65 Year Old Female with adrenal insufficiency due to ipilimumab

Endorama 2/13/2014
Milad Abusag, MD

HPI

- 65 year old F with PMH of hypothyroidism, Migraine, metastatic Melanoma
- Melanoma Dx 7/2003 in Rt forearm (s/p surgical resection), recurrent 5/2011 >> SQ nodules in back (resected) >>> few months later >>> supraclavicular LN, both legs nodules, new back nodules.
- Treated with ipilimumab for 1 year.
- Last dose of ipilimumab was 8/2012
- Doing well until 8/2013
- Wt loss (30 pounds)
- Generalized fatigue, decrease energy
- No headache, no hyperpigmentation
- Found to have 8 am cortisol 0.8

PMH:

- ✓Metastatic melanoma
- ✓Hypothyroidism
- ✓Migraine

Family History:

- ✓Father NHL
- ✓DM (mother).

Surgical history:

- ✓Surgical resection for melanoma

Social history

- ✓Never smoke, no alcohol, no illicit drugs.

Home medications

- ✓**Prednisone 3.25 mg am, 2.5 mg PM**
- ✓**Ibuprofen 200 mg po Q 8hrs PRN**
- ✓**Synthroid 150 mcg daily.**
- ✓**Omeprazole 20 mg daily**
- ✓**Miralax PRN**
- ✓**Imitrex PRN for headache**

ROS

Constitutional: Fatigue, generalized weakness, and Wt loss

HENT: No blurred vision, no VF defect, No sore throat, no headache

Neck: No neck swelling or tenderness

Cardio/pulm: No CP, no palpitation, no orthopnea or PND

GI: No N/V/D, no constipation, no melena or hematochezia

GU: Negative

Skin/MSK: no hyperpigmentation, + multiple cutaneous nodules

Neuro: no numbness, no tingling, asymmetrical weakness.

On examination

Vitals: BP 107/78 | Pulse 78, no fever, RR 14. wt 48.5 kg, BMI 19.5

General: awake alert, setting comfortable on exam table

HEENT: normocephalic non traumatic, no pallor, no jaundice. Normal VF confrontation test.

Neck: supple, no LN enlargement, no thyromegaly

CVS/Pulm: clear equal air entry no added sounds, S1 + S2, no murmur.

Abd: soft lax, no organomegaly, no tenderness, audible bowel sounds.

Skin: warm, multiple cutaneous nodules on torso and extremities, no hyperpigmentation , no vitiligo

Neuro: CN intact, sensation normal, DTR normal.

Psych: normal mood, and affect

General labs

Test	Result (12/2013)
CBC	Normal
Glucose	97
Na	142
K	3.5
Carbon Dioxide	26
Anion gap	11
BUN	16
Cr	0.7
GFR (Calc)	>90
Ca	8.7
Albumin	4.1
ALT	16
AST	18
ALP	50

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Endocrine workup

Test/date	11/2013 (outside)	12/2013
TSH (0.4 – 4.5 mcu/ml)	8.18	3.0
FT4 (0.8 – 1.8 ng/dl)	1.6	1.88
FSH (23-116 miu/ml)	65	
LH mIU/ml)	34	
GH (ng/ml)	0.1	
PRL (4.8 – 23.3 ng/ml)	14.3	
Cortisol (8:55am) mcg/dl	0.8	0.6
ACTH	8	7
IGF-1 (41 – 279 ng/ml)	77	
Aldosterone (< 21 ng/dl)	<1.1	6.1
Renin (0.6 – 3.0 ng/ml/hr)		1.4
ACTH stim test	0.8 >> 3.9 (30 min) >>5.4 (60min)	
DHEA-S (8-390)	2 mcg/dl	
Adrenal Ab		- Ve

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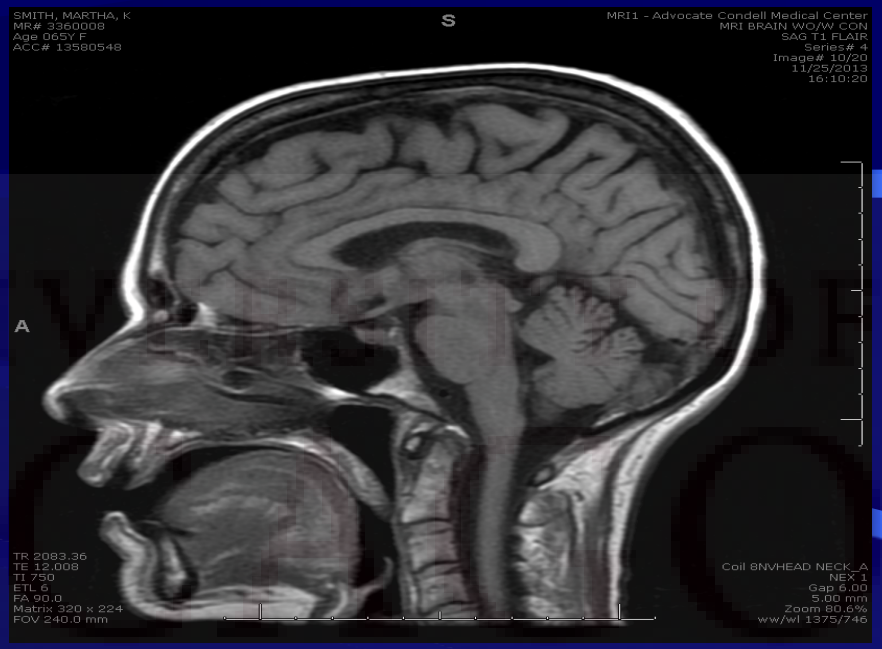
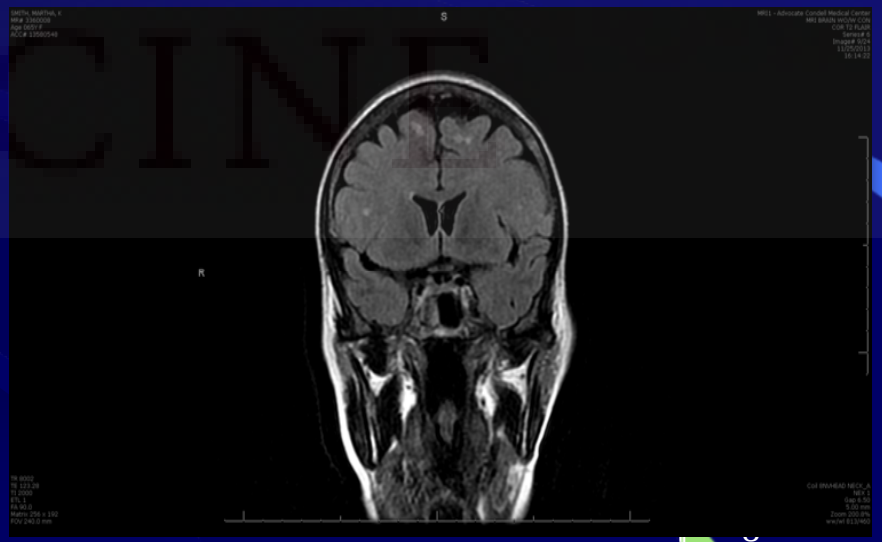
Radiology

CT Abdomen 11/15/2013

normal adrenal glands, no mass

MRI brain 11/25/2013





Clinical Qs

1. What is pathophysiology of ipilimumab induced adrenal insufficiency?
2. What is the incidence of ipilimumab induced adrenal insufficiency ?

Pathophysiology

- Ipilimumab is a fully human monoclonal antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4).
- Approved by the FDA for the treatment of metastatic melanoma and renal cell carcinoma.
- Proliferation of T lymphocytes and secretion of interleukin 2 are attenuated by CTLA-4
- Autoimmune adrenalititis is rare but autoimmune hypophysitis has been reported in up to 17% of patients with melanoma treated with this therapy

Very few case report on ipilimumab induced autoimmune adrenalititis

Ipilimumab-induced autoimmune adrenalitis

Le Min, Nageatte Ibrahim

A 56-year-old woman presented with fatigue and headache after receiving four doses of ipilimumab, a monoclonal antibody against cytotoxic T-lymphocyte antigen 4, for the treatment of metastatic melanoma. Low morning serum concentrations of corticotropin (<1·1 pmol/L [reference range 2·2–13·2 pmol/L]) and cortisol (41·4 nmol/L [reference range 165·5–662·2 nmol/L]), combined with pituitary enlargement, were consistent with hypophysitis-related secondary adrenal insufficiency. Treatment with a replacement dose of hydrocortisone was initiated. Before ipilimumab treatment, her adrenal glands (circled) were normal in size (figure A). A subsequent surveillance CT scan of the abdomen showed bilateral enlargement of adrenal glands (figure B). Her serum cortisol and aldosterone concentrations did not respond to cosyntropin stimulation, which indicated primary adrenal insufficiency. 6 weeks later, her adrenal glands normalised in size (figure C). The dynamic size change of the adrenal glands suggests ipilimumab-related autoimmune adrenalitis. Although secondary adrenal insufficiency is a fairly common endocrinopathy related to ipilimumab treatment, the identification of primary adrenal insufficiency that could coexist with secondary adrenal insufficiency is important.

Contributors

LM was the lead clinician in charge of managing this patient's ipilimumab-related endocrinopathies, and NI was the lead clinician in charge of managing this patient's melanoma. Both authors contributed equally to the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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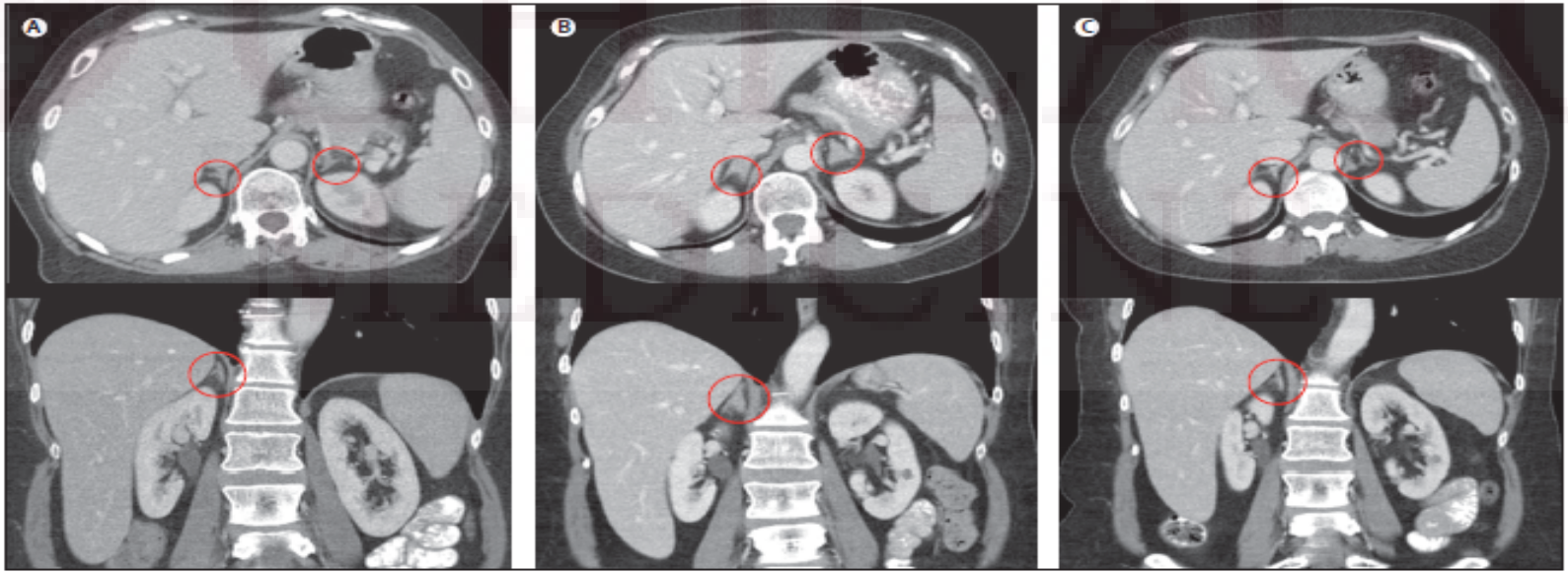


Figure: **CT scans of the abdomen show the change in size of adrenal glands (circled) during treatment**
(A) Before ipilimumab. (B) 16 weeks after ipilimumab initiation. (C) 22 weeks after ipilimumab initiation.

More commonly ipilimumab induced hypo-physitis

Demographic Data and Magnetic Resonance Imaging Results in 7 Patients With Adrenal Insufficiency While Treated With Ipilimumab

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Sex	Male	Male	Male	Male	Female	Male	Male
Age, y	64	44	57	55	70	55	64
Time of presentation (weeks after initiating ipilimumab)	6	12	9	8	12	12	10
Reason for referral	Fatigue and headache	Fatigue, and headache	Headache, and high fever	Low energy, headache, and lightheadedness	Fatigue and headache	Hypotension	Malaise, anorexia, and lethargy
On LT4 before ipilimumab	Yes	Yes	No	No	Yes	Yes	No
Findings on MRI brain	Normal	Normal	Normal	Enlarged pituitary	Enlarged pituitary	Normal	Normal

Ipilimumab and hypophysitis, Endocr Pract. 2012; 18 (No. 3)

More commonly ipilimumab induced hypo-physitis

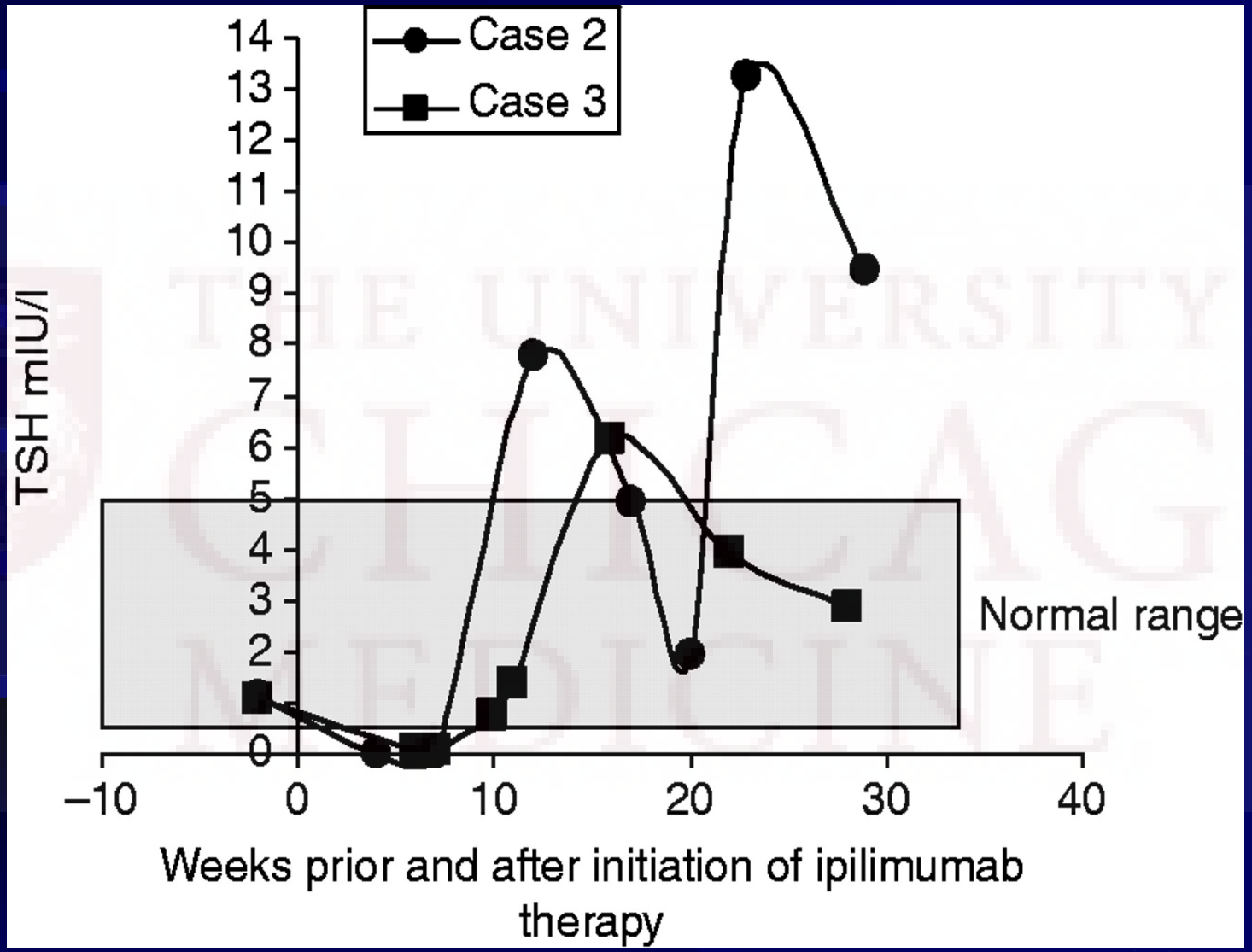
Laboratory Values of 7 Patients Before Ipilimumab Therapy Was Initiated and at Presentation With Secondary Adrenal Insufficiency

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6		Patient 7	
time	Before	AP	Before	AP	Before	AP	Before	AP	Before	AP	Before	AP	Before	AP
ACTH (AM)	…	<10	…	<10	…	<10	…	<10	…	<10	…	<10	…	<10
Cortisol (AM)	…	0.77	…	0.6	…	0.9	…	0.9	…	1.1	…	0.5	…	0.45
TSH	5.2	0.07	1.66	0.086	0.86	0.28	1.6	0.45	…	<0.01	1.3	0.22	1.1	2.4
FT4	1.2	1.5	1.1	0.5	…	0.5	0.8	0.5	…	0.94	…	1.1	…	1.2
T. testosterone	…	3034	3010	710	…	…….	…	……	…	…	…	1449	…	…
LH	…	13.5	…	0.8	…	7.2	…	1.1	…	…	…	3.2	…	…
IGF-1	…	52	…	355	…	77	…	56	…	173	…	…	…	…

- Ipilimumab mainly affect mainly corticotroph and thyrotroph cells

Ipilimumab and hypophysitis, Endocr Pract. 2012; 18 (No. 3)

Common Thyroid abnormality with ipilimumab



Change in TSH in two cases before and after ipilimumab therapy.

Back to my patient

1. Started on Hydrocortisone replacement (15 mg AM and 5 mg pm).
2. Advised for medical alert bracelet
3. Sick days role and stress dose steroid discussed with the patient
4. Planning to do MRI pituitary but she wanted to go on her trip to Paris first

Summary and recommendations

- ✓ life-threatening endocrine disorders (hypopituitarism, adrenal insufficiency, hypogonadism and hypothyroidism) have been reported
- ✓ Hypophysitis reported in up to17%, primary adrenal insufficiency (≤1%), hypothyroidism (around 2-5%)
- ✓ The median onset for endocrine disorders was 11 weeks long-term hormone replacement therapy has been required in many cases
- ✓ Monitor for signs of hypophysitis, adrenal insufficiency and thyroid disorders (eg, abdominal pain, fatigue, headache, hypotension, mental status changes, unusual bowel habits).
- ✓ Monitor TSH, free T_4 and cortisol levels (morning) at baseline, prior to dose, and as clinically indicated.

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Thank you

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02/13/2014