PRINCE OF SONGKLA UNIVERSITY

Interhospital conference

Onnicha Suntornlohanakul M.D.

Case presentation

A 27 -yr- old Thai female, previously healthy.

CC: Referred due to hip fracture

PI: Three weeks PTA, she got a motorcycle accident lead to a right hip fracture with an abnormal radiologic and basic blood test results. Thus, she was referred to us.

Her past medical and personal history were unremarkable.

Her family history was also unremarkable.

Case presentation

GA: A Thai female, good consciousness

V/S: BT 36 ^{0}C BP 130/78 mmHg PR 70/min RR 16/min

HEENT: mildly pale conjunctivae, no blue sclera

normal teeth, no neck mass, no jaw mass

CVS, RS and Abdomen: unremarkable

Neuro exam: Motor grade V all extremities, DTR 2+ all (except fracture site)

MSK: normal stature, no gross deformity, no tenderness

Skin: no hyperpigmentation

Investigation

BUN/Cr: 17.5/1.12

Na 137.1, K 3.6, Cl 101.7, HCO_3^- 18.0

Calcium 15.2, Phosphorus 3.3 , Alb 4.3

ALP 272 (39-117 U/L)

PTH 1304 pg/mL

Localization 8/2558

- Ultrasound: Lt. parathyroid gland 1.2*1.2*3 cm

- MIBI: Two hyperfunctioning parathyroid glands
  - below left thyroid lobe
  - behind right thyroid lobe

Management 2558

- Normal pituitary hormones
- MRI pituitary: normal

Management 2558

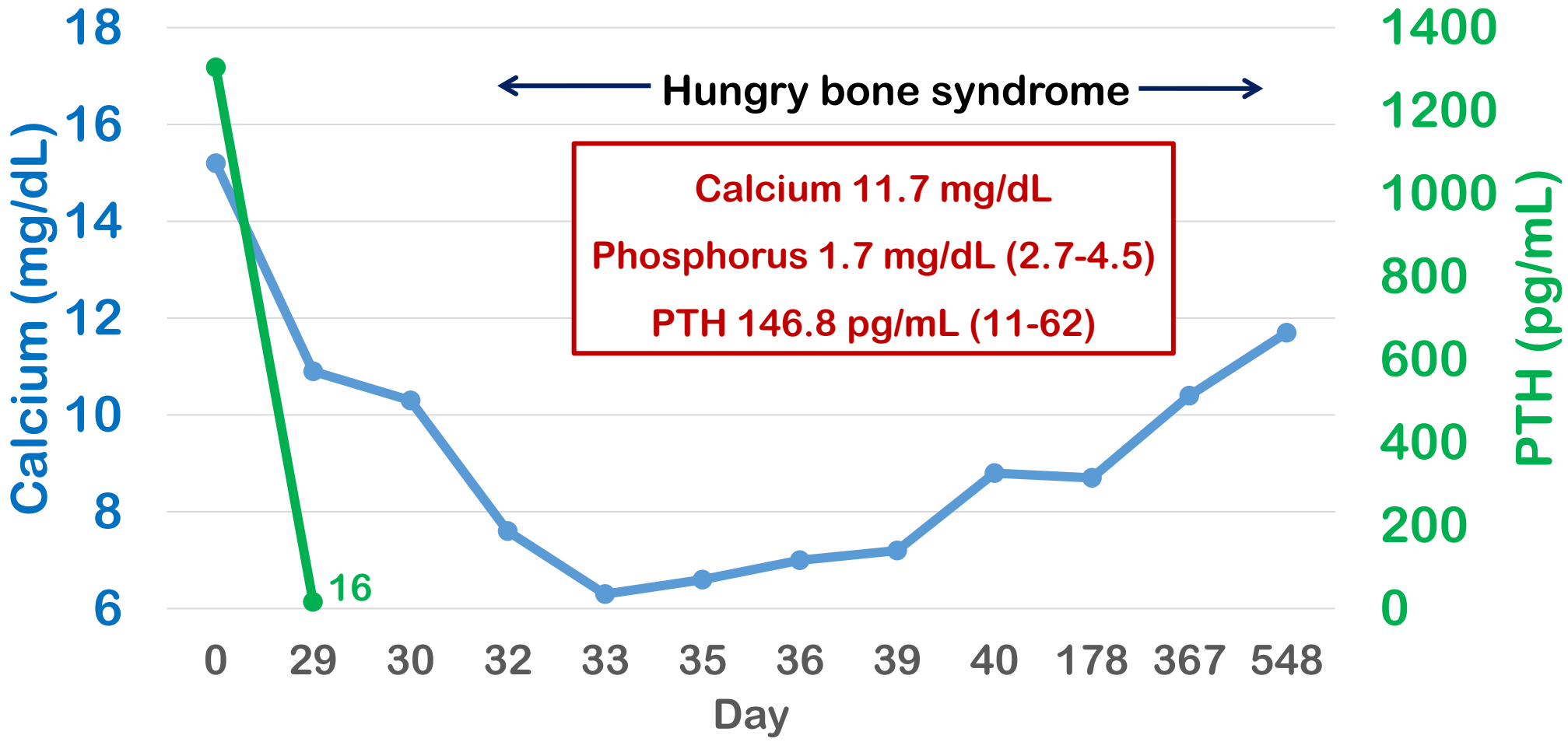
Lt.lobectomy with ischmectomy with subtotal parathyroidectomy (2 glands) with iPTH monitoring 1212 → 169.9 (10 minutes)

Pathological Dx

- Lt. thyroid: nodular goiter
- Rt.Parathyroid gland (superior): one parathyroid gland
- Lt. Parathyroid gland (inferior): parathyroid adenoma, size 1.8 cm
  - Mitosis 0/10 HPF
  - No definite area of lymphovascular or perineural invasion

PRINCE OF SONGKLA UNIVERSITY

Management 2558



PRINCE OF SONGKLA UNIVERSITY

Diagnosis + Management

Fellow 2

"Recurrent hyperparathyroidism"

Management 2560

- An ultrasound and 99mTC-sestamibi: negative in the neck or thoracic areas
- A CT of the chest including neck: 2 suspicious nodules in the left thyroid bed.

Management 2560

RE-explore neck with parathyroidectomy, thymectomy

Rt. lobectomy; iPTH monitoring (2nd operation)

Pathological Dx

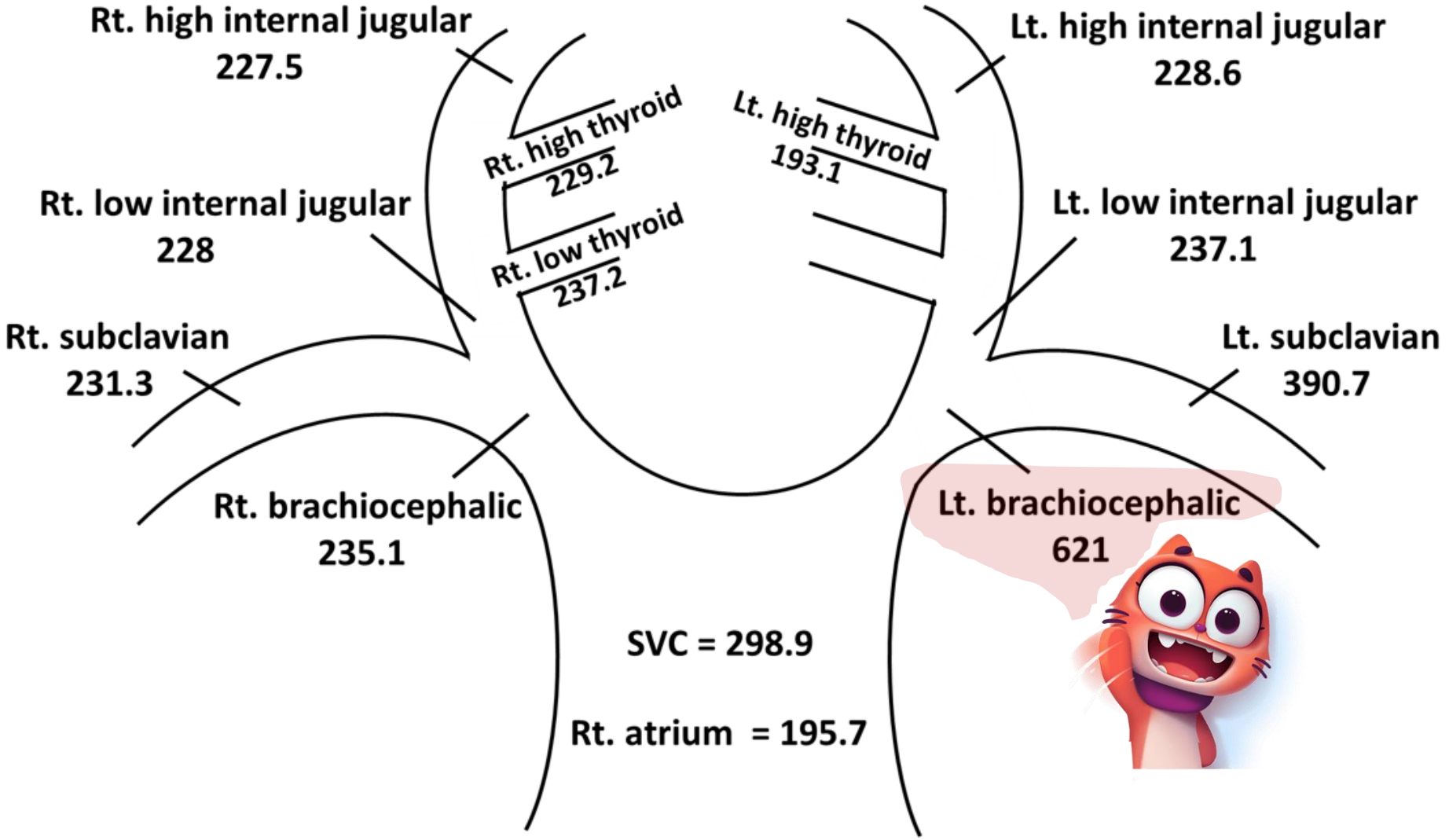
- Right thyroid lobe: thyroid gland with small part of one parathyroid gland
- Left superior parathyroid gland
- Benign thymus, no parathyroid tissue in thymus

PRINCE OF SONGKLA UNIVERSITY

Management

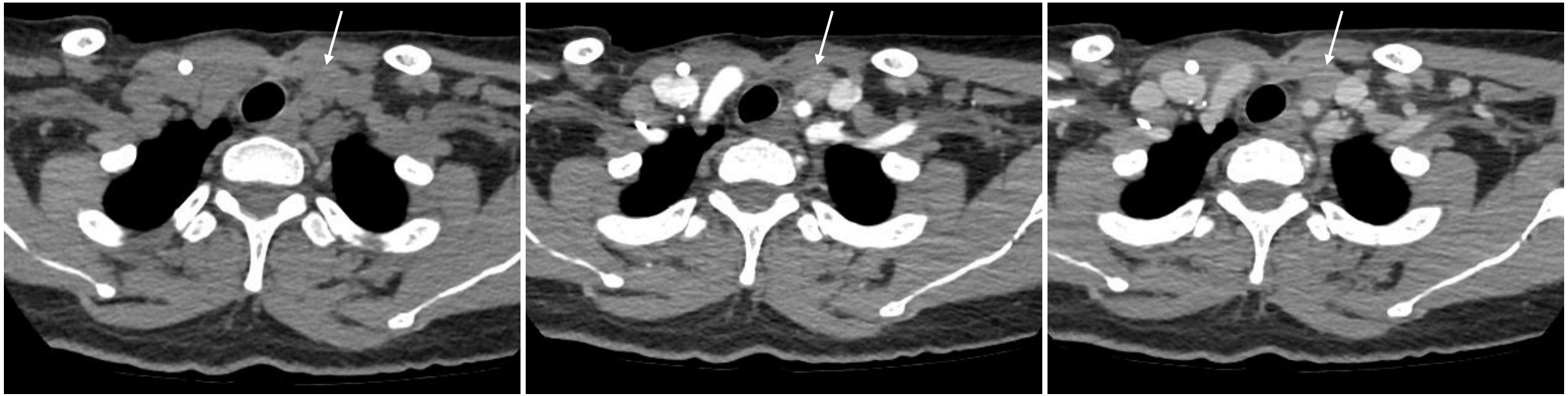
Fellow 2

SVS PTH


Rt. high internal jugular
227.5
Rt. high thyroid
229.2
Lt. high thyroid
193.1
Lt. high internal jugular
228.6
Rt. low internal jugular
228
Rt. low thyroid
237.2
Lt. low internal jugular
237.1
Rt. subclavian
231.3
Lt. subclavian
390.7
Rt. brachiocephalic
235.1
Lt. brachiocephalic
621
SVC = 298.9
Rt. atrium = 195.7

4D CT

Nonenhanced phase | Arterial phase | Delayed phase



- Parathyroid adenoma at left lower neck, deep to left strap muscle and just superomedial to the left int.jugular-brachiocephalic vein
- Another similar-appearing nodule at slightly superomedial aspect to the larger parathyroid adenoma

PET scan

- Negative

Management 6/2562

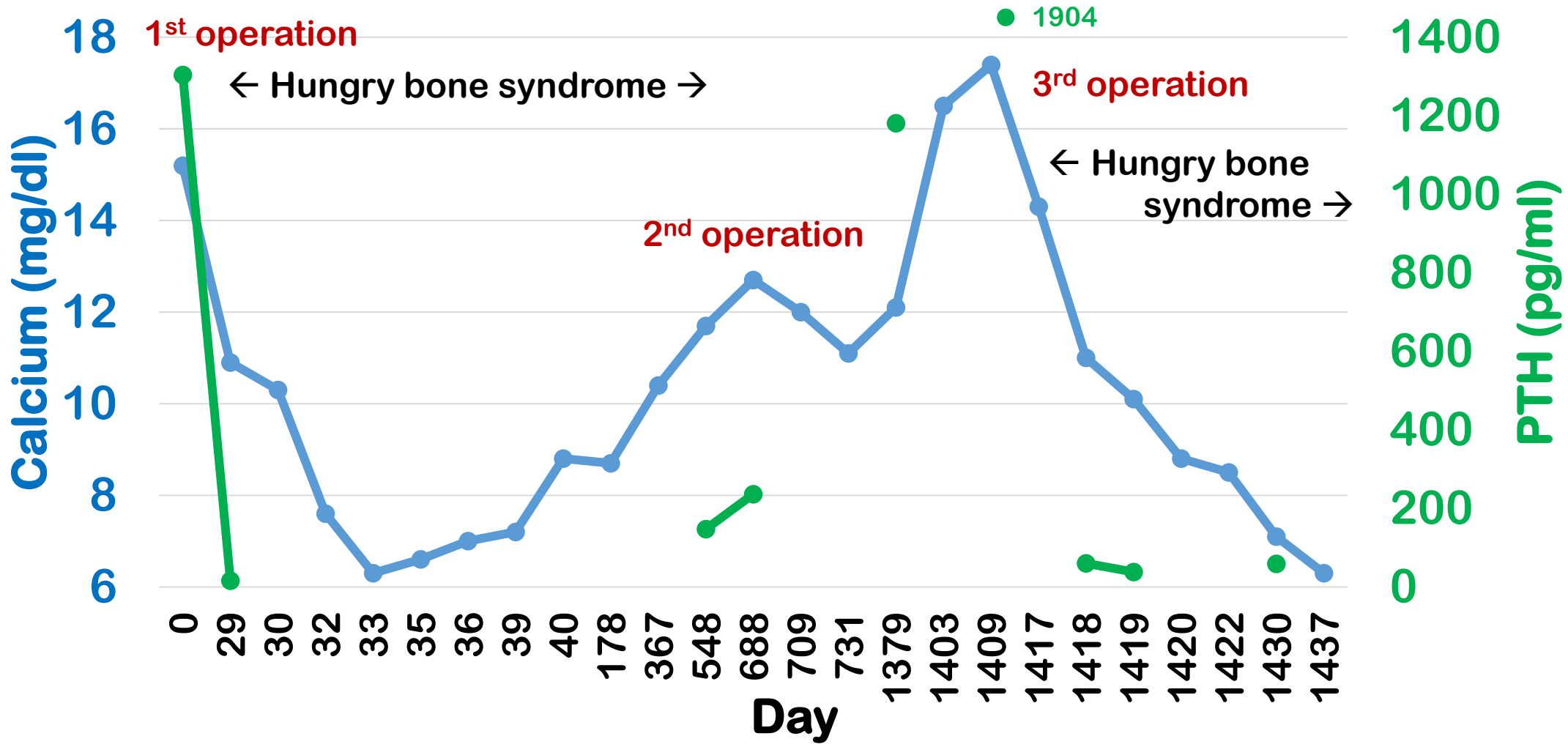
Lt.parathyroidectomy with iPTH monitoring (3rd operation)

Pathological Dx

- Lt.Parathyroid gland: Parathyroid hyperplasia x II (medial and lateral)
- Lymph node: Not lymph node

  Parathyroid gland hyperplasia with some mitotic activity

Review lab and Mx



PRINCE OF SONGKLA UNIVERSITY

12/2562

Recurrent hyperparathyroidism

- Localization by 4DCT and SVS PTH

→ Parathyroid adenoma at left lower neck

Mx: bilateral neck exploration with cervical tissue dissection

(4^{th} operation)

Mx: S/P re-explored bilateral neck with left parathyroidectomy with median sternotomy and thymectomy with iPTH monitoring

(5^{th} operation)

PRINCE OF SONGKLA UNIVERSITY

4-6/2563

- Intractable hypercalcemia despite of cinacalcet

  7 tabs / day and Bisphosphanates
- Nephrogenic DI + AKI (need Hemodialysis)
- Pancreatitis suspected from hypercalcemia

Refer BKK 6/63

Revision Lt. parathyroidectomy with gamma probe

with iPTH monitoring with Lt.claviculectomy

iPTH 1640 → 568 → 349 pg/mL intraoperation

Calcium 16.1 → 11.6 in 3 days (PTH 179 pg/mL)

PRINCE OF SONGKLA UNIVERSITY

Refer BKK 6/63

Pathology

Lt.Parathyroid glnd: Parathyroid carcinoma, low grade, invasion to adjacent structure (skeletal muscle)

Tumor size 3*2*1.5 cm

Mitotic count 12 mf/10 HPFs, Ki-67 20%

No lymphovascular / perineural invasion identified

Margin +

PRINCE OF SONGKLA UNIVERSITY

Final Dx

Supernumerary, ectopic parathyroid lesion
+ Parathyroid carcinoma

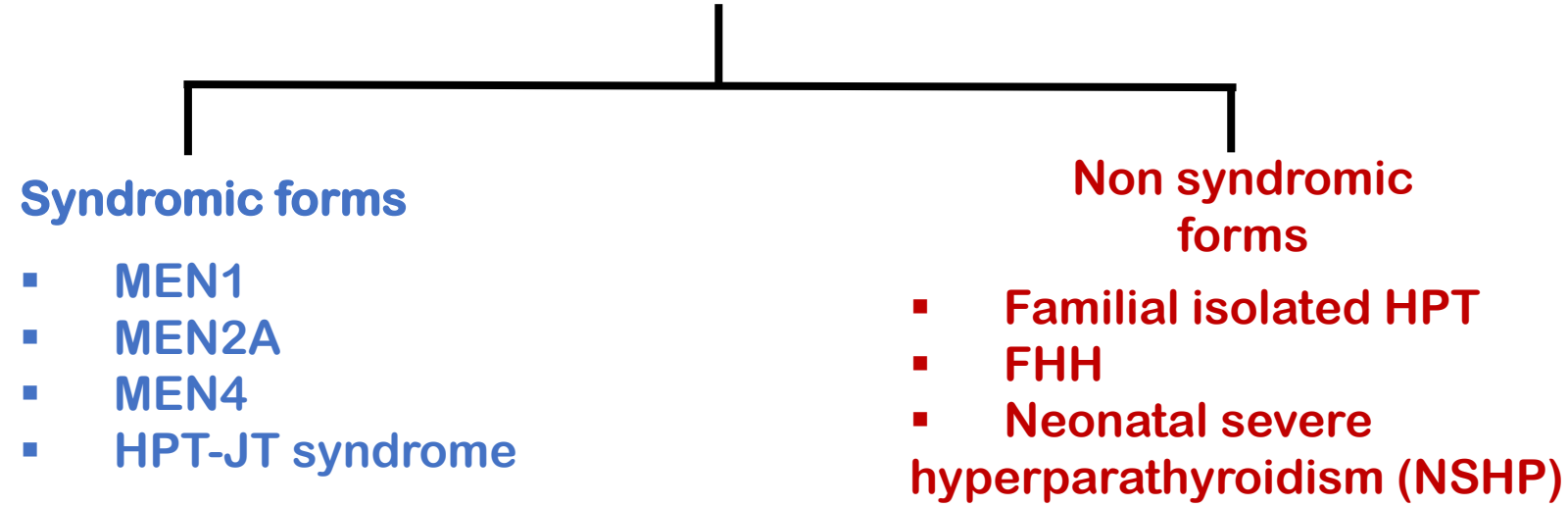
PHPT

- **Primary hyperparathyroidism (PHPT):** benign single parathyroid adenoma (80%)

  Multiple parathyroid adenoma/multiglandular hyperplasia (15-20%)

  Parathyroid carcinoma (1%)

- Sporadic PHPT (90-95%) *vs.* Familial inherited parathyroid disorders (5-10%)



Clinical Cases in mineral and bone metabolism 14.1 (2017): 60.

Indication for genetic testing in PHPT

Young age (< 30 y)

Syndromic findings / positive family Hx

Multigland disease (≥ 2 glands)

Parathyroid carcinoma

Nature Reviews Disease Primers 2.1 (2016): 1-16.

VALUES OF GENETIC TESTING

1. Confirm clinical diagnosis → screening associated tumor
2. Implementation of appropriate treatment eg.-
   - → Early PTX in HPT-JT
   - → Avoid minimal invasive parathyroid surgery in MEN1
   - → Early prophylaxis thyroidectomy in MEN2, MEN3
   - → Not Sx in FHH
3. Identify family members : screening for tumor detection
4. Identify 50% of familial members who do not harbor the familial germline mutation : reassure

Syndrome	Mean age of onset	Parathyroid pathology	Clinical treatment
MEN1 **MENIN**	20-25 years	Multiglandular hyperplasia and/or adenoma	Subtotal parathyroidectomy of hyperplastic and/or adenomatous parathyroids; or total parathyroidectomy with healthy tissue reimplantation in the non-dominant forearm, in case of pathological involvement of all four parathyroids
MEN2A **RET**	Over 30 years	Single or multiglandular hyperplasia and/or adenoma	Specific resection on only the hyperplastic and/or adenomatous parathyroids
MEN4 **CDKN1B**	Over 45 years	Single or multiglandular hyperplasia and/or adenoma	Specific resection on only the hyperplastic and/or adenomatous parathyroids
FHH **CASR, GNA11, AP2S1**	All ages	Multiglandular mildly hyperplastic parathyroids	Parathyroidectomy is not only unnecessary but also inappropriate, since it does not cure FHH-associated hypercalcemia
NSHPT **CASR**	At birth or within the first six months of life	Multiglandular markedly hyperplastic parathyroids	Total parathyroidectomy
HPT-JT **CDC73**	Over 30 years	Single or multiglandular (usually two glands) cystic adenoma. Carcinomas in 10-15% of cases	Subtotal parathyroidectomy of adenomatous and/or carcinomatous parathyroids, or total parathyroidectomy, with healthy tissue reimplantation in the non-dominant forearm, in case of adenoma involvement of all four parathyroids
FIPH	N.R.	Single or multiglandular adenoma	Subtotal parathyroidectomy of adenomatous parathyroids, or total parathyroidectomy, with healthy tissue reimplantation in the non-dominant forearm, in case of adenoma involvement of all four parathyroids

N.R. = not reported.

Clinical Cases in mineral and bone metabolism 14.1 (2017): 60.

Recurrent and persistent HPTH

Factors associated with persistent or recurrent HPTH

- Inexperience of the operating surgeon
- Ectopic or supernumerary glands
- Multiglandular disease (esp familial syndrome)
- Parathyroid carcinoma
- Parathyromatosis (Multiple nodules of benign functioning parathyroid tissue scattered throughout the neck and mediastinum)

Ectopic parathyroid adenoma (EPA)

- The prevalence of EPA is between 17.5 and 22% in unexplored patients with PHPT
- In re-operative patients, ectopic glands may comprise up to 66% of missed adenomas, making EPAs much more common in the re-operative setting than in the unexplored setting

Endocr Pract. 2018;24:589-598

Ectopic positions

- 28% - paraesophageal
- 26%- mediastinum
- 24%- intrathymic
- 11%- intrathyroidal
- 9%- carotid sheath
- 2%- high cervical position

Shen W.et al.Arch Surg 1996; 131:861-7.

Ectopic positions

- 28% - paraesophageal
- 26%- mediastinum
- 24%- intrathymic
- 11%- intrathyroidal
- 9%- carotid sheath
- 2%- high cervical position

Shen W.et al.Arch Surg 1996; 131:861-7.

4DCT

- In 4DCT, images are acquired in 4 phases: noncontrast, early arterial, late arterial, and delayed (venous)

- Parathyroid adenoma corresponds to an avidly enhancing (hyperdense) rounded lesion during the arterial phase

Endocr Pract. 2018;24:589-598

4DCT

- Good for ectopic adenomas and multigland disease
- Commonly used to detect suspected EPAs in the setting of failed initial parathyroidectomy but is also becoming the imaging of choice in many centers

- Limited ability to distinguish intrathyroidal adenomas and thyroid nodules (both enhance similarly on 4DCT)
- Reading requires experiences, contrast and radiation exposure

Endocr Pract. 2018;24:589-598

SVS PTH

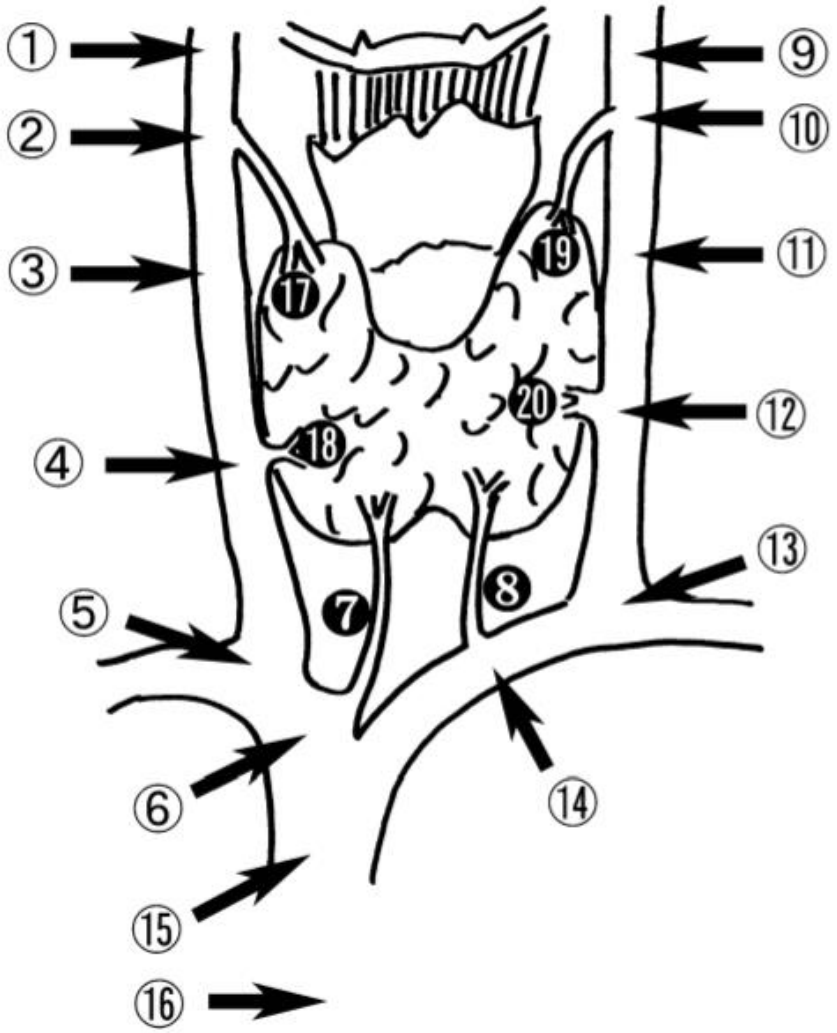


Table 1 Previous studies on venous sampling for primary hyperparathyroidism

Author	Year	Cases (*n*)	Sensitivity (%)	Indication
Jones [29]	2002	64	75	Persistent and recurrent
Estella [28]	2003	13	88.8	Persistent and recurrent
Udelsman [34]	2003	7	83	Persistent
Seehofer [33]	2004	21	90	Persistent and recurrent
Liew [31]	2004	9	78	Persistent and recurrent
Chaffanjon [27]	2004	23	94.7	Persistent and recurrent
Eloy [35]	2006	8	87.5	Primary
Reidel [32]	2006	51	83.3	Persistent and recurrent
Gimm [1]	2012	5	80	Persistent
Labastchi [30]	2015	31	89	Persistent

Japanese Journal of Radiology 35.8 (2017): 409-416.

Parathyroid carcinoma

- < 0.005% of all CA, < 1% of all parathyroid disorder
- Functioning parathyroid CA (90%)
- Inactivating somatic mutations of the CDC73 gene: the most frequent genetic alteration ranging from 66 - 100%
- Rb, p53, BRCA2, cyclin D1/parathyroid adenomatosis gene 1 (PRAD1), PI3K/AKT/MTOR pathway

Journal of Bone and Mineral Research 23.12 (2008): 1869-1880.
BMC endocrine disorders 19.1 (2019): 1-9.

Parathyroid carcinoma

	Benign HPTH	Parathyroid carcinoma
Female to male	3-4: 1	1:1
Average calcium(mg/dl)	<11.2	>14
Average PTH (ng/l)	mild elevation	3-10-fold elevation
Average age at presentation (yrs)	55	48
Palpable mass	rare	50-70%
Asymptomatic	80%	2%
Renal involvement	<20%	56-84%
Radiological bone change	<5%	34-91%

JCEM 86.2 (2001): 485-493.

Diagnosis

- Clinical and biochemical
- Imaging study
- Macroscopic finding
- Histology (microscopic finding)
- Immunohistochemical markers

PRINCE OF SONGKLA UNIVERSITY

Histology

- Present of lobular architecture separated by fibrous trabeculae
- Cytological atypias
- Mitotic figures
- Presence of vascular invasion
- Capsular invasion with extension to adjacent tissues
- Presence of metastases

Management

- En bloc excision

JCEM 86.2 (2001): 485-493.

PRINCE OF SONGKLA UNIVERSITY

Conclusion

Localization of parathyroid lesion in recurrent/persistent hyperparathyroidism is “mandatory”.

Supernumerary glands are not uncommon. Therefore, intraoperative parathyroid monitoring cannot be avoided.

Histological diagnosis should be performed by keen pathologist in order to give diagnosis of parathyroid carcinoma.

PRINCE OF SONGKLA UNIVERSITY

Thank you for your attention