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Case Report

Successful Management of Cushing Syndrome From Ectopic ACTH Secretion in an Adolescent With Osilodrostat

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Abstract

A previously healthy 11-year-old male was found to have a mass in the pancreatic head after several months of abdominal pain and jaundice. Pathology was consistent with a World Health Organization grade 2 pancreatic neuroendocrine tumor. He developed refractory hypertension and was found to have Cushing syndrome from ectopic ACTH secretion, with oligometastatic liver disease. He underwent surgical resection of the pancreatic tumor and metastases. Postoperatively, his Cushing syndrome resolved, but it reemerged 1 year later in the setting of disease recurrence. He was not a candidate for bilateral adrenalectomy. Ketoconazole therapy was inadequate and he was started on metyrapone, lanreotide, cabergoline, and spironolactone. Although this regimen was well-tolerated, his Cushing syndrome recurred 4 months later as his metastatic disease burden increased. Osilodrostat was begun and the dose was gradually increased in response to his uncontrolled Cushing syndrome. Osilodrostat resulted in rapid improvement and eventual normalization of his urinary free cortisol at a dose of 18 mg twice daily. He had no adverse effects. This rare case highlights the successful off-label use of osilodrostat, a medication intended for refractory Cushing disease in adult patients, in a pediatric patient with Cushing syndrome caused by ectopic ACTH secretion.

Key Words: pediatric, Cushing syndrome, osilodrostat, ectopic ACTH secretion

Abbreviations: CD, Cushing disease; CS, Cushing syndrome; MRI, magnetic resonance imaging.

Introduction

Cushing syndrome (CS), resulting from excess production of the adrenal glucocorticoid hormone cortisol, can have multiple systemic effects including central adiposity, facial plethora, hypertension, glucose intolerance, hypokalemia, proximal muscle weakness, growth failure, and psychological impacts. CS has an estimated incidence of 0.7 to 2.4 cases per million people per year, with children and adolescents comprising only 10% of the diagnoses [1]. Approximately 75% to 90% of pediatric CS is secondary to ACTH overproduction by a pituitary adenoma, also known as Cushing disease (CD), whereas 15% is caused by autonomous cortisol secretion by the adrenal glands [1]. Ectopic ACTH production is a rare cause of CS and represents less than 1% of adolescent CS [1]. Pancreatic neuroendocrine tumors account for less than 15% of cases of ectopic ACTH production [2].

Hypercortisolism caused by ectopic ACTH secretion can be severe and challenging to manage [2]. Osilodrostat, an 11-beta-hydroxylase inhibitor, is indicated for adults with CD who have failed or are not candidates for pituitary surgery. Reports have described its effectiveness for treating CS in adults with ectopic ACTH production [3]. To our knowledge, this is the first report describing osilodrostat use in an adolescent with CS because of ectopic ACTH secretion.

Case Presentation

A previously healthy 11-year old male presented with 6 months of scleral icterus and 3 months of intermittent abdominal pain. He was diagnosed with a 5.3-cm intermediate-grade neuroendocrine tumor of the pancreatic head and was initially treated with 4 cycles of neoadjuvant capecitabine and temozolomide. He developed hypertension and hyperglycemia 2 months after his diagnosis, which was attributed to acute illness and pain. Approximately 10 months after initial diagnosis, he acquired *Pseudomonas* bacteremia and had severe, refractory hypertension (180/110 mm Hg) and hyperglycemia (11.1-19.43 mmol/L, 200-350 mg/dL). He also had physical features of CS, including facial plethora and central adiposity.

Diagnostic Assessment

Laboratory evaluation for CS revealed elevated ACTH and cortisol, with loss of diurnal variation based on serial assessment (Table 1). Dexamethasone suppression testing showed lack of cortisol suppression. Magnetic resonance imaging (MRI) and positron emission tomography revealed a new subcentimeter enhancing hepatic lesion. A 24-hour urinary free cortisol was not obtained at the time of diagnosis and pituitary MRI was deferred given the known pancreatic neuroendocrine tumor. Testing for multiple endocrine neoplasia type 1 was negative.

Treatment

The patient's CS was treated with ketoconazole and lanreotide before he underwent a modified Whipple procedure and

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hepatic lobectomy (Fig. 1). Pathologic evaluation showed a minority of neoplastic cells were positive for ACTH on immunohistochemistry (Fig. 1). Postoperatively, his cortisol normalized and he did not require treatment with hydrocortisone. His CS recurred approximately 1 year postoperatively with characteristic examination findings and laboratory values. New hepatic and retroperitoneal metastases were visualized on MRI scans. Ketoconazole was briefly restarted with a dose of 300 mg twice daily, but it was discontinued because of lack of efficacy and interactions with everolimus. He was evaluated for bilateral adrenalectomy, but he was not a good candidate because his extensive previous abdominal surgery and uncontrolled CS. His CS was temporarily controlled on lanreotide (120 mg subcutaneous monthly), cabergoline (0.5 mg twice weekly), spironolactone (75 mg daily), and metyrapone (750 mg twice daily) with the additional use of sunitinib (24 mg daily) for his metastatic disease. He also required potassium supplementation and insulin therapy.

Because of progression of his metastatic liver disease, the patient underwent staged bilobar bland embolization of his hepatic metastases at age 14 years. The bland embolizations were separated by 4 weeks, during which time sunitinib was held for a total of 9 weeks. Although the procedures were well tolerated, his CS did not improve and in fact worsened, necessitating an increase in metyrapone to 1000 mg twice daily. Following bland embolization, the size and enhancement of the hepatic metastases decreased with resolution of Ga68-DOTATATE uptake in hepatic lesions; however, his

Table 1. ACTH and cortisol levels at diagnosis and postoperatively

	7 AM	7 PM	Dexamethasone suppression test (1 mg)	8 AM postoperative day 1
ACTH (15-66 pg/mL; 3.3-14.5 pmol/L)	118 pg/mL; 26 pmol/L	155 pg/mL; 34.1 pmol/L		14 pg/mL; 3.1 pmol/L
Cortisol (5-25 µg/dL; 137.5-687.5 nmol/L)	33.9 µg/dL; 935.4 nmol/L	42.0 µg/dL; 1159.2 nmol/L	35.9 µg/dL; 990.8 nmol/L	11.9 µg/dL; 328.4 nmol/L

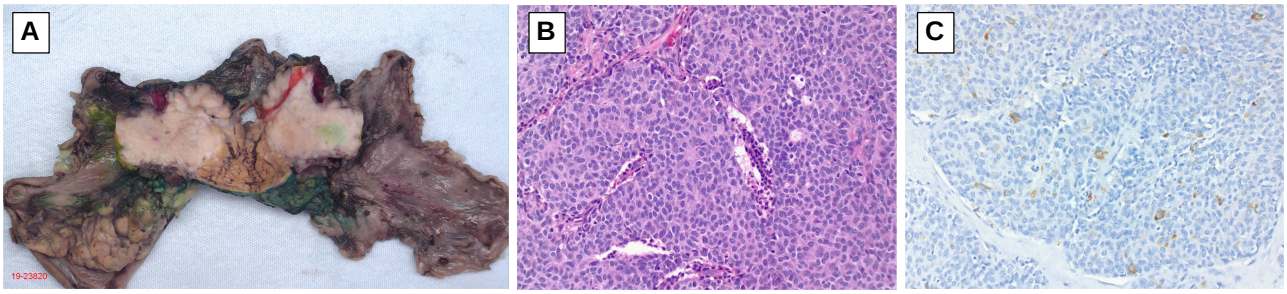

Figure 1. Gross specimen of pancreatic neuroendocrine tumor (A), microscopic specimen with hematoxylin and eosin stain of well-differentiated tumor (B), microscopic specimen with immunohistochemistry staining (brown), indicating a minority of cells positive for ACTH (C).

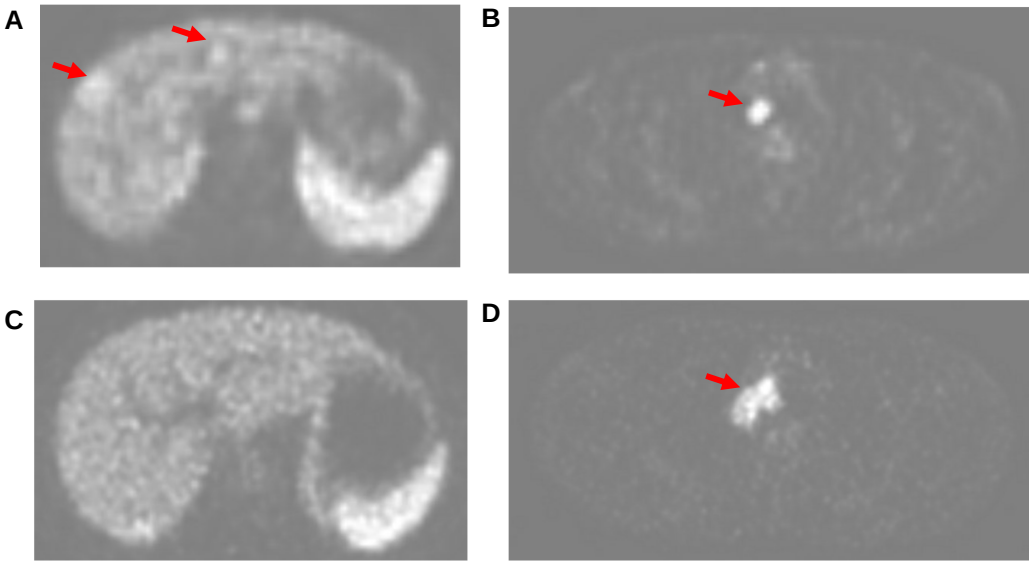

Figure 2. Positron emission tomography scan with Ga-68 DOTATATE before (A and B) and after (C and D) bland hepatic embolizations. Following bland embolization, the size and enhancement of hepatic metastases decreased (A and C) and nodal metastases advanced (B and D) with indication of enhancing metastatic activity with arrows.

nodal metastases advanced with an increase in Krenning score (Fig. 2).

Despite the increase in metyrapone dosage, the patient's 24-hour urinary free cortisol level reached 2481.24 nmol/day (899 mcg/24 hours; relative risk, 11.04-154.56 nmol/day or 4-56 mcg/24 hours). Therefore, osilodrostat was started at a dose of 2 mg twice daily with plans to increase by 4 mg per day every 2 weeks until adequate control of his CS was achieved. Lanreotide, cabergoline, spironolactone, and metyrapone were continued during this titration. The patient was monitored for potential adverse effects of osilodrostat including QTc prolongation on electrocardiogram, hypokalemia, hypertension, adrenal insufficiency, fatigue, headaches, vomiting, abdominal pain, and diarrhea. Twenty-four-hour urinary free cortisol levels were obtained approximately every 2 weeks to guide dose escalation (Fig. 3). His QTc remained normal and he tolerated dose escalation well without side effects. After 2 months of treatment, osilodrostat was increased by 4 mg per day weekly, instead of every 2 weeks, because of continued severe CS.

Outcome and Follow-up

The patient's 24-hour urinary free cortisol level normalized at a dose of 18 mg twice daily, approximately 5 months after the initiation of osilodrostat. His CS features, including central adiposity, hypertension, hypogonadism, fatigue, weakness, and difficulty concentrating, greatly improved. Within 2 weeks of the normalization of his urinary free cortisol, the patient experienced fatigue, hypoglycemia, decreased appetite, diarrhea, and decreased blood pressure. Metyrapone and spironolactone were immediately discontinued and he was started on a mildly supraphysiological dose of hydrocortisone (15 mg/m^2/day to prevent adrenal crisis). The osilodrostat dose was not immediately adjusted following development of hypocortisolism, given the discontinuation of metyrapone. He remains on osilodrostat approximately 12 months after initiation of this therapy and 9 months after control of his CS was achieved.

Since his initial diagnosis, weight and body mass index have fluctuated with rises and falls in his cortisol levels (Fig. 4). His

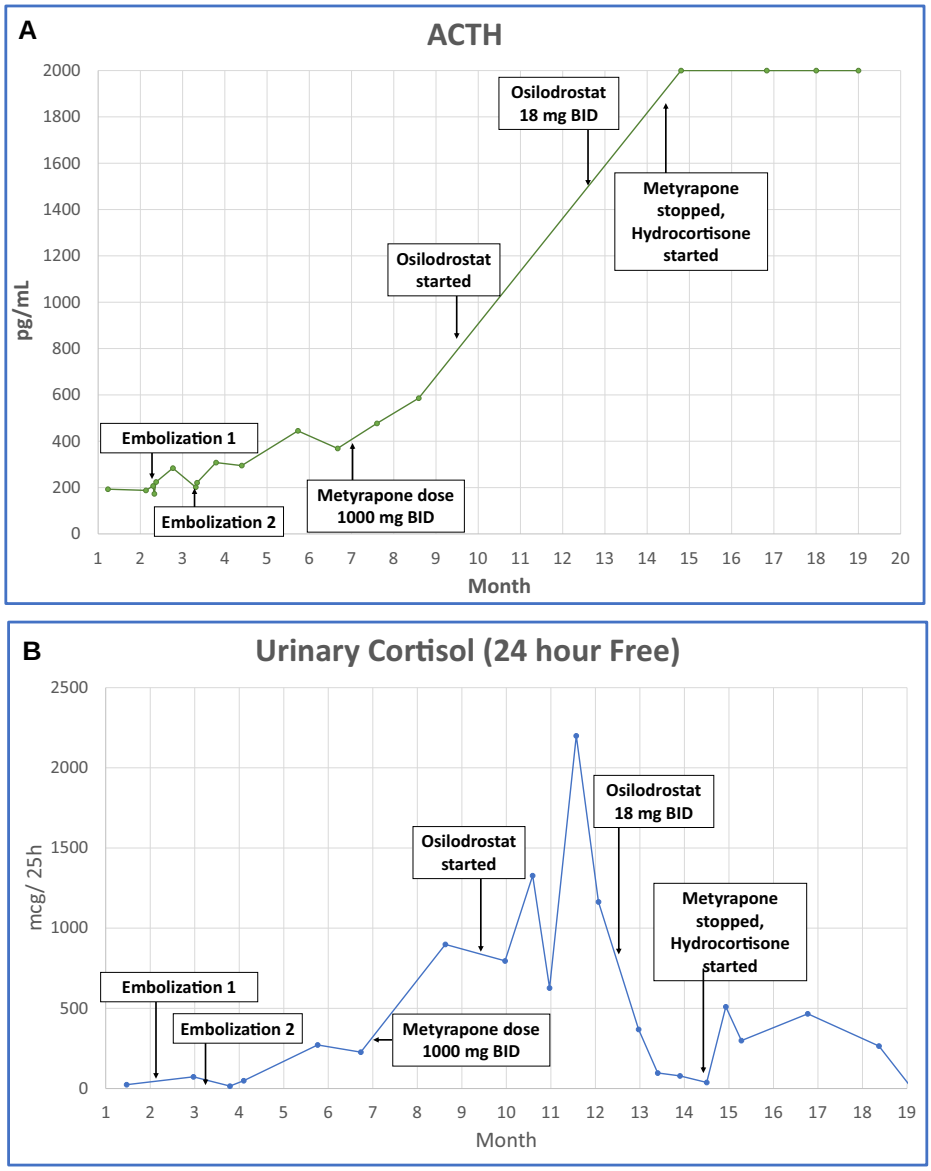

Figure 3. Impact of bland embolization procedures and medical therapy on ACTH (A) and 24-hour urinary free cortisol (B) levels.

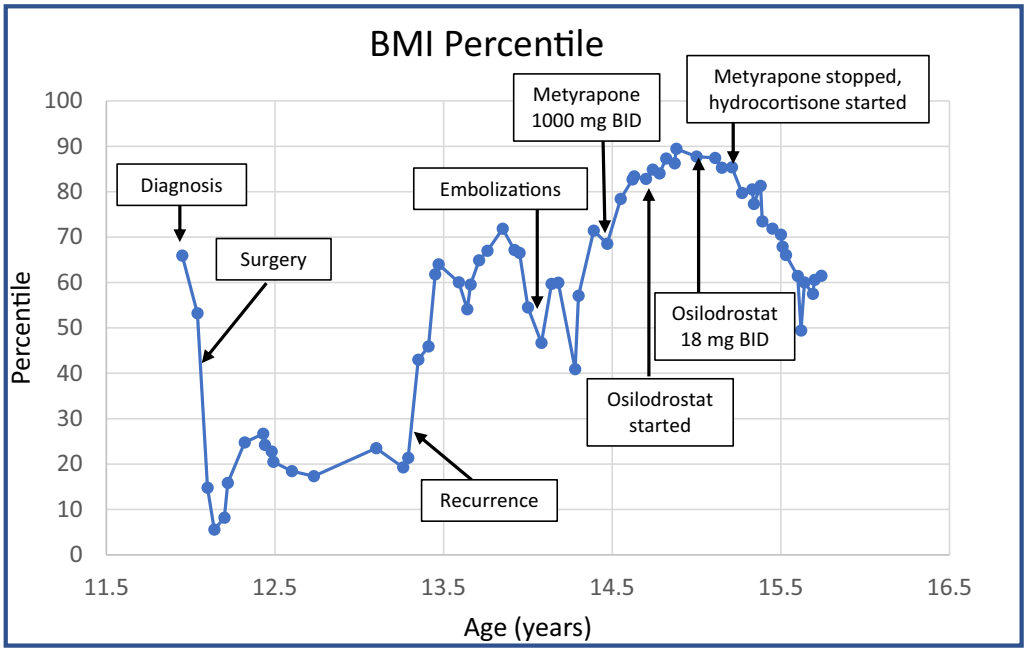

Figure 4. Impact of the patient's Cushing syndrome and his subsequent treatments on his body mass index percentile.

body mass index *z*-score was 0.41 when his CS was diagnosed, peaked at the *z*-score 1.25 2 months after starting osilodrostat, and decreased to *z*-score 0.15 12 months after starting osilodrostat. He had normal pubertal development, with the exception of periods of hypogonadotropic hypogonadism when his cortisol levels were markedly elevated. Although osilodrostat can cause signs of hyperandrogenism in female patients, no additional virilization was appreciated in our pubertal male patient during treatment.

The current dose of osilodrostat is 20 mg twice daily in our now-15-year-old patient who is approximately 50 kg. Since osilodrostat initiation, the ACTH levels have been extremely elevated (>400 pmol/L, >2000 pg/mL). Subsequently, the patient has experienced significant skin hyperpigmentation.

Discussion

Ectopic ACTH secretion is a rare cause of CS, with few cases reported in children and adolescents [4]. Additionally, pancreatic neuroendocrine tumors are an uncommon cause of ectopic ACTH secretion [2]. Thus, this case combines 2 rare phenomena, which, in addition to the novel management strategies, warrant further discussion.

Our patient developed hypertension and hyperglycemia that may have represented CS just 2 months after diagnosis; however, his CS was not recognized or tested for until 10 months after diagnosis. Delayed diagnosis is common in ectopic ACTH secretion causing CS, with a mean time to diagnosis of 14 months [5]. Heightened awareness of the signs and symptoms of pediatric CS can aid in earlier recognition to prevent complications.

Per the Endocrine Society Clinical Practice Guideline on the Treatment of CS, surgical resection of causative lesion(s) is the recommended first-line therapy [6]. Surgery resulted in an initial remission of CS in our patient (of approximately 1 year's duration). Treatment options following recurrence include (1) surgical resection of ACTH-secreting neuroendocrine tumors, (2) bilateral adrenalectomy, or (3) medical therapy [2]. Because of his metastatic disease burden, surgical resection was not possible in our patient. Bilateral adrenalectomy was determined to be nonfeasible because of his high surgical risk.

Our patient underwent staged bland embolization of his hepatic metastases to lessen ACTH production. Use of bland embolization for management of ACTH-secreting metastases has not been previously reported in a pediatric patient. Although the procedure was well-tolerated and successfully reduced the size of hepatic metastases, the patient's nodal disease worsened and CS did not improve. It is possible that the nodal progression was driven by the need to temporarily hold sunitinib to improve the efficacy of embolization.

Despite medical therapy, our patient developed evidence of severe hypercortisolism, with urinary free cortisol level more than 5 times the upper limit of normal. This state is considered a life-threatening endocrine emergency with high risk of complications [2]. Therefore, we proceeded with osilodrostat use, which was off-label because it is neither approved in the pediatric population nor for the indication of ectopic ACTH production. Based on a prior study, we were hopeful that osilodrostat, an 11-beta-hydroxylase inhibitor with improved potency and a longer half-life compared with metyrapone, would be effective in achieving eucortisolism in our patient [3]. Given the lack of experience in the pediatric population, we increased the dose of osilodrostat per the manufacturer's guidelines (increasing by 4 mg every 2 weeks). Higher starting doses and faster titrations have been reported in adult patients with severe hypercortisolism from ectopic ACTH secretion to more rapidly normalize cortisol levels [3].

Serum cortisol measurements may be falsely elevated in patients taking metyrapone or osilodrostat because of increased levels of the cortisol precursor 11-deoxycortisol. This interference and overestimation can be avoided by highly specific techniques such as liquid chromatography mass spectrometry and gas chromatography mass spectrometry or through urinary free cortisol measurement. Urine free cortisol levels were

monitored in our patient and a normal level was achieved at an osilodrostat dose of 36 mg/day. This dose was greater than is required for many adult patients with CD [7], but less than the maximum dose of osilodrostat (30 mg twice daily). Based on case series, high doses of osilodrostat are often needed to treat ectopic ACTH secretion [3]. Further study of osilodrostat in the pediatric population will help determine potential differences in pharmacokinetics compared with adult patients [8].

To our knowledge, this is the first reported case of using osilodrostat to successfully manage CS caused by ectopic ACTH secretion in a pediatric patient. The therapy has been well-tolerated despite high doses with no apparent side effects apart from mild adrenal insufficiency, which was treated with hydrocortisone. Clinical trials of osilodrostat in the pediatric population are ongoing, which will further elucidate its effectiveness for pediatric CS that cannot be surgically cured.

Learning Points

- Cushing syndrome (CS) caused by ectopic ACTH production is rare and can be severe because of markedly elevate cortisol levels.
- Osilodrostat has higher potency than other steroidogenesis inhibitors and should be considered in patients with poorly controlled CS not amenable to surgical management.
- Osilodrostat was well tolerated in an adolescent with CS caused by ectopic ACTH secretion, although it required high doses to normalize cortisol levels.

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Contributors

All authors made individual contributions to authorship. K.B. led the development of this manuscript. D.V.M. provided critical review of this manuscript. L.P. led conceptualization of this case report and provided critical review of the manuscript. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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