Interhospital conference Case 1

Siriraj Hospital

“ขาซ้ายบวม 1 เดือน ก่อนมาโรงพยาบาล”

Case

Patient Information

ผู้ป่วยชาย	อายุ 62 ปี
ภูมิลำเนา	จังหวัดเชียงราย
อาชีพ	ไม่ได้ประกอบอาชีพ
อาการสำคัญ	ขาซ้ายบวม 1 เดือน ก่อนมาโรงพยาบาล

-ประวัติต่อไปนี้ได้มาจากผู้ป่วยและเวชระเบียน มีความน่าเชื่อถือมาก-

Case

Present Illness

3 years PTA

Diagnosis Ureteric stone from right flank pain
Film KUB found radio-opaque calculi at Rt. renal pelvis

- BP 155/65 mmHg
- FBS 113 mg/dL, LDL 189 mg/dL
- K 4.1 mmol/L, HCO3 29 mmol/L

Diagnosis: HT, DLP and Prediabetes

Treatment: Enalapril 5 mg/d, Amlodipine 5 mg/dL

During follow-up

- **K 2.9-3.5 mmol/L**, HCO_3 28-36 mmol/L
- Cr 0.7 mg/dl
- FBS 131 mg/dl, HbA1c 6.7%

Diagnosis: Diabetes mellitus

Treatment: Metformin 500 mg/day

1.5 years PTA

Developed left eye ptosis without proximal muscle weakness

- AChR positive, K 2.2 mmol/L

Diagnosis: AChR Ab positive Ocular MG

Treatment: Mestinon, **prednisolone(5) 2x1 pc**
KCl (500) 1x2 pc

Then Worsening of ocular MG and uncontrolled DM
(HbA1C 6.7% -> 8.6%)

Treatment:

- Prednisolone 20 mg/d
- MFM 500 -> 1000 -> 2000 mg/d
- Pioglitazone 30 mg/d, Glipizide 10 mg/d

Case

Present Illness

3 months PTA

Back pain with radiculopathy

- MRI L-S Spine: **compression fracture at T12 and L2**, no cord signal change

Treatment

- Teriparatide SC

1 month PTA

Multiple brownish plaque at right forearm

Skin biopsy: *Microsphaeropsis arundinis*

Diagnosis: Sporotrichosis from Dematiaceous mold

Present

Admit for ventral hernia surgery

- **Left leg edema for 1 month**

Consult endocrine

- Glycemic control
- Evaluation history of vertebral compression fracture

Case

Additional history

- ไม่มีภาวะซึมเศร้า อ่อนเพลีย นอนไม่หลับ ความต้องการทางเพศลดลง สมาธิสั้น หงุดหงิดง่าย
- ไม่สีผิวคล้ำขึ้นหรือแผลเป็นคล้ำขึ้น
- น้ำหนักเพิ่มขึ้นจากเดิม 64 ⟶ 70 kg ภายใน 1 ปี
- ไม่มีขี้หนาว เหนื่อยง่าย ผิวแห้ง ขาบวม ตะคริว ไม่มีอาการขนหัวหน่าวหรือขนรักแร้ร่วงผิดปกติ
- ไม่มีขี้ร้อน ไม่มีใจสั่น/มือสั่น/กินจุก
- การมองเห็นปกติ
- ผู้ป่วยหยุดยา prednisolone 1 เดือนก่อนมาโรงพยาบาลเอง เนื่องจากกังวลเรื่องกระดูกหลังหัก

- ปฏิเสธยาชุด สมุนไพร ยาต้ม ยาลูกกลอนหรืออาหารเสริม
- Social drinking เลิกมานาน 10 ปี
- Smoking < 5 pack year เลิกมา > 20ปี
- มีบุตร 3 คน บุตรทุกคนแข็งแรงดี อายุ 33, 31 และ 29 ปี ตามลำดับ

Case

Current Medications

- Metformin (500)	1x2	PO pc
- Atorvastatin (40)	1x1	PO hs
- Spironolactone (25)	1x1	PO pc
- CaCO3 (1,000)	1x1	PO pc
- Vitamin D2 (20,000)	1 cap	PO weekly
- Mestinon (60)	2x4	PO ac, hs
- Azathioprine (50)	1/2x1	PO pc
- Enoxaparin	0.6 ml	SC q 12 hr

Case

Physical Examination

Vital sign	BT 36°C, PR 90 bpm, RR 20/min, BP 118/96 mmHg BW 66 kg, Ht 162 cm, **BMI 25 kg/m^2**
GA	Alert, well-cooperative, no pallor, no jaundice, **round face**, **supraclavicular fullness, dorsocervical fat pad,** no facial plethora, no truncal obesity
Skin	No bruise and ecchymosis, no purplish striae, thin skin, **acanthosis nigricans at neck**, no hirsutism, no hyperpigmentation, **multiple discrete brownish plaque with some erythematous nodules on right forearm, multiple hypopigmented discrete lesions at chest area and upper back**
CVS	PMI at 5th ICS lateral to MCL, no LV/RV heaving, normal S1/S2, no murmur
RS	Clear, equal breath sound

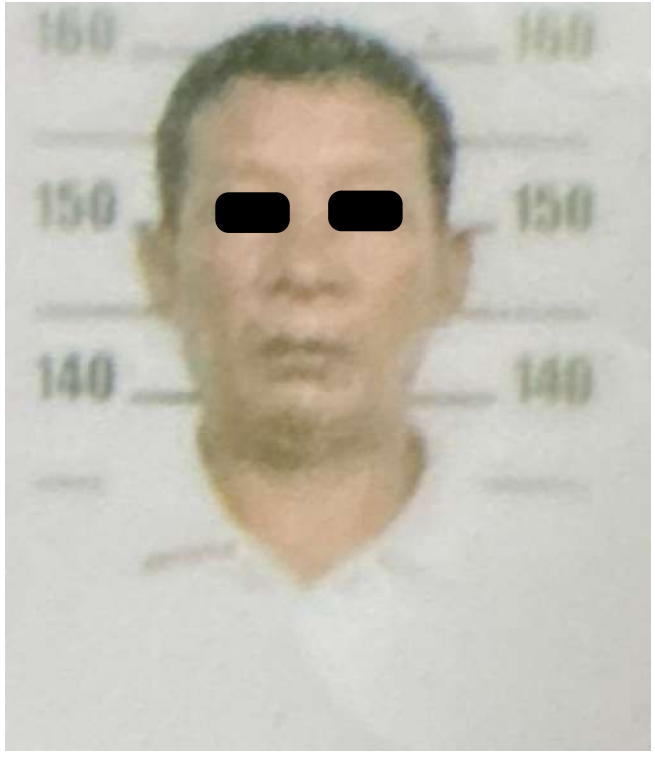
Case

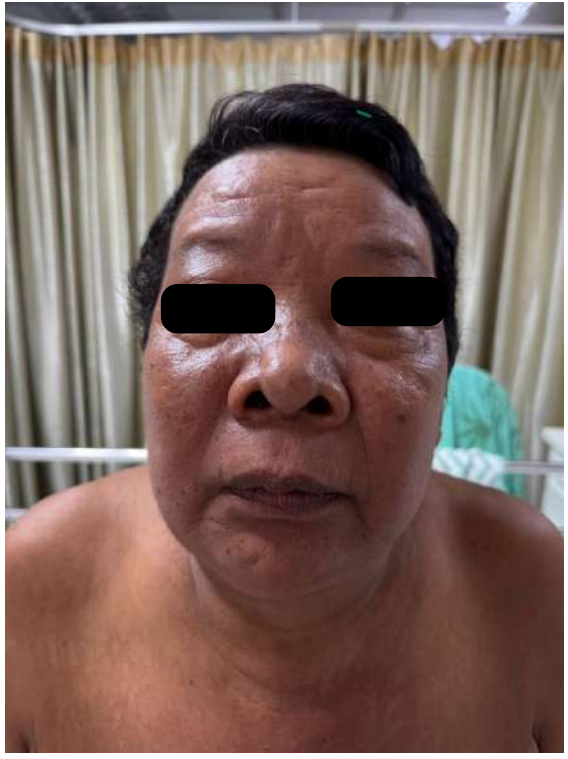
Physical Examination

Abdomen	No surgical scar, no striae, mild distension abdomen, normoactive BS, no tenderness, no hepatosplenomegaly, no palpable mass
Nervous system	Normal consciousness, orientation to time place person No VF defect, full EOM, left eye ptosis Motor power grade 5 all extremities, intact sensory system, DTR 2+ all
LN	No palpable lymphadenopathy
Extremities	**Pitting edema left leg, Homan's sign positive left leg**

Case

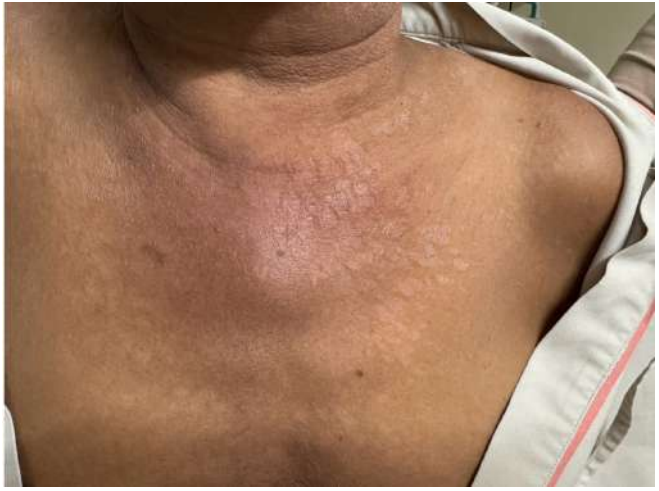
Physical Examination

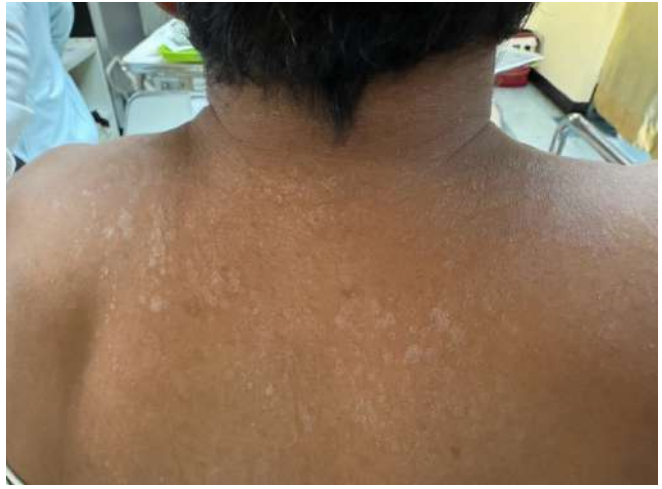


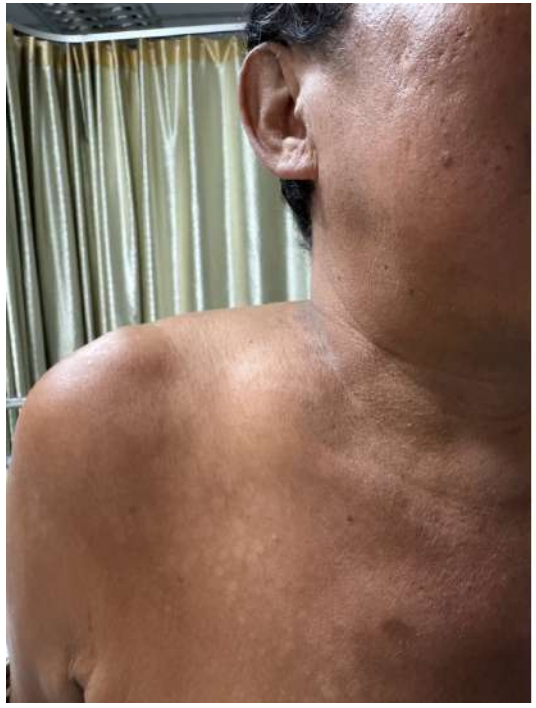


Case

Physical Examination (Skin)







Case

Physical Examination (Skin)

Investigation

Complete Blood Count

Hb	14.6	g/dl
Hct	46.4	%
WBC	11,240	/ul
Neutrophil	60	%
Lymphocyte	34	%
Monocyte	4.3	%
Eosinophil	0.9	%
Basophil	0.3	%
Platelet	277,000	/ul

Investigation

Blood Chemistry

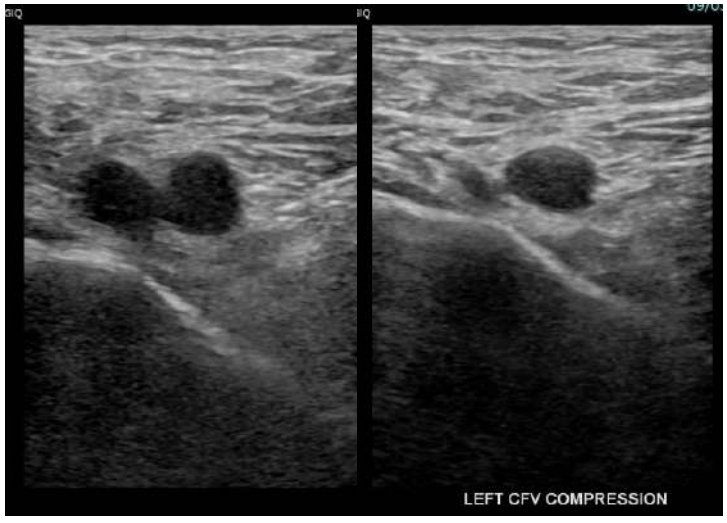
Cr	0.6	mg/dl
Na	140	mmol/L
K	3.4	mmol/L
Cl	99	mmol/L
HCO_3	28	mmol/L

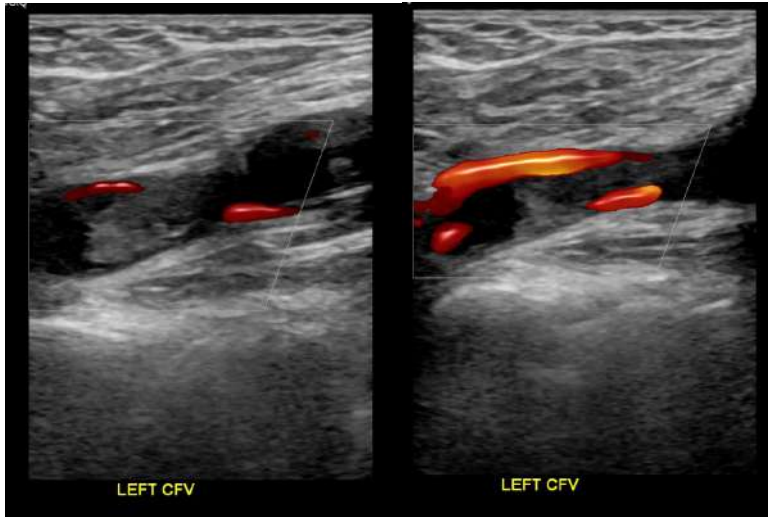
Glucose	120	mg/dl
HbA1c	7.4	%
Cholesterol	256	mg/dl
Triglyceride	219	mg/dl
HDL-c	35	mg/dl
LDL-calculated	177	mg/dl

TCa	10.0	mg/dl	(8.8-10.2)
PO_4	2.5	mg/dl	(2.5-4.5)
PTH	41.80	pg/ml	(15-65)
25 OHD	39.7	ng/ml	

Investigation

Ultrasound doppler left lower extremity





Impression

- **Acute occlusive DVT** of the left common-femoral vein
- No DVT in right femoropopliteal veins
- No DVT in the visible portions of right calf vein

Case

Problem List

A 62-year-old man scheduled for ventral hernia surgery

Case

Problem List

A 62-year-old man scheduled for ventral hernia surgery

1. DVT Left leg for 1 month
2. Superficial fungal skin infection for 1 month
3. Non-traumatic vertebral compression fracture at T12/L2 diagnosed 3 months ago
4. Weight gain 6 kg in 1 year
5. Worsening diabetes control 1.5 years
6. Hypokalemia with metabolic alkalosis
7. Physical examination: signs of Cushing syndrome ???
8. U/D: DM, HT, DLP, AChR-Ab positive ocular MG

Investigations and Diagnosis

Investigation

Lab Investigation

8.00 AM cortisol	20.8	ug/dl
2-day LDDST	23.5	ug/dl
LNSC	Day 1 = 0.652 Day 2 = 1.500	ug/dl (<0.274)

	Day 1	Day 2
Urine free cortisol (19-317 ug/day)	825.86	1,363.61
24-hr Urine Cr (mg/kg/day)	12.64	10.65

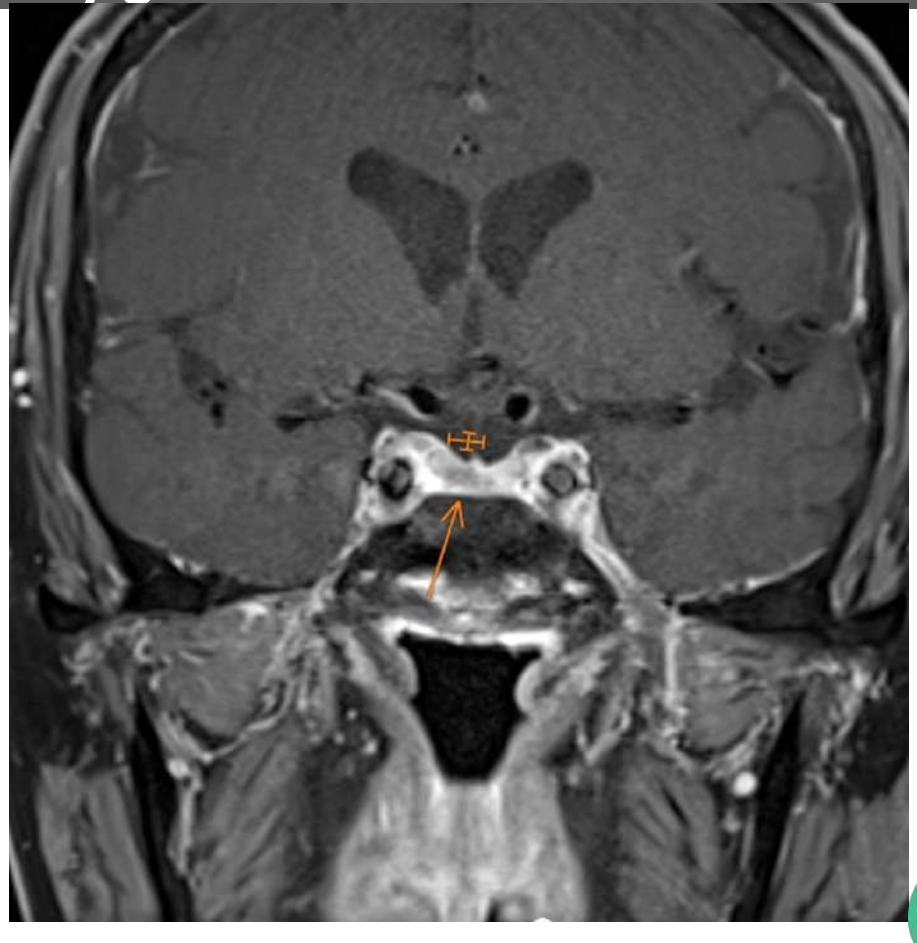
ACTH	128.9,	93.98	pg/ml

Investigation

MRI pituitary gland

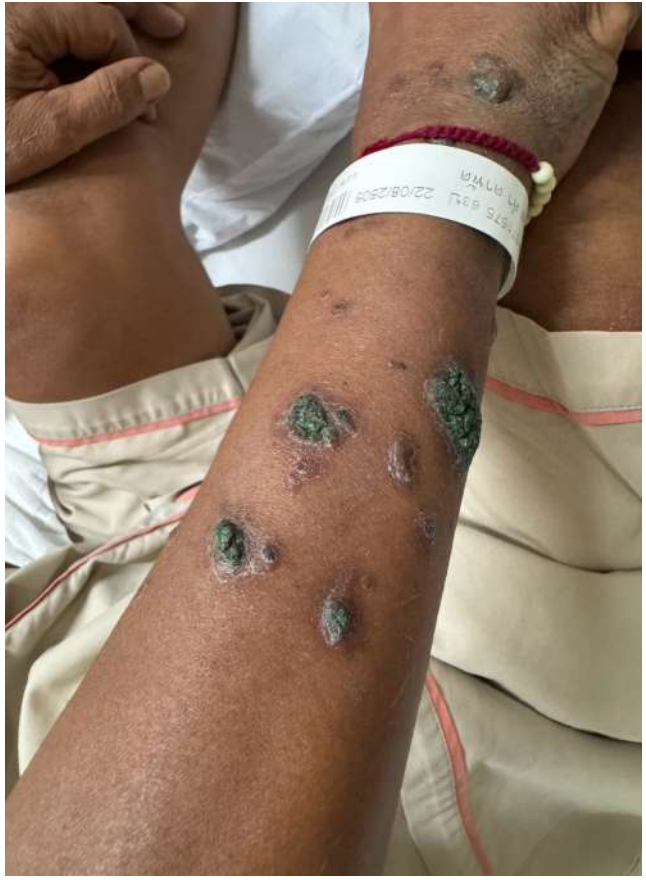
MRI Pituitary Gland

- A well-defined intermediate signal on T1W and T2W with relatively less enhancement, measured **about 0.5x0.3 cm at right sided pituitary gland, suspected pituitary microadenoma**
- The rest of pituitary gland and posterior bright spot are unremarkable
- Normal position of pituitary stalk



Coronal T1 with Gadolinium Dynamic Phase

Case Progression



Superficial fungal skin infection

Treatment:

- Itraconazole(200) 1x2 po pc

Case

Problem List

A 62-year-old man scheduled for ventral hernia surgery

1. **ACTH dependent Cushing syndrome**
2. **Pituitary microadenoma 0.5x0.3 cm**
3. **Fungal infection (on treatment Itraconazole)**
4. **DVT left leg on enoxaparin**
5. **Osteoporosis with vertebral fracture**

Next ???

Investigation

Desmopressin Test

Time	ACTH (pg/mL)	Cortisol(ug/mL)	Na (mEq/L)
0	47.49	21.4	139
15	61.41	22.1	140
30	54.35	22.5	139
45	87.35	21	143
60	94.31	21	141
90	80.85	21.6	141
120	83.04	21.4	139

ACTH 47.49 -> 94.31 pg/ml
Increase 98%

Investigation

8-mg Overnight HDDST

- **Baseline 8 AM cortisol 20 ug/dl**
- **8.00 AM after 8 mg Dexamethasone 16.9 ug/dl**

Cortisol 20 -> 16.9 ug/dl
Decrease 15.5%

Investigation

Bilateral Inferior Petrosal Sinus Sampling (BIPSS)

LNSC 0.714 ug/dl (positive), midnight serum cortisol 17.7 ug/dl

	ACTH					Prolactin				
	Rt	Lt	FV	R/F	L/F	Rt	Lt	FV	R/F	L/F
-5	125.7	131.7	96.64	1.3	1.36	104	58.6	10.10	10.3	5.8
-2	140.60	139.30	105.9	1.33	1.31	126	44.80	9.62	13.1	4.66
0										
2	147.80	146.20	96.43	1.53	1.52	97.80	109	9.3	10.52	11.72
5	146.80	153.40	107.80	1.36	1.42	52	85.8	10.3	5.04	8.33
10	142.60	155.90	110.30	1.29	1.41	25.5	78	10.9	2.34	7.15

Normalized ACTH/PRL IPS/P < 0.7

Basal ACTH IPS/P < 2
Peak ACTH IPS/P < 3

Baseline PRL IPS/P > 1.8

Diagnosis

Cushing syndrome from ectopic ACTH

NEXT ?????

Investigation

Anatomical imaging

CT chest

- No anterior mediastinal mass detected
- Enlarged right thyroid lobe with an unclear hypo-enhancing nodule size 3 cm containing internal calcification
- No pulmonary mass or lymphadenopathy observed
- Both adrenal glands appear normal

CT whole abdomen

- No detectable of abdominal mass.
- No detectable of the overt HCC
- The 0.6 cm ureteric stone at lower ureter, and above right uretero-vesical junction about 3 cm and causing partial ureteric obstruction and mild hydroureter.
- The small calyceal stone, 0.3 cm at right kidney
- Bilateral renal cysts, up to 1 cm
- The small duodenal diverticulum at 3rd part duodenum.
- The fat containing ventral hernia (epigastrium), and the small fat containing umbilical hernia.
- Degenerative change of spine and multiple levels of vertebral body compression.

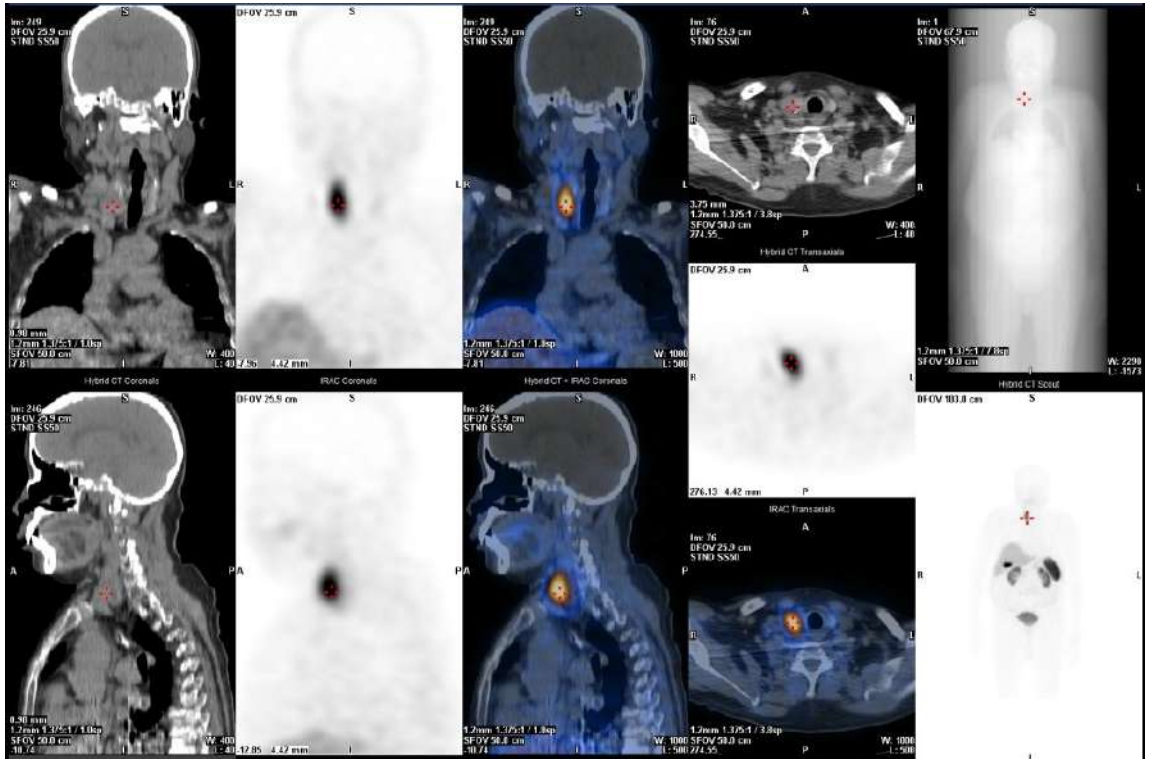
Investigation

Somatostatin Receptor Scan

Investigation

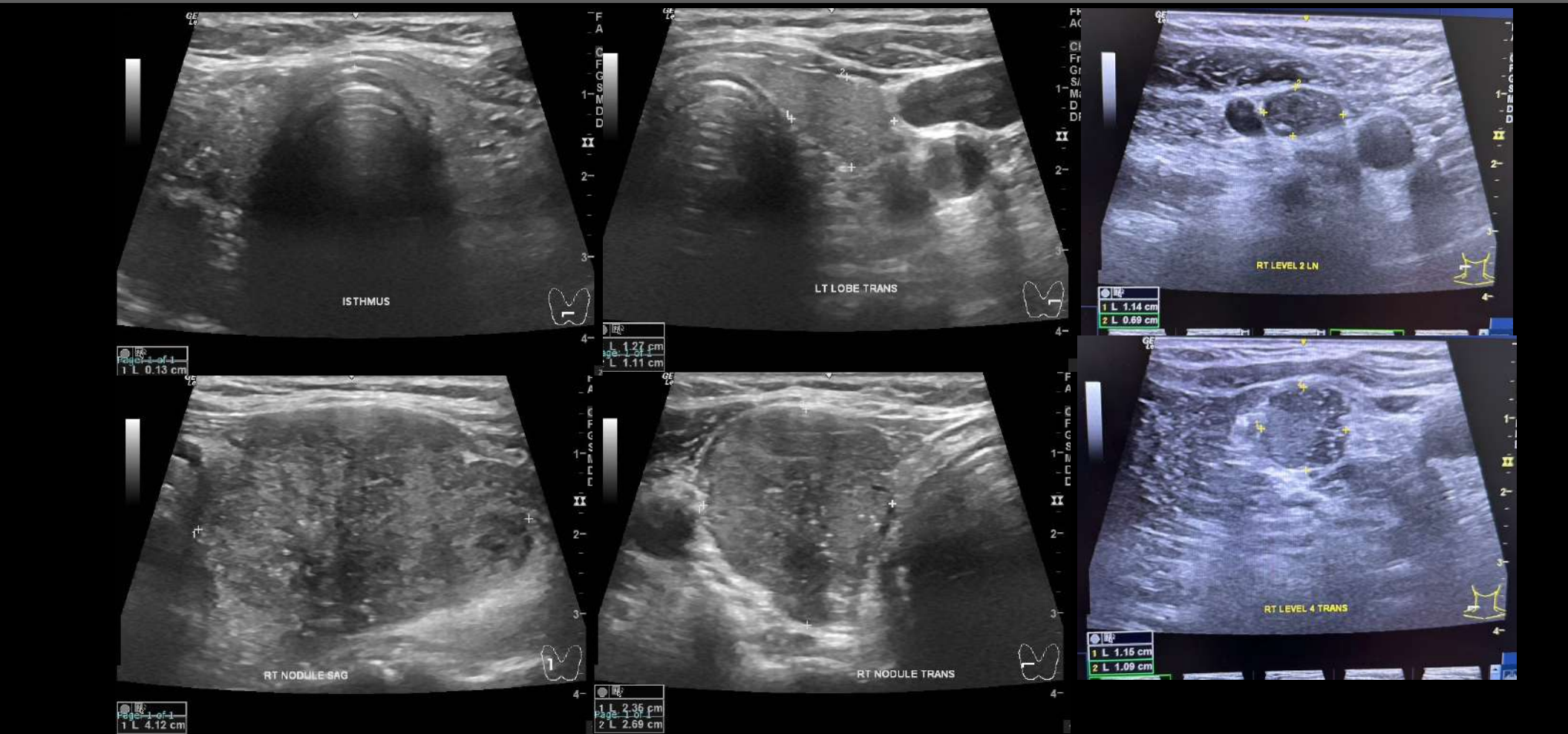
Somatostatin Receptor Scan

- **A focally intense radiotracer uptake at right lobe of thyroid gland**, which SPECT/CT images show an enlarged right thyroid lobe with a focal intense uptake at lateral aspect. Probably an ectopic ACTH tumor at lateral aspect of right thyroid lobe
- No suspicious uptake elsewhere that might suggest functioning tumor



Investigation

US Thyroid

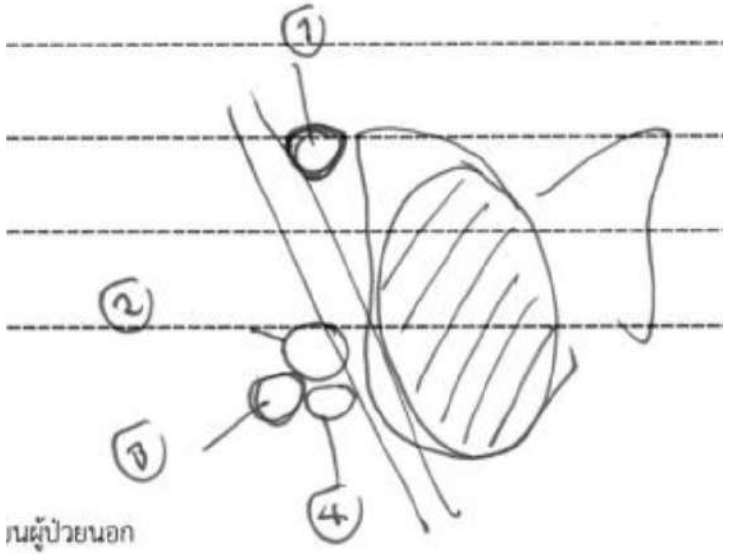


Investigation

US Thyroid

U/S Thyroid

- Isthmus width 0.13 cm
- **Rt. lobe is occupied almost entirely by hypoechoic nodule with irregular border, microcalcification and increased vascularity size 2.35 x 2.69 x 4.12 cm.**
- Lt. lobe measures 1.27 x 1.11 x 2.49 cm. Homogeneous echotexture, no nodules.
- **Multiple round shape hypoechoic lymph nodes with microcalcification at Rt. Cervical region level II (1) and IV (2,3,4)**



Investigation

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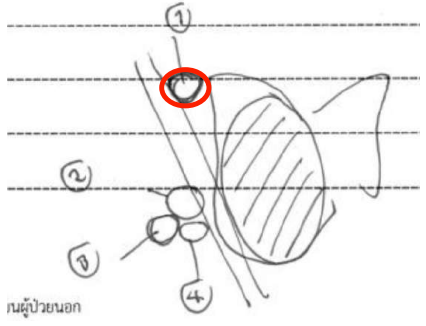
U/S-guided FNA of Rt. Thyroid nodule and Rt. Cervical LN level II (4/9/68)

- **Pathology** :
  - Rt. Thyroid nodule – Suspected medullary thyroid carcinoma (MTC)
  - Rt. Cervical LN level II – Metastatic carcinoma



Diagnosis

Medullary thyroid carcinoma with ectopic ACTH

NEXT ?????

Investigation

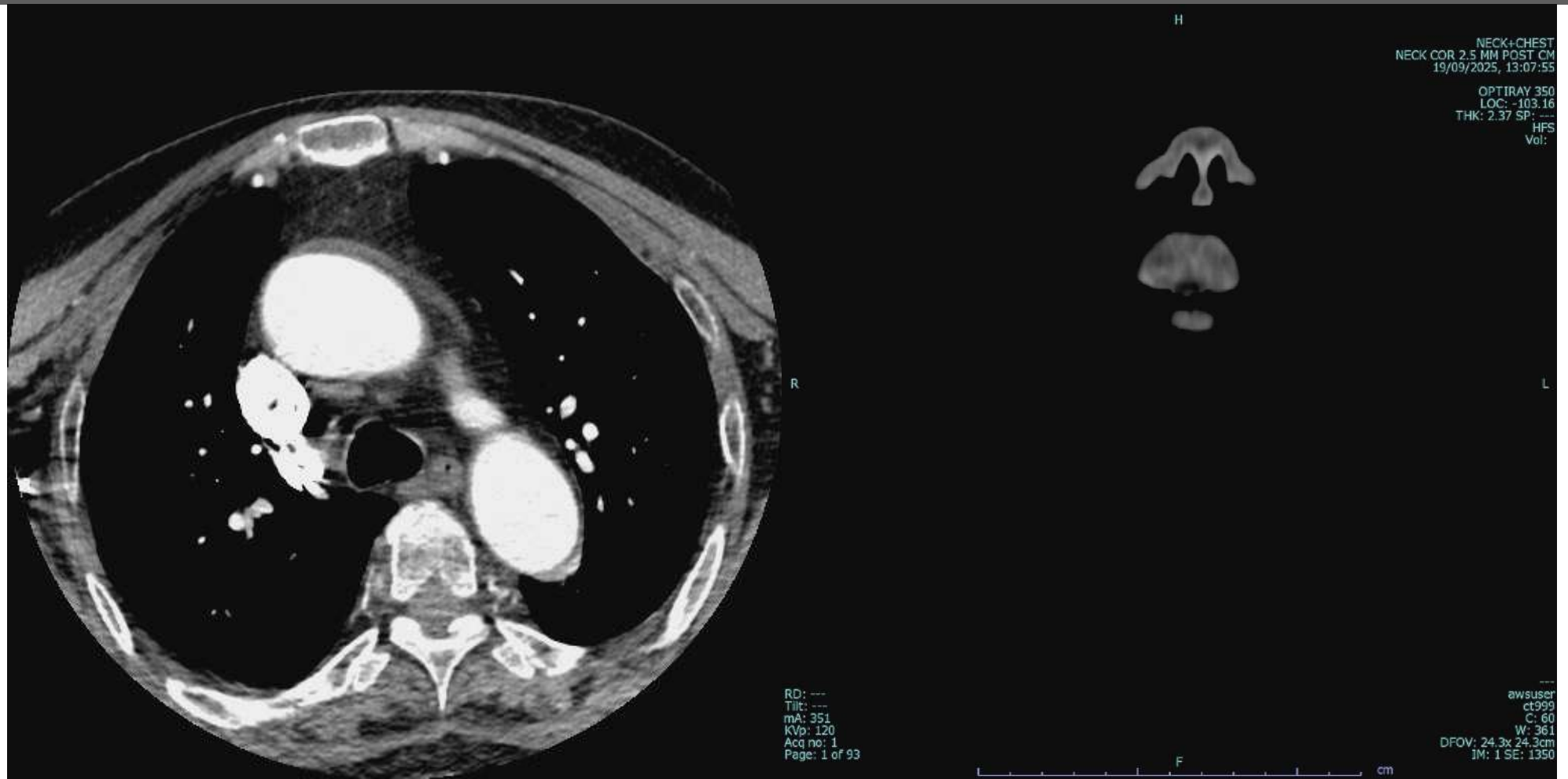
Special Investigation

Calcitonin	1,609	pg/ml	(0-9.52)
CEA	11.60	ng/ml	(0-3.4)

24-hr urine metanephrine	<50,	<50	ug/day (<350)
24-hr urine normetanephrine	56.63,	50.28	ug/day (<600)
24-hr urine dopamine	832.95,	747.88	ug/day (80-480)
24-hr urine Cr	13,	15	mg/kg/day

Investigation

CT Neck with chest



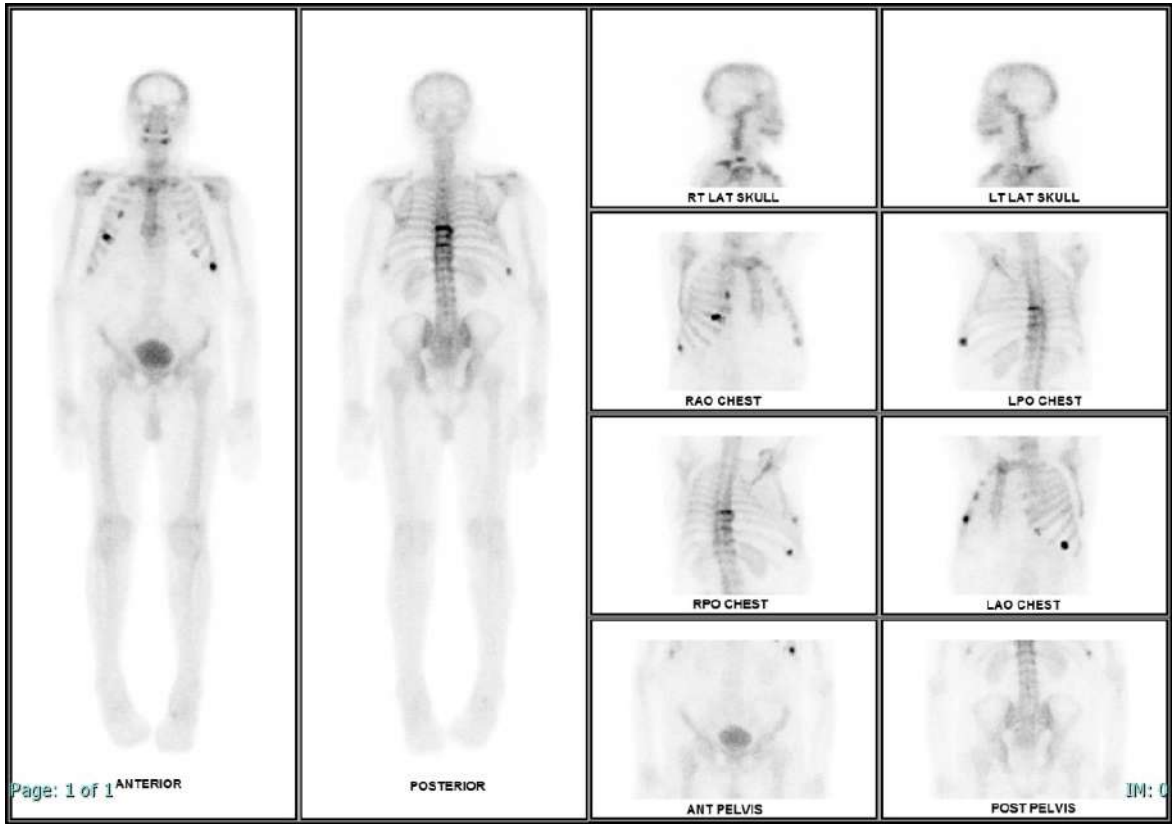
Investigation

CT Neck with Chest

- **A 3.4 x 2.4 x 4.6 cm ill-defined enhancing nodule with internal calcification at Rt. Thyroid lobe**
- **A few significant enlarged Rt. Cervical lymphadenopathy size up to 1.4 cm in short axis at Rt. supraclavicular region**, probably nodal metastasis
- No evidence of pulmonary metastasis
- A 0.3-cm calcified nodule at the superior segment of RLL could be calcified granuloma
- Mild dilated ascending aorta
- Enlarged size of main pulmonary artery, suspected pulmonary hypertension
- A 0.6-cm hypodense lesion at hepatic segment 8
- A few bilateral renal cysts
- Bilateral gynecomastia
- Compression Fracture of T3-T12 and L1 level

Investigation

Bone scan



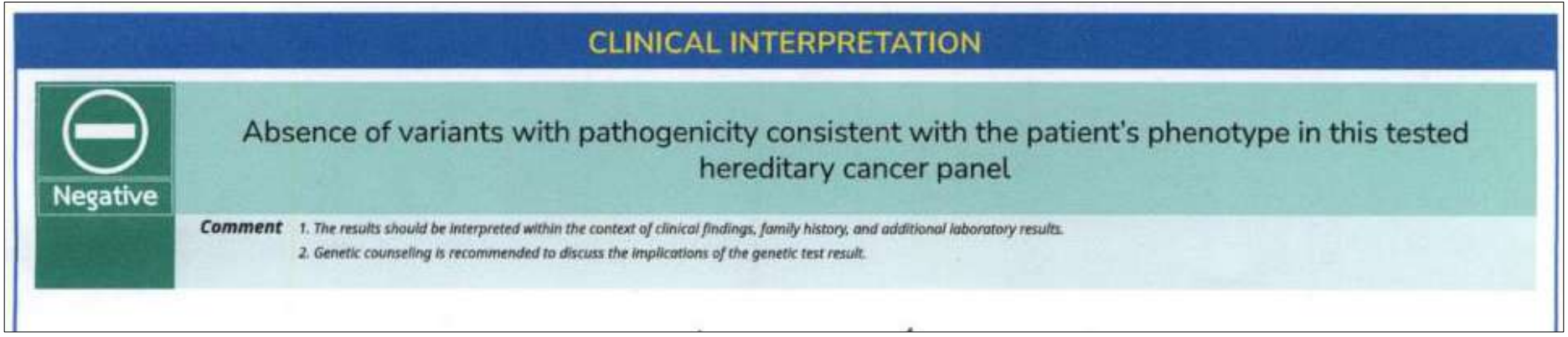
- **Increased radiotracer uptake at anterior left 6 th and 8th ribs**, **anterior right 3rd**, **5th, 9th ribs** is suggestive of bone metastasis.

- **Increased radiotracer uptake at T8-T10 vertebrae** is likely post treatment change, however residual tumor or bone metastasis cannot be excluded.

- The rest of the skeleton appears unremarkable

Investigation

Genetic testing



CLINICAL INTERPRETATION

Negative

Absence of variants with pathogenicity consistent with the patient's phenotype in this tested hereditary cancer panel

Comment *1. The results should be interpreted within the context of clinical findings, family history, and additional laboratory results.*

2. Genetic counseling is recommended to discuss the implications of the genetic test result.

Case Progression

Operation: Total thyroidectomy with bilateral central node dissection with bilateral lateral neck dissection

Intra-op finding:

- Thyroid gland with mass 2 cm at Rt. Lobe thyroid without gross extrathyroidal extension
- Enlarged Rt. Paratracheal LN size up to 1 cm with Lt. Cervical LN level II-IV size up to 1.5 cm

Patho report:

Diagnosis
A) Thyroid gland, total thyroidectomy:
- Medullary thyroid carcinoma
- Size: 4.1x3.3x2 cm
- Site: Right lobe
- Focality: Unifocal
- Mitosis 8/2 sq.mm
- Tumor necrosis: Present
- Lymphatic invasion: Present
- Angioinvasion: Present
- Perineural and neural invasion: Present
- Extrathyroid extension:
  - Microscopic extension into perithyroidal soft tissue
  - No involvement of striated muscle
- Presence of tumor deposit in perithyroidal soft tissue
- Margin: Involved by tumor at anterior and posterior
- Remaining thyroid: No remarkable change
- Parathyroid tissue: Present; No involvement by tumor
- Regional lymph node:
  - Metastatic carcinoma (1/1 node)
  - No extranodal extension
  - Largest metastatic deposit 0.27 cm

B) Soft tissue, labeled "right paratracheal LN", dissection:
- Fibrovascular and adipose tissues with no involvement by tumor
- No lymph node received

C) Lymph node, labeled "right lateral cervical LN level 2-5", dissection:
- Metastatic carcinoma (9/16 nodes)
- Presence of extranodal extension
- Largest metastatic deposit 2.4 cm

D) Lymph node, labeled "left lateral cervical LN level 2-5", dissection:
- Negative for metastatic carcinoma (15 nodes)

E) Lymph node, labeled "central node", dissection:
- Metastatic carcinoma (7/7 nodes)
- Presence of extranodal extension
- Largest metastatic deposit 1.3 cm

Immunohistochemical Results
The tumor cells show immunoreactivity as follow:
TTF-1: positive
Thyroglobulin: negative
PAX8: positive
Chromogranin and INSM1: positive
Calcitonin: Positive
Ki-67: 10.9% (manual count)

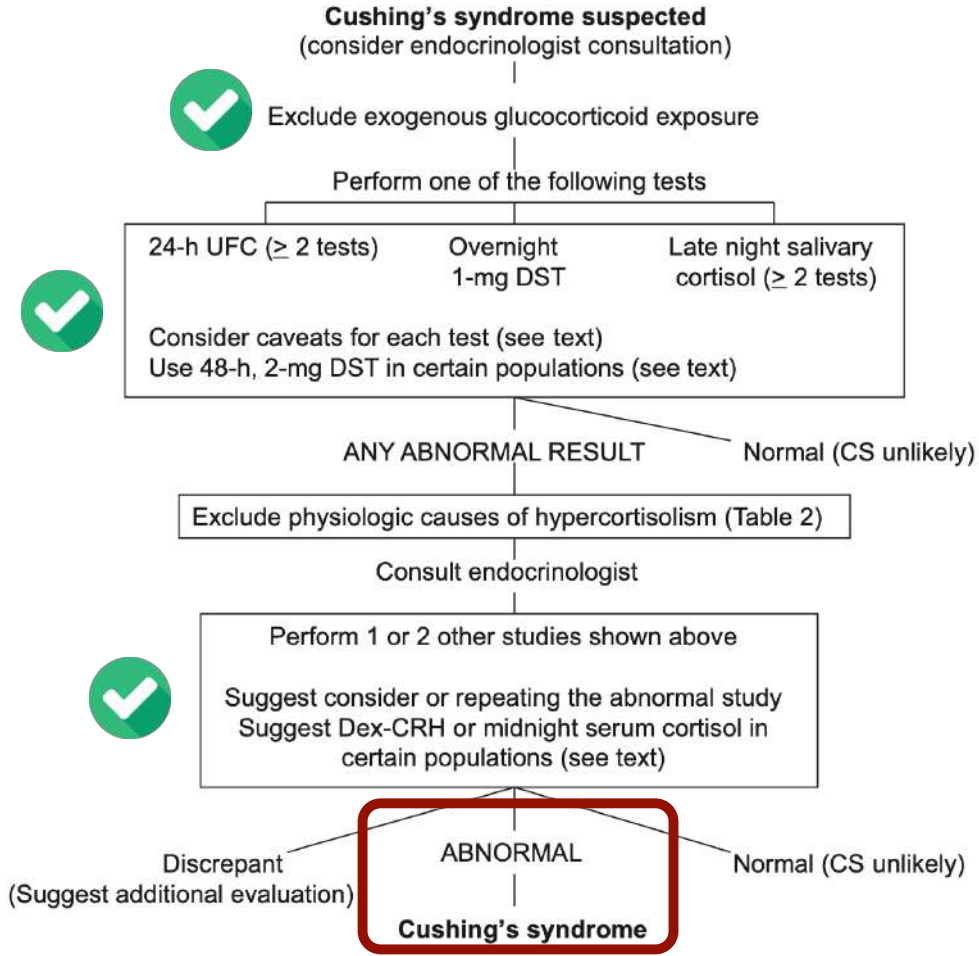
Case Progression

	Pre-op	Post-op Day 6	Post-op 1 month	Post-op 2 month
Calcitonin (0-9.52 pg/ml)	1,609		33.10	29.60
CEA (0-3.4 ng/ml)	11.6		2.83	2.83
8AM cortisol (ug/dl)	17.6	0.6		
ACTH (pg/ml)	140.60	24.87	6.57	7.33

Review

Case

Work-up Results



Morning cortisol = 20.8 mcg/dL (Alb 3.9 g/dL)

Exclude Exogenous Cushing Syndrome

Late-night salivary cortisol (LNSC)

Day 1 = 0.652 ug/dl (<0.274)

Day 2 = 1.500 ug/dl

Standard LDDST

Basal serum cortisol 23.5 ug/ml

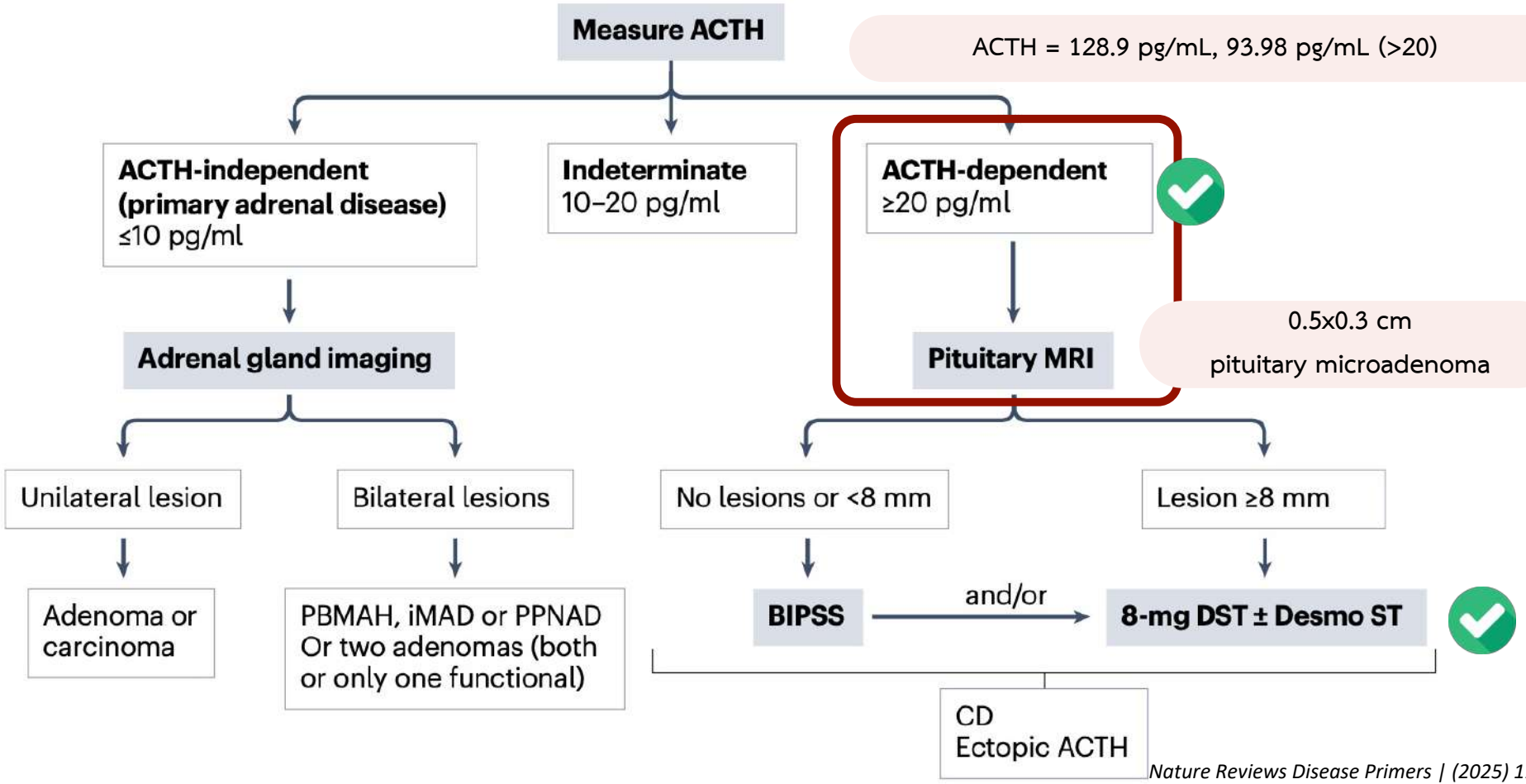
24-hr urine free cortisol

Day 1: 825.86 mcg/24 hr (Urine Cr 12.6 mg/kg/d) (19-317)

Day 2: 1,363.61 mcg/24 hr (Urine Cr 10.6 mg/kg/d)

Subtypes of Cushing's Syndrome

Localization of Tumor



Nature Reviews Disease Primers | (2025) 11:4

Investigation for Cushing's Syndrome

Test to Differentiate Causes of ACTH-dependent Cushing's

Bilateral Inferior Petrosal Sinus Sampling (BIPSS)

DDAVP 10 mcg

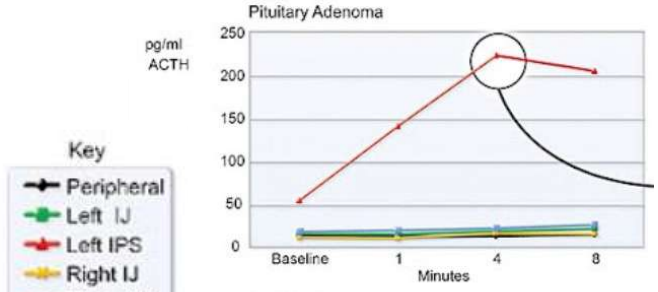
Yes

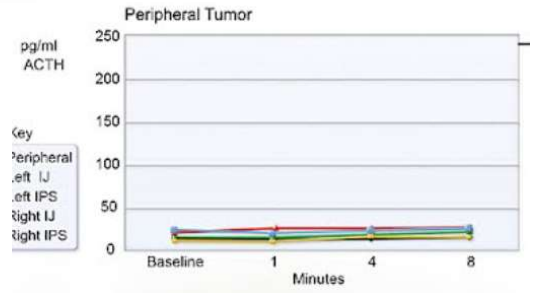
IPS:PV
ACTH > 2:1 (pre-ACTH) or
> 3:1 (post-ACTH)

No

Cushing Disease

Ectopic Cushing Syndrome





Consider fail catheterization if IPS:PV Prolactin < 1.8

Investigation for Cushing's Syndrome

BIPSS Limitations

False Positive
(Interpreted as Pituitary CS)

- Normal population
- Pseudo-Cushing state
- Factitious hypercortisolemia
- Adrenal Cushing with mild hypercortisolemia
- Cortisol blocking drug (e.g. ketoconazole, metyrapone)
- Bilateral adrenalectomy
- Ectopic CRH-secreting tumor

False Negative
(Interpreted as Ectopic CS)

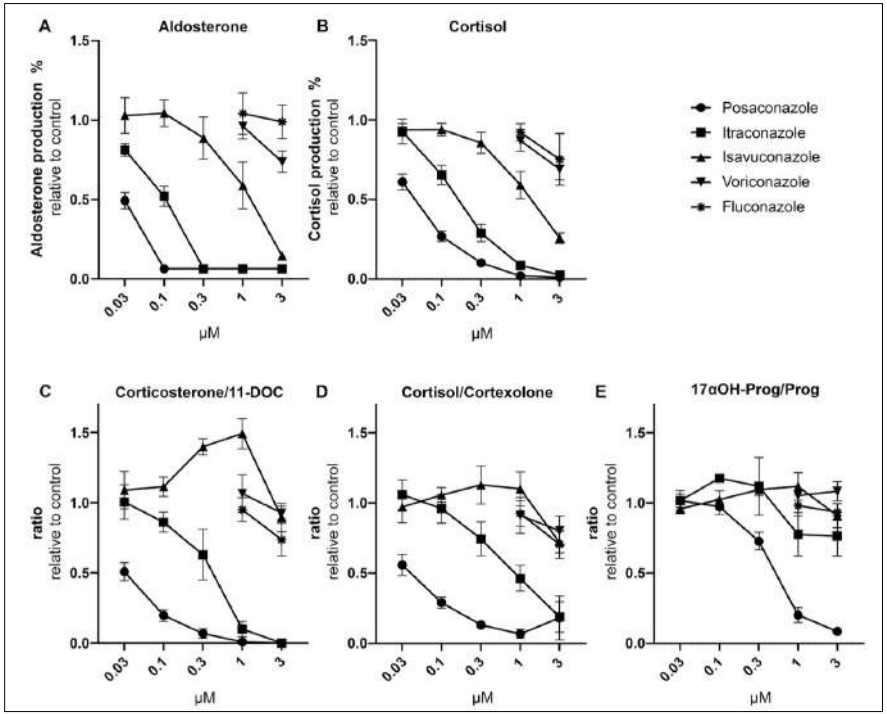
- Aberrant pituitary drainage
- Incorrect IPSS technique
- Failed cannulation at IPS
- Low ACTH response after CRH/DDAVP

J Clin Endocrinol Metab. 2004 Aug;89(8):3752-63

Investigation for Cushing's Syndrome

Itraconazole

1. <u>Inhibition of CYP11B1 (11b-hydroxylase)</u>
   - Decrease conversion of 11-deoxycortisol -> cortisol
   - Decrease negative feedback of ACTH
   - Increase precursor steroid (DOC, 11-deoxycortisol)



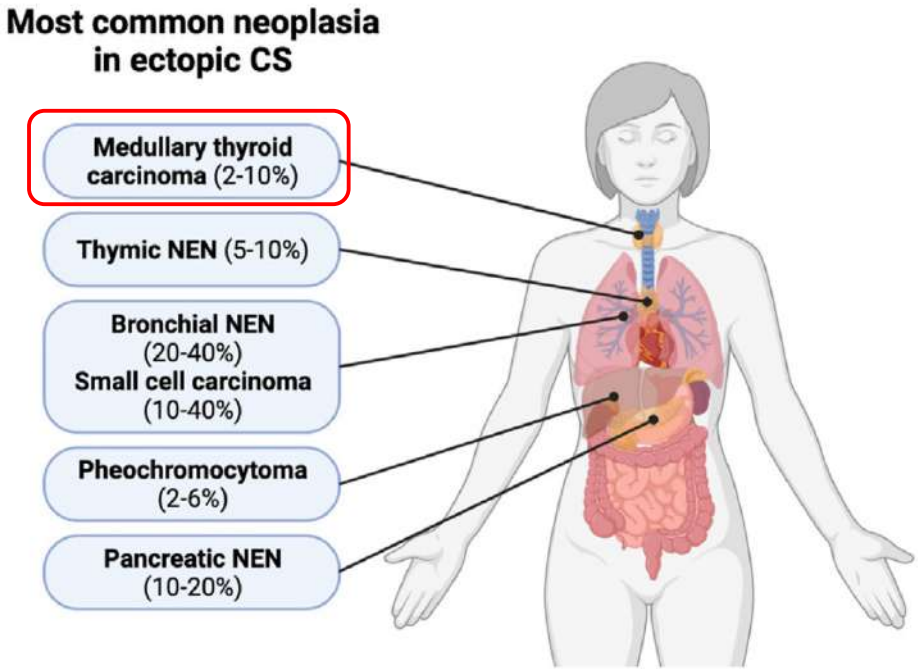
Current Research in Toxicology 5 (2023) 100119

Overview of Ectopic Cushing's Syndrome (ECS)

Overview of Ectopic Cushing's Syndrome (ECS)

Etiology of Cushing syndrome

Cushing's disease	
ACTH dependent	50–80% of all CS
Cause	ACTH-producing pituitary adenoma (100%)
Adrenal CS	
ACTH independent	15–25% of all CS
Cause	Cortisol-producing adrenocortical adenoma (80%)
	Primary bilateral macronodular adrenocortical hyperplasia (<5%) Primary pigmented nodular adrenocortical disease (<5%)
	Adrenocortical carcinoma (10%)
Ectopic CS	
ACTH dependent	10–20% of all CS
Cause	Bronchial neuroendocrine neoplasia (20–40%)
	SCLC (10–40%)
	Pancreatic neuroendocrine neoplasia (10–20%) Thymic neuroendocrine neoplasia (5–10%) Pheochromocytoma (2–6%) MTC (2–10%) Other NEN[a] (1–15%) Occult (10–20%)



Ragnarsson et al., Trends Endocrinol Metab. 2024; 35(4):347–360

Imaging modalities in patients with ECS

Sensitivity ~66%

Modality	Merit	Pitfalls
CT cervical-thoracic-abdominal and pelvic	Easily available Inexpensive Identifies around two-thirds of all tumours causing ECS First choice in most patients with ECS Radiologists well familiar with the modality	Cannot identify some ECS Cannot evaluate the functional status of tumour Ionized radiation Intravenous contrast given (normal kidney function required, risk for contrast reaction)
Magnetic resonance tomography	No ionized radiation, thus the imaging modality of choice when frequent imaging is required First choice if CT cannot be done	Identifies only up to half of all ECS Poor performance for NENs in lungs Cannot evaluate the functional status of a tumour Cannot be used in patients with metallic implants Good radiological skills needed
^{111}In-pentetreotide scintigraphy (Octreoscan)	Been used for long time Identifies functional tumours Second choice if ^{68}Ga-SSTR PET/CT or other new modalities are not available	Cannot identify around half of all ECS Radioactive tracer used Not sensitive in highly proliferative NENs Expensive Not widely available
^{68}Ga-SSTR PET/CT	Identifies most NENs Can recognize if tumour is functional Second choice	Not widely available Radioactive tracer used Intravenous contrast given (normal kidney function required, risk for contrast reaction) Not sensitive in highly proliferative NENs Expensive
^{18}F-FDG-PET/CT	Sensitive for highly proliferative NENs The most widely available PET/CT Third choice	Identifies only half of all NENs Radioactive tracer used Intravenous contrast given (normal kidney function required, risk for contrast reaction) Expensive
^{68}Ga-SSTR-PET/MRI	Similar as ^{68}Ga-SSTR-PET/CT	Similar as ^{68}Ga-SSTR-PET/CT but less sensitive for bronchial NENs Cannot be used in patients with metallic implants Not widely available Expensive
^{18}F-DOPA-PET/CT	Identifies more than half of all NENs Can recognize if the tumour is functional Fourth choice	Many NENs not detected Uses radioactive tracer Intravenous contrast given (normal kidney function required, risk for contrast reaction) Not sensitive for highly proliferative NENs Expensive Not widely available
^{131}I/^{123}I-metaiodobenzylguanidine (MIBG)	Been used for long time Can recognize if a tumour is functional Method of choice for patients with suspected ACTH-producing pheochromocytoma where ^{68}Ga-SSTR-PET/CT is not available otherwise last choice	Most ECS not detected Radioactive tracer used Not sensitive for highly proliferative NENs Expensive Not widely available

Sensitivity ~82%

Ragnarsson et al., Trends Endocrinol Metab. 2024; 35(4):347–360

Ectopic Cushing's Syndrome

Treatment

- Goals of treatment are **resolution of hypercortisolism** and **tumour control**
- The only definite cure of ECS is **complete excision** of causative
- Postoperative hypocortisolism is expected with postoperative glucocorticoid replacement therapy
- Recovery HPA axis typically 6-18 months
- In case of metastatic or occult ECS, medical therapy using adrenal steroidogenesis inhibitors, glucocorticoid receptor blockage and/or adrenolytic agents can be provided
- Bilateral adrenalectomy is an option for rapidly and effectively elimination hypercortisolism

Trends in Endocrinology & Metabolism, April 2024, Vol. 35, No.4

MTC with ECS

Treatment and Outcomes

- MTC with ECS: multihormonal dedifferentiation of C cells
- **0.6-0.7%** of 1640 MTC cases found **ectopic ACTH**
- **90%** having **distant metastases** at diagnosis

Retrospective cohort study in 3 German and 1 Swiss referral centers

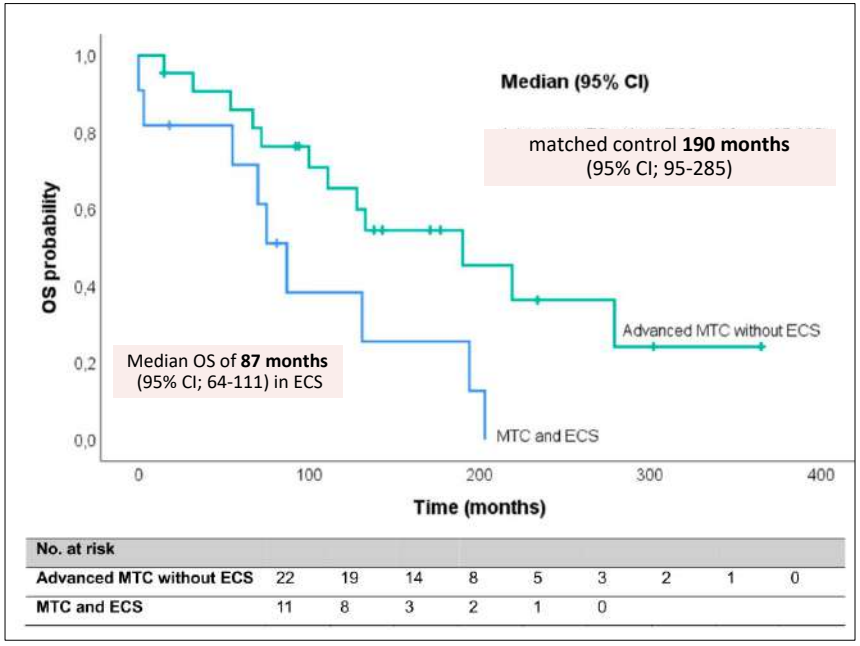
Treatment

- 8/11 (73%) specific therapy
- 8 Adrenostatic therapy (metyrapone, ketoconazole, mitotane)
- 4 Bilateral adrenalectomy
- 1 Multikinase inhibitor
- All treated patients achieved biochemical control
- 3/11 (27%) BSC

Survival: Worse survival with ECS

Causes of death

- Tumor progression
- Complications of hypercortisolism (infection, thrombosis)



Matched by sex, age at diagnosis, tumor stage, calcitonin doubling time

Cancers 2023, 15, 2403
JCEM, 2025, Vol. 110, No.9.
Clinical Endocrinology. 2022;96:847–856.


THANK
YOU