisolism
- Metastatic adrenocortical carcinoma managed with osilodrostat

Clinical Relevance

This case illustrates use of osilodrostat to treat severe hypercortisolism from metastatic adrenocortical carcinoma. It serves as a reference for clinicians considering block-and-replace treatment of Cushing syndrome using steroidogenesis inhibition and glucocorticoid replacement. Other pertinent cases of off-label osilodrostat use to manage Cushing syndrome due to various non-pituitary causes are reviewed

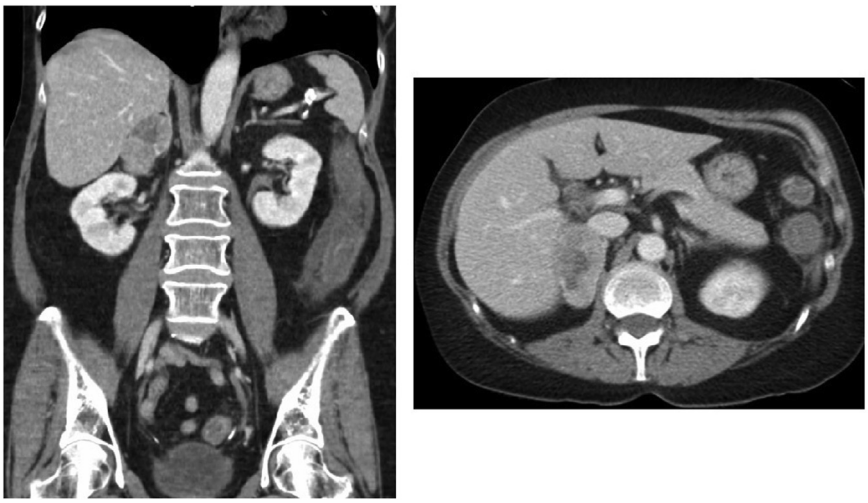

Fig. 1. An initial computed tomography scan of the abdomen and pelvis with contrast demonstrating a 5.6 × 3.5 × 5.1 cm right adrenal mass.

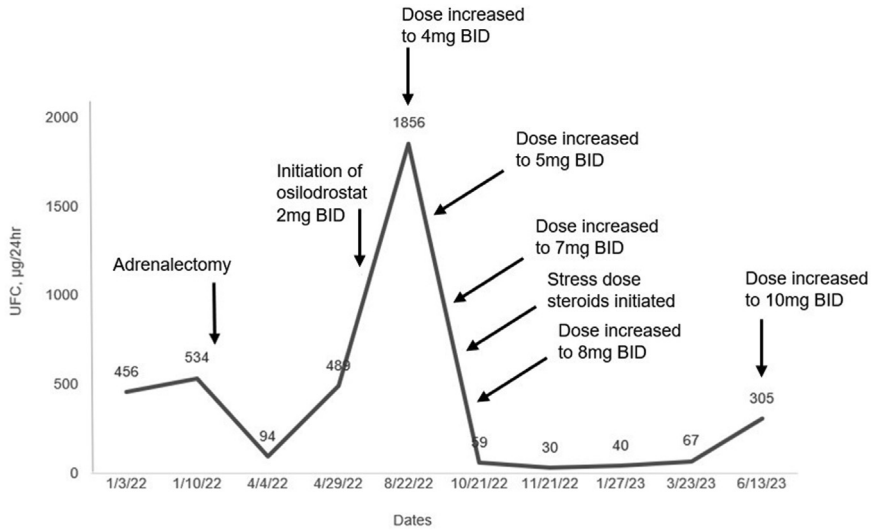

Fig. 2. The 24-hour urinary free cortisol trends during treatment course, relative to osilodrostat dose. Note that the episode of adrenal insufficiency was not captured by this data as it was diagnosed based on a morning serum cortisol level.

Discussion

ACC is a rare but devastating cause of ACTH-independent Cushing syndrome. Guidance of treatment can be difficult due to lack of data and variable patient response to therapy. Stage 3-4 disease at diagnosis, resection status >R0, and high pathologic grade (Ki-67 >10% and >20 mitoses) are known factors associated with unfavorable prognosis.[1,3] Despite positive prognostic features, our patient developed metastatic disease 5 months postoperatively. Although initial management with surgery has curative potential, 40% to 70% of patients experience disease recurrence despite complete resection, and even patients with stage 1-2 ACC have a widely ranging 60% to 80% 5-year survival rate after resection; these variable responses necessitate adjuvant treatment for many.[3,4] Mitotane is recommended adjuvant therapy for stage 3-4 or any high-grade ACC with Ki-67 index >10%. Data are mixed regarding mitotane's benefit for recurrence-free survival in stage 3-4 ACC, and the 2021 ADIUVO trial showed no benefit from mitotane toward recurrence-free survival in stage 1-3, low-grade ACC.[5-7] For those who develop metastatic disease refractory to adjuvant treatment (up to 75% of cases), controlling associated hypercortisolism is important for mitigating morbidity and mortality.[8] Recent pharmacologic developments in steroidogenesis inhibition provide an off-label consideration for medical management. Osilodrostat is a steroidogenesis inhibitor that blocks action of 11β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2) to inhibit production of cortisol and aldosterone in the adrenal glands (see Fig. 3).[2,9] Osilodrostat was approved by the FDA in 2020 to treat patients with Cushing disease who are not surgical candidates or have not responded to pituitary surgery.[10]

Osilodrostat has been described in several case reports for treatment of nonpituitary Cushing syndrome due to ACC, ectopic ACTH production in small cell lung cancer and epidermal growth factor receptor mutated lung adenocarcinoma as well as unknown primary source, ACTH-independent primary bilateral macronodular adrenocortical hyperplasia, and in a case of cyclic ACTH-dependent Cushing syndrome that developed in relationship to pembrolizumab treatment.[11-17] One report illustrates preoperative use of osilodrostat to reduce hypercortisolism due to ACC prior to adrenalectomy.[16] Another describes use of osilodrostat in combination with etomidate to control severe hypercortisolism unresponsive to initial osilodrostat monotherapy.[17] In one case of ectopic Cushing syndrome, high-dose osilodrostat (20 mg/d) was initiated and titrated to maximum dose of 60 mg/d in block-and-replace strategy to gain rapid control of severe hypercortisolism requiring ICU admission.[18]

Aside from individual case reports, there are few studies investigating osilodrostat use in non-pituitary Cushing syndrome. One retrospective study included 33 patients with paraneoplastic Cushing syndrome who received osilodrostat monotherapy or combination osilodrostat with ketoconazole or metyrapone, and documented significant reduction in urinary free cortisol, as well as improvement in comorbidities related to hypercortisolism (hypertension, hyperglycemia, and hypokalemia). Patients were treated with a dose titration strategy, immediate block-and-replace regimen, or dose titration before block-and-replace dosing with glucocorticoid replacement. Adrenal insufficiency was reported in 8 patients, and authors emphasized the importance of patient education about adrenal insufficiency and providing access to stress dose glucocorticoid replacement with this known risk of treatment.[19] Another study examined osilodrostat use in 9 patients with adrenal and ectopic Cushing syndrome. Of the 7 patients who completed the study, 6 achieved mean 24-hour urine free cortisol level below the upper limit of normal by week 12 of treatment. Adrenal insufficiency was reported in 7 patients.[20]

These publications help to document the utility of osilodrostat in treating various etiologies of nonpituitary hypercortisolism with varying dosage regimens. Sample sizes in formal studies remain small, likely in part due to the rarity of this disease entity. Common side effects of treatment include accumulation of cortisol precursors with symptoms of mineralocorticoid or androgen excess, as well as adrenal insufficiency. US Food and Drug Administration guidelines for osilodrostat dosing recommend to target a cortisol level within normal range, with cessation of therapy and dose reduction if adrenal insufficiency occurs.[2,10] Off-label dosing using a block-and-replace regimen has been described in several cases and appears to be a reasonable option for rapidly controlling severe hypercortisolism. It is also a treatment approach that should be considered when clinical situations result in variable cortisol production such as cyclic Cushing syndrome and metastatic ACC. This approach allows for the avoidance of adrenal insufficiency in the setting of rapidly decreasing cortisol levels or unpredictable cortisol production.

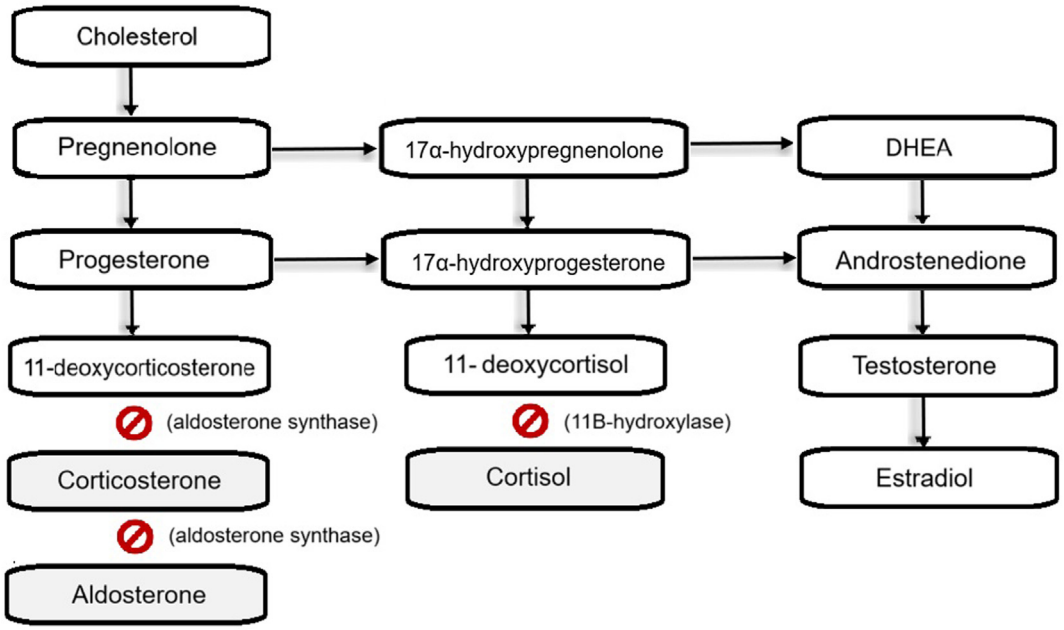

Fig. 3. Steroidogenesis pathway and inhibition of 11β-hydroxylase and aldosterone synthase by osilodrostat.

For our patient, other options for steroidogenesis inhibition such as ketoconazole and metyrapone were considered, but osilodrostat was selected for rapid control of cortisol production due to the sudden development of severe hypercortisolism. The patient tolerated the treatment well, and while receiving block-and-replace dosing she maintained suppression of cortisol levels on a stable dose of osilodrostat until metastatic disease burden increased, which correlated biochemically with increasing urinary cortisol levels. With currently limited data available, we hope to see continued examination of osilodrostat use in nonpituitary Cushing syndrome. Further studies are warranted to investigate efficacy and tolerability in larger groups of patients with hypercortisolism from non-pituitary sources.

Disclosure

The authors have no conflicts of interest to disclose.

Consent

Patient has provided informed consent for preparation of this case report.

Authorship Contributions

All authors made individual contributions to authorship. K.R. was involved in the writing and manuscript submission. C.P. and A.B. contributed in writing and editing. All authors were involved in the management of this patient. All authors reviewed and approved the final draft.

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