45 year old woman with facial swelling and hypokalemia

Katie Stanley, MD

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HPI

- Developed swelling of face, abdomen, and legs 3 weeks prior to admission
- Had developed depressive symptoms 6 mos prior
- Saw PCP who did CT a/p which showed 7.1 cm mass near pancreas, bilateral adrenal enlargement, retroperitoneal LAD
- Bx done of retroperitoneal LN c/w neuroendocrine tumor
- Became progressively confused, possibly hallucinating after diagnosis

HPI

- Scheduled to see endocrine surgeon
  - Pt drove separately to appt, lost her way, crashed into parked car, admitted
- Found to have potassium 2.4 as well as hyperglycemia which was new
- Seen by endocrine surgeon who stated tumor was inoperable given proximity to aorta
- Random serum cortisol 348, ACTH 348, urine cortisol 13,609
- Medical management vs. bilateral adrenalectomy recommended
- Txf to U of C for second opinion

Other History

- PMH
  - Hypothyroidism
  - Endometriosis
  - Hx ovarian cystectomy
  - Hx tubal ligation
- Home Medications
  - LT4 75 mcg daily, recently decreased from 88 mcg
  - Kdur 40 meq daily
  - Amiloride 5 mg daily
  - Lexapro 5 mg daily
- Family History
  - ALS in mother and other distant relative
  - No cancer or endocrine tumors
- Social History
  - Married with 2 sons
  - Originally from Poland, came to US age 18
  - Difficult childhood
  - Quit smoking 7-10 yrs ago
  - Rare EtOH

Review of Systems

- Constitutional: **Weight loss 20lbs in the last 2-3 weeks.** Poor appetite. +Fatigue. No fevers, chills.
- Eyes: No change in vision.
- ENT: No thirst. +Facial swelling.
- Respiratory: No shortness of breath, cough.
- Cardiovascular: No chest pain, palpitations. +leg swelling.
- Gastrointestinal: No nausea, vomiting, abdominal pain, diarrhea. **+Abdominal distention, constipation.**
- Genitourinary: No dysuria, urinary frequency. **Menopause at the age 42.**
- Musculoskeletal: **No weakness.**
- Skin: **+Acne face, upper chest. Easy bruising.**
- Neurological: No headache. No peripheral neuropathy.
- Psych: **+behavioral problems, +confusion, +agitation.**

Physical Exam

- Wt 55.3 kg; Ht 167 cm; BMI 19.83; T36.4; HR 89; BP 126/89
- Constitutional: Patient appears well-developed, well-nourished, in no acute distress. Face mildly swollen.
- Eyes: Conjunctivae are not injected. Sclerae anicteric. Pupils are equal, round, and reactive to light. Extraocular movements are intact.
- ENT: Mucous membranes moist.
- Neck: Supple. No thyromegaly or nodules palpated.
- Cardiovascular: Regular rhythm and rate. No murmurs appreciated. Intact distal pulses.
- Respiratory/Chest: Normal respiratory effort. No wheezes or crackles.
- Gastrointestinal/Abdomen: Normoactive bowel sounds. Soft, nontender, nondistended.
- Musculoskeletal/extremities: No peripheral edema. 5/5 strength in proximal extremities.
- Neurological: Alert and oriented to person, place, but not date. Normal deep tendon reflexes.
- Skin: Skin is warm and dry. No acanthosis nigrans noted. **+Acne (face, upper chest), hirsutism (upper lip). Multiple petechiae and ecchymoses(arms, abdomen).**
- Psychiatric: Normal mood, behavior, and affect.

Initial Labs

- Na 141, K 4.3, Cl 106, HCO3 27, CUN 21, Cr 0.6, Ca 8.4, Mg 1.9, PO4 2.3, Prot 5.1, Alb 3.3, Bili 1.2, Alk phos 64, AST 11, ALT 24
- WBC 7.6, Hgb 12.0, Plts 137
- INR 1.3
- A1c 6.0
- TSH 0.26, FT4 1.37, T3 40
- 6 am ACTH 199, cortisol 151.2
- Chromogranin A 70

Hospital Course

- Presentation, laboratory findings, imaging findings consistent with ectopic ACTH syndrome from retroperitoneal neuroendocrine tumor
- Initial recommendations: 24 urine free cortisol, surgical evaluation, Bactrim for PCP prophylaxis, plan to start medical therapy after urine collection to bridge to removal of tumor or b/l adrenalectomy

Hospital Course

- 24 hour urine cortisol 3520
- Started on ketoconazole 200 mg bid on HD 4 after urine collection completed
- Heme/onc team started octreotide 200 mcg q8h
- Plan for EUS to better elucidate location of tumor per surgery
- HD 5 Pt became suddenly mute and uncooperative, restricted and nonreactive affect
- CT unremarkable, EEG diffuse slowing
- Psych- presentation c/w retarded catatonia
  - Improved with Ativan

Hospital Course

- Paraneoplastic panel sent
- Waxing and waning mental status
- Paraneoplastic panel, anti-NMDA receptor Ab negative
- Ketoconazole titrated up as cortisol remained significantly elevated
- EUS- resectable, bx c/w well differentiated neuroendocrine tumor
  - Did not stain for ACTH
- Plan for Whipple by surg onc
- Bradycardic to 40s on HD 12->stopped octreotide

Hospital Course

- Surgery on HD 15
  - Resected 3 masses: 6 x 5 cm paracaval, 4 x 3 peri-pancreatic, 3 x 2 cm near duodenum, pancreaticoduodenectomy
- **PATHOLOGY**
- Started stress dose hydrocortisone at beginning of surgery
- Developed hypotension near end of surgery
- Hypotension continued postoperatively, developed lactic acidosis
  - Hydrocortisone 100 mg IV q6
- Postoperative course complicated by coagulopathy, postoperative hemorrhage
  - Return to OR early the following morning

Hospital Course

- Continued to be coagulopathic at first but hemodynamically stable
- Hydrocortisone decreased as clinical status improving
- Catatonia recurred POD #2, POD #3
  - Hydrocortisone 50/25/25 IV q8
  - Mute, stereotyped mouth movements, writing nonsensical characters
- More alert and verbal POD #4
  - HC 30/15/15 IV q8

Hospital Course

- Mental status continues to improve

Date	2/21 3p POD 0	2/21 8p	2/22 4a	2/23 4a	2/24 4a
ACTH	112	100	13	<5	6.9

- 3/2 (POD #9) ACTH 22.4 Cortisol 14.4
- 3/4 (POD #11) ACTH 6.5 Cortisol 72.4

How often do ectopic ACTH producing tumors stain for ACTH?

Analysis of 44 pts who presented with ectopic ACTH syndrome 1969 to 2001 at a British hospital

Tumor size (range, cm)	Localization (no.)	Immunostaining (no.)
0.8–6	Bronchial carcinoid (12)	ACTH (7/12), bombesin (3/12), CgA (2/12), NSE (1/12)
3–4	Thymic carcinoid (2)	ACTH (2/2), LPH (2/2), LHRH-GHRH (1/2)
2.5–3.5	MTC (3)	Negative for ACTH (1/3), bombesin (1/3), calcitonin (2/3)
2–3.5	Small cell colon (2)	ACTH (1/2), serotonin, CgA, NSE (1/2)
3	Pheochromocytoma (1)	
4–7	Pancreatic carcinoid (3)	ACTH (3/3), gastrin (1/3), LPH (1/3), CgA, NSE, MSH, 5HT (1/3)
	Never found (5)	
Multiple	Small cell lung (7)	
1	Mesothelioma (1)	
	Disseminated (2)	
1–2	Lymph node NET (2)	ACTH (2/2), CgA (1/2), bombesin (1/2)

23 out of 31 stained for ACTH

How often do ectopic ACTH producing tumors stain for ACTH?

Series of 18 samples from surgery or autopsy

Table 3 *Results of immunocytochemical investigations*

Case No	*Tissue studied*	*Antibodies*		
		Neuron specific enolase	*N-POMC*	*ACTH*
Group 1				
1	Primary tumour	2	0	0
	Liver metastasis	2	0	0
2	Lymph node metastasis	2	0	0
3	Primary tumour	2	0	0
	Lymph node metastasis	2	0	0
4	Primary tumour	0	0	0
5	Liver metastasis	3	0	0
6	Primary tumour	3	0	0
	Liver metastasis	3	0	0
Group 2				
7	Primary tumour	3	1	1
8	Liver metastasis	3	1	0
9	Primary tumour	1	2	2
10	Primary tumour	2	1	1
11	Primary tumour	3	3	3
12	Lymph node metastasis			2
13	Primary tumour	3	2	2
	Primary tumour (recurrence)	2	2	2
14	Primary tumour			1
15	Primary tumour	3	1	0
16	Primary tumour	3	1	0
17	Primary tumour	3	0	0
18	Lymph node metastasis	3	0	0

Staining: 0 = negative; 1 = very few cells positive; 2 = many cells positive, but less than 50%; 3 = greater than 50% of cells positive.

7/18 stained for ACTH

Total of 10/18 for POMC-derived peptides

Hypotheses:

1. Larger molecular wt precursor forms
2. Heterogeneity of cells
3. Rapid secretion-> insufficient storage to stain

What is catatonia?

- Inability to move normally despite full physical capacity
- Occurs in context of psych or medical disorder
- Features: immobility, mutism, stupor, negativism, wavy flexibility, posturing, purposeless motor activity, staring, mannerisms, stereotypy
- Treatment with lorazepam, ECT

Cushing's and catatonia?

- Psychiatric manifestations more common in neuroendocrine tumors than small cell tumors
- No cases described of endogenous Cushing's syndrome and catatonia
- Case report of prednisone associated catatonia
  - 62 yo F with multiple myeloma on 60 mg prednisone
  - Agitation->depression after 2 wks despite decrease in dose to 40 mg
  - Catatonia as decreased to 20 mg
  - Received final dose of 10 mg the following day and then began to resolve

Mortality in ectopic ACTH syndrome

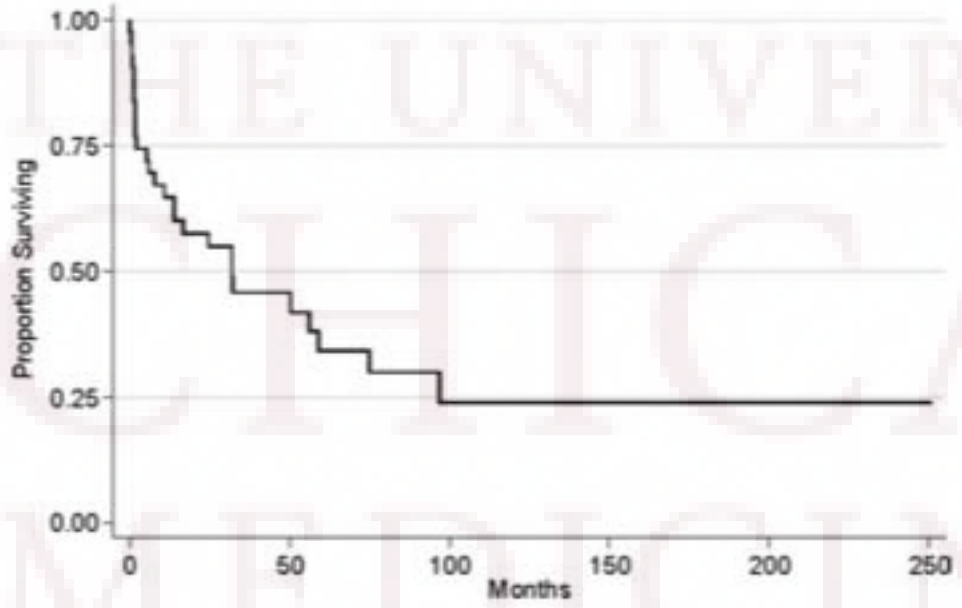
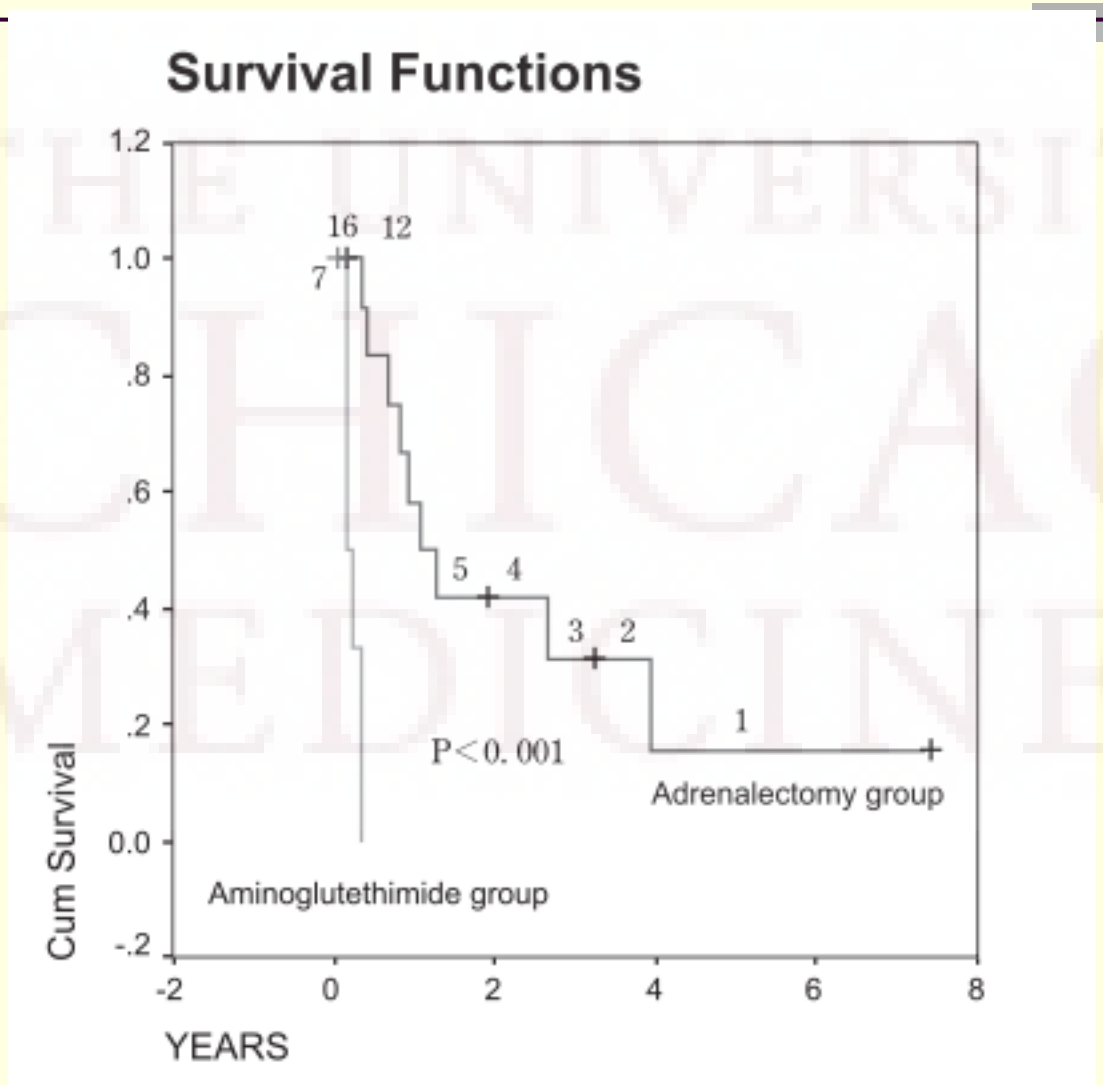


Figure 1. This Kaplan-Meier curve illustrates overall survival for the entire series (n = 43). The median overall survival was 32.2 months.

23.3% with infectious complications
14% with symptomatic VTE
62.8% death rate during follow up- progression of malignancy, infection, PE

Mortality with Adrenalectomy?



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