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Case Report

Utilization of bilateral percutaneous microwave ablation of the adrenal glands in ectopic Cushing's syndrome ☆,☆☆

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ABSTRACT

Ectopic Cushing's syndrome (CS) is rare and difficult to cure when the source is elusive. Medical management is complex and often times contraindicated in the medically complex patient. We present a complicated case of ectopic CS where bilateral percutaneous microwave ablation (MWA) of the adrenal glands successfully cured hypercortisolism when surgery and medical therapies were contraindicated. A 71-year-old male was diagnosed with ectopic CS after adrenocorticotropic hormone-dependent hypercortisolism persisted after hypophysectomy despite a positive gradient of >3 on inferior petrosal sinus sampling. An ectopic source was not identified. Surgery and medical therapies were contraindicated due to comorbidities and drug interactions. Bilateral MWA of the adrenal glands was performed. Postprocedurally cortisol levels declined and the patient was clinically adrenally insufficient at 6 months. Bilateral MWA of the adrenal glands can prove to be an effective treatment option for ectopic CS when surgical resection and medical therapies are ineffective or contraindicated.

Introduction

Cushing's syndrome (CS) is associated with significant morbidity and mortality [1]. The ultimate goal is cure by surgical resection of the primary source [2]. In ectopic CS, however, identification of the primary source can be difficult, with a 1–20-year delay in finding the tumor and up to 16% of cases the tumor is not found [3]. Medical therapy is recommended to treat hypercortisolism if surgery is delayed or contraindicated

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Table 1 – Laboratory results before and after trans-sphenoidal pituitary surgery and bilateral adrenal gland percutaneous microwave ablation.

Analyte	Normal range	Before TSS	1 week post first TSS	1 week post second TSS	6 months post MWA	8 months post MWA	16 months post MWA
ACTH	1.58-13.93 pmol/L	17.56	21.96	13.71		24.2	5.72
8 AM cortisol	220.7-634.5 nmol/L	714.5	717.3	811.1	126.9	171.1	33.1
24-hour urine cortisol	(<165.6 nmol/d	396.3	645.0		42.8		
Prolactin	2.1-17.7 μg/L	22.3	7.6	0.8			
IGF-1	3.28-31.7 nmol/L	18.08	22.4	18.34			
Thyroxine free	10.3-21.88 pmol/L	18.02	12.87	12.87			15.45
TSH	(0.35-4.49 mIU/L	0.67	0.19	0.02			
LH	1.7-8.6 IU/L	<0.1	4.2	0.2			0.6
FSH	1.7-12.4 IU/L	0.9	5.6	1.4			0.7
8 AM testosterone	7.67-24.85 nmol/L			0.66			<0.1

TSS, trans-sphenoidal pituitary surgery; MWA, bilateral adrenal gland percutaneous microwave ablation; ACTH, adrenocorticotropic hormone; IGF-1, insulin like growth factor-1; TSH, thyroid stimulating hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone.

Table 2 – Inferior petrosal sinus sampling results.

Time	Location	ACTH level (pmol/L)	Location	ACTH level (pmol/L)	Location	ACTH level (pmol/L)
0852	Right CS	11.3	Left CS	16.35	Right CFV	17.95
0853	Right CS	15.07	Left CS	16.87	Right CFV	17.27
0855	Right distal IPS	17.89	Left distal IPS	22.88	Right CFV	18.35
0856	Right distal IPS	20.0	Left distal IPS	18.3	Right CFV	18.81
0857	Right Prox IPS	20.11	Left Prox IPS	17.69	Right CFV	17.69
0900	CRH administered					
0902	Right Prox IPS	26.8	Left Prox IPS	57.44	Right CFV	16.61
0905	Right Prox IPS	50.53	Left Prox IPS	71.35	Right CFV	19.27
0910	Right Prox IPS	37.0	Left Prox IPS	45.32	Right CFV	26.6

ACTH, adrenocorticotropic hormone; CS, cavernous sinus; CFV, common femoral vein; IPS, inferior petrosal sinus; Prox, proximal; CRH, corticotropin-releasing hormone.

[2,4]. Medical management, however, is complex, as all available treatment modalities have numerous side effects, require intense follow-up for medication titration, are either expensive or difficult to source, and have lower efficacy rates compared to surgery [2,4]. Here, we present a complicated case of ectopic adrenocorticotropic hormone (ACTH)-dependent CS successfully treated with bilateral percutaneous microwave ablation (MWA) of the adrenal glands.

Case presentation

A 71-year-old male with a past medical history of hypogonadotropic hypogonadism, obesity (BMI 39.5 kg/m^2), type 2 diabetes mellitus (T2DM) diagnosed 4 years prior, and obstructive sleep apnea diagnosed 1 year prior, initially presented for management of T2DM. The patient reported significant weight gain, thinning of the skin, and easy bruising which prompted evaluation and confirmation of ACTH-dependent CS (Table 1). A pituitary protocol brain MRI was unable to identify a discrete pituitary lesion.

Three months after initial presentation, he developed abdominal wall cellulitis, sepsis, and a DVT for which he was started on apixaban 5 mg twice a day. He underwent inferior petrosal sinus sampling 6 months after initial presentation, which was significant for a central-to-peripheral plasma ACTH gradient of 3.7 after corticotropin-releasing hormone administration (Table 2). He was started on ketoconazole 200 mg every 8 hours while awaiting surgery. Trans-sphenoidal surgery was performed 11 months after initial presentation. Pathology revealed pituitary hyperplasia with positive staining for ACTH. However, he had persistent hypercortisolism after initial surgery (Table 1) and was restarted on ketoconazole 200 mg every 8 hours.

He underwent repeat trans-sphenoidal surgery with hypophysectomy and distal stalk resection 15 months after initial presentation, for which the pathology showed pituitary gland composed of small cells with minimal pleomorphism. ACTH staining was positive in many of the pituitary cells. A reticulin stain demonstrated expanded acini focally. Unfortunately, elevated ACTH and cortisol levels persisted despite the development of central hypothyroidism and a decrease in prolactin post operatively (Table 1). These findings confirmed ectopic Cushing's syndrome. Possible ectopic sources were an incidental 10 mm lung nodule and a 3 cm thyroid nodule

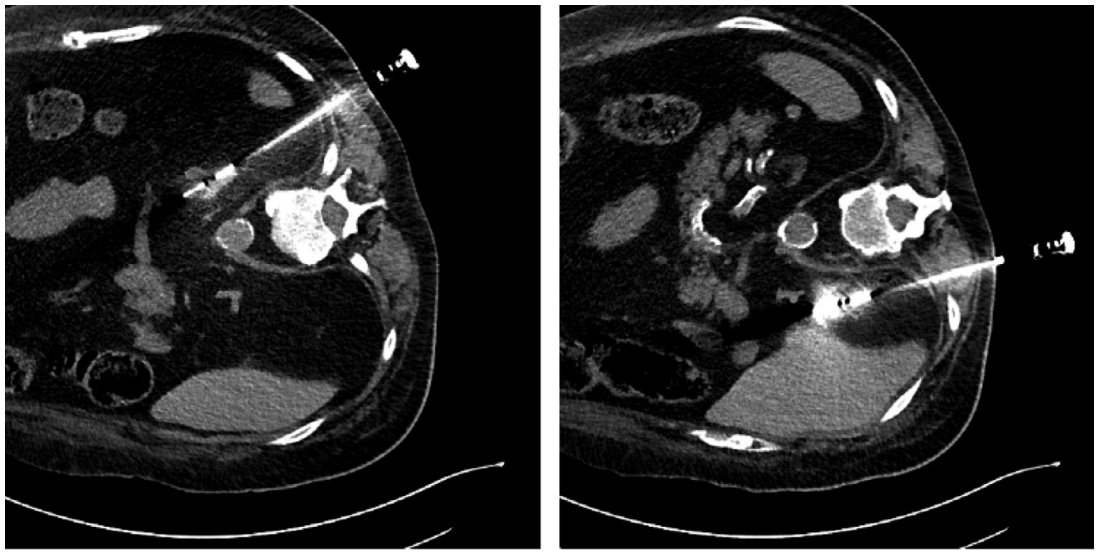

Fig. 1 – Real-time CT-guided images of bilateral adrenal gland percutaneous microwave ablation.

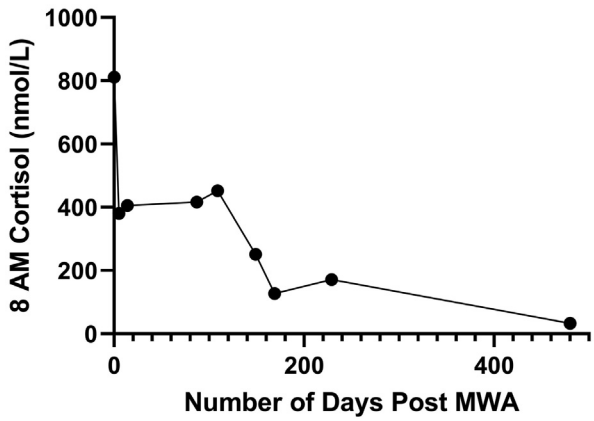

Fig. 2 – Serum cortisol concentrations after percutaneous microwave ablation (MWA) of both adrenal glands.

that were both noted on prior scans. Unfortunately, due to his multiple comorbidities, surgical resection of the lung nodule, thyroid nodule or both adrenal glands were too risky. After a multidisciplinary team meeting which included endocrinology, neurosurgery, interventional radiology, family members and the patient, bilateral MWA of the adrenal glands was performed (Fig. 1) after pre-procedure alpha blockade with doxazosin. The procedure was uncomplicated except for a brief (45 seconds) period of hypertension with systolic blood pressure reaching 200 mmHg.

After bilateral adrenal gland MWA, the patient had an immediate decrease in serum cortisol levels (Fig. 2). On MWA post-op day 5, the patient was started empirically on hydrocortisone and fludrocortisone due to symptoms of adrenal insufficiency with nausea and hypotension. These were tapered off as an outpatient over the course of 4 months given an 0800 AM serum cortisol of 16.4 ug/dl, which was measured off hydrocortisone for 24 hours. Six months after his MWA, he was hospitalized for septic shock due to pneumonia, and was found to have a low 0800 AM serum cortisol of 4.6 ug/dl (Table 1), with a low sodium of 131 mmol/L (136-144 mmol/L) and a high potassium of 5.1 mmol/L (3.3-5.0 mmol/L). He was treated with stress dose steroids, and then restarted on hydrocortisone and fludrocortisone for primary adrenal insufficiency. He had 2 repeat 8 AM cortisol concentrations off hydrocortisone which were both consistent with adrenal insufficiency (Table 1).

At his 1- and 2-year follow-up post-MWA of his adrenal glands, he was improving clinically. He had 13 kg weight loss with improvements in both his blood pressure and glycemic control. He continues on hydrocortisone and fludrocortisone replacement.

Discussion

Here, we present a complicated case of ectopic CS whose hypercortisolism was successfully cured with bilateral adrenal MWA. Surgery is the primary treatment modality for CS. In ectopic CS, however, the source can be elusive [3]. In our case, inferior petrosal sinus sampling suggested a pituitary source. Despite anterior hypophysectomy, our patient's hypercortisolism persisted. Given his overall comorbidities, prompt treatment of his hypercortisolism was of utmost importance. Unfortunately, the risks associated with both medical therapy and open bilateral adrenalectomy were too risky. Bilateral adrenal gland MWA was therefore the best and least invasive option to effectively treat his hypercortisolism.

Medical treatment of CS consists of osilodrostat, mitotane, mifepristone, ketoconazole, and/or metyrapone. All options are associated with significant side effects and have many drug interactions [5]. In our case, concomitant use of ketoconazole and apixaban can result in elevated levels of apixaban predisposing to bleeding. Our patient's cardiac and thrombosis comorbidities made the use of other medical options too risky. In addition, metyrapone was not easily accessible and

Table 3 – Published case reports on utilization of bilateral adrenal ablation to treat hypercortisolism.

Age (yrs) sex	Etiology	Year and origin[a]	Prior treatment	Type of ablation	Response to bilateral adrenal ablation
25 Male	CD	2020, Poland	TSS (x3)	Radiofrequency ablation	Serum cortisol decreased from 1087 to 140.7. Required hydrocortisone. Developed AI postoperatively. Body weight reduction, blood pressure normalization, bone mineral density improvement at 18-24 months [12].
48 Female	CD	2020, Poland	TSS (x1), Cyber Knife	Radiofrequency ablation	Serum cortisol decreased from 1001.4 to 267.6. Body weight reduction, improved glycemic control, blood pressure normalization at 18-24 months [12].
43 Female	CD	2020, Poland	TSS (x2), Gamma Knife	Radiofrequency ablation	Serum cortisol decreased from 794.5 to 206.9. Body weight reduction, blood pressure normalization, improved glycemic control, bone mineral density improvement at 18-24 months [12].
35 Female	CD	2020, Poland	TSS (x1)	Radiofrequency ablation	Serum cortisol decrease from 880 to 129.7. Required hydrocortisone. Developed AI postoperatively. Body weight reduction at 18-24 months [12].
38 Female	CD	2016, Brazil	TSS (x1), radiotherapy	Percutaneous ethanol ablation	Failed to respond and required continued medical treatment [11].
70 Male	Ectopic ACTH, pancreatic NET	2020, Poland	Liver surgery and PRRT	Radiofrequency ablation	Serum cortisol decreased from 1727 to 441. Improved glycemic control, normal blood pressure, normal potassium levels at 18-24 months [12].
63 Female	Ectopic ACTH, Occult	2017, Canada	None	Microwave ablation	Serum cortisol decreased from 3322 to 333.8. Improvement in weight, normal potassium levels. Underwent laparoscopic adrenalectomy at 6 months after MWA [13].
66 Female	Ectopic ACTH, Metastatic medullary thyroid cancer	2015, USA	Thyroid surgery and chemotherapy.	Microwave ablation	Serum cortisol decreased from 2759 to 44.1. Required hydrocortisone. Developed AI postoperatively. Weakness improved, but patient died from complication of metastatic cancer 8 weeks after procedure [14].
73 Female	Ectopic ACTH, Occult.	2015, USA	Bilateral partial adrenalectomy.	Microwave ablation	Serum cortisol decrease from 1269 to 52.4. Required hydrocortisone. Developed AI postoperatively. Lost to follow-up [14].
66 Male	Ectopic ACTH, Occult	2015, Australia	Percutaneous ethanol ablation (x1)	Retrograde venous ethanol ablation	Serum cortisol decreased from 1479 to 150.1. Required hydrocortisone. Developed AI within 12 months. Clinically improved at 12 months [15].

CD, Cushing's disease; TSS, trans-sphenoidal pituitary surgery; PRRT, peptide receptor radionuclide therapy; MWA, microwave ablation; AI, adrenal insufficiency.
Cortisol reported as nmol/L.
[a] Year article was published and country of authors.

rapidity to improve hypercortisolism was critical. Ventilation was to be avoided, thus etomidate was not chosen. Etomidate is also a bridge therapy and unable to be used long term. In one cohort with 76 patients with ectopic CS, only 13% (n = 7) treated with medical therapy had normalization of cortisol [6]. On the other hand, all who underwent surgical bilateral adrenalectomy had biochemical cure [6].

Bilateral adrenalectomy is recommended when medical therapy is contraindicated or if hypercortisolism is severe and surgical resection of the source is unattainable [4,5]. Adrenal gland ablation is a less invasive approach for patients who may not be good candidates for surgery or medical therapy, or have failed conventional therapy or other treatment modalities. Thermal ablation, including cryoablation, radiofrequency ablation (RFA) and MWA, is primarily utilized to treat focal oncologic lesions. MWA uses electromagnetic energy in the microwave range to agitate water molecules resulting in frictional heat and cellular death via necrosis, whereas RFA uses electrical current produced by a radiowaves [7,8]. The primary use of thermal ablation of the adrenal glands is in the treatment of primary or metastatic adrenal neoplasms. There are several successful case studies treating functional unilateral

adrenal neoplasms with thermal ablation [9]. In one report, there was a 100% response rate with unilateral RFA to treat 13 functional adrenal tumors (primary hyperaldosteronism, n = 10; pheochromocytoma, n = 1; cortisol-secreting tumors, n = 1; testosterone-secreting tumor, n = 1) [9]. In a slightly smaller case series (n = 11), there was a 91% resolution when unilateral RFA was used to treat functional adrenal tumors (primary hyperaldosteronism, n = 9 and cortisol-secreting tumor, n = 2) [10].

While there are several studies reporting unilateral adrenal gland ablation, there are scattered case reports of bilateral adrenal gland ablation. A review of the literature was only able to identify 4 cases reported in the literature of patients who have undergone a bilateral adrenal MWA for ACTH dependent hypercortisolism, 5 cases utilizing RFA, and 2 cases treated with alcohol ablation (Table 3). As in our case, nearly all patients had already failed conventional therapy prior to undergoing bilateral adrenal ablation. Most patients had a good response after the procedure with only 1 patient out of 11 who had undergone bilateral alcohol ablation failing to show significant decrease in cortisol levels and required medical treatment afterward [11]. One patient who underwent MWA responded to therapy, but then underwent surgical bilateral adrenalectomy after improving clinically [4]. All the patients who underwent either bilateral MWA or RFA had a decrease in cortisol levels. Of those undergoing MWA/RFA, all patients had good clinical outcomes with weight loss, improved blood pressure and glycemic control, resolution of electrolytes abnormalities and increased bone mineral density. Half of the patients who underwent bilateral adrenal gland ablation developed adrenal insufficiency requiring steroid replacement, suggesting significant destruction of the adrenal gland tissue. The time to adrenal insufficiency, however, was variable. Either adrenal insufficiency occurred immediately after surgery or the timing was difficult to deduce because patients were started on hydrocortisone preemptively. In our case, the time to develop adrenal insufficiency took several months after bilateral adrenal gland MWA. Larger studies are needed to determine the range of time for patients to developed adrenal insufficiency after bilateral adrenal ablation.

Conclusion

Bilateral adrenal gland MWA effectively cured hypercortisolism in our patient with ectopic CS. Despite our patient's medical complexities, bilateral adrenal gland MWA induced a clinical cure without the increased risks associated with bilateral adrenalectomy and complexities of medical management in high-risk patients. Bilateral adrenal MWA should be considered as an effective treatment modalities for CS.

Patient consent

A written, informed consent from the patient was obtained to publish the patient's case in this journal.

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