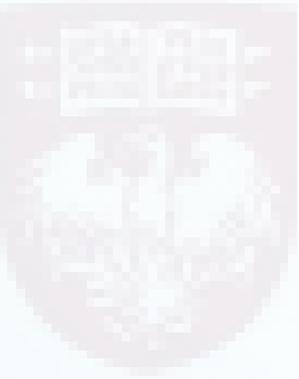




THE UNIVERSITY OF
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MEDICINE &
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“83 Year-old Woman Presenting with Altered Mental Status and Hypercalcemia”

Dr. Dickens does not have any relevant financial relationships
with any commercial interests.



ENDORAMA: Case 1

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Objectives

1. Review presentation of and diagnostic approach to hypercalcemia
2. Discuss management of severe hypercalcemia and evidence for use of loop diuretics
3. Evaluate evidence for vitamin D replacement in primary hyperparathyroidism
4. Review pre-operative localization studies in primary hyperparathyroidism and incidence of ectopic parathyroid adenomas

Chief complaint

83 year old woman with a PMH of CVA, HTN, and complete heart block s/p pacemaker presents to the ER with lip swelling and altered mental status.

HPI: Patient lives in a nursing home since a recent admission for CVA and on the morning of admission was noted to have new lip lesions and swelling. She was also somnolent and less interactive than usual (baseline AAOx1, interactive).

PMH: CVA one month ago, HTN, complete heart block s/p pacemaker

PSH: None

ROS: Unable to obtain

Meds:

- Aspirin 81mg daily
- Atorvastatin 80mg daily
- Fluconazole 200mg
- Nystatin oral swish

Social Hx: No T/E/D. Lived with family until recent admission with CVA, since then has been in a nursing home.

Family Hx: Unable to obtain

Physical exam

VITALS: Temp 36.6, BP 106/67, HR 83, RR 22, O2 sat 98 on 2L NC, BMI 24.2

General: Not in distress

ENT: Erythematous papules and open pustules on the lip and R chin with yellow crusting. Whitish/yellow thick coating on tongue and lower gums. Three small white lesions on L lower lip. Raised erythematous welts on R cheek

CV: Regular rhythm and rate, no murmurs, rubs, or gallops

Pulmonary: Clear to auscultation bilaterally with poor effort

GI: Normoactive bowel sounds, not visibly distended, **RUQ tenderness**. No mass. No hepatosplenomegaly

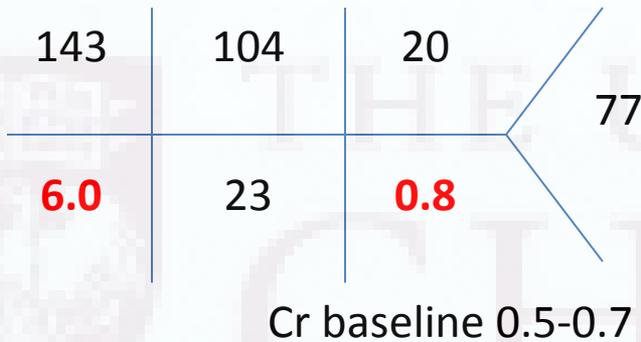
GU: No suprapubic tenderness. Foley in place draining clear yellow urine

MSK: Edema in bilateral lower extremities (R>L) with venous stasis skin changes. Decreased bulk and tone

Neuro: **Somnolent. Opens eyes to verbal stimuli, withdraws to pain in all extremities. Intermittently follows one step commands. RUE contracted with spasticity and increased tone. R facial droop. Myoclonus in the bilateral upper extremities**

Skin: Sacrum with erythema, no ulceration

Admission Labs



Ca **14.0**
Mg 2.2
Ph **2.2**

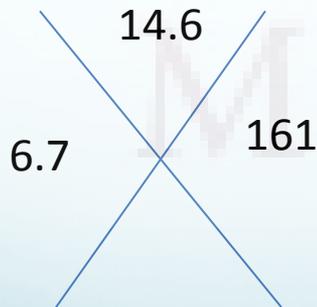


EKG: NSR, nonspecific ST
abnormality, QTc 430

Lactic acid= 1.6

Troponin= <0.03

TSH= 0.63



Neutrophils 76%

Blood cultures x2: pending

UA: Negative LE, negative nitrites,
1+ ketones, occasional WBC, no
bacteria, many hyaline casts

Hypercalcemia

- Presentation: anorexia, N/V, pancreatitis, AKI, weakness, AMS, shortened QT interval
- Severity:
 - Mild Ca <12
 - Moderate Ca 12-14
 - Severe Ca >14
- Etiology: 90% is caused by primary hyperparathyroidism or malignancy

Table 1 Causes of Hypercalcemia

Parathyroid disease

Primary hyperparathyroidism due to benign PTH adenoma, PTH carcinoma, or PTH multiglandular hyperplasia as part of multiple endocrine neoplasia syndromes

Tertiary hyperparathyroidism

Malignancy

Parathyroid hormone related protein (humoral hypercalcemia of malignancy)

Local osteolysis mediated by cytokine release

Lytic bone metastasis.

Multiple myeloma

Ectopic production of 1, 25 dihydroxyvitamin D by the tumor (eg, lymphoma)

Endocrinopathies

Adrenal insufficiency

MEN 1, 2A

Thyrotoxicosis

Pheochromocytoma

VIPoma

Granulomatous disease

Tuberculosis

Sarcoidosis

Endemic mycosis: histoplasmosis, coccidioidomycosis

Leprosy

Crohn's disease

Berylliosis

Medications

Estrogens

Lithium

Thiazide diuretics

Excess vitamin D or vitamin A ingestion

Miscellaneous

Familial hypocalciuric hypercalcemia

Immobilization

MEN = multiple endocrine neoplasia; PTH = parathyroid hormone.

- Additional labs
 - **PTH = 356**
 - 25-OH vitamin D = 13
 - 1,25-Dihydroxy vitamin D = 19
 - PTHrP = 0.4
 - SPEP = normal
- Hydration with 1L NS, then maintenance fluids at 83cc/hour
- Ca 14.0 -> 12.9 -> 12.3 -> 12.4

Management of hypercalcemia

- Goals of management
 - Lower calcium
 - Correct dehydration
 - Decrease osteoclast-mediated bone resorption
 - ** treat underlying etiology
- Emergent management:
 - IV 0.9%NS 4-6L over 24 hours → expect a 1.6-2.4 mg/dL reduction with IVF
 - Loop diuretics only if volume overload develops
 - Consider IV bisphosphonates
 - Zoledronic acid 4mg over 15min
 - Pamidronate 30–90mg (depending on severity of hypercalcaemia) at 20mg/h
 - Ibandronic acid 2–4mg
 - Second line treatments
 - Glucocorticoids
 - Calcimimetics, denosumab, calcitonin
 - Parathyroidectomy

Loop diuretics in hypercalcemia

- Mechanism: block Ca re-absorption in the ascending limb of the loop of Henle to induce calciuresis
- Review in 2008 assessed the evidence for “forced saline diuresis” in hypercalcemia and current clinical recommendations
 - Fourteen articles, most recent in 1983
 - Average furosemide dose 1120mg over 24 hours (range 240mg – 2400mg)
 - Normalization of Ca in 14 of 39 cases, but only occurred rapidly in 2 patients (within 6-12 hours)
 - Significant complications

“Furosemide should be relegated to the management of fluid overload, which should be rare if one focuses on appropriate rehydration rather than trying to induce forced diuresis.”

Table 2. Textbook Recommendations

Source (Reference)	Fluid	Furosemide	Bisphosphonate
<i>Emergency Medicine Manual</i> (26)	Normal saline, 5–10 L	Yes, 40 mg	Not mentioned
<i>Tintanalli's Emergency Medicine: A Comprehensive Study Guide</i> (27)	Normal saline volume repletion	Yes, 40–100 mg every 2–4 h	Not mentioned
<i>Harrison's Principles of Internal Medicine</i> (28)	Normal saline, 4–6 L over 24 h	Yes; no dose given	Should be considered for patients with cancer
<i>Current Medical Diagnosis and Treatment</i> 2008 (29)			Standard of care
<i>Clinical Anesthesia</i>			Standard of care
<i>Principles of Internal Medicine for the General Practitioner</i>			Standard of care
<i>ACP Medication Handbook</i>			Standard of care
<i>ACP Medication Handbook</i>			Simplified
<i>Cecil Medicine</i> (35)	Normal saline, 200–300 mL/h	Yes; no dose given	Standard for cancer-associated hypercalcemia
<i>Brenner & Rector's The Kidney</i> (36)	Normal saline	Yes, no dose given, strong fluid statement	May be reasonable
<i>Greenspan's Basic and Clinical Endocrinology</i> (37)	Normal saline, 500–1000 mL in the first hour, then 25–500 mL/h	Yes, to avoid fluid overload	First choice for most patients after initial therapy
<i>Clinical Oncology</i> (38)	Normal saline	Reserved for fluid overload	Mainstay of therapy
<i>Washington Manual of Medical Therapeutics</i> (39)	Normal saline, 3–4 L in first 24 h	No, except for fluid overload	Administer early
<i>Hospital Medicine</i> (40)	Normal saline	“Contraindicated” unless fluid overload	Primary therapy with fluids
UptoDate (41)	Normal saline	Loop diuretic “out of favor”; use for overload	Concurrent with saline

“First-line therapy is aggressive intravenous fluid resuscitation. Once the patient is volume replete, an intravenous loop diuretic should be added if the calcium level has not normalized.” – MKSAP 17

Back to our patient: AMS evaluation

- CXR = Marked interval improvement in patchy bilateral airspace opacities with residual diffuse interstitial opacity suggestive of edema and possibly fibrosis
- CT head = chronic subdural hematoma (stable from prior imaging), age-indeterminate small vessel ischemic disease
- EEG = no seizures
- Oral lesion swab positive for HSV-1
- Cheek lesion swab positive for **VZV**
- CSF examination
 - **102 WBC (81% lymph, 0% neut)**, 9 RBC
 - Glucose 60, Protein 50
 - Bacterial and fungal cultures negative, HSV negative, **VZV positive**, enterovirus negative, VDRL negative, cryptococcus negative

Management

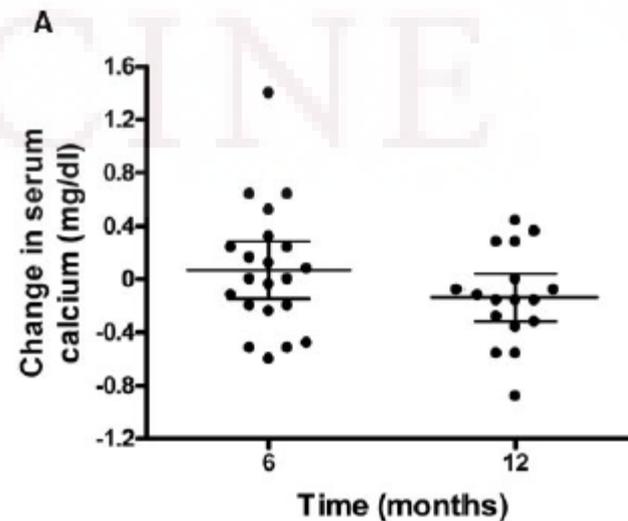
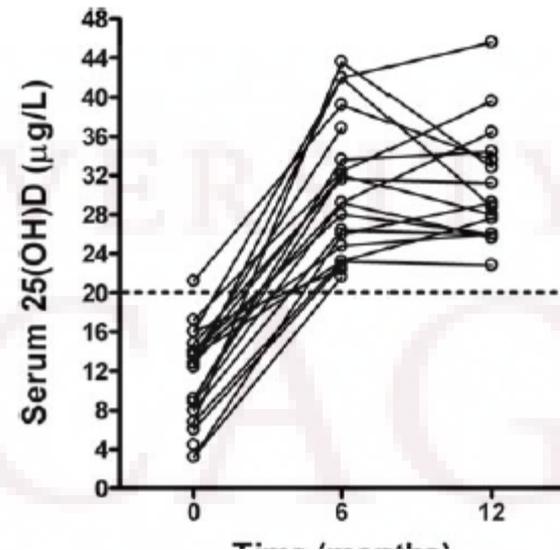
- Hypercalcemia
 - Hydration with maintenance IVF, free water flushes via dobhoff tube
 - Pamidronate 30mg x1
 - Cinacalcet 30mg BID -> uptitrated to 90mg TID
- Vitamin D deficiency
 - D3 1,000 IU daily
- VZV encephalitis
 - IV acyclovir
 - Clindamycin (for overlying impetigo)

Vitamin D deficiency in hyperparathyroidism

TABLE 1. Baseline characteristics of patients with primary hyperparathyroidism

Characteristic	Value
Gender (M/F)	2/19
Age (yr)	68.3 ± 12.7
Serum calcium (mg/dl) [mmol/liter]	10.8 ± 0.5 [2.70 ± 0.12]
Serum phosphate (mg/dl) [mmol/liter]	2.8 ± 0.6 [0.89 ± 0.19]
Serum creatinine (mg/dl) [mmol/liter]	0.92 ± 0.23 [0.08 ± 0.02]
PTH (pg/ml) [pmol/liter]	138 ± 79 [12.4 ± 7.1]
Serum 25(OH)D (μg/liter) [nmol/liter]	11 ± 5 [28 ± 13]
Serum 1,25(OH) ₂ D (pg/ml) [pmol/liter]	54 ± 25 [134 ± 62]
Serum ALP (U/liter)	105 ± 29
Urine N-telopeptides (nmol BCE/mmol creatinine)	54 ± 25
24-h urinary calcium (mg/d) [mmol/d]	232 ± 148 [5.8 ± 3.7]
L1-L4 BMD (g/cm ²)	1.02 ± 0.16
L1-L4 BMD (T score)	-1.4 ± 1.3
Femoral neck BMD (g/cm ²)	0.78 ± 0.18
Femoral neck BMD (T score)	-1.7 ± 1.5

Data are mean ± SD. M, Male; F, female.



Meta-analysis: vitamin D repletion in PHPT

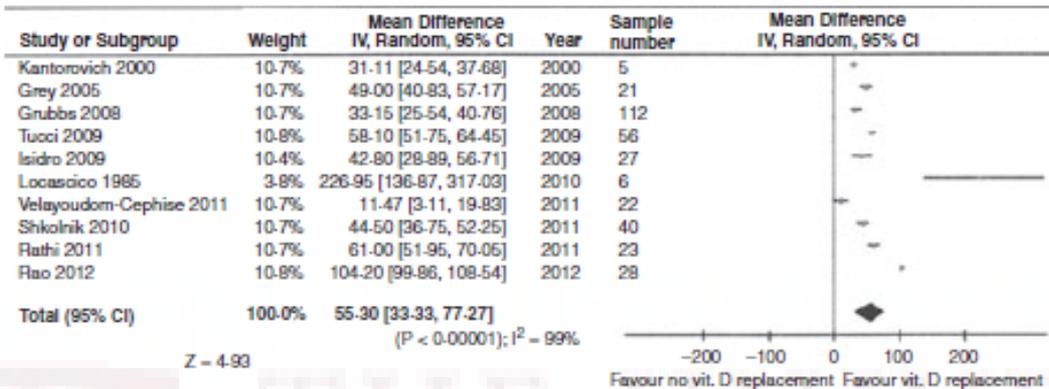
Table 1. Characteristics of included studies

First author, year, ref no	Study type	Country	Number of participants	Mean age	Intervention	Duration and dose	Mean pre/post 25(OH)D [nmol/l]	Mean (SD) Serum PTH level [pmol/l]	Mean (SD) Serum calcium level [mmol/l]	Follow-up period
LoCasiccio, 1985 ¹⁴	Obs.	Italy	6	28–51*	25-OH-D3	50 µg/day for 1 month	38.3/265.2	170.8 (80.9)	2.8 (0.2)	4 weeks
Kantorovich, 2000 ¹⁵	Obs.	USA	5	78	Vitamin D2	50 000 U/twice weekly for 5 week	21.4/52.5	9.62 (2.5)	2.5 (0.2)	1.25 months
Grey, 2005 ¹⁶	Obs.	New Zealand	21	68.3	Cholecalciferol	50 000 U/week for month and thereafter once a month for 12 months	28/77	12.4 (7.1)	2.7 (0.1)	12 months
Grubbs, 2008 ¹⁷	Obs.	USA	112	58	Ergocalciferol	50 000 U/tab. Dose and duration as per directed by surgeons. Median cumulative dose-400 000 U	45.9/79.1	15.7 (9.9)	2.7 (0.1)	Median duration 28 days
Isidro, 2009 ¹⁸	Obs.	Spain	27	67.5	Calcifediol	480–960 IU/day for 12 months	28.7/71.5	16.6 (12.1)	2.7 (0.1)	12 months
Tucci, 2009 ¹⁹	Obs.	USA	56	63.6	Ergocalciferol	50 000 U/week for 8 weeks followed by 800/day to 100 000 U/month	36.4/94.5	13.1 (5.1)	2.7 (0.1)	34 weeks (8.5 months)
Velayoudom-cepheise, 2011 ²⁰	Obs.	France	22	66.8	Ergocalciferol or cholecalciferol	800–1200 U/day for 3 months or 100 000 U/month	28.1/39.5	17.2 (18.8)	2.7 (0.2)	6 months
Rathi, 2011 ²¹	Obs.	UK	23	59	Cholecalciferol	20 000 IU per week for 12 weeks	14.8/75.8	21.9 (11.0)	NA	3 months
Shkolnik, 2010 ²²	Obs.	Israel	40	63	NA	NA	38.5/83	11.7 (3.6)	2.6 (0.1)	NA
Rao, 2012 ²³	Obs.	UK	28	69	Various forms	Variable dosage	32.2/136.4	13.7 (1.3)	2.6 (0.03)	18 ± 2 months

Obs., observational; NA, information not available.

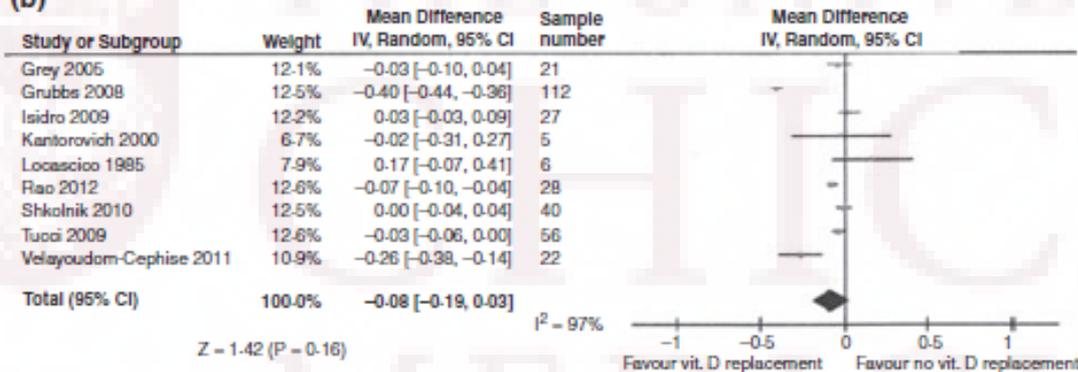
*Mean age not available, data are in range

(a)



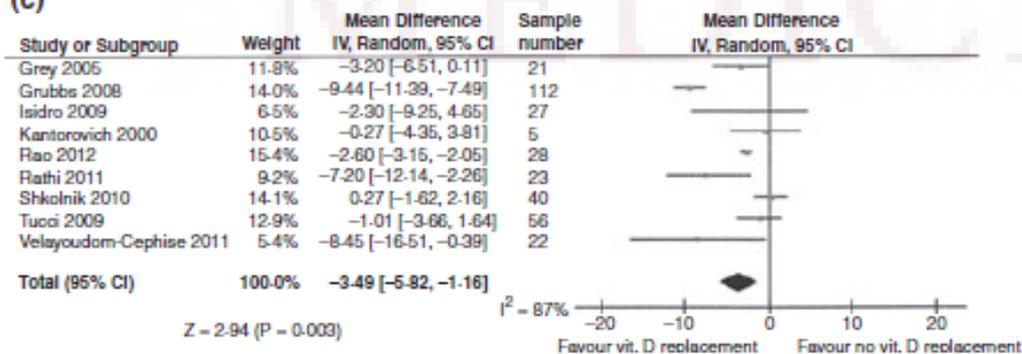
Serum 25-OH Vitamin D

(b)



Serum Calcium

(c)



Serum PTH

Surgical Consult → Localizing Studies

- Thyroid ultrasound
 - Right lobe 4.4 x 2.4 x 1.9 cm
 - Left lobe 4.3 x 2.1 x 1.6 cm
 - Isthmus 0.1cm
 - Right lobe is heterogeneous. No dominant nodules
 - Left lobe is heterogeneous. No dominant nodules.
 - No suspicious adenopathy. R level 3 lymph node visualized with a fatty hilum measuring 1.4 x 1.5 x 0.4 cm
- Impression: No evidence of a parathyroid adenoma visualized on this study.

Pre-op localization

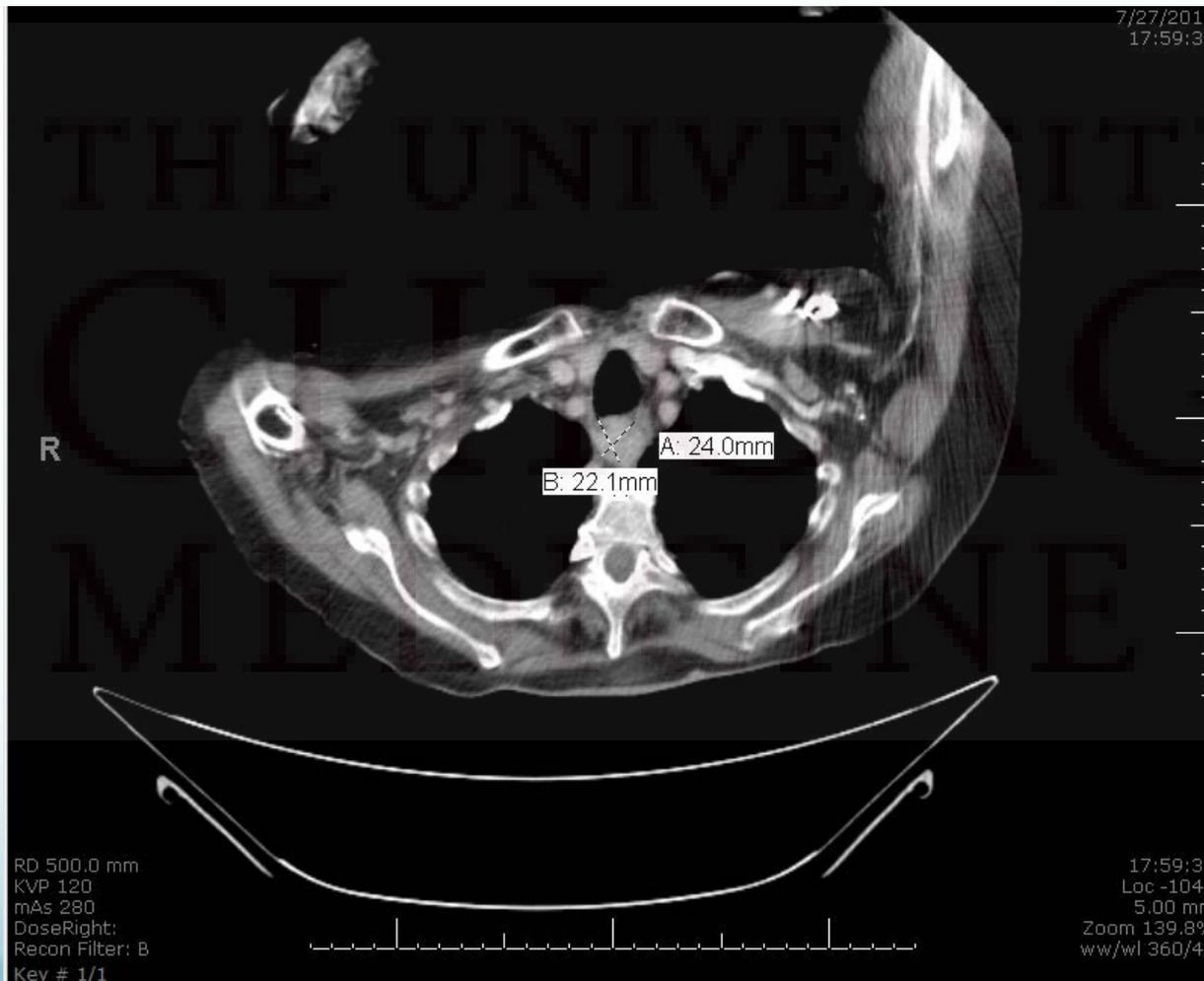
- Imaging modalities:
 - Neck ultrasound (unrevealing 10-20% of cases)
 - Nuclear medicine scintigraphy parathyroid scan
 - CT scan
- Meta-analysis in 2012 investigated accuracy of these 3 techniques for pre-op localization
- 43 studies included: 19 ultrasound, 9 sestamibi-SPECT, 4 4D-CT

Imaging modality	Sensitivity	PPV
Ultrasound	76.1%	93.2%
Sestamibi-SPECT	78.9%	90.7%
4D-CT	89.4%	93.5%

CT scan from admission...

- CT chest/abdomen/pelvis with contrast
 - Superior mediastinal soft tissue mass adjacent to esophagus. Etiology is unknown, may represent a primary nasopharyngeal mass, metastatic adenopathy, and/or less likely a diverticulum. Upper GI study may be helpful to exclude the possibility of small diverticulum

CT chest



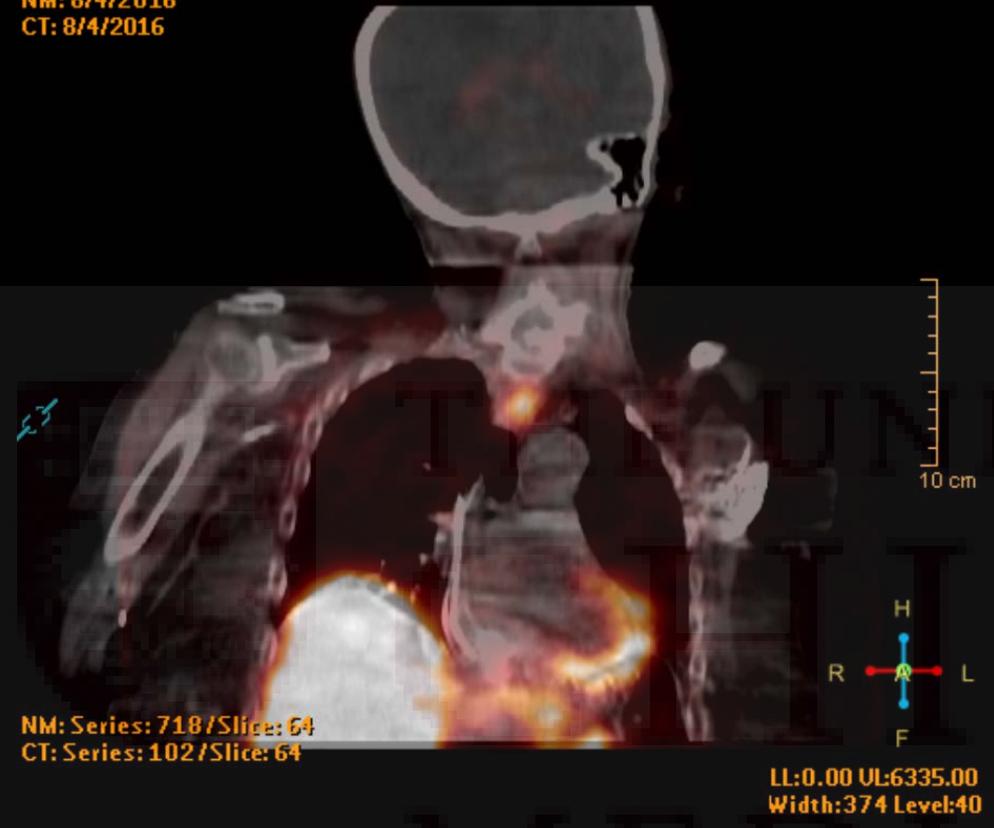
NM parathyroid imaging with SPECT and CT anatomical localization

- 21.4 mCi Tc-99m sestamibi injected
- Early and delayed planar and early SPECT/CT images were acquired through portions of the neck and thorax
- On early SPECT, a focus of increased tracer uptake is localized in the retrotracheal area in the superior mediastinum, posterior to the lower pole of the right thyroid lobe.
- Impression: Concern for ectopic parathyroid adenoma in the retrotracheal superior mediastinum

NM: RECON TOMO / TRANS-OSEM-AC
CT: CTTRANS 3.2
NM: 8/4/2016
CT: 8/4/2016

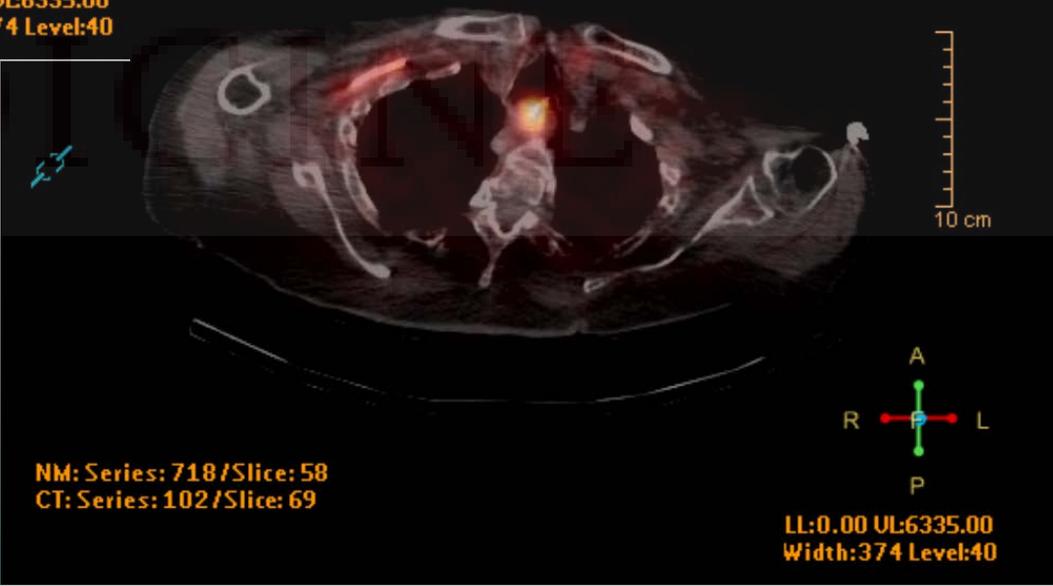
BVXCT_
Fused Coronal

NM parathyroid imaging with SPECT



ON TOMO / TRANS-OSEM-AC
ANS 3.2
2016
2016

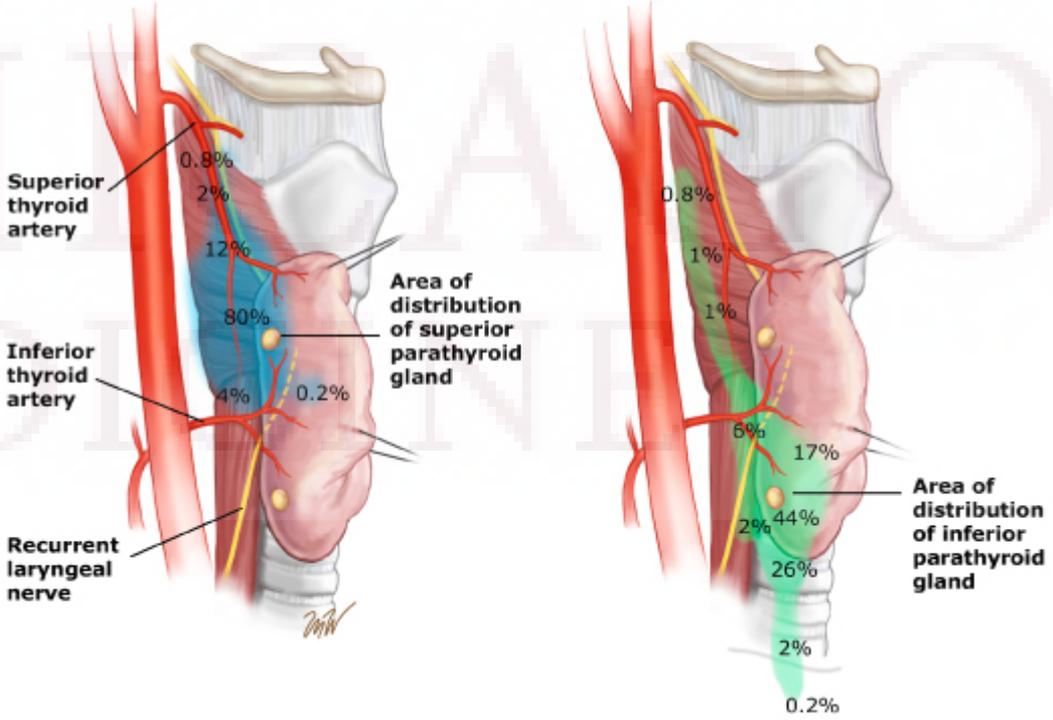
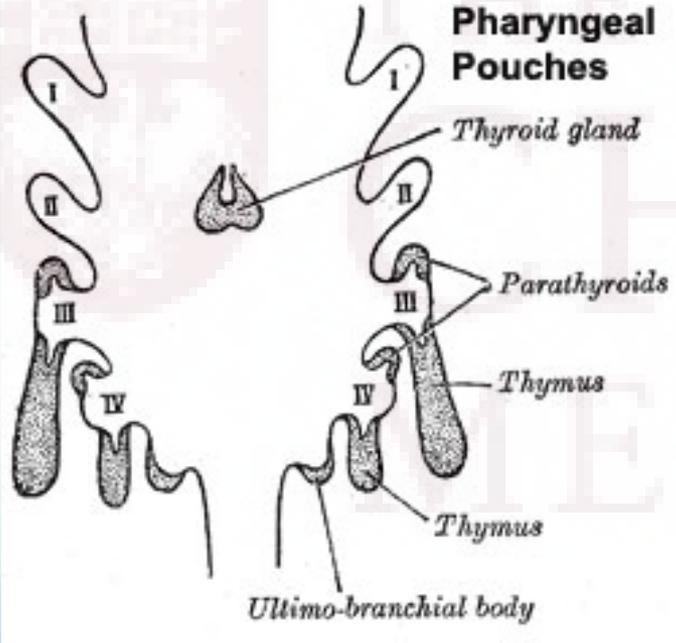
BVXCT_TC169
Fused Transverse TRANS-



Normal Parathyroid Development and Anatomy

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Locations of parathyroid glands



Ectopic parathyroid adenoma

- Case series from 1978-2007 reported 252 patients with severe hypercalcemia due to hyperparathyroidism
 - 8% of adenomas were located ectopically
- Study in 2013 analyzed 1,562 patients who underwent surgery for primary hyperparathyroidism
 - 346 (22%) had ectopically located adenoma
 - Most common locations were thymus (38 %), retroesophageal region (31%), intrathyroidal (18%)

Table 1 Location of 202 ectopic parathyroid glands and comparison of MIBI and US accuracy ($p = 0.009$)

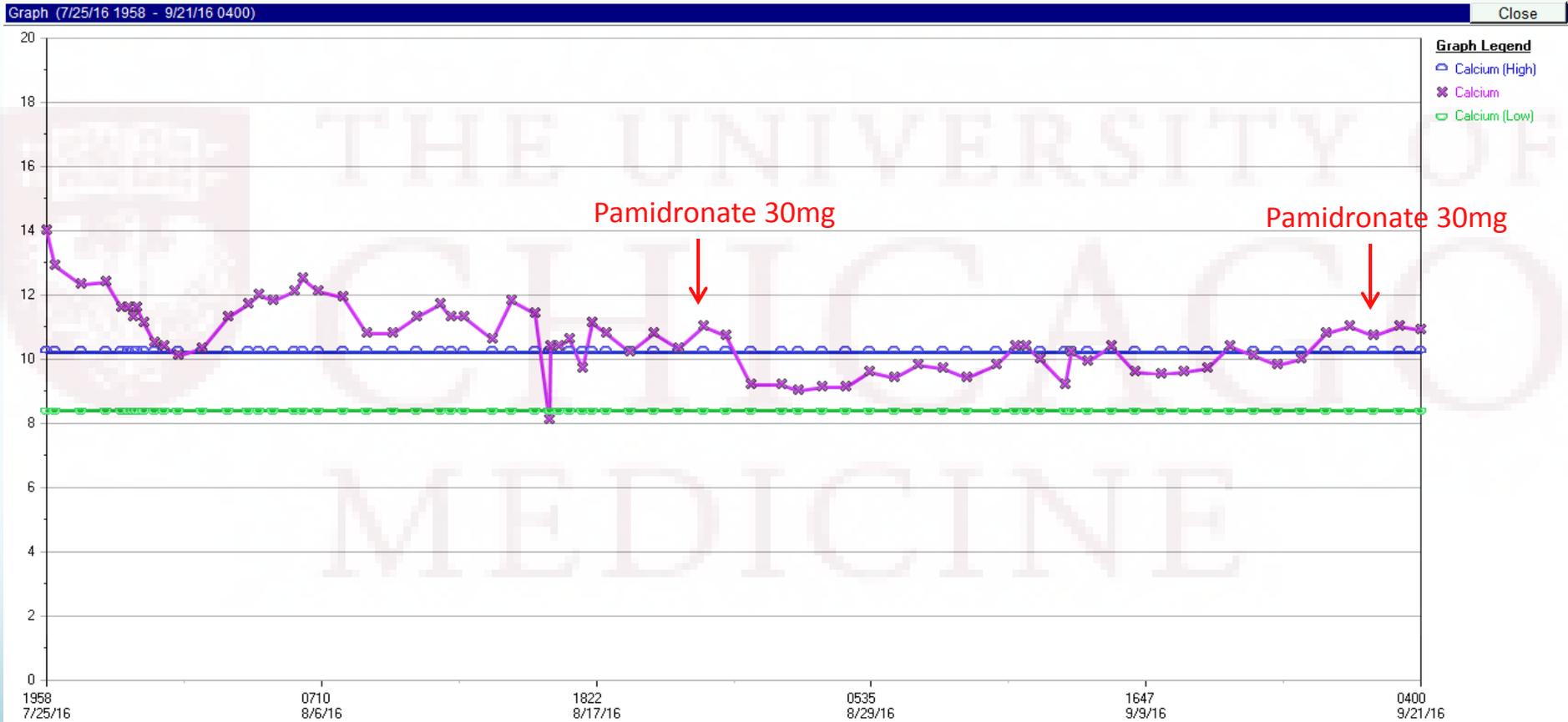
Location of ectopic glands	No. of ectopic glands	MIBI: no. correct (161/197) Overall sensitivity 89 %, PPV 90 %	US: no. correct (35/65) Overall sensitivity 59 %, PPV 90 %
Thymus	77 (38 %)	61/74 (82 %)	11/23 (48 %)
Retroesophageal sites	62 (31 %)	54/61 (89 %)	11/19 (58 %)
Intrathyroidal sites	37 (18 %)	28/36 (78 %)	10/12 (83 %)
Mediastinal sites	13 (6 %)	11/13 (85 %)	0/2 (0 %)
Undescended	8 (4 %)	6/8 (75 %)	3/4 (75 %)
Carotid sheath	5 (3 %)	1/5 (20 %)	0/3 (0 %)

MIBI technetium-99m-sestamibi, *US* ultrasonography, *PPV* positive predictive value

Hospital course

- ENT discussed with family, surgical resection would have high morbidity. Defer surgery.
- IR unable to place G tube due to lack of safe window/hiatal hernia. Required continuous IVF for hydration
- For hypercalcemia, Pamidronate re-dosed 4 weeks after initial dose. Continued Cinacalcet at 90mg BID and vitamin D3 at 500IU daily.

Calcium trend



Discharged to NH... missed Endocrinology follow up

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