In The Name of God

Case Presentation

Dr.Khadijeh Tabatabaei Lotfi

11 December 2023

Patient ID:

- Gender: Man
- Age: 56-year-old
- Source of History: Patient's Wife, Reliable
- Married
- Born & Live in Ardebil
- Job: Worker

Chief complaint:

- Leg edema and abdominal obesity & muscle weakness

Present illness:

- A 56 year old man with problems starting 1.5 to 2 months ago with Leg edema and abdominal obesity & progressive muscle weakness
- Inability to go up stairs

Present illness:

- The onset of hypertension and diabetes in the last 1.5 to 2 months
- White sores (oral thrush) at the beginning of the patient's problems in the last 1.5 to 2 months

Present illness:

- The patient was admitted to the heart department for further investigation due to blood pressure and edema
- During hospitalization, due to high blood pressure and hypokalemia, which was discovered in the hospital, the patient was referred to the endocrinology service and was admitted to Imam Ardebil Hospital from Aban 22nd to Azar 2nd.

PI:

1402/08/18

Immunoassays-Endocrinology

Test		Result	Unit	Refrence Range
ACTH	↑	124.3	pg/ml	7.2 - 63.6
Aldosteron (Supine)		18.20	ng/dL	4 - 31
Renin(Supine)	↓	3.20	uIU/ml	4.2 - 59.7

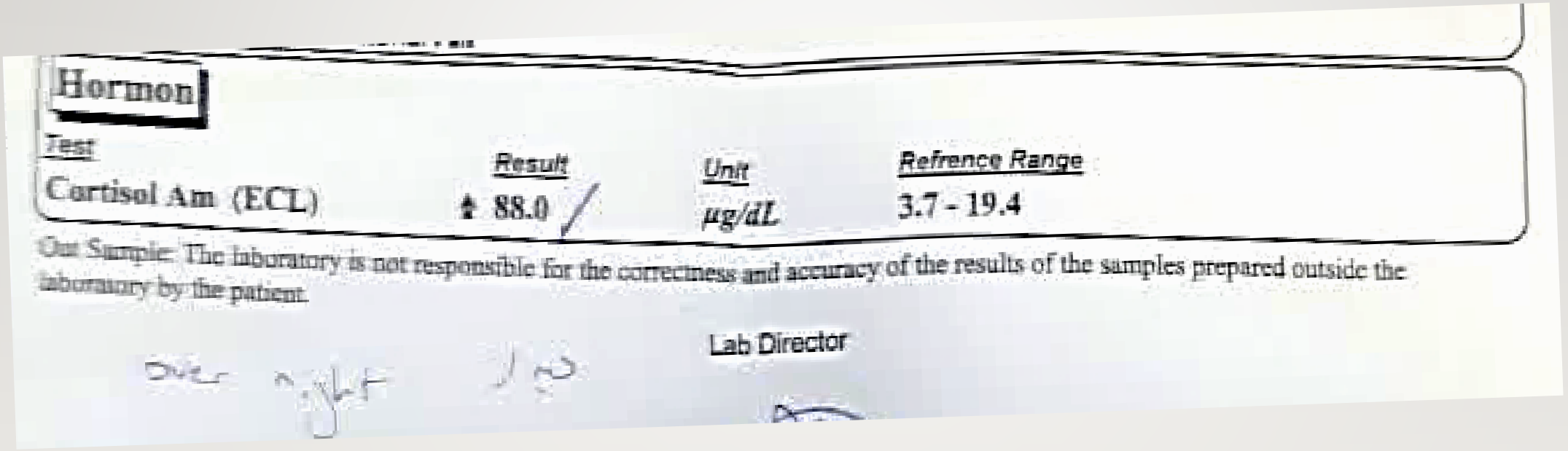
Normal ranges are according to the patients sex and age.

Hormon

Test		Result	Unit	Refrence Range
Cortisol Am (ECL)	↑	>60	µg/dL	6.2 - 19.4

PI:

1402/08/25



Hormon

Test	Result	Unit	Refrence Range
Cortisol Am (ECL)	↑ 88.0	µg/dL	3.7 - 19.4

Out Sample: The laboratory is not responsible for the correctness and accuracy of the results of the samples prepared outside the laboratory by the patient.

Lab Director

PI:

1402/08/29

Urine Biochemistry

Test	Result	Unit	Refrence Range
Urine Volume (24 hrs)	▲ 3200	ml/24hrs	800 - 1800
Cortisol (24 hrs urine)	▲ >1000	ug/24 hrs	4.3 - 176

Normal ranges are according to the patients sex and age.

Hormon

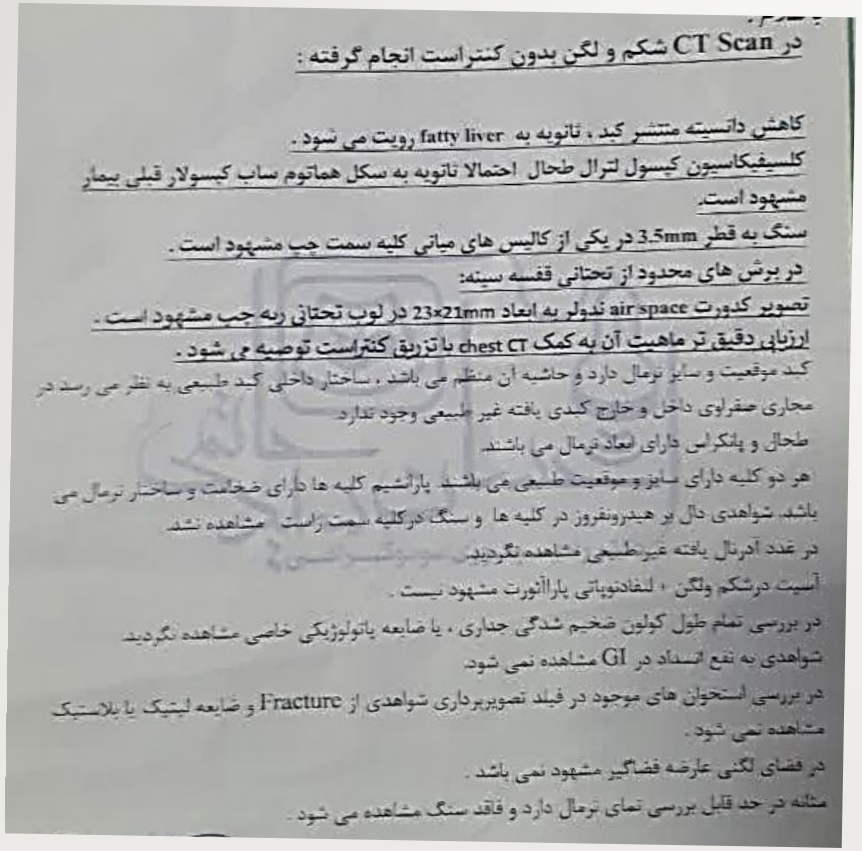
Test	Result	Unit	Refrence Range
Cortisol Am (ECL)	▲ 98.0	µg/dL	3.7 - 19.4

PI:
High-dose dexamethasone suppression tests

- Urine volume = 3200 ml/24h (800-1800)
- UFC > 1000 µg/dl (4.3-176)
- Cortisol 8 AM = 94 µg/dl

PI:

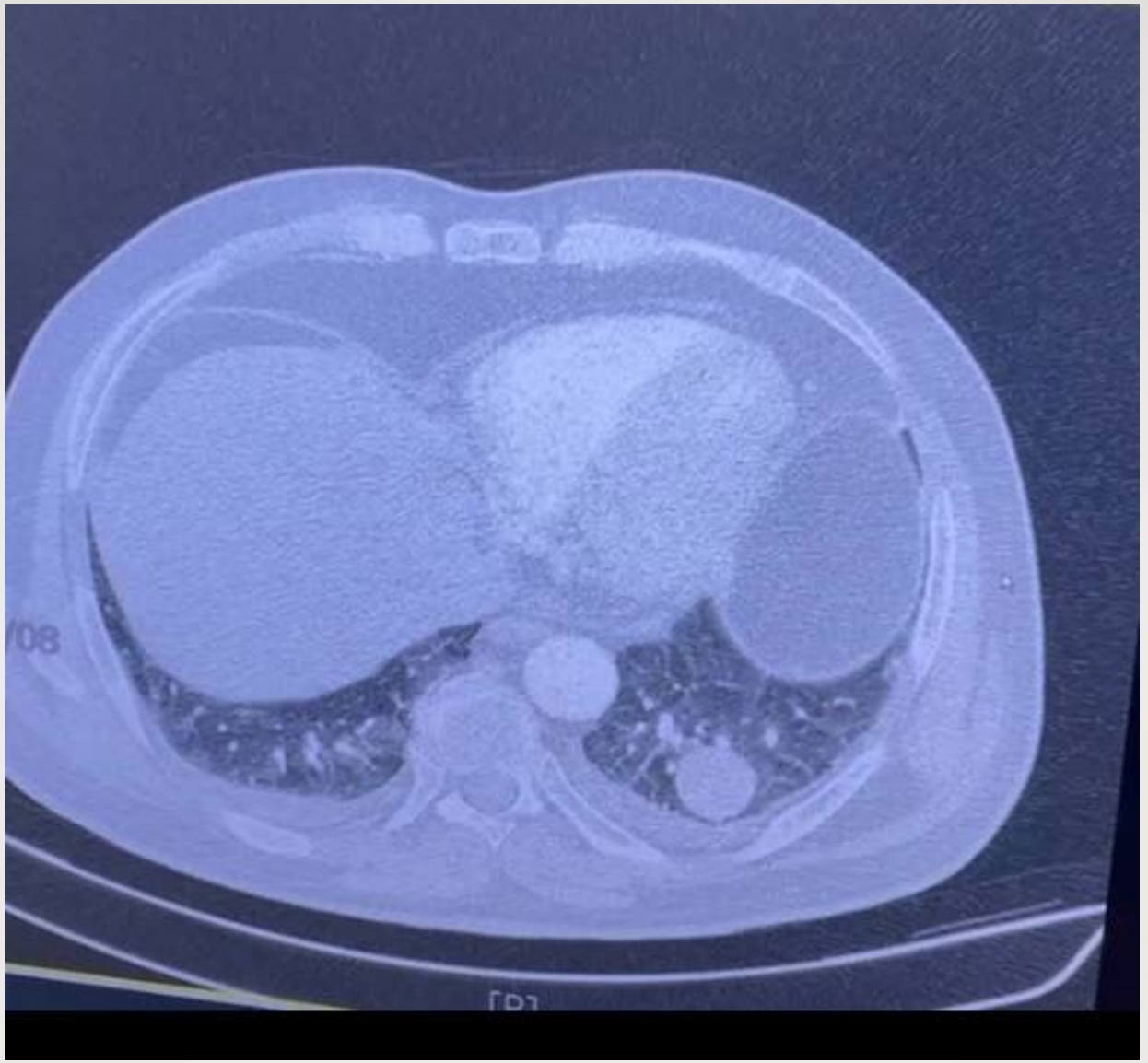
Abdomino pelvic CT Scan without Contrast 1402/08/14



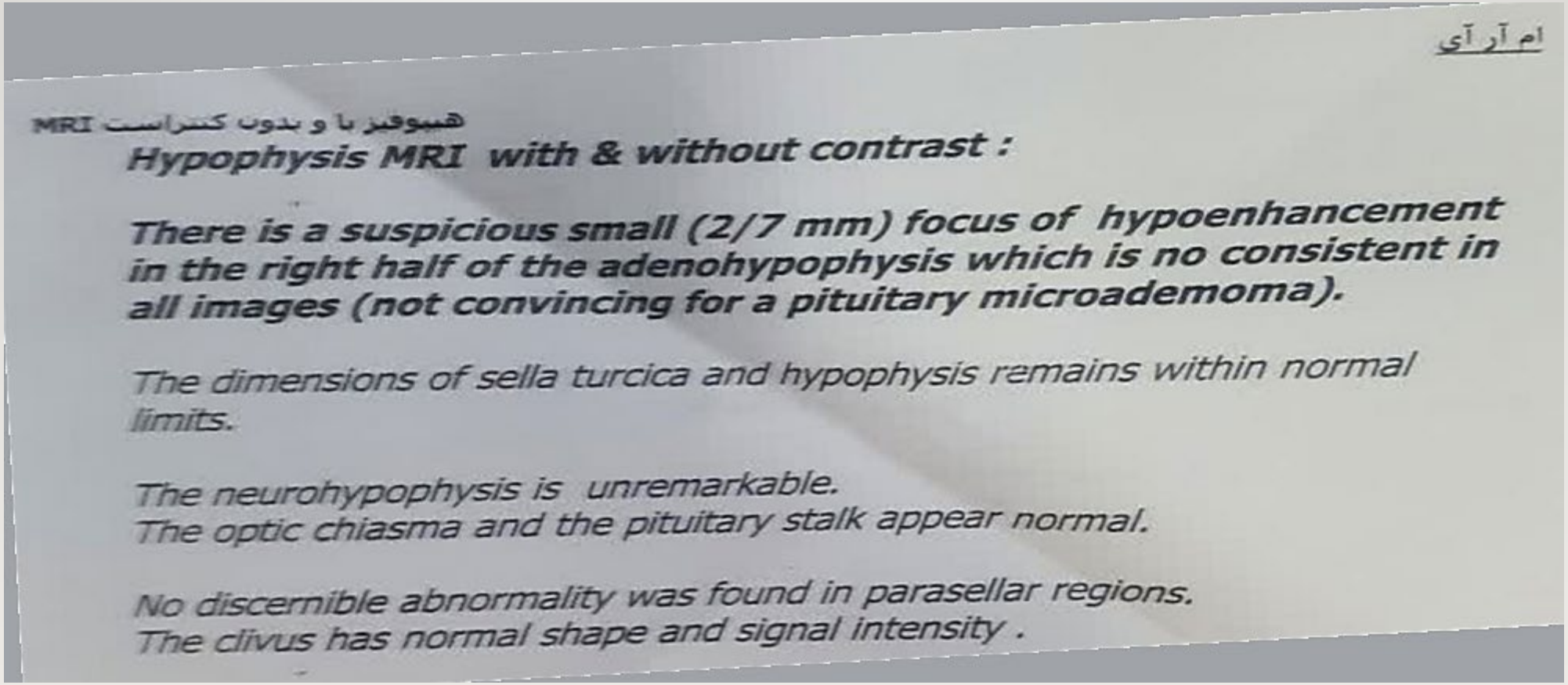
در CT Scan شکم و لگن بدون کنتراست انجام گرفته :

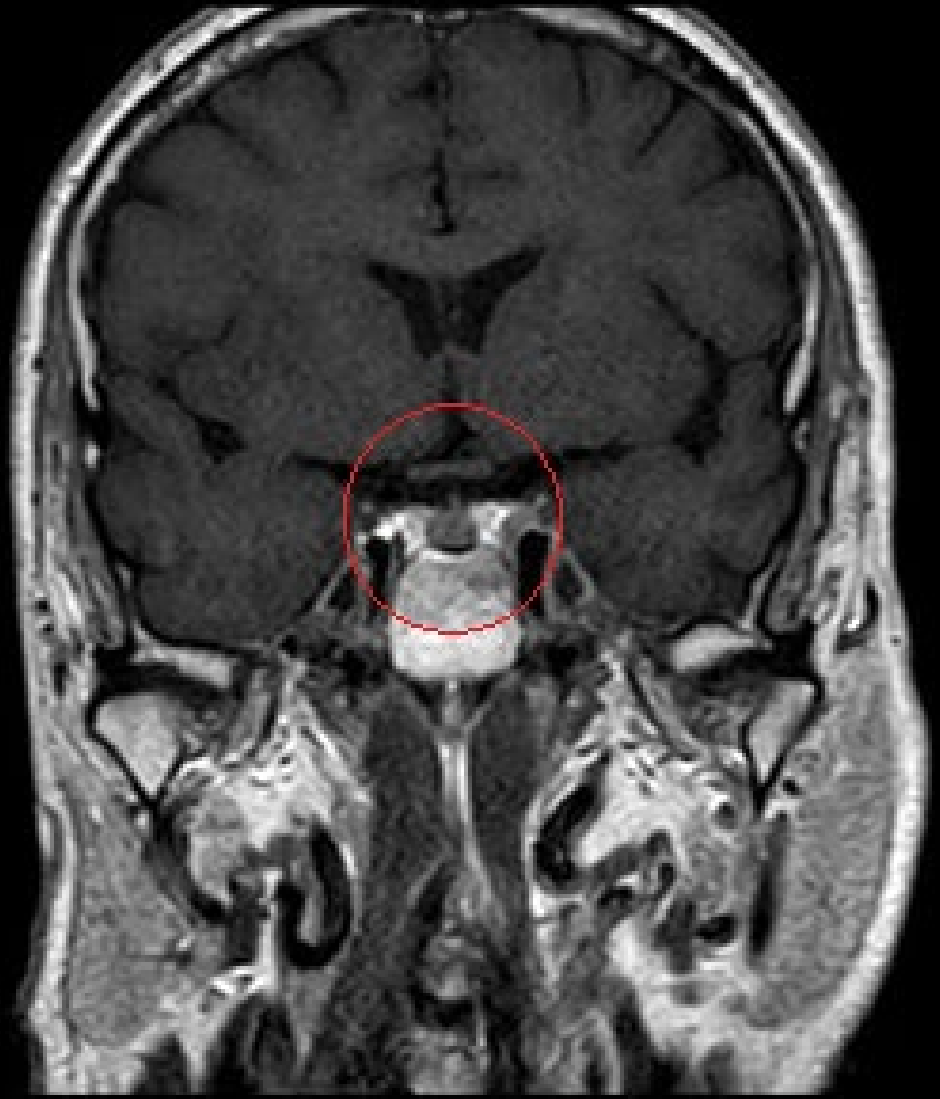
کاهش دانسیته منتشر کبد ، تانویه به fatty liver رویت می شود .
کلسیفیکاسیون کپسول لترال طحال احتمالا تانویه به سکل هماتوم ساب کپسولار قبلی بیمار مشهود است.
سنگ به قطر 3.5mm در یکی از کالیس های میانی کلیه سمت چپ مشهود است .
در برش های محدود از تحتانی قفسه سینه:
تصویر کدورت air space ندولر به ابعاد 23x21mm در لوب تحتانی ریه چپ مشهود است .
ارزیابی دقیق تر ماهیت آن به کمک chest CT با تزریق کنتراست توصیه می شود .
کبد موقعیت و سایز نرمال دارد و حاشیه آن منظم می باشد ، ساختار داخلی کبد طبیعی به نظر می رسد در مجاری صفراوی داخل و خارج کبدی یافته غیر طبیعی وجود ندارد
طحال و پانکراس دارای ابعاد نرمال می باشند.
هر دو کلیه دارای سایز و موقعیت طبیعی می باشند پارانشیم کلیه ها دارای ضخامت و ساختار نرمال می باشد. شواهدی دال بر هیدرونفروز در کلیه ها و سنگ درکلیه سمت راست مشاهده نشد.
در غدد آدرنال یافته غیرطبیعی مشاهده نگردید.
آسیت درشکم ولگن ، لنفادنوپاتی پاراآئورت مشهود نیست .
در بررسی تمام طول کولون ضخیم شدگی جداری ، یا ضایعه پاتولوژیکی خاصی مشاهده نگردید.
شواهدی به نفع انسداد در GI مشاهده نمی شود.
در بررسی استخوان های موجود در فیلد تصویربرداری شواهدی از Fracture و ضایعه لیتیک یا بلاستیک مشاهده نمی شود .
در فضای لگنی عارضه فضاگیر مشهود نمی باشد .
مثانه در حد قابل بررسی نمای نرمال دارد و فاقد سنگ مشاهده می شود .

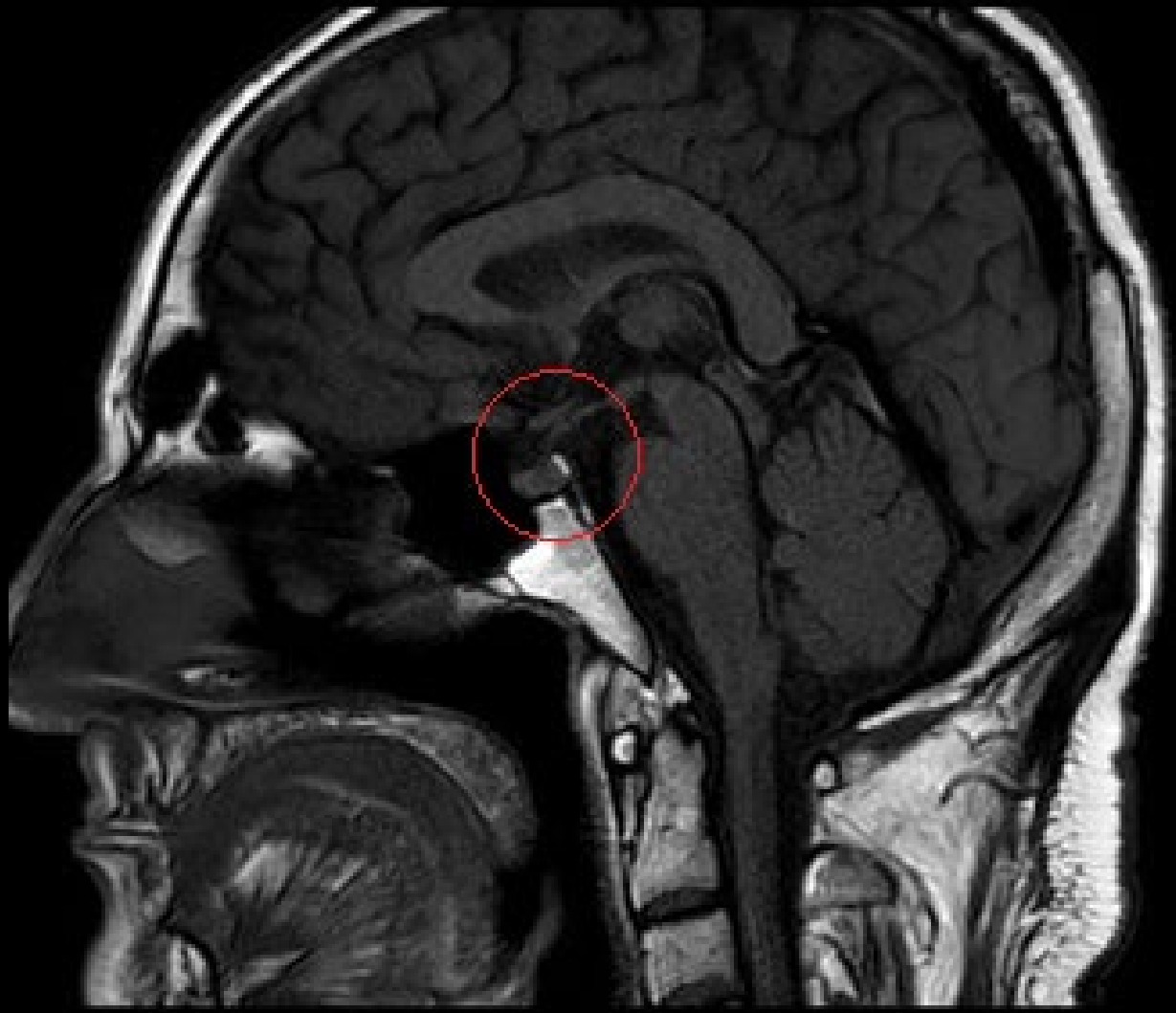
تصویر کدورت air space ندولر به ابعاد 23x21mm در لوب تحتانی ریه چپ



Hypophysis MRI with & without Contrast
1402/09/01







PI:

- The patient was referred to Taleghani hospital on Azar 4th.
- The patient had a potassium level of 1.9 mEq/L at the beginning of hospitalization in this center, and after correcting potassium and controlling blood sugar and blood pressure, an Octreotide scan was performed.

PI: 1402/09/04

Testnde	Result	
W.B.C	13,100	/micL
Poly	85%	
Lymph	10%	
Mono	3%	
Eos	2%	
Hemoglobin	14	g/dl
PLT	89,000	/micL
Urea	43	mg/dl
Cr	1	mg/dl
ESR	4	mm/hr
CRP	8.7	Index
TSH	0.2	micIU/ml

Test	Result	
Na	129	m.mol/L
K	1.9	m.mol/L
SGOT	63	u/I
SGPT	98	u/I
Alb	3.3	g/dl
Mg	1.8	mg/dl
Ca	8	mg/dl
P	1.6	mg/dl
Ptt	20	
INR	0.84	
Uric Acid	2.3	mg/dl
Free PSA	0.2	

PI:

VBG

Test / Result	1	2	3	4
PH	7.59	7.60	7.56	7.59
H_3O_3	44	48	28.5	35
P_{CO_2}	45.9	49	32.5	37

PI:

1402/09/05

WHOLE BODY SCAN AND SPECT BY 99mTc - HYNIC- OCTREOTIDE

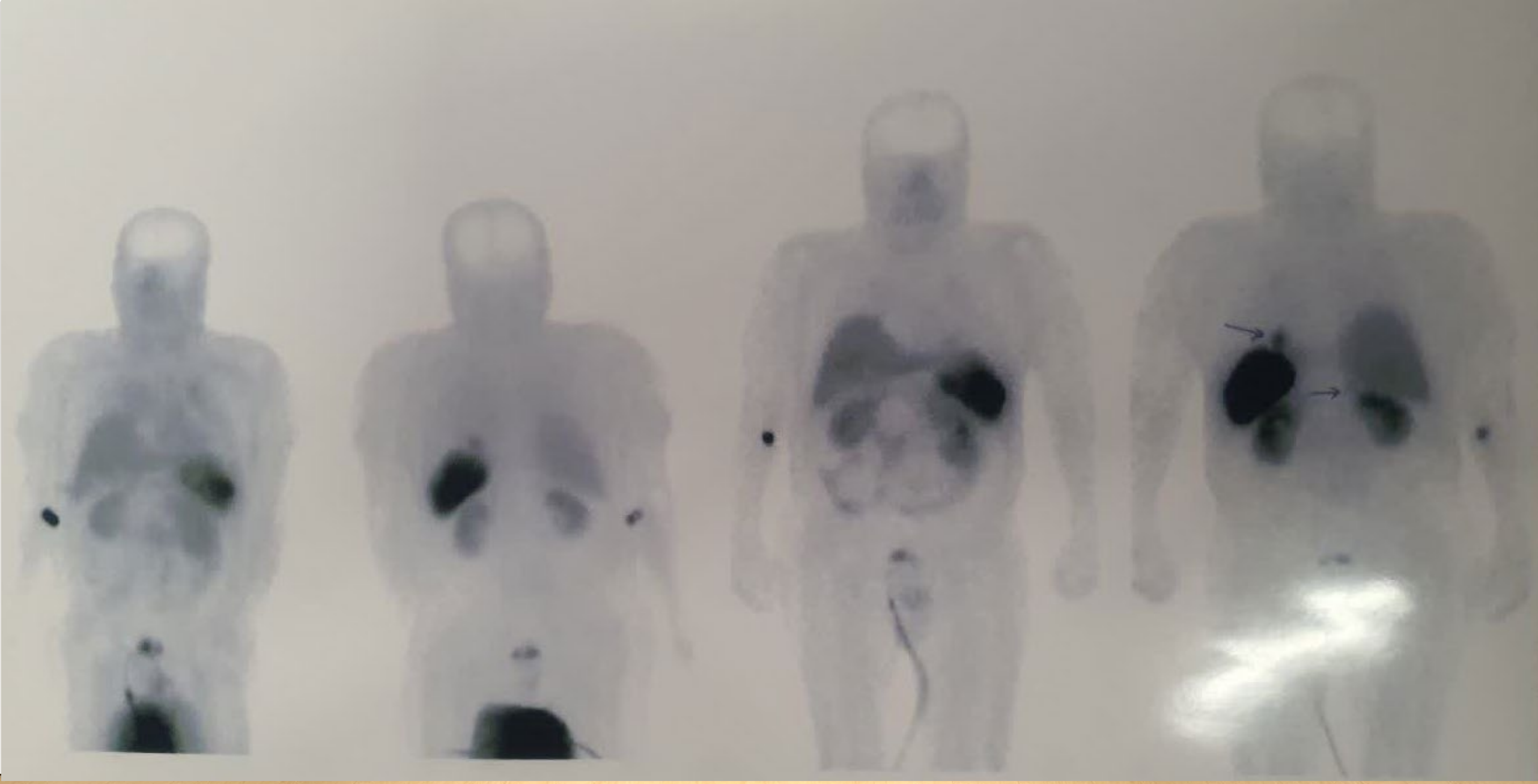
0.5 and 2 hours after IV injection of 99mTc - HYNIC TOC, scanning was performed in anterior and posterior projections.

Whole body planar scan and SPECT from abdomen and pelvis show an abnormal round collection of radioactivity **at the posterior aspect of the base of left lung above the spleen as well as above the right kidney at the region of right adrenal gland.**

The remainder of the body is unremarkable.

IMPRESSION:

- **Scan is positive for octreotide-avid tumoral lesion at the posterior aspect of the base of left lung above the spleen.**
- **Mild uptake above the right kidney at the region of right adrenal gland can be due to hyperplastic adrenal gland or normal variation.**
- Correlation with CT scan is recommended.

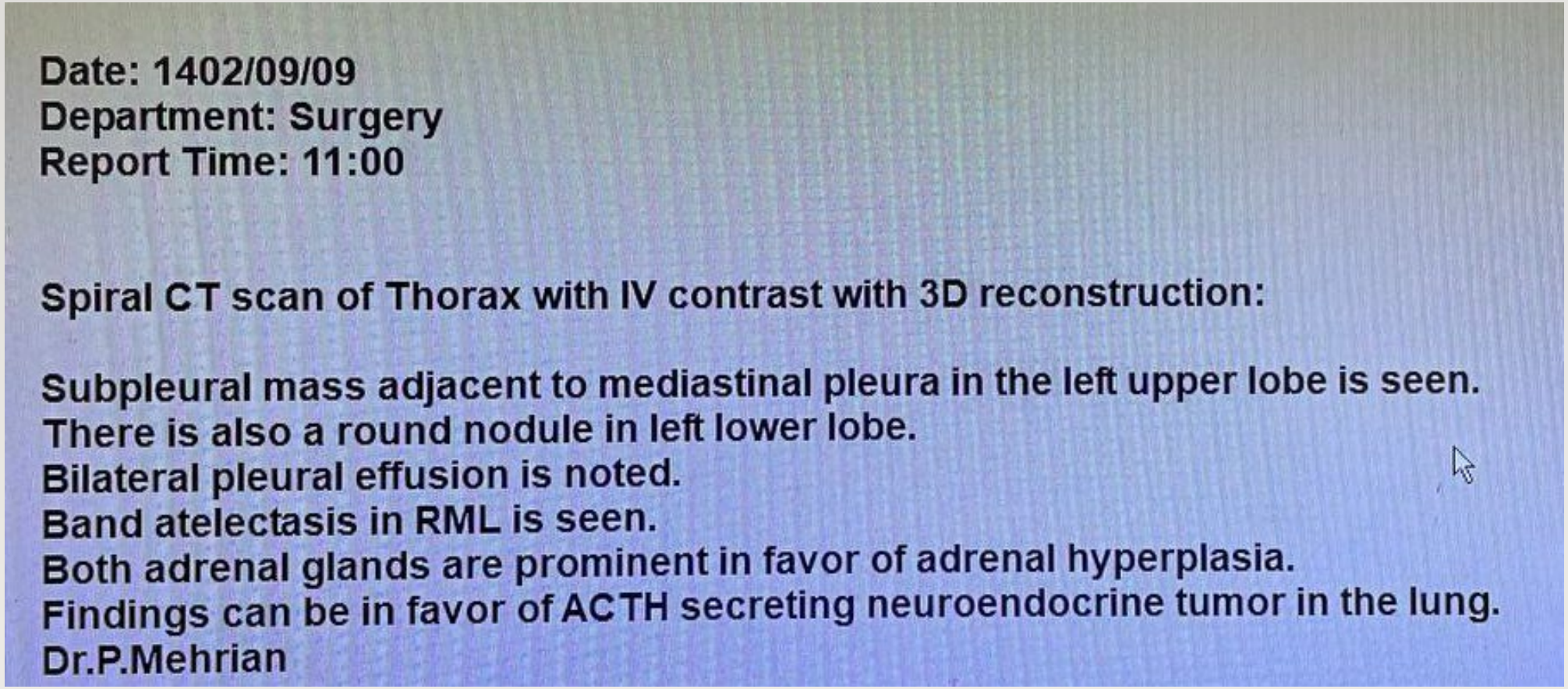


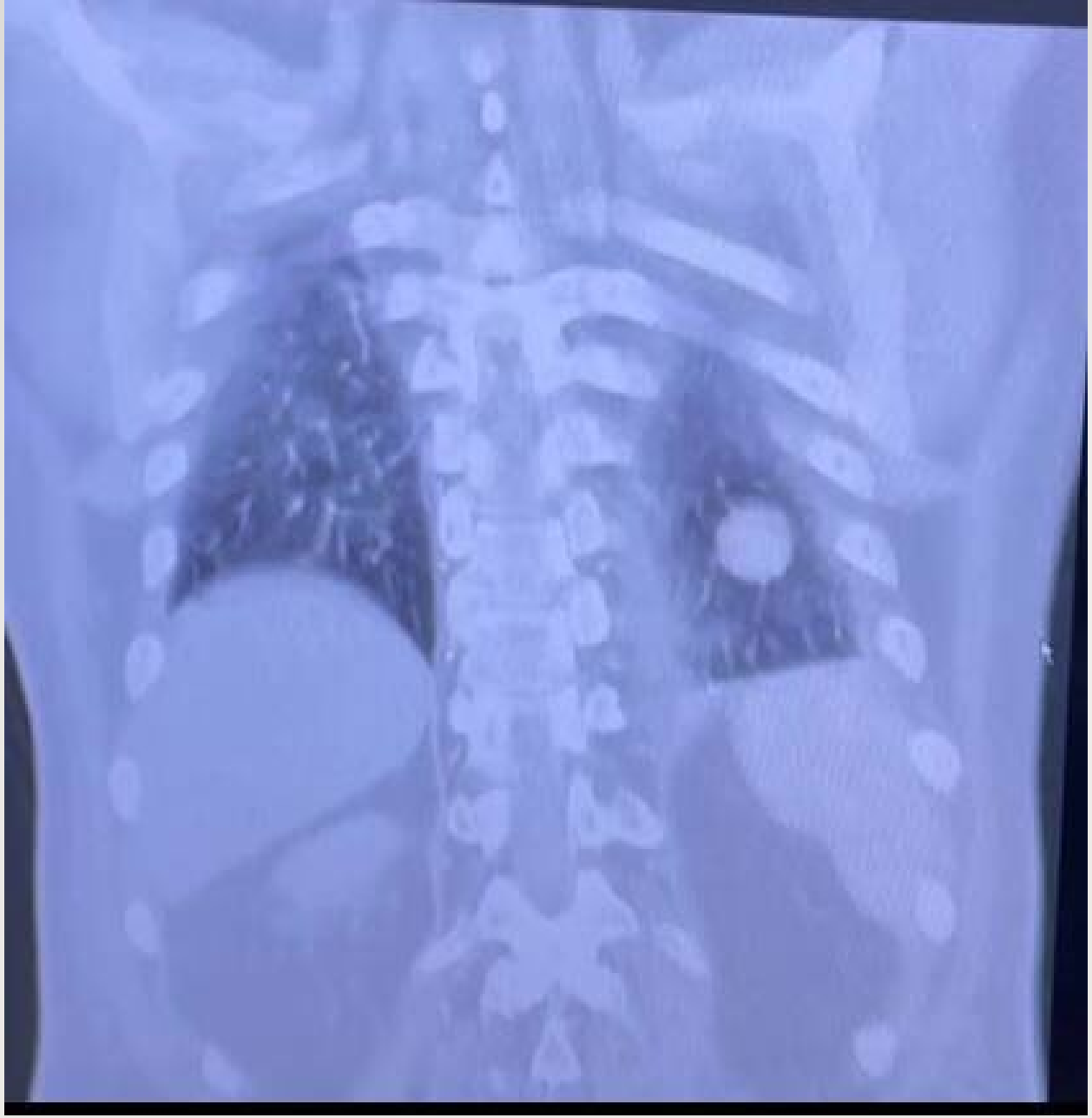
PI:

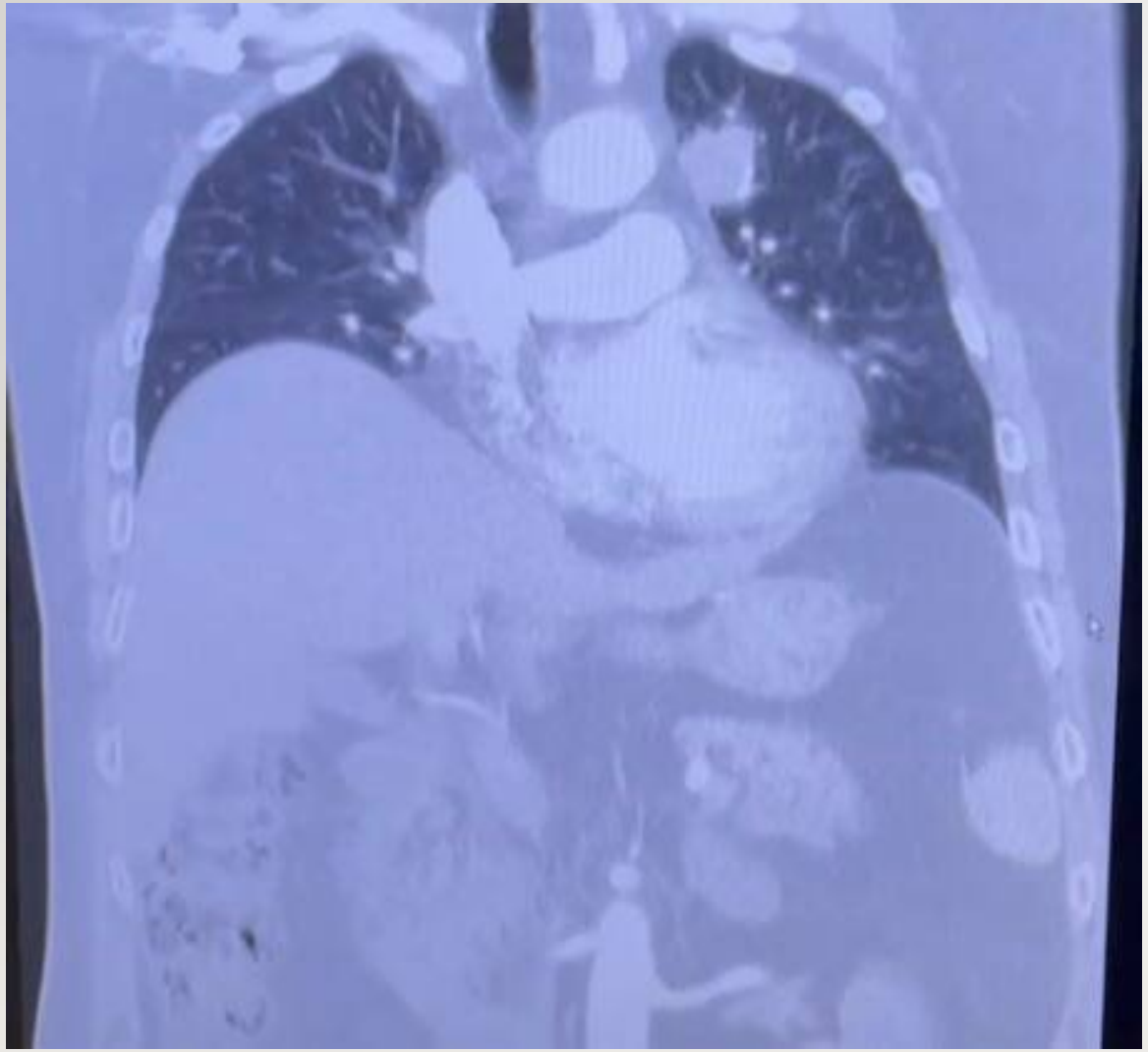
- The patient was sent to Masih Deneshvari Hospital on Azar 7th and underwent surgery on Azar 9th after a CT scan of the lungs with contrast.

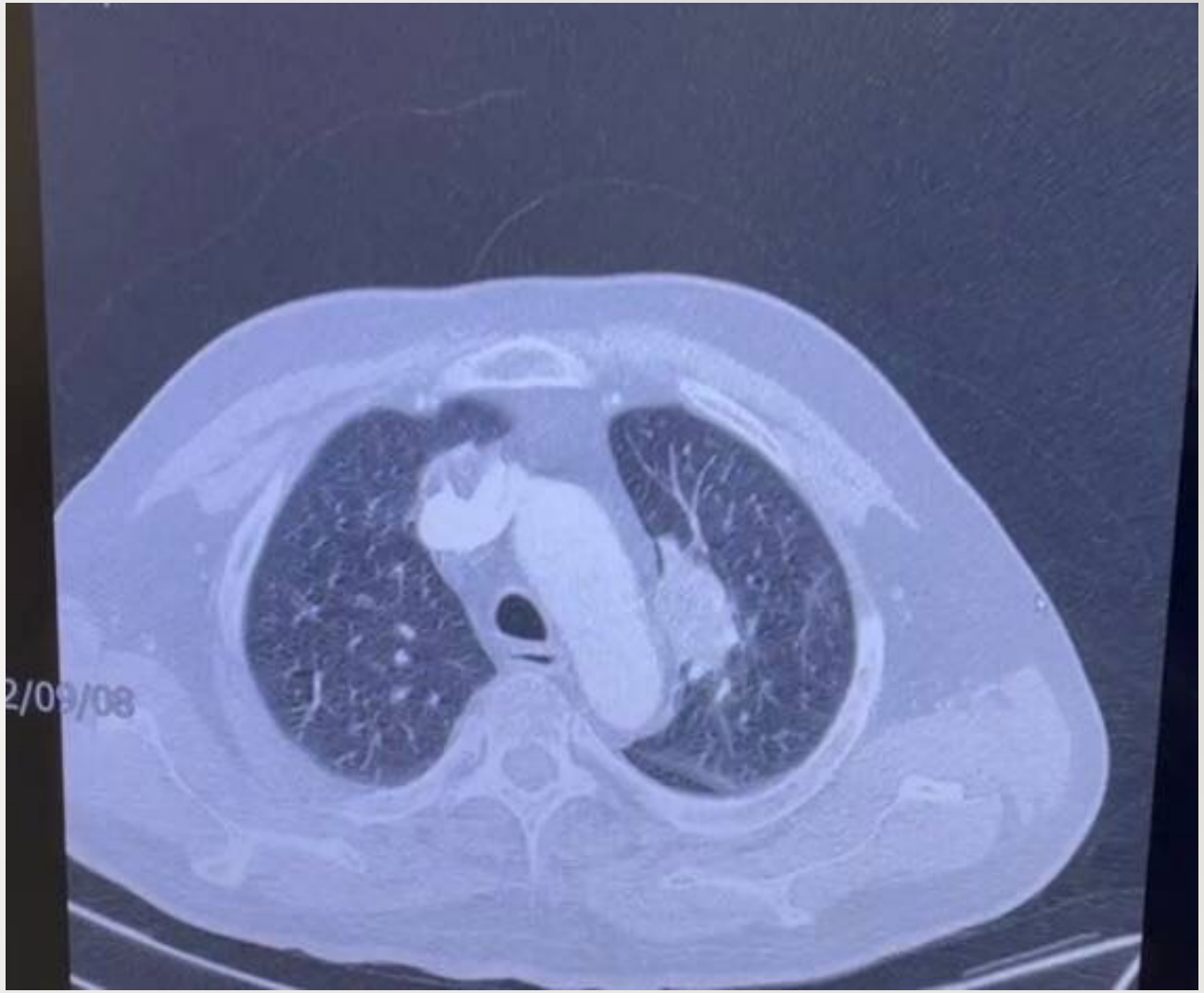
PI:

Spiral CT Scan of thorax with IV Contrast
Masih Danshvari









PI:

Description of surgery
1402/09/09 -Masih Danshvari

بیمار بدنبال اکتوپیک ACTH و توده LUL و توده LUL و پتاسیم ۲.۵ پتاسیم و DM , HTN نوکاردو و پلاکت ۵۰ هزار به طور اورژانسی جهت جراحی رزکسیون توده ریه به نظر سبب ترشح اکتوپیک ACTH به OR منتقل شد.

تشخیص بعد از عمل : چسبندگی ریه به مدیاستن و APEX در محل توده LUL سگمان اپیکو پوستریور و مجاور ناف LUL .توده کپسول دار
Post - OP Diagnosis: عمق پارانشیم LUL.بیمار تحمل One lay نداشت سرعمل افت sat مداوم می داد

نوع عمل جراحی : توراکوتومی پوستروالترال چپ فضای ۵ام. سگمنتکتومی اپیکو پوستر پلور LUL حاوی توده LUL/. انوکلئاسیون توده LLL . رزکشن گوه ای پارانشیم مجاور توده LUL که انوکلئه شد. رزکسیون دنده ۴ ام پارشیل اکستراپلورال . دایسکشن لنف نود مدیاستن و ارسال جایگاه ۹و۸و۱۱ .برونکوسکوپی عمل مستقل
Kind of Operation:

پس از بیهوشی جنرال برونکو شد که پاتولوژی واضح اندوتراکنال و اندو برونشیال نداشت. دابل لومن تعبیه شد توسط بیهوشی بیمار در

پوزیشن لترال دکوبیتوس راست داده شد توراکوتومی پوسترولترال چپ فضای ۵ام انجام شد. قسمت خلفی دنده ٤ام اکستراپلورال برداشته

Specimen: Yes ☐ NO ☐ نمونه برداشته شده: بلی ☐ خیر ☐ تعداد

شد. بیمار اصلا تحمل one lay نداشت افت sat داشت و مجبور شدیم لنفادپاتی یا ریه را با لانگ گاز بخوابانیم یا لنفادپاتی دو ریه کرده و

سپس برای دقایقی one lay کرده ریه را جراحی کنیم توده LUL در عمل پارانشیم بود در صورتی که می خواستیم رزکسیون گوه ای کنیم

شرح عمل و مشاهدات / Procedure and Findings: قسمت بادی از لوب تحتانی از ابتدا توده کپسول دار LUL انوکلئه شد. و سپس پارانشیم مجاور آن رزکسیون گوه ای شد با کارتریج

اندو gIA بنفش با توجه به این شرایط که بیمار دو توده یکی در LUL و یکی در LLL داشت و تحمل رزکسیون لوبکتومی یا پنومونکتومی

نداشت تصمیم گرفتیم توده ناف LUL که از سگمان اپیکال منشا گرفته بود را هم سگمنتکتومی کنیم که چسبندگی شدید ریه به APEX و

مدیاستن و فرنیک داشت که آزاد شد. دو شریان سگمان اپیکو پوستریول پلور و ورید آن جداگانه با سیلک دوصفر کات شد. سپس

سگمنتکتومی با سه عدد کارتریج بنفش GIA اندو شد دایسکشن لنف نود مدیاستن شد. جایگاه ۱۱ و۸ و۹ جهت پاتولوژی ارسال شد. بیمار

شمارش گازها و لوازم قبل از عمل و بعد از آن منطبق می باشد؟

پس از کارتریج ... پیدا کرد که ورید ... خونریزی دریافت کرد که اصلاح شد. شست و شو شد. هموستاز

شد. با شمارش گاز و وسیله LOng gaz دو لوله سینه تعبیه شد. لازم به ذکر است که نه از توده LUL و نه از توده LLL پاتولوژی

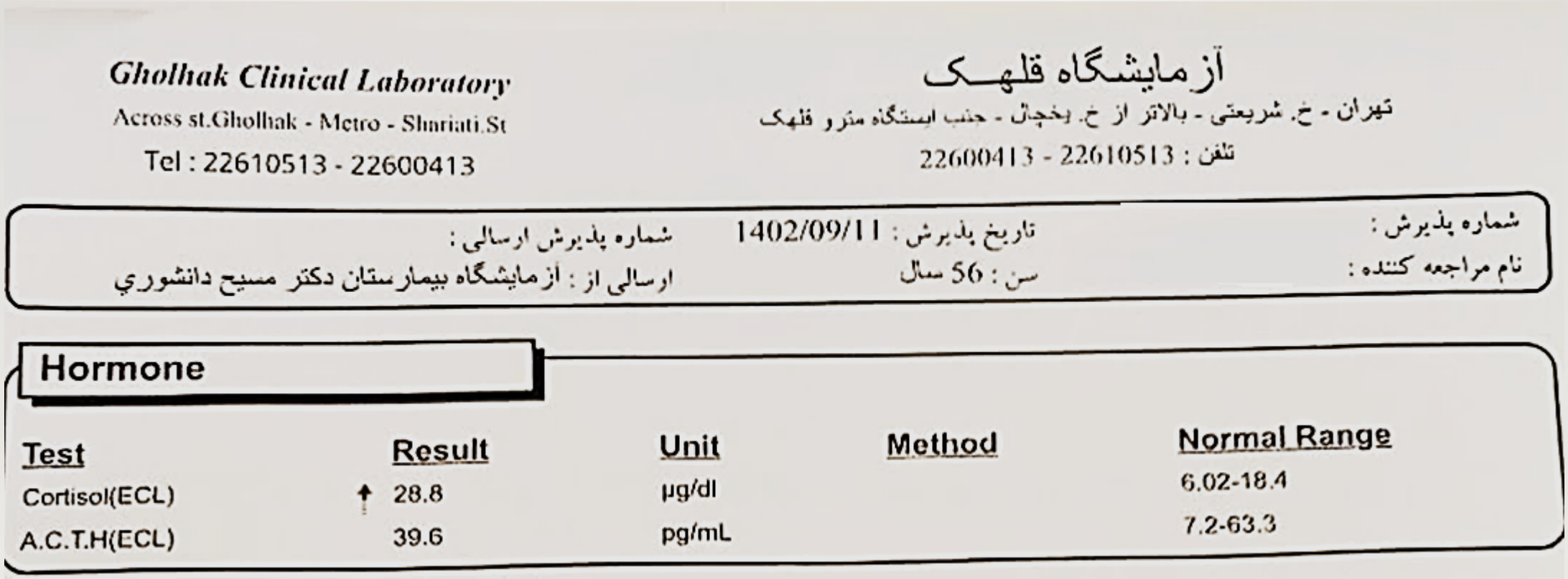
Count of Swabs/Instrument is Correct? Yes ☐ No ☐

نداشتیم قبل از عمل و با توجه در اسلش ... با تشخیص ASTH, Actopic، کاندید جراحی شد. و قفسه سینه لایه به لایه بسته

شد. پانسمان شد.

PI:

1402/09/11
(Lab Test 2 days after surgery)



Gholhak Clinical Laboratory
Across st.Gholhak - Metro - Shariati.St
Tel : 22610513 - 22600413

آزمایشگاه قلهک
تهران - خ. شریعتی - بالاتر از خ. پخچال - جنب ایستگاه مترو قلهک
تلفن : 22610513 - 22600413

شماره پذیرش :
نام مراجعه کننده :

تاریخ پذیرش : 1402/09/11
سن : 56 سال

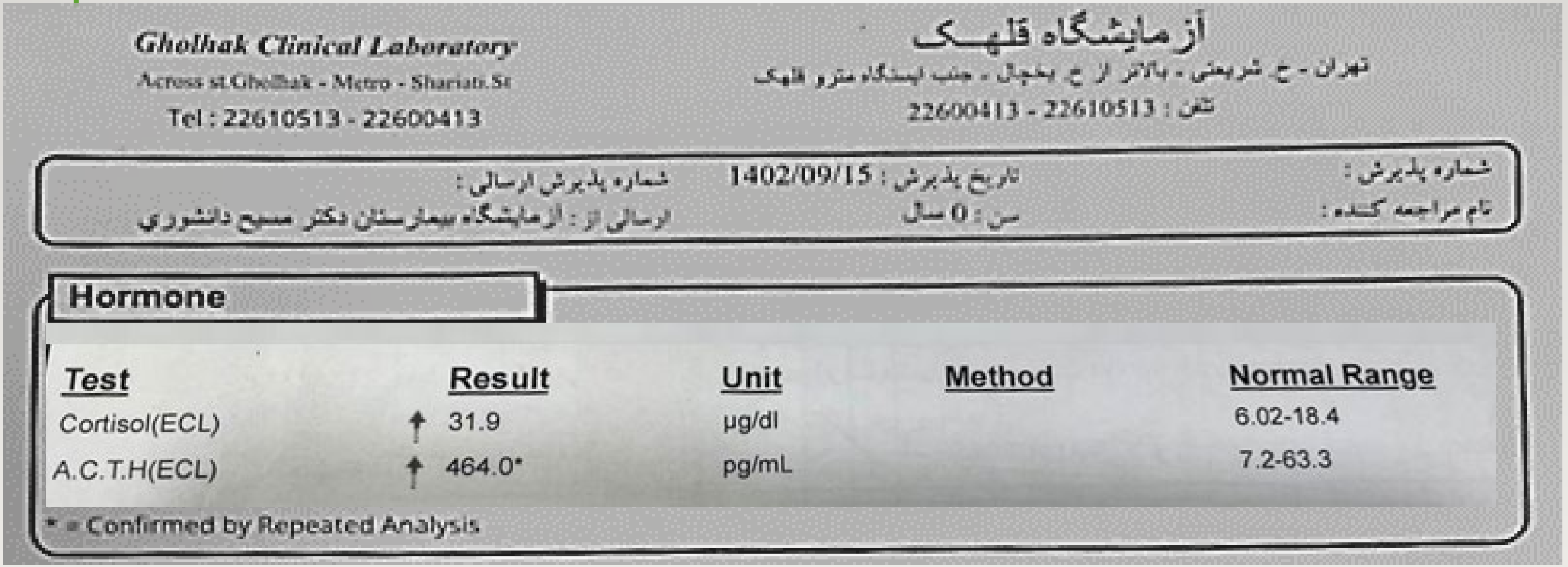
شماره پذیرش ارسالی :
ارسالی از : آزمایشگاه بیمارستان دکتر مسیح دانشوری

Hormone

Test	Result	Unit	Method	Normal Range
Cortisol(ECL)	↑ 28.8	µg/dl		6.02-18.4
A.C.T.H(ECL)	39.6	pg/mL		7.2-63.3

PI:

1402/09/15
(Lab Test 6 days after surgery)



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آزمایشگاه قلهک
تهران - خ. شریعتی - بالاتر از خ. بخچال - جنب ایستگاه مترو قلهک
تلفن : 22610513 - 22600413

شماره پذیرش :
نام مراجعه کننده :

تاریخ پذیرش : 1402/09/15
سن : 0 سال

شماره پذیرش ارسالی :
ارسالی از : آزمایشگاه بیمارستان دکتر مسیح دانشوری

Hormone

Test		Result	Unit	Method	Normal Range
Cortisol(ECL)	↑	31.9	µg/dl		6.02-18.4
A.C.T.H(ECL)	↑	464.0*	pg/mL		7.2-63.3

* = Confirmed by Repeated Analysis

PMH

- Inguinal hernia surgery and lithotripsy 7 months ago

DH

- The patient did not use any special medicine before the recent problem, but he was discharged from Imam Ardabil Hospital on December 2 with the following prescription.
  - Insulin Lantus 28
  - Insulin Novo rapid (30-22-34)
  - Tab Ketoconazole 200 BD
  - Tab Losartan H BD 50/12.5 BD
  - Tab Ca-D BD
  - Tab Aldactone 100 BD

Habitual History

- About 2 months before the onset of the disease, the patient used herbal teas and herbal ointments (due to hypopigmented skin lesions from 8 months ago).
- Smoking, alcohol and opium negative

FH

- Prostate cancer in the patient's father (controlled)
- The patient's mother died 25 years ago due to ESRD
- The patient's sister underwent hysterectomy at the age of 48 due to endometrial cancer (unmarried).

ROS

- Muscle weakness
- Insomnia and fatigue and Decreased libido and impotence
- White ulcerated lesions of the mouth and dysphagia to liquids
- Weight loss(10 kg in the last 1.5 to 2 months) with edema of both legs and abdominal obesity
- Hypopigmented skin lesions on fingers, elbows and feet since 8 months ago
- Psychiatric manifestations (depression, psychosis, cognitive impairment, memory, and irritability):Negative
- Easy Bruising and Acne & Hirsutism: Negative

Physical Examination

- A middle-aged man, ill
- BP: 155/95 mmHg PR: 70/min RR:18/min SPO2: 86% (with O_2:95%)
- BMI: 25.3 Height :160cm Weight : 65 kg
- Round face: Negative Plethora: Negative
- Dorsocervical fat pad: Negative
- Stria: Negative
- Thin skin and easy bruising: Negative
- Pigmentation: Negative (Hypopigmented skin lesions on fingers, elbows and feet)
- Lung auscultation: clear
- A soft, uniformly large abdomen without mass & pain
- Force of muscles: Lower limbs: 4/5 Upper limbs: 5/5, 4/5
- Pitting edema in both legs: +3

Problem List

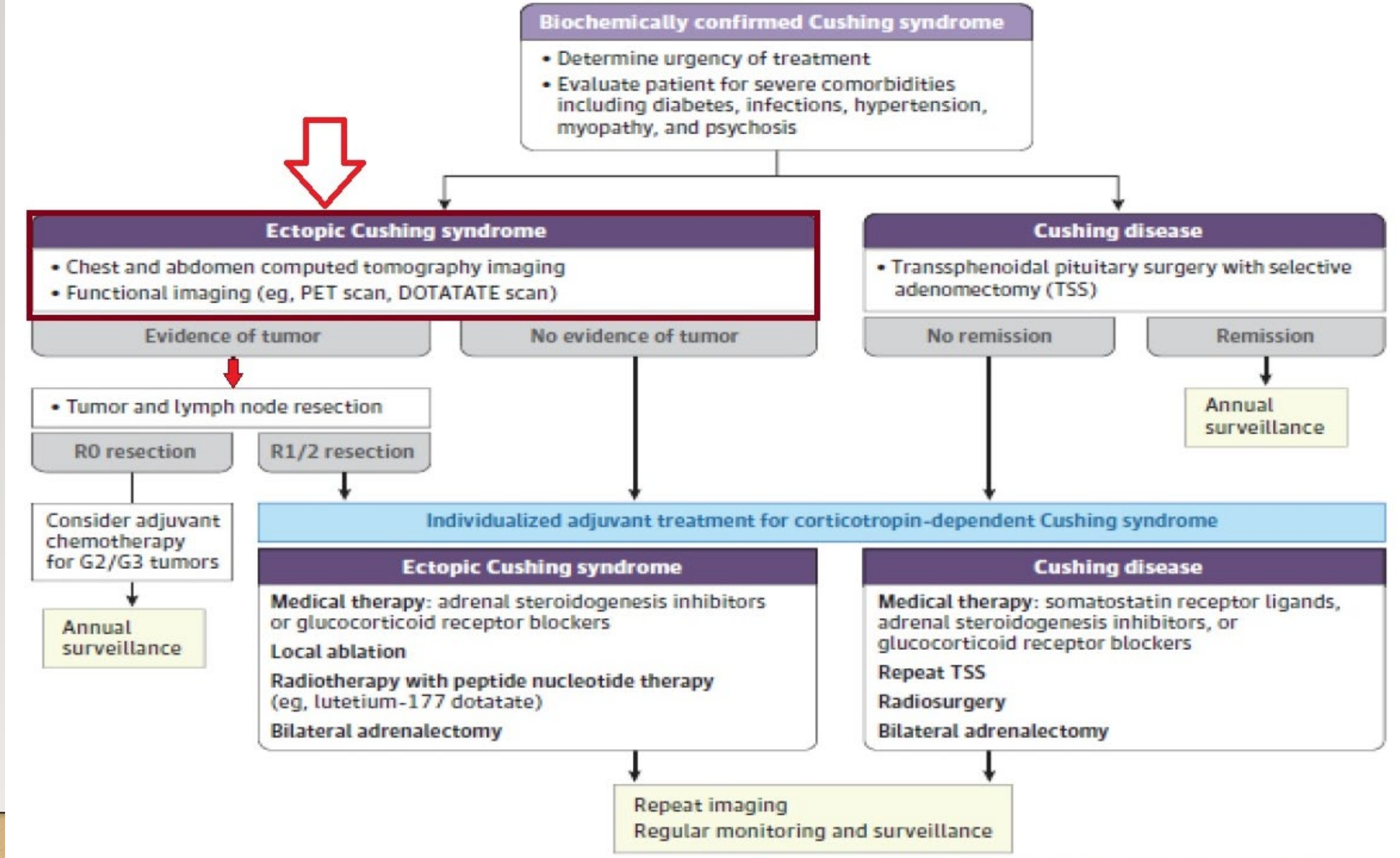
- Leg edema and abdominal obesity & muscle weakness, Weight loss(10 kg in the last 1.5 to 2 months)
- New onset HTN & DM
- Hypokalemia and metabolic alkalosis
- High cortisol >60 µg/dl, UFC >1000 µg/24h, ACTH = 124 *p*g/ml
- HDDST : Non-suppressed
- Pituitary microadenoma? (2.7 mm)
- Octreotide scintigraphy: Positive for octreotide-avid tumoral lesion at the posterior aspect of the base of left lung
- CT of the chest: Subpleural mass (left upper lobe) a round nodule (left lower lobe)

Our Questions

- 1. How can we differentiate between the subtypes of Cushing's syndrome?
- 2. What is the definition of remission and late remission in the context of Cushing's syndrome?
- 3. How can we localize the culprit lesion in this case of Cushing's syndrome?
- 4. What is the best management protocol for this case of Cushing's syndrome?

D/D

- Ectopic Cushing's Syndrome
- Cushing Disease


Biochemically confirmed Cushing syndrome
• Determine urgency of treatment
• Evaluate patient for severe comorbidities including diabetes, infections, hypertension, myopathy, and psychosis
Ectopic Cushing syndrome
• Chest and abdomen computed tomography imaging
• Functional imaging (eg, PET scan, DOTATATE scan)
Cushing disease
• Transsphenoidal pituitary surgery with selective adenomectomy (TSS)
Evidence of tumor
No evidence of tumor
No remission
Remission
• Tumor and lymph node resection
Annual surveillance
R0 resection
R1/2 resection
Consider adjuvant chemotherapy for G2/G3 tumors
Annual surveillance
Individualized adjuvant treatment for corticotropin-dependent Cushing syndrome
Ectopic Cushing syndrome
Medical therapy: adrenal steroidogenesis inhibitors or glucocorticoid receptor blockers
Local ablation
Radiotherapy with peptide nucleotide therapy (eg, lutetium-177 dotatate)
Bilateral adrenalectomy
Cushing disease
Medical therapy: somatostatin receptor ligands, adrenal steroidogenesis inhibitors, or glucocorticoid receptor blockers
Repeat TSS
Radiosurgery
Bilateral adrenalectomy
Repeat imaging
Regular monitoring and surveillance

Tumor Type	Approximate Incidence (%)
Small cell lung carcinoma	50
Non–small cell lung carcinoma	5
Pancreatic neuroendocrine tumors	10
Thymic neuroendocrine tumors	5
Lung neuroendocrine tumors	10
Other neuroendocrine tumors	2
Medullary carcinoma of thyroid	5
Pheochromocytoma and related tumors	3
Rare carcinomas of prostate, breast, ovary, gallbladder, colon	10

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7

The definition of remission and recurrence of Cushing's disease

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[b] *Neuroendocrinology Clinic, Department of Endocrinology and Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico*

Remission After Surgery

- The current consensus defines remission as a low post-surgical SC and some studies include normalization of the 24-h UFC and LNSC.
- The role of ACTH levels in either confirming remission or confirming recurrence is still controversial.
- The combination of tests and the proper timing for testing for the optimal identification of remission is not clear.

Remission After Surgery

- Delayed remission occurs in around 5.6% of patients but is not likely to happen in patients with immediate postsurgical cortisol >10 µg/dl.

REVIEW

CURRENT OPINION

Functional imaging in ectopic Cushing syndrome

Seda Grigoryan[a], Anca M. Avram[b], and Adina F. Turcu[c]

Purpose of review
Ectopic adrenocorticotropic hormone (ACTH)-secreting tumors are commonly small, yet they often lead to fulminant forms of Cushing syndrome. High-resolution functional imaging modalities, such as [^{68}Ga]-DOTATATE, have been recently introduced in clinical practice for the identification of neuroendocrine tumors. In this review, we focus on the performance of [^{68}Ga]-DOTATATE as a tool for localizing primary and metastatic sources of ectopic Cushing syndrome (ECS).

Recent findings
Prompt surgical removal of ectopic ACTH-secreting tumors is the mainstay of therapy in patients with ECS. Detecting such tumors with conventional cross-sectional imaging is often unsuccessful, owing to their small size. [^{68}Ga]-DOTATATE has been approved in 2016 by the Federal Drug Administration for imaging well differentiated neuroendocrine tumors. Data regarding the performance of [^{68}Ga]-DOTATATE for detecting ectopic ACTH-secreting tumors remain limited, in part owing to the recent introduction of this imaging modality in clinical practice, and in part because of the low prevalence of ECS. Nevertheless, [^{68}Ga]-DOTATATE has been reported to be useful in identifying primary and metastatic ectopic ACTH-secreting lesions that were not apparent on other imaging studies, impacting the clinical care of many patients with ECS.

Summary
[^{68}Ga]-DOTATATE-based imaging, which targets the somatostatin receptors abundantly expressed in neuroendocrine tumors, has generally high, although variable resolution in detecting the source(s) of ECS.

Keywords
[^{68}Ga]-DOTATATE PET/CT, Cushing syndrome, ectopic adrenocorticotropic hormone syndrome, somatostatin receptor

KEY POINTS

- Early diagnosis and localization of ECS-causing tumor(s) is critical, as such patients have the highest mortality of all other forms of Cushing syndrome.
- Identification of ectopic ACTH-secreting tumors is commonly challenging, because of their small size.
- [68Ga]-DOTATATE is a high-resolution imaging modality targeting somatostatin receptors, which was approved by the FDA in November 2016, for localizing well differentiated neuroendocrine tumors.
- [68Ga]-DOTATATE has been shown to be successful in identifying both primary and new metastatic sources of ECS missed by anatomical cross-sectional imagining, such as CT/MRI, or by octreotide-based imaging.

KEY POINTS

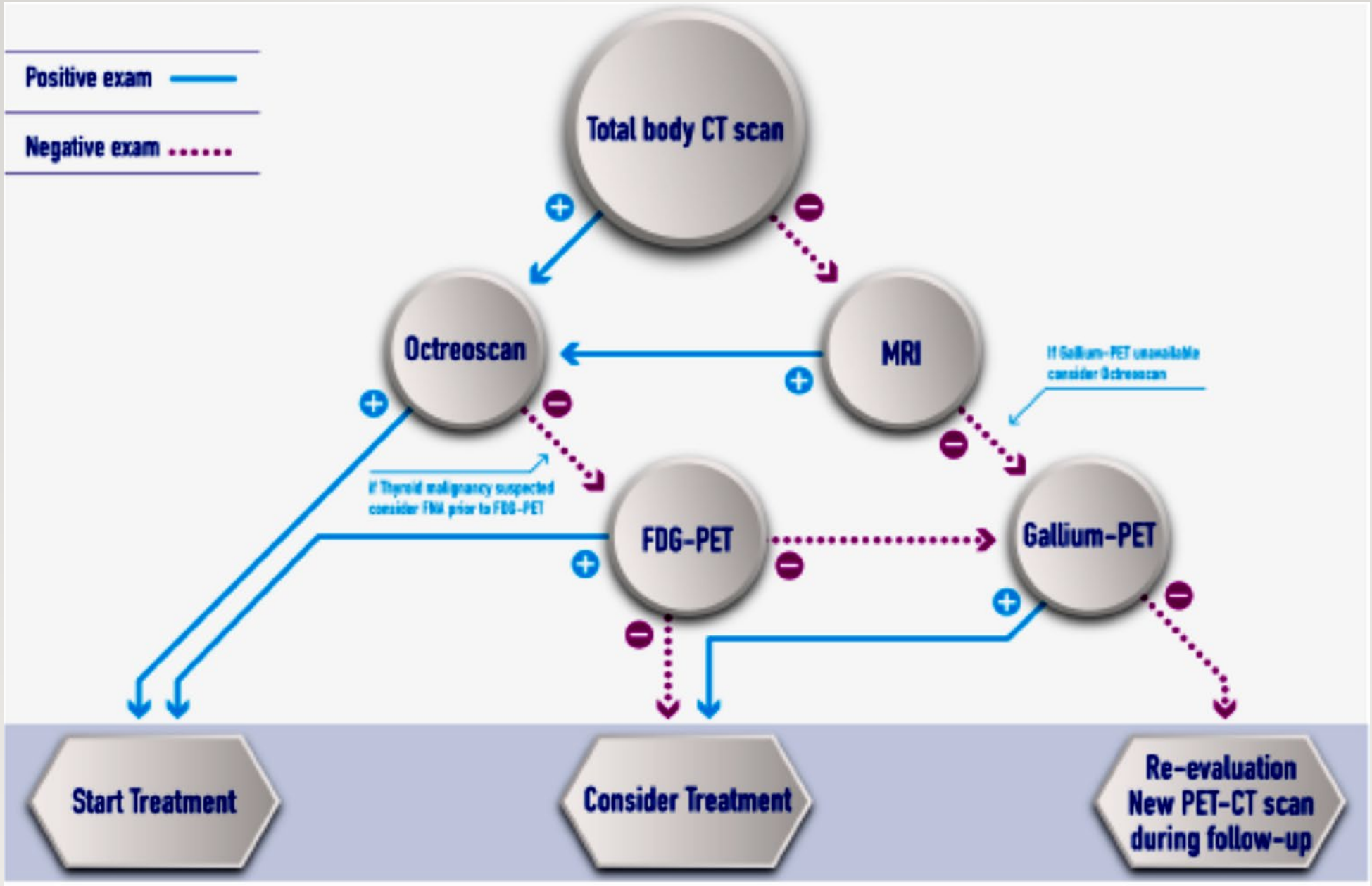
- Data regarding the performance of [68Ga]-DOTATATE PET/CT imaging specifically in ECS have grown over the recent years, yet they remain limited.
- This is in part due to the low prevalence of ECS, but also to the relatively recent FDA approval of [68Ga]-DOTATATE PET/CT imaging and to its scarce availability.

Table 2. Diagnostic accuracy for each imaging technique in all patients, in those with proven histology, and in overt and covert patients.

All patients (n = 231)	CT	MRI	OCT	FDG-PET	F-DOPA-PET	MIBG	^{68}Gallium-SSTR-PET/CT
Sensitivity % (95% CI)	66.2% (59.5–72.3)	51.5% (41.9–60.9)	48.9% (41.5–56.3)	51.7% (41.5–61.8)	57.1% (36.6–75.5)	30.8% (12.7–57.6)	81.8% (61.5–92.7)
	137/207	53/103	84/172	46/89	12/21	4/13	18/22
True Positive	63.7%	50.5%	48.3%	51.1%	54.5%	26.7%	78.3%
	137/215	53/105	84/174	46/90	12/22	4/15	18/23
False negative	33.6%	47.6%	50.6%	47.8%	40.9%	60%	17.4%
	70/215	50/105	88/174	43/90	9/22	9/15	4/23
False positive	3.7%	1.9%	1.1%	1.1%	4.5%	13.3%	4.3%
	8/215	2/105	2/174	1/90	1/22	2/15	1/23
Histologically confirmed (n = 188)							
Sensitivity % (95% CI)	81.1% (74.5–86.3)	73.4% (61.9–82.2)	62.9% (54.6–70.7)	65.7% (54–75.8)	65.0% (43.3–81.9)	40% (16.8–68.7)	81.8% (61.5–92.7)
	137/169	52/71	85/135	46/70	13/20	4/10	18/22
True Positive	77.4%	71.2%	62.0%	64.8%	61.9%	33.3%	78.3%
	137/177	52/73	85/137	46/71	13/21	4/12	18/23
False negative	18.1%	26%	36.5%	33.8%	33.3%	50%	17.4%
	32/177	19/73	50/137	24/71	7/21	6/12	4/23
False positive	4.5%	2.7%	1.5%	1.4%	4.8%	16.7%	4.3%
	8/177	2/73	2/137	1/71	1/21	2/12	1/23
Overt (n = 121)							
Sensitivity % (95% CI)	98.3% (93.9–99.5)	92.9% (81.0–97.5)	63.5% (52.9–72.9)	71.1% (55.2–83)	53.9% (29.1–76.8)	37.5% (13.7–69.4)	70% (39.7–89.2)
	113/115	39/42	54/85	27/38	7/13	3/8	9/13
True positive	97.4%	92.9%	62.1%	71.1%	50,0%	30%	69.2%
	113/116	39/42	54/87	27/38	7/14	3/10	9/13
False negative	1.7%	7.1%	35.6%	28.9%	42.9%	50%	30.8%
	2/116	3/42	31/87	11/38	6/14	5/10	4/13
False positive	0.9%		2.3%		7.1%	20%	
	1/116		2/87		1/14	2/10	
Covert (n = 67)							
Sensitivity % (95% CI)	43.6% (31.4–56.7)	44.8% (28.4–62.4)	64.0% (50.1–75.9)	59.4% (42.3–74.5)	85.7% (48.7–97.4)	50% (9.5–90.6)	100% (61–100)
	24/55	13/29	32/50	19 /32	6/7	1/2	9/9
True positive	39.3%	41.9%	64.0%	57.6%	85.7%	50%	90.0%
	24/61	13/31	32/50	19/33	6/7	1/2	9/10
False negative	50.8%	51.6%	36.0%	39.4%	14.3	50%	
	31/61	16/31	18/50	13/33	1/7	1/2	
False positive	9.8%	6.5%		3.0%			10.0%
	6/61	2/31		1/33			1/10

Table 3. Sensitivity (95% CI) of diagnostic techniques in primary source localization according to tumor site.

Site (positive finding)	CT +	MRI +	OCT +	FDG-PET +	FDOPA-PET +	MIBG +	^{68}Gallium-SSTR-PET/CT +
Lung	79.4% (70.3–86.2)	66.7% (48.8–80.8)	60.9% (50.2–70.8)	54.6% (38.0–70.2)	71.4% (45.4–88.3)	50% (9.5–90.6)	77.8% (45.3–93.7)
	77/97	20/30	50/82	18/33	10/14	1/2	7/9
Thymus, Mediastinum	85% (63.9–94.8)	62.5% (30.6–86.3)	85.7% (60.1–96.0)	62.5% (30.6–86.3)	33.3% (6.2–79.2)	nd	50% (15.0–85.0)
	17/20	5/8	12/14	5/8	1/3		2/4
Pancreas	85.7% (60.1–96.0)	87.5% (52.9–97.8)	66.7% (35.4–88)	100% (61–100)	nd	Out of 1 case: 0 TP, 1 FN	100% (34.2–100)
	12/14	7/8	6/9	6/6			2/2
Adrenal gland	100% (72–100)	100% (57–100)	60% (23.1–88.2)	100% (44–100)	100% (20.7–100)	50% (15–85)	nd
	10/10	5/5	3/5	3/3	1/1	2/4	
Gastrointestinal Tract	90% (59.6–98.2)	71.4% (35.9–91.8)	50% (21.5–78.5)	57.1% (25.1–84.2)	100% (20.7–100)	nd	100% (34.2–100)
	9/10	5/7	4/8	4/7	1/1		2/2
Thyroid	80% (37.6–96.4)	100% (20.7–100)	66.7% (20.8–93.9)	100% (43.9–100)	nd	Out of 3 cases:	100% (34.2–100)
	4/5	1/1	2/3	3/3		0 TO, 1 FP, 2 FN	2/2
Carotid glomus, Atrium, Para-aortic region	33.3% (6.2–79.2)	33.3% (6.2–79.2)	80% (37.6–96.4)	100% (34.2–100)	nd	nd	nd
	1/3	1/3	4/5	2/2			
Head: Ethmoidal-Paranasal-Sphenoid- Sinus, Olfactory bulb, Skull base etc.	57.1% (25.1–84.2)	87.50% (52.9–97.8)	80% (37.6–96.4)	71.4% (35.9–91.8)	Out of 1 case:	nd	100% (43.9–100)
	4/7	7/8	4/5	5/7	0 TP, 1 FN		3/3
Abdomen/other (abdominal paraganglioma, ovary)	60% (23.1–88.2)	66.7% (20.8–93.9)	20% (3.6–62.5)	100% (20.7–100)	nd	100% (34.2–100)	nd
	3/5	2/3	1/5	1/1		2/2	


Positive exam
Negative exam
Total body CT scan
Octreoscan
MRI
If Gallium-PET unavailable consider Octreoscan
If Thyroid malignancy suspected consider FNA prior to FDG-PET
FDG-PET
Gallium-PET
Start Treatment
Consider Treatment
Re-evaluation New PET-CT scan during follow-up

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Recent Updates on the Diagnosis and Management of Cushing's Syndrome

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Cushing's syndrome, a potentially lethal disorder characterized by endogenous hypercortisolism, may be difficult to recognize, especially when it is mild and the presenting features are common in the general population. However, there is a need to identify the condition at an early stage, as it tends to progress, accruing additional morbidity and increasing mortality rates. Once a clinical suspicion is raised, screening tests involve timed measurement of urine, serum or salivary cortisol at baseline or after administration of dexamethasone, 1 mg. Each test has caveats, so that the choice of tests must be individualized for each patient. Once the diagnosis is established, and the cause is determined, surgical resection of abnormal tumor/tissue is the optimal treatment. When this cannot be achieved, medical treatment (or bilateral adrenalectomy) must be used to normalize cortisol production. Recent updates in screening for and treating Cushing's syndrome are reviewed here.

Keywords: Cushing syndrome; Hydrocortisone; Adrenocorticotropic hormone

TREATMENT

- The goal of treatment is to normalize cortisol levels or its action at the receptors
- Control of patient's glucose, Blood pressure and K.
- Treat any comorbid condition.

TREATMENT

- Severe hypercortisolism carries a high risk for infections and thrombotic phenomena, and may be life-threatening. In general, monotherapy is not effective in this setting.
- A few small studies have investigated combination therapy, and suggest that aggressive use of multiple agents may be effective.

Endocrinology, Diabetes & Metabolism CASE REPORTS

L Gonzalez Fernandez and others

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Ectopic Cushing's syndrome: clinical, diagnostic, treatment and follow-up outcomes of 12 cases of lung ectopic ACTH

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Table 1 Epidemiological and clinical data.

Case number	Gender	Age (years)	Symptoms and signs	Laboratory tests alterations	Time to diagnosis (months)
1	M	62	Proximal myopathy, Cushingoid phenotype, weight gain, osteoporosis/fractures, asthenia, hyperpigmentation, oedema of limbs, unusual infections, constitutional syndrome	↓ K; ↑ALP, GGT, ALT, AST; ↑leucocytes; DM	2
2	M	29	Facial plethora, proximal myopathy, striae, Cushingoid phenotype, weight gain, osteoporosis/fractures, asthenia, oedema of limbs, hypertension, nephrolithiasis, psychiatric disorders, gynecomastia	None	24
3	F	40	Capillary fragility, Cushingoid phenotype, weight gain, osteoporosis/fractures, asthenia, hypertension, menstrual disorders	↓ K	12
4	M	68	Cushingoid phenotype, weight gain, oedema of limbs, hypertension, gynecomastia	↓ K; DM; DL.	2
5	M	31	Proximal myopathy, striae, Cushingoid phenotype, weight gain, asthenia, hypertension	↓ K; ↑ ALP, GGT, ALT, AST; DM	12
6	M	50	Facial plethora, proximal myopathy, capillary fragility, Cushingoid phenotype, weight gain, asthenia, oedema of limbs, hypertension, psychiatric disorders, gynecomastia	↓ K; ↑ALP, GGT, ALT, AST; ↑leucocytes; DM; DL	2
7	F	77	Proximal myopathy, asthenia, oedema of limbs, hypertension, psychiatric disorders	↓ K; ↑leucocytes; DM; DL	2
8	M	61	Facial plethora, proximal myopathy, capillary fragility, asthenia, oedema of limbs, hypertension	↓ K; ↑leucocytes; DM; DL; ↑ALT, AST	1
9	M	76	Proximal myopathy, capillary fragility, osteoporosis/fractures, hyperpigmentation, oedema of limbs, hypertension, nephrolithiasis, unusual infections, deep vein thrombosis	↓ K; ↑leucocytes; DM; DL	4
10	F	61	Proximal myopathy, capillary fragility, weight gain, asthenia, hypertension, unusual infections	↓ K; ↑ALP, GGT, ALT, AST; ↑leucocytes; DM	1
11	F	61	Capillary fragility, Cushingoid phenotype, oedema of limbs, hypertension, virilisation	↓ K; ↑leucocytes	1
12	M	66	Capillary fragility, asthenia, oedema of limbs, hypertension	↓ K; ↑leucocytes; DM	4

Table 3 Localization studies.

Case number	CT	MRI	OctreoScan	FDG-PET/CT	^{68}Ga- PET/CT	Pituitary gland MRI	Final diagnosis
1	14.4 mm nodule in left lung. Liver metastases. Gastroenterohepatic lymphadenopathy	-	Positive. Hypercaptation in primary tumour	Positive. Hypermetabolism in primary tumour and loco-regional lymphadenopathy	-	No findings	Lung carcinoid
2	No findings	No findings	Negative	Negative	Positive. Right pulmonary nodule	No findings	Lung carcinoid
3	-	7 mm lingular nodule	Positive. Hypercaptation in primary tumour	-	-	Pituitary microadenoma 7 mm size	Lung carcinoid
4	Nodule in LUL of lung	-	Negative	-	-	Pituitary microadenoma 5 mm size	SCLC
5	8 mm nodule in RLL of the lung.	-	Negative	Negative	-	No findings	Lung carcinoid
6	85 mm right parahilar mass. Mediastinal lymphadenopathy, pleural, liver and adrenal metastases	-	-	-	-	-	SCLC
7	Bilateral adrenal hyperplasia. Left adrenal nodule of 14 mm	-	Positive. Hypercaptant left lung area	Positive. Hypermetabolic lesion in the left lung	-	No findings	Unknown origin
8	96 mm subcarinal mass infiltrating and compressing surrounding structures (superior vena cava, left atrium, oesophagus, main bronchi, right main pulmonary artery)	No findings at pancreatic-liver level	-		-	-	SCLC
9	17 mm nodule in LUL of the lung	-	Positive. Hypercaptation in primary tumour		-	-	Lung carcinoid
10	20 mm nodule in RUL of the lung	14 mm cystic lesion in the pancreas compatible with a mucinous tumour	Positive. Hypercaptation in primary tumour		-	Right pituitary microadenoma 5 mm size	Lung carcinoid
11	Multifocal and bilateral lung metastases. Liver metastases and peritoneal implants.	-	-		-	-	SCLC
12	44 mm mass in RUL of the lung.	-	-	-	-	-	SCLC

Table 4 Pathological anatomy results.

Case number	Size (cm)[a]	Localization	Grade	Ki67 index (%)	Mitotic count (10 HPF)	TNM	Final diagnosis
1	NA[b]	Lung	G2	1–5	<2	Stage IV	Atypical carcinoid
2	1.7	Lung	G1	3	-	Stage IA2 (pT1b pN0 cM0)[c]	Typical carcinoid
3	2	Lung	G2	10	-	Stage IIIA (pT1b pN2 cM0)[c]	Atypical carcinoid
4	2	Lung	-	-	-	Stage IV	SCLC
5	1.3	Lung	G1	-	<2	Stage IA (pT1b pN0 cM0)[d]	Typical carcinoid
6	NA[b]	Lung	-	-	-	Stage IV	SCLC
7	-	Lung	-	-	-	-	Unknown origin. No finding of tumour cells (necrotic tissue).
8	9.6	Lung	G3	90	-	Stage IV	SCLC
9	1.7	Lung	G1	1	-	Stage IA2 (pT1b pN0)[c]	Typical carcinoid
10	2	Lung	G1	2	-	Stage IA2 (pT1b pN0)[c]	Typical carcinoid
11	NA	Lung	-	-	-	Stage IV	SCLC
12	4.4	Lung	G3	90	-	Stage IV	SCLC

Table 5 Hypercortisolism treatment.

Case number	1st line treatment		2nd line treatment		3rd line treatment		Final state of CS
	Drug	Response	Drug	Response	Drug	Response	
1	Metyrapone (250 mg TID)+ long-acting SST analogue (pasireotide 0,6 mg BID SC)	P	-	-	-	-	Uncontrolled
2	Ketoconazole (200 mg TID)	CC	-	-	-	-	Cured
3	Ketoconazole (200 mg TID)	P until Qx	Ketoconazole (200 mg TID) + long acting SST (octreotide 20 mg/ 28d SC)	P until Qx	Ketoconazole (200 mg TID) + long acting SST (octreotide 20 mg/28d SC) + metyrapone (500 mg BID)	P until Qx	Cured
4	Ketoconazole (200 mg BID)	PC	-	-		-	Uncontrolled
5	Ketoconazole (NA)	P until Qx	-	-	-	-	Cured
6	Ketoconazole (400 mg BID)	P	Ketoconazole (400 mg BID) + metyrapone (250 mg TID)	P	-	-	Uncontrolled
7	Ketoconazole (200 mg TID)	P	-	-	-	-	Uncontrolled
8	Ketoconazole (200 mg TID)	P	Metyrapone (250 mg TID)	PC	-	-	Uncontrolled
9	Metyrapone (500 mg BID)	PC until Qx	-	-	-	-	Cured
10	Ketoconazole (200 mg BID)	PC until Qx	-	-	-	-	Cured
11	Ketoconazole (200 mg TID)	P	-	-	-	-	Uncontrolled
12	Metyrapone (500 mg QID)	P	-	-	-	-	Uncontrolled

Table 6 Antitumour treatment.

Case number	1st line treatment		2nd line treatment		Final state of neoplastic disease
	Therapy	Response time	Therapy	Response time	
1	Sunitinib+ long-acting SST analogue (Octreotide LAR)	TP: 8 months	SST analogue (Pasireotide)	TP: 4 months	Dead (TP)
2	Qx	CR	-	-	Disease-free
3	Qx+ long-acting SST	-	Chemotherapy (carboplatin etoposide)	CR: 30 months	Remission
4	Chemotherapy (carboplatin-etoposide)	PR: 11 months	Chemotherapy (topotecan)[a]	TP: 10 months[a]	Dead (TP)
5	Qx	CR	-	-	Disease-free
6	Chemotherapy (carboplatin-etoposide)	TP	-	-	Dead (TP)
7	Qx	-	-	-	Dead (CCS)
8	Chemotherapy (carboplatin-etoposide)	TP: 1 month	Chemotherapy (camptothecin-11)	TP: 1 month	Dead (TP)
9	Qx	CR	-	-	Disease-free
10	Qx	CR	-	-	Disease-free
11	Chemotherapy (carboplatin-etoposide)	TP: 3 months	Radiotherapy	TP: 2 months	Dead (TP)
12	Chemotherapy (carboplatin-etoposide)	TP: 1 month	-	-	Dead (CCS)

Thanks for your attention

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Emerging diagnostic methods and imaging modalities in cushing's syndrome

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TABLE 1 Diagnostic accuracy and limitations of traditional first-line biochemical tests, as well as the newer hair tests used for the diagnosis of Cushing's syndrome (14–18).

Test	Sensitivity	Specificity	Disadvantages
Low-Dose Dexamethasone Suppression Test	>95%	80-85%	• Variation in absorption and metabolism of dexamethasone (e.g., P450 enzyme system interactions, liver or renal disease) between patients may influence results • False positives in women taking oral contraceptive pills and during pregnancy due to increased cortisol binding globulin (CBG) • Poor performance in differentiating from nonneoplastic hypercortisolism • Incompliance may cause a false-positive result • No possibility to test cortisol levels in retrospect as is useful in cyclic CS
Late Night Salivary Cortisol	90-98%	90-100%	• False positives in patients who smoke or use chewing tobacco, and with direct contamination of the saliva with exogenous steroids • Influenced by abnormal sleep-wake cycles • False positives in patients of older age and those with hypertension and diabetes mellitus • False positives in foods that contain glycyrrhizic acid (e.g., licorice, teas) • No possibility to test cortisol levels in retrospect as is useful in cyclic CS
24 Hour Urine Free Cortisol	70-75%	40-90%	• Potential for improper collection • Day-to-day intra-patient variability, often requiring repeated measurements • Possible contamination • Poor performance in differentiating from nonneoplastic hypercortisolism • Measurements influenced by gender, age, urinary volume, sodium intake, and renal function • No possibility to test cortisol levels in retrospect as is useful in cyclic CS
Hair Cortisol	81%	88%	• Limited if no or little scalp hair is present • Method is not yet widely available and, therefore, samples often need mailing to expert laboratories
Hair Cortisone	87%	90%	• Limited if no or little scalp hair is present • Method is not yet widely available and, therefore, samples often need mailing to expert laboratories

TABLE 2 Summary of non-invasive strategies and reported diagnostic accuracies for differentiating Cushing's Disease and ectopic ACTH syndrome (33, 83, 85–87).

Strategy	Positive Result Suggestive of CD	Sensitivity	Specificity
Individual tests			
CRH Stimulation Test (83)	• >35% increase in ACTH concentration after CRH administration	90%	90%
High-Dose Dexamethasone Suppression Test (85)	• >50% suppression of cortisol concentrations	81%	66.70%
Pituitary MRI (33)	• Lesion compatible with a pituitary adenoma identified on standard MRI by two experienced radiologists	46-49%	33-50%
Combination tests			
CRH Stimulation Test + Desmopressin Stimulation Test (86)	1. >17% increase in cortisol and >37% increase in ACTH following CRH stimulation 2. >18% increase in cortisol and >33% increase in ACTH following desmopressin stimulation	73%	93%
CRH Stimulation Test + Desmopressin Stimulation Test + Pituitary MRI (86)	1. >17% increase in cortisol and >37% increase in ACTH following CRH stimulation 2. >18% increase in cortisol and >33% increase in ACTH following desmopressin stimulation 3. Pituitary lesion compatible with a pituitary adenoma on MRI	49.70%	100%
CRH Stimulation Test + High-Dose Dexamethasone Suppression Test (87)	1. >72% increase in ACTH following CRH administration 2. >52.7% decrease in cortisol following dexamethasone administration	75.60%	100%

Advances in imaging techniques

- **Anatomical Imaging:**
  - **CT**
  - **Standard MRI(6 mm)**
  - **postcontrast Golden-Angle Radial Sparse Parallel sequencing obtained on a 3T magnet is well suited to achieve sub millimetric (approximately 0.8 mm)**

Despite all the advancement in pituitary MRI, up to 40% of cases are "MR imaging–negative"

Advances in imaging techniques

- Molecular Positron Emission Tomography (PET) Imaging:
  - **11C-Methionine (MET) PET**
  - **18F-Fluoroethyl-L-Tyrosine (FET) PET**
  - **68Ga-CRH PET**
  - **68Ga-DOTATATE PET/CT or PET/MRI**

Advances in imaging techniques

- Using artificial intelligence (AI), specifically machine learning and deep learning algorithms, as a diagnostic tool for imaging analysis to enhance tumor assessment and improve diagnostic accuracy.

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Approach to the Patient

Approach to the Patient: Diagnosis of Cushing Syndrome

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Differentiation Between CD and Ectopic ACTH Secretion

- Pituitary MRI is used for detecting pituitary adenomas. Compared with conventional MRI, which can only detect 36% to 63% of pituitary microadenomas in patients with CD
- High-resolution 3T-MRI with 3-dimensional spoiled gradient-echo sequence is characterized by thinner sections and superior soft-tissue contrast and can detect adenomas as small as 2 mm
- 68Ga CRH PET-CT scan was able to correctly identify 100% of CD cases, including culprit lesions less than 6 mm in size

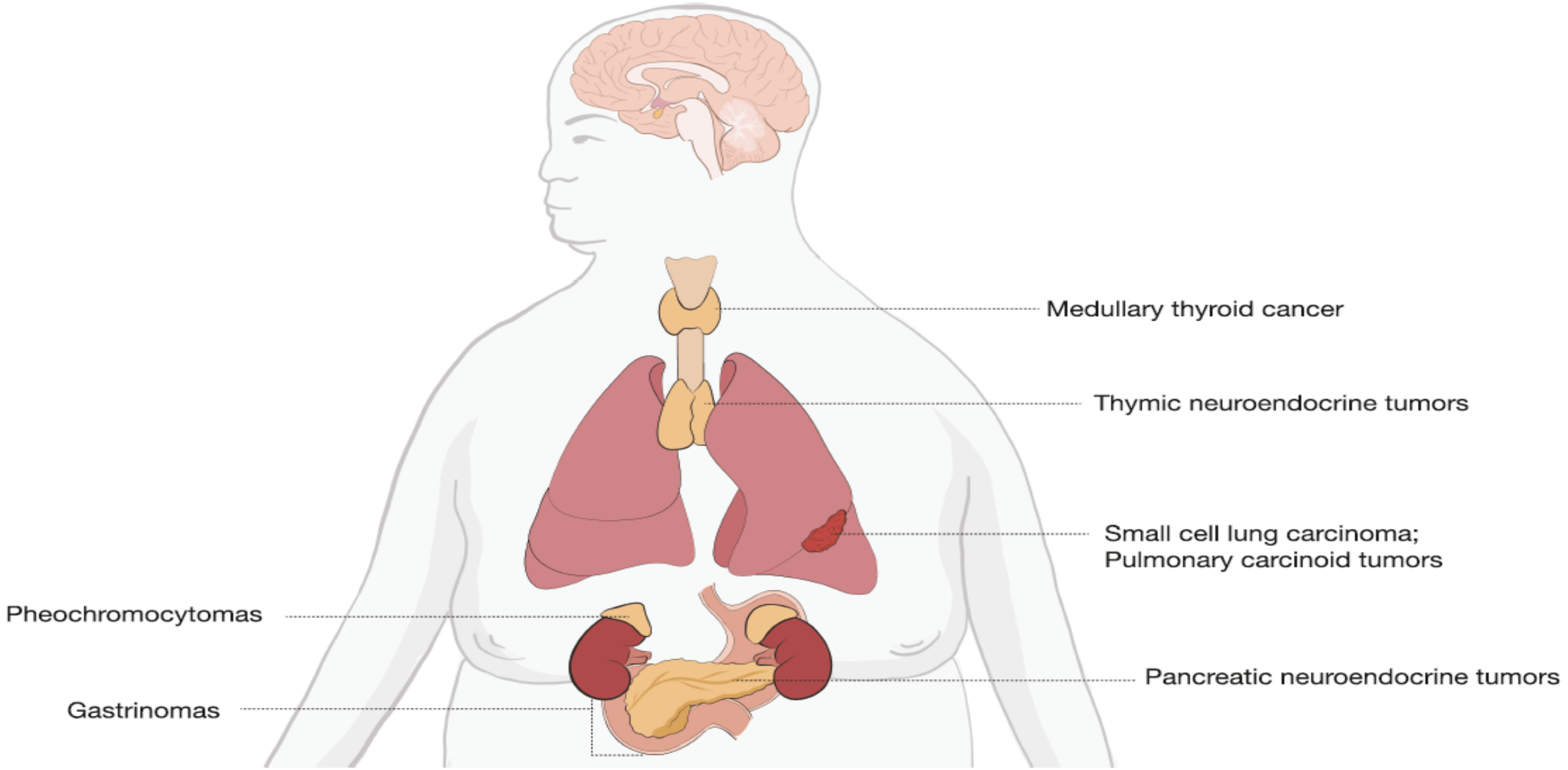

Figure 3. Sources of ectopic ACTH secretion. Based on Lacroix et al (2).

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- In cases in which results are inconclusive for Cushing disease, evaluation for EAS should be considered .
- Whole-body thin-slice CT scans (cervical, thoracic, abdominal, and pelvic regions) should be performed initially to evaluate for tumors suggestive of EAS.
- Second-line tests include functional imaging using 68Ga-PET/CT or 18FDG PET/CT scans, which can be used to detect occult tumors, reinforce tumors seen on CT scan as being neuroendocrine, or contribute to the workup of metastatic tumors.