73 F WITH TYPE 2 DIABETES PRESENTING WITH LEFT SIDED WEAKNESS

Endorama 01/14/2016

Raj Jain

HPI

- 73 F with DM, hypertension, atrial fibrillation on warfarin who presented with vomiting, diarrhea, hyperglycemia
- EMS took blood sugar which was in the 490s
- Initial evaluation in the emergency room reveals left sided weakness and altered

Extended past medical history

PMH: DM2, hypertension, hyperlipidemia, atrial fibrillation

PSH: None

Home medications: benazepril, lovastatin, metoprolol-XL, warfarin, novolog 70/30 50 units qAM, 25 units qPM

Allergies: no known drug allergies

Social history / family history: not obtainable secondary to mental status

Initial physical examination (per neuro)

Vitals: T 36, HR 104-125, BP 153-215/63-155, R 16, SpO2 95-100 RA, BMI 35.5

Gen: no acute distress

CV: RRR, no m/g/r

Lungs: CTAB, no crackles

Abd: Soft, non-tender, BS present

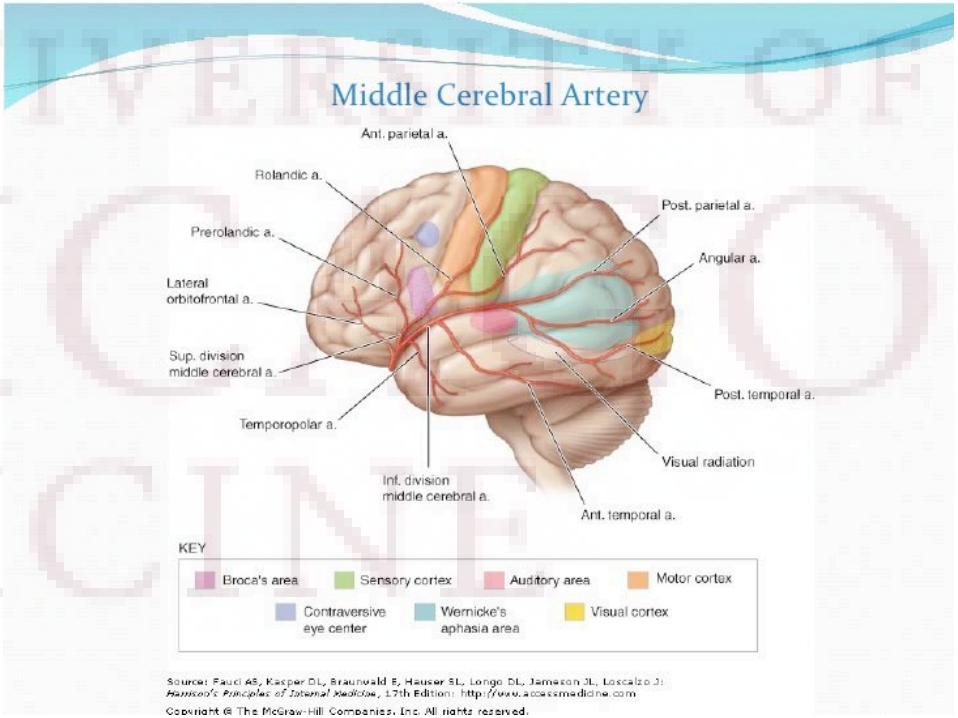
Ext: no edema, extremities warm, 2+ distal pulses

Skin: No rashes or bruising or ulcers

Neuro exam (abbreviated): A&O x 3, tracks, follows commands, able to name objects, PERRL, +gaze preference to right, does not respond to visual threat on the left, left lower facial weakness, does not move LUE

MCA Syndrome

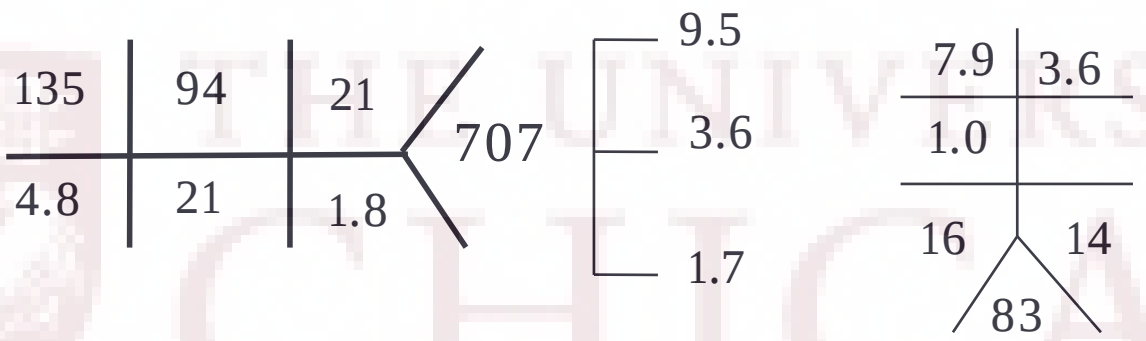
- Hemiparesis or hemiplegia of the lower half of the contralateral face
- Hemiparesis or hemiplegia of the contralateral upper and lower extremities
- Sensory loss of the contralateral face, arm, and leg
- Ataxia
- Speech impairments/aphasia
- Perceptual deficits e.g. hemispatial neglect



Initial management

- Patient last seen normal 1.5-2 hours ago
- Immediate head CT showed no bleeding
- tPA administered

Labs



A1c 10.1%
Beta-hydroxybutyrate 0.73 (Reference: <0.30 mmol/L)
LDL 60

Patient goes for an angiogram…

Findings:

1. Right CCA: normal, no arterial luminal narrowing.
2. Right ICA: minimal delay in right MCA branches, distal portion, including right MCA. No evidence of large MCA branch occlusion.

Summary

1. Multifocal small delayed filling of right MCA distal branches. However, major intracranial arteries are well visualized
2. No significant arterial luminal stenosis. No aneurysm.
3. Endovascular thrombectomy not performed.

Etiology of her neurologic deficits?

- Neurology Attending attestation:

"We hypothesize her neurological syndrome is not due to a vascular lesion but most likely seizures in the setting of profound hyperglycemia…"

Hyperglycemia-induced seizures?

- Seizures related to hyperglycemia have been described in case reports – focal seizures are most common

TABLE 2. *Seizures in nonketotic hyperglycemia*

Reference	Seizure type (number of patients)		
	Generalized	Partial motor	Occipital
DiBenedetto et al., 1965		1	
Maccario et al., 1965	1	6	
Feagin, 1966	1		
Jackson and Forman, 1966		3	
Feagin, 1968		1	
Henry and Bressler, 1968		1	
Kolodny and Sherman, 1968		1	
Lotz and Geraghty, 1968	1		
Maccario, 1968	1	6	
Daniel et al., 1969		3	
Goldberg and Sanbar, 1969		1	
Maccario and Messis, 1969			1
Gerich et al., 1971	1		
Whelton et al., 1971	1		
Arieff and Carroll, 1972	3		
Singh et al., 1973		5	
Gabor, 1974		1	
Aquino and Gabor, 1980		2	
Singh and Strobos, 1980		21	
Carter et al., 1981		1	
Venna and Sabin, 1981		3	
Berkovic et al., 1982		3	
Grant and Warlow, 1985		5	
Sowa and Pituck, 1989			1
Brick et al., 1989		5	
Total	9	69	2

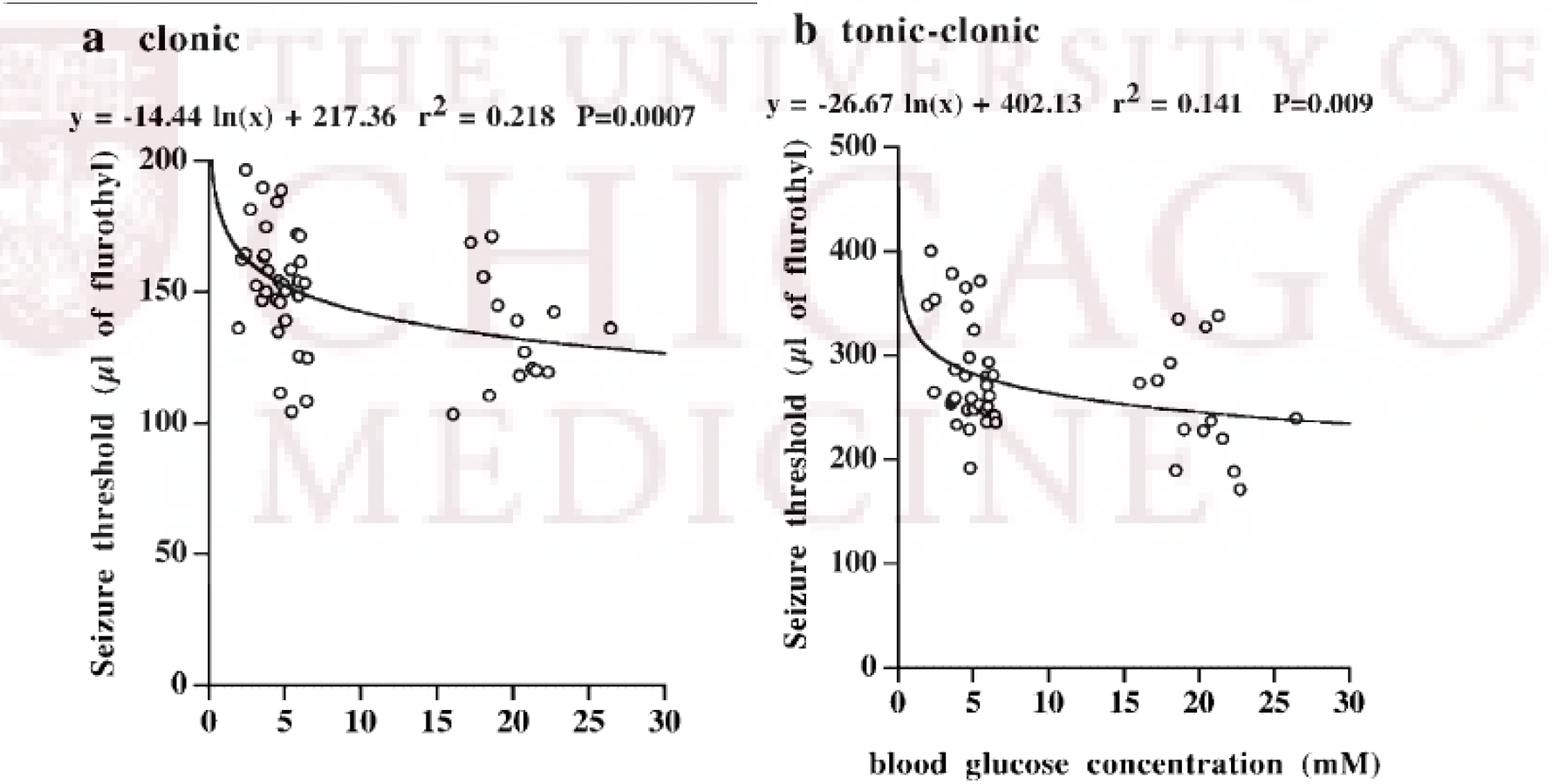
Harden et al. Hyperglycemia presenting with occipital seizures. Epilepsia 1991;32.2:215-20.

An example

Case 5. A 65-year-old, right-handed woman with IDM began experiencing episodes of confusion of several minutes' duration. On presentation in the emergency room, she had a generalized major motor seizure. The GPE was unremarkable. She was obtunded, and spontaneous movements on the right side of the body were diminished. Frequent complex partial seizures (CPS) of 1- to 2-minutes' duration occurred, characterized by a blank stare, with unresponsiveness, lip smacking, and automatisms consisting of waving of the right arm. She was intermittently confused until all seizures stopped. Blood sugar levels varied rapidly from 167 to 827 mg/dl in the first 24 hours. Despite therapy with phenytoin and carbamazepine with therapeutic levels, the seizures persisted. By the fifth hospital day, the level of serum glucose remained in the 120 mg/dl range, and her mental status cleared, with the seizures and hemiparesis subsiding.

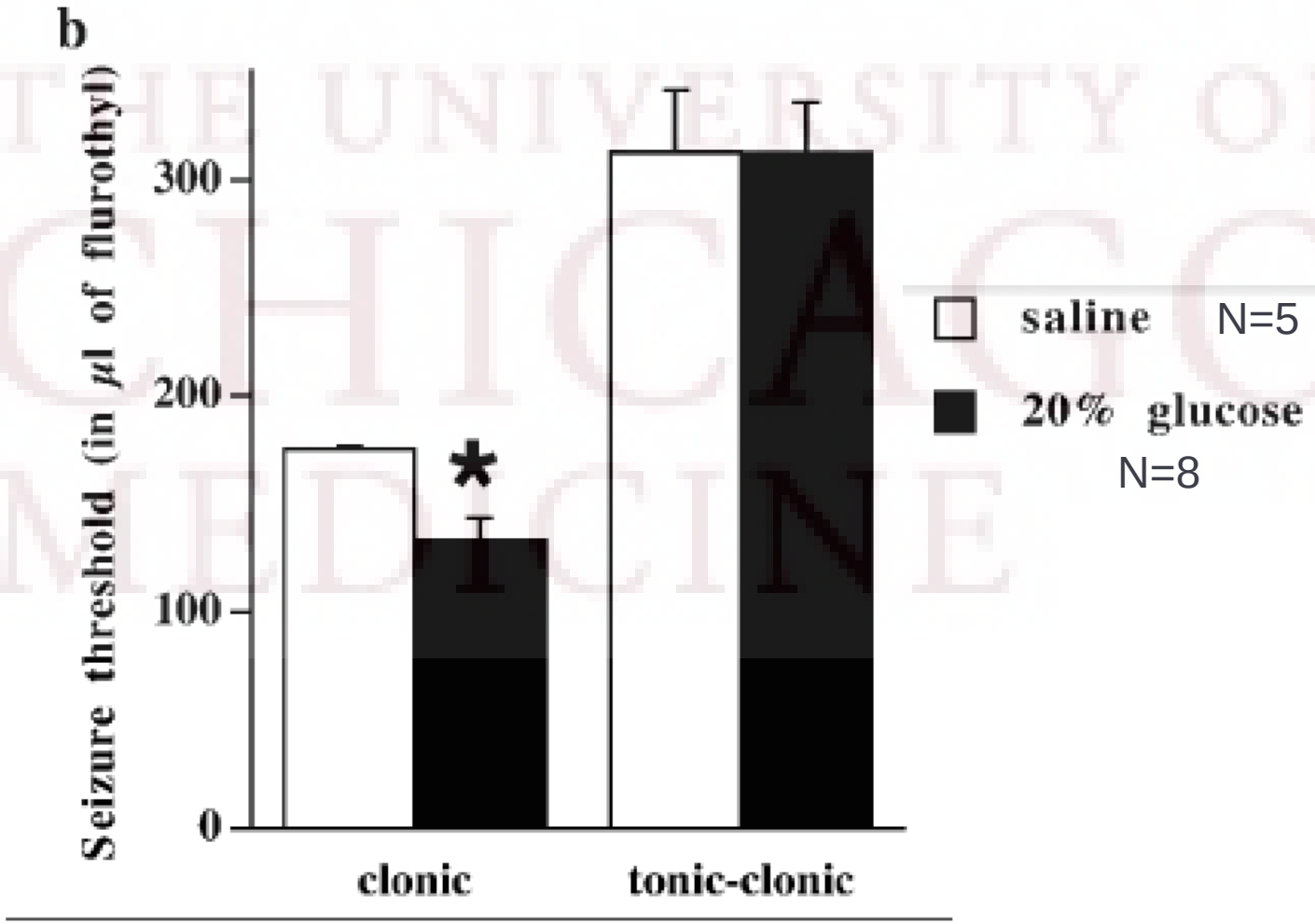
Brick et al. Reflex epilepsy and non-ketotic hyperglycemia in the elderly: a specific neuroendocrine syndrome. Neurology 1989;39:394-399.

Correlation between Extracellular Glucose and Seizure Susceptibility in Adult Rats



Schwechter et al. Correlation between extracellular glucose and seizure susceptbility in adult rats. Ann Neurol 2003;53:91-101.

Correlation between Extracellular Glucose and Seizure Susceptibility in Adult Rats



Schwechter et al. Correlation between extracellular glucose and seizure susceptbility in adult rats. Ann Neurol 2003;53:91-101.

Mechanism?

- Underlying focal cerebral ischemia?
  - Suggested by underlying focal vascular lesions in some patients
  - Focal venous sludging or thrombosis due to hyperglycemia, hyperosmolarity, dehydration, or combination of?
  - Hyperglycemia in animal models decreases cerebral blood flow
- Hyperosmolarity does not need to be present
- Less likely to occur with DKA - Acidosis encourages formation of GABA and inhibits CNS electrical activity

Stahlman et al. Neurologic manifestations of non-ketotic hyperglycemia. J Tenn Med Assoc 1998;81(2): 77-80.

EEG

Impression: This EEG is an abnormal study recorded in the obtunded state. Background slowing is consistent with moderate encephalopathy. No focal, lateralizing, or epileptiform activity is seen and no seizures are recorded.

However, patient was on an insulin drip and BS were in the 160s

Patient course continued…

- Within 24 hours, patient's facial and extremity weakness, as well as gaze preference, are completely resolved

Do you agree with their diagnosis?

Patient's course continued

- Endocrinology consulted for DM2 management
- Patient initially requiring an insulin drip and increased requirements from baseline (over 100 units of insulin per 24 hours) but decreased after 1-2 days
- Patient's mental status improving and patient transferred to the general floor

Nine days after admission, however, patient develops new rash, fever to 38.9, leukocytosis to 27

Patient's course continued…

- Rash was rapidly evolving so derm was consulted.
- "Patient noted to be erythrodermic with partially tense bullae with slightly cloudy fluid prominent on extremities... Positive facial edema. Full thickness erosion noted on left arm in area of previous bandaid"
- Biopsies were taken
- Initial clinical diagnosis was drug hypersensitivity syndrome (DRESS) vs. staph scalded skin syndrome vs. less likely Stevens Johnson Syndrome/TEN
- Patient transferred to the burn unit for wound care

Skin Biopsy - Pathology

FINAL PATHOLOGIC DIAGNOSIS: Features of necrolytic erythema.

The differential diagnosis includes the necrolytic migratory erythema of glucagonoma and nutritional deficiency of trace elements such as zinc (acrodermatitis enteropathica) and selenium. Clinical-pathological correlation is recommended.

Glucagonoma

- Extremely rare – 1 in 1-20 million
- Typically present in the 5th decade, 20% associated with MEN1
- Clinical features: weight loss, glucose intolerance or DM, necrolytic migratory erythema, chronic diarrhea, venous thrombosis, dilated cardiomyopathy
- Tumors can secrete other neuroendocrine hormones – in 21 patients with pathology proven glucagonoma, 11 had increased levels of another hormone (VIP, gastrin, 5-HIAA, insulin, calcitonin, ACTH)

Wermers et al. The Glucagonoma Syndrome: clinical and pathological features in 21 patients. Medicine 1996; 75.2:53-63

Most common clinical characteristics

TABLE 1. Presenting clinical characteristics of 21 patients with the glucagonoma syndrome

Characteristic	No. of Patients
Male	11
Female	10
NME	14
Diabetes mellitus	8
Weight loss	15
Diarrhea	6
Stomatitis	6
Abdominal pain	3
Nausea	3
Neuropathy	1
History of thrombosis	3
Psychiatric history	1
MEN	1

MEN = multiple endocrine neoplasia; NME = necrolytic migratory erythema.

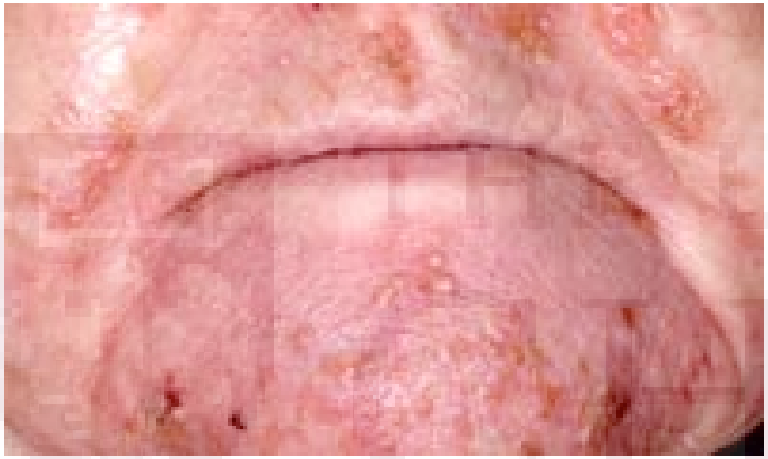
Demographics & Glucagon levels

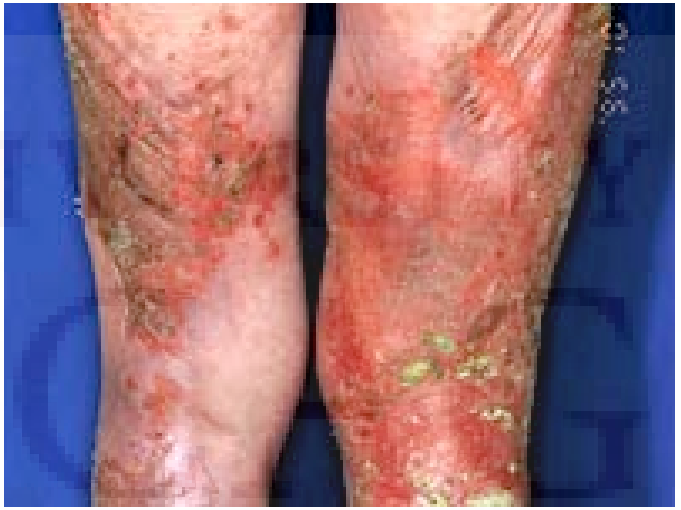
TABLE 2. Clinical and laboratory features in 21 patients with the glucagonoma syndrome

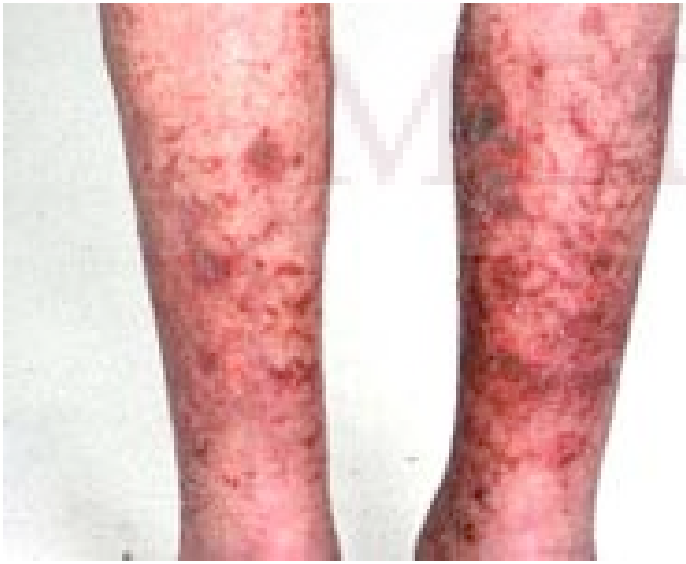
Patient	Age (yr)	Sex	Serum Glucagon (pg/mL)	DM	NME	Hypoamino-acidemia
1	30	F	10,916	+	+	ND
2	65	M	14,000	+	+	+
3	34	M	733	+	+	+
4	59	F	2,340	+	+	ND
5	44	M	3,790	+	+	+
6	54	M	693	+	+	ND
7	70	F	580	+	+	+
8	46	M	5,600	+	+	+
9	57	F	14,300	+	+	+
10	73	F	2,200	+	+	ND
11	50	M	3,000	+	+	ND
12	52	M	260	−	+	ND
13	51	F	84*	+	+	†
14	43	M	2,100	+	+	ND
15	64	M	6,550	+	+	+
16	61	F	510	−	+	ND
17	33	M	1,400	−	+	ND
18	28	F	610	+	+	−
19	71	F	470	−	+	ND
20	64	M	120‡	+	+	ND
21	66	F	760	+	+	ND

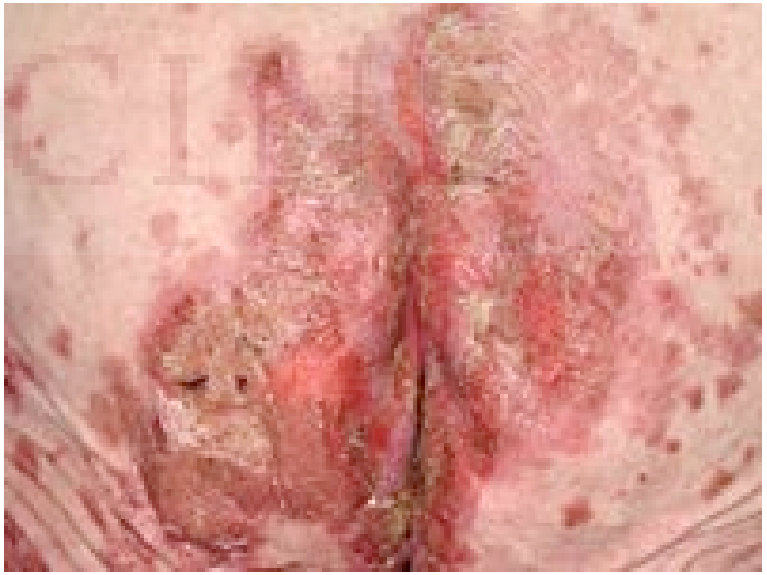
Abbreviations: DM = diabetes mellitus; ND = not done; NME = necrolytic migratory erythema; + = present; − = absent.
* Later, 283 pg/mL.
† Only 2 amino acids decreased.
‡ Later, 250 pg/mL.

Necrolytic migratory erythema









Necrolytic migratory erythema

- Evolves over 7-14 days and presents in waves (e.g. twice per year) & often has been occurring for years at presentation
- Begins as small erythematous macules and papules that extend to involve the perineum, lower extremities, and perioral regions. Areas then blister and central erosions develop
- Often intensely pruritic and can become superinfected with Candida or Staph
- Hypothesized by some to be related to vitamin or fatty acid deficiencies that result from the glucagonoma itself (i.e. persistent stimulation of carbohydrate metabolism / catabolic state)

Pathology perspective

“The findings of necrolytic migratory erythema include parakeratosis accompanied by vacuolation and pallor of the mid and upper keratinocytes, these findings are not typically seen in DRESS, and they usually are not within the same differential diagnosis.

Typically in DRESS we would see findings more characteristic of even a pustular psoriasis (which does not fit the clinical background) or findings more consistent with a hypersensitivity reaction, which has features that do not usually overlap with the findings in necrolytic migratory erythema.

The pallor and vacuolization of the mid to upper keratinocytes is fairly classic for necrolytic migratory erythema, with these findings also seen in acrodermatitis enteropathica, glucagonoma syndrome, necrolytic acral erythema, Hartnup disease and other more rare conditions.”

Dr. Ruiz de Luzuriaga (Pathology)

More labs

Lab	Value	Reference
Glucagon*	169	<=80 pg/mL
Gastrin	71	<100 pg/mL
Serotonin	<30	<=230 ng/mL
VIP	24	<75 pg/mL
Insulin**	9.7	2.6-24.9 mcU/mL
PTH	165	15-75 pg/mL
Cortisol	21.7	ug/dL
C diff	**POSITIVE**	
Creatinine	**3.7**	

*Glucose 201 at time of draw
**Glucose 139 at time of draw

What now?

- What would your next step in management be? Imaging?

Repeat glucagon level

Lab	Value	Reference
Glucagon*	119	<=80 pg/mL

*Glucose 187 at time of draw

Secondary causes of elevated glucagon levels?

- DKA
- Hyperosmolar non-ketotic state
- Cushing syndrome
- Trauma or burns
- MI
- Sepsis
- Liver failure
- Renal failure
- Abdominal surgery
- Fasting

Nutritional labs

Zinc 0.59 (Reference 0.66-1.10 ug/mL)

Selenium 114 (Reference 80-142 ng/mL)

Vitamin A 23.7 (Reference 32.5-78.0 ug/dL)

Vitamin B12 662 (240-900 pg/mL)

25-Vitamin D <7 ng/mL

Vitamin E 7.9 (Reference 5.5-17.0 mg/L)

Transferrin 99 (168-302 mg/dL)

Pre-albumin 12 (Reference 21-41 mg/dL)

Albumin 2.6 (3.5-5.0 g/dL)

Zinc

"… the zinc level may be within normal limits in a deficiency dermatitis that nevertheless responds to zinc replacement therapy. This paradoxical finding is in part a result of the tight regulation of plasma zinc, which comprises only 0.1% of the body's total zinc stores. Thus, accurately measuring the body's zinc status is difficult."

Maverakis et al. Acrodermatitis enteropathica and an overview of zinc metabolism. J Am Acad Dermatol 2007;56:116-24.

Clinical Course continued…

- Patient started on PO zinc, in addition to vitamin D, thiamine, vitamin A, and multivitamin
- Patient's rash and mental status improved. She continued to receive wound care, transferred to the general floor
- Patient was eating minimally but refused feeding tube at discharge
- Discharged to subacute rehabilitation

References

Harden et al. Hyperglycemia presenting with occipital seizures. Epilepsia 1991;32.2:215-20.

Brick et al. Reflex epilepsy and non-ketotic hyperglycemia in the elderly: a specific neuroendocrine syndrome. Neurology 1989;39:394-399.

Schwechter et al. Correlation between extracellular glucose and seizure susceptbility in adult rats. Ann Neurol 2003;53:91-101.

Wermers et al. The Glucagonoma Syndrome: clinical and pathological features in 21 patients. Medicine 1996; 75.2:53-63

Maverakis et al. Acrodermatitis enteropathica and an overview of zinc metabolism. J Am Acad Dermatol 2007;56:116-24.

Kovacs et al. Necrolytic migratory erythema. J Cutan Pathol 2006;33:242-245.