

# Mifepristone Treatment of Cushing's Syndrome in a Pediatric Patient

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Cushing's syndrome (CS) in the pediatric population is challenging to diagnose and treat. Although next-generation medical therapies are emerging for adults with CS, none are currently approved or used in children. Here we describe the first use of mifepristone, a glucocorticoid receptor antagonist, to treat CS in a pediatric subject. The patient, a 14-year-old girl with an 18-month history of metastatic neuroendocrine carcinoma, suffered from fatigue, profound myopathy, irritability, and depression. She was found to have hypertension, hypokalemia, and worsening control of her preexisting type 1 diabetes. In this report, we detail our clinical evaluation that confirmed CS caused by an ectopic adrenocorticotrophic hormone secreting tumor. Surgical and radiation therapies were not pursued because of her poor functional status and limited life expectancy, and medical treatment of CS was indicated for symptom relief. Mifepristone treatment provided rapid improvement in glycemic control, insulin resistance, and hypertension as well as significant diminishment of her myopathy and fatigue. Hypokalemia was managed with an oral potassium replacement and dose escalation of spironolactone; no other significant adverse effects were observed. Despite successful palliation of Cushing's signs and symptoms, the patient died of progression of her cancer. This case demonstrates the safety and efficacy of mifepristone treatment in a pediatric patient with symptomatic, ectopic CS. We conclude that, in appropriate pediatric patients with CS, glucocorticoid receptor antagonism with mifepristone should be considered to control the effects of hypercortisolism and to improve quality of life.

Cushing's syndrome (CS) results from excess glucocorticoid hormone in the circulation. In the pediatric population, outside of the exogenous use of glucocorticoids (ie, prednisone, dexamethasone, and hydrocortisone) for treating a variety of diseases, CS is rare but often considered in diagnostic evaluations, particularly in overweight patients. These evaluations are challenging because, whereas most children with CS have weight gain, a number of other classic signs that are readily apparent in the adult population, such as muscle weakness and cognitive changes, are absent or significantly more subtle in children. Thus, excluding CS based on clinical

signs is difficult in children. However, an additional strong indicator of CS that occurs selectively in the pediatric population is the decrease in, or sometimes the complete abatement of, the growth velocity. Therefore, any child who is gaining weight but has poor linear growth should be evaluated for CS.

As mentioned, the majority of pediatric CS cases are iatrogenic, related to supraphysiologic glucocorticoid levels from drug treatment of other medical conditions.<sup>1</sup> By contrast, endogenous CS (hereafter referred to as CS in this article) causes include corticotropin-independent adrenal tumors and primary adrenocortical

## abstract

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Dr Banerjee compiled the pertinent clinical data for the report and drafted and revised the manuscript; Drs Marina and Katznelson reviewed and revised the manuscript; Dr Feldman was primarily responsible for all aspects of the case report; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of this work.

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hyperplasia, as well as corticotropin-dependent causes, including Cushing's disease (pituitary adenoma) and ectopic corticotropin production from tumors arising outside of the pituitary.<sup>1</sup> Although these cancers are rare, the patients often present with CS, a fact that can compel physicians to perform a challenging complete workup for CS to exclude the possibility of these associated diseases.

Once confirmed in a patient, the treatment of CS remains a challenge. In pediatric patients, as in adults, first-line treatment is to surgically resect the source of excess cortisol or corticotropin production. For corticotropin-dependent CS, endonasal microadenectomy for a pituitary adenoma or resection of the ectopic corticotropin-producing tumor would be indicated. For corticotropin-independent CS, adrenalectomy is indicated to remove the cortisol-producing adrenal pathology. Unfortunately, patients with unresectable corticotropin-producing tumors often have a difficult course, with profound morbidities resulting from uncured CS or second-line therapies including bilateral adrenalectomy and pituitary irradiation. Although a number of pharmacologic agents are used for adults with CS,<sup>2</sup> none of these agents have been tested in pediatric subjects with CS, including cases with ectopic CS.<sup>3</sup> Mifepristone is commonly recognized as an abortifacient (RU486) due to its antagonism of the progesterone receptor. However, it is also a competitive antagonist of glucocorticoid action at the glucocorticoid receptor (GR), prompting its development as a treatment of CS.<sup>4-7</sup> In a recent trial, the administration of mifepristone resulted in improvement in hypertension and hyperglycemia control in adults with CS. On the basis of this study, mifepristone was recently approved by the US Food

and Drug Administration (FDA) for adults with endogenous CS and hyperglycemia.<sup>5,8,9</sup> Here we report the first use of mifepristone in a pediatric patient with CS. We found that mifepristone successfully mitigated the comorbidities of CS, including insulin resistance, hypertension, and myopathy.

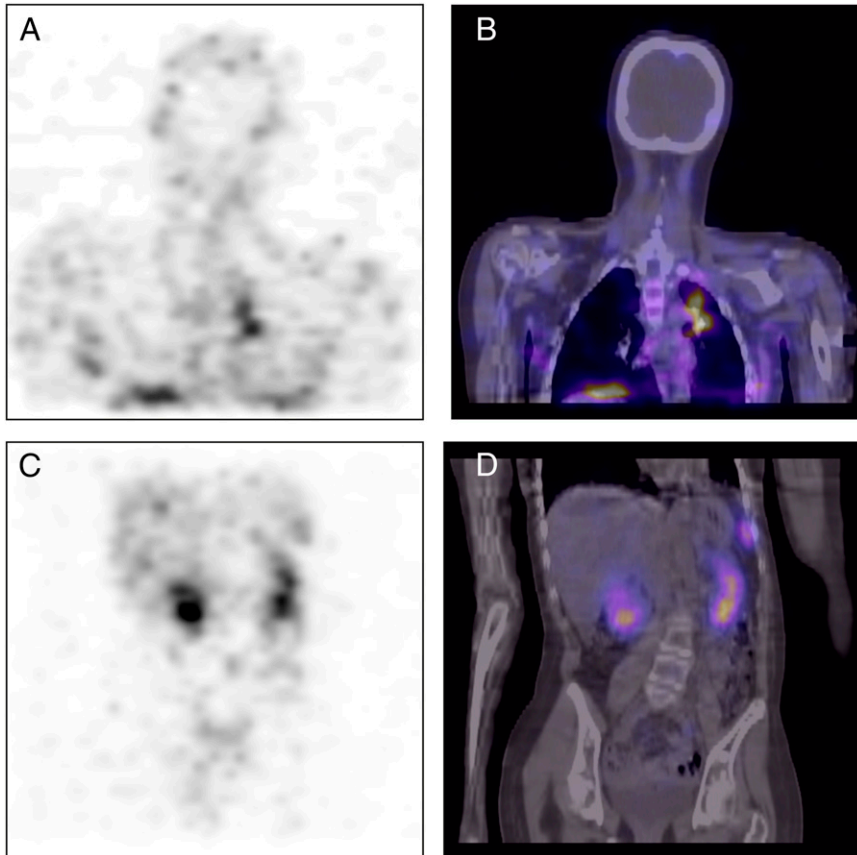
### THE CASE

A 14-year-old African-American girl with a 5-year history of type 1 diabetes presented to our hospital for a second opinion regarding the treatment of a metastatic neuroendocrine tumor. Approximately 18 months before presentation, she was seen at a local hospital for a persistent cough. A chest computed tomography (CT) scan revealed a left upper lobe consolidation, and she was treated with oral antibiotics. Six months later she was referred to the pulmonary clinic for persistent cough. A CT scan revealed a left upper lobe mass encasing the pulmonary artery and compressing the main pulmonary artery, hilar lymphadenopathy, and adjacent satellite nodules. A CT-guided lung biopsy identified a neuroendocrine carcinoma with a Ki-67 proliferation index of 10%. Immunostaining revealed that the neoplasm was positive for pancytokeratin, synaptophysin, chromogranin, and transcription termination factor, RNA polymerase I, but negative for Wilms tumor 1, S100, myogenin, CD99, desmin, CD45, octamer-binding transcription factor 4, and terminal deoxynucleotidyl transferase, consistent with a neuroendocrine carcinoma of lung origin.

Additional CT scans showed no other spread, and a brain MRI was normal. However, a pelvic MRI revealed sclerotic lesions, and an upper back skin-punch biopsy identified metastatic neuroendocrine carcinoma consistent with stage IV (T3N2M1b) disease. There was no family history of genetic disorders. Diagnostic

genetic testing for *MEN1* mutations, as well as screening for 14 genes that are mutated in hereditary cancer syndromes (ColoNext; Ambry Genetics, Aliso Viejo, CA), was negative. Treatment was initiated with external beam radiation to the lung mass and mediastinum (4900Gy/23 fractions over ~1 month) followed by 4 cycles of cisplatin and etoposide. Temozolomide therapy initiated shortly thereafter was stopped after severe nausea and anorexia. In addition, ~9 to 12 months before presentation, the patient began to require increasing insulin dosing with worsening blood sugar control. In retrospect, the initiation of this process was likely an early sign of her developing CS. Ultimately, her hemoglobin A1c reached 12.5% (normal: <5.7%), and finger-stick blood glucose measurements typically ranged in the 400 to 500s (mg/dL). Her insulin regimen was increased to 28 U insulin glargine daily and 22 to 25 U insulin lispro per meal. Her total daily insulin requirement of >2.2 U/kg per day was consistent with severe insulin resistance.

At presentation, the patient complained of facial swelling, difficulty swallowing, muscle weakness, and difficulty standing, as well as generalized severe fatigue and irritability. Physical examination revealed a Cushingoid, thin child with moon facies, facial acne, hirsutism (fore lip), and supraclavicular fat pads. She was afebrile (36.9°C) but hypertensive (blood pressure ranges: 135–150/85–90 mm Hg) and tachycardic (pulse: 100–110 beats per minute). Her height was 1.55 m (16.8th percentile) and weight was 44.9 kg (24th percentile), with a BMI of 18.7 (36th percentile). A neurologic examination was notable for proximal muscle weakness (4/5 hips, shoulder). She did not display plethora, skin bruises, striae, or edema. A brain MRI revealed cerebral lesions consistent with metastatic



**FIGURE 1**

<sup>111</sup>In octreotide scintigraphy SPECT (A) and SPECT-CT (B) chest coronal images revealed uptake in the left mediastinum consistent with pathologically established neuroendocrine tumor. Physiologic uptake is seen in the diaphragm. SPECT (C) and SPECT-CT (D) abdominal coronal images in the same plane are shown. No uptake is seen in the liver despite widely metastatic disease on previous CT and biopsy-proven disease below the diaphragm. Physiologic uptake is present in the kidneys and spleen. SPECT, single-photon emission computed tomography.

disease. An octreotide scan showed octreotide-avid lesions above but not below the diaphragm (Fig 1). A biopsy of a subcutaneous abdominal nodule revealed a neuroendocrine tumor with immunostaining positive for synaptophysin and chromogranin but negative for TTF-1. This finding suggested dedifferentiation from the primary tumor that might explain the differences in the octreotide uptake results on imaging studies. Laboratory testing showed severely elevated urine free cortisol levels (4073  $\mu\text{g}$  per 24 hours [normal: <50]) and serum cortisol levels (62  $\mu\text{g}/\text{dL}$  [normal: 4–24]) and inappropriately elevated plasma corticotropin levels (229 pg/mL [normal: 10–60]). After a high-dose (8 mg) overnight dexamethasone

suppression test, morning serum cortisol and plasma corticotropin levels remained elevated (36  $\mu\text{g}/\text{dL}$  and 151 pg/mL, respectively). Given the unequivocal nature of the clinical scenario and laboratory studies in this particular patient, a repeat dexamethasone suppression test was not required; the constellations of clinical findings and studies were all consistent with corticotropin-dependent CS.

After the administration of 100  $\mu\text{g}$  octreotide, plasma corticotropin levels did not change (baseline: 142 pg/mL; 4 hours: 133 pg/mL; 6 hours: 137 pg/mL; 8 hours: 156 pg/mL [normal: 10–60]). Long-acting-release, 30-mg intramuscular octreotide was initiated to control tumor growth. To palliate the

consequences of hypercortisolemia, we considered medical therapy with mifepristone, a glucocorticoid antagonist.<sup>8</sup> Because mifepristone is FDA approved for the treatment of CS in adults but not in children, a patient-specific emergency-investigation new-drug application was submitted to the FDA and approved for our patient. The institutional review board approved the use of mifepristone for this subject.

Mifepristone was initiated at an oral dose of 300 mg daily. As predicted from its mechanism of action, both plasma corticotropin and serum cortisol levels increased (Table 1). Within 7 days of starting the mifepristone, the patient's insulin sensitivity rapidly and dramatically improved. Her insulin glargine was tapered to 16 U/day, and her insulin-to-carbohydrate ratio was reduced to 1 unit insulin lispro per 50 g. Consistent with rapid improvement in insulin sensitivity, her total insulin requirement decreased to 0.75 U/kg per day. With the hopes of continued clinical improvement and consistent with protocols used in the adult population, her dose of mifepristone was increased to 300 mg twice daily after 2 weeks of therapy. The patient's blood pressure normalized as did the alanine aminotransferase levels (Table 2). However, the patient developed worsening hypokalemia with serum levels of 2.3 to 2.6 mmol/L (normal: 3.5–5.5 mmol/L), which was managed by increasing the dose of spironolactone to 50 mg twice daily and adding a potassium replacement of 60 mEq daily (Table 2).

Despite the improvement in her CS, the patient's overall condition worsened and she was placed on hospice care, although she remained on mifepristone for the continued management of CS-related morbidities. She died several weeks later.

**TABLE 1** Serum Cortisol and Plasma Corticotropin Levels Before and After Initiation of Treatment With Mifepristone

	Days Relative to Start of Mifepristone Administration						
	-394	-22	-21	-2	0	6	15
Serum cortisol, $\mu\text{g/dL}$		158	151	61.5		>150.0	>120.0
Plasma corticotropin, $\text{pg/mL}$	40	35.5	32.8	229		439	449

## DISCUSSION

We describe a pediatric case of ectopic CS caused by a neuroendocrine carcinoma. Because of the challenging nature of the case, we assembled a multidisciplinary team, including consultation and joint decision-making with adult endocrinology and oncology colleagues, a strategy advocated by experts in the field.<sup>3</sup> The overall functional status and life expectancy of this patient required that we pursue a therapeutic option that was easily available, rapid-acting, and with minimal expected side effects. Thus, surgical treatment with bilateral adrenalectomy was not pursued. We obtained a patient-specific emergency-investigation new-drug to use mifepristone in

a pediatric patient and implemented therapy within days of presentation to our hospital. Mifepristone successfully improved the clinical management of her CS and palliated a number of her symptoms related to hypercortisolemia, although the patient succumbed to her primary disease. Because of the short duration that the patient was receiving therapy, and the confounding aggressive disease that required blood transfusions, measurements of hemoglobin A1c and growth velocity in this patient during treatment would not be informative but are recommended if a patient stays on therapy for at least 3 months.

A number of medical therapies are now available for adults with CS. Unfortunately, nearly all of these

agents have therapeutic limitations or side effects that preclude their use in specific patients.<sup>2</sup> Among medical treatment options, side-effect profiles, efficacy, and rapid onset of disease control made etomidate, pasireotide, mitotane, metyrapone, and ketoconazole less attractive treatment choices in this case. The somatostatin analog long-acting-release octreotide was tried to control tumor growth, but, on the basis of the lack of an acute plasma corticotropin response to subcutaneous octreotide, we did not expect long-term octreotide administration to improve the CS.

Direct GR antagonism is an attractive therapeutic target in endogenous CS, in contrast to commonly used drugs that block adrenal steroid synthesis and/or secretion, including mitotane, ketoconazole, and metyrapone. These agents frequently have side effects and/or are not approved by regulatory agencies for the treatment of CS, even in adults, requiring limited use off-label. For example, mitotane treatment is frequently associated with dose-related, common gastrointestinal and neurologic symptoms and abnormal liver function tests. Metyrapone is not commercially readily available for therapeutic use in the United States. Ketoconazole is only effective in ~50% of subjects and often causes severe side effects including hepatotoxicity, rash, and gastrointestinal symptoms.<sup>2</sup> We also considered pasireotide, a recently approved treatment of CS in adults, but because of worsening of glucose tolerance reported as a side effect, and the higher reported clinical efficacy rate for mifepristone, we decided to use mifepristone in this case.

After the addition of mifepristone, the patient showed rapid improvement in her hyperglycemia, insulin resistance, hypertension, and myopathy. There was an expected increase in serum cortisol and plasma corticotropin, consistent with successful GR

**TABLE 2** Vital Signs and Laboratory Results Before and After Mifepristone Treatment

	Before Treatment	Weeks on Mifepristone Treatment	
		1 Week	2 Weeks
<b>Vital signs</b>			
Systolic blood pressure, mm Hg	132	—	117
Diastolic blood pressure, mm Hg	87	—	81
Heart rate, beats per minute	102	—	112
Weight, kg	44.8	—	45
<b>Laboratory results (reference range)</b>			
Sodium (135–145 mmol/L), mmol/L	142	145	142
Potassium (3.5–5.5 mmol/L), mmol/L	3.8	2.6	4.1
Chloride (96–109 mmol/L), mmol/L	104	102	103
Carbon dioxide (20–30 mmol/L), mmol/L	29	36	35
Urea nitrogen (5–25 mg/dL), mg/dL	9	6	10
Creatinine (<1.2 mg/dL), mg/dL	0.8	0.8	0.9
Glucose (70–100 mg/dL), mg/dL	260	72	122
Anion gap (5–15 mmol/L), mmol/L	9	7	4
Calcium (8.5–10.5 mg/dL), mg/dL	8.2	8.4	8.5
Total bilirubin (<1.4 mg/dL), mg/dL	0.3	0.8	1.5
AST (<40 U/L), U/L	54	52	60
ALT (<80 U/L), U/L	122	96	75
Alkaline phosphatase (<400 U/L), U/L	279	277	304
Albumin (3.5–5.0 g/dL), g/dL	2.5	2.8	2.3
Total protein (6.0–9.0 g/dL), g/dL	6.3	6.5	6.3
Globulin (2.0–5.0 g/dL), g/dL	3.8	3.7	4

ALT, alanine aminotransferase; AST, aspartate aminotransferase; —, no data.



antagonism and improved CS control.<sup>8</sup> The patient developed profound hypokalemia, a known side effect of mifepristone, but this was readily treated with spironolactone and an oral potassium replacement. We did not observe other adverse effects of mifepristone.

This case demonstrates the use of mifepristone in ectopic CS, and uniquely in a pediatric patient. Because many of the agents used to treat CS work through different molecular mechanisms, including inhibition of steroid hormone synthesis and secretion, adrenolysis, inhibition of corticotropin secretion, and direct GR antagonism, combination therapy might perform synergistically in particular patients.<sup>10</sup> In addition, the variety of agents available for the treatment of CS allows for the rational use of specific agents for personalized therapy in individual patients on the basis of side-effect profiles and comorbidities. Regrettably, information regarding specific combinations of therapy regimens is lacking because of the rarity of cases.<sup>2</sup> This lack of data is particularly pronounced in the pediatric setting. Thus, the use and reporting of agents, alone or in combination, are critical toward the development of successful therapies in this population. Our description of the safe, effective use of mifepristone in a pediatric patient demonstrates that mifepristone can

be considered in pediatric patients with endogenous hypercortisolism, particularly when surgical cure is not possible and other forms of medical treatment are contraindicated.

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#### ABBREVIATIONS

CS: Cushing's syndrome  
CT: computed tomography  
FDA: Food and Drug Administration  
GR: glucocorticoid receptor

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