A THIN 50-YEAR-OLD WOMAN WITH AN ADRENAL INCIDENTALOMA AND OSTEOPOROSIS

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History of Presenting Illness

- 50-year-old female with a history of Hashimoto's thyroiditis with hypothyroidism, primary ovarian insufficiency, and osteoporosis
- Referred for a second opinion of elevated cortisol
- Cortisol assessed as part of work up for a stable 3.4 x1.8 cm adrenal mass which was discovered on abdominal CT for appendicitis 3 years prior

History of Presenting Illness

- Her main complaint is poor sleep
- Often awakens with palpitations and headaches
- Thin (BMI 20) and has not gained any weight recently but does feel her face may look rounder in photos
- Recent muscle cramps related to pilates; no muscle weakness
- Denies acne or hirsutism but may have some scalp hair loss
- Denies alcohol abuse or illicit drug use

Past Medical and Surgical History

- Hashimoto's thyroiditis
  - On Nature Thyroid
- Primary Ovarian Failure
  - Regular menstrual cycles until age 40 when menses ceased
  - First pregnancy at age 37; able to achieve pregnancy on her own
  - Second pregnancy at age 40 was a result of egg donation after 3 failed IUI attempts
  - AMH was 0.02
  - FSH 82.2 at age 49
  - She has not been on estrogen replacement
- Osteoporosis
  - Diagnosed at age 48 (April 2017)
  - Lumbar spine T-score -3.6, Femoral neck T-score -3.7, Hip T-score -2.7
  - Was on forteo with only mild improvement in vertebral BMD so was switched to tymlos but insurance would not cover
  - Had lumbar fusion December 2017
  - Not currently on any osteoporosis agents
  - Work up also revealed hypercalciuria and she is on HCTZ

Medication

- Nature thyroid 32.5 mg
- Probiotics
- Cholecalciferol 10,000 international units daily
- Calcium citrate 500 mg daily
- HCTZ 12.5 mg
- Rhodiola
- Nutrafol
- Licorice root powder
- Vitamin B complex
- Ashwagandha
- Montelukast
- Flonase

Family and Social History

Family History

- Mom
  - Breast Cancer
- Paternal Grandmother
  - Breast Cancer
- Sister
  - Hashimoto’s
- Nieces
  - Hashimoto’s

Social History

- Lives with husband and two daughters
- One of her children has autism
- She drinks alcohol one to two times per month

Physical Exam

- Vitals
  - 108/71 mmHg
  - 66 bpm
  - 55.9 kg
  - 165.1 cm
  - 20.4 kg/m^2
- General
  - Thin lady
  - Normal, non-rounded facies without plethora
- CVS: S1+S2, RRR
- Resp: CTA
- GI:
  - No striae
  - No central adiposity
- MSK:
  - No dorsocervical fat pad
  - No atrophy/thinning of upper or lower extremities
  - No edema
- Skin
  - No bruising
  - No acne
  - No hirsutism or androgenic alopecia

Imaging from Initial Work Up

- June 2017: Adrenal MRI
  - The right adrenal mass is retrospectively stable in size measuring 3.4 x 1.8 cm. The
    mass demonstrates loss of signal on the out of phase images relative to the in phase images compatible with an adrenal adenoma. A small left adrenal adenoma measuring 7 mm is stable.

What next?

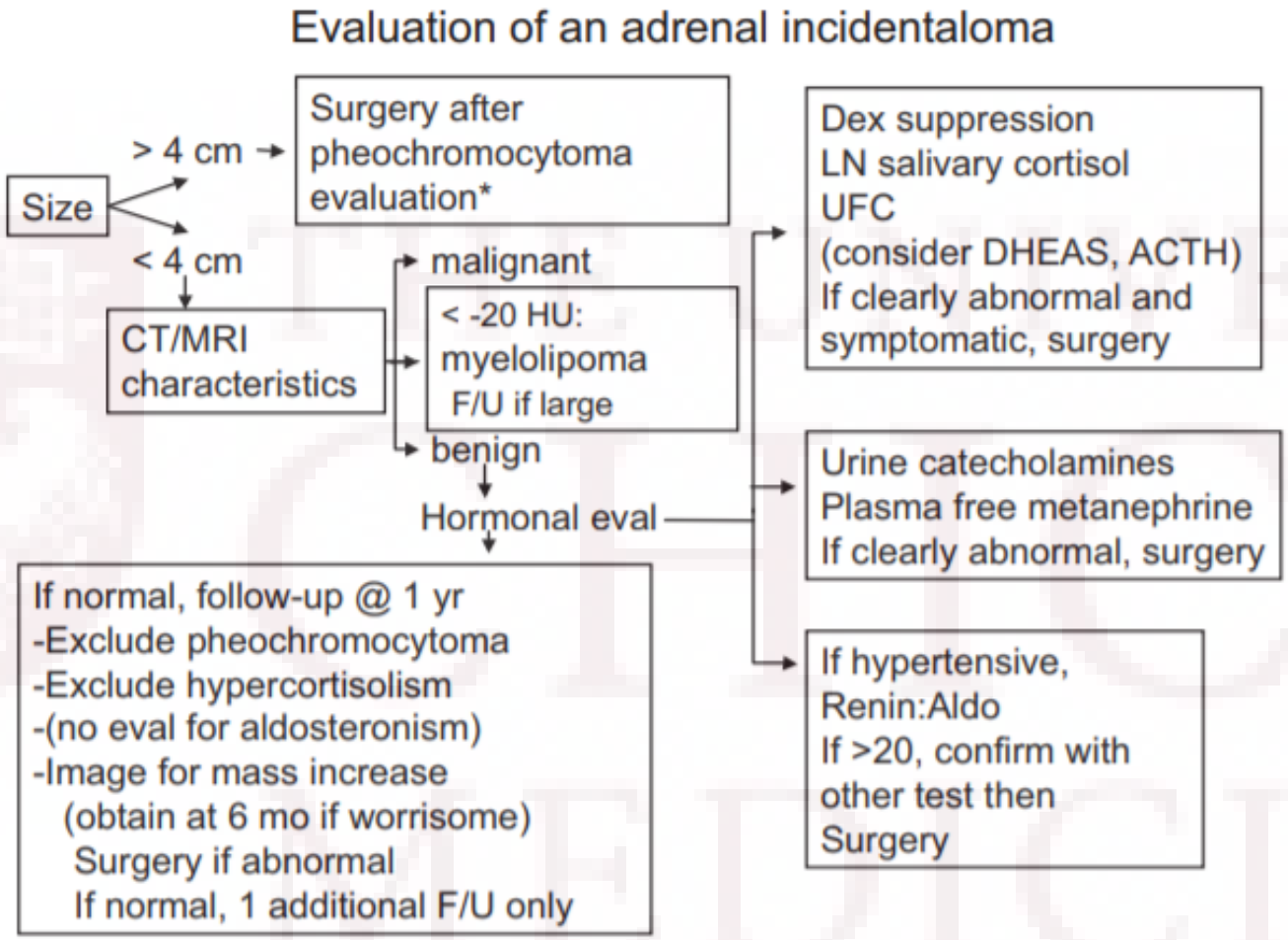

FIG. 1. Suggested evaluation of an incidentally found adrenal mass. *, Surgery for large masses without a cause that requires resection, *e.g.* tuberculosis. LN, Late-night; Aldo, aldosterone; Dex, dexamethasone; F/U, follow-up; eval, evaluation; mo, months.

Nieman LK *et al.* JCEM 2010

Labs from Initial Work Up (November 2018)

- Glucose 212
- HbA1c 5.5%
- BUN 11
- Creatinine 0.65
- Na 139
- K 4
- Cl 103
- CO2 27
- Calcium 9.5
- 25-OH vit D 43
- TSH 0.945

- Plasma metanephrines
  - Metanephrine: 50 (≤ 57 pg/mL)
  - Normetaneperhine 129 (≤148 pg/mL)
  - Total metaneperhine 179 (≤205 pg/mL)

- Midnight Salivary Cortisol x2
  - 0.16 (normal ≤ 0.09 mcg/dl)
  - 0.19

- 1 mg Dexamethasone Suppression Test
  - ACTH 19 pg/mL
  - Cortisol 13.1 mcg/dL

Possible Interpretation

- Evidence for hypercortisolemia on labs but ? no features consistent with Cushing's syndrome
- If adrenal source of hypercortisolemia would expect a suppressed ACTH level
- Biotin supplements can increase cortisol levels and patient is on biotin from nutrafol hair supplements

Further work up

- Biotin held for 2 weeks
- 1 mg dexamethasone suppression test repeated
- ACTH 20 pg/mL
- Cortisol 9.8 mcg/dL
- Dexamethasone level 109 ng/dL (normal after overnight suppression test 180-950 ng/dL)

Pituitary MRI

- No pituitary lesions or enlargement

Further Thoughts

- Low dexamethasone level suggest that she may be a somewhat fast metabolizer but clearly took medication and despite that her ACTH and cortisol levels are higher than expected given dexamethasone level
- Depression screening negative but high levels of stress and very poor sleep so does she have pseudo-Cushing's?
- Does she have glucocorticoid resistance?

Findling, J *et al.* *European Journal of Endocrinology* 2017. *176*(5), R205-R216

Non-neoplastic-physiologic hypercortisolism (formerly known as pseudo-Cushing's syndrome)

- Phenotype similar to neoplastic hypercortisolism
  - Alcoholism and alcohol withdrawal
  - Chronic kidney disease
  - Depression/neuropsychiatric disease
  - Glucocorticoid resistance
  - Uncontrolled diabetes mellitus
- Phenotype not similar to neoplastic hypercortisolism
  - Starvation/malnutrition—anorexia nervosa
  - Pregnancy
  - Chronic intense exercise

Diagnosing Pseudo-Cushing's

- Dexamethasone-suppressed CRH test
  - 0.5 mg of dexamethasone q6 hr x2 day
  - 2-hr after last dexamethasone dose 1 mcg/kg CRH given
  - Serum ACTH and cortisol measured −15, −5, 0, 15, 30, 45, 60, 90, and 120 minutes
  - Cortisol >1.4 mcg/dL likely true Cushing's
- Vasopressin stimulation test
  - Corticotroph adenomas express specific vasopressin receptors
  - Desmopressin acetate administration can stimulate ACTH secretion in patients with Cushing's disease but will have minimal effect in those who have pseudo-Cushing's
  - ACTH and cortisol levels measured before and +15, + 30 and +60-min after 10 mcg IV DDAVP given
  - ACTH >6 pmol/L likely true Cushing's

Diagnosing Pseudo-Cushing's

- Comparing the tests
- Giraldi *et al. Clinical Endocrinology.* 2007
- N=32 patients with Cushing's syndrome and 23 with pseudo-Cushing's syndrome, all patients has mild hypercortisolism of UFC of <690 nmol/24 hr
- 1 and 2 mg dexamethasone suppression test failed to identify those with pseudo-cushing's
- Dexamethasone-CRH suppression tests classified pseudo-Cushing's with 100% sensitivity but only 81.5% specificity (84% diagnostic accuracy)
- The desmopressin stimulation test classified all but two patient's with pseudo-cushing's (81.5% sensitive, 90% specific, 85% diagnostic accuracy)

Glucocorticoid Resistance

- Familial receptor-mediated disorder
- Increased androgen and cortisol production in otherwise healthy, usually thin adults
- Patients do not usually have typical Cushing's features
- Tend to present more with mineralocorticoid excess
- Features of androgen excess and fertility issues
- In one case study, half of patients complained of fatigue (n=5, Charmandari *et al*. *JCEM.* 2004)
- Generally slightly increased to high normal ACTH and elevated cortisol levels
  - In one study, almost half had normal ACTH (Vitellius *et al.* Euro J Endrinol. 2020)
  - More severe cases ACTH may be in 1000s (McMahon SK *et al.* JCEM 2010)
- Treatment
  - Dexamethasone at midnight to suppress ACTH activation of mineralocorticoid and androgen production
  - Titrate to normalize androgens, blood pressure and potassium

Back to Our Patient: Testing

- DHEA-S 11.4 mcg/dL (normal 34.5-256)
- Total testosterone <7 pg/mL (normal <60)
- Free testosterone <1 pg/mL (normal <9)
- Testosterone binding globulin 162
- CBG (9:15 AM): 3.0 mg/dl (normal 1.7-3.1)
- Serum free cortisol: 1.2 mcg/dl (normal 0.1-1.8)
- % free cortisol: 7% (normal 2.3-9.5%)
- Serum cortisol 17 mcg/dL (normal 8 AM 8-19
  4 PM 4-11)

Cushing’s Syndrome Suspected

- Hypercortisolemia by overnight dex suppression test and late evening salivary cortisol
- No risk factors for pseudo Cushing and presentation and data not consistent with glucocorticoid resistance
- Severe osteoporosis not responsive to anabolic agents is consistent with catabolic form of Cushing’s syndrome
- Evidence for glucose intolerance based on intermittently elevated glucose despite normal body weight and normal A1c also suggestive of Cushing’s sydrome
- Low DHEA-S, adrenal mass and normal pituitary MRI supports adrenal source of cortisol excess despite frequent elevated ACTH

Osteoporosis and Cushing's Syndrome

- 31.6% of women with Cushing's present with OP and 46.8% of men ($p<0.05$) (Giraldi FP *et al. Clinical Endocrinol.* 2003)
- The prevalence of subclinical hypercortisolism among patients with low BMD and fractures was 10.8%
- The prevalence of subclinical hypercortisolism in patients with osteoporosis (those with vertebral fractures and/or T-score of 2.5 or less) was 4.8%. (Chiodini *et al. Annals Int Med.* 2007)

Osteoporosis and Cushing's Syndrome

Table 2. **Odds Ratios for Osteoporosis and Vertebral Fracture***

Risk Factor	Odds Ratio for Osteoporosis (95% CI)*†	*P* Value	Odds Ratio for Vertebral Fracture (95% CI)‡	*P* Value
Cortisol level after 1-mg overnight dexamethasone suppression test (per 1-μg/dL increase)	3.37 (1.78–6.43)	<0.001	1.70 (1.04–2.79)	0.035
Age (per 1-year increase)	1.06 (1.02–1.10)	<0.001	1.06 (1.02–1.10)	0.002
Sex (male vs. female)	2.52 (0.74–8.48)	0.138	3.40 (1.18–9.71)	0.023
BMI (per 1-kg/m^2 increase)	0.945 (0.88–1.02)	0.121	1.02 (0.95–1.11)	0.614
BMD at spine (L1 to L4) (per 1-unit decrease in T-score)	–	–	1.79 (2.40–1.34)	0.001

* Osteoporosis was defined as T-score of −2.5 or less and/or vertebral fractures. BMD = bone mineral density; BMI = body mass index.
† Hosmer–Lemeshow goodness of fit $P = 0.67$, and c-statistic = 0.74.
‡ Hosmer–Lemeshow goodness of fit $P = 0.75$, and c-statistic = 0.76.

Chiodini *et al. Annals Int Med.* 2007

Immulite-Assay

- Two site “sandwich” technique
- Selected antibodies that bind to N-terminal and C-terminal epitopes of ACTH
- Two case series published of spuriously high ACTH levels
  - Greene LW *et al.* 2019: N=5
  - Donegan DM *et al.* 2019: N=12
- In many cases, elevated ACTH lead to further unnecessary invasive testing and in one case pituitary surgery
- Other potential factors for spurious elevation of ACTH were interference with heterophile antibodies, human anti-animals antibodies, rheumatoid factor/autoantibodies and pro-opiomelanocortin and ACTH fragments

Immulite-Assay

Greene *et al. JES.* 2019.

Case	Reason for Referral	Initial Adrenal Testing	ACTH(Immulite)	Imaging	Additional Testing and Procedures	Initial Diagnosis	ACTH (2nd Method)	Final Diagnosis
1	Weight gain Hypertension Fatigue Anxiety Bruising Irregular menses Infertility	Normal AM cortisol, elevated LNSC and UFC, positive LDDST Elevated ACTH(Immulite) after LDDST and HDDST	Elevated (122–203 pg/mL)	Normal pituitary MRI ×2 3rd MRI positive	IPSS ACTH(Immulite) positive (Table 2) Pituitary surgery (neoplasm ACTH staining negative)	Cushing disease	ACTH(Cobas) normal (16–38 pg/mL)	No Cushing syndrome
2	Striae Weight gain Moon facies Gestational diabetes	Elevated UFC, LNSC, LDDST	Normal (40 pg/mL) and elevated (62 pg/mL)	Pituitary MRI, 5-mm microadenoma Abdominal MRI, adrenal nodule DOTATE negative ×2	JVS ACTH(Immulite) no gradient IPSS ACTH(Immulite) no gradient Adrenal vein sampling Left adrenal vein cortisol > right Serum DHEAS low	Occult ectopic ACTH-dependent Cushing syndrome	ACTH(AIA) decreased (2–5 pg/mL)	Adrenal (ACTH-independent) Cushing syndrome
3	Fatigue Muscle weakness Hypertension Prediabetes Osteoporosis Renal calculi	Normal/elevated UFC Elevated LNSC Positive LDDST	Elevated (78–143 pg/mL)	Right adrenal nodule Pituitary MRI 1–2-mm lesion MIBG uptake in adrenal nodule DOTATATE normal	JVS ACTH(Immulite) elevated but no gradient IPSS ACTH(AIA) low and no gradient	Occult ectopic ACTH-dependent Cushing syndrome	ACTH(AIA) decreased (2–4 pg/mL)	Adrenal (ACTH-independent) Cushing syndrome
4	Weight gain Facial rounding Hirsutism Striae Supraclavicular fullness	Elevated UFC, LNSC Positive LDDST	Normal (17–21 pg/mL)	Possible 3-mm pituitary lesion Right adrenal mass (HU 40)		Cushing disease	ACTH(Cobas) decreased (1 pg/mL)	Adrenal (ACTH-independent) Cushing syndrome
5	EtOH abuse Cirrhosis Bruising Muscle atrophy Edema	Normal UFC Elevated LNSC Positive LDDST	Elevated (367–1031 pg/mL)	Pituitary MRI normal		Ectopic ACTH syndrome	ACTH(Cobas) decreased (7 pg/mL) ACTH(AIA) normal (14 pg/mL)	Ethanol-induced hypercortisolism

To convert ACTH to pmol/L, multiply by 0.2202.

Abbreviations: EtOH, ethanol; HDDST, high-dose DST suppression test; HU, Hounsfield units; IPSS, inferior petrosal sinus sampling; JVS, jugular venous sampling; LDDST, low-dose DST suppression test; MIBG, metaiodobenzylguanidine; UFC, urine free cortisol.

Immulite-Assay

Laboratory assessment performed in those patients with ACTH assay interference.

	Siemens ACTH (Reference range, 10–60 pg/mL)				HBT (pg/mL)	Roche ACTH (Reference range, 7.2–63.3 pg/mL)
Patient	Original ACTH	Repeat ACTH	X 2 dilution	X 4 dilution		
1	56	34.8	50.8	100.4	27.5	< 1
2	19	13.7	25.6	42.4	20.3	1.76
3	142	145	51*	82*	NP	20
4	98.5	NP	550	730	292	1.9
5	14	15	24.6	66.4	7.2	< 1
6	21	22	30	56	154	1.3
7	137	127	97.2	72.4	NP	48.44
8	95	93	77.6	160	NP	24
9	138	98	290	632	NP	8.9
10	261	NP	NP	238	930 (1.89 Cobas)	1.74
11	60	49	80	88	67	22
12	77	70	140	172	98	5.6

Abbreviations used: ACTH, corticotropin; HBT, heterophile blocking tube, NP, not performed.

* Dilution performed was 5- and 10-fold.

Donegan DM *et al. Clinical Biochemistry.* 2019

Back to Our Patient

- ACTH repeated using Roche assay at UCM and was 1.6
- Her HbA1c prior to surgery was 5.8%
- Patient underwent right adrenalectomy 10/2019
  - Pathology revealed adrenal cortical adenomas (3.5 and 1.0 cm), entirely excised
  - The sections show two nodules adjacent to each other raising possibility of adrenal nodular hyperplasia. Both nodules show extensive areas of cells with eosinophilic cytoplasm
- She received stress dosing prior to surgery and then was placed on maintenance hydrocortisone
- Postoperatively reported dramatic improvement in insomnia
- Labs
  - Glucose 72
  - Na 144
  - K 144
  - A1c 5.8%
  - ACTH 4.9
- Advised repeat DEXA scan in 18 months
- Re-assess HPA axis in several months
- Lost to follow up

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