Interhospital Conference
Case 1

F1 Kaemkan Paechotrattnakul
F2 Kusuma Phimson
Advisor : Asst. Prof. Sirinart Sirinvaravong
Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University

Patient Profile

ผู้ป่วยหญิง	อายุ 45 ปี
ภูมิลำเนา	กรุงเทพมหานคร
อาชีพ	พนักงานบริษัท

Chief complaint

ปวดต้นขา 2 ข้าง เดินกะเผลก 2 ปีก่อนมา รพ.

Present illness

2 ปี ปวดบริเวณต้นขาด้านในทั้ง 2 ข้างเวลาเดิน เดินกะเผลก ค่อยๆเป็นมากขึ้นเรื่อย Pain score 5/10 ปฏิเสธประวัติอุบัติเหตุกระทบกระแทกมาก่อน รักษาด้วยยาแก้ปวดตามอาการ อาการพอดีขึ้นบ้าง ยังเดินกะเผลก ทำงานได้ปกติ

Present illness

2-3 เดือนที่ผ่านมา ปวดมากขึ้นเรื่อยๆ Pain score 8/10 ลุกจากท่านั่งและขึ้นบันไดลำบาก (ต้องจับราวบันไดเพื่อเหนี่ยวตัวขึ้น) ยังเดินได้แต่กะเผลก จึงมาตรวจกับศัลยแพทย์กระดูก ตรวจพบ x ray ผิดปกติ จึงส่งมาหาสาเหตุเพิ่มเติม

Past history

- History of elevated ALP ตั้งแต่ 2563 รักษาที่ รพ.แห่งหนึ่ง
  - US upper abdomen: Liver normal size, no hepatic mass, normal gallbladder and no intrahepatic duct dilatation
- DLP

Personal history

- Denied smoking, alcohol drinking
- Denied history of herbal use
- Denied history of consanguineous marriage
- Denied history of fracture

Family history

- No family history of Fracture
- Denied bone disease in family members

Current medication

- Ursolin (250) 1 x 2 o pc
- Pentifylline (400) 1 x 1 o pc
- Fenofibrate (200) 1 x 1 o pc

(Since 4/2023)

Physical examination

Vital sign: BT 37.4 c, PR 86 BPM, RR 14 /min, BP 116/79 mmHg

BW 54.2 kg Height 152 cm. BMI 23.4 kg/m^2

GA: no dysmorphic feature

HEENT: not pale conjunctivae, anicteric sclerae, no thyroid gland enlargement, no palpable neck mass

LN: no lymphadenopathy

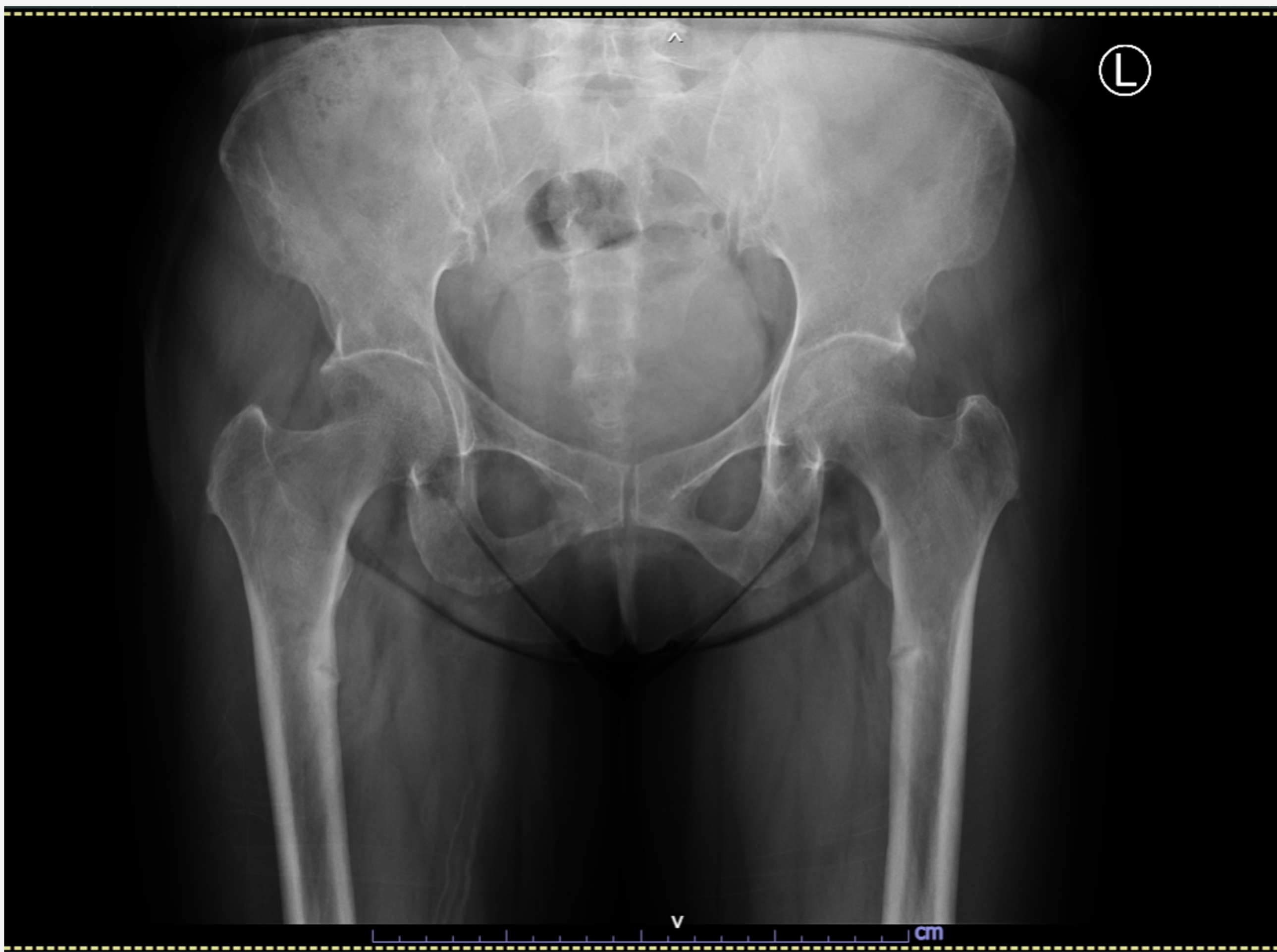
Physical examination

CVS: normal S1S2, no murmur
RS: lung clear and equal breath sound both lungs
Abdomen: no distension, not tender
Extremities: no edema, limit ROM in both Hip due to pain, mild tender both anterior superior iliac spine
Skin: no hypo/hyperpigmentation, no rash

Physical examination

Nervous System:

- E4V5M6 pupil 3 mm RTLBE
- Cranial nerves: Intact
- Motor system: Normotonia
- Motor power: Deltoid and hip flexors – grade IV/V
  Otherwise within normal limit
- Reflex 2+ all
- Sensory intact by pinprick sensation



Film Pelvis - Finding?

History & Physical examination ?

Additional history

- No polyuria, polydipsia or constipation
- No history of fragility fracture
- No history of height loss
- No history of KUB stone
- Regular menstruation
- No family history of abnormal calcium metabolism

Additional Physical examination

Height: 152 cm as baseline

HEENT: No blue sclerae, no acromegalic feature, no cushingoid appearance

Breast: No galactorrhea, no palpable breast mass

Back: No kyphosis

Extremities: No shortening of leg

Problem list

Problem list

- Chronic progressive Hip pain for 2 years
- Antalgic gait and proximal muscle weakness
- Pseudofractures on pelvic X-Ray
- History of elevated ALP without no biliary tract abnormality

Differential Diagnosis

Investigations

CBC

Hb (g/dL)	14.7 (12.0-16.0)	WBC (/cumm)	9660 (4000-10,000)
Hct (%)	43.8 (36.0-47.0)	Neutrophil (%)	68.2
MCV (fl)	85.5 (80.0-95.0)	Lymphocyte (%)	26.2
		Monocyte (%)	4.3
		Eosinophil (%)	0.9
		Basophil (%)	0.4
		Platelet count(/cumm)	454,000 (140,000-450,000)

Blood Chemistry

BUN	**7.2**	**mg/dL**
Creatinine	**0.52**	**mg/dL**
Sodium	**141**	**mmol/L**
Potassium	**3.5**	**mmol/L**
Chloride	**111**	**mmol/L**
CO2	**22**	**mmol/L**

Liver Function Test

Total protein	**8.1**	**g/dL**	**AST**	**20**	**U/L**
Albumin	**4.3**	**g/dL**	**ALT**	**19**	**U/L**
Globulin	**3.4**	**g/dL**	**ALP**	**415.9**	**U/L**
Total bilirubin	**0.48**	**mg/dL**			
Direct bilirubin	**0.27**	**mg/dL**			

Blood Chemistry

Gamma glutamyl transferase	**19 U/L**	**(5-36)**

Blood Chemistry

Total calcium	11.7	mg/dL	(8.4-10.2)
Albumin	4.3	g/dL	(3.5-5.2)
Phosphate	1.6	mg/dL	(2.3-4.7)

Blood Chemistry

PTH	895	pg/mL
25(OH)D	8	ng/mL

Thyroid Function Test

FT4	1.11	ng/dL	(0.70-1.48)
TSH	0.902	uIU/mL	(0.35-4.94)

I

V1

II

V2

III

V3

aVR

V4

aVL

V5

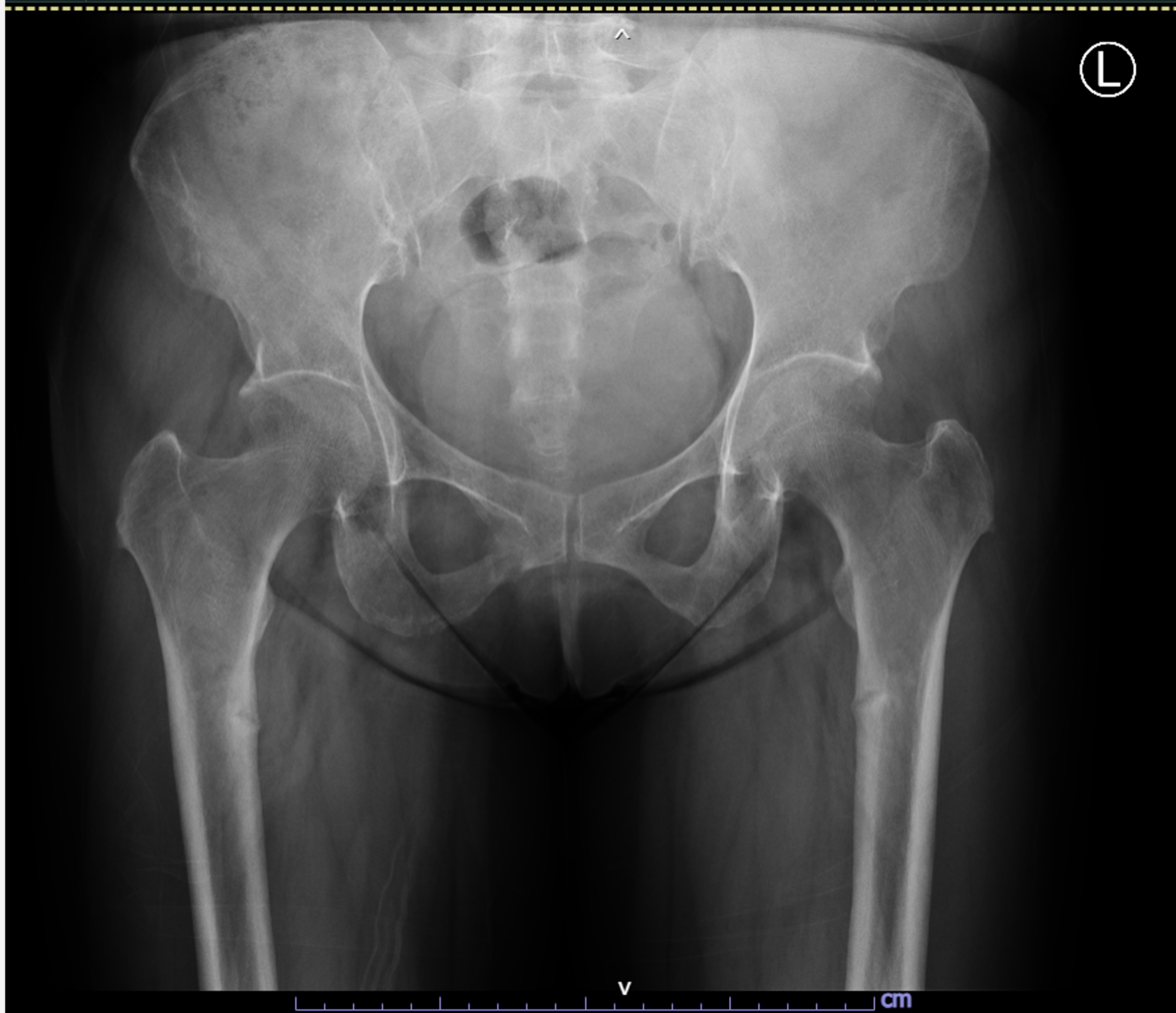
aVF

V6

2350K 03-10 07-01 Dept.: Exam:

Problem list

- PTH-dependent hypercalcemia
- Vitamin D deficiency
- Antalgic gait and proximal muscle weakness
- Pseudofractures on pelvic X- Ray



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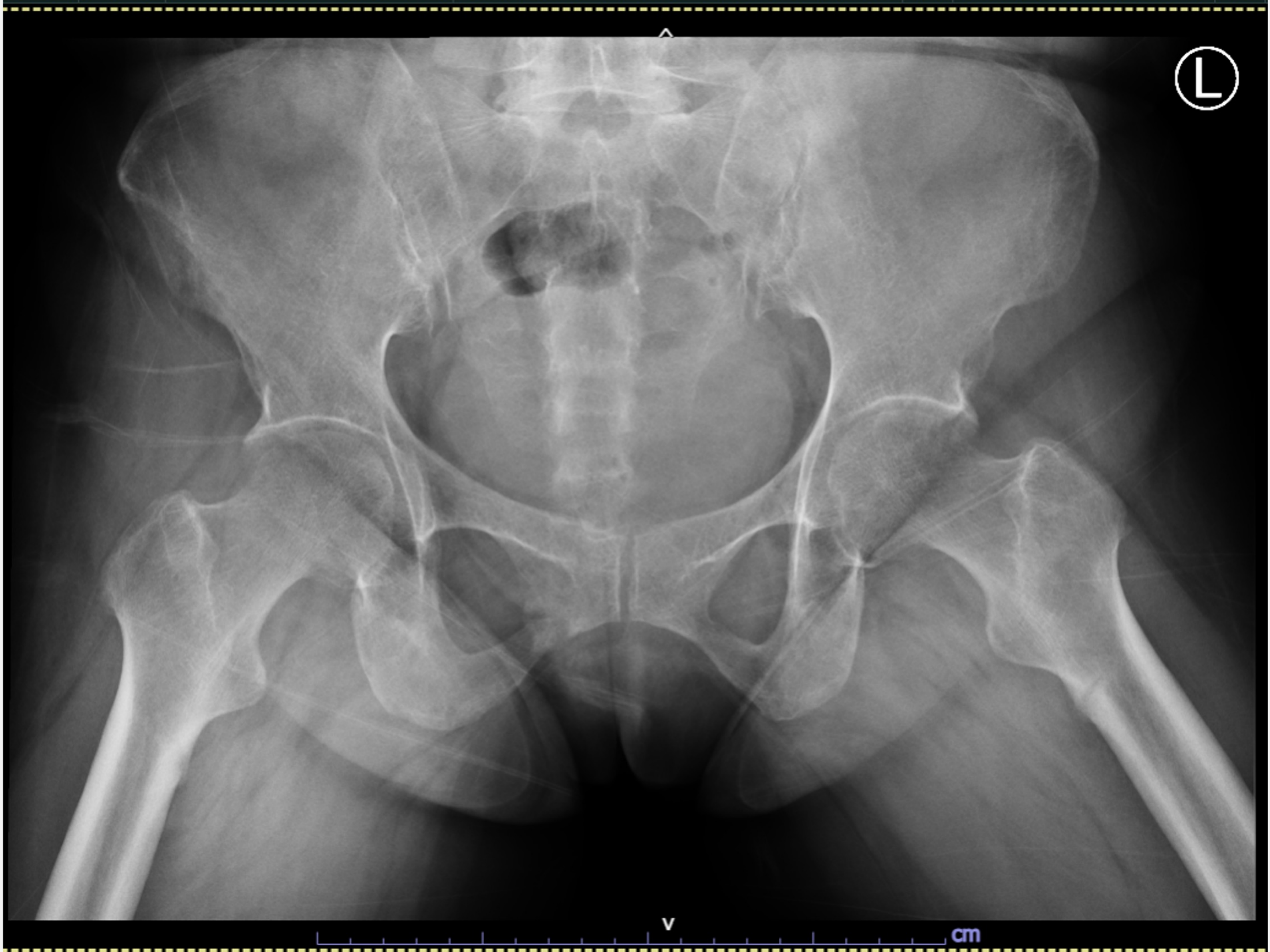
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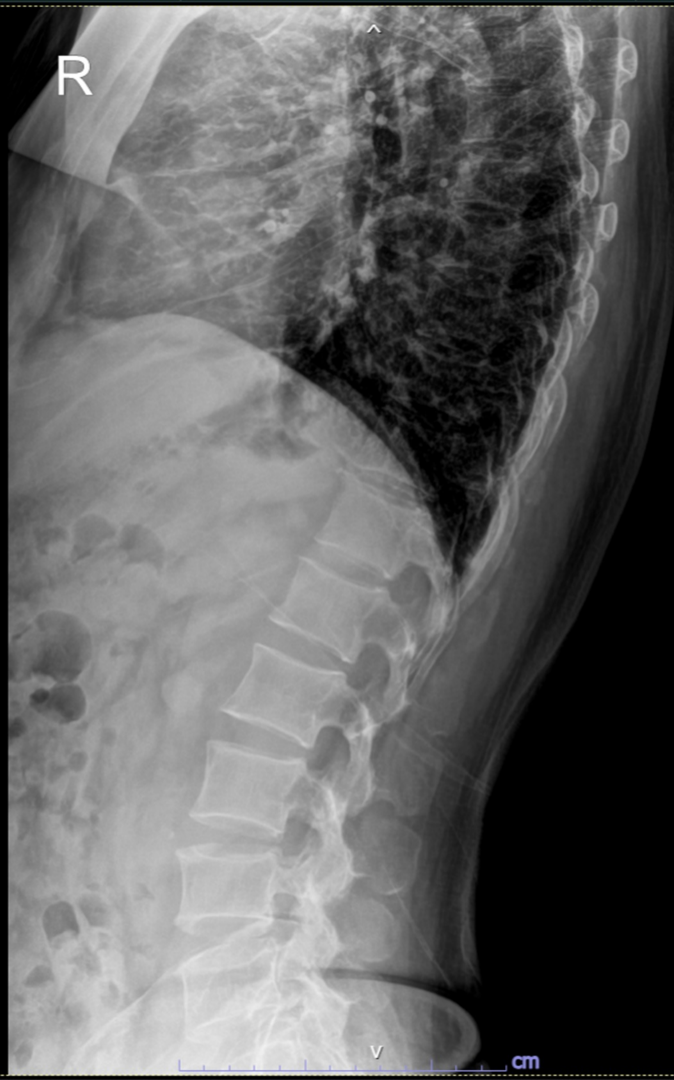
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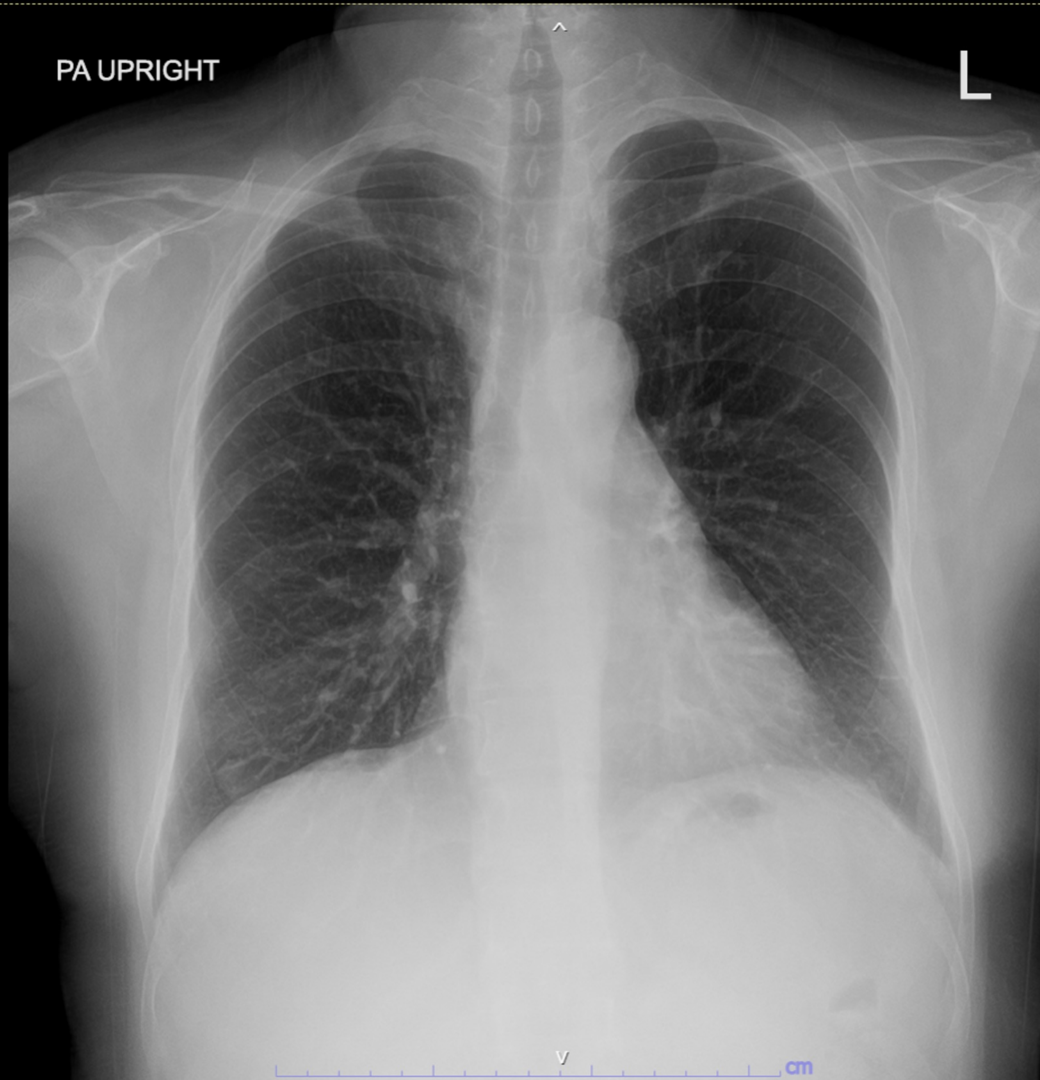
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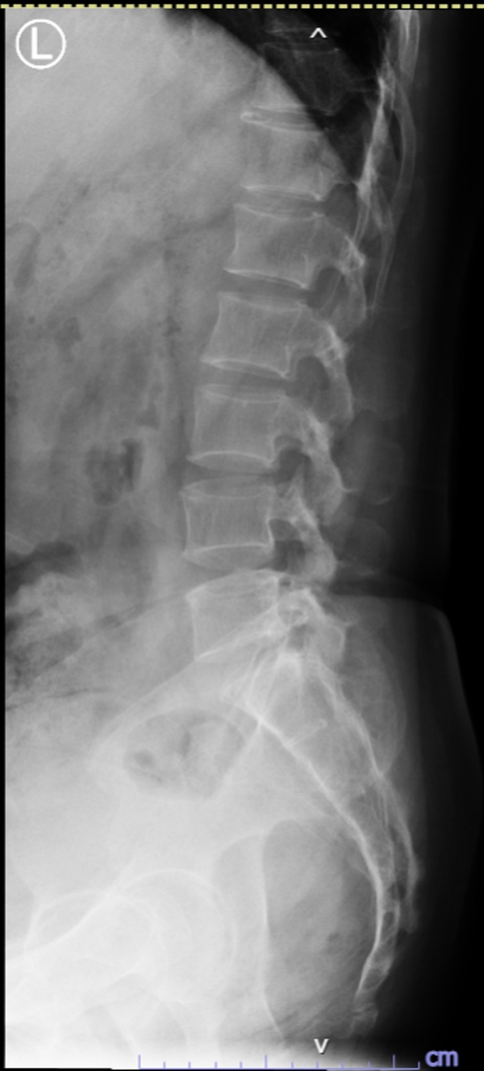
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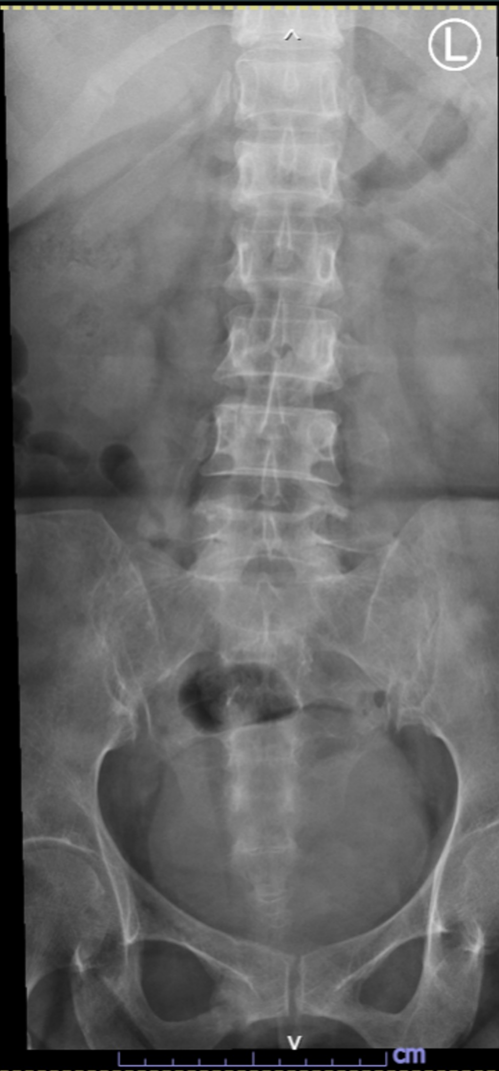
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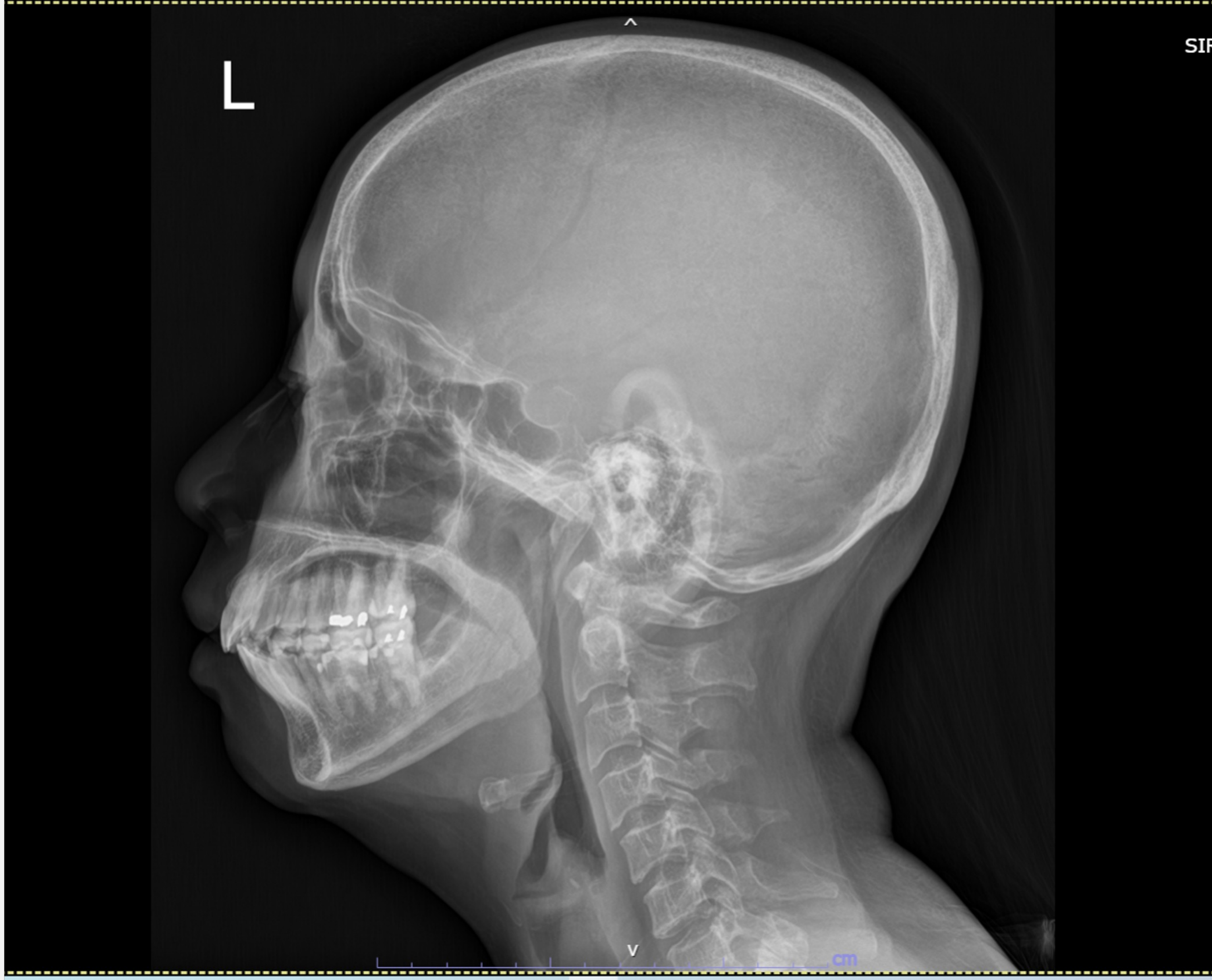
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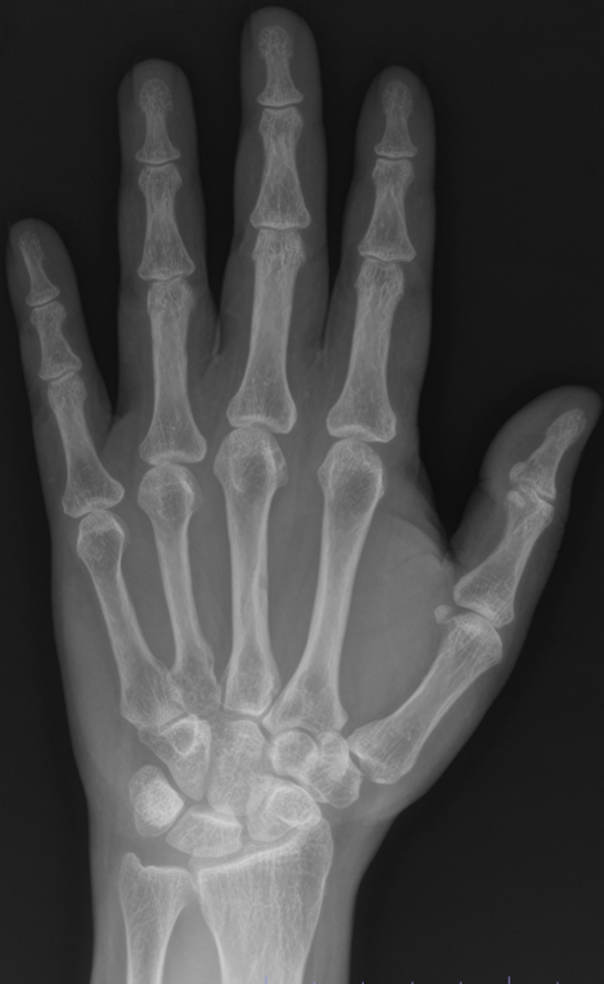
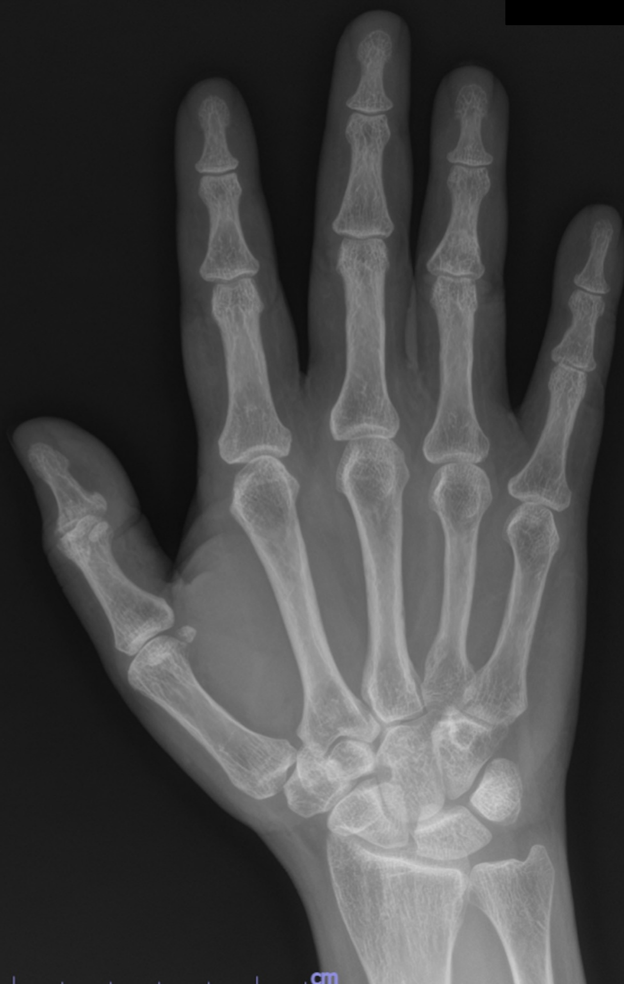
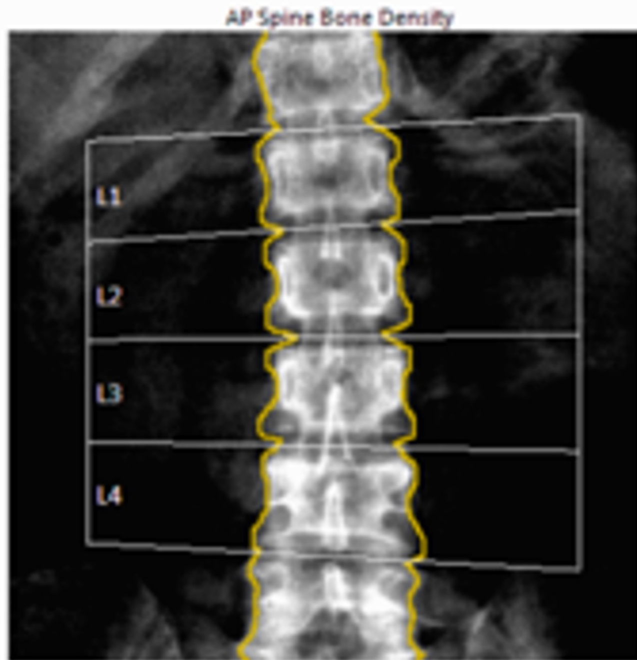
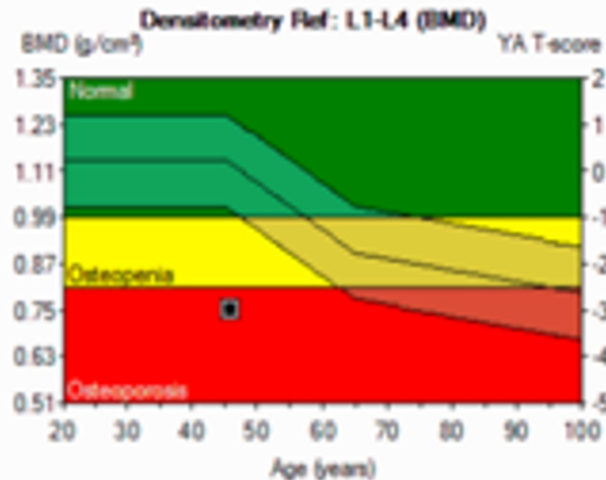




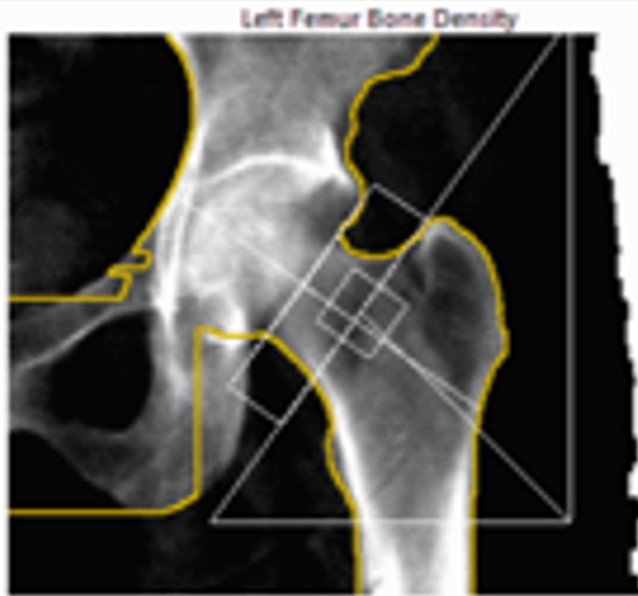


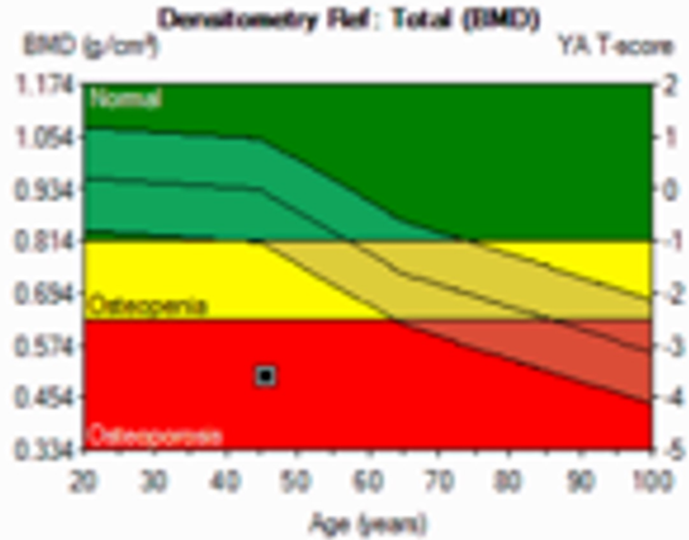


Region	BMD[1] (g/cm²)	Young-Adult[2] (%)	Young-Adult[2] T-score	Age-Matched[3] (%)	Age-Matched[3] Z-score
L1	0.650	61	-3.4	60	-3.6
L2	0.696	62	-3.5	61	-3.7
L3	0.783	70	-2.8	69	-2.9
L4	0.844	75	-2.3	74	-2.4
L1-L2	0.674	62	-3.5	61	-3.6
L1-L3	0.713	65	-3.2	64	-3.4
L1-L4	0.750	68	-3.0	67	-3.1
L2-L3	0.741	66	-3.2	65	-3.3
L2-L4	0.778	70	-2.8	69	-3.0
L3-L4	0.816	73	-2.5	72	-2.7

L1-L4	Z score	-3.1

DXA Scan

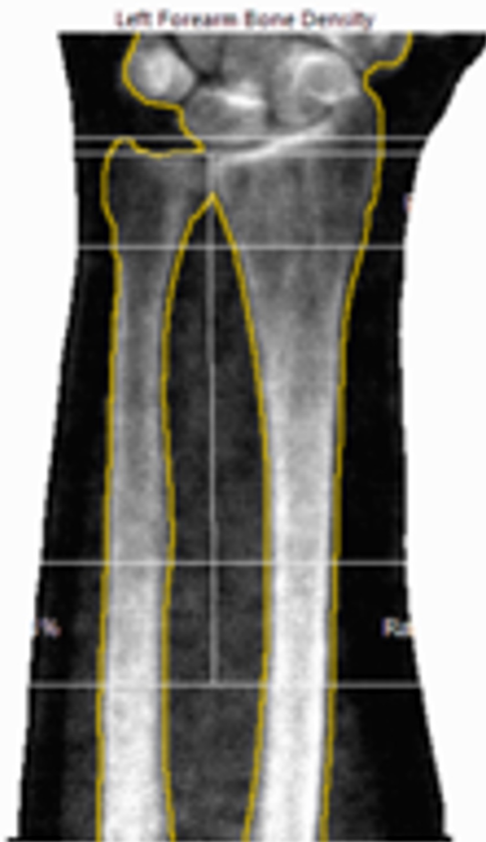


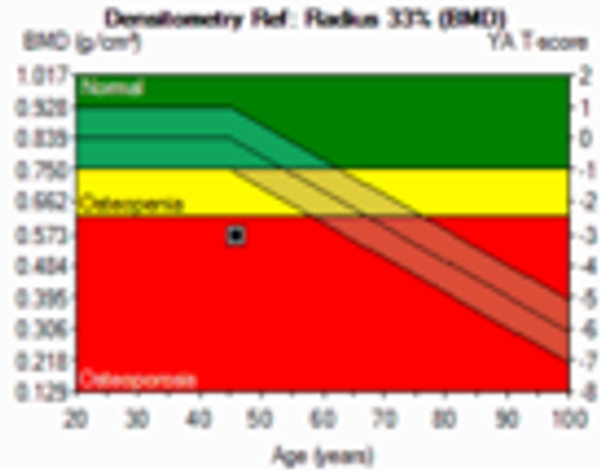


Femoral neck	Z score -3.2
Total Hip	Z score -3.5

Region	BMD[1,6] (g/cm²)	Young-Adult[2] (%)	Young-Adult T-score	Age-Matched[3] (%)	Age-Matched Z-score
Neck	0.472	52	-3.6	55	-3.2
Upper Neck	0.414	-	-	-	-
Lower Neck	0.529	-	-	-	-
Wards	0.327	37	-4.3	40	-3.8
Troch	0.358	48	-3.6	47	-3.6
Shaft	0.619	-	-	-	-
Total	0.502	54	-3.6	55	-3.5

DXA Scan

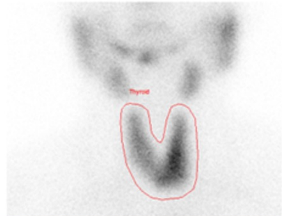


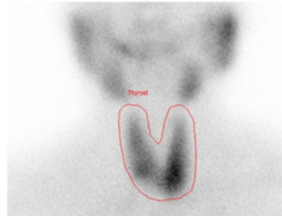


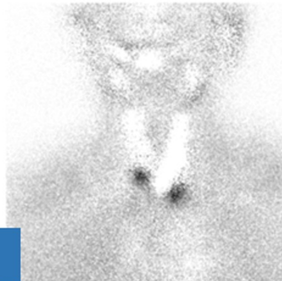
Region	BMD (g/cm²) [1]	Young-Adult [2] (%)	Young-Adult T-score	Age-Matched [3] (%)	Age-Matched Z-score
Radius UD	0.231	52	-4.7	53	-4.6
Ulna UD	0.146	-	-	-	-
Radius 33%	0.562	67	-3.2	68	-3.0
Ulna 33%	0.464	-	-	-	-
Both UD	0.199	-	-	-	-
Both 33%	0.514	-	-	-	-
Radius Total	0.373	58	-4.6	58	-4.4
Ulna Total	0.302	-	-	-	-
Both Total	0.344	-	-	-	-

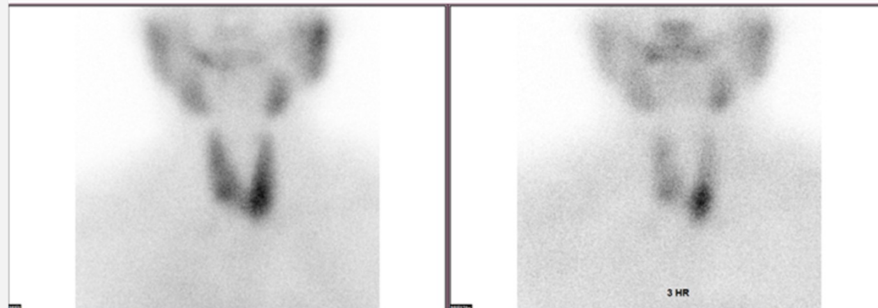
Left forearm Z score-3.0

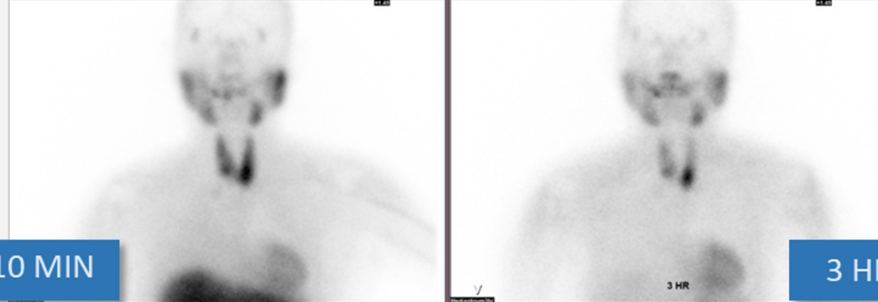
DXA Scan



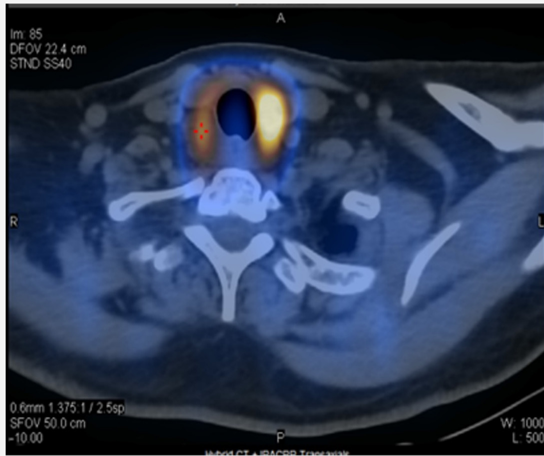


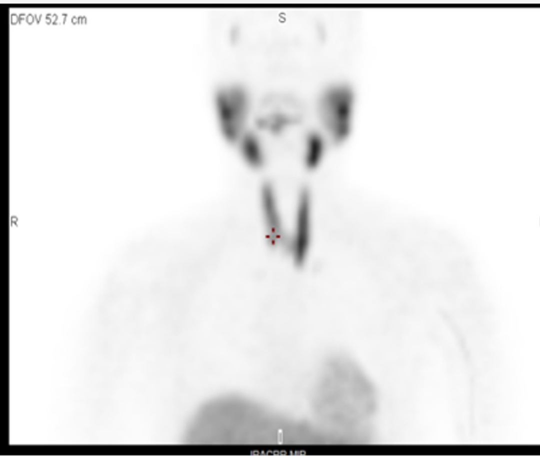




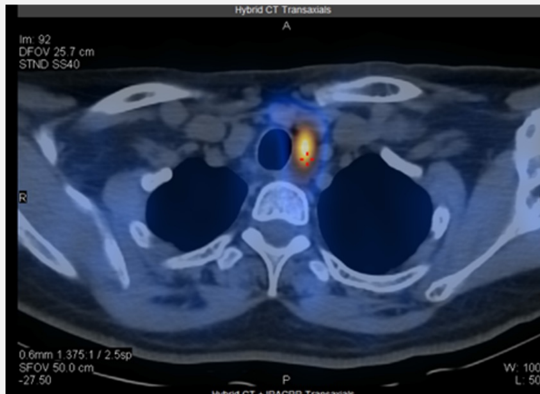


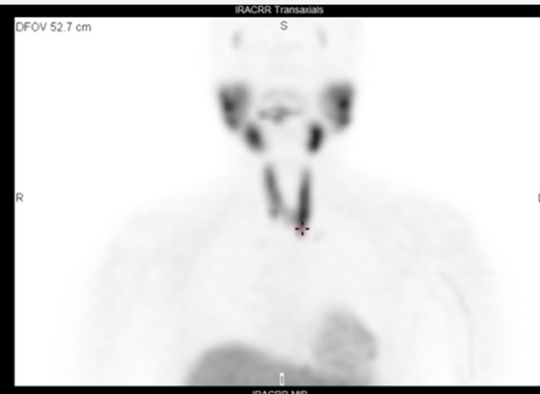
Parathyroid Scan





Right lower



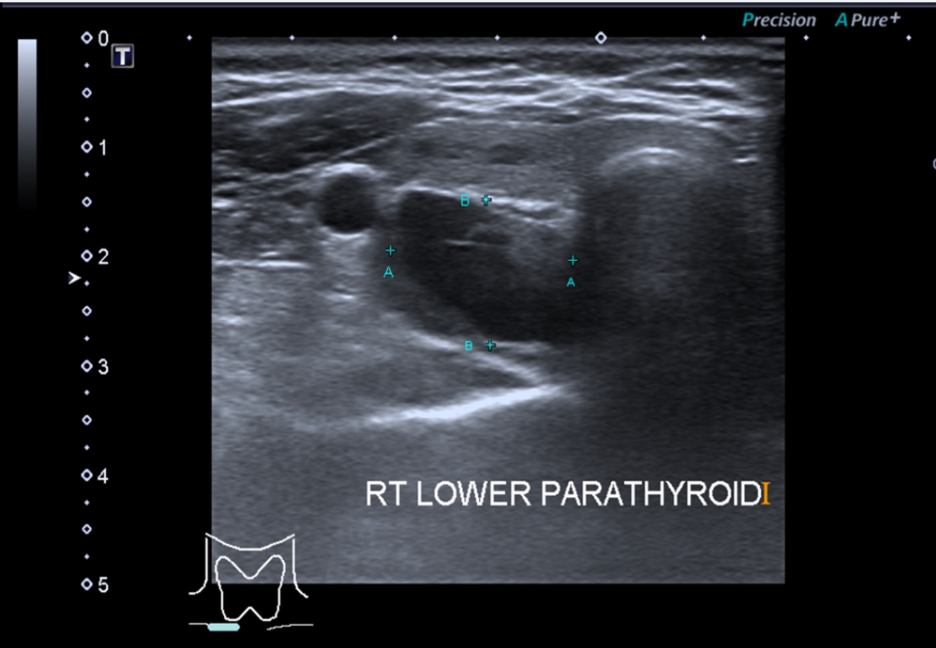


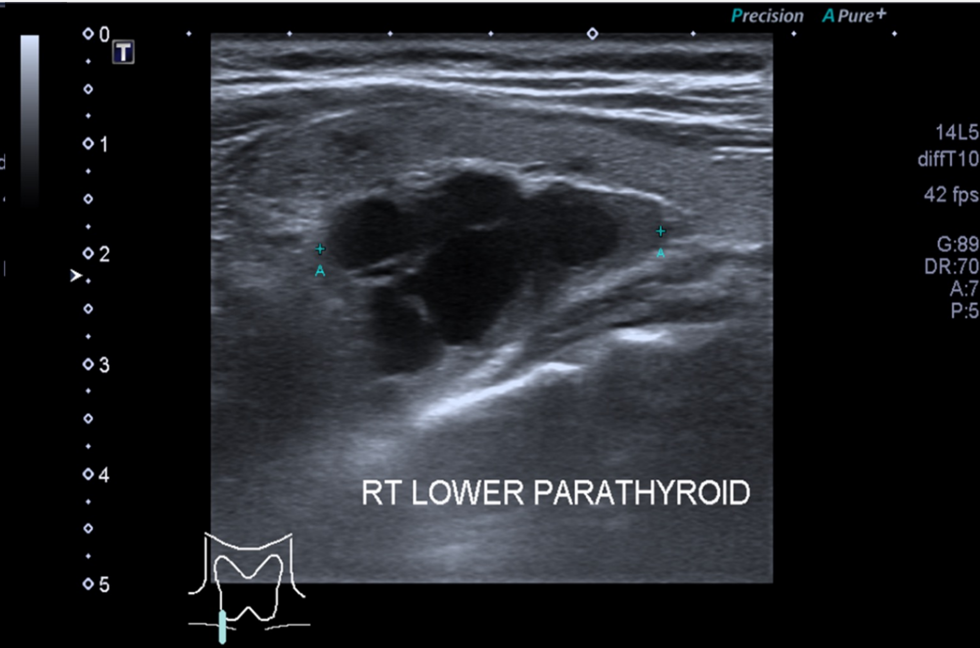
Left lower

Dual-phase 99mTc-sestamibi with SPECT/CT

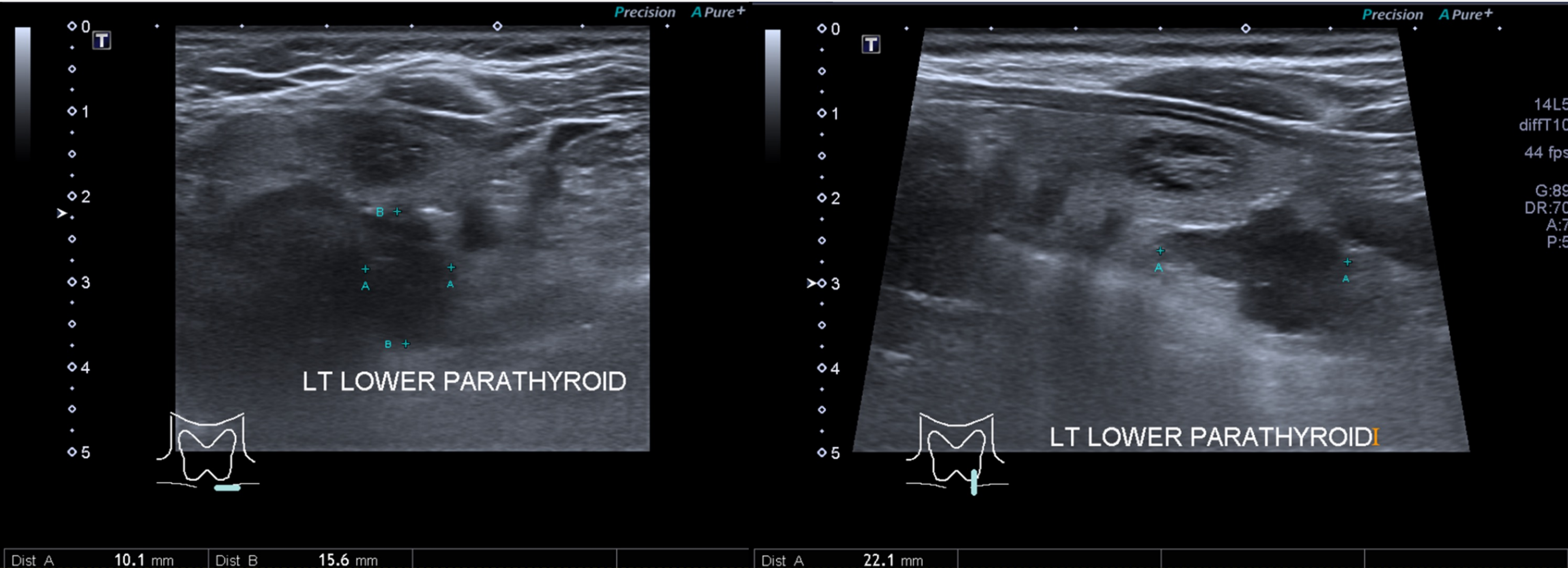
Parathyroid Scan

- Two hyperfunctioning parathyroid glands at lower pole of both thyroid lobes
- No definite evidence of an ectopic hyperfunctioning parathyroid gland





Neck Ultrasound



Neck Ultrasound

Neck Ultrasound

Normal-size thyroid gland with homogeneous echotexture of thyroid parenchyma

Several spongiform nodules at left lobe of thyroid with the largest one at left lower pole, measuring 1.6 x 0.7 x 1.5 cm

A right upper parathyroid adenoma (posterior to mid pole of right thyroid lobe), 1.8 x 1.3 x 3.9 cm

A left lower parathyroid adenoma (posterior to lower pole of left thyroid lobe), 1.0 x 1.6 x. 2.2 cm

Problem list

- PTH-dependent hypercalcemia
- Vitamin D deficiency
- Antalgic gait and proximal muscle weakness
- Pseudofractures on pelvic X- Ray

Osteomalacia

Diagnosis ?

Double Parathyroid Adenomas with Osteomalacia?

Management

Management

Endocrine evaluation

- Preoperative localization of parathyroid adenomas
    - Ultrasound neck
    - Parathyroid scan (Dual-phase 99mTc-sestamibi with SPECT/CT)
- Role of genetic testing in young patients especially in individuals with more than one parathyroid adenoma
    - MEN1

Management

Surgical management

- The extent of surgery: parathyroidectomy and standard bilateral neck exploration
- Intraoperative nerve monitoring
- Intraoperative PTH monitoring

Progression

- **Right upper and left lower parathyroidectomy with NIM was performed**
- **Patho:** Parathyroid adenomas
- **No surgical complications**

- **Hungry bone syndrome**

Progression

	Pre op	หลังตัด Parathyroid	Post op Day 1	Post op Day 2	Post op Day 3	Post op Day 7
Calcium (mg/dL)	12.5	10.5	9.6	8.4	8.0	9.0
PTH (pg/mL)	713	48.40	26.4		50.2	47.8
PO4 (mg/dL)	2.0	1.4	1.0	1.6	2.1	2.0
25(OH)D (ng/mL)	13					18
CalTab (1.5)				1 x 3	2 x 3	1 x 3
VitD2 (20000)	3caps/wk	3caps/wk	3caps/wk	3caps/wk	3caps/wk	3caps/wk
Calcitriol (0.25)					1 x 2	1 x 2

Pre op

Post op

CLINICAL INTERPRETATION

VUS

A heterozygous variant of uncertain significance (VUS) was found in *MEN1* gene (c.857G>A, p.Gly286Glu).

Inconclusive: Based on currently available information, it is unclear whether the variant is pathogenic or benign.

Comment:

1. ***Medical management decisions should not be based on a VUS.***
2. ***Targeted testing for family members to clarify clinical significance and recontacting laboratory for reclassification updates are recommended.***
3. *The results should be interpreted within the context of clinical findings, family history, and additional laboratory results.*
4. *Genetic consultation and genetic counseling are recommended to discuss the implications of the genetic test result.*

This report has been reviewed and approved by: ______________ (Manop Pithukpakorn, M.D., ABMG)

คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

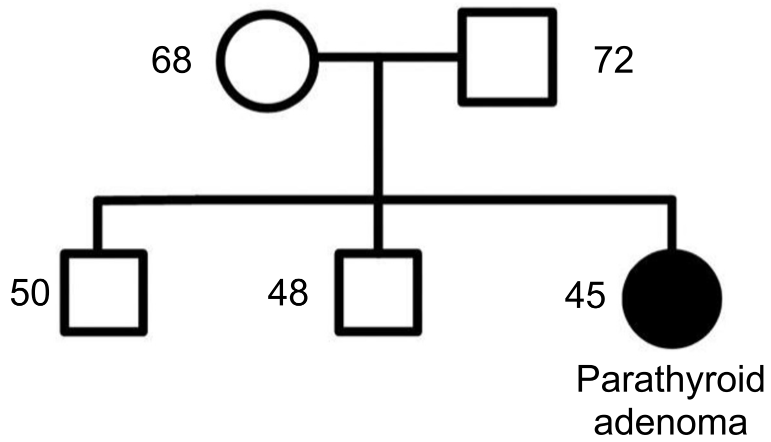
RESULTS : Variant Analysis

Gene Information	Inheritance Model	Variant Information		ClinVar	Effect Predictors	gnomAD POPMAX	Gene-Phenotype Consistency	Variant Classification
MEN1 NM_000244.4	Dominant	c.857G>A p.Gly286Glu	Heterozygous missense_variant	Uncertain significance 2907409	Damaging, Conserved, REVEL : 0.965	-	Strong	Uncertain Significance/FP PM2, PM5, PP3

RESULTS : CNV Analysis

Analytical Technique	Region of Interest (ROI)	Analysis Result
NGS CNV Analysis	Coding sequence of gene panel	Negative

- *Statistic Information: Percentage depth of coverage at 50x (99.6%), 100x (98.7%), 250x (88.6%), Mean depth of coverage: 828x (Max: 2,844x, Min: 0x), Median MQ: 60*
- *Benign, Likely Benign, Silent and Intronic variants with no evidence towards pathogenicity are not included in this report.*
- *FP = Favor pathogenic, LB = Leaning benign, REVEL = Rare Exome Variant Ensemble Learner*



68
72
50
48
45
Parathyroid adenoma

Double adenoma

- Double Adenoma has historically been considered a distinct diagnosis, as patients could be cured after the removal of two affected parathyroid glands
- However, persistent and recurrent disease rates in DA are reported at 4% and 7%, respectively
- Some experts suggest that DA may actually represent asymmetric or asynchronous hyperplasia, which has significant implications for treatment

Goodsell, Kristin E., et al. Double adenoma as a cause of primary hyperparathyroidism: Asymmetric hyperplasia or a distinct pathologic entity?
The American Journal of Surgery, vol. 222, no. 3, Jan. 2021, pp. 483–89

Double adenoma

- Patients with true DA can achieve a cure after the removal of two abnormal glands, while those with asymmetric hyperplasia remain at higher risk for persistence or recurrence
- Due to the uncertainty about whether DA and asymmetric hyperplasia are distinct conditions, patients require careful intraoperative observation and close postoperative follow-up with serum calcium monitoring, as they may be more likely to need reoperation

Goodsell, Kristin E., et al. Double adenoma as a cause of primary hyperparathyroidism: Asymmetric hyperplasia or a distinct pathologic entity?
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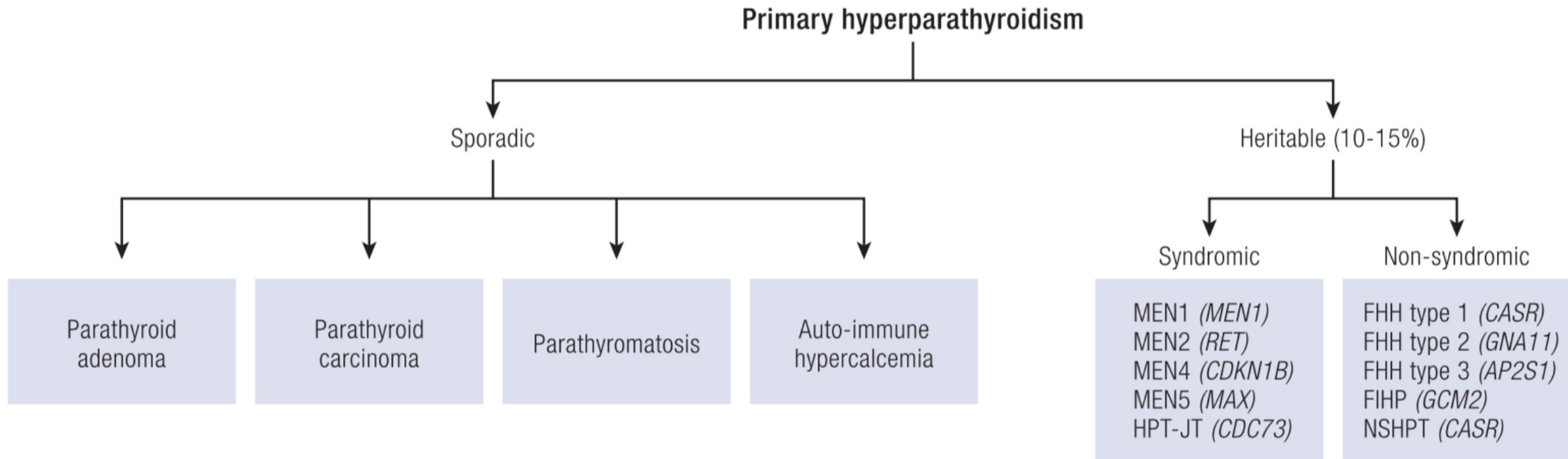
Clinical spectrum of PHPT



> 90% sporadic and caused by

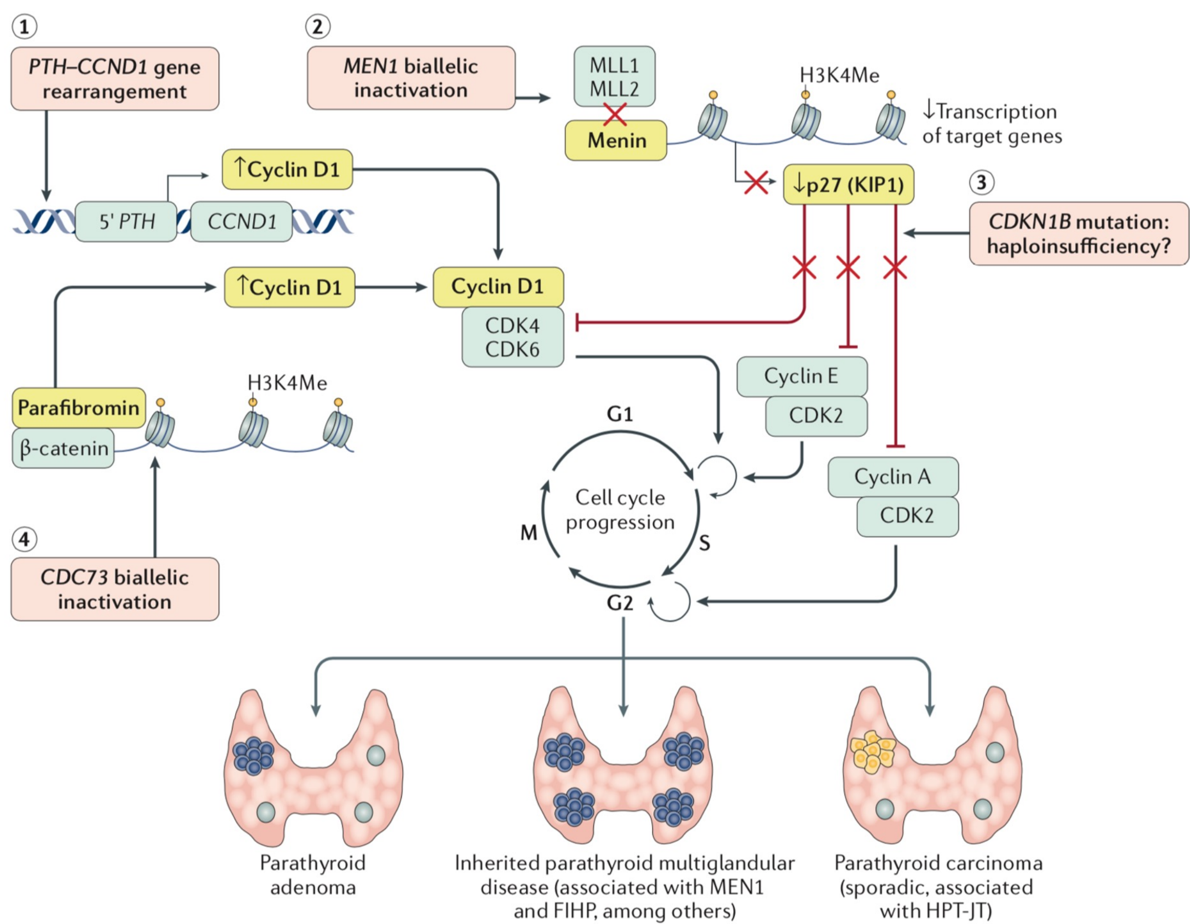
- Solitary benign adenoma (85–90%)
- Multi glandular involvement (5-10%)
- Parathyroid carcinoma (<1%)

Smita Jha, William F Simonds, Molecular and Clinical Spectrum of Primary Hyperparathyroidism, *Endocrine Reviews*, Volume 44, Issue 5, October 2023, Pages 779–818

Genetics of PHP

- Genetic counseling and evaluation
  - Patients < 30 years with PHPT
  - Multigland disease by history or imaging
  - Family history of hypercalcemia or syndromic diseases
    - MEN1, MEN2A, MEN4
    - HPT-JT syndrome
  - Atypical parathyroid adenoma and parathyroid carcinoma

Molecular mechanisms of tumorigenesis



Bilezikian, J., Cusano, N., *et al.* Primary hyperparathyroidism. *Nat Rev Dis Primers* 2, 16033 (2016). https://doi.org/10.1038/nrdp.2016.33

Coexisting osteomalacia and PHPT

- The requirement of vitamin D may be increased in PHPT
  - Increased renal synthesis of 1,25-OHD, which in turn increasing the catabolism of 25-OHD via hepatic inactivation and biliary excretion
  - Long standing hyperparathyroidism causes phosphaturia and hypophosphataemia which may contribute to the development of osteomalacia

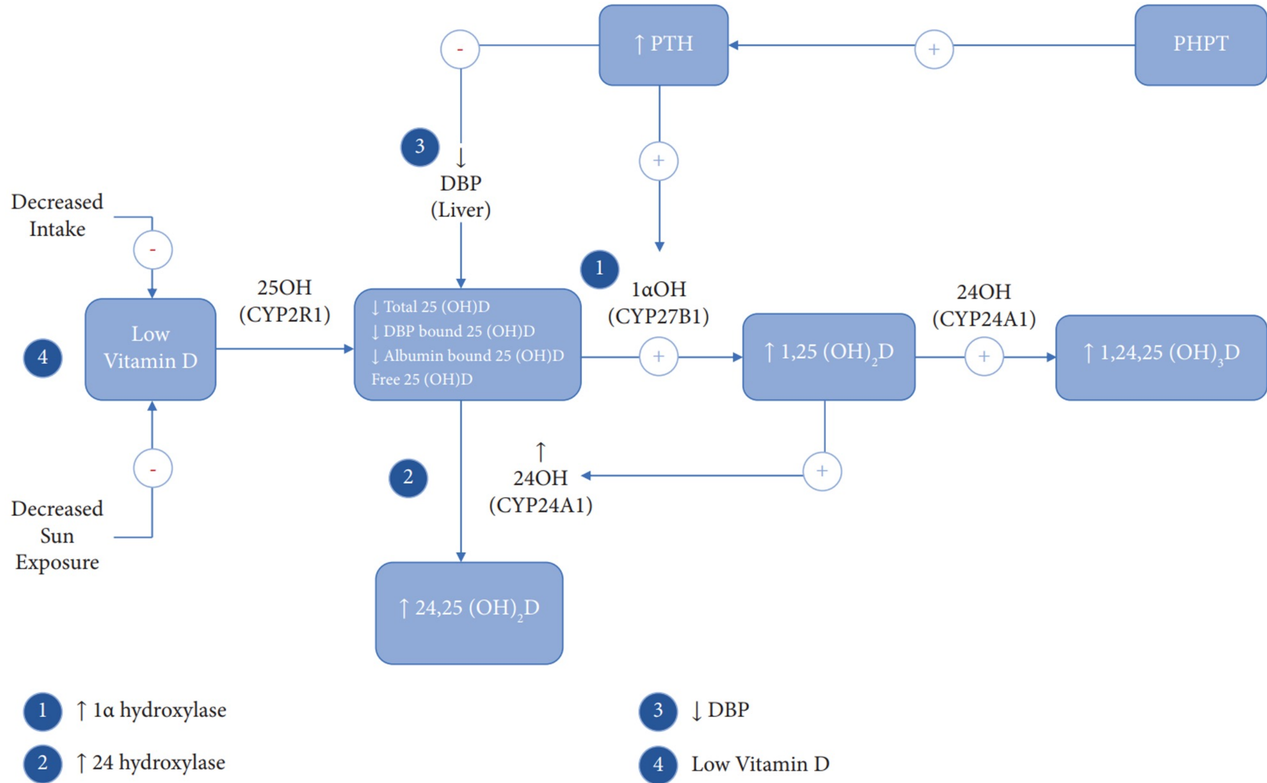


FIGURE 1: Potential mechanisms of low 25(OH)D levels in PHPT. PHPT: primary hyperparathyroidism; PTH: parathyroid hormone; DBP: vitamin D-binding protein; 25(OH)D: 25-hydroxyvitamin D; $1,25(OH)_2D$: 1,25-dihydroxyvitamin D; $24,25(OH)_2D$: 24,25-dihydroxyvitamin D; 1αOH: 1-alpha hydroxylase; 24 OH: 24 hydroxylase.

Niharika Yedla, et al. **Vitamin D Deficiency and the Presentation of Primary Hyperparathyroidism: A Mini Review.** International Journal of Endocrinology, vol. 2023, 11 Dec. 2023, pp. 1–8

Case Report #1

- An 86-year-old woman, history of a 20-year untreated PHPT developed generalized bone pain, pseudofracture of midshaft of left femur
- Laboratory examinations:
    - Elevated serum calcium, ALP, and PTH levels
    - Serum inorganic phosphate was below normal and 25-hydroxyvitamin D levels were low-normal

Kaplan FS, Soffer SR, Fallon MD, Haddad JG, Dalinka M, Raffensperger EC. Osteomalacia as a very late manifestation of primary hyperparathyroidism. Clin Orthop Relat Res. 1988 Mar;(228):26-32. PMID: 3342577

Case Report #1

- Undecalcified transiliac bone biopsy specimen following tetracycline double labeling: osteomalacia and osteitis fibrosa
- Following treatment with vitamin D and phosphate
  - Serum inorganic phosphate level rose to normal
  - Decrease in bone pain, and the pseudofracture healed
  - Serum calcium, ALP, and PTH level remained elevated

Kaplan FS, Soffer SR, Fallon MD, Haddad JG, Dalinka M, Raffensperger EC. Osteomalacia as a very late manifestation of primary hyperparathyroidism. Clin Orthop Relat Res. 1988 Mar;(228):26-32. PMID: 3342577

Case Report #2

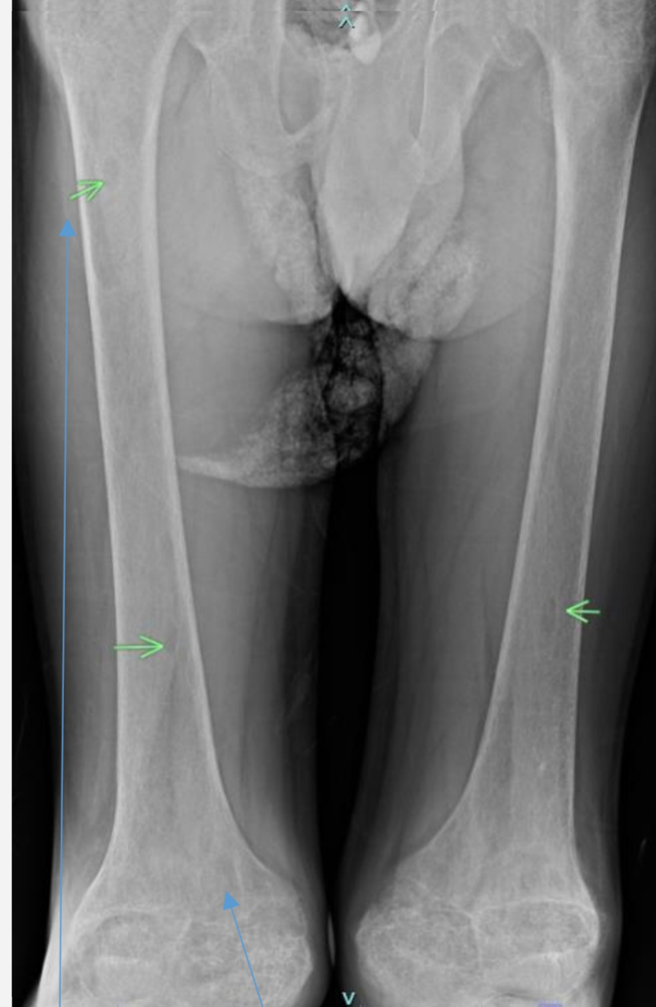
- A 15-year-old boy, history of right wrist fracture and progressive skeletal deformity and difficulty walking for 1 year
- Refer from secondary care center:
  - Initial lab PTH 3572 pg/mL, 25(OH)D 9.3 ng/mL
  - $CaCO_3$ 600 mg 1*2, Vitamin D2 20,000 IU 3 caps weekly
- PE: pectus carinatum, bell-shaped chest, rachitic rosary, kyphoscoliosis, deformity of both wrists and both shoulders, bowlegs and knocked knees

Case from Division of Endocrinology & Metabolism, Department of Pediatrics, Siriraj Hospital

Case Report #2

- Lab at Siriraj: Calcium 12.9 (8.5-10.2) mg/dL, P 2.4 (2.7-4.9) mg/dL, albumin 4.2 g/dL, PTH 2141 pg/mL, Mg 1.8 mg/dL (1.7-2.2), 25(OH)D 19.20 ng/mL, ALP 4172 U/L
- US KUB
  - Few bilateral small calyceal stones, up to 6 mm, without hydronephrosis. A 3-cm vesical stone with extension to bladder neck
- Parathyroid scan
  - A 0.9 x 1.8 x 4.0-cm hyperfunctioning parathyroid tissue along the posterolateral aspect of left thyroid lobe

Case from Division of Endocrinology & Metabolism, Department of Pediatrics, Siriraj Hospital



Case from Division of Endocrinology & Metabolism, Department of Pediatrics, Siriraj Hospital

Osteoporosis treatment after PTX

- Studies show the improvement of BMD in the lumbar spine and hip within the first year after parathyroidectomy
- Therefore, the decision to treat osteoporosis has usually been delayed until a follow-up bone densitometry scan (DXA) at least **one year after parathyroidectomy**

Khine Mon Swe, Alexander Chiu, Elaine Pelley, FRI690 Should Treatment For Osteoporosis Be Started In Patients With Primary Hyperparathyroidism Within The First Year After Parathyroidectomy?, Journal of the Endocrine Society, Volume 7, Issue Supplement_1, October-November 2023

Skeletal change after PTX

- The mean BMD of LS, FN, and TH increased significantly from the baseline to the first, from the baseline to the second, and from the baseline to the third year after PTX
- Neither radial third BMD nor TBS experienced significant changes during follow-up

Arboiro-Pinel, Rosa, et al. Primary Hyperparathyroidism: Assessment of the Effects of Parathyroidectomy Using Dual X-Ray Absorptiometry, Trabecular Bone Score, and Dual X-Ray Absorptiometry–Based Three-Dimensional Modeling. Endocrine Practice, vol. 30, no. 4, Apr. 2024, pp. 340–347

Table 10. Effect of Surgery on Bone Mineral Density by DXA in Primary Hyperparathyroidism

Site	Lumbar spine	Femoral neck	Total hip	1/3 radius
Mean difference	4.82 (2.55 to 7.09)[a]	3.18 (−0.95 to 7.31)[a]	4.41 (2.62 to 6.20)[a]	0.28 (−1.25 to 9.58)[b] −1.47 (−10.13 to 7.19)[c]
Trial[c]	4	3	2	2[b]; 1[c]
Patient[c]	258	208	103	136[b]; 53[c]

Data presented as MDs with 95% CIs.
DXA = dual-energy X-ray absorptiometry.
[a]At 2–5 years.
[b]At 1–5 years.
[c]At 2 years.

Ye, Zhikang, et al. The Efficacy and Safety of Medical and Surgical Therapy in Patients with Primary Hyperparathyroidism: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Journal of Bone and Mineral Research, vol. 37, no. 11, 17 Oct. 2022, pp. 2351–2372.

Table 2. Changes in BMD before and after surgery in patients with severe hyperparathyroidism.

Site	Parameter	Both sexes and total	Before surgery	6 months after surgery	1 year after surgery	2 years after surgery	P value[a]	P value[b]	P value[c]
L1–L4*	BMD (g/cm^2)	Men	0.74 ± 0.14	0.90 ± 0.15	1.02 ± 0.09	1.09 ± 0.07	0.003	0.039	0.007
		Women	0.62 ± 0.18	0.87 ± 0.19	1.04 ± 0.35	1.33 ± 0.32	0.031	0.156	0.117
		All	0.69 ± 0.17	0.89 ± 0.16	1.03 ± 0.21	1.21 ± 0.24	<0.001	0.011	0.012
	T-score	Men	−2.83 ± 1.21	−1.60 ± 1.43	−0.20	0.20	0.011	–	–
		Women	−4.26 ± 1.48	−2.03 ± 1.81	−0.55 ± 2.62	1.75 ± 2.76	0.041	0.143	0.122
		All	−3.42 ± 1.48	−1.77 ± 1.51	−0.43 ± 1.86	1.23 ± 2.15	<0.001	0.032	0.046
	Z-score	Men	−2.72 ± 1.31	−1.37 ± 1.63	0.30	0.60	0.018	–	–
		Women	−3.89 ± 1.23	−1.58 ± 1.62	−0.10 ± 2.26	2.35 ± 2.47	0.036	0.139	0.131
		All	−3.20 ± 1.37	−1.45 ± 1.53	0.03 ± 1.62	1.77 ± 2.02	<0.001	0.022	0.040
Total hip	BMD (g/cm^2)	Men	0.55 ± 0.13	0.69 ± 0.14	0.89 ± 0.04	0.92 ± 0.01	0.003	0.139	0.081
		Women	0.52 ± 0.17	0.65 ± 0.10	0.75 ± 0.10	0.84	0.012	0.016	–
		All	0.54 ± 0.14	0.67 ± 0.12	0.82 ± 0.10	0.89 ± 0.05	<0.001	0.002	0.008
	T-score	Men	−3.19 ± 0.93	−2.13 ± 1.16	−0.90	−0.40	0.016	–	–
		Women	−3.64 ± 1.35	−2.68 ± 0.88	−1.80 ± 0.85	−1.10	0.022	0.021	–
		All	−3.39 ± 1.12	−2.35 ± 1.04	−1.50 ± 0.79	−0.75 ± 0.49	<0.001	0.002	<0.001
	Z-score	Men	−3.01 ± 0.90	−1.93 ± 1.25	−0.60	0.00	0.017	–	–
		Women	−3.40 ± 1.22	−2.45 ± 0.85	−1.55 ± 0.92	−0.40	0.027	0.021	–
		All	−3.18 ± 1.03	−2.14 ± 1.09	−1.23 ± 0.85	−0.20 ± 0.28	<0.001	0.007	0.010

Data are shown as mean ± standard deviation. Values without a standard deviation only represent one patient.
[*]Mean of L1–L4; [a]6 months after surgery vs before surgery; [b]1 year after surgery vs before surgery; [c]2 years after surgery vs before surgery. T-score of >−2.5 to −1 indicates osteopenia; T-score of <−2.5 indicates osteoporosis.
BMD, bone mineral density.

Lu, Shuai, et al. "Changes in Bone Mineral Density after Parathyroidectomy in Patients with Moderate to Severe Primary Hyperparathyroidism.
The Journal of International Medical Research, vol. 48, no. 10, 31 Oct. 2020

Thank you