Interhospital conference
Case 4

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PATIENT IDENTIFICATION

- ผู้ป่วยหญิงไทยคู่ อายุ 44 ปี
- อาชีพแพทย์
- สิทธิการรักษา บัตรทอง
- อาการสำคัญ : อ่อนแรง 2 เดือน ก่อนมาโรงพยาบาล

PRESENT ILLNESS

- 2 เดือนก่อน มีอาการอ่อนแรงเวลาลุกจากเก้าอี้ หรือขึ้นบันได อาการเป็นๆหายๆ น้ำหนักลดลง 2 กก. ในช่วงดังกล่าว ไม่มีอาเจียน ไม่มี bowel habit change ไม่มีไอเรื้อรัง

Physical examination

V/S: BT 37.8 °C, BP 120/80 mmHg, RR 18/min, PR 70 bpm

HEENT: Mildly pale conjunctivae, anicteric sclerae, no thyroid gland enlargement

NS: Alert, Motor deltoid grade IV both sides, bicep and triceps V,

Hip flexion gr IV both sides, Hip extension/Knee flexion/Knee extension V, DTR 2+

Investigations:

CBC: Hb 10.1 g/dL, Hct 29.3 %, MCV 94.9 fL, WBC 25,729 cells/mm3 (N 93%, L 4 %), platelet 209,000 cells/mm3

Na 130 mmol/L, K 3.0 mmol/L, Cl 99 mmol/L, HCO3 27 mmol/L, BUN 15 mg/dL, Cr 0.45 mg/dL

History taking

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PRESENT ILLNESS

- 2 เดือน ก่อนมา รพ. ญาติสังเกตว่ามีอาการอ่อนแรงเวลาลุกจากเก้าอี้หรือขึ้นบันได อาการเป็นๆหาย ๆ กินได้น้อย เบื่ออาหาร น้ำหนักลด 2 กก. (จาก 35 > 33 กก.) ไม่มีอาเจียนหรือท้องเสีย ไม่มี bowel habit change ไม่มีไอเรื้อรัง

- 1 เดือน ก่อนมา รพ. มีอาการปวดศีรษะตื้อ เป็นช่วงๆ นานครั้งละประมาณ 10 นาที ช่วงปวดศีรษะวัดความดันได้ 170/100 mmHg หลังนั่งพักอาการปวดศีรษะหายได้เอง ความดันจะลดลงมาเป็น 120/80 mmHg ไม่ได้ทานยาลดความดัน ไม่ได้ไปรักษา

- 3 สัปดาห์ ก่อนมารพ ขณะยืนอยู่มีอาการชักเกร็งกระตุกทั้งตัวประมาณ 1 นาที ไม่มีอาการผิดปกตินำมาก่อน ไม่มีไข้ ไม่มีประวัติอุบัติเหตุ ไปที่ รพ. เอกชน แพทย์ได้ใส่ท่อช่วยหายใจ เนื่องจากซึมมาก

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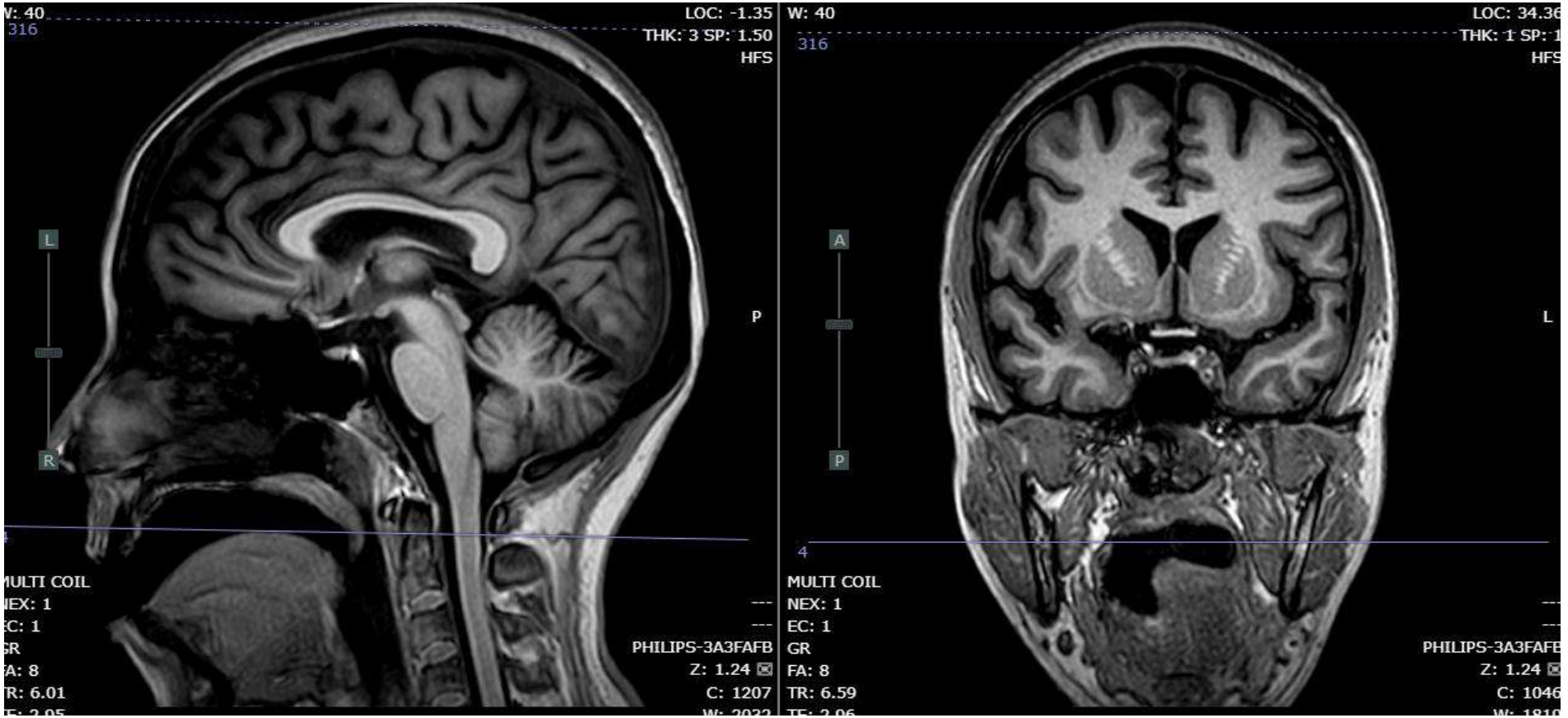
PRESENT ILLNESS

At รพ เอกชน

- BP 180/100 mmHgม HR 90 bpm, RR 18/min, T 37.3 C
- ตรวจพบ Na 128 mmol/L, K 1.3 mmol/L, Cl 102 mmol/L HCO3 26 mmol/L

MRI brain with contrast



Impression:

1. Hypersignal intensity at bilateral insular and hippocampus on FLAIR and T2W image suspected seizure from metabolic cause
2. No acute intracranial abnormality. No evidence of focal mass lesion, intracranial hemorrhage or acute infarction

PRESENT ILLNESS

- LP : OP 10 cmH2O, CP 11 cmH2O
  - RBC 2, WBC 0, Protein 33, Glucose 176
  - Autoimmune panel >> negative in serum & CSF
  - CSF for viral panel >> negative

- ได้รับการรักษาโดยการให้ยาความดันโลหิต และแก้ไขเรื่องเกลือแร่ผิดปกติ
- หลังให้การรักษาผู้ป่วยตื่นเป็นปกติ ทำตามสั่งได้ ถอดท่อช่วยหายใจได้ ไม่มีชักซ้ำ
- ญาติต้องการส่งตัวมาที่รพ.ธรรมศาสตร์

CURRENT MEDICATION จากรพ.เอกชน

- Doxazosin(2) 1X1 po hs
- Hydralazine(25) 1X3 po pc
- KCL tab(500) 3X4 po pc
- Multivitamin 1X2 po pc
- Vitamin B Complex 1X3 po pc

PRESENT ILLNESS

- ไม่มีหน้ากลมแดง ไม่มีหน้าท้องแตกลาย มีจ้ำเลือดผิดปกติหลังการเจาะเลือด
- ไม่มีหน้าตาเปลี่ยนหรือมือเท้าใหญ่ผิดปกติ ไม่มีเปลี่ยนไซส์รองเท้า/แหวน
- ไม่มีใจสั่น หน้าซีด แต่มีอาการปวดศีรษะ ความดันสูงเป็นพักๆ
- ไม่มีนอนกรน มีหยุดหายใจขณะหลับ
- ไม่มีขี้ร้อน ไม่มีใจสั่น ไม่มีเหงื่อออกมากผิดปกติ
- มีน้ำหนักลด 2 kg ใน 3 เดือน 35 > 33 kg (max BW 42 kg)
- มีผื่นขึ้นตามตัว+ใบหน้า เริ่มมีอาการประมาณ 3 สัปดาห์ช่วงที่นอน รพ. ไม่คัน
- ไม่มีประวัติใช้อาหารเสริม สมุนไพร ยาลูกกลอน
- เริ่มมีประจำเดือนอายุ 13 ปี เดิมประจำเดือนมาตรงรอบทุกเดือน รอบละ 3 วัน แต่ไม่มา 2 เดือน

  ไม่มีกินยาคุมกำเนิด ไม่มีบุตร ไม่เคยแท้ง

FAMILY HISTORY

บิดา

- U/D : HT, ESRD on HD
- ประวัติเส้นเลือดหัวใจตีบ วินิจฉัยเมื่ออายุ 50 ปี ได้รับการผ่าตัด Bypass
- ประวัติก้อนที่ต่อมหมวกไต ความดันโลหิตสูง และเคยมีประวัติเกลือแร่โพแทสเซียมในเลือดต่ำ (ไม่ได้ work up เพิ่มเติม)
- เสียชีวิตเมื่ออายุ 78 ปี จาก MI

มารดา

- No known U/D
- เสียชีวิตเมื่ออายุ 64 ปี ไม่ทราบสาเหตุ (Sudden death)

พี่ชาย

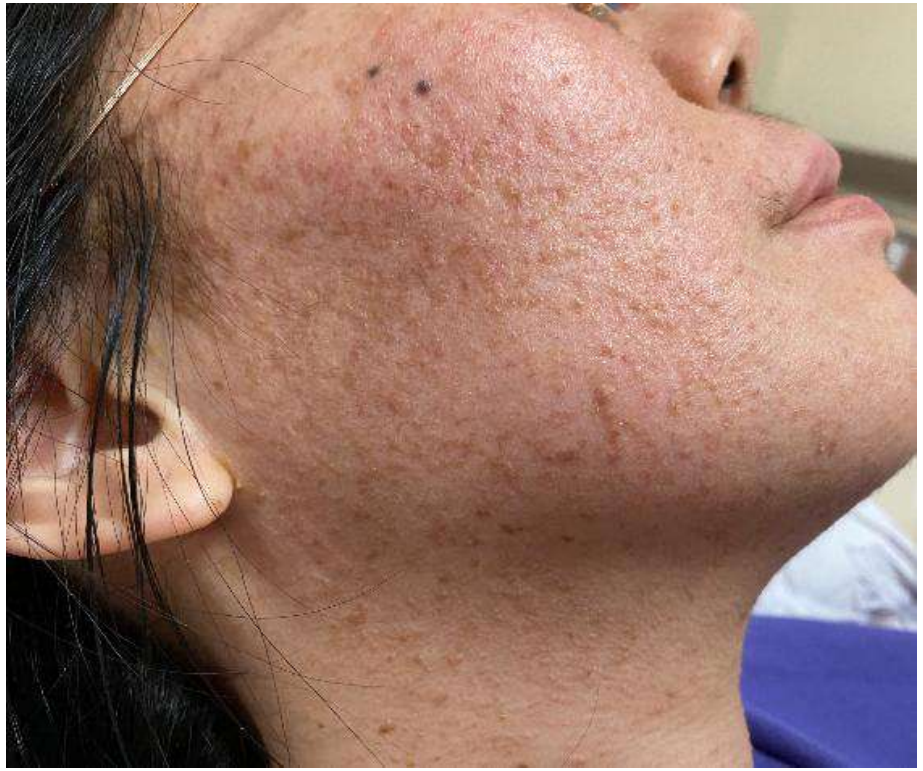
- U/D: HT (ปัจจุบันอายุ 45 ปี)

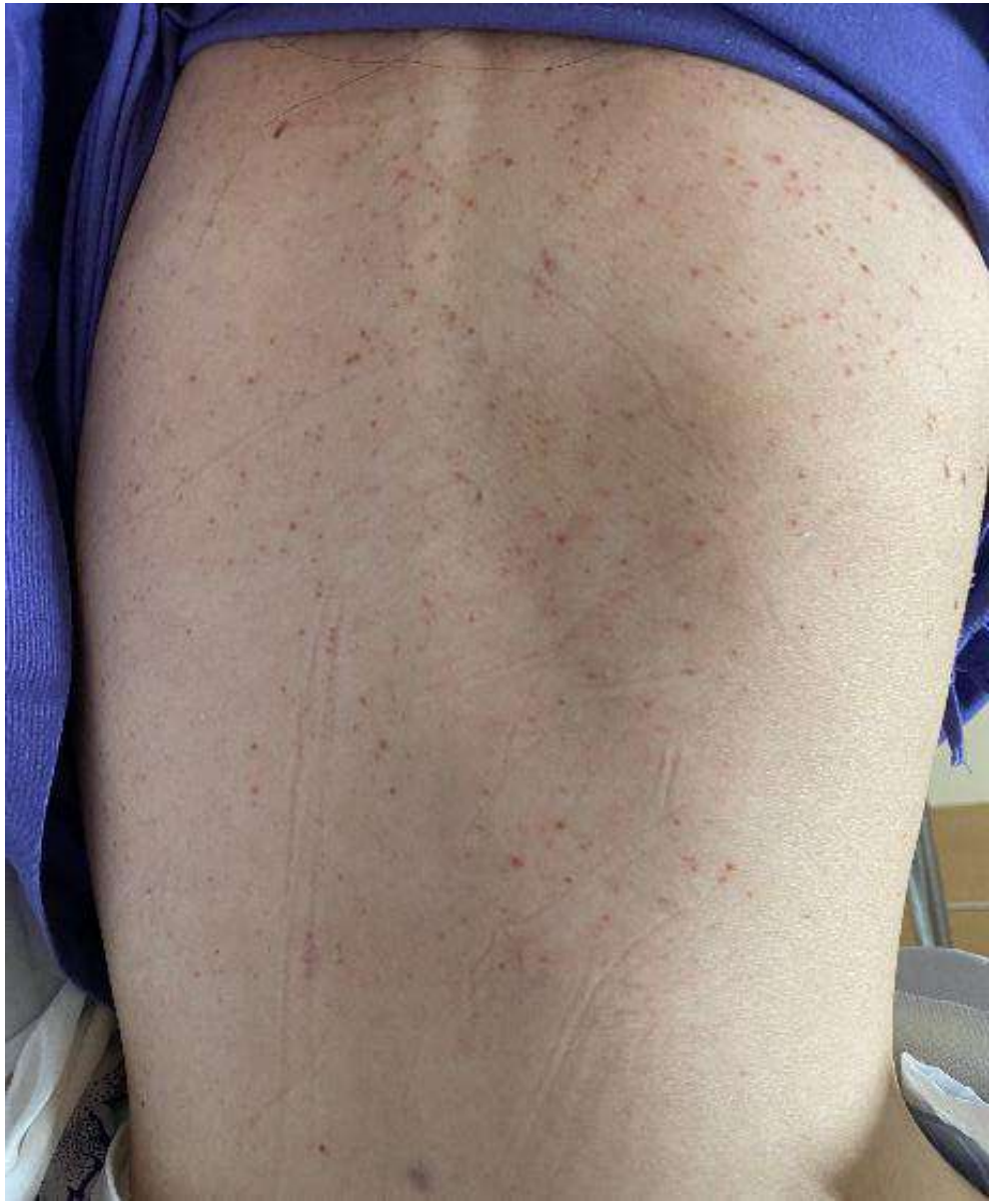
Physical Examination

PHYSICAL EXAMINATION

- Vital signs: BP 160/100 mmHg (no difference in 4 extremities), PR 100 BPM, RR 20/min, BT 37.8 C
- Body weight: 35 kg, Height 160 cm, BMI 13.6 kg/m^2
- GA: a middle-aged female, good consciousness, no acromegalic features
- HEENT: mildly pale conjunctiva , anicteric sclerae, no thyroid gland enlargement, no fullness of supraclavicular fat pad, no dorsocervical hump
- CVS: apical impulse at Lt 5th ICS MCL, no heaving, no thrill, normal S1 S2 , no murmur
- RS: normal chest contour, normal breath sound, no adventitious sound both lungs
- Abdomen: normal contour, soft, not tender , no palpable mass , no hepatosplenomegaly, no purplish striae
- LN: no cervical, axillary and inguinal LN enlargement
- Ext: no edema
- Skin: multiple small erythematous papule at face trunk and back, no skin hyperpigmentation

PHYSICAL EXAMINATION





multiple small erythematous papule at face trunk and back

PHYSICAL EXAMINATION

Neurological examination:

- Alert, follow command, orientated to time-place-person
- Motor power:
  - Upper extremitries : Deltoid grade IV both sides , Bicep and triceps V/V both sides
  - Lower extremitries : Hip flexor gr IV both sides, Hip extensor ,Knee flexor ,Knee extensor V/V both sides
- Sensory all intacted
- DTR 2+ all

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PROBLEM LISTS

PROBLEM LISTS

1. **New onset hypertension for 1 month (with intermittent headache)**
2. Proximal muscle weakness for 2 months
3. Profound weight loss for 1 month
4. Multiple papule at face, trunk, back for 3 weeks
5. Evidence of severe hypokalemia
6. 1st degree relative of adrenal mass (with hypokalemia)

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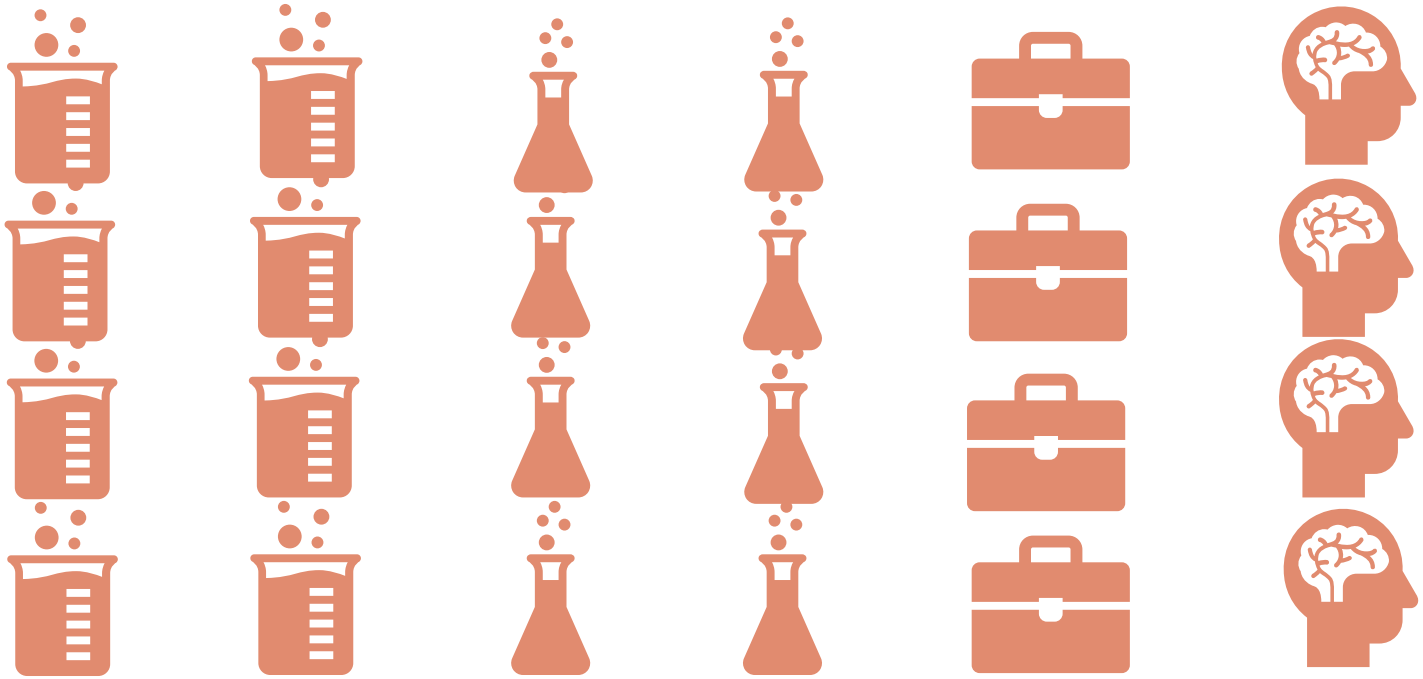
INVESTIGATIONS



INVESTIGATIONS

Serum Electrolytes

Lab	Result	Unit
Na	134	mmol/L
K	3.3	mmol/L
Cl	99	mmol/L
HCO3	27	mmol/L
Ca	8.5	mg/dL
PO4	2.3	mg/dL
Mg	1.9	mg/dL
BUN	15	mg/dL
Cr	0.45	mg/dL

- KCL tab(500) 3X4 po pc

Urine Electrolytes

Lab	Result	Unit
Na	35	mmol/L
K	32.5	mmol/L
Cl	58	mmol/L
PO4	24	mmol/L
Cr	12.51	mg/dL

- **TTKG : 14** **UK/UCr 260** -> renal K loss

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INVESTIGATIONS

Liver function test

Lab	Result	Unit
AST	53	U/L
ALT	118	U/L
ALP	150	U/L
Albumin	2.73	g/dL
Globulin	2.27	g/dL
TP	5.02	g/dL
TB	0.41	mg/dL
DB	0.11	mg/dL

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INVESTIGATIONS

Complete blood count

Lab	Result	Unit
Hb	10.1	g/dL
Hct	29.3	%
MCV	94	fl
WBC	25,729	/uL
Neutrophil	93	%
Lymphocyte	4	%
Monocyte	2.8	%
Eosinophil	0.7	%
Platelet	209,000	/uL

Lab	Result	Unit
ferritin	148	ng/mL
Iron	75	mg/dL
TIBC	212	mg/dL

Lab	Result
Reti.count	6.64%

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INVESTIGATIONS

HbA1C

Lab	Result	Unit
HbA1C	6.0	
FBS	120	mg%

Lipid profile

Lab	Result	Unit
Cholesterol	183	mg/dL
LDL	98	mg/dL
HDL	65	mg/dL
Triglyceride	155	mg/dL

INVESTIGATIONS

Hormone

Lab	Result	Unit
PAC	14.5	ng/dL
DRC	173	uIU/mL
K	3.8	mmol/L

INVESTIGATIONS

Hormone

Lab	Result	Unit	Reference range
FT3	1.22	pg/mL	2-4.4
FT4	0.775	ng/dL	0.93-1.7
TSH	0.807	uIU/mL	0.27-4.2

INVESTIGATIONS

Lab	Result	Unit
8.00 AM cortisol	183	ug/dL
ACTH	504	pg/ml

Lab	Result	Unit	Reference range
DHEA-s	946	ug/dL	(60.9-337)

Diurnal variation

Time	Cortisol (ug/dL)	ACTH (pg/ml)
8.00	183	504
16.00	206	
24.00	187	403 (Awake)

24 hr Urine Free Cortisol

Lab	Result	Unit	Reference range
24hr UFC day1	5142.8	ug/24hr	(21-143)
24 hr urine Cr day1	421	mg/24hr	
24hr UFC day2	3049.6	ug/24hr	(21-143)
24 hr urine Cr day2	325.36	mg/24hr	

Late Night Salivary Cortisol

Lab	Result	Unit	Reference range
Late night salivary cortisol	51.43	ug/dL	(0-0.41)

1 mg Dexamethasone-suppression Test

Lab	Result	Unit	Reference range
cortisol	178	ug/dL	(0-0.41)

INVESTIGATIONS

Plasma metanephrine, normetanephrine, 3-methoxytyramine

Lab	Result		Unit	Reference range
	Day1	Day2		
Plasma metanephrine	326.23	238.84	pg/mL	(0-73.17)
Plasma noremetanephrine	81.68	55.9	pg/mL	(0-174.59)
Plasma 3-methoxytyramine	2.32	<1	pg/mL	(0-15.05)

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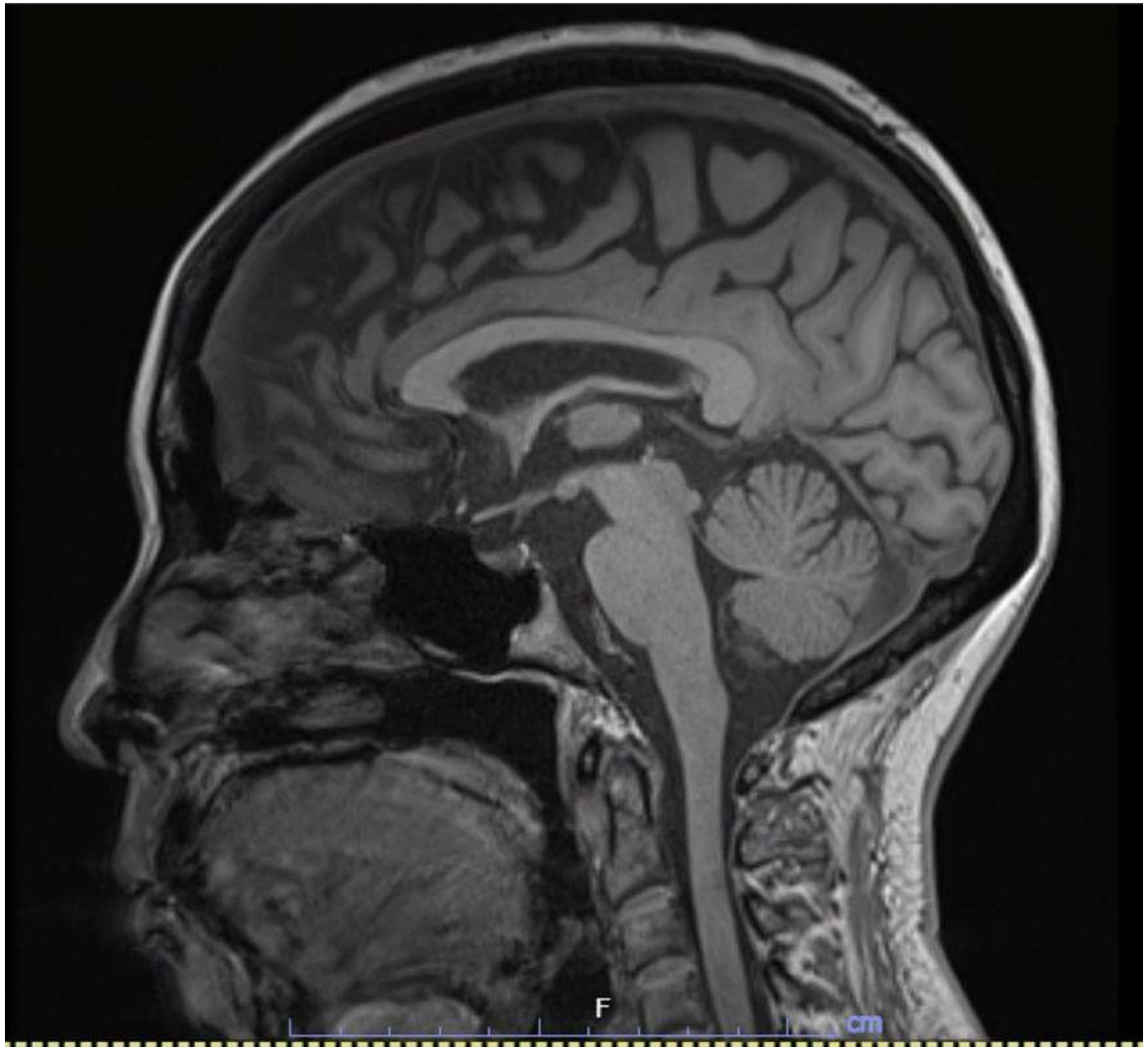
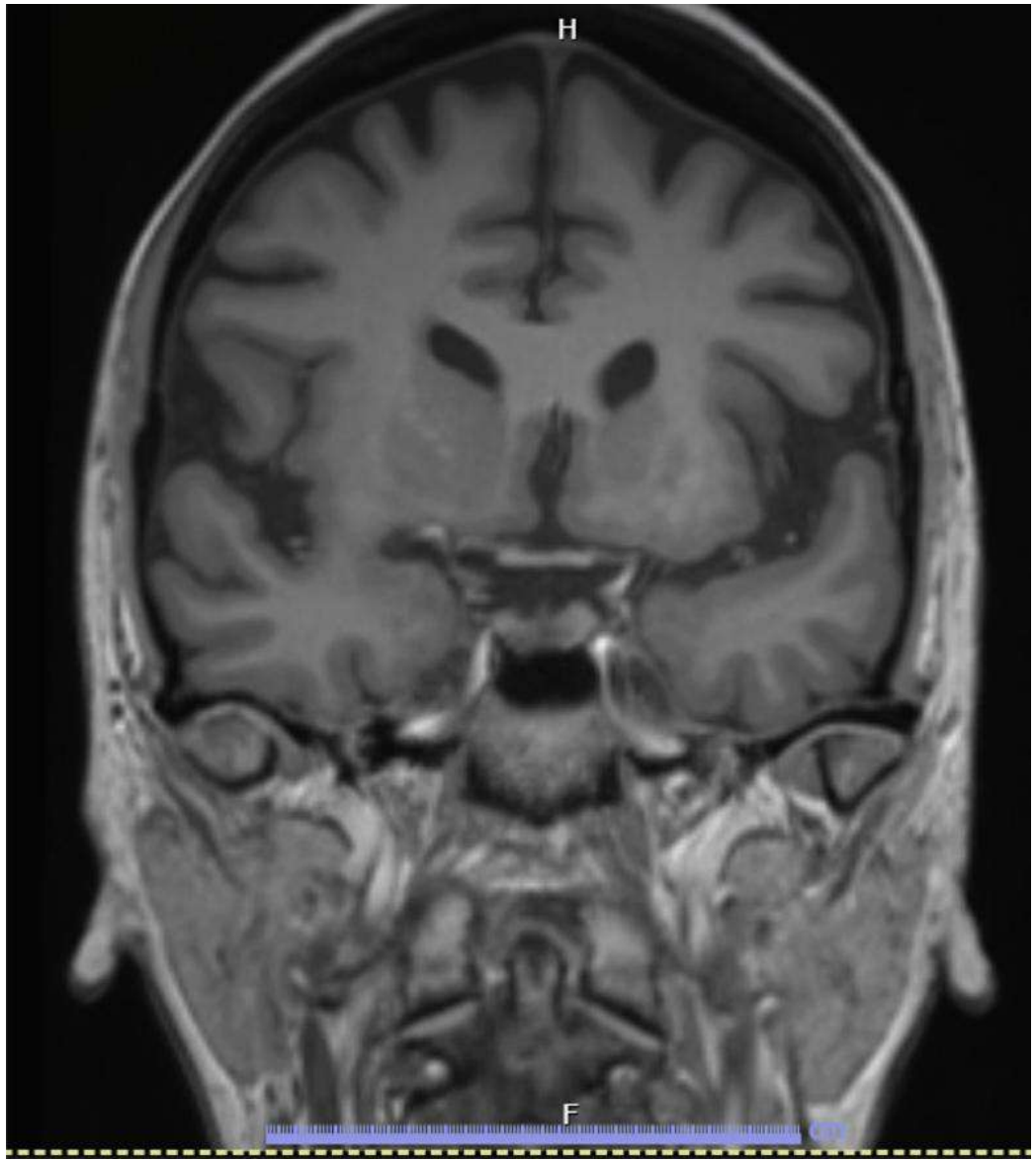
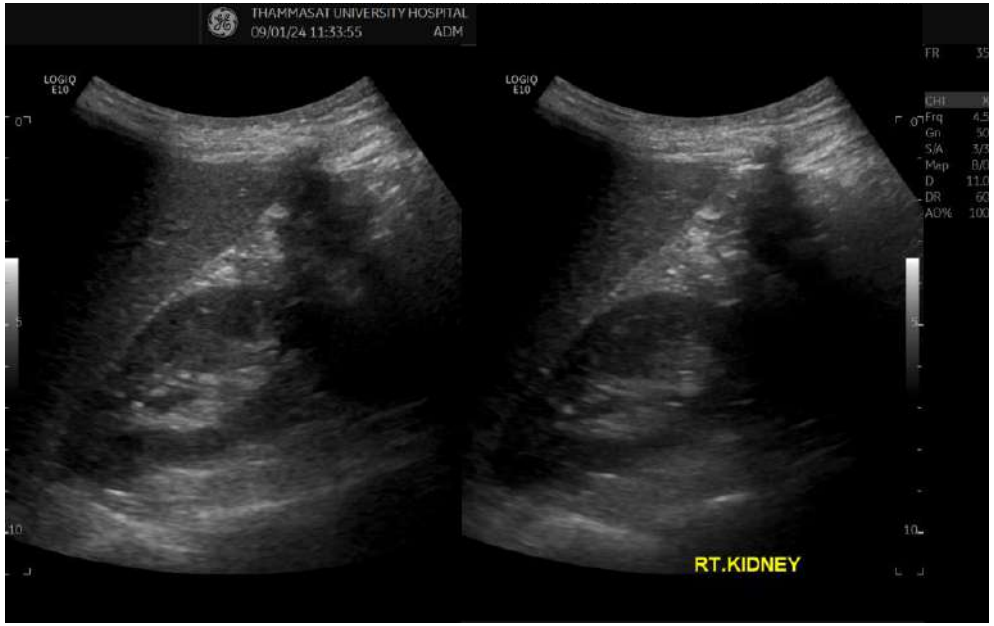
MRI Brain

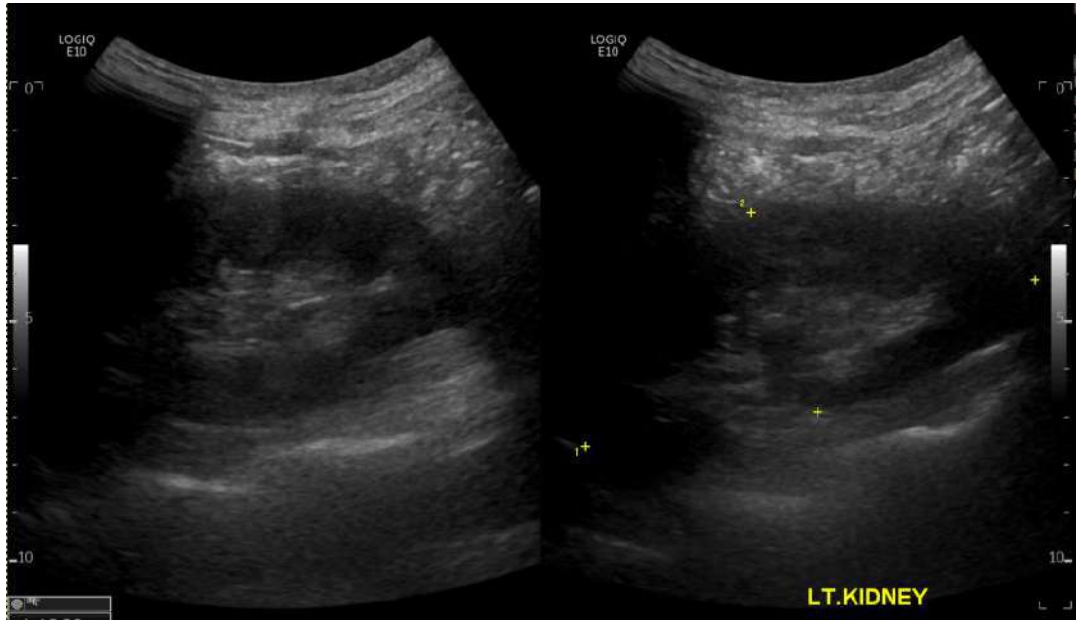




Review MRI : X- ray : not seen pituitary adenoma

Doppler U/S Renal artery





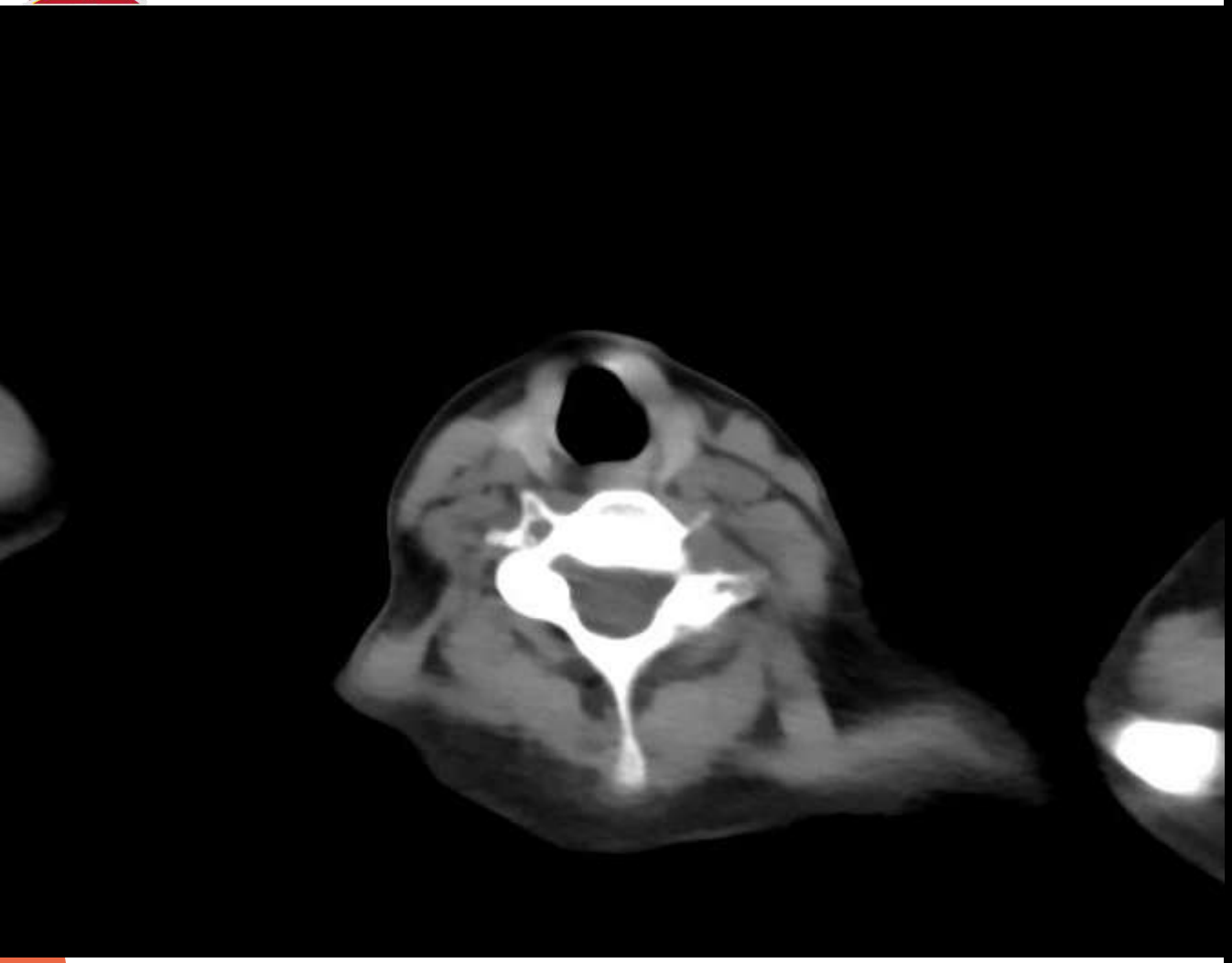
FINDINGS

-No dilated pelvicalyceal systems or stone is seen.
-Rt and Lt renal size are 8.7x3.8 cm.
and 10.0x4.4 cm.
-Doppler US shows normal vasculature at both kidneys

IMPRESSION :

1. No definite evidence of renal artery stenosis at both kidneys are detected
2. Mild increased echo of both kidneys are likely mild renal parenchymal disease.

CT chest with whole abdomen



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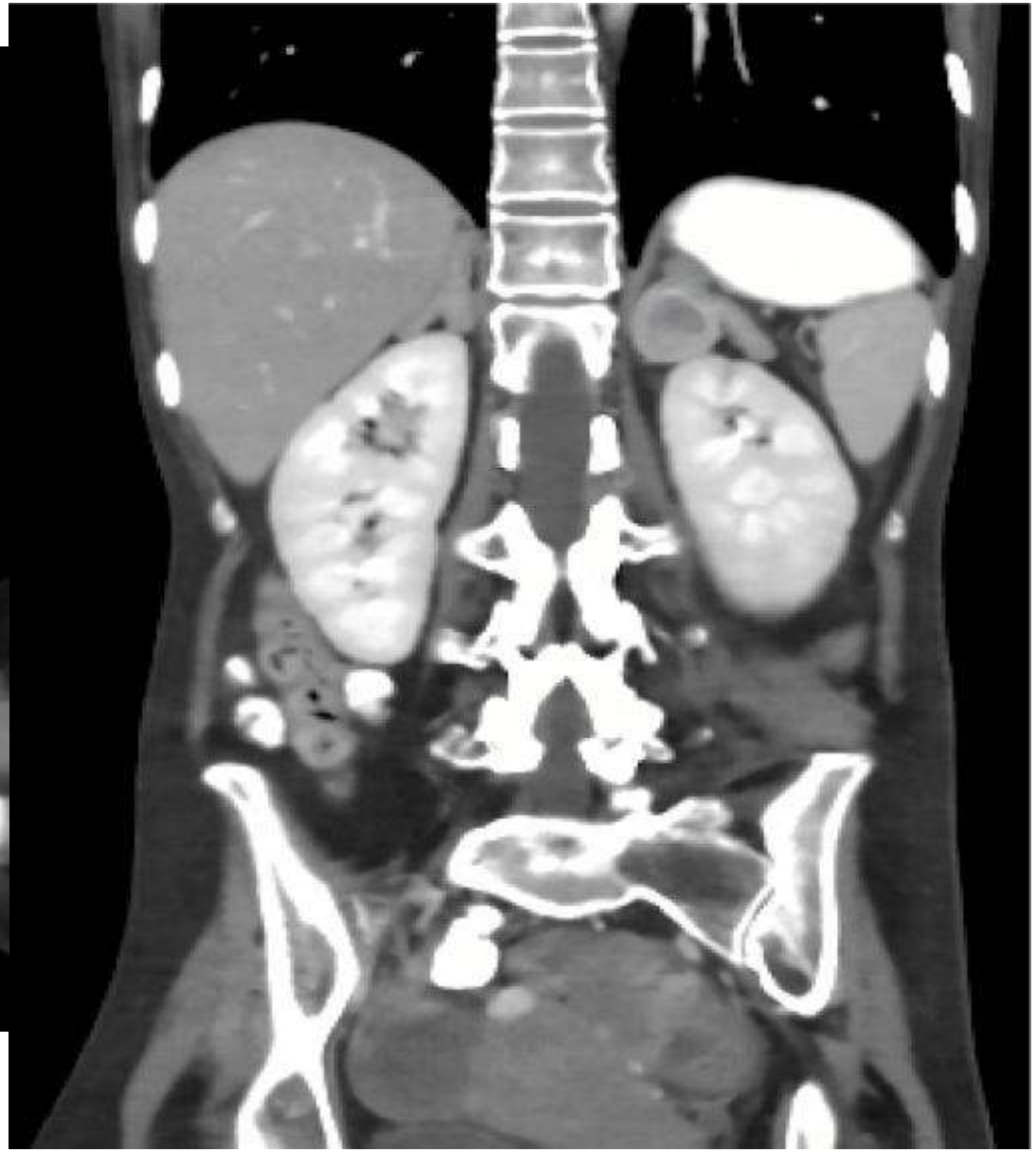

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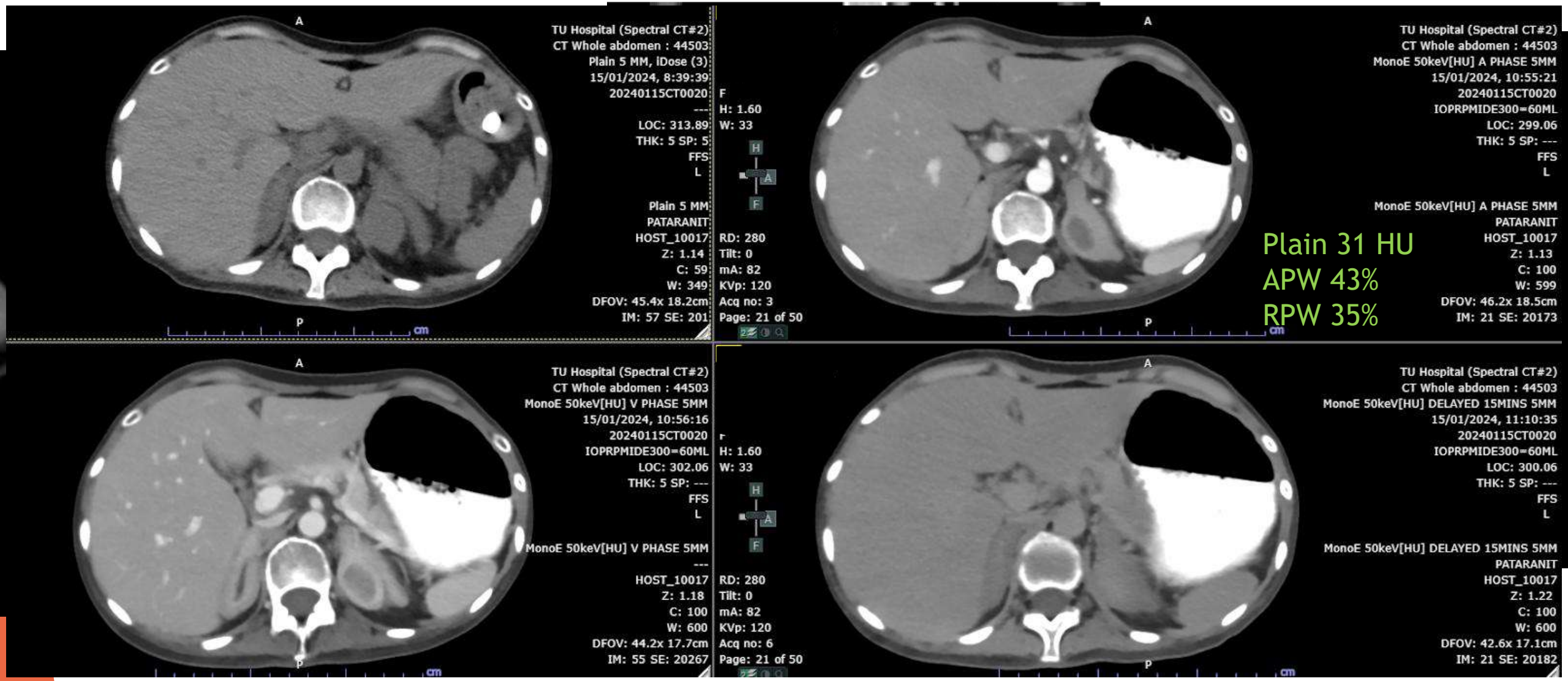
CT chest with whole abdomen



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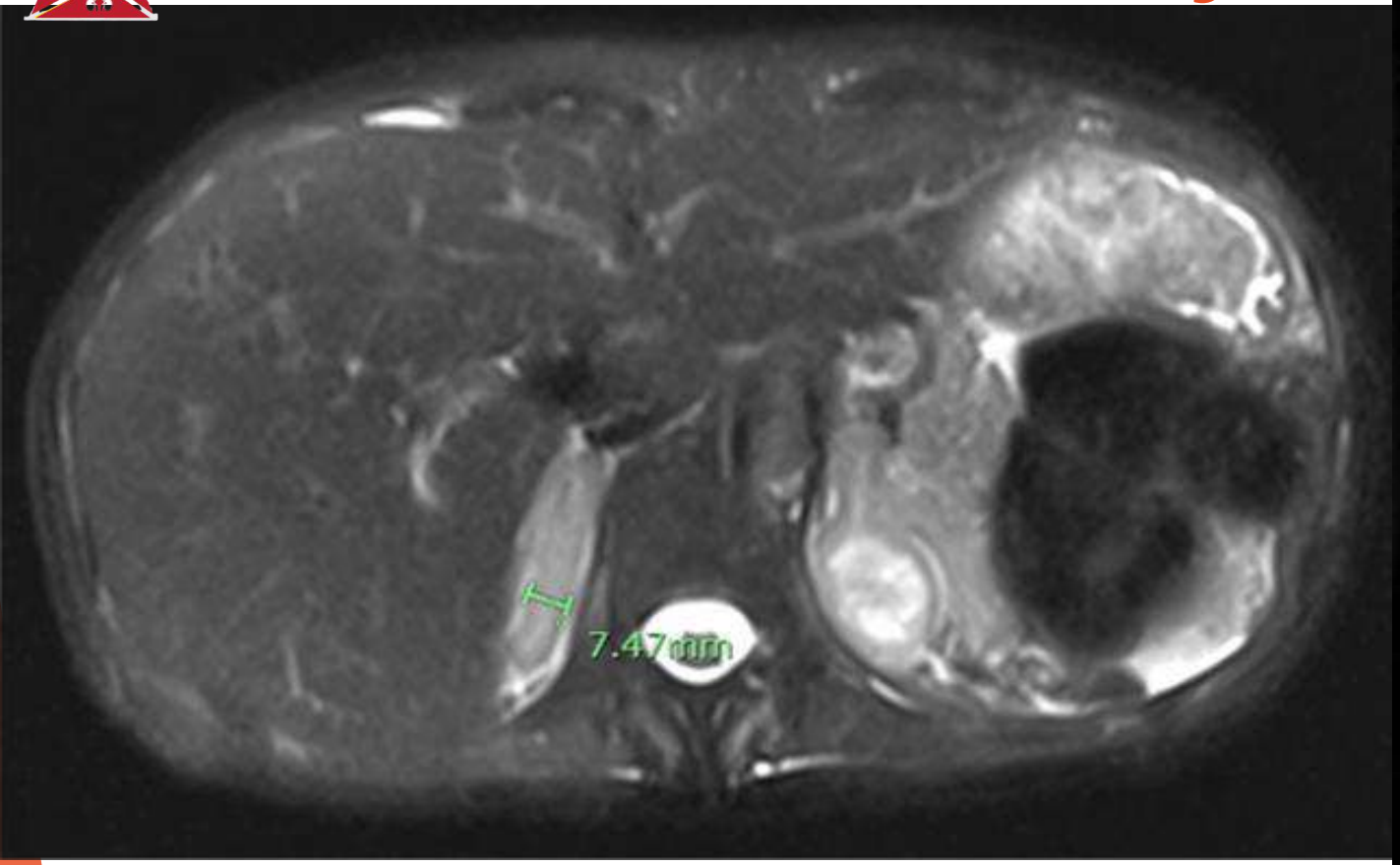
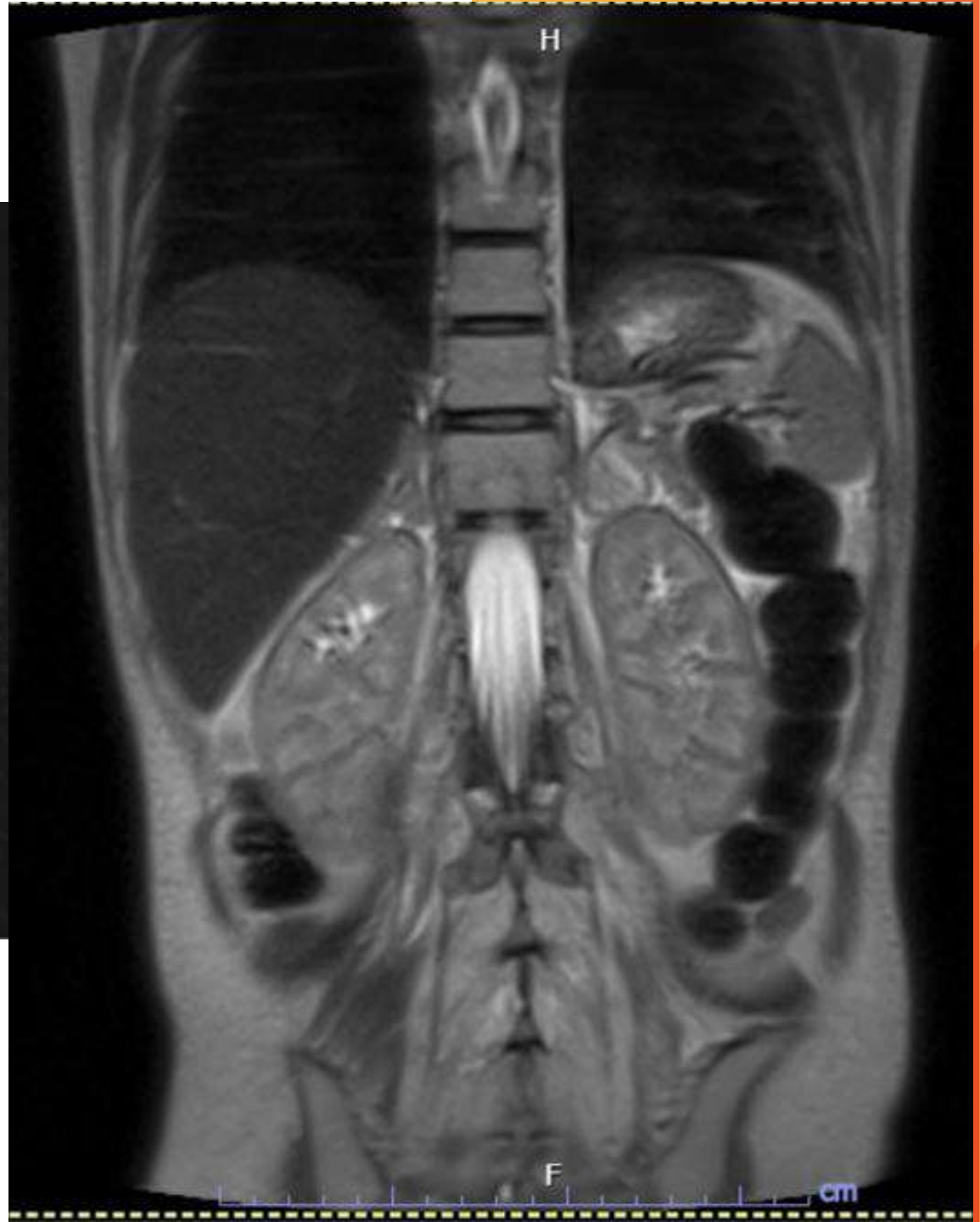
MRA Renal artery



T2



CT chest with whole abdomen

- <u>CT whole abdomen findings</u>:

  Adrenal glands:

  - Diffuse thickening of bilateral adrenal glands is seen, probably adrenal hyperplasia.
  - Stable well-defined complex cystic appearing mass at medial limb of left adrenal gland, measured about 2.0x3.4 cm.
    - Demonstrable arterial rim hyperenhancement with internal progressive enhancement of solid portion.
    - Internal hyperdense content on noncontrast image corresponding with features of subacute Hemorrhage on previous MRI. (T1 and T2-hyperintensity at the dependent part).
    - Hyperintense signal on T2W at previous MR.

Left adrenal pheochromocytoma is firstly considered.
Other less likely differential diagnosis includes adrenocortical carcinoma.

MRA Renal arteries

1. Diffuse enlargement of bilateral adrenal glands with mild increased enhancement are found, considering **for bilateral adrenal hyperplasia**
2. **Mild irregular narrowing** at distal part of main right renal artery and upper-lower segmental branches are found
3. Mild irregular narrow at upper and lower main left renal artery upper, with irregular narrow at upper and lower segmental branch of left renal artery

no RAS

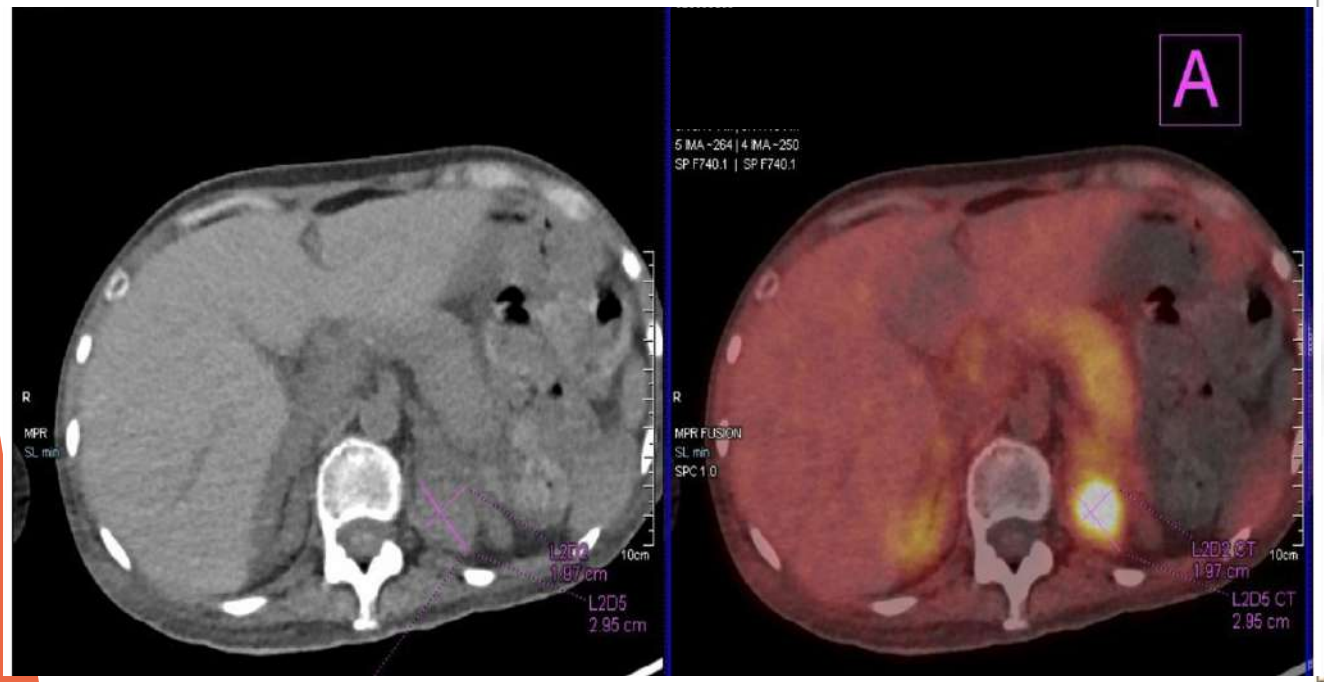
INVESTIGATIONS

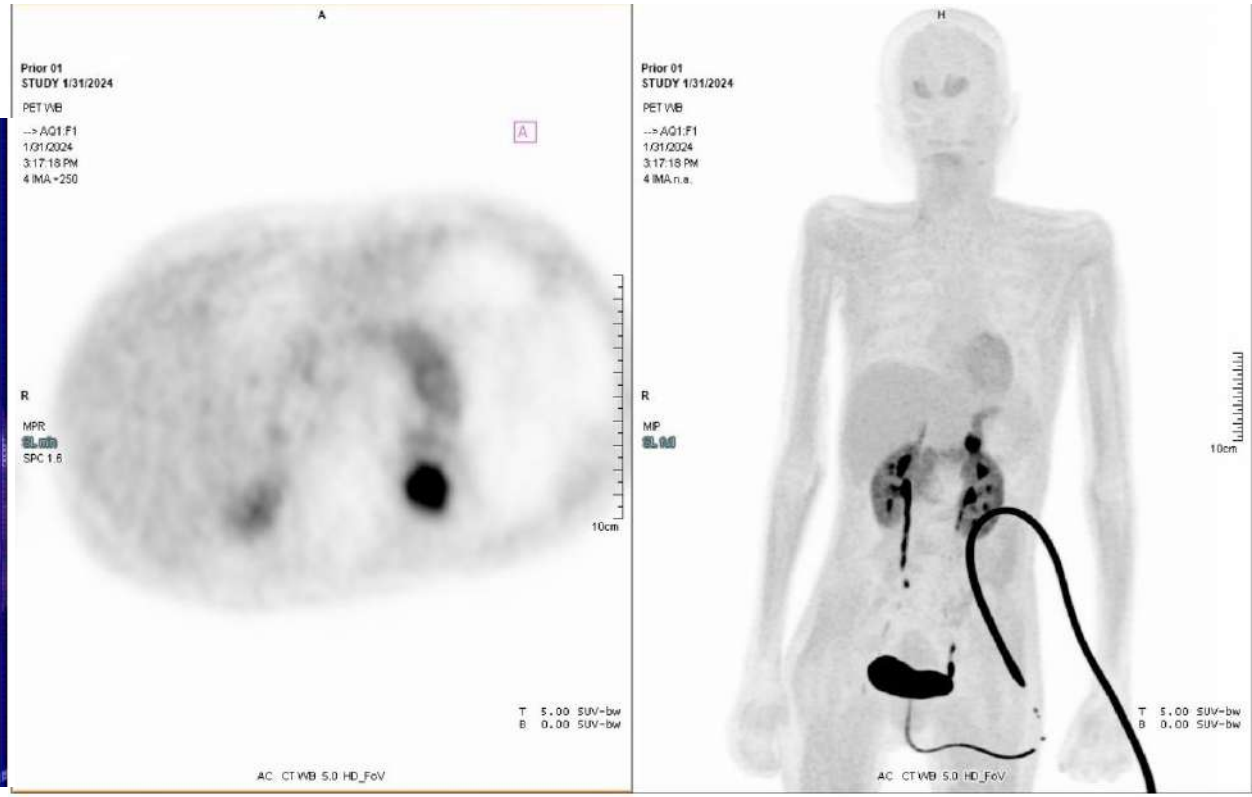
Echocardiogram

- Good LVEF , no valvular heart disease

INVESTIGATIONS

18F-DOPA PET/CT





- Likely 3.0x2.0-cm FDOPA-avid pheochromocytoma at medial limb of left adrenal gland.
- Probably bilateral adrenal hyperplasia.
- No evidence of extra-adrenal FDOPA-avid tumor/metastases in the examined region.

THAMMASAT UNIVERSITY HOSPITAL

Klongluang , Patumthani

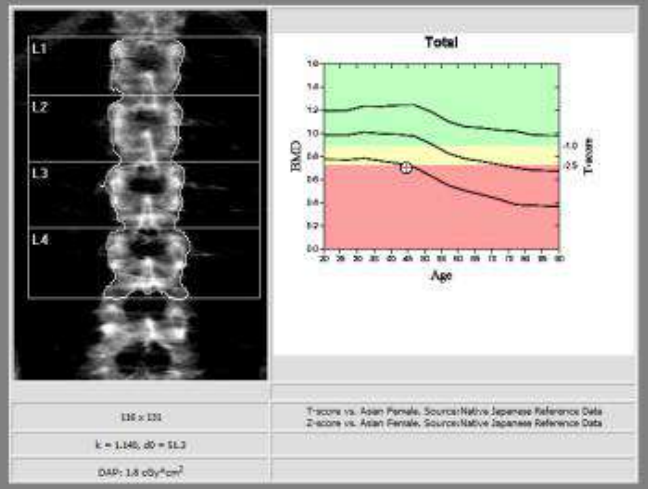
Telephone: 0-2926-9068-70

Bone mass density 2 part (Lumbar sp

Patient Information:

[redacted]

Identifier 2:	
Postal Code:	
Sex:	Female
Ethnicity:	Asian
Height:	160.0 cm
Weight:	33.0 kg
DOB:	04.07.1979
Age:	44
Menopause Age:	
Referring Physician:	



Scan Information:

Scan Date:	06 February 2024 - A0206240K
Scan Type:	f Lumbar Spine
Analysis Date:	06.02.2024 09:35
Analysis Protocol:	Spine
Report Date:	06.02.2024 09:38
Institution:	THAMMASAT UNIVERSITY HOSPITAL
Operator:	mai
Model:	Horizon W (S/N304432M)
Comment:	
Software version:	13.6.0.7

Results Summary:

Region	Area [cm²]	BMC [(g)]	BMD [g/cm²]	T-score	PR (Peak Reference)	Z-score	AM (Age Matched)
L1	9.52	6.25	0.656	-2.7	68	-2.2	70
L2	10.76	7.92	0.736	-2.1	75	-1.6	77
L3	11.33	8.34	0.736	-2.6	71	-2.0	73
L4	12.78	8.62	0.675	-3.0	66	-2.4	68
Total	**44.39**	**31.13**	**0.701**	**-2.6**	**70**	**-2.1**	**72**

Total BMD CV 1.0%, ACF = 1.020, BCF = 0.995, TH = 5.728

Fracture Risk: High; WHO Classification: Osteoporosis

Comment:

HOLOGIC®

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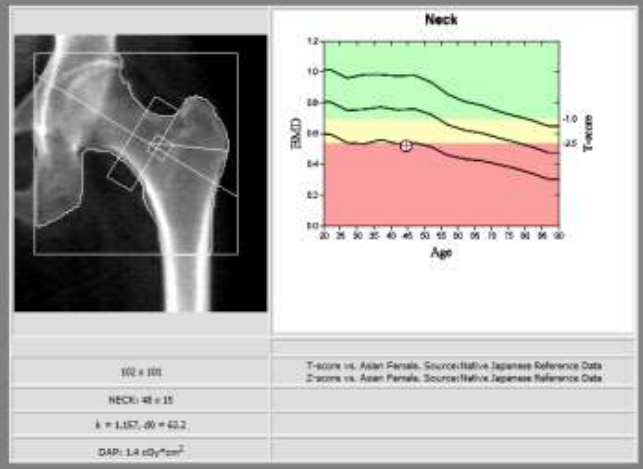
Menopause Age:	
Referring Physician:	



Scan Information:

Scan Date:	06 February 2024 - A0206240L
Scan Type:	f Left Hip
Analysis Date:	06.02.2024 09:37
Analysis Protocol:	Hip
Report Date:	06.02.2024 09:38
Institution:	THAMMASAT UNIVERSITY HOSPITAL
Operator:	mai
Model:	Horizon W (S/N304432M)
Comment:	
Software version:	13.6.0.7

Results Summary:

Region	Area [cm²]	BMC [(g)]	BMD [g/cm²]	T-score	PR (Peak Reference)	Z-score	AM (Age Matched)
Neck	**4.48**	**2.33**	**0.520**	**-2.6**	**65**	**-2.1**	**69**
Troch	6.98	3.71	0.532	-1.1	83	-0.9	86
Inter	16.83	13.92	0.827	-1.2	83	-1.1	84
Total	28.29	19.96	0.706	-1.3	83	-1.1	85
Ward's	1.03	0.47	0.458	-2.0	69	-1.1	79

Total BMD CV 1.0%, ACF = 1.020, BCF = 0.995, TH = 3.541

WHO Classification: Osteoporosis

FRAX® WHO Fracture Risk Assessment Tool

10-year Fracture Risk[1]	
Major Osteoporotic Fracture	**2.6%**
Hip Fracture	**1.2%**

Reported Risk Factors:
Thailand, T-score(WHO)=-2.8, BMI=12.9

[1] FRAX® Version 3.08. Fracture probability calculated for an untreated patient. Fracture probability may be lower if the patient has received treatment.

Comment:

HOLOGIC®

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Faculty of Medicine, Thammasat University

PROBLEM LIST

- New onset HT with spell with hypokalemic metabolic alkalosis
- Severe hypercortisolism with elevated ACTH levels
- Elevated metanephrine
- Imaging : Left pheochromocytoma

Left pheochromocytoma with ectopic ACTH secretion

Management?

Management

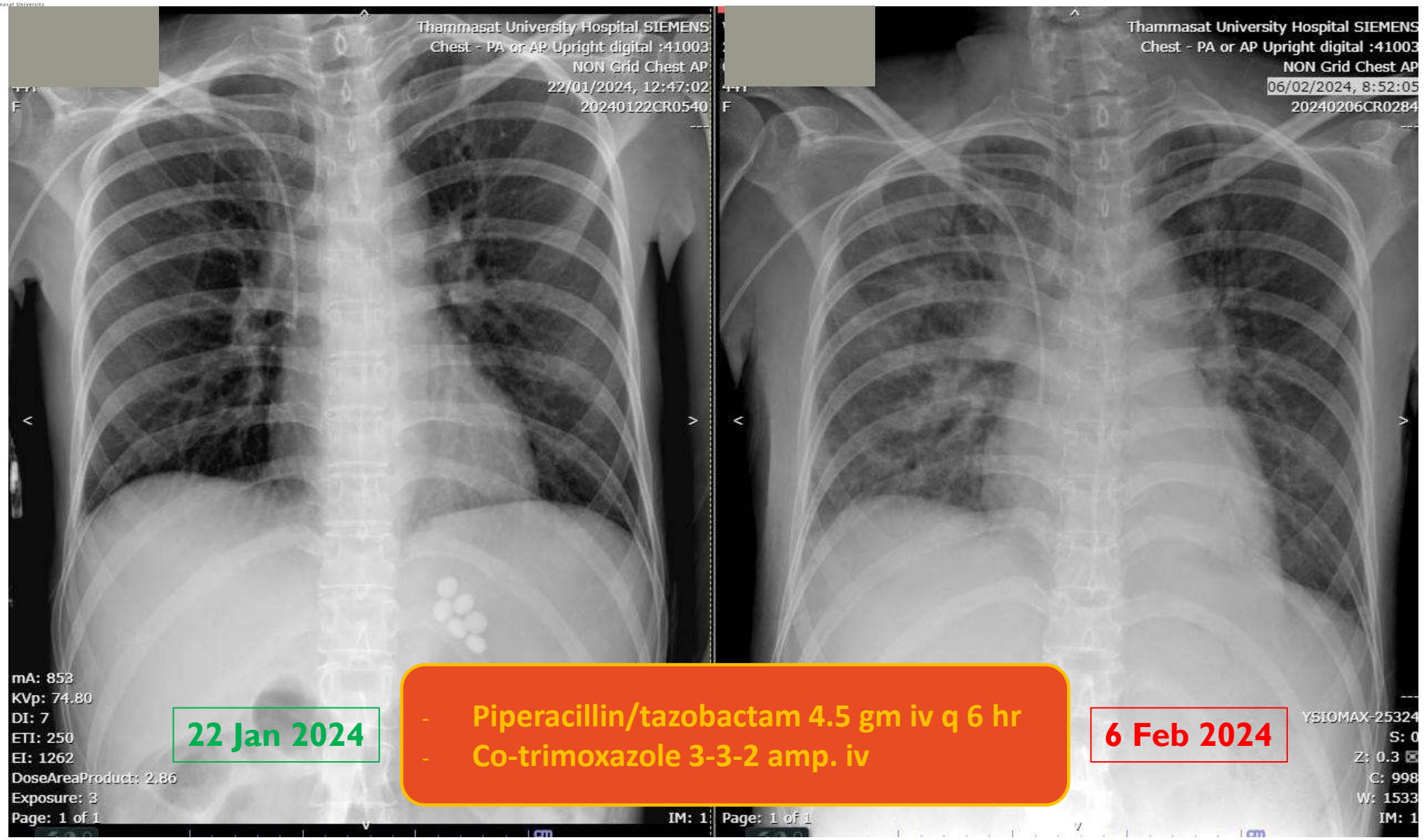
Pheochromocytoma

- Doxazosin 7 to 14 days
- High-sodium diet and fluid
- monitoring blood pressure, heart rate, and blood glucose

Hypercortisolism

- **Venous thromboembolism**
- **Risk for opportunistic infection**
  - Prophylactic treatment with trimethoprim–sulfamethoxazole
- **Hypertension with hypokalemia**
  - Spironolactone
- **Diabetes mellitus**

RIGHT LUNG PNEUMONIA WITH SEPTIC SHOCK



22 Jan 2024

- Piperacillin/tazobactam 4.5 gm iv q 6 hr
- Co-trimoxazole 3-3-2 amp. iv

6 Feb 2024

PROGRESSION

- **start etomidate (2mg/ml) iv drip 0.5 ml/hr (1 mg/hr) due to severe hypercortisolism with infection**
- monitor cortisol level q 6 hr + monitor RAAS score

Time	cortisol	Etomidate
10.32	43	0.5 ml/hr (0.025 mg/kg/hr)
24.00	40	1 m//hr (0.05 mg/kg/hr)
6.00	13.6	0.5 ml/hr (0.025 mg/kg/hr)
12.00	11.5	0.2 ml/hr. (0.01 mg/kg/hr)
18.00	15	
23.00	25.4	0.4 ml/hr (0.02 mg/kg/hr)
6.00	26.4	off
Set OR for adrenalectomy		

Multidisciplinary conference
(Endocrine, ID, Anes, UroSx)
Urgency adrenalectomy

PREOPERATIVE MANAGEMENT

- Doxazosin 4 mg/day
- E.KCL 30 ml oral bid pc
- Hydrocortisone 200 mg iv drip before operation
- Monitor CBG intra-op q 1 hr

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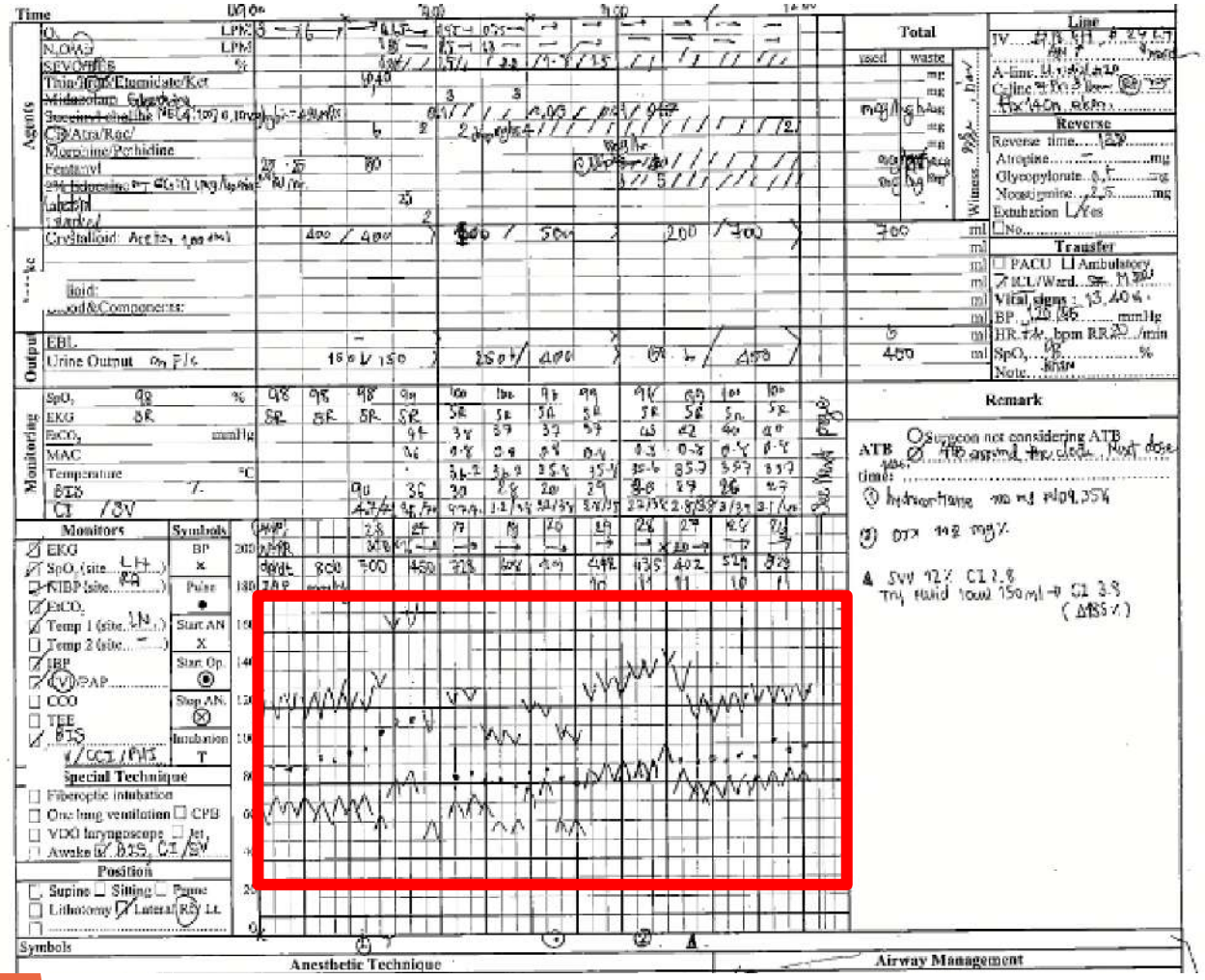
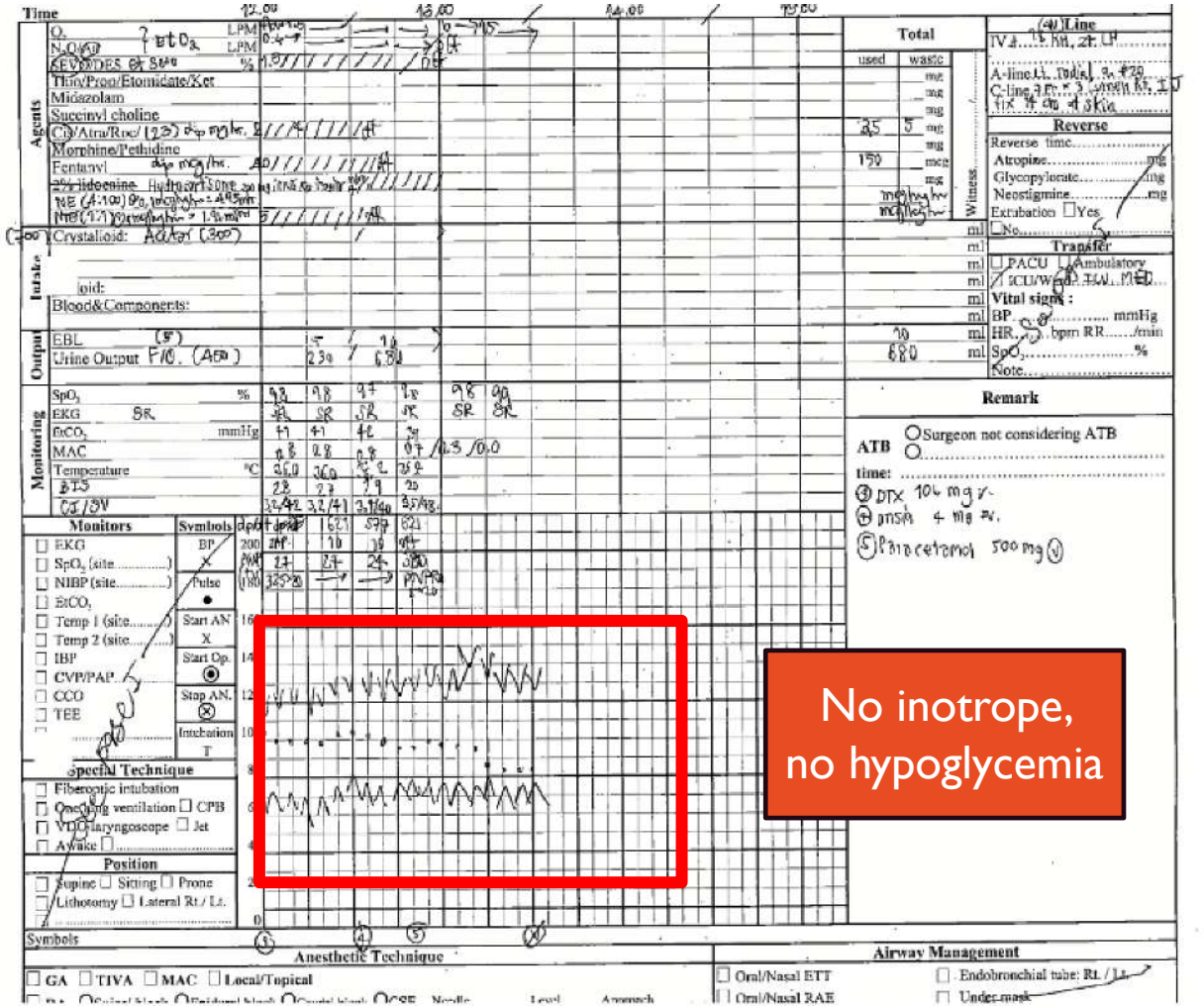
ANESTHETIC RECORD



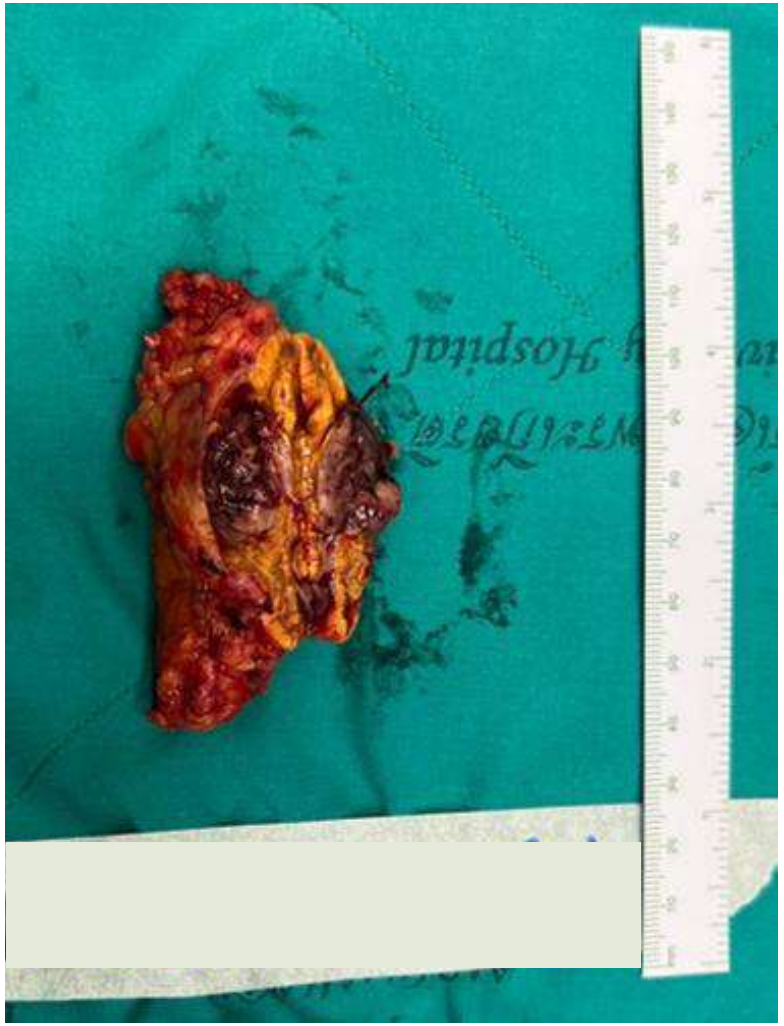


LAPAROSCOPIC LT ADRENALECTOMY

Finding :
left adrenal gland with mass about 3 cm at the middle
Separated mass at posterior aspect of left adrenal gland

Procedure :

- Patient placed in flank after vascular access and anesthesia
- Camera port incision was done at left lateral aspect of rectus muscle, gas was insufflated
- Working ports were inserted under camera guidance
- White line of Toldt was dissected and large bowel then mobilized, kidney and its Gerota's fascia was identified
- Left adrenal vein was identified and isolated
- Left adrenal gland was dissected from superior aspect
- Left adrenal vein was then clamped and dissected of adrenal gland continue at inferior aspect
- Specimen was then removed via working port, fortune drain was placed
- Abdominal sheath was closed with PDS 2-0, skin was closed with Monosyn 4-0



PATHOLOGY

A) Left adrenal gland, Laparoscopic adrenalectomy:

- Pheochromocytoma (see GAPP and PASS scores)
- Size: 3.3x1.9x1.4 cm
- Location: Adrenal medulla
- Mitotic figure: 1-2/10 HPFs

IHC study : ACTH positive
Ki67 : 1-2% in the tumor area (Score=1)

- No capular invasion seen
- Presence of vascular invasion
- No necrosis seen
- Uninvolved radial resection ma
- Unremarkable adrenal cortex

GAPP score
Histological pattern
- Zellballen --> score = 0

Cellularity
- High (> 250 cells/U) --> score = 2

Comedonecrosis
- Absence --> score = 0

Vascular or capsular invasion
- Presence (vascular invasion) --> score = 1

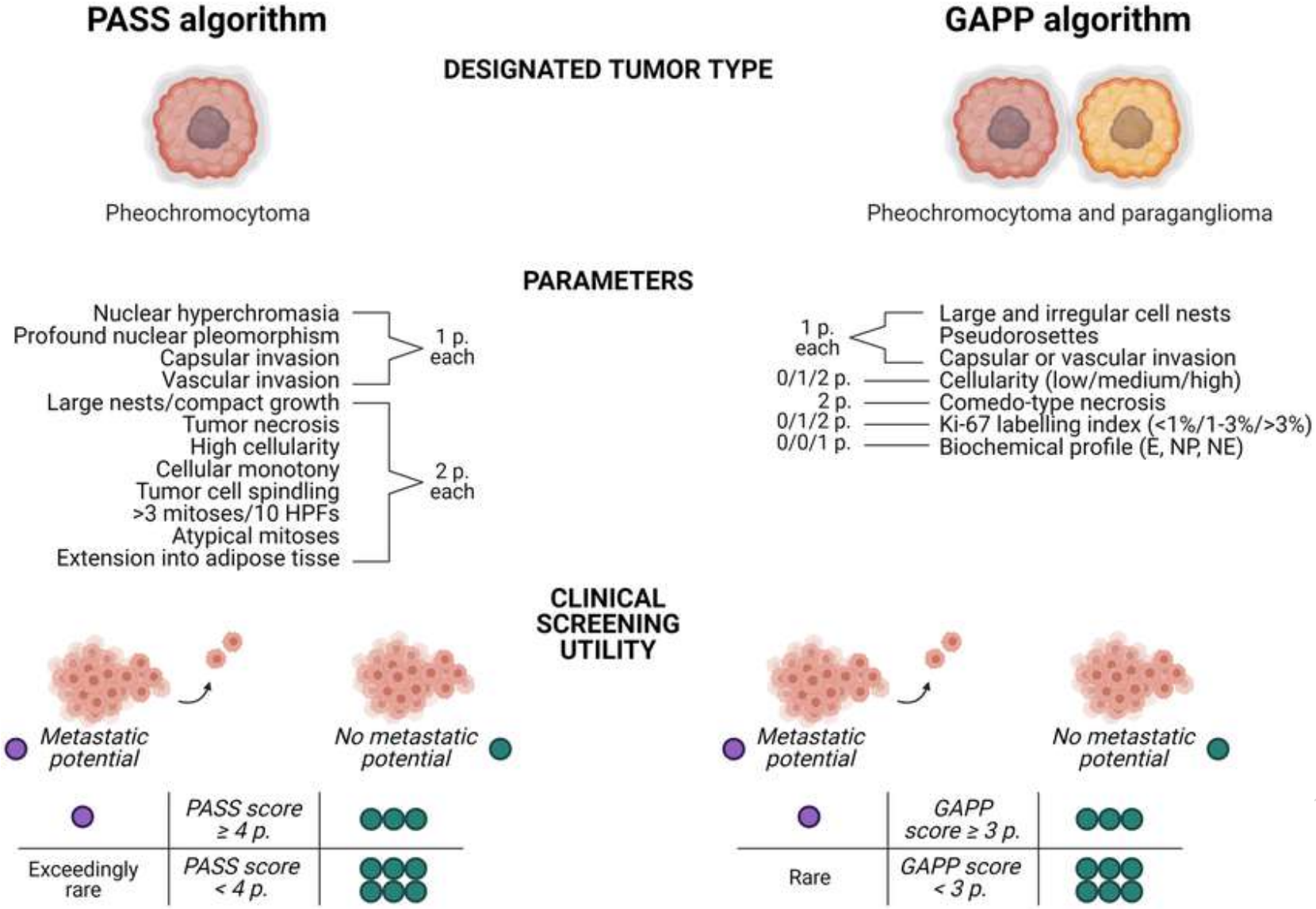
Ki67 labeling index --> N/A (Not performed)
Catecholamine type --> N/A

PASS score
Large nest/diffuse growth --> score = 0
Central/confluent necrosis --> score = 0
High cellularity --> score = 2
Cellular monotony --> score = 0
Tumor cell spindling --> score = 0
Mitotic index --> score = 0
Atypical mitosis --> score = 0
Periadrenal adipose tissue invasion --> score = 0
Vascular invasion --> score = 1
Capsular invasion --> Score = 0
Nuclear pleomorphism --> score = 0
Nuclear hyperchromasia --> score = 0

GAPP score 3, PASS score 3

ACTH-Producing Pheochromocytoma

Tumor characteristics



Endocrine Pathology (2021) 32:228–244

POSTOPERATIVE

Blood pressure 100–120/60–70 mmHg (No HT-drug)
Pulse rate 80–100 / min
Temperature 38°C
Respiratory rate 16

Creatinine 0.3 mg/dL
Potassium 4.3–4.5 mmol/L
No hypoglycemia (CBG 90–130 mg/dL)
On intermittent pneumatic compression

After stop hydrocortisone 24 hours
- ACTH levels: 18.9 pg/mL
- Serum cortisol: 6.39 mcg/dL
- Late night salivary cortisol: 0.0544 mcg/dL (0-0.41)
- DHEA-S: 5.23 mcg/dL

→ **Steroid replacement** (hydrocortisone 10 mg/day, 3 doses regimen)

POSTOPERATIVE biochemical profiles

Post-op 4 weeks

•Plasma metanephrine	15.12 pg/mL (0-73.17)
•Plasma normetanephrine	13.51 pg/mL (0-174)
•Plasma 3-Methoxytyramine	<1.00 pg/mL (0-15.05)

Normalize catecholamine

Post-op 8 weeks (stop hydrocortisone 24 hours)

•BW 40 kg, BP 129/84 mmHg

•serum K 3.5 mmol/L

Recovery AI

•8 AM cortisol 6.11 mcg/dL → 1 mcg ACTH stimulation test: cortisol = 14.1, 15.8, 15.6, 14.7 mcg/dL

•Basal ACTH level 49.4 pg/mL

•PAC: 5.94 ng/dL, DRC: 9.69 uIU/mL

•FT3 1.23, FT4 0.932, TSH 0.77 → normal TFT

•Minimally increase monomorphic acne at face

Genetic testing : pending

Ectopic Cushing's syndrome

- **most often caused by NENs in the thorax or upper abdomen** (50–80% of tumors causing ECS are intrathoracic)
- **Occult ECS** refers to the 10–20% of patients with ECS where the ACTH source cannot be found > **Bronchial NENs are presumed to account for most occult ECS**
- Ectopic CRH-producing tumors are extremely rare and most often ACTH is co-produced
- **Ectopic CRH secretion** may confound the results of inferior petrosal sinus sampling (IPSS) as pituitary-to-peripheral venous ACTH gradient is similar to that in patients with ACTH-producing pituitary adenoma

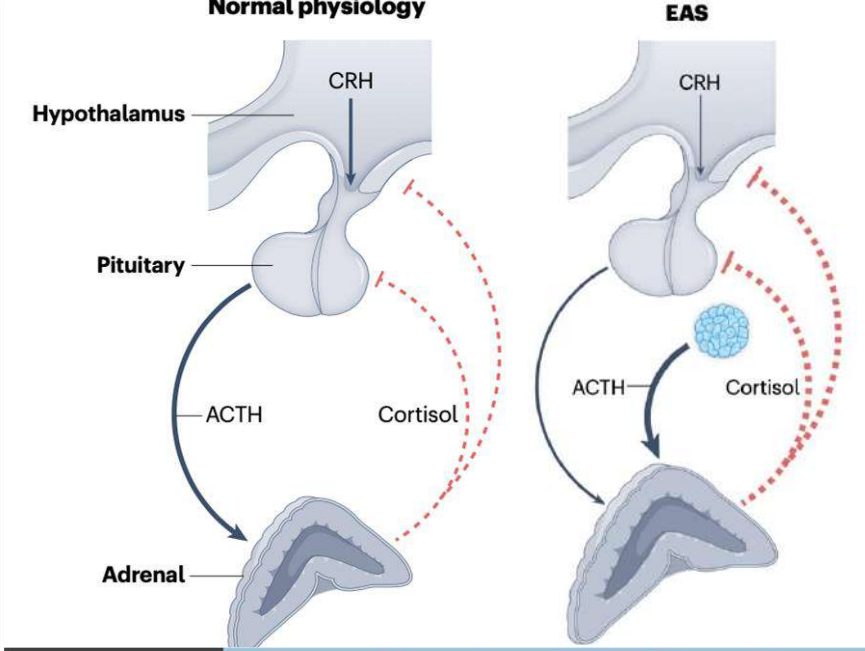


TABLE 13.7 Tumors Associated With Ectopic Adrenocorticotropic Hormone Syndrome

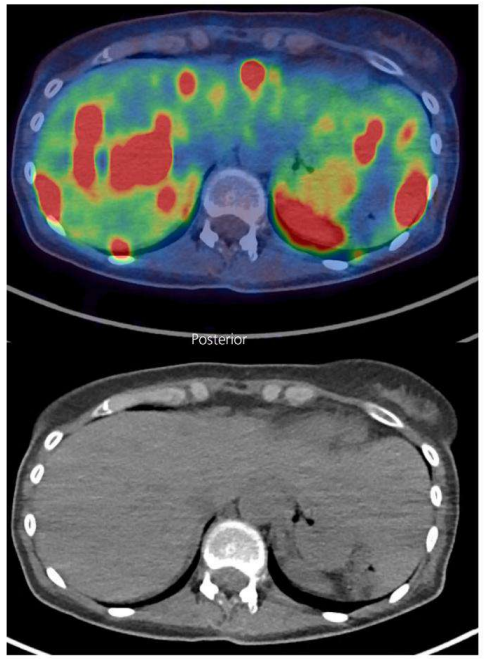
Tumor Type	Approximate Incidence (%)
Lung neuroendocrine tumors	20–40
Small-cell lung carcinoma	5–20
Occult neuroendocrine tumors	10–20
Pancreatic/intestinal neuroendocrine tumors	10–15
Thymic neuroendocrine tumors	5–10
Other neuroendocrine tumors	5–10
Medullary carcinoma of thyroid	5–10
Pheochromocytoma and related tumors	5

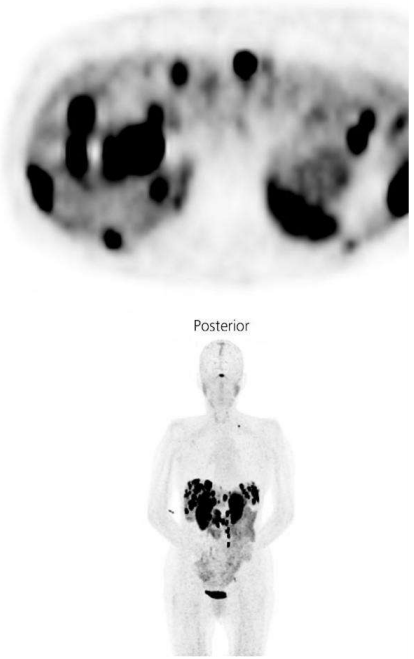
Cushing syndrome. *Nat Rev Dis Primers* **11**, 4 (2025)

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

IMAGING TO DETECT CAUSATIVE NENS IN ECS

- **The diagnostic performance of CT is superior to MRI in ECS**
- Bronchial NENs can be difficult to identify since they are often small (<15 mm) and located close to pulmonary vessels
- **Functional imaging can be used for three purposes in ECS:**
  1. identify an occult tumor when conventional imaging has failed
  2. to determine if a tumor identified by CT/MRI is a true NEN
  3. for cancer staging





Functional imaging

Neuroendocrine ACTH-secreting tumors take up **18-F-dihydroxy-phenyl-alanine (18F-DOPA),** and have **somatostatin cell surface receptors**

- 111In-pentetreotide scintigraphy (Octreoscan)
- 18F-FDG PET/CT
- 68Ga-DOTA-TATE PET/CT
- 18F-DOPA PET/CT

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

ACTH-Producing Pheochromocytoma

From Meta-analysis 99 case reports (up to 2020)

- Female: Male = 2:1
- Age ranged from 38-59 years (median age, 49 years)
- Unilateral, 59% Lt adrenal gland, HU 4-100 (mean 61)
- Onset ranged from 1 month to 5 years

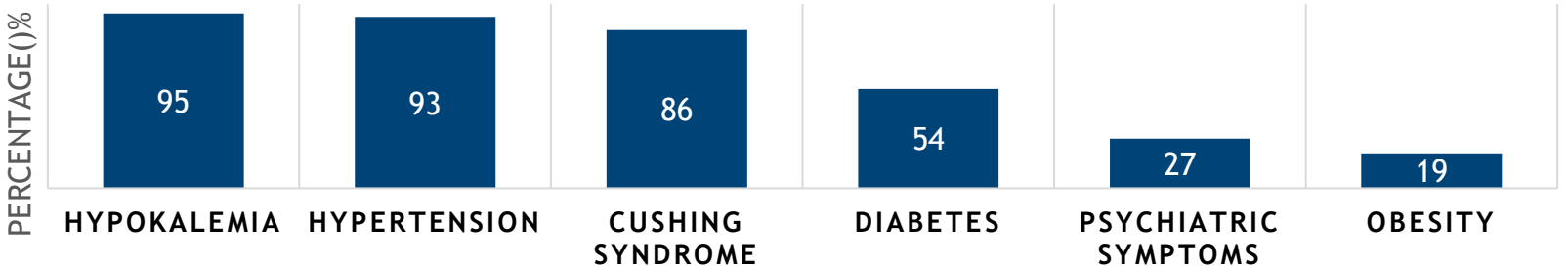


Table 1. Patient and tumor characteristics of 99 individuals with ACTH and CRH-secreting pheochromocytomas

Variable	Result	Number reporting
Female sex, n (%)	65 (69)	98
Median age, years	49 (38, 59.5)	99
Symptomatic, n (%)	77 (81)	97
Duration of symptoms, months	6 (2, 12)	68
Cushing syndrome, n (%)	79 (86)	92
Psychiatric symptoms, n (%)	22 (27)	83
Hypertension, n (%)	87 (93)	94
Diabetes, n (%)	50 (54)	92
Mean BMI, kg/m^2	24 (±5.1)	19
Obese[a] (BMI ≥ 30), n (%)	4 (19)	21
Median largest tumor diameter, cm	3.8 (3, 5)	81
Tumor laterality, n (%)		92
Right	29 (32)	
Left	54 (59)	
Bilateral	9 (10)	
CT imaging, n (%)	79 (90)	85
Mean tumor Hounsfield units	61 (±35)	11
MRI imaging, n (%)	26 (30)	85
MIBG scintigraphy, n (%)	30 (34)	85
PET scan, n (%)	15 (18)	85
Tumor expression,[b] n (%)		84
ACTH	78 (93)	
CRH	4 (5)	
ACTH and CRH	2 (2)	
Familial syndrome present,[c] n (%)	6 (12)	51
Surgical approach, n (%)		72
Open	36 (50)	
Laparoscopic	36 (50)	
Preoperative alpha blockade, n (%)	52 (87)	60
Median days on alpha blockade	14 (6, 18)	15
Malignant, n (%)	2 (3.5)	55

Journal of the Endocrine Society, Volume 2, Issue 7, July 2018, Pages 621–630
Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 2, 598–608

ACTH-Producing Pheochromocytoma

- Another features
  - 5% **Central hypothyroidism**
    - without overt evidence of thyroid dysfunction
    - Mechanism :
      - **glucocorticoid-mediated hypothalamic and thyrotroph inhibition**
      - **diminished peripheral deiodination**
      - **lowering hypothalamic TRH expression**
    - Normalization of the thyroid hormones occurred after the adrenalectomy
  - muscle weakness, hirsutism

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ACTH-Producing Pheochromocytoma

Table 2. Biochemical characteristics and patient outcomes of 99 individuals with ACTH and CRH-secreting pheochromocytomas

Variable	Preoperative	Postoperative	*P*	Number reporting
Mean systolic blood pressure, mmHg	170 (±32)	121 (±17)	<0.01	68/11
Mean diastolic blood pressure, mmHg	102 (±20)	76 (±14)	<0.01	67/10
Improvement in hypertension postoperatively, n (%)		59 (97)		NA/61
Median ACTH, pmol/L 282 pg/ml	62.8 (22.4, 93.3)	3.1 (2, 5.6)	<0.01	81/35
Median CRH, ng/L	127.4 (76.1, 178.7)			2/NA
Median random serum cortisol, nmol/L	1666 (931.6, 2400)	405.5 (133.9, 642.5)	<0.01	53/19
Median morning serum cortisol, nmol/L 50 mcg/dL	1399 (908.1, 2202.9)	349.3 (124.1, 404.9)	<0.01	38/12
Median morning serum cortisol post 1mg dexamethasone, nmol/L 42 mcg/dL	1189 (315.9, 1875)			31/NA
Median urinary cortisol nmol/24 h	5500 (1500, 10 292)	145.0 (46.9, 237.2)	<0.01	50/17
Median plasma metanephrine, pmol/L 132 pg/mL	460 (108.0, 821.0)			17/NA
Median plasma normetanephrine, pmol/L 92 pg/mL	321.0 (71.5, 1302.9)			19/NA
Median urinary epinephrine, nmol/24 h	611.7 (240.9, 1403.6)			29/NA
Median urinary norepinephrine, nmol/24 h	1558.8 (689.4, 3961.4)			30/NA
Median urinary metanephrine, nmol/24 h	7801.4 (4664.1, 13 444.4)			30/NA
Median urinary normetanephrine, nmol/24 h	7199.8 (2501.6, 13 725.4)			18/NA
Median urinary dopamine, nmol/24 h	2654.9 (1848.0, 9211.5)			14/NA
Hypokalemia, n (%)	45 (83)			54/NA
Median serum potassium, mmol/L	2.7 (2.1, 3)	3.8 (3.8, 4.1)	0.02	54/5
Improvement in diabetes postoperatively, n (%)		21 (100)		NA/21
Treatment with insulin, n (%)	29 (78)	4 (50)	0.23	35/8
Hemoglobin A1c, %	8.3 (6.5, 10.1)	5.5 (5.4, 5.5)	<0.01	21/3
Median chromogranin A, mcg/L	52.5 (15.3, 761.2)			6/NA
Median aldosterone, pmol/L	163.7 (28.9, 215.4)			11/NA
Median follow up time, months	6 (2, 18)			47/NA
Survival at publication, n (%)	70 (88)			80/NA

Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 2, 598–608

ACTH-Producing Pheochromocytoma

Tumor characteristics

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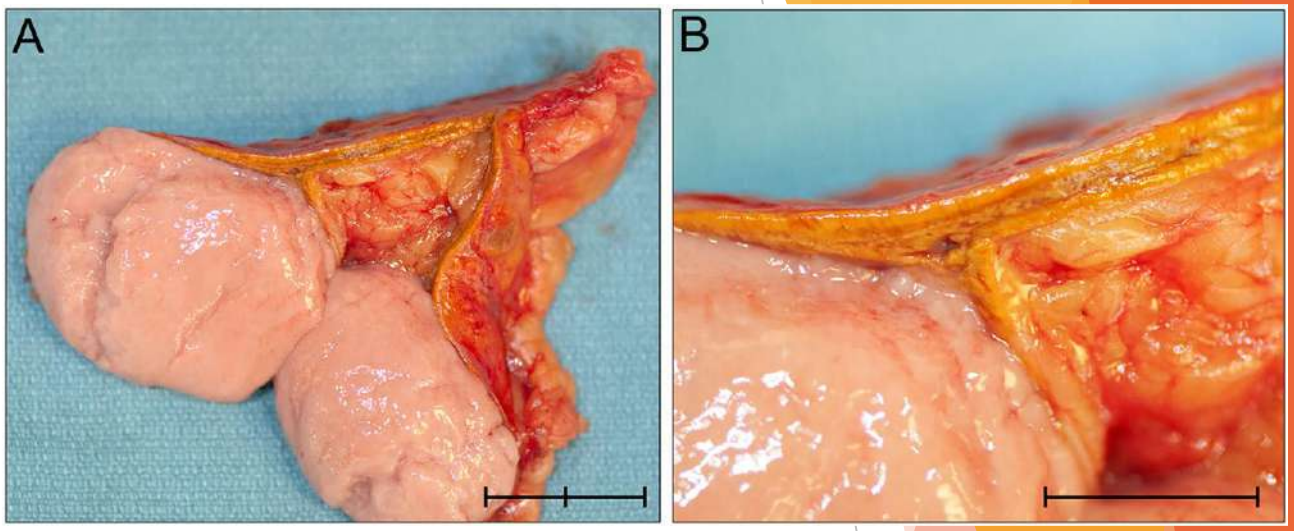


Figure 5
Gross specimen of the left adrenal gland and pheochromocytoma with homogenous tan-pink cut surface (A) (2.0 cm scale bar). (B) The interface between adjacent bright-yellow adrenal cortex and pheochromocytoma (1.0 cm scale bar).

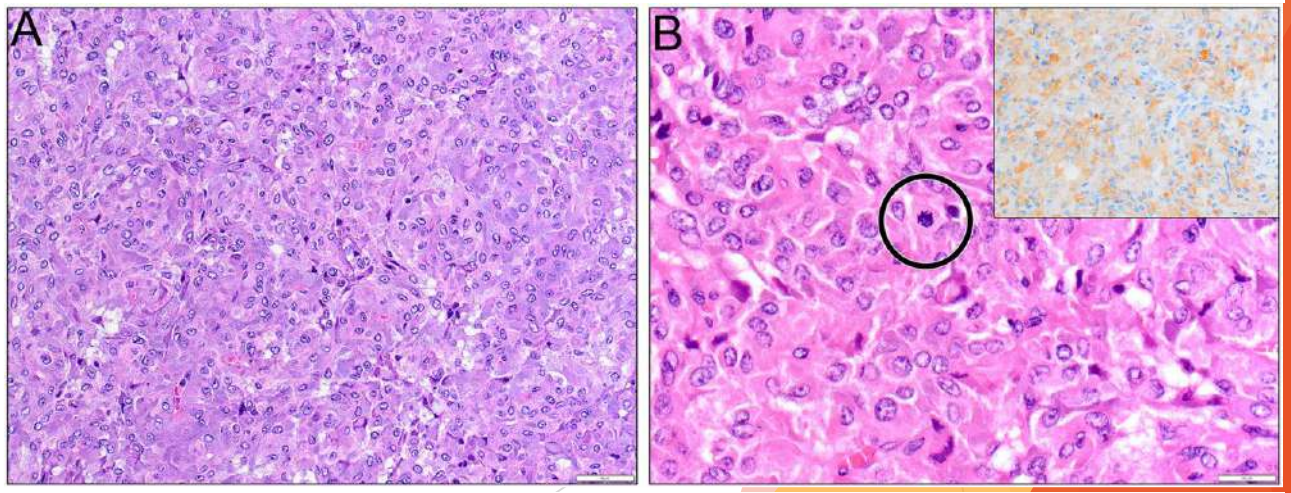
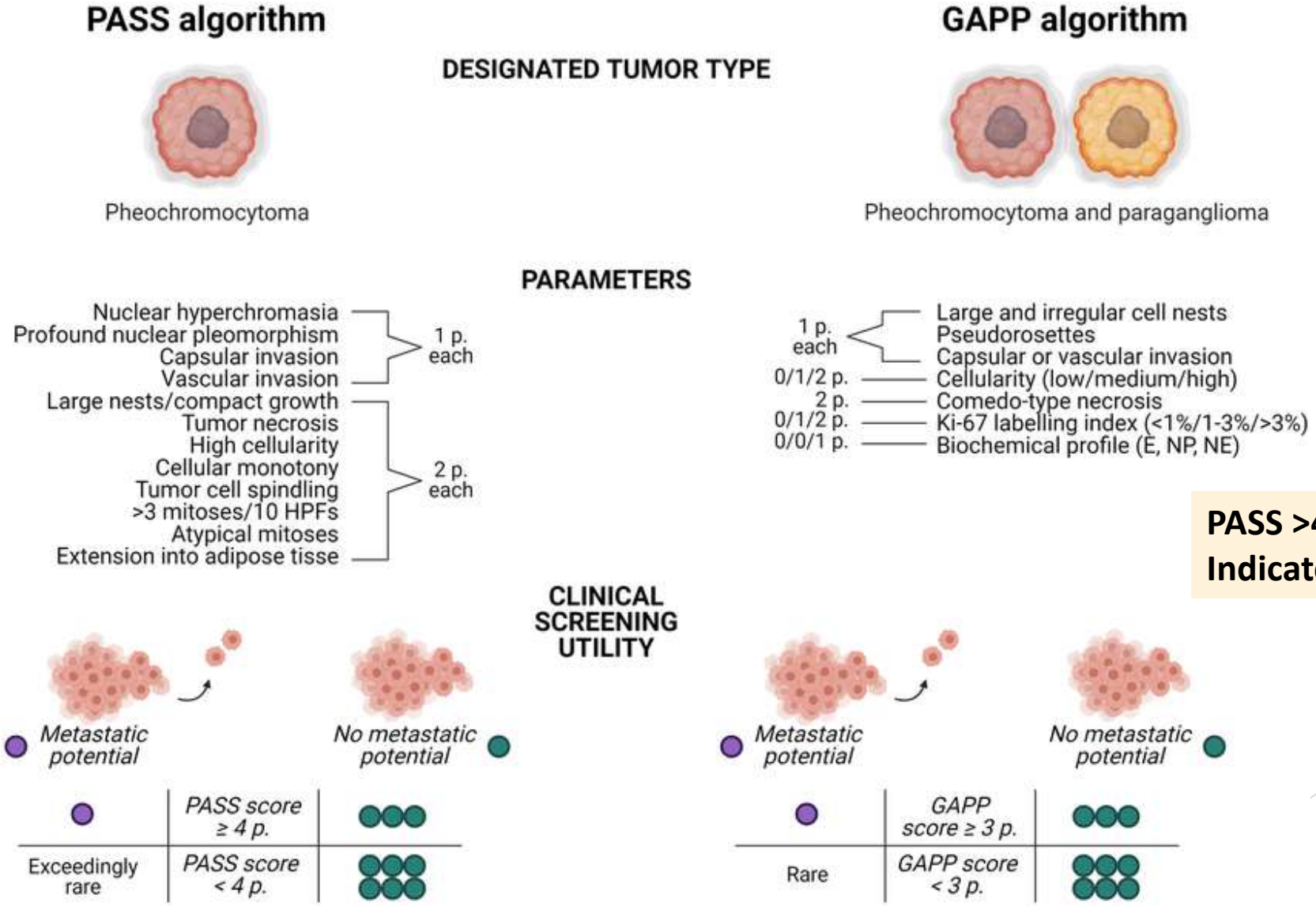


Figure 6
(A and B) Microscopy showing a classical appearance of pheochromocytoma with Zellballen architecture comprised large cells with granular amphophilic cytoplasm. Mitoses were readily identifiable (B, circle) (8/10 HPF) without atypical forms. Lesional cells showed ACTH expression by immunohistochemistry (B, insert) (magnification A ×200, B ×400).

ACTH-Producing Pheochromocytoma

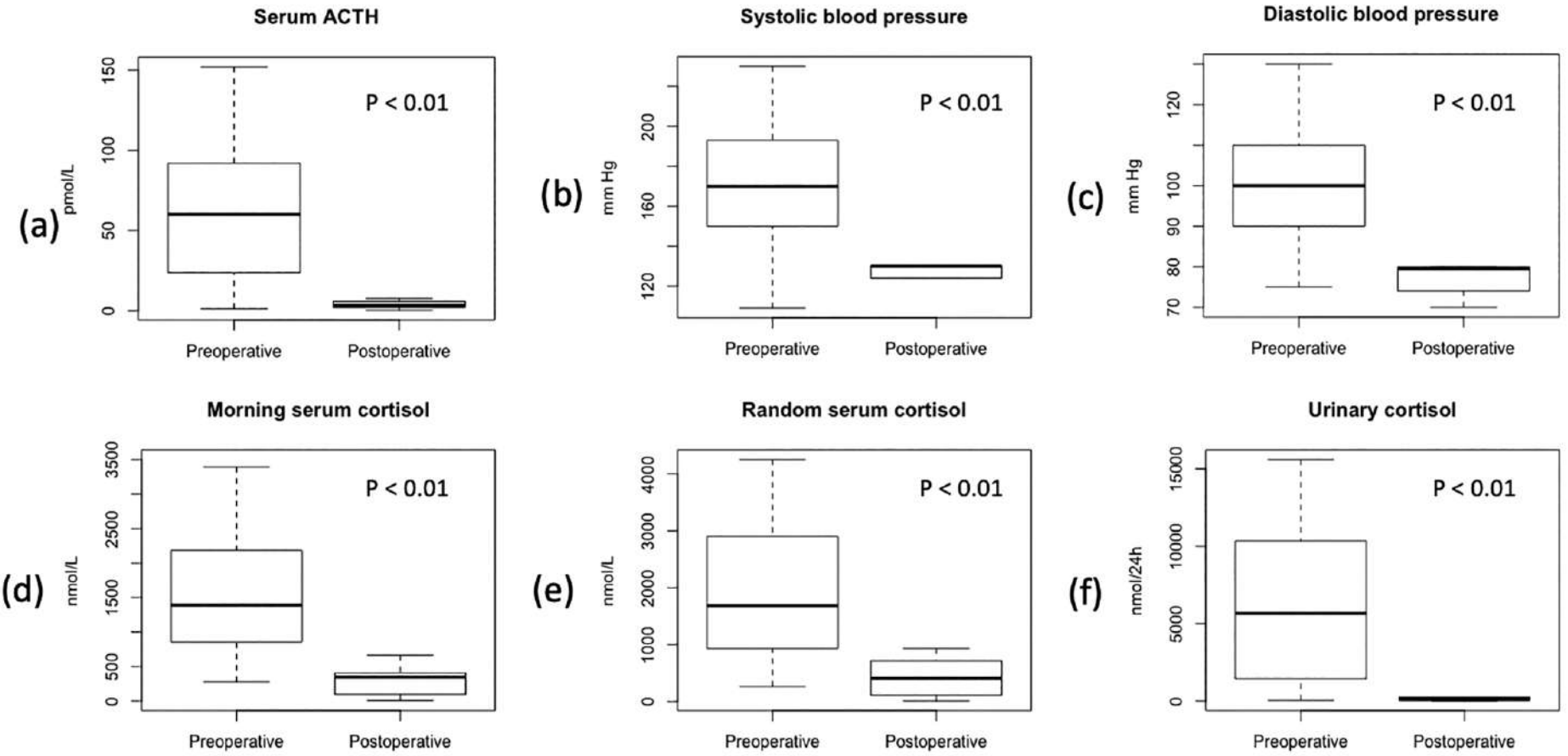
Tumor characteristics



PASS >4, GAPP>3
Indicates potential malignant behavior

Endocrine Pathology (2021) 32:228–244

Pre-op VS Post-op biochemical profiles



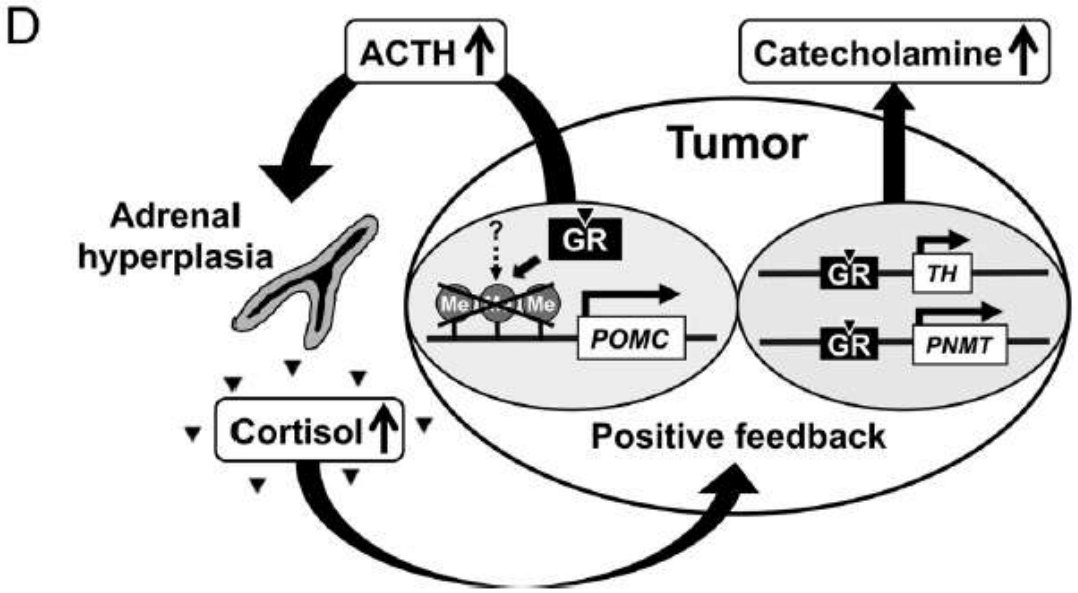
Postoperative biochemical Normalised

-Serum ACTH 95%,
-Morning serum cortisol 75%
-Urinary cortisol 97%
-Serum potassium levels
-HbA1c

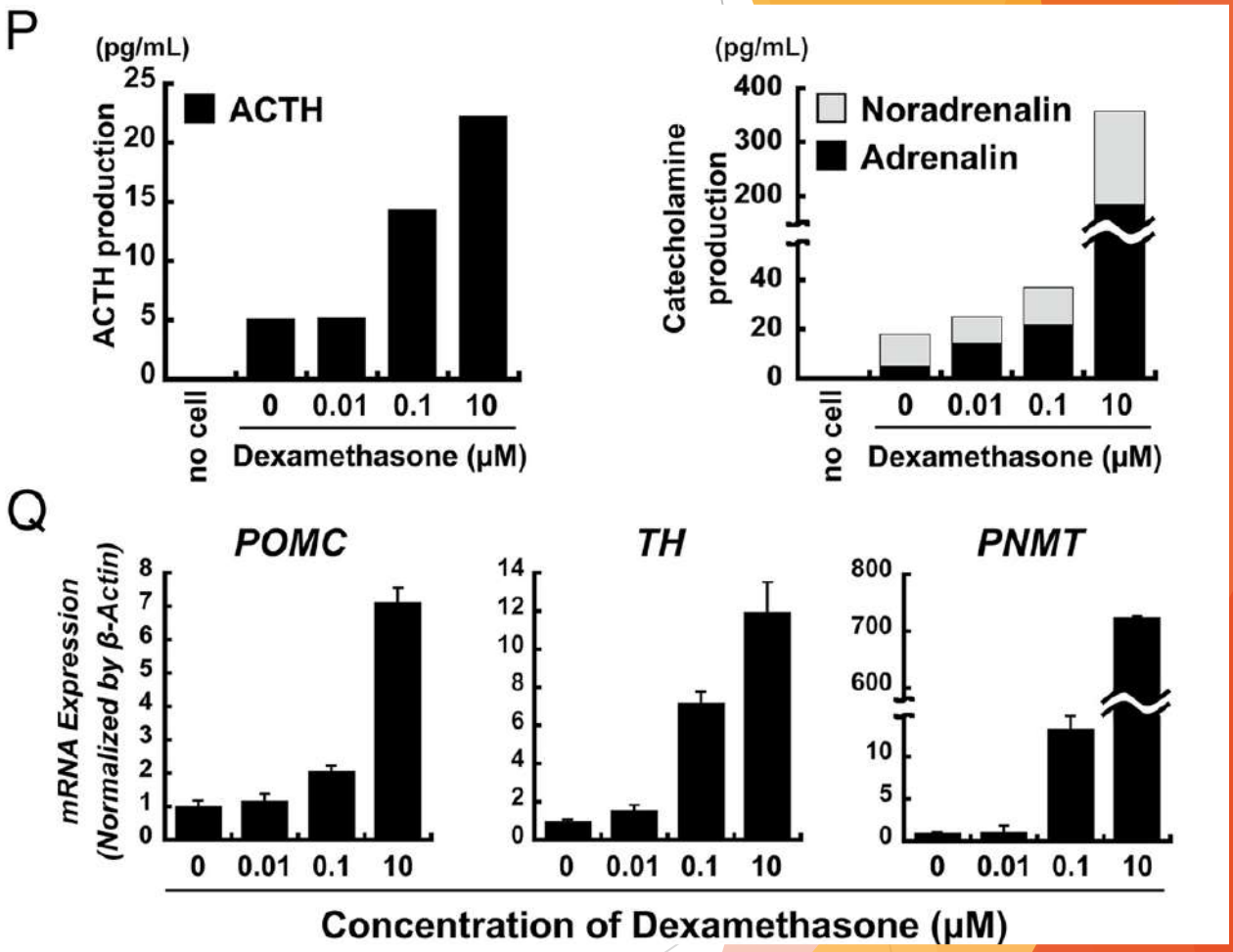
- Glucocorticoid supplementation for a median of 1.5 months after surgery

Journal of Clinical Endocrinology & Metabolism, 2021, Vol. 106, No. 2, 598–608

ACTH-Producing Pheochromocytoma



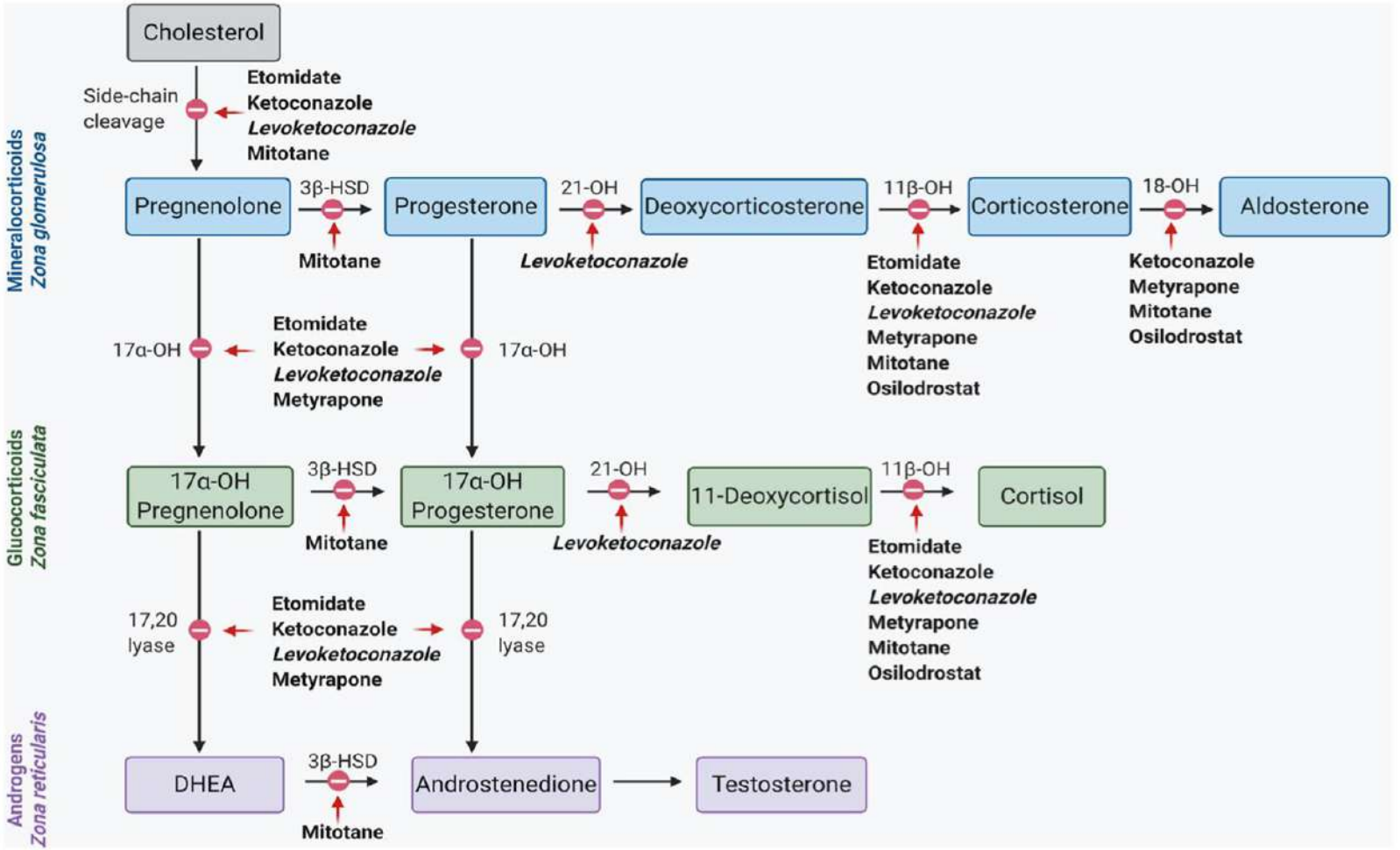
- ACTH up-regulation with paradoxical response to glucocorticoid, possibly through the hypomethylation of the *POMC* promoter



J Clin Endocrinol Metab, March 2016, 101(3):841–846

TREATMENT

- Goals of treatment are **resolution of hypercortisolism and tumor control**
- Only definitive cure of ECS is **complete excision** of the causative NEN
- Resolution of hypercortisolism can be achieved with medical therapy using adrenal steroidogenesis inhibitors, glucocorticoid receptor blockade and/or adrenolytic agents such as mitotane
- Bilateral adrenalectomy, now often performed via retroperitoneal approach, is another option to rapidly and effectively eliminate hypercortisolism



Best Practice & Research Clinical Endocrinology & Metabolism 35 (2021)

SURGERY

- **Surgical excision** of the ACTH-producing tumor is the ideal treatment when visible on imaging and not metastatic
- A good preoperative functional status, comprising normal ambulation and absence of active infection or thromboembolic disease, portends a favorable surgical outcome
- **Preoperative cortisol lowering therapy is often needed to improve the patient's operative risk and to prevent postoperative complications**
- **Postoperative hypocortisolism** is expected in patients where the underlying tumor has been successfully removed and should be managed with glucocorticoid replacement (avoid adrenal crisis)
- Recovery of the hypothalamic–pituitary– adrenal axis typically takes 6–18 months

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

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Table 3 | Pharmacological treatment of CS

Class and individual agents	Onset of action[a]	Preferred aetiological indication	Possible use in severe CS	FDA regulatory approval	Adverse effects (less common effects)
Steroidogenesis inhibitors					
Metyrapone	Hours to days	Any aetiology of CS	Yes, alone or with ketoconazole	Off-label	GI (hirsutism, HT, hypokalaemia, AI)
Osilodrostat	Days to weeks	Any aetiology of CS	Yes	Approved	Nausea, headache, AI, ↑QTc (HT)
Ketoconazole	Hours to days	Any aetiology of CS	Yes, associated with metyrapone	Off-label	GI, inhibits CYP3A4; male hypogonadism, ↑LFTs, (↑QTc; hepatic dyscrasia)
Levoketoconazole	Days	Any aetiology of CS	Unknown	Approved	GI, ↑LFTs, inhibits CYP3A4 (↑QTc)
Mitotane	Months; long half-life	ACC, and less frequently other aetiologies of CS	No, because of delayed onset of action	Adrenolytic; approved for adrenal cancer	GI, CNS, low WBC and T_4, ↑LFTs, gynaecomastia, ↑CBG, inhibits CYP3A4, teratogenic
Etomidate	Hours	Ectopic ACTH secretion and ACC (severe hypercortisolism)	Yes, in ICU	Off-label	Requires monitoring in ICU
Agents that inhibit ACTH release from CD tumour					
Cabergoline	Weeks	CD	No, low efficacy in severe hypercortisolism	Off-label	GI, asthenia, dizziness, ↓impulse control and/or ↑compulsive behaviours
Pasireotide	Days	CD	No, low efficacy in severe hypercortisolism	Works best if UFC less than twice normal; approved	↑Glucose, diarrhoea, nausea, cholelithiasis (transient ↑LFTs, ↑QTc interval)
Pasireotide extended release	Weeks	CD	No, low efficacy in severe hypercortisolism	Works best if UFC less than twice normal; approved	Diarrhoea, nausea, cholelithiasis, ↑glucose (transient ↑LFTs, ↑QTc interval)
Agent that antagonizes cortisol action at its receptor					
Mifepristone	Days to weeks	Any aetiology of CS	Yes, as a single treatment	Approved for glucose intolerance and CS	Fatigue, hypokalaemia, nausea, oedema, arthralgias, headache, endometrial thickening; CYP3A4 inhibitor, abortifacient

ACC, adrenal cortical cancer; ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency; CBG, corticosteroid-binding globulin; CD, Cushing disease; CNS, central nervous system; CS, Cushing syndrome; GI, gastrointestinal; HT, hypertension; ICU, intensive care unit; LFT, liver function test; QTc, corrected QT interval; T_4, thyroxine; UFC, urinary free cortisol; WBC, white blood cell count. [a]Onset of action varies depending on intrinsic potency, half-life, speed of upward titration and duration of exposure.

Cushing syndrome. *Nat Rev Dis Primers* **11**, 4 (2025)

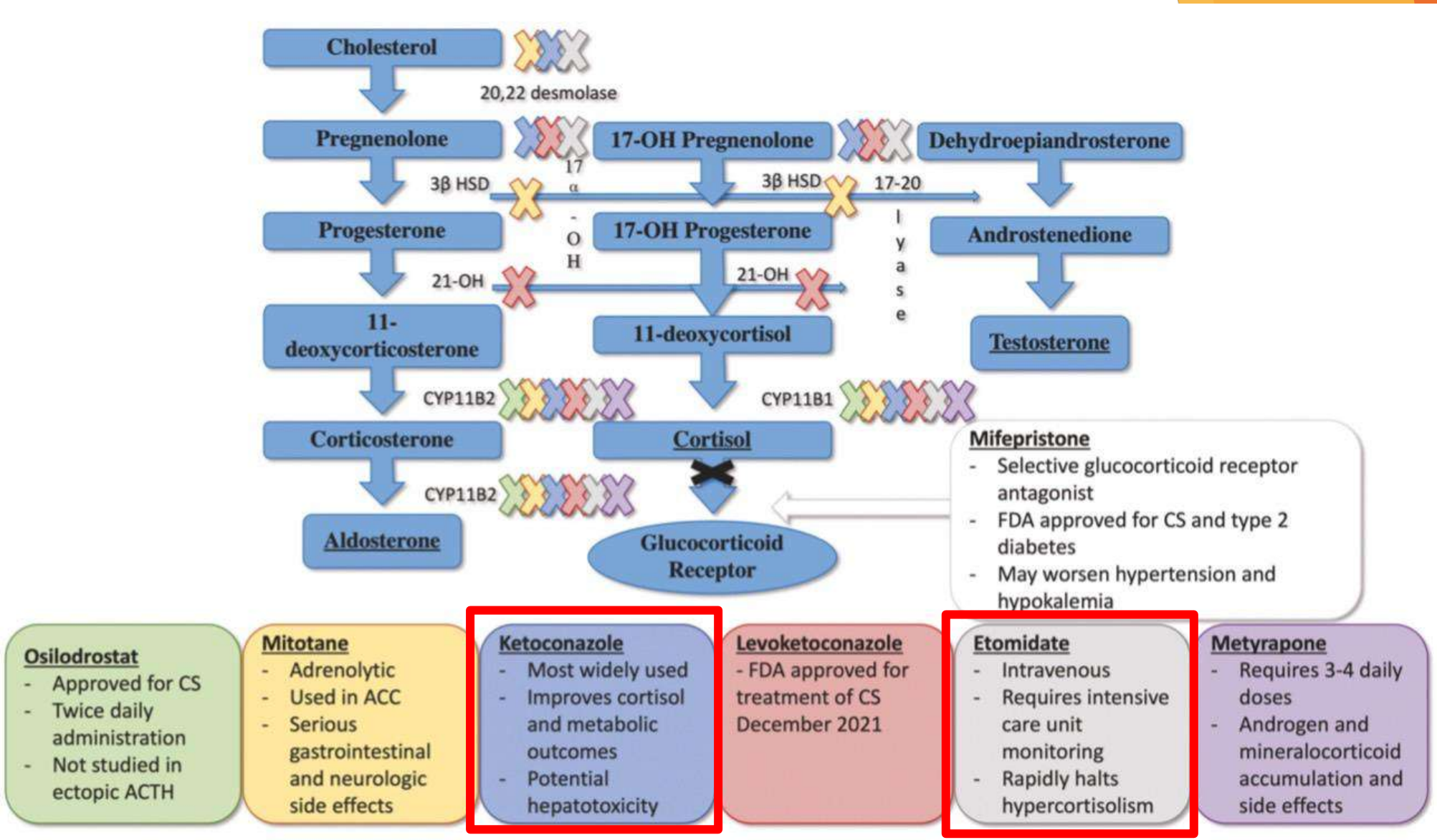

Figure 1. Cortisol synthesis inhibitors and receptor blockers. Sites of inhibition are demarcated by "X," color matched to the boxes below with the corresponding drug. Abbreviations17α-OH, 17α hydroxyprogesterone; 21-OH, 21-hydroxylase; 3β HSD, 3β-hydroxysteroid dehydrogenase; ACC, adrenal cortical carcinoma; CS, Cushing syndrome; CYP11B1, cytochrome P450 family 11 subfamily B member 1; CYP11B2, cytochrome P450 family 11 subfamily B member 2.

ETOMIDATE

Table 2 Treatment of hypercortisolism with etomidate recommendations.

Etomidate infusion rate options	Blockade	Target cortisol level	Biochemical monitoring	Other
0.04–0.05 m/kg per h = 2.5–3.0 mg/h	Partial	Titrate to serum cortisol 500–800 nmol/l in physiologically stressed patient, 150–300 nmol/l in non-physiologically stressed patient	Potassium level	Sedation scoring initially every 2 h then every 12 h after first 24 h
0.5–1.0 mg/h	Complete (will need steroid replacement)	<150 nmol/l	Cortisol level Potassium level Cortisol level	Sedation scoring initially every 2 h then every 12 h

18-30 mcg/dL

5.4 mcg/dL

- Etomidate, **inhibits 11β-hydroxylase at subhypnotic doses** and **reduces cortisol secretion immediately**
- Etomidate is administered intravenously and the dose **titrated against serum cortisol or given in a block–replace regimen**
- Etomidate may be used when an immediate effect is needed, especially where oral administration is not possible
- **Starting dose was consistently 0.02 mg/kg/h if cortisol level was not trending to goal, then the infusion rate was adjusted in increments of 0.01 to 0.02 mg/kg/h to achieve desired cortisol levels**
- The infusion rate was not up titrated more frequently than every 6 hours, A maximum allowed infusion rate was set at 0.3 mg/kg/h

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ACTH-Producing Pheochromocytoma

- **Early diagnosis** is the key
- should be suspected in any patient with **ACTH-dependent Cushing syndrome** when workup is suggestive of an **ectopic source along with an adrenal mass** on imaging
- **Pheochromocytoma should be ruled out in any adrenal mass** even in the absence of typical symptoms of catecholamine excess
- **Genetic testing should be considered** in any patient with pheochromocytoma because 40% of patients have an underlying genetic mutation, especially if there are other suggestive features, such as a family history or young age

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