MON-0439: Case Presentation: Improved Activities of Daily Living, Normal Mood and Quality of Life: 4 years of Treatment Data in a Pre-menopausal woman with Cushing's Disease

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BACKGROUND

Endogenous Cushing's Syndrome (CS) is a complex endocrine disorder caused by prolonged exposure to elevated cortisol (hypercortisolism) leading to serious multisystem manifestations. Patients with CS may exhibit truncal obesity, diabetes mellitus, hypertension, early onset of osteoporosis, gonadal dysfunction, and neuropsychiatric and neurocognitive disorders. Physical manifestations may include round, swollen or flushed face (moon facies), bruising, impaired healing, striae, muscle pain and weakness, excess body hair, menstrual irregularities, dorsocervical fat pad (buffalo hump) and lack of libido. The therapeutic goal of normalizing cortisol levels is difficult for patients with CS. Transsphenoidal pituitary surgery is initially successful in 65–90% of patients with Cushing's disease (CD) with 11%–34% of patients experiencing persistent hypercortisolism or recurrence postoperatively. In circumstances when surgery is unsuccessful, or contraindicated or when rapid treatment of hypercortisolemia is required, medical treatment is needed to treat the effects of excess cortisol while ameliorating the metabolic dysfunction associated with CS.

Medical History

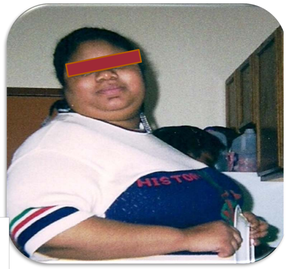
- 40 year old female diagnosed with Cushing's Disease
- Transsphenoidal surgery
- Gamma knife irradiation
- Past failed trials of Cabergoline and Ketoconazole
- Obesity, BMI : 43.8
- type 2 diabetes
- Hyperlipidemia
- Hypothyroidism
- Hypertension
- acanthosis nigricans
- polycystic ovaries
- Anovulation and amenorrhea
- Muscle weakness
- Depression
- Anxiety
- Impaired quality of life

Case Discussion

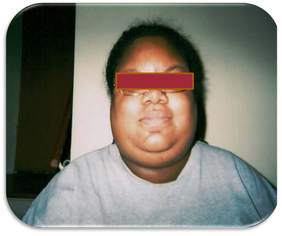
This case highlights 5 years of Mifepristone (MIFE) therapy in a premenopausal female (PT) who was unable to work or care for her family due to uncontrolled CD.

- 5 Year history of depression, fatigue and inability to manage activities of daily living
- PT underwent transsphenoidal surgery followed by gamma knife irradiation a year later due to persistent tumor on MRI , CS remained uncontrolled
- Participated in SEISMIC, a 24-week open label Mifepristone (MIFE) study. MIFE is a selective glucocorticoid receptor (GR) antagonist with no clinical effect on the mineralocorticoid receptor (MR)
- MIFE dose started at 300mg/d and then escalated to 1200mg/d, later reduced to 600mg based on clinical response and tolerability
- Cortisol and ACTH remained elevated as expected with MIFE use
- At Week 24 PT experienced vaginal bleeding with increased endometrium and decreased HCT
- PT referred to Gynecologist, D&C performed but bleeding continued despite stopping therapy for 5 weeks
- Hypertension improved , medication load reduced with normalization of B/P readings. After one year of MIFE therapy, metroprolol SR 50 mg qd was added to control hypertension
- To continue the beneficial effects of MIFE, PT elected to undergo a hysterectomy
- Due to MR activation by excess cortisol, K declined and supplementation was initiated, spironolactone added at Mo 36
- Significant glycemic control was achieved while on MIFE. At baseline, PT required 400 units of insulin daily & Metformin 500 mg bid. By 8 Mo: no diabetic medication: blood sugars, H A1c within normal range
- PT demonstrated substantial weight loss
- PT currently remains stable on 600mg MIFE. Other medications include: Potassium chloride Tab 20 meq bid and Spironolactone 100 mg tid to treat Hypokalemia and Lisinopril 20 mg bid & metroprolol SR 50 mg qd for hypertension.

Relevant data across time



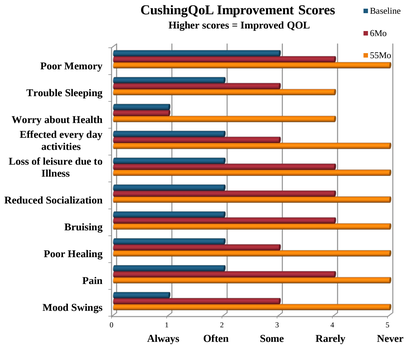
Pre Treatment
Wt: 122.9 kg
BMI: 43.8
Waist: 123.0 cm

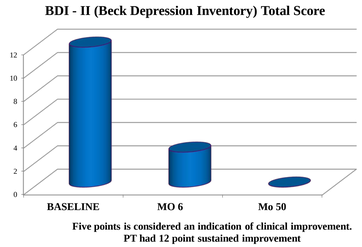


Current
Wt: 106.2 kg
BMI: **38.1**
Waist: 117.8 cm

Visit, (Mo. =month)	Dose MIFE (MG)	H A1c	Blood Pressure (S/D)	Weight (kg)	BMI (kg/m2) Height= 167.5	Waist circum (cm)	Endometrial Thickness (mm)	HCT % (35-46%)	K+ MEQ/L (3.5-5.3)	Event
PRE MIFE	0	8.7	130/80	122.9	43.8	123	3	37.8	4	
MO 6 SEISMIC	600	5.9	106/64	110.7	39.5	113.2	55	34.9	3.9	
Wash out 6 weeks	0	6.7	129/87	108.7	38.7	115	33	35	4.2	
Mo 9	600		130/80	107	38.1			35.4	3.5	Mirena IUD, D&C
Mo 16	600	6.6	118/84	111.4	39.7		HYST	29.9	3.5	Hysterectomy left sal-ooph
Mo 24	600	5.8	138/84	108.4	38.6		"NA/ Rt overy only	36.8	3.3	K+ oral start
Mo 30	600	5.2	130/80	103.4	36.9		"		3.3	D/C hyperglycemic drugs
Mo 36	0/ 600		152/80	98.7	35.2		"	38.6	2.6	FDA approval Korlym K+ oral increase , Spironolactone added
Mo 55	600	5	146/92	106.2	38.1	117.8	"		2.9	Continues on B/P meds, Oral K+, Spironolactone

Quality of Life





PT went from mild depression and anxiety to normal mood. QOL was assessed at various times during the MIFE treatment period using a specific validated Cushing's QOL questionnaire. The lower the score the greater the impact of QOL. PT showed significant improvement across all domain scores with an overall QOL improvement of 2.5 times above baseline

Conclusion

- While taking MIFE, a PR modulator, endometrial changes may occur which may require gynecologic evaluation
- Hypokalemia and HTN may need monitoring and intervention due to mineralocorticoid receptor activation
- CD induced diabetes may improve during long term MIFE treatments: 400 units of insulin daily now managed by diet and exercise, no medication
- Significant improvements in glucose tolerance: -3.7% H A1c, Weight: -16 Kg; BMI; -5.7 kg/m2, waist circumference -10cm
- Beck Depression Inventory (BDI – II) improved from mild levels of depression and anxiety to normal mood. CushingQoL scores increased 2.5 times from baseline with improvement in all measured areas of QoL
- PT returned to a normal, active life with capability to care for her family and maintain a full time job

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