IN THE NAME OF GOD

CASE PRESENTATION

A 64-year-old patient was referred because of hypercalcemia

Patient ID:

- A 64-year-old man
- Married and has a 27-year-old daughter
- cheif complaint : referred because of hypercalcemia
- Source of history: himself

Present illness

- The patient visited a nephrologist 5 years ago due to gradual weight loss, fatigue, hypertension, and intermittent epistaxis. He also reports a history of polydipsia, nocturia, and urinary dribbling

- In the workup, the nephrologist requests the following laboratory tests :

Present illness

Lab data 1398

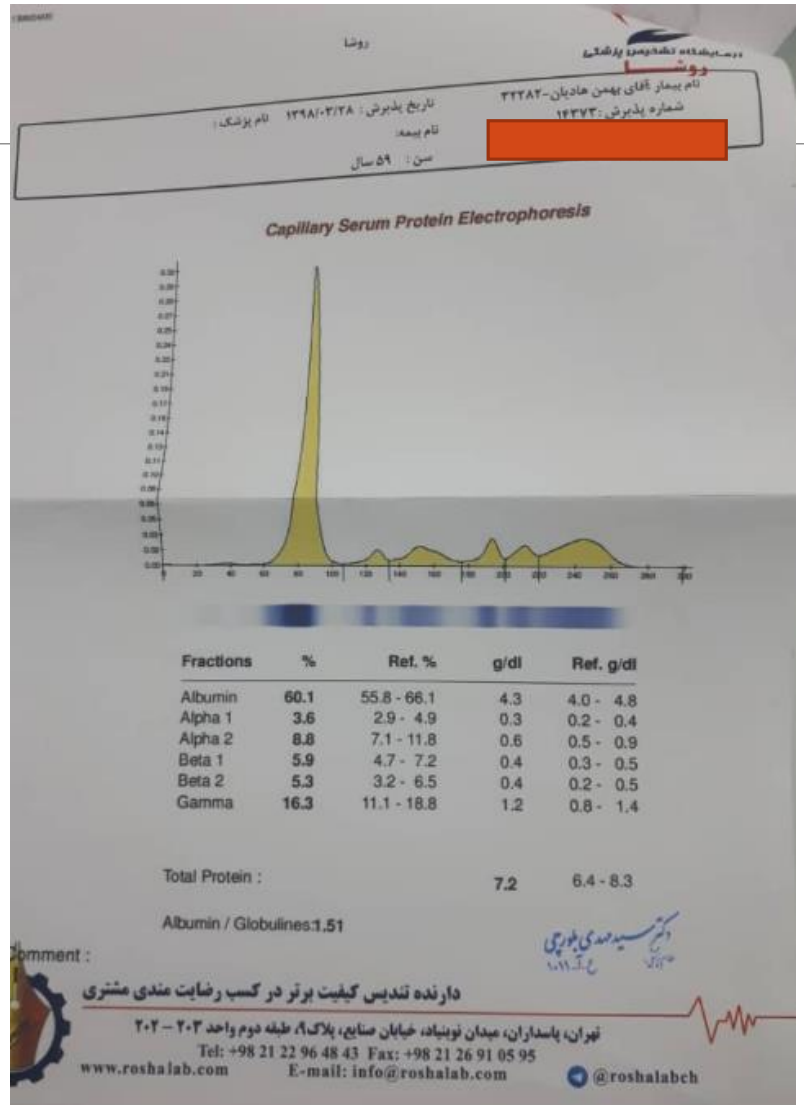
PSA (TOTAL)	CBC	Cr	Ca	P	iPTH	25(OH)VIT D	ALK	Albumin	U/A
1.1 ng/mL	wbc:5800 hb:15g/dL plt:217000	2.2 mg/dL	10.9 mg/dL	3.3 mg/dL	5.4 pg/mL	29.6 ng/mL	133 u/L	4.3 gr/dL	SG:1015 PH:6 RBC:8-10 WBC:5-8 Crystal:ca-oxalat

Present illness

Lab data 1398

24hr Urine	Rheumatology/ work up	Uric acid	TFT	LFT	FBS	Lipid Profile	ESR	Serum protein Electrophoresis
V:2400 Cr:1303mg Ca:218mg	Negative	7.4 mg/dL	NL	NL	96 mg/dL	TG:157 mg/dL Cho:154 mg/dL	4	Total pro:7.2 Alb:60% Alpha1:3.6% Alpha2:8.8% Beta1:5.9% Beta 2:5.3% Gamma:16%

Present illness



روشا

آزمایشگاه تشخیص پزشکی
روشا

نام بیمار آقای بهمن هادیان-۳۲۲۸۲
شماره پذیرش :۱۴۳۷۳

تاریخ پذیرش : ۱۳۹۸/۰۳/۲۸ نام پزشک :
نام بیمه:
سن : ۵۹ سال

[redacted]

Capillary Serum Protein Electrophoresis

Fractions	%	Ref. %	g/dl	Ref. g/dl
Albumin	60.1	55.8 - 66.1	4.3	4.0 - 4.8
Alpha 1	3.6	2.9 - 4.9	0.3	0.2 - 0.4
Alpha 2	8.8	7.1 - 11.8	0.6	0.5 - 0.9
Beta 1	5.9	4.7 - 7.2	0.4	0.3 - 0.5
Beta 2	5.3	3.2 - 6.5	0.4	0.2 - 0.5
Gamma	16.3	11.1 - 18.8	1.2	0.8 - 1.4

Total Protein : 7.2 6.4 - 8.3

Albumin / Globulines:1.51

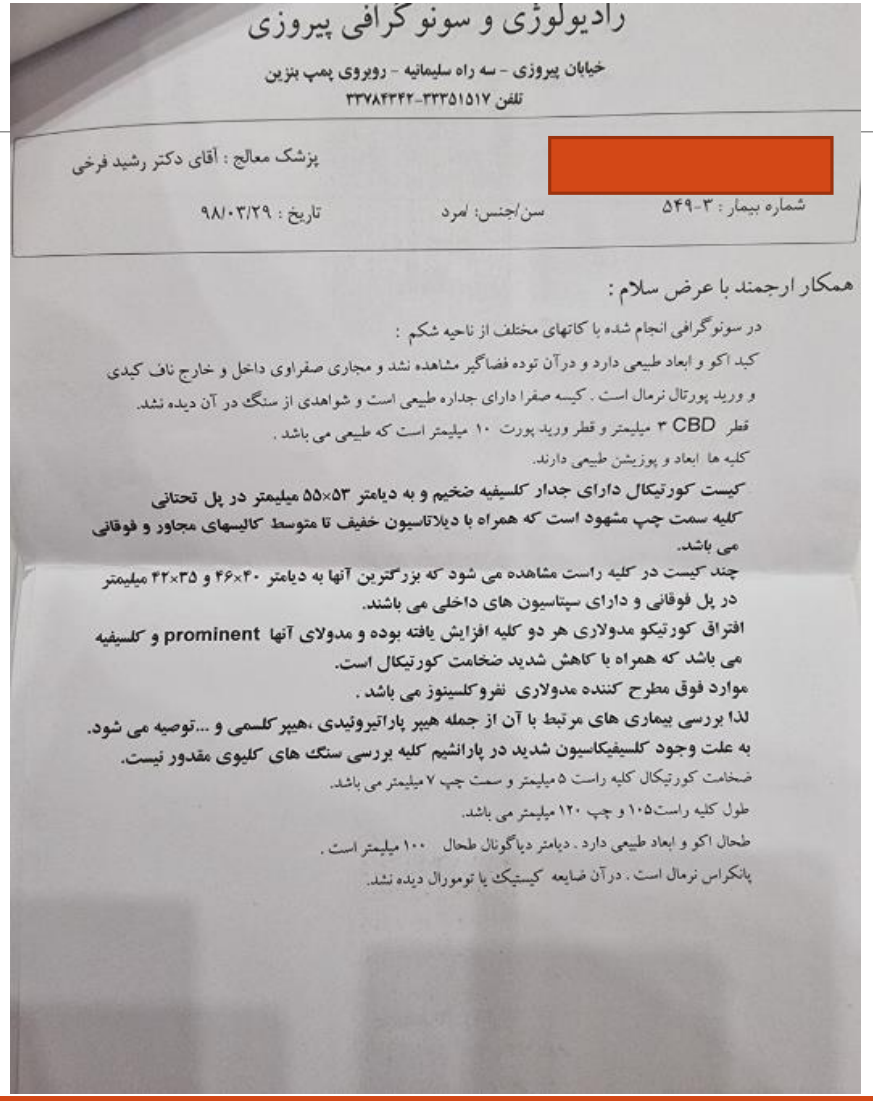
Comment :

دکتر سید مهدی بلوچی

دارنده تندیس کیفیت برتر در کسب رضایت مندی مشتری

تهران، پاسداران، میدان نوبنیاد، خیابان صنایع، پلاک۸، طبقه دوم واحد ۲۰۳ – ۲۰۲
Tel: +98 21 22 96 48 43 Fax: +98 21 26 91 05 95
www.roshalab.com E-mail: info@roshalab.com @roshalabch

Present illness



رادیولوژی و سونوگرافی پیروزی

خیابان پیروزی - سه راه سلیمانیه - روبروی پمپ بنزین

تلفن ۳۳۷۸۴۳۴۲-۳۳۳۵۱۵۱۷

پزشک معالج : آقای دکتر رشید فرخی

[redacted]

شماره بیمار : ۳-۵۴۹ سن/جنس: /مرد تاریخ : ۹۸/۰۳/۲۹

همکار ارجمند با عرض سلام :

در سونوگرافی انجام شده با کاتهای مختلف از ناحیه شکم :

کبد اکو و ابعاد طبیعی دارد و درآن توده فضاگیر مشاهده نشد و مجاری صفراوی داخل و خارج ناف کبدی و ورید پورتال نرمال است . کیسه صفرا دارای جداره طبیعی است و شواهدی از سنگ در آن دیده نشد.

قطر CBD ۳ میلیمتر و قطر ورید پورت ۱۰ میلیمتر است که طبیعی می باشد .

کلیه ها ابعاد و پوزیشن طبیعی دارند.

کیست کورتیکال دارای جدار کلسیفیه ضخیم و به دیامتر ۵۳×۵۵ میلیمتر در پل تحتانی کلیه سمت چپ مشهود است که همراه با دیلاتاسیون خفیف تا متوسط کالیسهای مجاور و فوقانی می باشد.

چند کیست در کلیه راست مشاهده می شود که بزرگترین آنها به دیامتر ۴۰×۴۶ و ۳۵×۴۲ میلیمتر در پل فوقانی و دارای سپتاسیون های داخلی می باشند.

افتراق کورتیکو مدولاری هر دو کلیه افزایش یافته بوده و مدولای آنها prominent و کلسیفیه می باشد که همراه با کاهش شدید ضخامت کورتیکال است.

موارد فوق مطرح کننده مدولاری نفروکلسینوز می باشد .

لذا بررسی بیماری های مرتبط با آن از جمله هیپر پاراتیروئیدی ،هیپرکلسمی و ...توصیه می شود.

به علت وجود کلسیفیکاسیون شدید در پارانشیم کلیه بررسی سنگ های کلیوی مقدور نیست.

ضخامت کورتیکال کلیه راست ۵ میلیمتر و سمت چپ ۷ میلیمتر می باشد.

طول کلیه راست۱۰۵ و چپ ۱۲۰ میلیمتر می باشد.

طحال اکو و ابعاد طبیعی دارد . دیامتر دیاگونال طحال ۱۰۰ میلیمتر است .

پانکراس نرمال است . درآن ضایعه کیستیک یا تومورال دیده نشد.

Present illness

After work up by The nephrologist ,The patient was Treated with;

- Enalapril 10mg BID
- Alopurinol 100mg Daily
- Tamsulosin 0.4mg Qhs.

The Patient was not Followed up until 1401 due to Covid Pandemic

Present illness

Lab data1401

PSA total	CBC	Cr	Ca	P	iPTH	25(OH)Vit D	ALK	Albumin	Uric acid
1.65 ng/ml	WBC:7000 Hb:14.9 Plt:237000	2.1 mg/dL	11.4 mg/dL	2.5 mg/dL	3 Pg/mL	65 ng/mL	126 U/L	4 gr/dL	9.1 mg/dL

Present illness

- During the follow-up, the patient is referred to an endocrinologist by the nephrologist.
- During these 5 years, the patient experienced a weight loss of ten kilograms and still exhibits symptoms of fatigue, polydipsia, and urinary symptoms such as nocturia, dribbling, feeling of incomplete emptying of urine, and decreased urine flow. However, the patient's hypertension was controlled with Enalapril 10mg twice daily.

Family Hx:

- His parents are cousins.
- Positive history of kidney stones in the patient's father, brother, and sister.
- The patient is unaware of the cause of his father's death.
- The patient's mother passed away due to esophageal cancer.

Family Hx:

- His older brother was hospitalized due to respiratory distress during the COVID-19 pandemic. Unfortunately, he passed away during hospitalization due to progressive renal failure that necessitated hemodialysis. He died after three sessions of hemodialysis.

DRUG Hx:

- Enalapril 10 mg BD
- Allopurinol 100mg Daily
- Tamsolusin 0.4mg Daily

Review of Systems

Headache(+) visual problem(-)

Weight loss(+) hotflashes(-) sexual problem(-)

Skin: pigmentation(+) diaphoresis(-) skin dryness(+)

Ears, nose, mouth : (no problem)

Cardiovascular: (HTN)

Review of Systems

Respiratory: (no Problem)

Gastrointestinal: constipation(+)

Musculoskeletal: (no problem)

Neurological: (no problem)

Psychiatric:(no problem)

Physical Examination

- **General Appearance:**
  - The patient is a 64-year-old man who appears well and non-toxic.

- **Vital signs at the time of presentation:**
  - Blood Pressure (BP): 120/70 mmHg
  - Heart Rate (HR): 65 beats per minute
  - Temperature (T): 36.5°C

Physical Examination

- Oxygen Saturation (SpO2): 96%
- Weight: 60 kg
- Height: 168 cm
- Body Mass Index (BMI): 21 kg/m²

- **Skin:**
  - Dryness

Physical Examination

- **Head and Neck:**
  - No pallor or cyanosis observed.
- **Lung:**
  - clear
- **Heart:**
  - Normal S1 S2
- **Abdomen:**
  - soft, no Hepatomegaly, no splenomegaly
- **Extremitis**:
  - Muscle power Normal

1403 Lab data

CBC	Ca	P	Cr	Vit D (25oH)	ALB	iPTH	ALP	ESR	ACE level
WBC:7000 Hb:15g/dl Plt:243000	Total:12.6 Ionized:6 (mg/dl)	3.1 mg/dl	2.6 mg/dl	68 ng/ml	4.9 gr/dl	7.2 pg/ml	58 u/l	11	16.5 u/l

1403 Lab data

24hr urine	TFT	ACTH(8AM)	Cortisol(8AM)	Pro Electrophoresis, Serum
V:3000 Cr:1410mg Ca:267mg Weight:60kg Clearance Cr:37.6ml/min Metanephrine:121mcg Normetanephrine:630mcg	NL	18Pg/ml	9mcg/dl	Total Protein:7.9gr/dl ALBUMIN:59.3% Alpha 1:3.8% Alpha 2:10.3% Beta 1:6.5% Beta 2:4.7% Gamma 15.4%

Problem List

64-year-old-man

iPTH Independent Hypercalcemia

Hypercalciuria/Nephrolithiasis

CKD

Family HX Nephrolithiasis

Renal Cysts

Agenda

DDX iPTH independent hypercalcemia?

Hypercalciuria,nephrolithiasis and nephrocalcinosis in this patient.

Which diagnosis is relevant for this Patient?

treatment options for this patient.

DDX IPTH Independent Hypercalcemia

- IPTH-independent hypercalcemia is characterized by elevated serum calcium levels in the presence of suppressed or inappropriately normal PTH levels. Common causes include:
  - Malignancy
  - Granulomatous disease
  - Endocrinopathy

DDX IPTH Independent Hypercalcemia

- Some less frequent causes are :
  - CYP24A1deficiency,associated with 24-Hydroxylase deficiency.
  - Foreign body granulomas.
- The diagnosis involves ruling out more common causes and identifying the specific underlying condition through laboratory tests, imaging, and sometimes genetic analysis.

DDX IPTH Independent Hypercalcemia

Hypercalcemia due to malignancy

- **Elevated PTHrp**
  - Solid tumors (Lung,head&neck, SCC, Rcc, Bladder)
  - PTHrP is a protein hormone that is structurally and functionally related to parathyroid hormone.

DDX IPTH Independent Hypercalcemia

Hypercalcemia due to malignancy

- **Local osteolytic hypercalcrmia**
  - Tumor cells produce cytokines that increase bone resorption and suppress bone formation, leading to increased calcium release into the bloodstream. It accounts for about 20% of hypercalcemia cases in cancer patients and commonly occurs in multiple myeloma and metastatic breast cancer.

DDX IPTH Independent Hypercalcemia

Hypercalcemia due to malignancy

- Excess production of 1,25-dihydroxyvitamin D by tumors can lead to increased intestinal calcium absorption and bone resorption
- Excess production of 1,25-dihydroxyvitamin D (1,25(OH)2D) is indeed a relatively rare phenomenon, accounting for around 1% of cases of hypercalcemia associated with malignancy.

DDX IPTH Independent Hypercalcemia

Hypercalcemia due to malignancy

Excess production of 1,25-dihydroxyvitamin D

The main mechanisms are:

1. Ectopic expression of the 1alpha hydroxylase enzyme by tumor cells can lead to increased conversion of 25-(OH)vitamin D to the active 1,25(OH)2D form. This phenomenon has been reported in cases of dysgerminomas and renal cell carcinoma.
2. Increased activity of 1alpha hydroxylase in macrophages or tumor-associated inflammatory cells within the lymphoma

DDX IPTH Independent Hypercalcemia

Granulomatous disease

- Hypercalcemia in granulomatous diseases such as sarcoidosis and tuberculosis is indeed caused by PTH-independent overproduction of 1,25-dihydroxyvitamin D by activated macrophages within the granulomas. This leads to increased intestinal calcium absorption and bone resorption, resulting in hypercalcemia. In this type of hypercalcemia, hypercalciuria is more common than overt hypercalcemia

- The frequency of hypercalcemia varies, reported in approximately 10% of sarcoidosis patients and up to 28% of tuberculosis patients in some series.

DDX IPTH Independent Hypercalcemia

Endocrinopathy

- **Hyperthyroidism:**

  Excess thyroid hormones can indeed increase bone turnover and resorption, leading to the release of calcium into the bloodstream. This can result in suppressed PTH levels.

- **Pheochromocytoma:**

  Some pheochromocytomas can indeed secrete PTHrP (parathyroid hormone-related protein), which can cause PTH-independent hypercalcemia.

- **Adrenal insufficiency**:

  Decreased cortisol production can lead to increased bone resorption and hypercalcemia, often with suppressed PTH levels

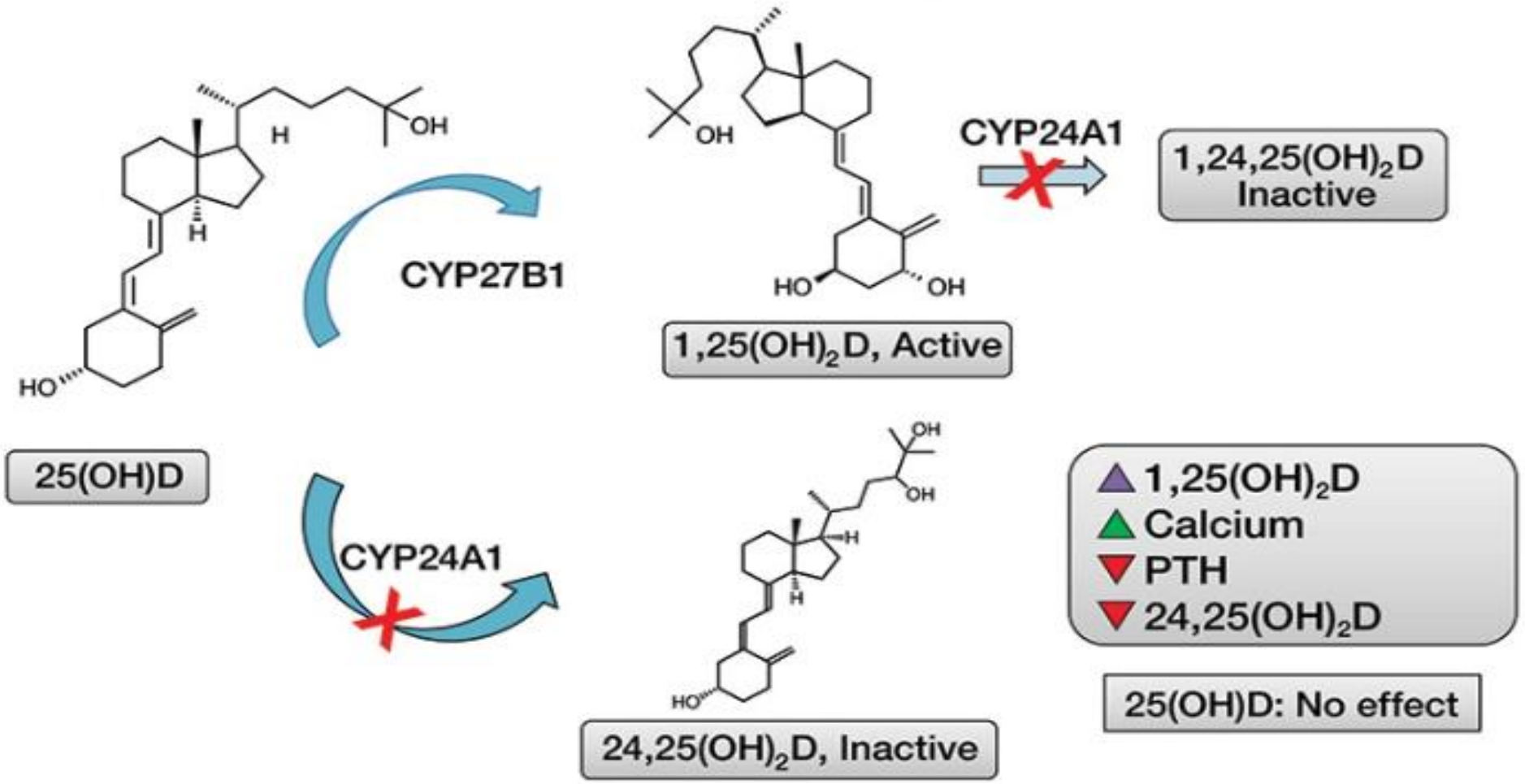
DDX IPTH Independent Hypercalcemia

1,25-(OH)2D-24 Hydroxylase deficiency

- 1,25-(OH)2D-24 hydroxylase (CYP24A1) deficiency is indeed a rare genetic disorder characterized by elevated levels of 1,25-dihydroxyvitamin D and hypercalcemia, which can lead to nephrocalcinosis and nephrolithiasis.

- mutations in the CYP24A1 gene, which encodes the 24-hydroxylase enzyme responsible for inactivating 1,25(OH)2D.

Loss of CYP24A1 Enzyme Function



Hypercalciuria, nephrocacinosis and nephrolithiasis in this patient

- What distinguishes this patient is nephrocalcinosis, which indicates that a chronic disease has occurred and requires a longer time to manifest. (Malignancy is almost ruled out)
- In sarcoidosis, nephrocalcinosis occurs in 5-13% of patients.
- The prevalence of nephrocalcinosis in CYP24A1 deficiency is notably higher, with 88.9% of patients exhibiting nephrocalcinosis. Comparatively, nephrocalcinosis is less common in sarcoidosis than in CYP24A1 deficiency.

Nephrocalcinosis and Renal cysts in this patient

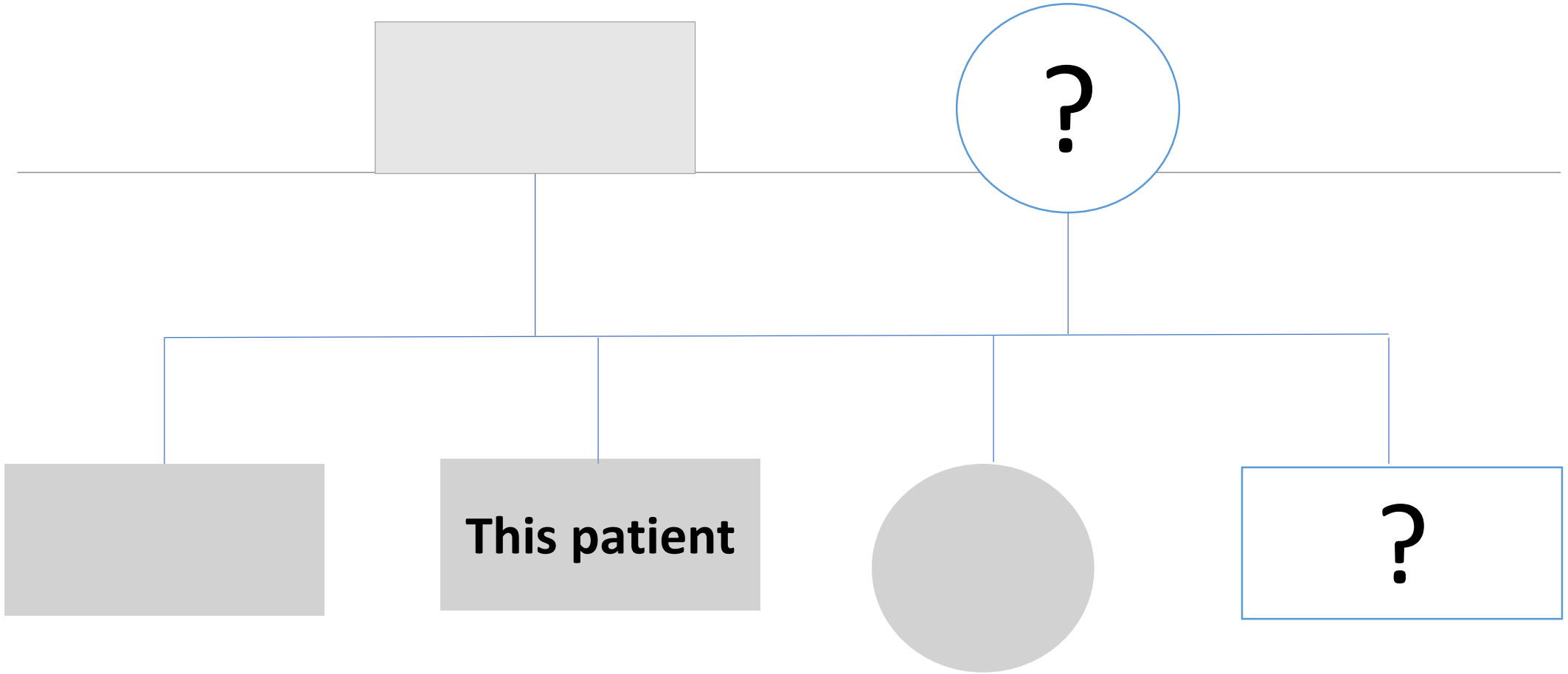
- Nephrocalcinosis is often associated with an increased prevalence of renal cysts. This relationship has been observed in patients with CYP24A1 deficiency, where there is a high prevalence of kidney cysts, with 38% of confirmed cases having medullary and/or corticomedullary junction cysts. The median age at first detected cyst was 37 years, and the mean number of cysts per patient was 5.3

Which diagnosis is relevant for this patient ?

- According to the 5-year history of the disease, physical examination, mild hypercalcemia, nephrocalcinosis, and laboratory tests, malignancy, granulomatous diseases such as sarcoidosis, and endocrinopathy are almost ruled out.

- family history of nephrolithiasis and renal failure in his father, brother, and sister, it seems that there is a monogenic genetic disease.

Inheritance of nephrolithiasis and renal failure in this patient's prdigree



Which diagnosis is relevant for this patient ?

- CYP24A1 deficiency, known as 24-hydroxylase deficiency (24HD), is characterized by hypercalcemia, nephrolithiasis, and nephrocalcinosis
- Loss-of-function variants in the CYP24A1 gene lead to impaired 24-hydroxylase activity, affecting the conversion of active vitamin D metabolites to inactive forms.
- Patients with 24HD may present with features such as hypercalcemia, nephrocalcinosis, and a positive family history, distinguishing them from other forms of vitamin D-mediated hypercalcemia and exogenous vitamin D toxicity

Diagnosis method

- Diagnosis of 24-Hydroxylase Deficiency (24HD) involves genetic testing to identify mutations in the CYP24A1 gene.
- Additionally ,biochemical profiles showing high active vitamin d metabolites,high or normal serum calcium and low PTH level , can suggest CYP24A1 mutation.

24-hydroxylase deficiency treatment

- Early diagnosis, appropriate treatment, and ongoing monitoring are crucial in managing 24-Hydroxylase Deficiency (24HD) to prevent complications associated with hypercalcemia, nephrolithiasis, and nephrocalcinosis.
- Vitamin D supplementation withdrawal and a low-calcium diet.
- The most frequent therapies included azoles (such as ketoconazole, fluconazole, or itraconazole) as modulators of CYP27B1 activity, and rifampin as a CYP3A4 inducer.

24-hydroxylase deficiency treatment

Rifampin,a potent inducer of the CYP3A4 enzyme,can provide an alternative pathway for the inactivation of 1,25-(OH)2D.

In two case studies,rifampin treatment at standard antituberculous dose(10mg/kg/day,up to 600mg daily)normalized serum calcium,phosphorus,and urinary calcium excretion in patients with biallelic CYP24A1 mutations.their results suggest that rifampin is an alternative treatment to consider in patients with recalcitrant hypercalcemia and/or hypercalciuria due to excessive 1,25 (OH)2D,but confirmation of this proposal should be explored with further studies.

References:

1.High prevalence of kidney cysts in patients with CYP24A1 deficiency

C Hanna, TA Potretzke, AG Cogal, YG Mkhaimer, PJ Tebben, VE Torres, JC Lieske…

Kidney International Reports, 2021•Elsevie DOI:10.1530/EJE-21-0713

2.Hypercalcemia due to ***CYP24A1*** mutations: a systematic descriptive review

D Cappellani, A Brancatella, R Morganti… - European Journal of …, 2022 academic.com

3. 24-Hydroxylase Deficiency Due to ***CYP24A1*** **Sequence Variants**: Comparison With Other Vitamin D–mediated Hypercalcemia Disorders

SM Azer, LE Vaughan, PJ Tebben… - Journal of the Endocrine …, 2021 - academic.oup.com

4. CYP3A4 Induction by Rifampin: An Alternative Pathway for Vitamin D Inactivation in Patients With *CYP24A1* Mutations

CP Hawkes, D Li, H Hakonarson… - The Journal of …, 2017 - academic.oup.com