Interhospital conference

Case 4

31-year-old woman
with abdominal pain for 6 months

F1 Thanasit Yingkamheang
F2 Chatrawee Yodmalai
Advisor: Assoc.Prof Taweesak Wannachalee

Patient Profile

ผู้ป่วยหญิงไทยโสดอายุ 31 ปี	อาชีพสัตวแพทย์
สิทธิการรักษา	ประกันสังคม รพ.อื่น
ภูมิลำเนา	จังหวัดกรุงเทพมหานคร

อาการสำคัญ **ปวดท้องด้านขวา 6 เดือนก่อนมารพ.**

Present Illness

Known case

- Rt ovarian cyst, Dx 2555
  On DMPA IM q 3 months

3 ปีก่อนมารพ.
Dx: Migraine, MDD

- Venlafaxine ER (37.5) 1x1 PO pc
- Nortriptyline (10) 1x1 PO hs

2 ปีก่อนมารพ.
น้ำหนักเพิ่มขึ้นจาก 45 เป็น 50 kg
ตรวจพบไขมันในเลือดสูง

6 เดือนก่อนมารพ.
ปวดท้องบริเวณด้านขวาล่าง

Work up -> CT whole abdomen

A

ABDOMEN, UPPER
2.5mm Pre CM
18/12/2021, 8:44:58

LOC: -40.50
THK: 2.50 SP: 2.50
FFS
Vol:

R L

RD: 293
Tilt: 0
mA: 240
KVp: 120
Acq no: 1
Page: 1 of 93

CT01
C: 35
W: 400
DFOV: 29.3x 29.3cm
IM: 1 SE: 2

P

A

ABDOMEN, UPPER
V-PHASE
18/12/2021, 9:33:20

LOC: -1.50
THK: 2.50 SP: 2.50
FFS
Vol:

R L

RD: 316
Tilt: 0
mA: 220
KVp: 120
Acq no: 2
Page: 1 of 88

CT01
C: 35
W: 400
DFOV: 31.6x 31.6cm
IM: 1 SE: 3

P

Present Illness

CT upper abdomen (18/12/64):

- A well-defined hypoechoic nodule at upper part of left adrenal gland size 1.7x1.3 cm Absolute wash out is 63%, 12-16 HU on plain scan
- Rt adrenal gland is intact
- Normal size appendix without CT evidence of appendicitis
- Thickening rim enhancing right paraovarian/adnexal hypodense lesion (3.1x2.3x2.4 cm) with surrounding suspected complicated cyst. Few left ovarian cysts (up to 1.5 cm) Suspicious few small cystic lesions in cul-de-sac posteriorly to the uterus

History taking?
Physical examination?

Present Illness

- ไม่มีรอยแตกลายบริเวณหน้าท้อง/ต้นขา
- หน้ากลมพอเดิม ไม่มีหน้าแดง ไม่มีแขนขาอ่อนแรง
- ไม่มีขนหน้าแข้งหรือหนวดหรือขนตามบริเวณใบหน้าเพิ่มมากขึ้น
- ไม่มีอาการปวดศีรษะ เหงื่อออก ใจสั่น เป็นๆหายๆ
- ไม่มีประจำเดือนตั้งแต่ฉีด DMPA
- ไม่เคยตรวจพบความดันโลหิตสูง
- ไม่เคยตรวจพบโพแทสเซียมในเลือดต่ำ
- ไม่มีซื้อยากินเอง ปฏิเสธประวัติกินยาสมุนไพร/ยาชุด
- น้ำหนักขึ้นจาก 45 เป็น 50 kg ในช่วง 2 ปี กินข้าว/ชานมไข่มุก/น้ำหวาน/น้ำอัดลมพอๆเดิม
- ตรวจสุขภาพประจำปีทุกปี เคยพบ LDL สูง กินยาลดไขมัน 2 ปี หลังจากนั้นไม่ได้กินต่อ เนื่องจากแพทย์แจ้งว่าลดลงแล้ว
- ไม่เคยตรวจพบน้ำตาลในเลือดสูง

Present Illness

ประวัติครอบครัว

- ปฏิเสธโรคเนื้องอกต่อมใต้สมอง/เนื้องอกต่อมหมวกไต/มะเร็ง/premature atherosclerosis ในครอบครัว

ประวัติส่วนตัว

- ไม่ดื่มสุรา ไม่สูบบุหรี่
- ไม่ใช้ยาต้ม ยาสมุนไพร หรือยาชุด

ประวัติยาและแพ้ยา

- ปฏิเสธประวัติแพ้ยาแพ้อาหาร

Physical examination

V/S: BT 36.6°C, HR 86 bpm, BP 123/71 mmHg, RR 20/min
Body weight 48.6 kg, Height 155 cm, BMI 20.2 kg/m^2

GA: A middle-aged woman, well co-operate, not pale, no jaundice, no edema, moon face, fullness of supraclavicular fat pad, no facial plethora, no dorsocervical hump

Skin: No petechiae, no striae, no acanthosis nigricans, no hyperpigmentation at gum, lips, buccal mucosa, palmar crease or knuckle

HEENT: No dry/moist skin, no loss of lateral 1/3 of eyebrow, no thyroid gland enlargement

CVS: PMI at 5th ICS MCL, no apical/parasternal heaving, normal S1S2, no murmur

RS: Clear and equal breath sounds both lungs

Physical examination

Abdomen: Soft, not tender, no guarding, no rebound tenderness, liver and spleen not palpable

NS: Alert, well cooperative, pupils 3 mm BRTL, motor power grade V all extremities

Lymph node: No superficial lymphadenopathy

Current medication

- DMPA 1 amp IM q 3 months
- Venlafaxine ER (37.5) 1x1 PO pc
- Nortriptyline (10) 1x1 PO hs

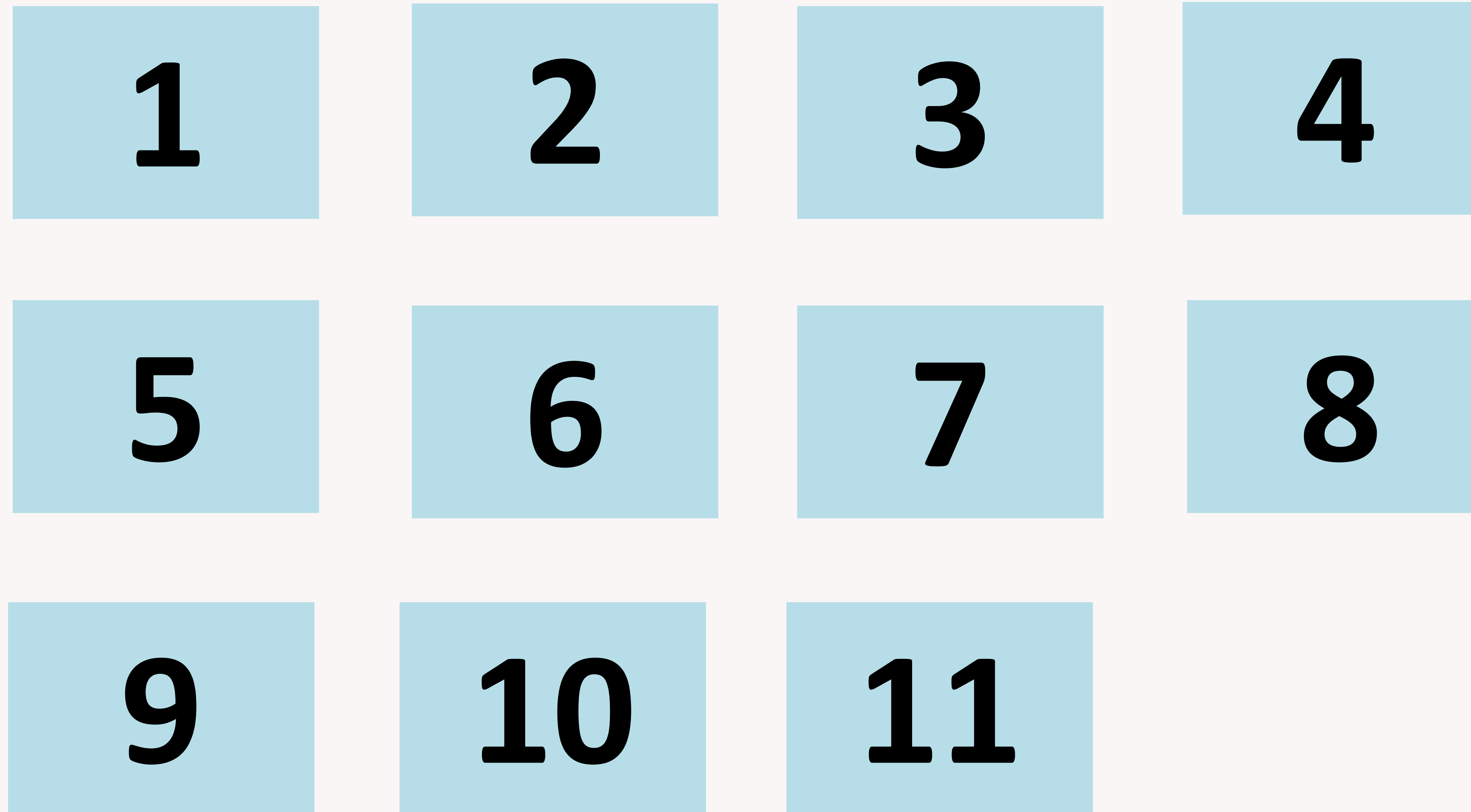
Problem list

A 31-year-old woman known case right ovarian cyst, major depressive disorder and dyslipidemia presented with

1. Left adrenal incidentaloma
2. Weight gain 5 kg for 2 years
3. Abnormal physical examination
   - Moon face, fullness of supraclavicular fat pad

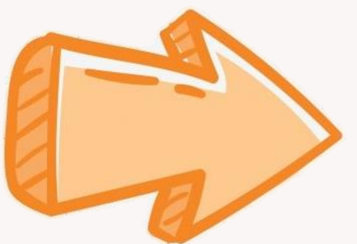
Investigation?

Investigation



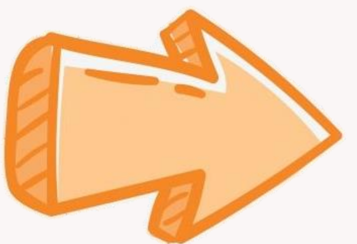
Investigation

- FBS 80 mg/dL, HbA_{1c} 5.1 %
- Cr 0.6 mg/dL, Na 139 mmol/L, K 3.7 mmol/L, Cl 103 mmol/L, HCO_3 22 mmol/L
- TC 234 mg/dL, LDL-C 151 mg/dL, TG 52 mg/dL, HDL-C 72 mg/dL



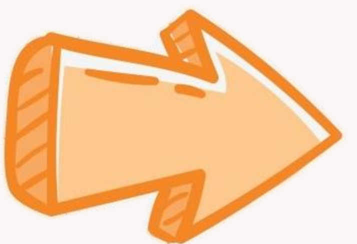
Investigation

- 8.00AM cortisol 12.2 mcg/dL
- Albumin 4.3 g/dL



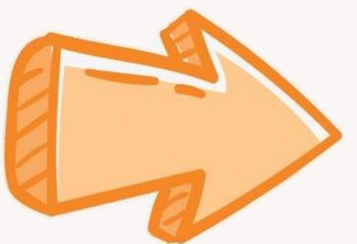
Investigation

- 1 mg DST 4.3 mcg/dL



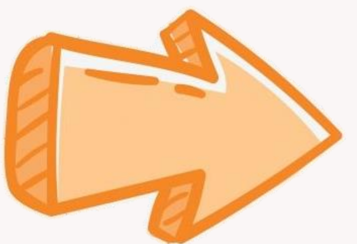
Investigation

- Standard LDDST 4.1 mcg/dL



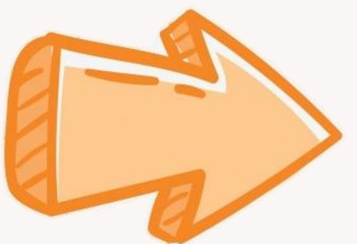
Investigation

- Standard HDDST
  8.6 -> 5.3 mcg/dL



Investigation

- Late night salivary cortisol < 0.054 mcg/dL x 2 days
(Ref. range < 0.274 mcg/dL)



Investigation

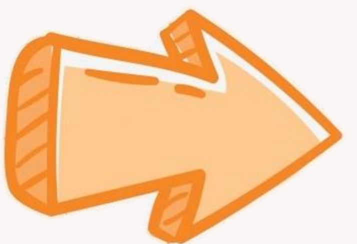
	Day 1	Day 2	Ref. range
24 hr. urine free cortisol (mcg/day)	59.48	76.82	0-150
24 hr. urine Cr (mg/dL)	32.6	44.1	
24 hr. urine volume (mL)	1950	1420	

Body weight 48 kg

Investigation

- DHEA-S

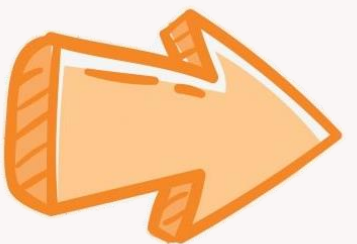
156.4 mcg/dL (98.8-340)



Investigation

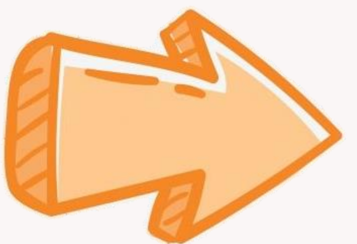
- PAC 11.90 ng/dL
- DRC 14.11 uU/mL

(K 3.7 mmol/L, BP 121/80 mmHg)



Investigation

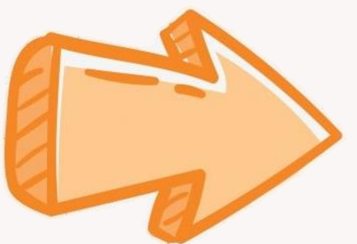
- ACTH < 5 pg/mL x 2 days



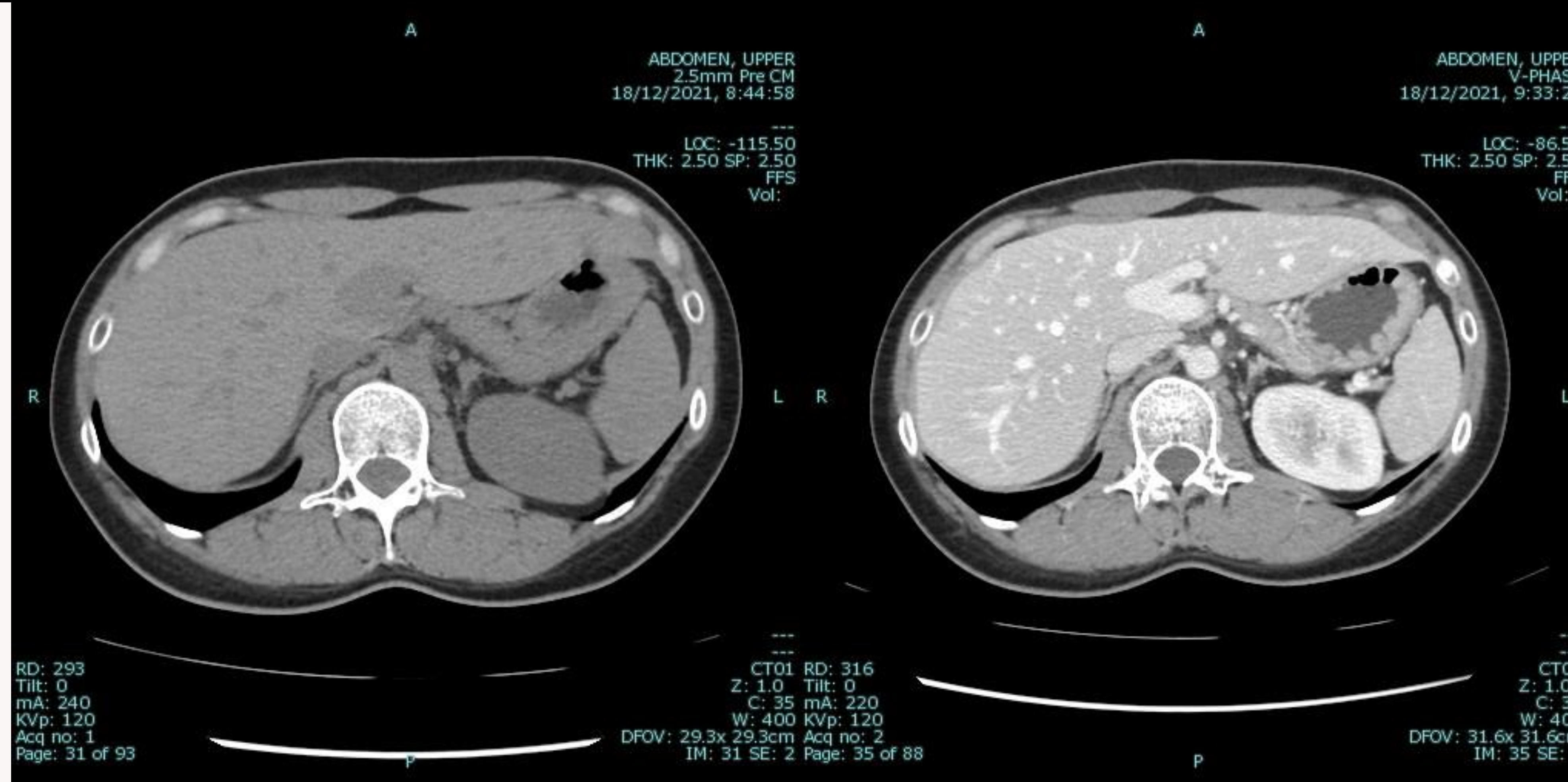
Investigation

	Day 1	Day 2	Ref. range
24 hr. urine metanephrine (mcg/day)	51.29	50.81	< 350
24 hr. urine normetanephrine (mcg/day)	266.94	233.35	< 600
24 hr. urine Cr (mg/dL)	52.4	33.1	
24 hr. urine volume (mL)	1879	2851	

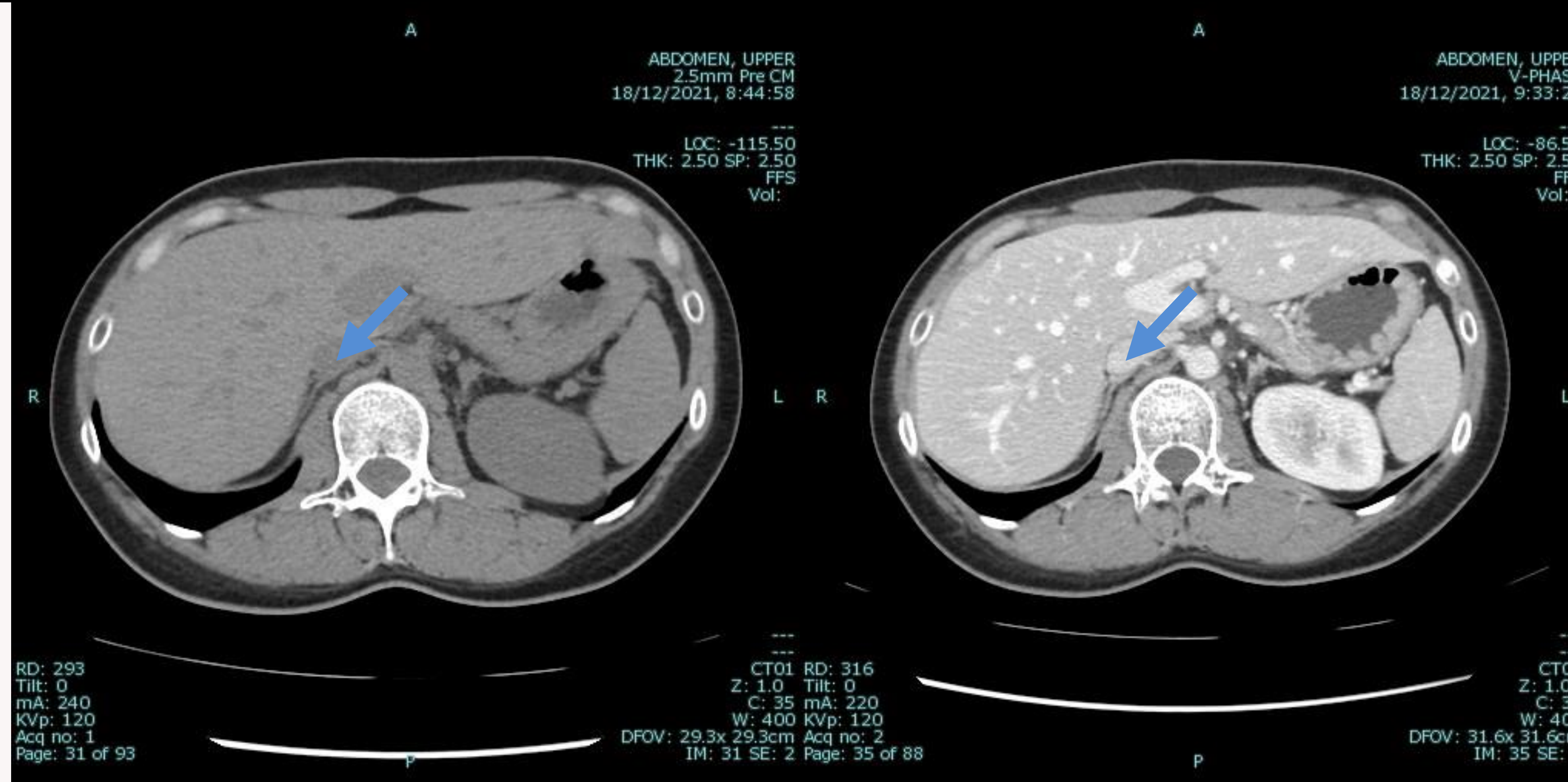
Body weight 48 kg

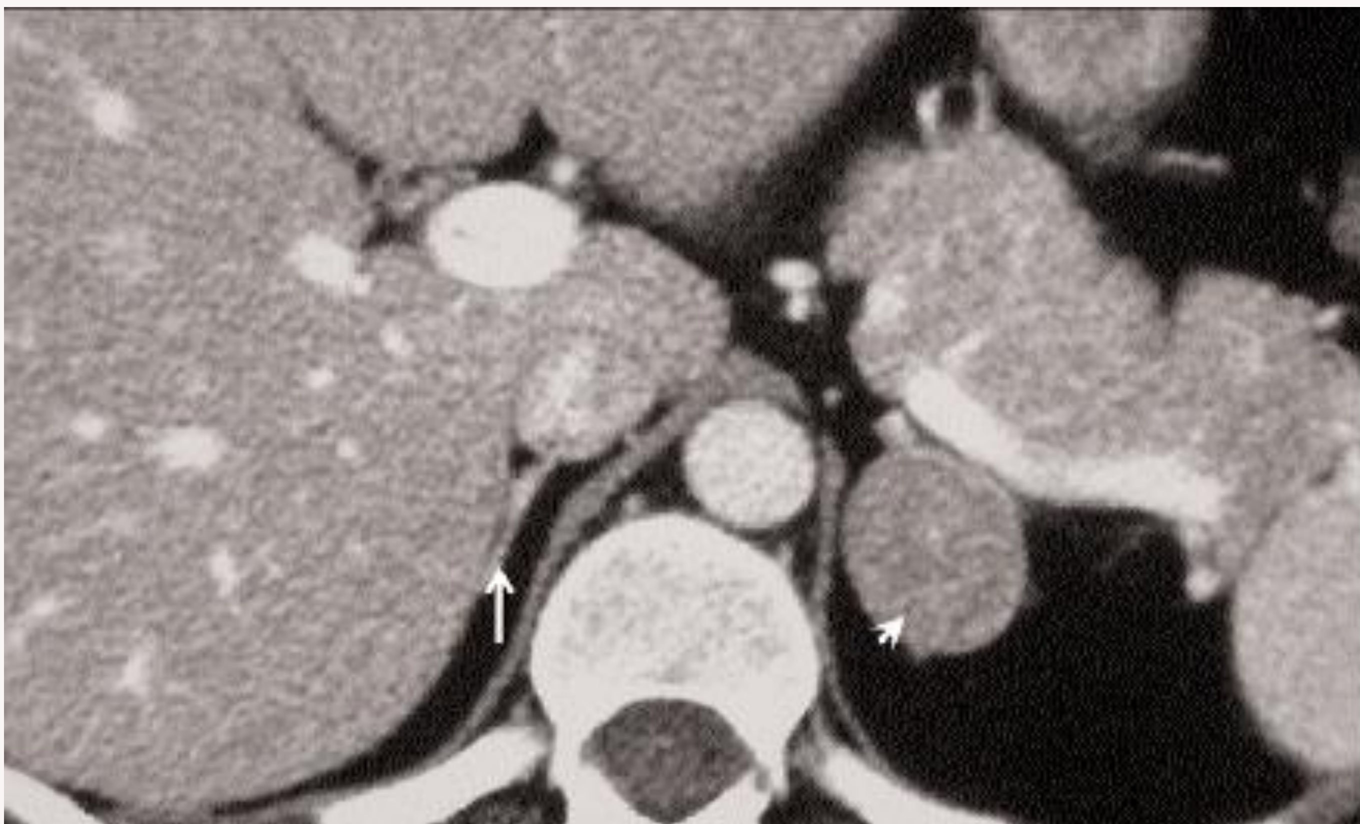


CT adrenal protocol (18/12/64)

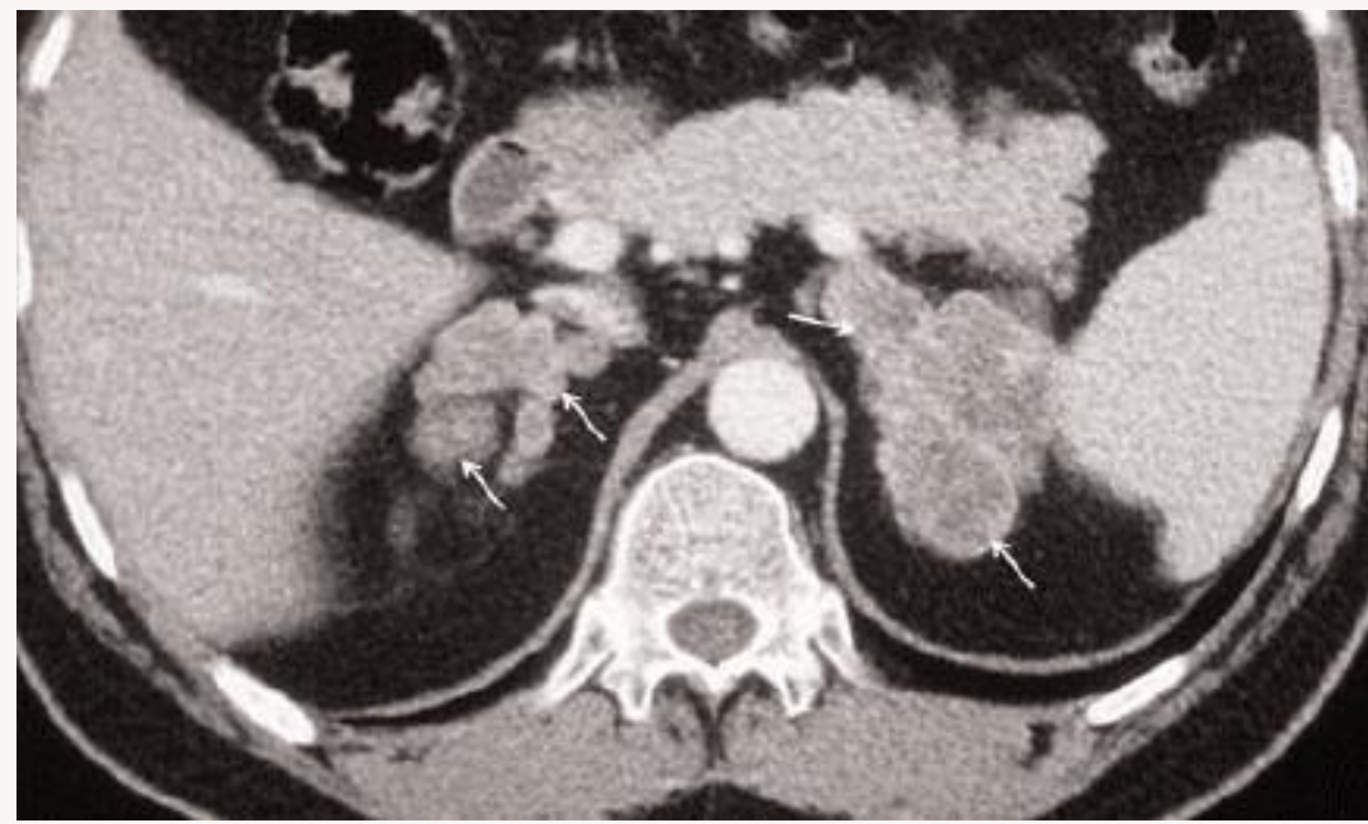


CT adrenal protocol (18/12/64)

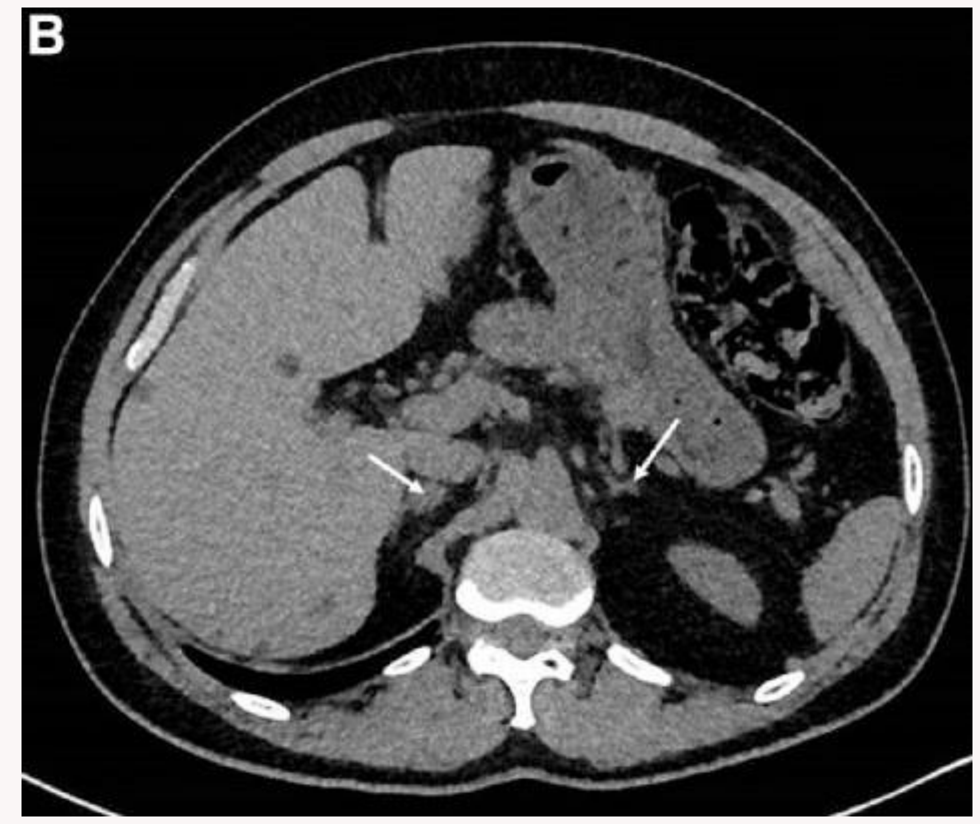




Adrenal adenoma



PBMAH



PPNAD

The Journal of Clinical Endocrinology & Metabolism, 2024, **109**, 2422–2432

Arq Bras Endocrinol Metab 2007;51/8

Provisional diagnosis and management?

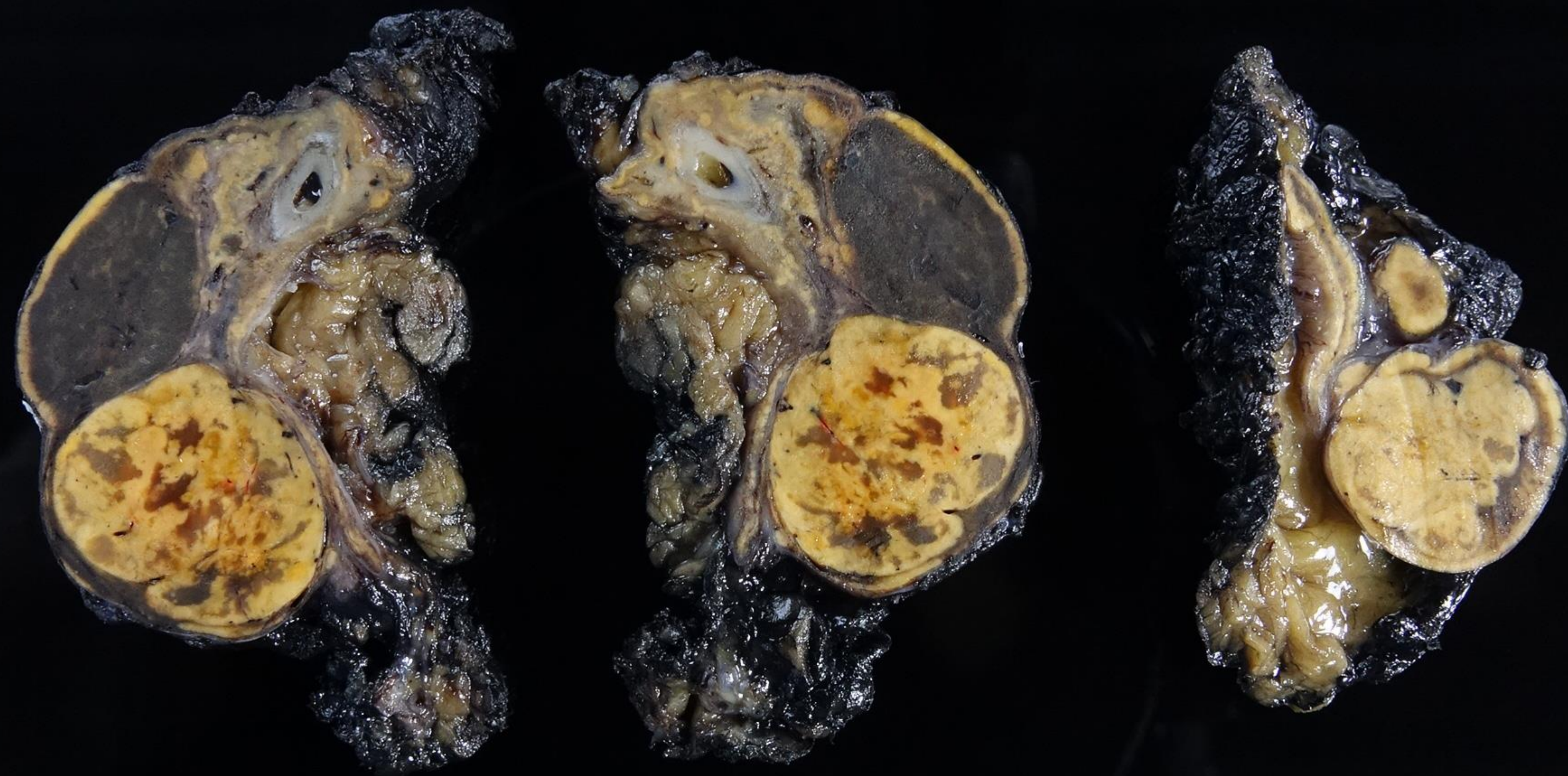
Provisional diagnosis & management

Left adrenal Cushing's syndrome (mild)

<u>Management</u>
Laparoscopic Lt adrenalectomy (2/5/65)
Intraoperative: hydrocortisone 200 mg + NSS 100 ml IV drip in 24 hr

Intraoperative findings:

- 2 cm well-defined, firm consistency nodule at medial part of Lt adrenal gland
- No lymphadenopathy
- No peritoneal nodule, no ascites



CENTIMETRES 1 2 3 4 5 6 7 8
DEPARTMENT OF PATHOLOG
SIRIRAJ HOSPITAL
S22010296

Differential diagnosis?

Pathology

Pathologic Diagnosis

Adrenal gland, left, adrenalectomy:

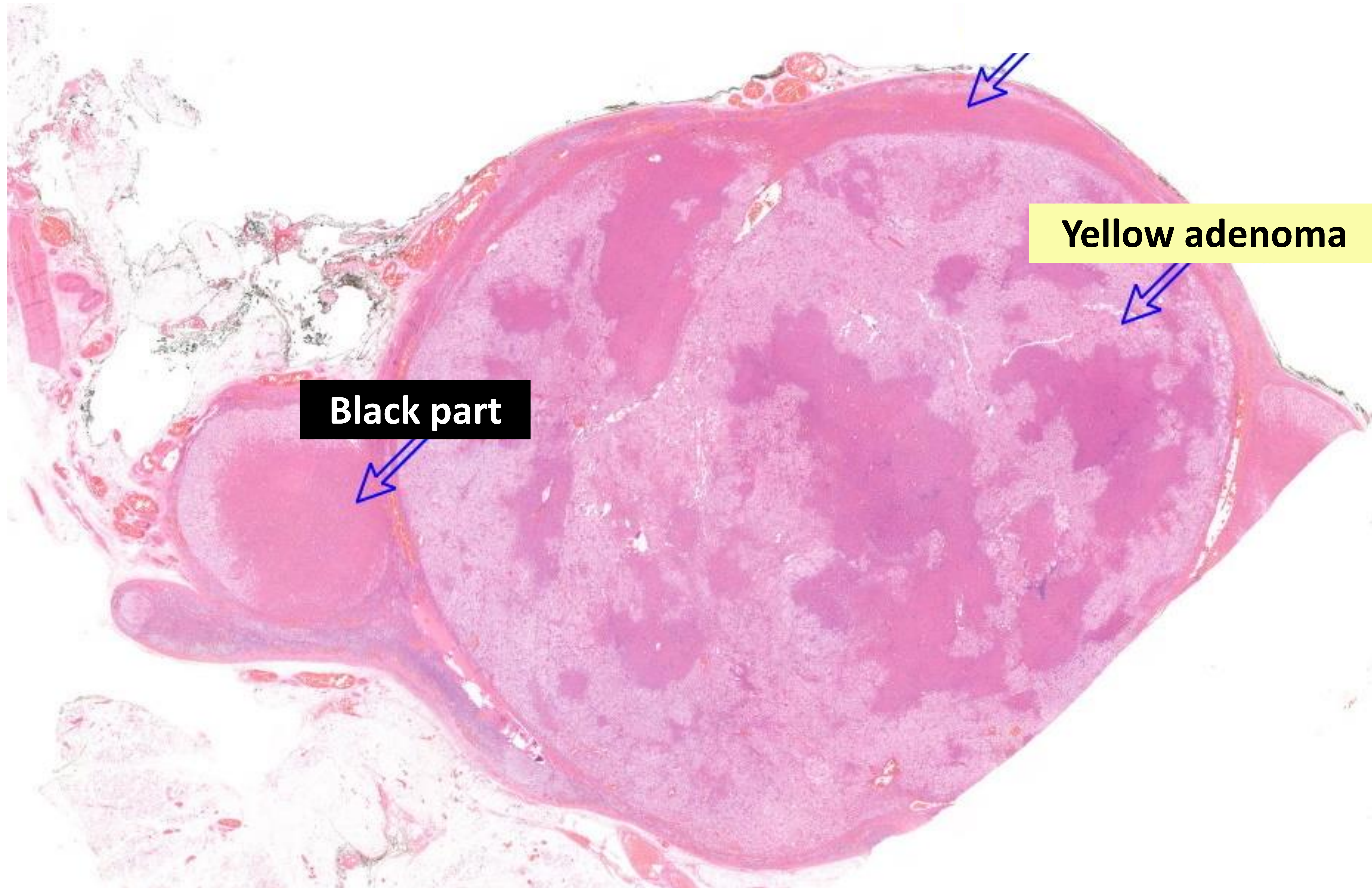
- Adrenal cortical adenoma
  - Size 1.7x1.3x0.9 cm
  - Fuhrman nuclear grade: 1/4
  - Mitosis 0-1/50 hf
  - Atypical mitosis: Not identified
  - Clear cell component: 70%
  - Diffuse architecture: Not identified
  - Tumor necrosis: Not identified
  - Venous invasion: Not identified
  - Sinusoidal invasion: Not identified
  - Capsular invasion: Not identified
- Remaining adrenal gland:
  - Pigmented cortical nodules, size 0.2-1.3 cm in maximal diameter
  - Cortical atrophy

Gross Description

The specimen is received in formalin, labeled with the patient's name, additional labeling "left adrenal gland" and a surgical number. It consists of an adrenal gland with periadrenal fat, totally measuring 5.5x2x2 cm and weighing 10.3 g. Serial sections show a rubbery well-circumscribed non-homogeneous yellowish and dark brown adrenal mass, measuring 1.7x1.3x0.9 cm. Adjacent to this mass is a 1.3x1.3x0.6 cm dark brown well circumscribed nodule. Area of necrosis or hemorrhage is not grossly present. Remaining adrenal gland shows two pigmented nodules, measuring 0.2 and 0.4 cm in greatest dimension. Cortical thickness of the remaining gland varies from 0.1-0.2 cm. Also received in the same container is a piece of irregular soft separate fibrofatty tissue, measuring 2.5x1.8x0.5 cm and shows no mass. Representatively submitted, after serial sectioning.

A1-A5 = mass with soft tissue resection margin (I each)

A6 = separate fatty tissue (II)



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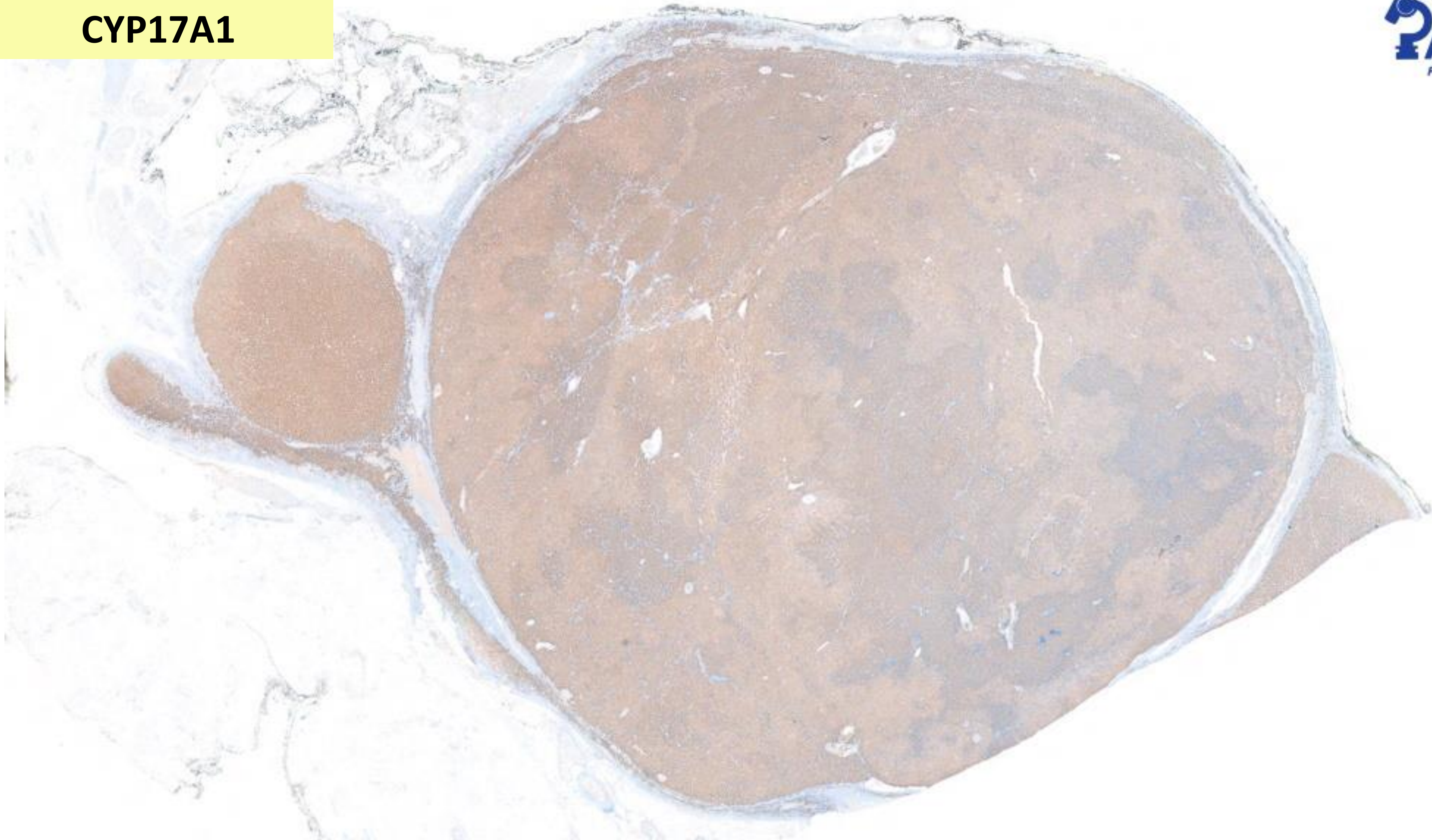
2.000 mm

Yellow adenoma CYP17A1



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2.000 mm

Yellow adenoma
CYP11B1

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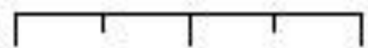

Yellow adenoma CYP11B2

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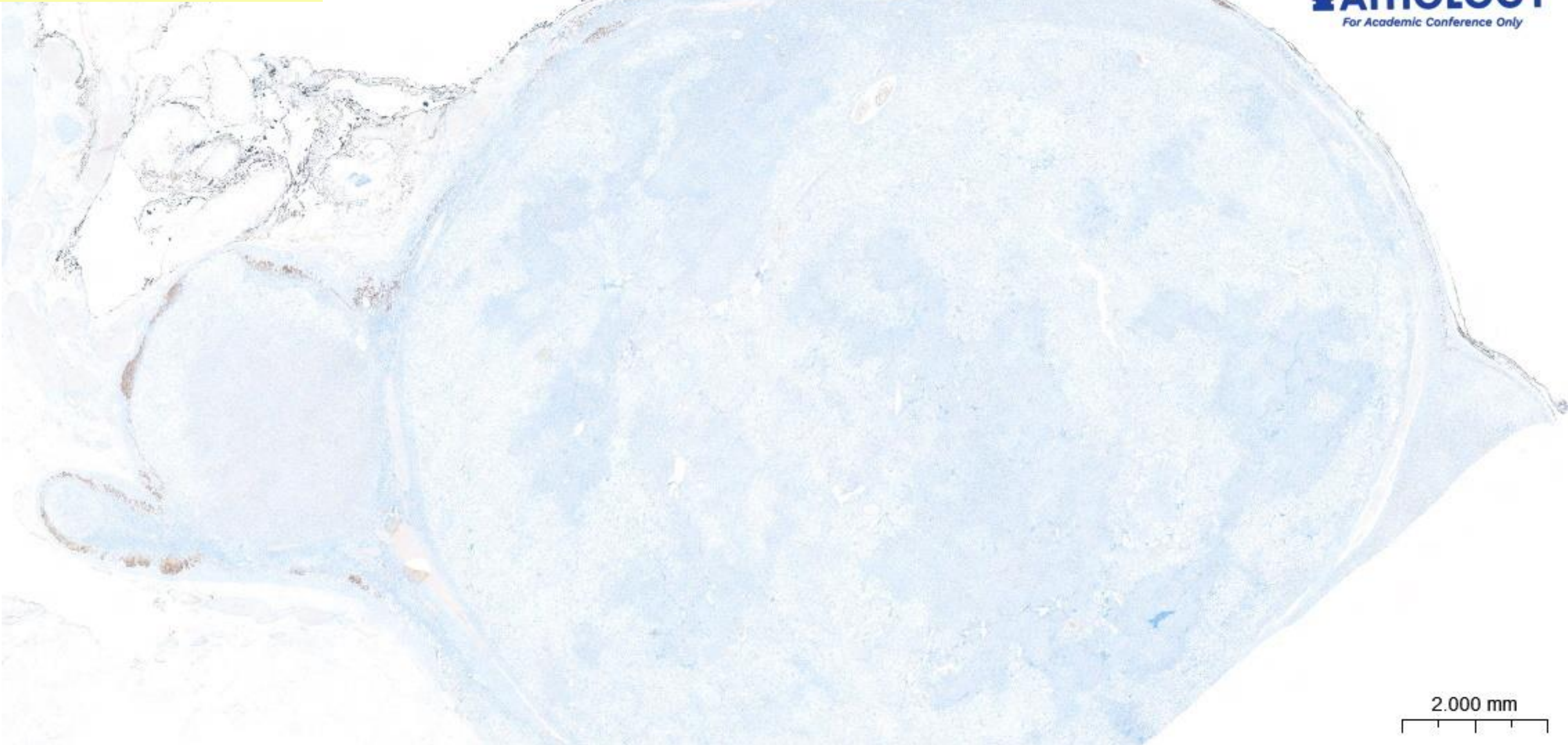
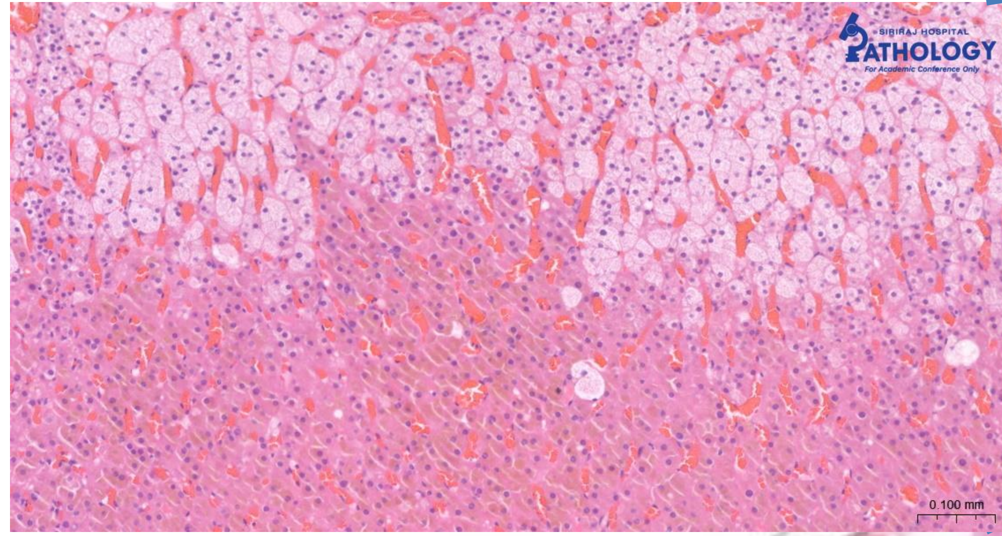


Black part



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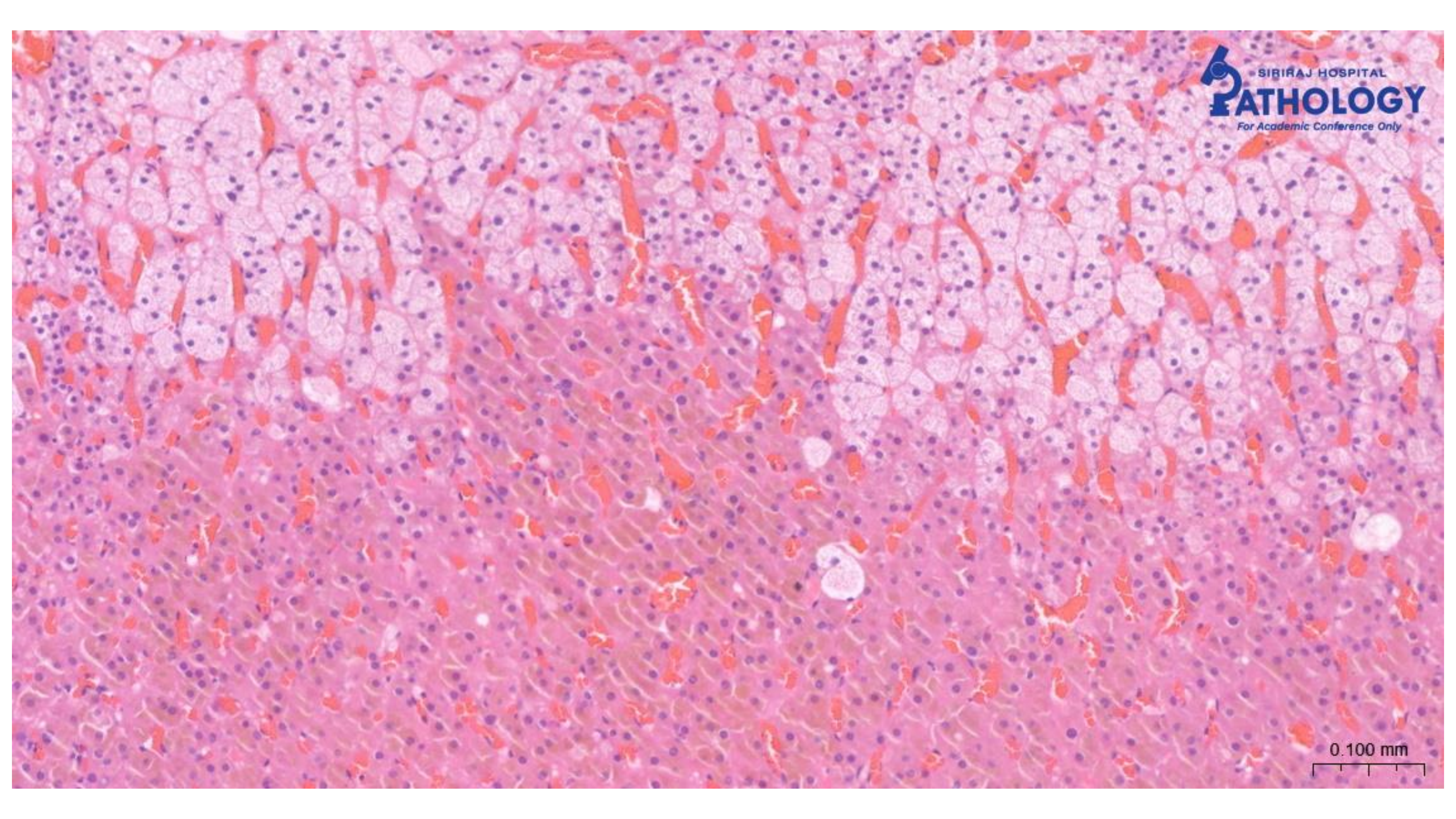
2.000 mm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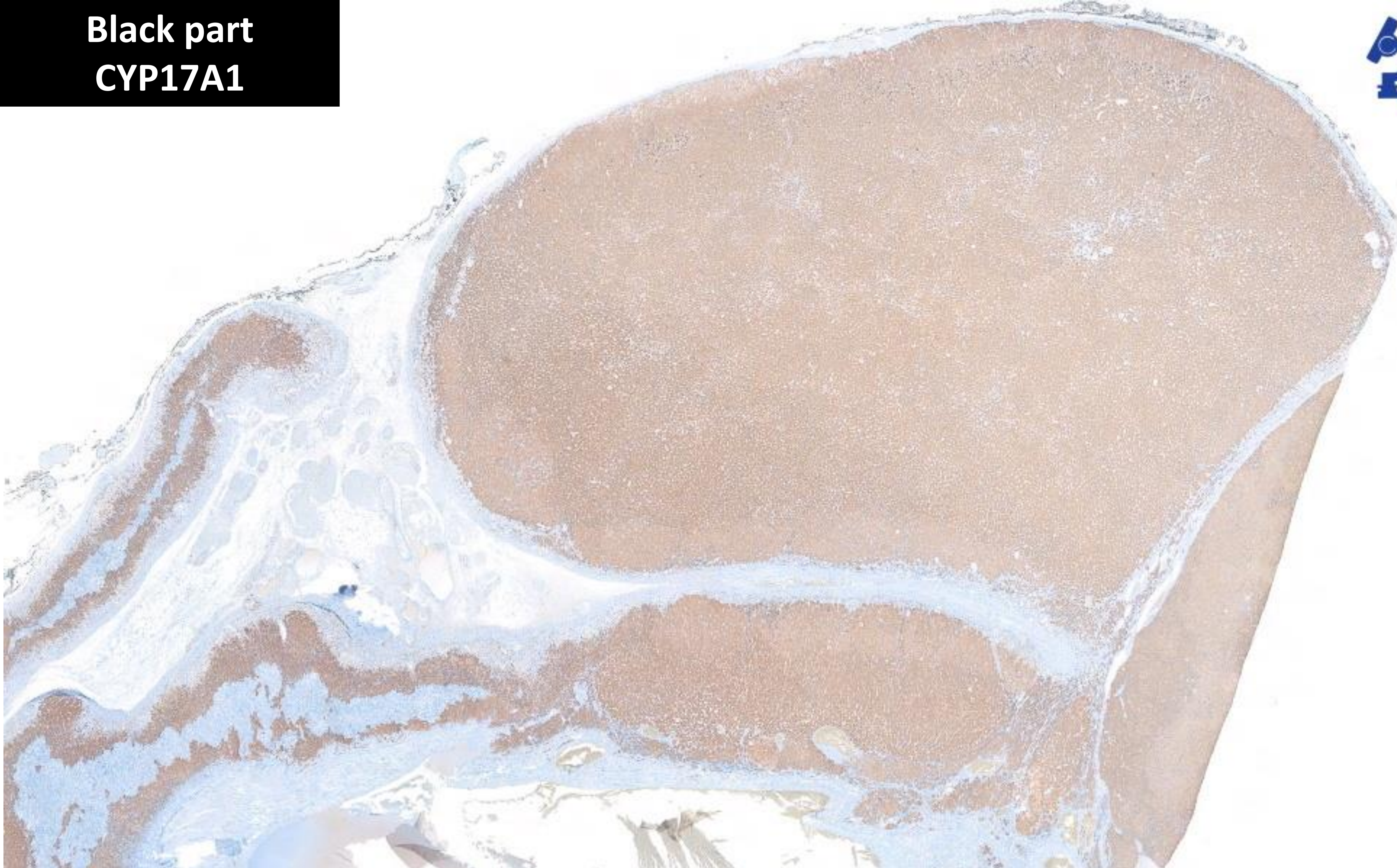
0.100 mm

Black part CYP17A1



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2.000 mm

Black part
CYP11B1

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Black part
CYP11B2

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Pathology

Immunohistochemical results

Performed in S22010296

The tumor shows CYP17+, CYP11B1+ and CYP11B2-.

The pigmented cortical nodules are CYP17+, CYP11B1+ and CYP11B2-.

The remaining adrenal gland shows several CYP11B2+ cell clusters in adrenal cortex.

(Refer to S22010296)

Diagnosis

Cushing's syndrome due to unilateral pigmented macronodular adrenocortical hyperplasia

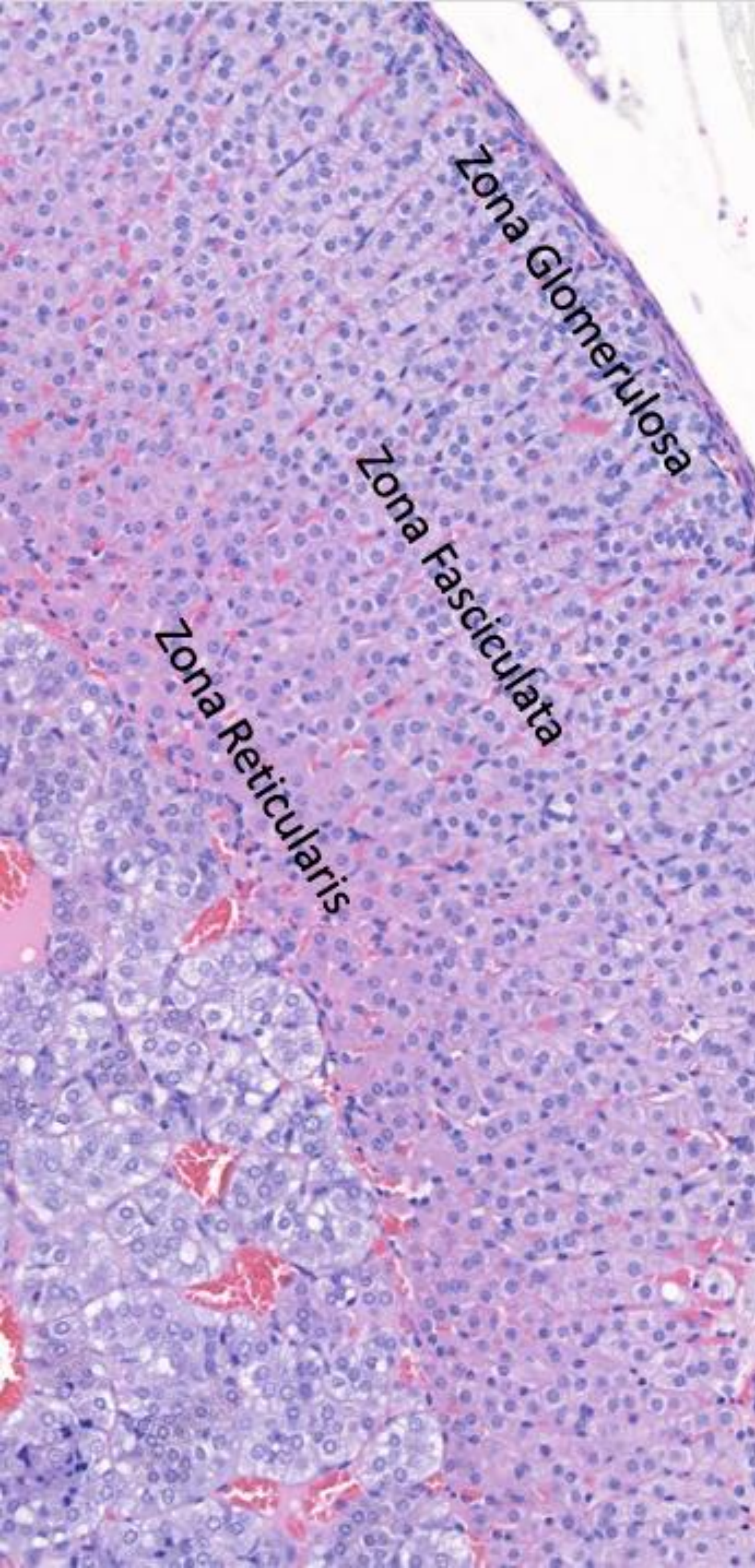
Progression

- BP 120/58 mmHg, BW 48 kg
- Lipid profiles: LDL 92-110 mg/dL
- 8.00AM cortisol = 11.9 mcg/dL

  1 mg DST = 1.0 mcg/dL

  ACTH 35.02 pg/mL

  LNSC negative



Adrenal cortex histology

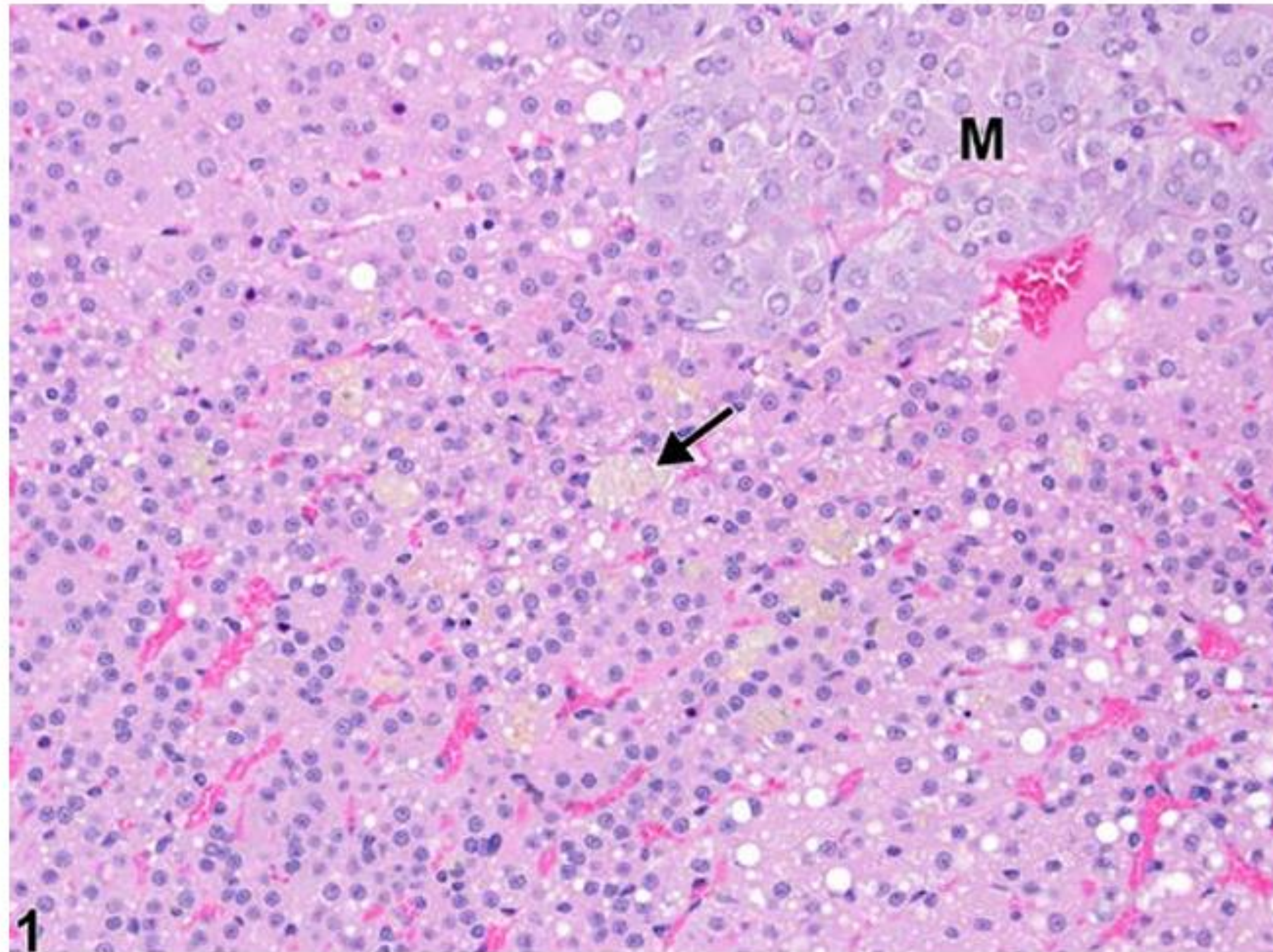
- Zona glomerulosa
  - Cells are polyhedral and arranged in clusters invested with a fine fibrovascular trabecular network that is continuous with the capsule
- Zona fasciculata
  - Cells are polyhedral and arranged in radial cord-like structures (laminae) separated by sinusoids
- Zona reticularis
  - Cells are polyhedral, lack the cord-like arrangement of the Zona fasciculata and are invested with tortuous sinusoidal structures

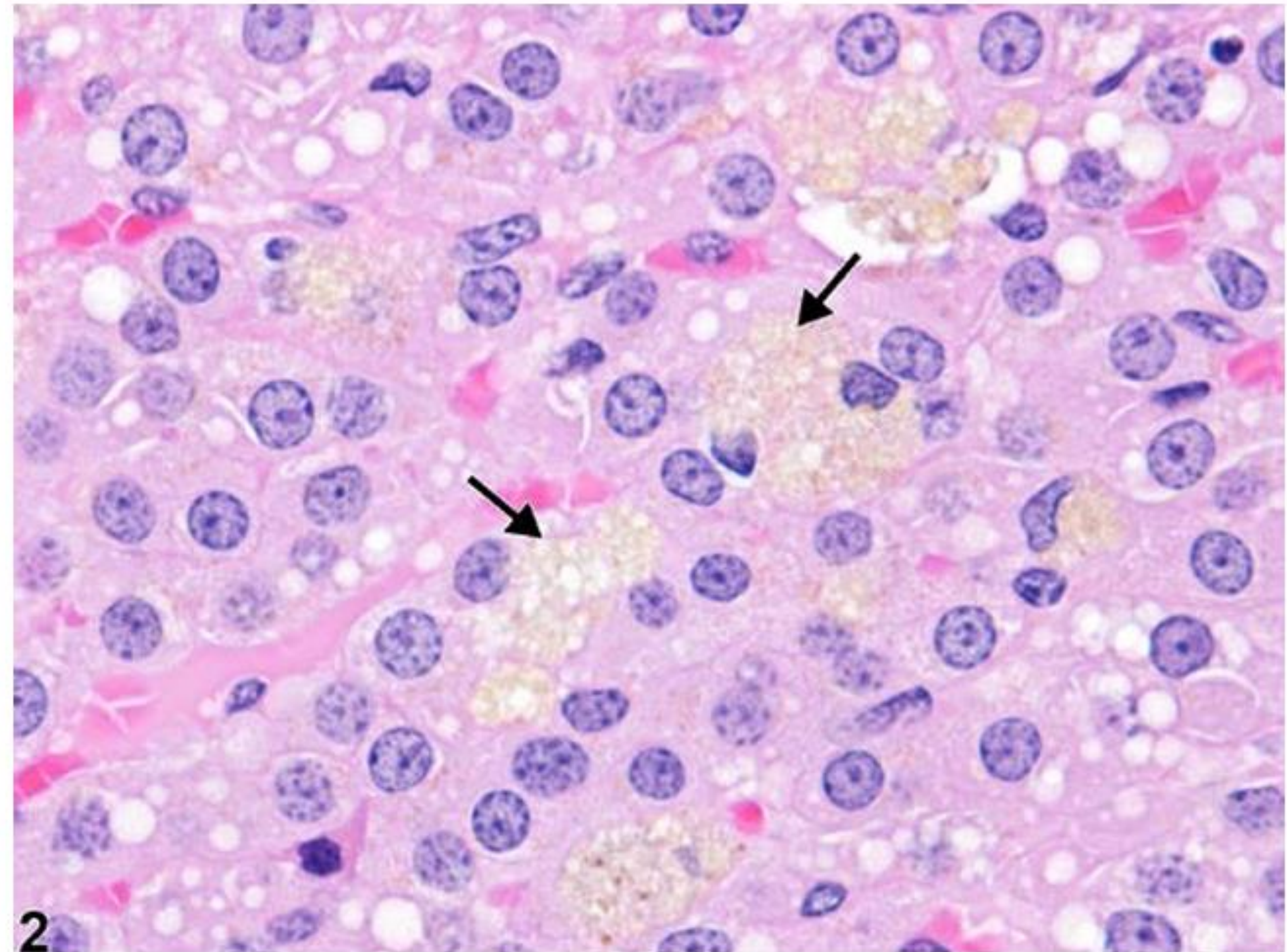
- ✓ Mitochondria = short and long tubular/vesicular cristae
- ✓ Lipofuscin granules
- ✓ ↑Lysosomes
- ✓ ↓ lipid droplets
- ✓ ↑ smooth endoplasmic reticulum and rough endoplasmic reticulum

Adrenal Gland: Histology, Anatomy, Physiology and Incidental Lesions Richard A. Peterson II, D.V.M., Ph.D.

Lipofuscin

- Lipofuscin is a pigmented, heterogenous byproduct of failed intracellular catabolism conventionally found within lysosomes or the cytosol of aging postmitotic cells

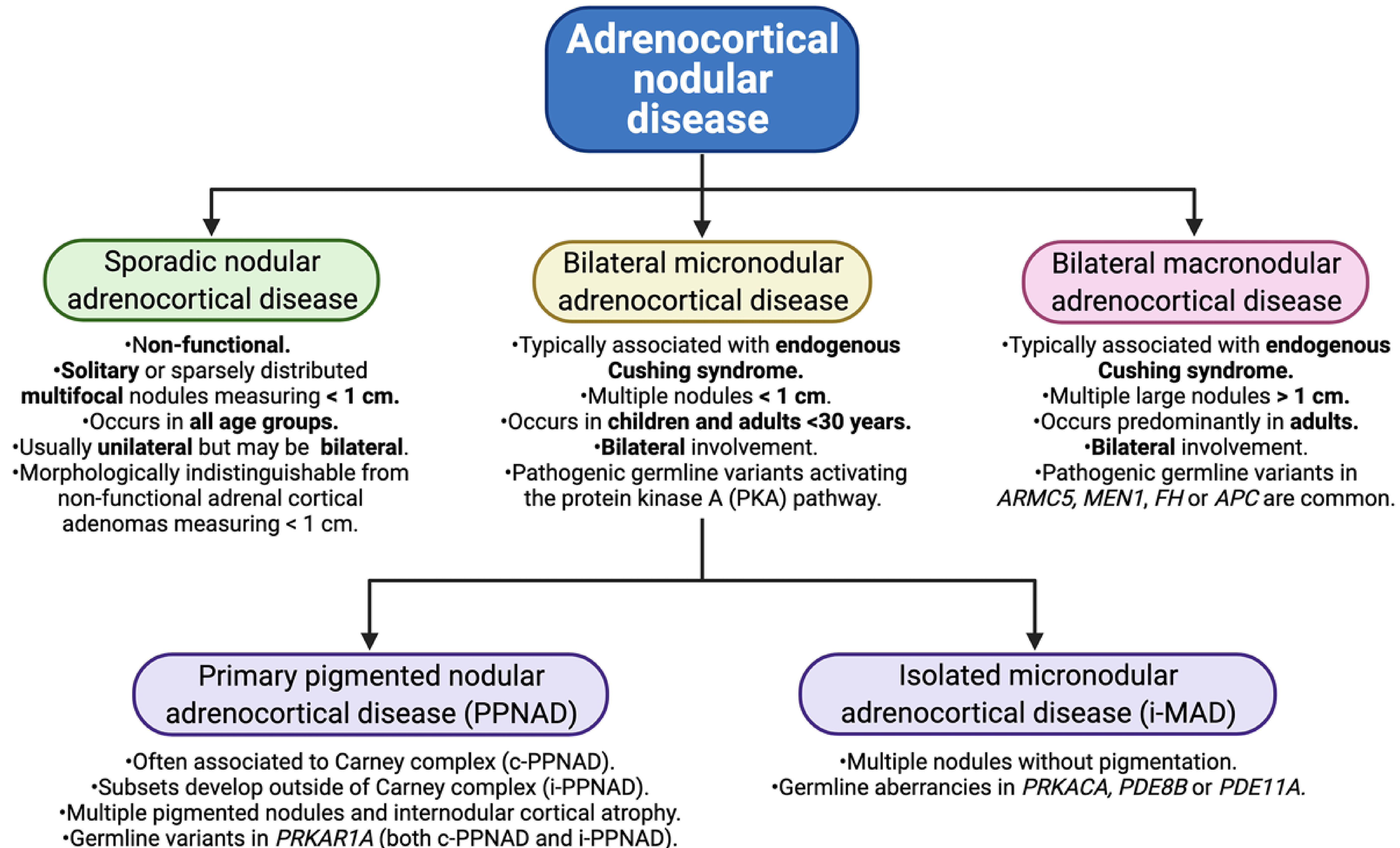




Mark J. Hoenerhoff, DVM, PhD, DACVP Associate Professor Veterinary Pathologist, In Vivo Animal Core Unit for Laboratory Animal Medicine University of Michigan

Histology, Lipofuscin, Alan N. Snyder; Jonathan S. Crane, 2023

Adrenocortical nodular disease



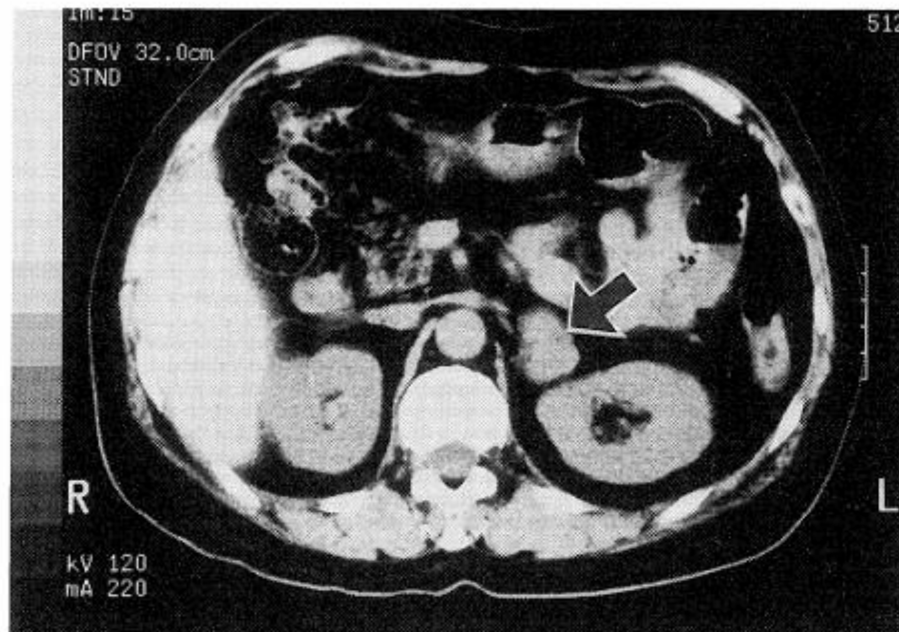
Endocrine Pathology (2022) 33:155–196

Cushing's Syndrome due to Unilateral Adrenocortical Hyperplasia

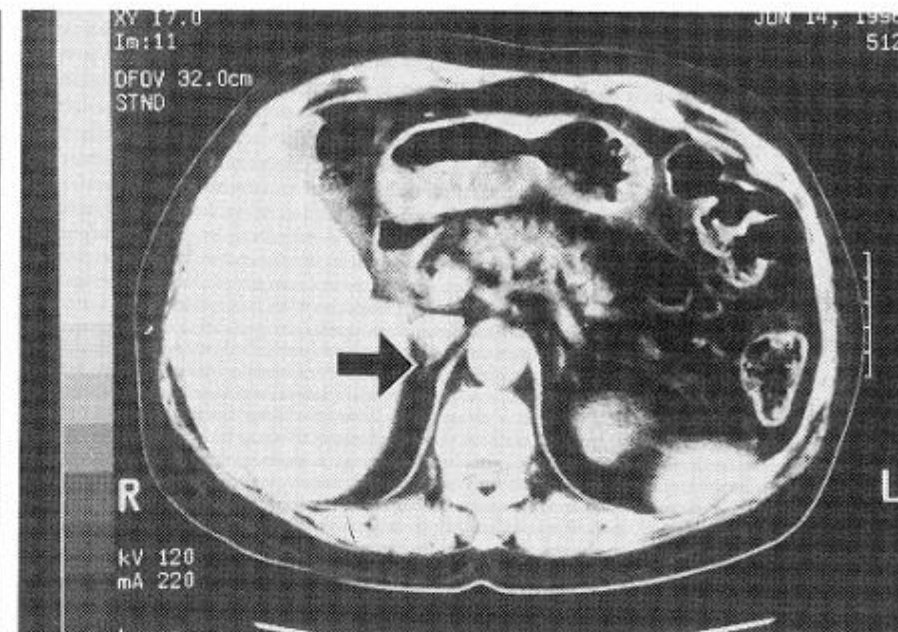
Fumio OTSUKA, Toshio OGURA*, Kazushi NAKAO, Nobuhiko HAYAKAWA, Yukari MIMURA, Takayoshi YAMAUCHI and Hirofumi MAKINO

Table 4. Dexamethasone Suppression Test

Day		0	1	2	3	4	5	6	7
Dexamethasone (*p.o.*)		–	–	2 mg	2 mg	8 mg	8 mg	–	–
Urinary 17-OHCS	(mg/day)	4.1	7.8	10.8	13.3	12.0	12.8	12.7	16.0
Urinary 17-KS	(mg/day)	2.9	4.0	3.7	3.7	2.7	2.6	3.2	4.7



A



B

The lack of ACTH elevation induced by CRH and the disappearance of circadian rhythm in serum cortisol disclosed the autonomous secretion of cortisol.

This phenomenon was also confirmed by the dexamethasone (2 or 8 mg/day) suppression test showing a paradoxical increase in urinary 17-OHCS excretion

Internal 385 Medicine Vol. 37, No. 4 (April 1998)

- The nodular hyperplasia in this case was distinguished from ACTH-independent macronodular hyperplasia tical (AIMAH) or primary pigmented nodular adrenocortical disease (PPNAD)
  - Markedly laterality of the adrenal gland in radiographic finding
- Only 5 cases well documented on Cushing' s syndrome due to ACTH-independent unilateral adrenal hyperplasia

Internal 385 Medicine Vol. 37, No. 4 (April 1998)

Black adrenal adenoma (BAA)

- ✓ Non functional neoplasms of unknown clinically significant
- ✓ Associated with different forms of hyperfunction of adrenal cortex such as subclinical or overt Cushing's syndrome and primary aldosteronism
- ✓ Most of the black adrenal adenomas, like in this case, cause ACTH-independent Cushing's syndrome, some cause primary hyperaldosteronism, and a few even result in masculinization

Non-functioning BAA is considered to be relatively high, with an incidence rate ranging from 10 to 37% at autopsy

Ann Nucl Med (2011) 25:812–817

Imaging on CT

- ✓ Poor in lipid (accumulates lipofuscin)
- ✓ Unenhanced CT cannot discriminate lipid-poor adenomas including BAAs from other tumors
- ✓ Short 5-min dynamic enhanced CT
  - PEW of 62.3% (C45%)
  - Relative PEW of 35.5% (C31%)
  - sensitivity and specificity 87 and 100%
- ✓ No significant signal intensity loss in MRI

Ann Nucl Med (2011) 25:812–817

TABLE 2. CT number of affected adrenal tissue and adjacent renal parenchyma in patients with Cushing's syndrome, Cushing's disease, and primary aldosteronism

Patient no.	CT number[a]		A – B
	Adenoma (A)	Kidney (B)	
Cushing's syndrome			
Type Y			
1	−1.2	36.9	−38.1
2	23.4	33.3	−9.9
3	18.4	34.2	−15.8
Mean ± SE	13.5 ± 7.5[b]	34.8 ± 1.1	−21.3 ± 8.6[c]
Type B			
6	37.4	35.8	1.6
7	29.4	32.2	−2.8
8	40.3	34.8	5.5
9	44.6	27.2	17.4
Mean ± SE	37.9 ± 3.2	32.5 ± 1.9	5.4 ± 4.3
Cushing's disease[d] (n = 3)			
Mean ± SE	28.9 ± 0.9	38.0 ± 1.5	−9.1 ± 0.6
Primary aldosteronism (n = 5)			
Mean ± SE	16.2 ± 3.3[e]	32.6 ± 2.1	−16.5 ± 3.1[e]

[a] EMI Hounsfield units (±1000).
[b] $P < 0.02$ *vs.* type B adenoma.
[c] $P < 0.025$ *vs.* type B adenoma.
[d] Left adrenal gland and kidney were examined.
[e] $P < 0.01$ *vs.* type B adenoma.

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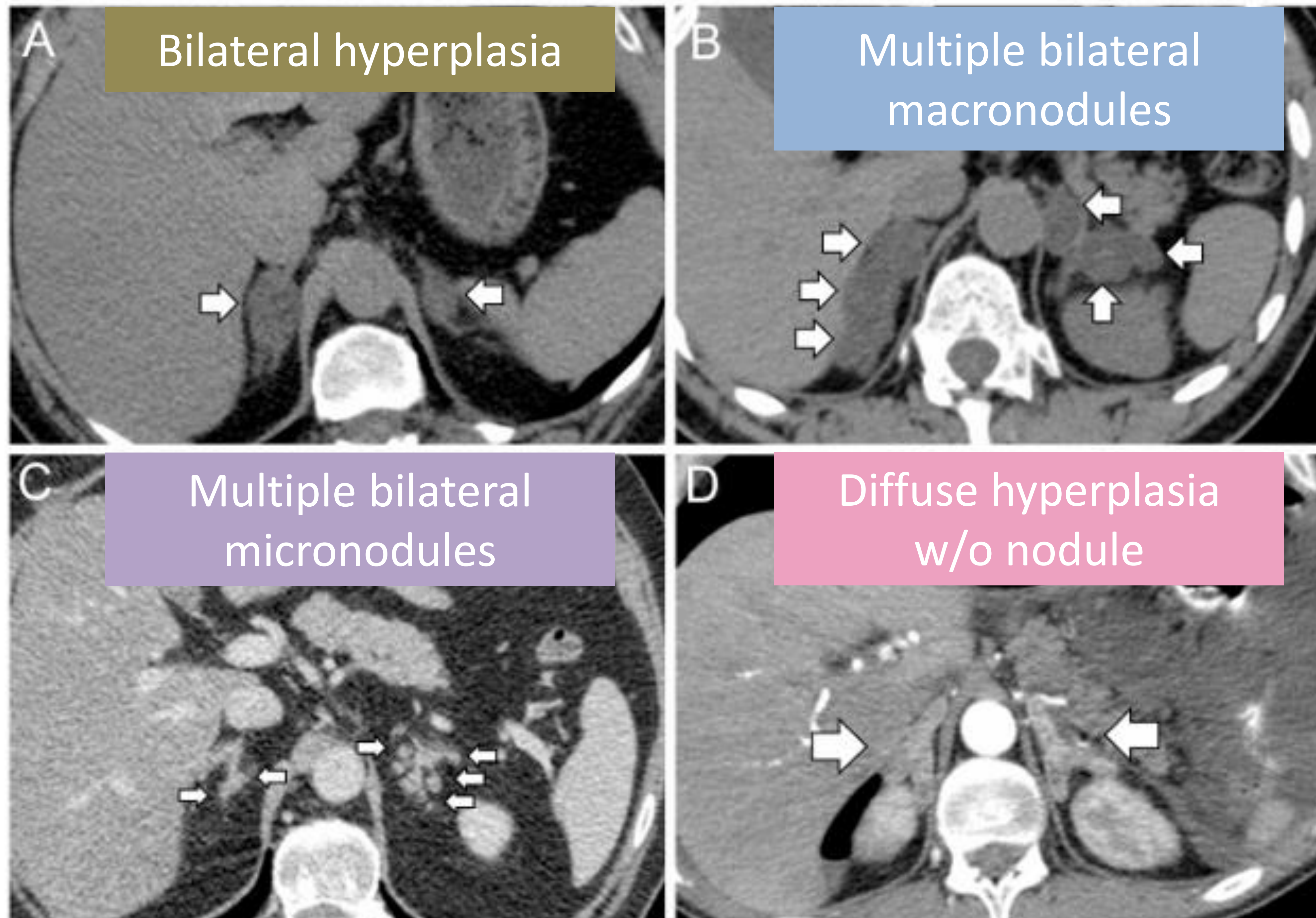
Hormonal assessment

- ✓Black adrenal adenoma is, we examined our pathology database between 1998 and 2014.
- ✓114 adrenal cortical tumors were found
  - ✓The average age of patients was 53 years (range 23-70)
  - ✓41 of the adenomas were aldosterone secreting
  - ✓23 cortisol-secreting
  - ✓1 androgen-secreting
  - ✓49 nonfunctional
- ✓The average adenoma size was 3.1 cm (range 0.2-27)

PBMAH

- The adrenal hyperplasia is slowly progressing
- Typically, hypercortisolism follows an insidious course and both tumor growth and cortisol excess progress gradually hampering the diagnosis in most cases by several years or decades



Endocrine-Related Cancer (2019) 26, R567–R581

Variations ranging from diffuse hyperplasia without clearly visible nodule, unique mass on each adrenal gland, to massively enlarged adrenals

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PBMAH

- No specific recommendation for imaging follow-up
- The European Endocrine Society recommends an individual follow-up of each adrenal incidentaloma bigger than 4 cm or spontaneous density above 10 UH (these two features being often observed in PBMAH), with subsequential imaging at 6 months

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Evolution of cortisol overtime

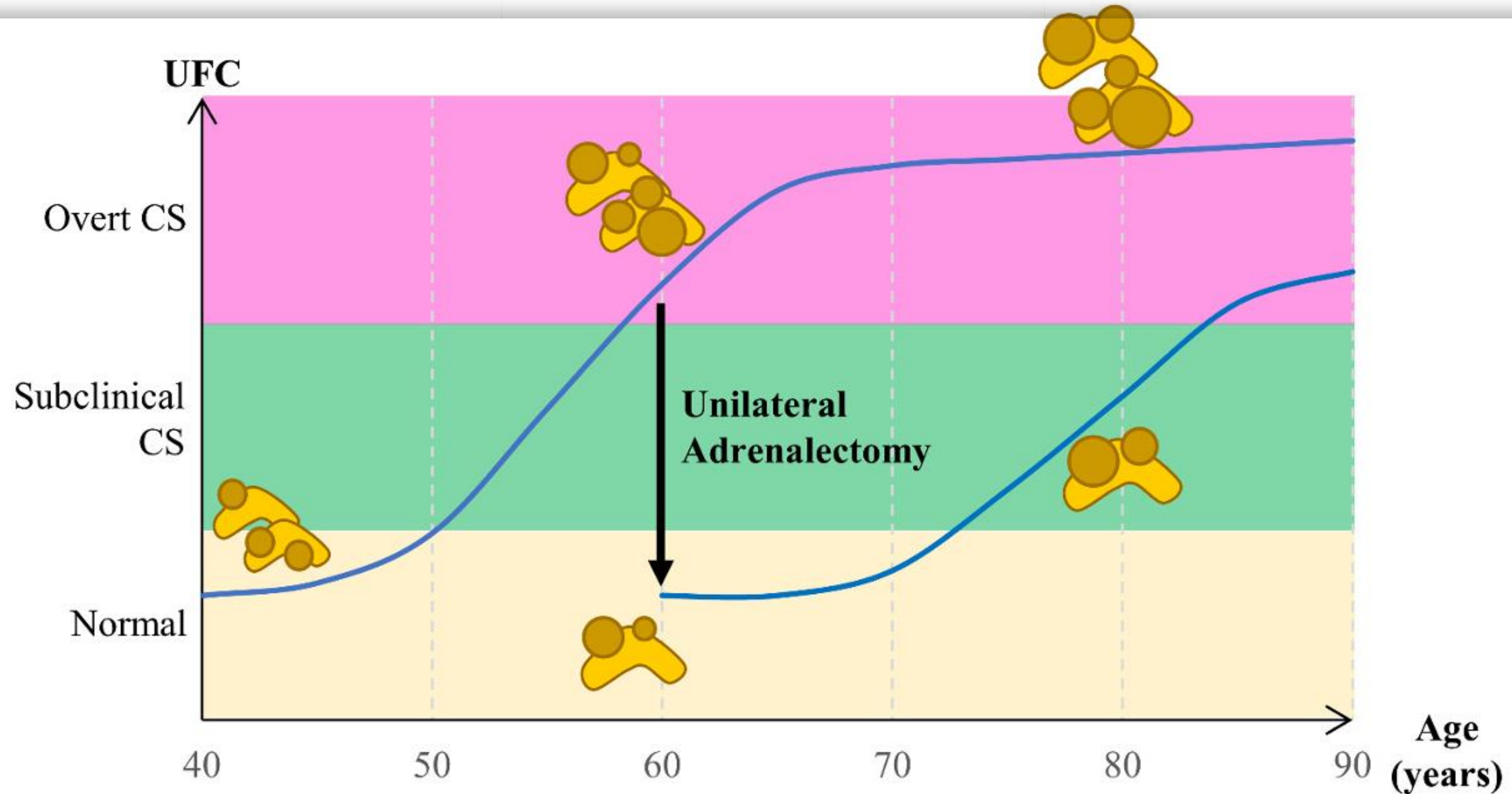

Figure 2. Evolution of cortisol secretion in bilateral adrenal hyperplasia over time and impact of unilateral adrenalectomy.

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	Adrenal CS adenoma	PPNAD	PBMAH	Black adenoma	This patient
Unilateral or Bilateral	Unilateral	Bilateral	Bilateral	Unilateral	Unilateral
Cause	Adrenal adenoma	Genetic mutation (commonly PRKAR1A)	Sporadic Germline mutation	Benign adrenal tumor that secretes cortisol	?
Clinical	CS	Childhood CS patients	CS Subclinical CS	May be asymptomatic or cause mild Cushing's symptoms	Mild CS
Imaging	Typically show adrenal masses Lipid rich adenoma	Underestimate the presence of bilateral adrenal gland involvement Small nodules	massively enlarged adrenals with multiple macronodules distorting the normal adrenal configuration	Unilateral adrenal mass Lipid poor adenoma	Unilateral adrenal mass with lipid poor adenoma
Histology Pathology	Cortical hyperplasia adenoma	Multiple adrenocortical nodules Cytoplasmic pigmentation Internodular cortical atrophy Lipofuscin	nodules are round or oval and occupy most of the adrenal cortex	Lipofuscin	Multiple adrenocortical nodules No cortical atrophy
Biochemical	CS	Paradoxical response of cortisol to DST	CS	Paradoxical response with DST	CS
Treatment	Unilateral adrenalectomy	Bilateral adrenalectomy	Adrenalectomy (larger)	Unilateral adrenalectomy	Adrenalectomy

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Thank you