THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

“57 Year Old Male with Hyperparathyroidism”

57 Year Old Male with Hyperparathyroidism

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Objectives

- Discuss primary vs secondary hyperparathyroidism
- Discuss lithium induced parathyroid dysfunction

Initial Presentation

- 57 year old male presented with hyperparathyroidism and osteoporosis
  - First visit in 6/2019
  - Diagnosed with osteopenia in 2014
  - No history of fractures
  - Remote history of kidney stones
  - Family history – father had osteopenia

Past Medical History

- Bipolar disorder
  - Previously on lithium (stopped in early 2000s) and valproate
  - Currently on lamotrigine
  - Started on levothyroxine by psychiatrist
- Stage 1 follicular lymphoma involving the left inguinal LN
  - Diagnosed in 3/2018
  - S/p radiation in 6/2018
  - PET/CT in 2019 showed complete remission
- Bicuspid aortic valve s/p replacement
- CKD stage 3, thought to be 2/2 lithium
- GERD

Levothyroxine treatment

- His psychiatrist put him on the thyroid hormone as adjuvant treatment for dysthymia
  - Started when he was on lithium treatment
  - Improvement in mood on levothyroxine

Other History

- Past surgical history
  - Aortic valve replacement in 2013
  - Tonsillectomy and adenoidectomy as child
- Social history
  - Denies tobacco, alcohol, illicit drugs
  - Works as property manager
  - Northwestern graduate in Economics, diagnosed with bipolar shortly after college
- Family history
  - Mother – Hashimoto's
  - Father – osteopenia, renal cell carcinoma
  - No family history of hip fractures

Other History

- Medications
  - Lamotrigine 100mg
  - Wellbutrin 300mg
  - Benztropine 0.5mg
  - Levothyroxine 50mcg
  - Aspirin 81mg
  - Famotidine 40mg
  - Finasteride 5mg
  - Vitamin D3 1000 IU daily
  - Calcitriol 0.25 twice weekly
- Allergies
  - Valproate
  - Olanzapine
  - Ziprasidone
  - Bactrim

Review of Systems:

- Constitutional: **+fatigue;** No fever, chills, activity change, weight change
- HEENT: No visual disturbance, hearing loss, congestion, sore throat, neck pain
- Resp: No cough, shortness of breath
- CV: No chest pain, palpitations, LE edema.
- GI: No nausea or vomiting. No abdominal pain, d/c, or blood in stool.
- MSK: No myalgias.
- Skin: No rashes or ulcers.
- Neuro: No seizures, syncope, headache, lightheadedness
- Endo: No heat/cold intolerance. No hair/skin changes noted.
- Heme: No adenopathy
- Psych: **Mood stable**

Physical Exam:

- Vitals: 74 kg, BMI 26, Temp 97.5, HR 74, RR 18, BP 110/72, SpO2 100%
- General: No apparent distress. Appears stated age.
- HEENT: No pharyngeal erythema. PERRL, EOMI.
- Neck: No neck tenderness. No thyromegaly or thyroid nodules appreciated.
- Cardiovascular: mechanical heart valve; regular rate and rhythm. No peripheral edema.
- Pulmonary/Chest: clear to auscultation bilaterally.
- Gastrointestinal: soft, non-tender, non-distended. No rebound or guarding.
- Musculoskeletal: normal range of motion of joints.
- Neurological: Alert & oriented, no focal deficits
- Skin: No apparent bald spots. No acanthosis nigricans.
- Psychiatric: normal mood, thought content, appropriate.

Review of previous labs

CHEM PROFILE

Component Name	12/4/2017	7/29/2017	4/20/2017	11/9/2015	4/15/2015	1/31/2013	1/27/2012	9/2/2011
Glucose	93	88	99	91	90	82	90	96
BUN	32 (H)	32 (H)	27 (H)	29 (H)	17	19 (H)	14	11
Creatinine	2.1 (H)	2.1 (H)	2.1 (H)	2.0 (H)	1.8 (H)	1.6 (H)	1.6 (H)	1.9 (H)
eGFR	33 (L)	33 (L)	33 (L)	37	42	49	49	40
Sodium	137	138	138	140	140	137	141	143
Potassium	4.6	4.0	4.4	4.6	4.5	4.2	4.3	3.6
Chloride	103	108	106	106	107	102	105	111 (H)
CO2	25	24	25	28	28	30	28	25
Calcium	9.8	9.7	9.3	10.5	10.3	9.3	9.4	8.8
Total Protein		6.7						
Albumin		3.7						
Total Bilirubin		0.9						
AST (SGOT)		19						
ALT (SGPT)		19						
Alkaline Phosphatase		94						

PARATHYROID

Component Name	12/4/2017	4/20/2017	11/9/2015	1/27/2012
Parathyroid Hormone (Intact)				88.5 (H)
PTH	179.8 (H)	189.8 (H)	136.4 (H)	

OTHER CHEM

Component Name	12/4/2017	4/20/2017	11/9/2015	1/27/2012
Uric Acid				
Phosphorus	3.0	3.1	2.9	2.8
Magnesium	2.1	2.2		1.9
Vitamin D 25-Hydroxy			78.1	

Initial Presentation

- Repeat labs on 6/21/19
  - Calcium 9.4
  - PTH 164
  - Phosphorus 2.3
  - GFR 39
  - 25-OH vitamin D 58
  - TSH 0.95
- Review of labs in EPIC over last year – calcium ranging 9.3 to 10.1

Labs

	Ref. Range	7/6/2019 08:35	7/25/2019 07:56	8/5/2019 13:47	8/16/2019 07:16	9/14/2019 10:38	10/15/2019 07:46	11/11/2019 13:04	12/5/2019 13:12
Inorganic Phosphate	Latest Ref Range: 2.5 - 4.4 mg/dL	2.8			3.3				
Calcium	Latest Ref Range: 8.4 - 10.2 mg/dL	9.6	10.0	10.1	10.2	10.2	10.2	9.8	9.8
eGFR, Non-African American	Latest Ref Range: >59 mL/min/BSA	39 (L)	39 (L)	37 (L)	33 (L)	34 (L)	34 (L)	34 (L)	37 (L)
25-Hydroxy Vitamin D	Latest Ref Range: 12 - 99 ng/mL								56
PTH, Intact	Latest Ref Range: 15 - 75 pg/mL	165 (H)			116 (H)		107 (H)		169 (H)
Thyrotropin	Latest Ref Range: 0.30 - 4.00 mcU/mL				2.00	1.88			0.94

Diagnostic Imaging

Procedure:	Procedure Date/Time:	Accession #	Patient Age at Exam:
XR DEXA SCAN AXIAL	3/8/2019 13:54 CST	XR-19-0142464	57 years

CPT code
77080

Your patient [redacted] completed a BMD test on 03/08/2019 using the Lunar Prodigy Advance DXA System (software version: 16 [SP 1]) manufactured by GE Healthcare. The following summarizes the results of our evaluation.

Height: 66.0 in.
Weight: 168.0 lbs.
Treatments:

DENSITOMETRY RESULTS:

Region	Date	T-score	BMD	%Change	Change(*)
Neck Left	03/08/2019	-3.2	0.655 g/cm2	-	
Neck Right	03/08/2019	-3.0	0.682 g/cm2	-	
Total Left	03/08/2019	-2.4	0.759 g/cm2	-	
Total Right	03/08/2019	-2.6	0.723 g/cm2	-	
L1-L4	03/08/2019	-0.9	1.113 g/cm2	-	
L2-L4	03/08/2019	-0.8	1.146 g/cm2	-	

ASSESSMENT:
The BMD measured at Femur Neck Left is 0.655 g/cm2 with a T-score of -3.2. This patient is considered osteoporotic according to World Health Organization (WHO) criteria. Fracture risk is high.

World Health Organization (WHO) criteria for post-menopausal, Caucasian Women:
Normal: T-score at or above -1 SD
Osteopenia: T-score between -1 and -2.5 SD
Osteoporosis: T-score at or below -2.5 SD

Bone Mineral Density

	BMD	T-score	Z-score
L1-L4 spine	1.123 g/cm2	-0.8	-0.4
Femoral neck	0.669 g/cm2	-3.1	-2.2
Forearm	0.979 g/cm2	-0.1	0.2

- FRAX based 10 year probability is 10.2% for major osteoporotic fractures and 3.3% for hip fracture.
- VFA was visualized from L5 to T3 and showed no fracture.

Clinic visits

- 6/19/19 appointment
  - Calcitriol stopped
  - Urine studies ordered
  - Patient to discuss with his psychiatrist to decrease levothyroxine from 50mcg to 25mcg
- 9/4/19 appointment
  - Levothyroxine was decreased to 25mcg and later increased to 50mcg by psychiatrist to help with dysthymia
  - Sestamibi scan ordered

	6/19/19	8/14/19	9/4/19
TSH	0.95	2.00	1.88

Urine Studies

	Ref. Range	7/6/2019 08:35
Collection Duration	Latest Units: h	24
Volume	Latest Units: mL	7,700
Rate	Latest Units: mL/min	5.347 (HH)
Urine Creatinine, Timed	Latest Ref Range: 1,000 - 2,000 mg/24hr	1,386
Urine Calcium, Timed	Latest Ref Range: 100 - 300 mg/24hr	<77 (L)
Urine Potassium, Timed	Latest Ref Range: 25 - 120 mmol/24hr	85
Urine Sodium, Timed	Latest Ref Range: 40 - 220 mmol/24hr	<231 (H)
Urine Phosphorus, Timed	Latest Ref Range: 400 - 1,300 mg/24hr	662

- Difficult to interpret 2/2 high volume and potential dilution
  - Possible nephrogenic DI in setting of prior lithium use?
  - Patient is hesitant to retest but would consider in the future.

Sestamibi scan

NM PARATHYROID IMG W/SPCT AND CT ANTMCL LCLZTN, 9/17/2019 11:00 AM

CLINICAL INFORMATION: Male 58 years old Reason: hyperparathyroidism; sestamibi History: hyperCa

TECHNIQUE: 21.2 mCi Tc-99m sestamibi was injected i.v. Early and delayed planar and early SPECT/CT images were acquired through portions of the neck and thorax. (The low-dose noncontrast CT was not of diagnostic quality and used only for attenuation correction and localization of the SPECT images).

COMPARISON: None.

FINDINGS: There is physiologic distribution of the radiopharmaceutical on early views with a faint focus of increased activity at the lower pole of the right thyroid on delayed views, suspicious for parathyroid adenoma.

IMPRESSION: Faint focus of increased activity at the lower pole of the right thyroid suspicious for parathyroid adenoma.

Does patient have primary vs secondary HPT?

Does patient have primary vs secondary HPT?

Primary HPT

- Lithium therapy can cause primary hyperparathyroidism
- Phosphorus levels have been low-normal which points away from secondary hyperparathyroidism
- Possible parathyroid adenoma on sestamibi scan

Secondary HPT

- Decreased GFR in 30-40s
- Mostly normocalcemic, besides one calcium of 10.5 in 2015 no evidence of hypercalcemia

Nephrology referral

- Patient was being seen by outside nephrologist for years
  - Had started patient on calcitriol 0.25mg twice weekly for years
  - We stopped calcitriol at 6/2019 appointment
  - Patient was referred to UCMC Nephrology department

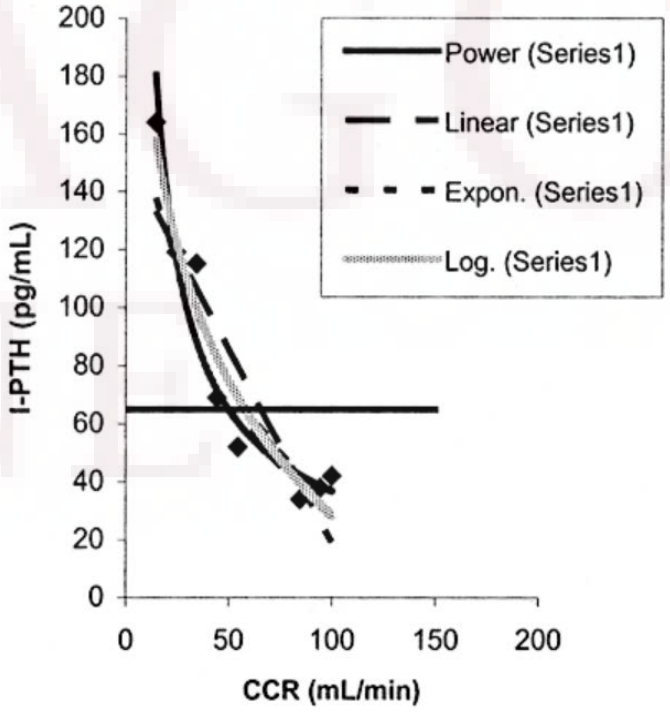
Nephrology referral

- Seen by Nephrology in 11/2019
  - Suspect hyperparathyroidism is not related to renal disease
  - Per note “At this degree of renal function would not expect secondary hyperparathyroidism and would expect calcium to be lower.”
  - Agree with stopping calcitriol
  - Consider cinacalcet

Table 15. Target Range of Intact Plasma PTH by Stage of CKD

CKD Stage	GFR Range (mL/min/1.73 m²)	Target “intact” PTH (pg/mL [pmol/L])
3	30-59	35-70 [3.85-7.7 pmol/L] (OPINION)
4	15-29	70-110 [7.7-12.1 pmol/L] (OPINION)
5	<15 or dialysis	150-300 [16.5-33.0 pmol/L] (EVIDENCE)

KDOQI guidelines 2003



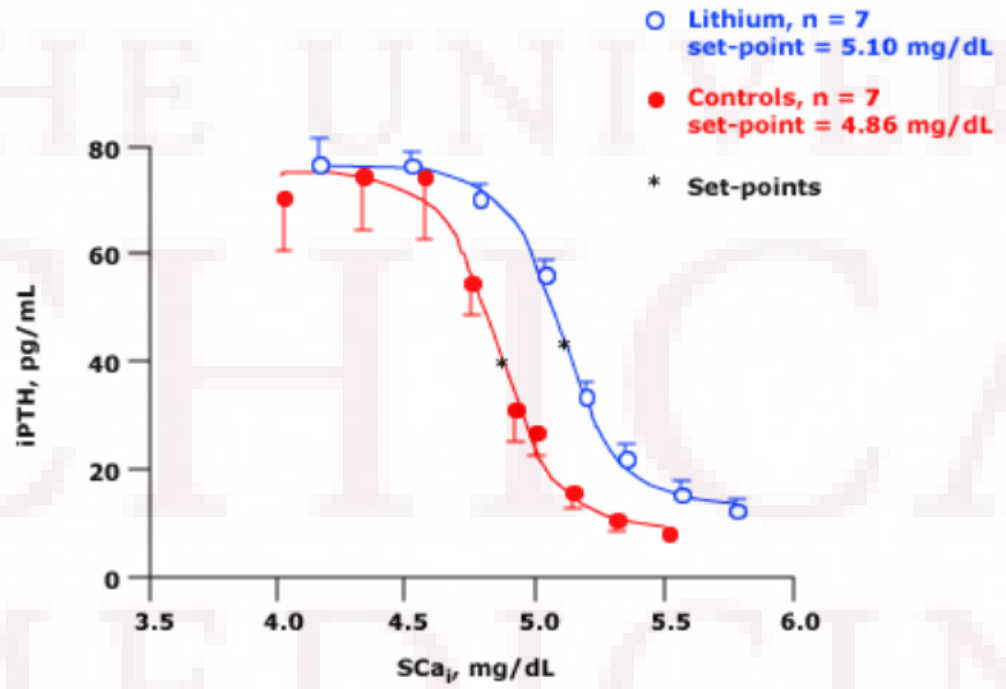
Lithium induced HPT

- Leading cause of hypercalcemia in lithium-treated patients
- The prevalence of hyperparathyroidism in chronic lithium users (>10 years) has been estimated at approximately 10–15%

Mechanism

- May directly stimulate PTH production
- Change in the calcium-sensing mechanism within the parathyroid gland, decreases parathyroid gland sensitivity to calcium
- Hypercalcemia might also be caused by hypocalciuria as a result of mild renal function impairment
- Lithium may lead to exacerbation of pre-existing primary hyperparathyroidism

Mean (±SD) calcium-PTH dynamics in normal subjects and patients receiving lithium carbonate



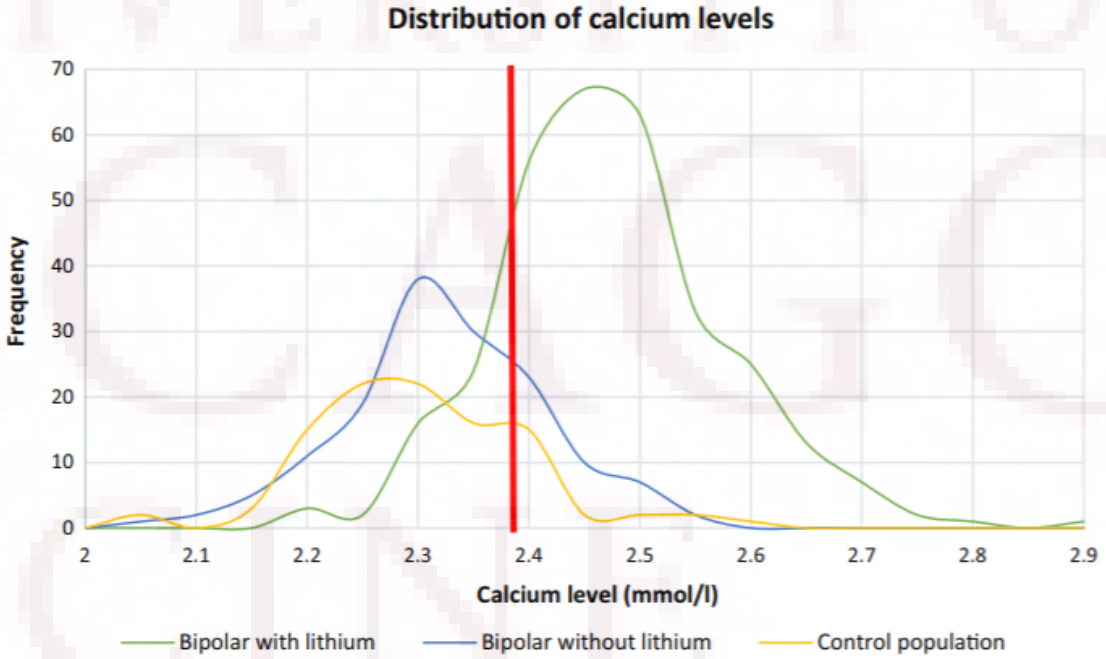
The curves were generated by measurements of serum PTH 30 minutes after serum ionized calcium concentrations had been raised or lowered by administration of calcium or citrate, respectively. The serum calcium-PTH curve is shifted to the right in the lithium-treated patients, and the

Meehan et al.

Meehan et al.

- Retrospective analysis
- 313 patients with bipolar disorder treated with lithium in central Sweden
- 148 BP without lithium and randomly selected control population of 102 individuals

Fig. 2 Distribution of calcium values for the three separate study groups. The available values included bipolar with lithium treatment ($n = 313$), bipolar without lithium ($n = 148$), population-based control group ($n = 102$). The median calcium value for the group as a whole was 2.37 mmol/l (illustrated with red line). Eighty-seven patients had P–Ca > 2.5 mmol/l; of those, eighty-two (94.3%) were bipolar patients with lithium treatment



Timing of HPT

- Patient developed HPT years after stopping lithium treatment
- No case reports found on developing HPT after lithium treatment was stopped
- Mallette et al. showed normalization of serum calcium is more likely to occur 1-4 weeks post-lithium withdrawal in patients with a relatively short duration of lithium use (less than a few years)
  - Less likely in patients receiving lithium for more than 10 years

Meehan et al.

Table 4 Demographic data, pre- and post-operative laboratory data including histopathological diagnoses and follow-up results of seven lithium-treated bipolar patients having undergone parathyroidectomy for hyperparathyroidism

Case no.	Sex	Age	Lithium duration at operation	No. glands identified	No. glands extirpated	Morphology	PTH before surgery (ref: 10–73)	Phosphate before surgery (ref: ♀ 0.8–1.5, ♂ 0.7–1.6)	Ca (ref: 2.10–2.50)		Crea (ref: ♀ 45–90, ♂ 60–105)		Thyroid disease	Cure at initial operation	Follow-up
									Before	After	Before	After			
1	F	65	28	3	1.5	Normal	106	0.99	2.73	2.47	92	77	Nontoxic goitre	No	12 years, recurrent
2	F	74	34	4	3	Hyperplasia	170	0.92	2.79	2.45	78	69	Multinodular goitre	No	7 years, recurrent
3	F	65	33	2	2	Hyperplasia	117	1.08	2.66	2.43	74	72	None	No	12 years, recurrent
4	M	50	14	4	2	Hyperplasia	67	n/a	2.75	2.02	109	109	Hypothyroidism	No	12 years, recurrent
5	M	55	29	2	1	Lipoadenoma	268	0.8	2.83	2.18	154	187	None	No	11 years, persistent[a]
6	M	62	36	2	1	Adenoma	102	n/a	2.69	2.47	107	111	Hypothyroidism	No	5 years, recurrent
7	F	46	19	4	2.5	Hyperplasia	66	n/a	2.67	2.32	81	97	Hypothyroidism	No	11 years, recurrent

[a]Patient re-operated 2016 with the extirpation of a further two parathyroid glands, weight 1820 mg; normocalcemic at latest follow-up

Table 1. Variables in patients treated with lithium for affective psychiatric disorders who developed primary hyperparathyroidism.

Patient no.	Gender	Age (years)	Duration of Li^{++} therapy (years)	Daily dose of Li^{++} (mg)	Parathyroid pathology	Location of enlarged gland(s)
1	F	66	11	900	Single adenoma	RS
2	F	57	21	600	Single adenoma	LI
3	F	74	24	300	Single adenoma	LS
4	F	59	7	300	Single adenoma	RI, IT
5	F	61	12	600	Single adenoma	LI
6	F	56	10	900	Single adenoma	RS
7	M	60	3	600	Single adenoma	RI
8	M	47	10	1600	Single adenoma	LI
9	F	58	7	450	Double adenoma	LS, LI
10	F	66	2	1200	Double adenoma	RI, LI
11	M	34	11	600	Four-gland hyperplasia	All
12	F	61	10	900	Double adenoma	RS, LI
13	F	58	12	300	Single adenoma	LI
14	F	51	5	600	Single adenoma	RI
15	M	63	9	900	Single adenoma	RI

RS: right superior; RI: right inferior; LS: left superior; LI: left inferior; IT: intrathyroidal; Li^{++}: lithium.

Awad et al.

- 15 patients with affective psychiatric disorders who were treated with chronic lithium therapy from 1982 to 1997, all of whom were operated on for primary hyperparathyroidism
- Mean age was 58 ± 10 years, the mean duration of lithium therapy 10.7 ± 6 years, and the mean preoperative calcium level 11.7 ± 0.5 mg/dl.
- Of the 15 patients, 14 (92%) had adenomas (11 single, 3 double), and 1 (8%) had four-gland hyperplasia

Normocalcemic PHPT

- PTH levels are elevated but serum calcium is always normal
  - Compared to occasional normocalcemia in patients with hypercalcemic PHPT
- Often found in patients undergoing evaluation for low bone density
- Secondary causes for hyperparathyroidism must be ruled out
- May occur early in the natural history of PHPT

▶**Table 1** Baseline characteristics of the 131 study patients.

Variable	Normocalcemic PHPT	Hypercalcemic PHPT	p-Value
Subjects (n)	25	106	
Age (years)	62 ± 12	67 ± 14	0.087
Sex ratio (male/female)	6/19	32/74	0.630
BMI (kg/m²)	27.6 ± 4.7	26.0 ± 5.4	0.206
Total corrected serum calcium (mmol/l)	2.34 ± 0.11	2.71 ± 0.20	0.000
Serum P (mmol/l)	0.98 ± 0.13	0.87 ± 0.19	0.006
Plasma 25-OH vitamin D (µg/l)	28 ± 9	20 ± 19	0.054
eGFR (ml/min)	80.52 ± 15.50	71.13 ± 22.68	0.017
Serum creatinine (mg/dl)	0.85 ± 0.17	0.99 ± 0.38	0.005
Urinary Ca (mmol/24 h)	4.9 ± 2.23	6.8 ± 4.8	0.016
Urine P (mmol/24 h)	25.1 ± 9.9	24.5 ± 11.01	0.866

Data expressed as mean ± SD; P: Phosphate; eGFR: Estimated glomerular filtration ratio; Reference range for serum calcium: 2.10–2.50 mmol/l; serum phosphate: 0.81–1.45 mmol/l; 25-OH vitamin D: 20–50 µg/l; serum creatinine: 0.66–1.28 mg/dl (men), 0.52–1.04 mg/dl (women); urinary Ca: 2.5–7.5 mmol/col.; urinary P: 13–42 mmol/col; Student's *t*-test and Pearson's chi-square test were used for statistical analysis of the quantitative variables and the qualitative variables, respectively. Level of significance: 5 %.

▶**Table 2** Clinical manifestations in normocalcemic and hypercalcemic PHPT.

	Normocalcemic PHPT	Hypercalcemic PHPT	p-Value
Nephrolithiasis	9 (25)	25 (106)	0.371
Fractures LS	3 (25)	14 (106)	0.599
Osteopenia	9 (16)	33 (77)	0.619
Osteoporosis	4 (16)	25 (77)	0.619
Bone disease	13 (16)	58 (77)	0.612
BMD LS (g/cm²)	0.95 ± 0.15	0.91 ± 0.19	0.398
T score LS	−0.92 ± 1.38	−1.38 ± 1.7	0.319
BMD LH (g/cm²)	0.80 ± 0.11	0.80 ± 0.17	0.991
T score LH	−1.26 ± 0.78	−1.40 ± 1.18	0.641

Data expressed as subjects (studied subjects in the group) or mean ± SD. The data for bone evaluation of 16 normocalcemic and 77 hypercalcaemic subjects were studied; LS: Lumbar spine; LH: Left hip; Bone disease is the sum of osteopenia and osteoporosis. Student's *t*-test and Pearson's chi-square test were used for statistical analysis. Level of significance: 5 %.

Pierreux et al.

- Cross-sectional, observational design
- Patients with PHPT in UZ Brussel between January 1st 2007 and December 31st 2016
- 131 patients were studied

Should the patient have surgery?

- Indications for parathyroidectomy per NIH guidelines
  - Serum calcium > 1.0 mg/dL above the upper limit of normal
  - Marked hypercalciuria (> 400 mg/day) or renal stones
  - **Creatinine clearance < 60**
  - **Bone density at hip, lumbar spine, or distal radius with T-score < -2.5**
  - Age < 50 years
  - Patient requesting surgery or for who surveillance and follow-up is not feasible or desired

Is this patient's osteoporosis caused by hyperparathyroidism?

- Other potential causes
  - Anti-epileptic drugs (history of valproate treatment)
  - Family history – father had osteopenia
  - Iatrogenic hyperthyroidism

Follow up visit

- Seen in 11/2019
- Likely primary (in the setting of remote prior lithium use) with component of secondary from CKD stage 3
- Referral to endocrine surgery
- Trial of cinacalcet 30mg BID
- Consider decrease in levothyroxine dose

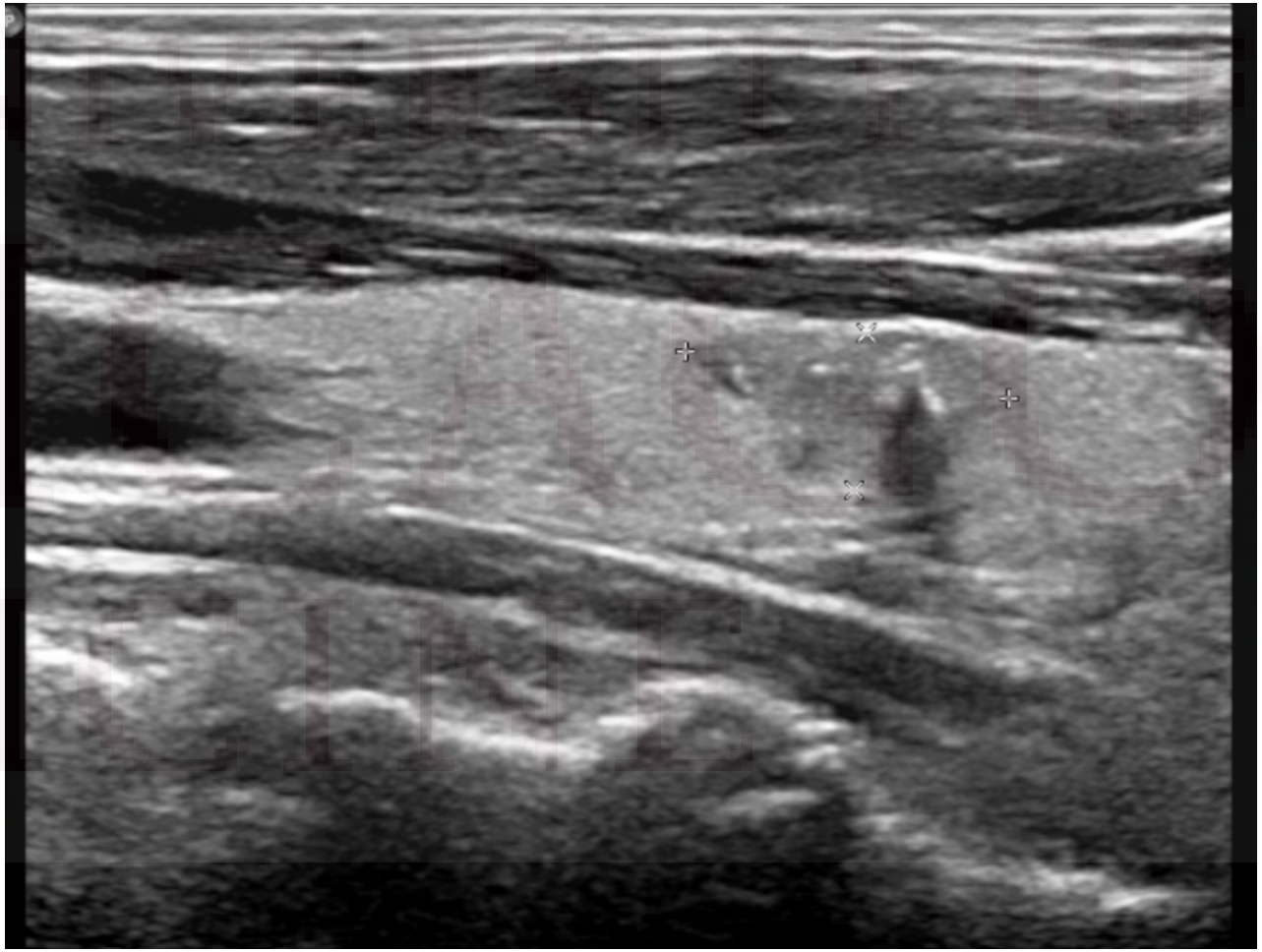
Endocrine surgery appointment

- Seen by Endocrine surgery in 12/2019
  - Plan for parathyroidectomy
  - Thyroid ultrasound ordered, now planning for FNA

Thyroid ultrasound

US THYROID, 12/20/2019

- RIGHT LOBE: There is a solid predominantly hypoechoic inferior right thyroid lobe nodule with slightly irregular margins and internal microcalcifications including a large shadowing coarse calcification. The nodule measures approximately 1.4 x 0.7 x 0.9 cm and demonstrates some internal vascularity.
- LEFT LOBE: No significant abnormality noted.
- ISTHMUS: No significant abnormality noted.
- IMPRESSION: 1.4 cm right thyroid lobe nodule is at least intermediate suspicion based on ATA criteria. Given size greater than 1 cm, FNA is recommended for further evaluation.



References

- Uptodate, Hyperparathyroidism
- Awad et al. Parathyroid Adenomas versus Four-gland Hyperplasia as the Cause of Primary Hyperparathyroidism in Patients with Prolonged Lithium Therapy. World J. Surg. 27, 486–488, 2003
- Babwah F, Buch HN. Normocalcemic primary hyperparathyroidism: a pragmatic approach. J Clin Pathol 2018;71:291–297
- Lowe et al. Normocalcemic Primary Hyperparathyroidism: Further Characterization of a New Clinical Phenotype. Journal of Clinical Endocrinology & Metabolism 92(8):3001–3005
- Mallette et al. Effects of lithium carbonate on human calcium metabolism. Arch Intern Med. 1986;146(4):770.
- Meehan et al. Lithium-Associated Hypercalcemia: Pathophysiology, Prevalence, Management. World J Surg (2018) 42:415–424
- Pierreux et al. Normocalcemic Primary Hyperparathyroidism: A Comparison with the Hypercalcemic Form in a Tertiary Referral Population. Horm Metab Res 2018; 50: 797–802