A case with hypercalcemia

Arefeh shahabi, MD

- A 62-year-old man came to ER due to progressive decrease in LOC started 2 days before his admission.
- The patient seemed ill, confused , disoriented and couldn’t communicate. But arousable.
- Vital signs:
- BP=90/70
- PR=90
- Not febrile
- spo2=98%(with o2 therapy)



- A precise physical exam was performed:
- There were no evidence of focal neurologic deficit, pupillary light reflex was normal.
- Fine crackles in lung
- Normal heart examination.
- 1+ pitting edema of the lower extremities.
- Flapping tremor was present in lower limbs

- **Past medical history :**

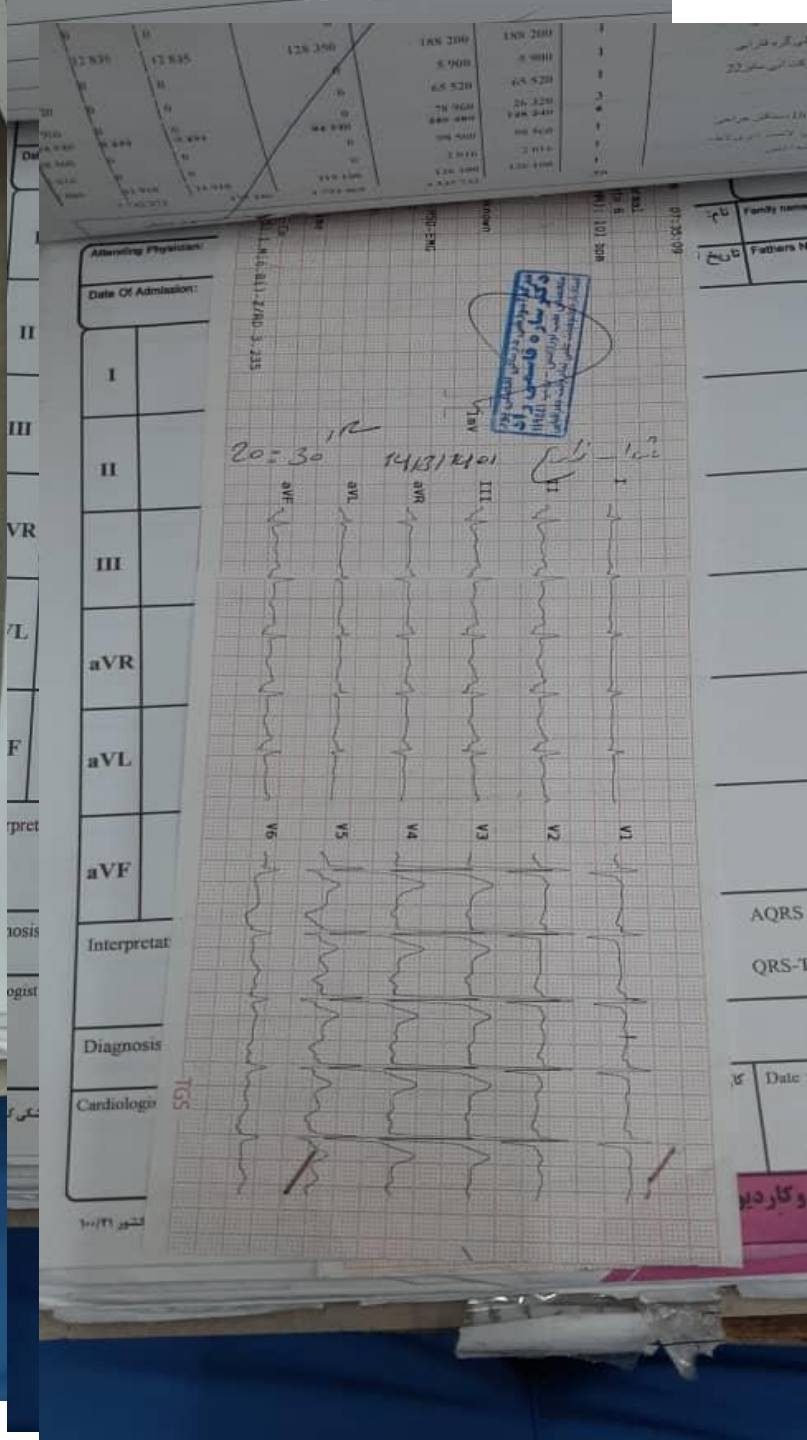
metastatic laryngeal cancer which underwent several sessions of chemotherapy .(he had a tracheostomy)

- **Social history:** opium addicted
- **Drug history:**

Cap pregabalin 75mg QHS

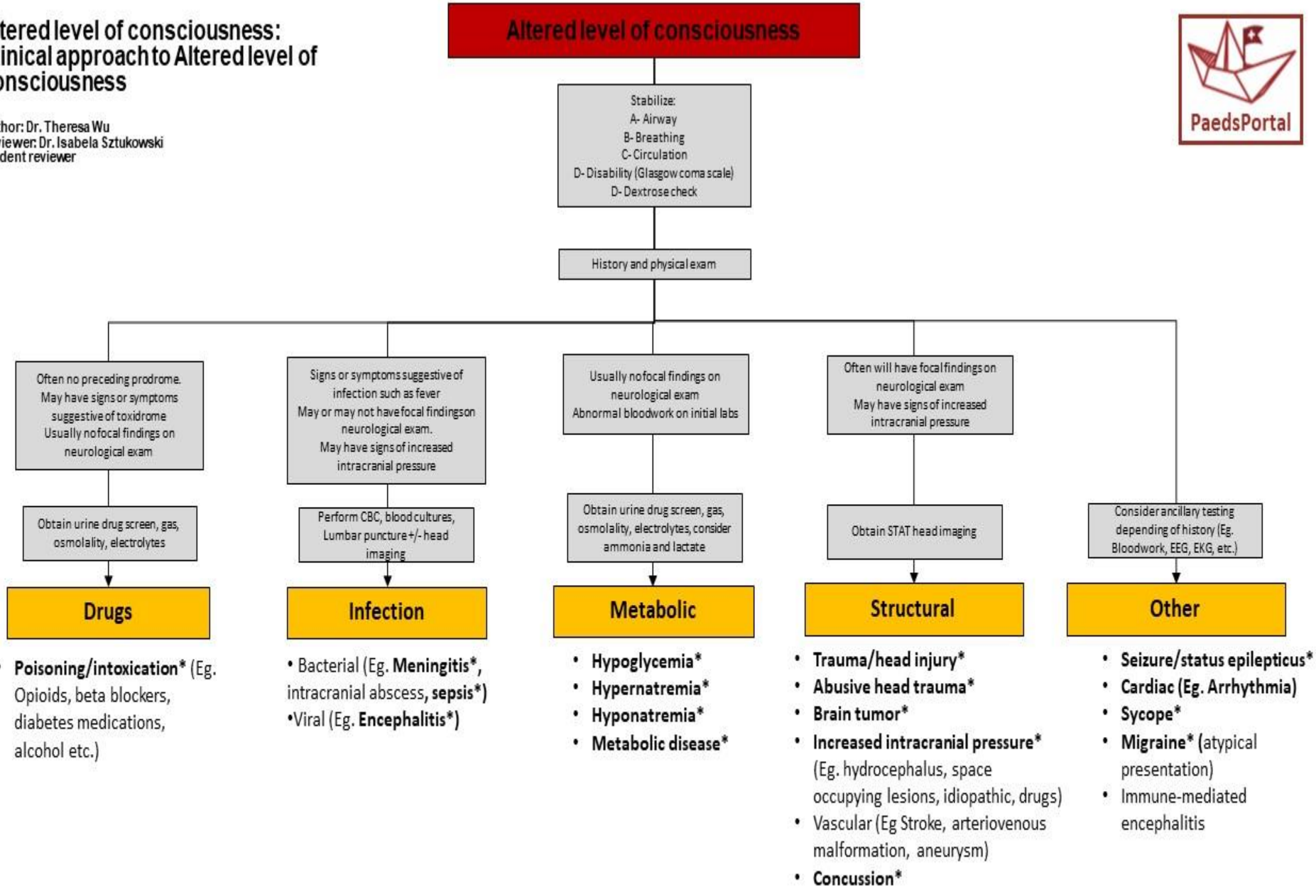
Tab Cotrimuxazole 400/80 Bid




Attending Physician:
Date Of Admission:
I
II
III
aVR
aVL
aVF
Interpretat
Diagnosis
Cardiologis
AQRS
QRS-T
Date

Altered level of consciousness: Clinical approach to Altered level of consciousness

Author: Dr. Theresa Wu
Reviewer: Dr. Isabela Sztukowski
Student reviewer



*Indicates Key Condition

This is not an exhaustive list of medical conditions.

What was the cause of decreased LOC?

- **Drug & toxins?**

No history , normal UA toxicology

- **Infection ?**

mucopurulent rhinorrhea, negative blood cultures

- **CNS?**

No FND, normal brain imaging, no neck stiffness



Metabolic causes?

- **Hypercarbia?/ hypoxemia?**

Pco2= 38 / spo2=98%

- **Hypo/hyper glycemia?**

BS=118

- **Liver failure?**

AST=24, ALT=6, Alkp= 270 , INR=1.1



- **Cardiac failure?**

No evidence

- **Renal failure?**

Cr=4.5, Urea= 200, k=5, flapping tremor present

- **Electrolyte disturbance?**

Na=135, Mg=2.0, P=4.5, *Ca+=6…7*

WBC	17.000
HB	7.8
PLT	224
Na	135
K	5
Ca++	7 (*2)
Mg	2
P	4.5
Cr	4.5
PH	7.40
PCO2	38
HCO3	20

Hypercalcemia signs & symptoms

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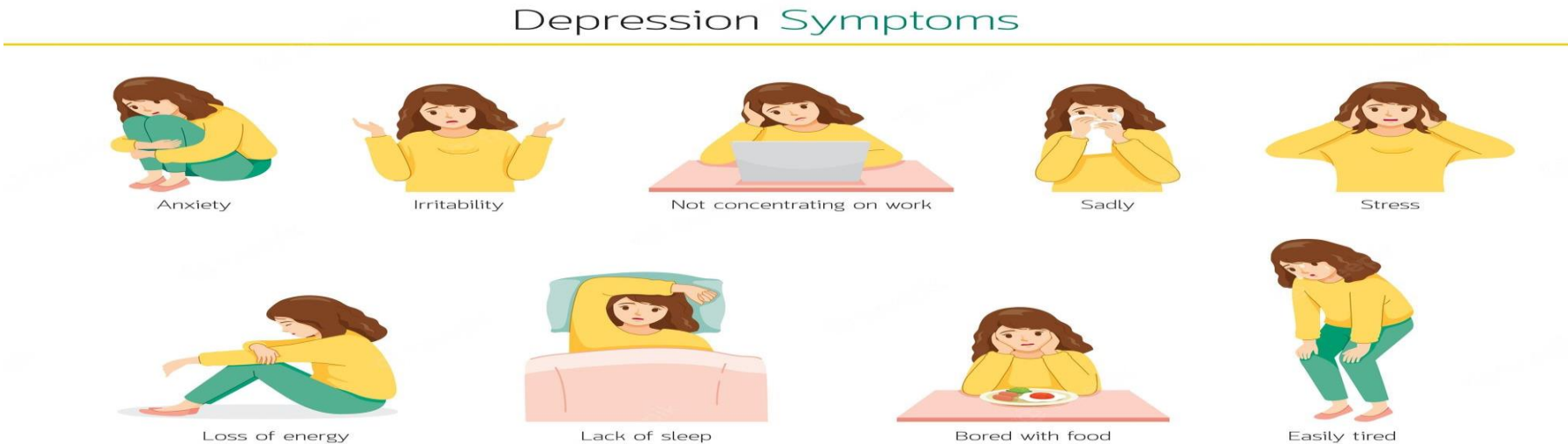
MEDINAZ

Clinical manifestation

- Patients with mild hypercalcemia (calcium above the upper limit of normal but <12 mg/dL [3 mmol/L]) may be asymptomatic, or they may report nonspecific symptoms, such as constipation, fatigue, and depression.
- A moderately elevated serum calcium of 12 to 14 mg/dL (3 to 3.5 mmol/L) may be well tolerated chronically, while an acute rise to these concentrations may cause marked symptoms, including polyuria, polydipsia, dehydration, anorexia, nausea, muscle weakness, and changes in sensorium
- In patients with severe hypercalcemia (calcium >14 mg/dL [3.5 mmol/L]), there is often progression of these symptoms

NEUROPSYCHIATRIC DISTURBANCES

- anxiety, depression, and cognitive dysfunction.
- More severe symptoms, including lethargy, confusion, stupor, and coma may occur in patients with severe hypercalcemia (calcium >14 mg/dL [3.5 mmol/L]) from any cause These symptoms are more likely to occur in older adults and in those with rapidly rising calcium concentrations



GASTROINTESTINAL ABNORMALITIES

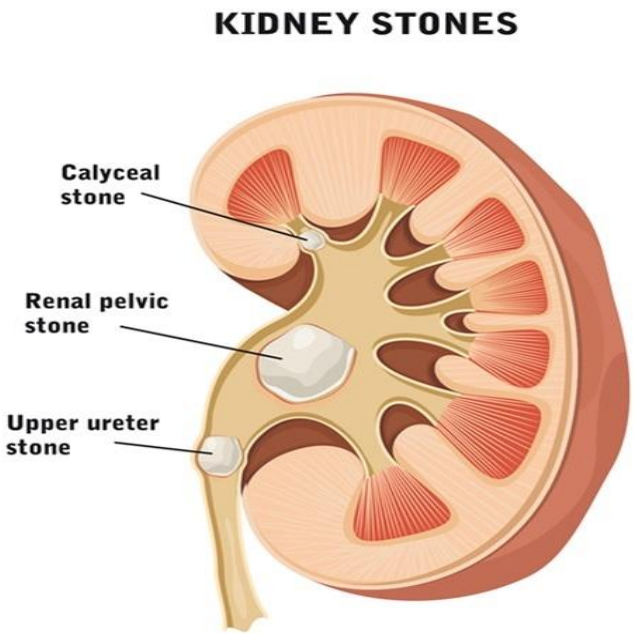
- constipation, anorexia, and nausea, occur commonly.

- Pancreatitis and peptic ulcer disease occur less frequently than other gastrointestinal



RENAL DYSFUNCTION

- polyuria (resulting from decreased concentrating ability in the distal tubule),
- nephrolithiasis,
- acute and chronic renal insufficiency

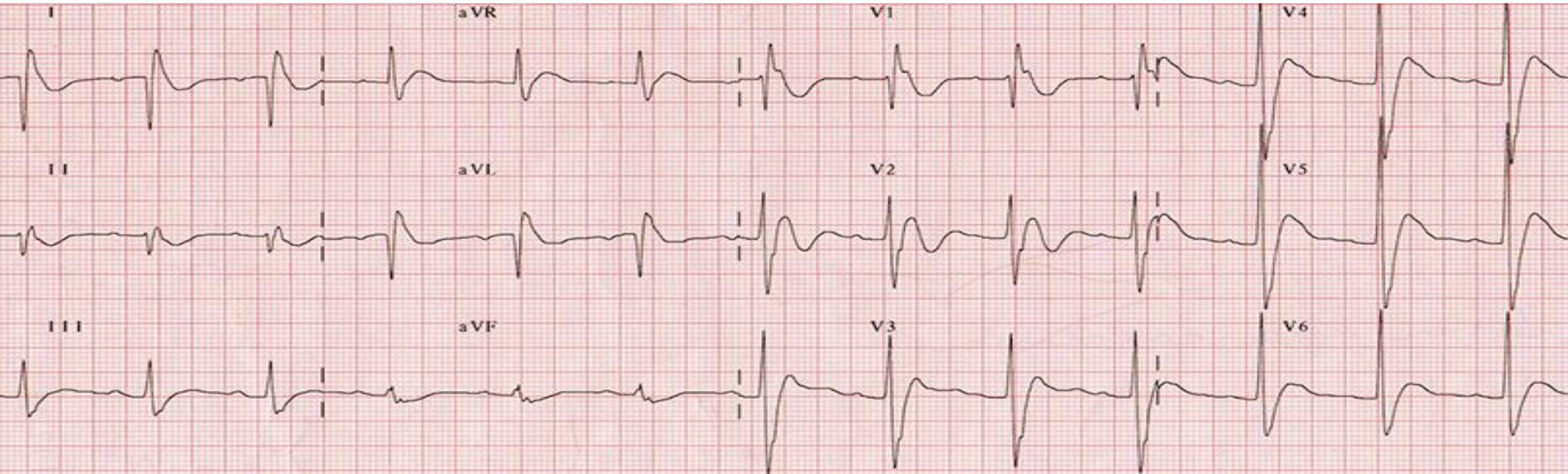




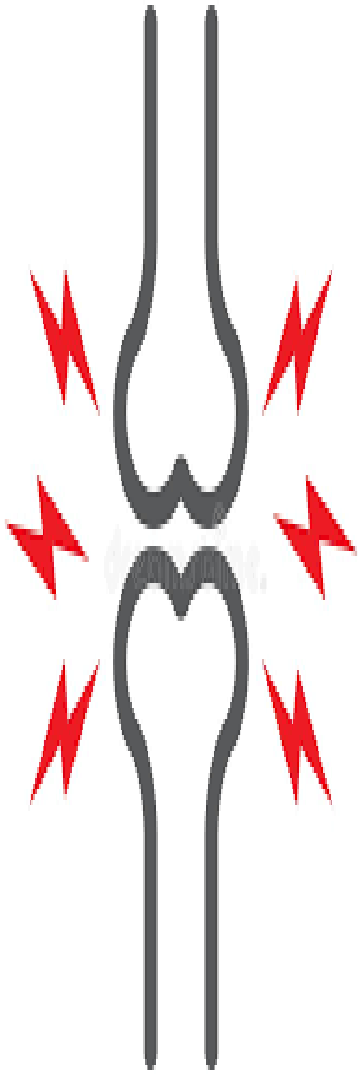
CARDIOVASCULAR DISEASE

- Acute hypercalcemia directly shortens the myocardial action potential, which is reflected in a **shortened QT interval** .
- arrhythmia has been described in patients with severe hypercalcemia.
- In addition, ST segment elevation mimicking myocardial infarction has been reported in such patients
- Longstanding hypercalcemia, as occurs in primary hyperparathyroidism, can lead to other cardiac abnormalities, including deposition of calcium

in heart valves, coronary arteries, and myocardial fibers; hypertension; and cardiomyopathy.



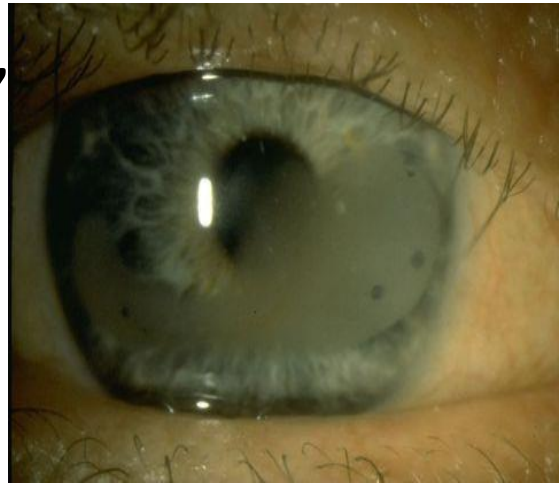
MUSCULOSKELETAL SYMPTOMS



- Profound muscle weakness was prominent in the original description of patients with hyperparathyroidism
- Bone pain can occur in individuals with hypercalcemia due to malignancy or primary hyperparathyroidism.
- A reduction in cortical bone mass may occur in individuals with hyperparathyroidism

PHYSICAL FINDINGS

- There are usually no specific physical findings of hypercalcemia other than those that might be related to an underlying disease, such as malignancy, and nonspecific findings related to dehydration.
- ***Band keratopathy***, a reflection of subepithelial calcium phosphate deposits in the cornea, is a very rare finding .



- It extends as a horizontal band across the cornea in the area that is exposed between the eyelids; It is usually detected by slit-lamp examination.



Diagnostic approach

- The first step in the evaluation of a patient with hypercalcemia is to verify with **repeat measurement** (total calcium corrected for albumin) that there is a true increase in the serum calcium concentration.
- If available, previous values for serum calcium should also be reviewed

- 40 to 45 percent of the calcium in serum is bound to protein, principally albumin. So don't forget the correction!

- The degree of hypercalcemia also may be useful diagnostically. Primary hyperparathyroidism is often associated with borderline or mild hypercalcemia (serum calcium concentration often below 11 mg/dL [2.75 mmol/L]). Values above 13 mg/dL (3.25 mmol/L) are unusual in primary hyperparathyroidism, although they do occur; they are more common in patients with malignancy-associated hypercalcemia. (

Clinical clues…

there are several features of the clinical evaluation
that may help to differentiate the etiology of hypercalcemia:

- Clinical findings that favor the diagnosis of primary hyperparathyroidism include an asymptomatic patient with chronic hypercalcemia, a postmenopausal woman, a normal physical examination, no other obvious cause of hypercalcemia (such as sarcoidosis), a family history of hyperparathyroidism, and evidence of multiple endocrine neoplasia. (
- Patients with hypercalcemia of malignancy often have higher concentrations of, and more rapid increases in, serum calcium and consequently are more symptomatic .
- A review of diet and medications (prescription and nonprescription drugs, herbal preparations, calcium and vitamin supplements) is important to assess for the milk-alkali syndrome and drug-induced hypercalcemia





Laboratory evaluation

- The initial goal of the laboratory evaluation is to differentiate parathyroid hormone (PTH)-mediated hypercalcemia (primary and tertiary hyperparathyroidism, and familial hyperparathyroid syndromes) from non-PTH mediated hypercalcemia (primarily malignancy, vitamin D intoxication, granulomatous disease)
- **Thus, once hypercalcemia is confirmed, the next step is measurement of serum PTH**

- **A frankly elevated PTH** concentration in the setting of hypercalcemia is likely the result of primary hyperparathyroidism
- **Mid- to upper-normal or minimally elevated parathyroid hormone**
- Ten to 20 percent of patients with primary hyperparathyroidism have a serum PTH concentration in the upper end of the normal range; such a "normal" level (ie, not suppressed but not frankly elevated) is also virtually diagnostic of primary hyperparathyroidism since it is still inappropriately high considering the presence of hypercalcemia .
- However, in this circumstance, the diagnosis of familial hypocalciuric hypercalcemia also should be considered, and urinary calcium excretion (24-hour urinary calcium or calcium-to-creatinine ratio) should be measured

Low-normal or low parathyroid hormone

- In the presence of low serum PTH concentrations (<20 pg/mL), PTH-related protein (PTHrp) and vitamin D metabolites should be measured to assess for hypercalcemia of malignancy and vitamin D intoxication .
- If PTHrp and vitamin D metabolites are also low, another source for the hypercalcemia must be considered
- Additional laboratory data (including serum protein electrophoresis [SPEP] for possible multiple myeloma, thyroid-stimulating hormone [TSH], vitamin A) may lead to the correct diagnosis

- **PTH-related protein**
- Humoral hypercalcemia of malignancy is one of the most common causes of non-parathyroid hormone (PTH)-mediated hypercalcemia. It should be particularly suspected if there is clinical evidence of malignancy, usually a solid tumor, and the hypercalcemia is of relatively recent onset.
- Thus, if the patient has longstanding hypercalcemia and a low serum PTH, one should consider one of the other non-PTH-mediated disorders rather than a malignancy .
- The diagnosis of humoral hypercalcemia of malignancy can be confirmed by demonstrating an elevated serum concentration of PTHrp .
- However, this assay *is usually not necessary for diagnosis*, since most patients have clinically apparent malignancy.
- Levels of PTH and 1,25-dihydroxyvitamin D (calcitriol) are usually appropriately suppressed in these patients



metabolites

Serum concentrations of the vitamin D metabolites, 25-hydroxyvitamin D (25[OH]D, calcidiol) and 1,25-dihydroxyvitamin D (calcitriol), should be measured if there is no obvious malignancy and PTH is not elevated.

- In patients **with elevated 1,25-dihydroxyvitamin D**, chest radiograph (looking for malignancy or sarcoidosis) may be helpful.
- Patients with granulomatous disease or lymphoma generally have widespread pulmonary and extrapulmonary disease. In the absence of such involvement, a systematic search for occult pulmonary, renal, hepatic, ocular, and bone marrow granulomas is indicated when no other cause for increased 1,25-dihydroxyvitamin D is apparent.

✓ Other tests

- The presence of low serum levels of PTH, PTHrp, and low or normal vitamin D metabolites suggests some other source for the hypercalcemia.
- In the absence of malignancy or increased PTHrp, unsuspected stimulation of bone resorption (as with *multiple myeloma, thyrotoxicosis, immobilization, or vitamin A toxicity) and unrecognized calcium intake in the face of renal insufficiency* (as in the milk-alkali syndrome) are the most likely candidates [



- Elevated serum calcium
- Check repeat (total calcium corrected for albumin or ionized calcium)
- Hypercalcemia confirmed by repeat measurement
- Measure intact PTH
  - Elevated → Primary hyperparathyroidism Δ
  - Mid to upper normal or minimally elevated* → Primary hyperparathyroidism likely, consider FHH ◇
  - Low-normal or low → Non-PTH mediated hypercalcemia
    - Measure:
      - PTHrP
      - 1,25-dihydroxyvitamin D
      - 25-hydroxyvitamin D
    - Is PTHrp elevated?
      - Yes → Humoral hypercalcemia of malignancy more likely §
      - No → Is 1,25-dihydroxyvitamin D elevated?
        - Yes → Lymphoma, granulomatous diseases (sarcoidosis, tuberculosis) more likely
        - No → Is 25-hydroxyvitamin D elevated? ¶
          - Yes → Vitamin D intoxication more likely
          - No → Measure:
            - SPEP
            - UPEP
            - Serum free light chain assay
            - Abnormal → Multiple myeloma
            - Normal → Assess for other diagnoses (vitamin A intoxication, hyperthyroidism)

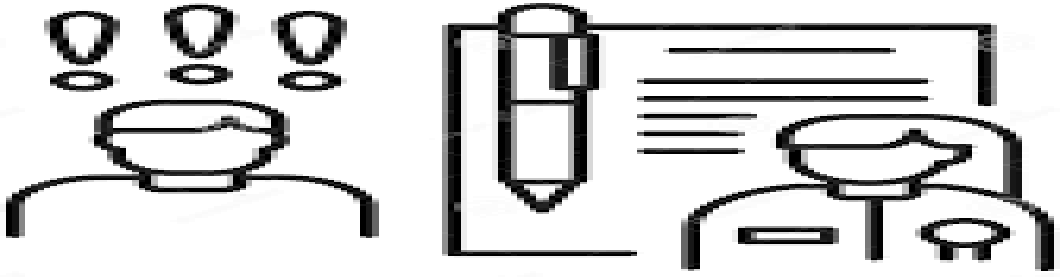
PTH mediated	Non-PTH mediated	Meds	Other
Primary hyoerparathyroidism	Malignancy: • PTHrp • Increased calcitriol • Osteolytic bone MTX	thiazids	Hyperthyroidism
MEN	Vitamin D intoxication	lithium	Acromegally
Familial isolated hyperparathyroidism	Chronic granulomatos disorders	Abaloparatide	Pheochromocytoma
Hyperparathyroidism-jaw tumor		Excessive vitA	Adrenal nsufficiency
FHH		Theophylline toxicity	Immobilization
Tertiary hyperparathyroidism(renal failure)			TPN
			Milk-alkali synd.

WBC	17.000							
HB	7.8							
PLT	224							
Na	135							140
K	5							4
Ca	7+	6.6	6.7	6.7	6	4.8	4.1	4
Mg	2							
P	4.5							3.9
Cr	4.5	2.9	1.9	1.5	1.2	0.7	1.1	0.9
PH	7.40							
PCO2	38							
HCO3	20							
PTH	6.25							
Vit D	17							



What did we do?

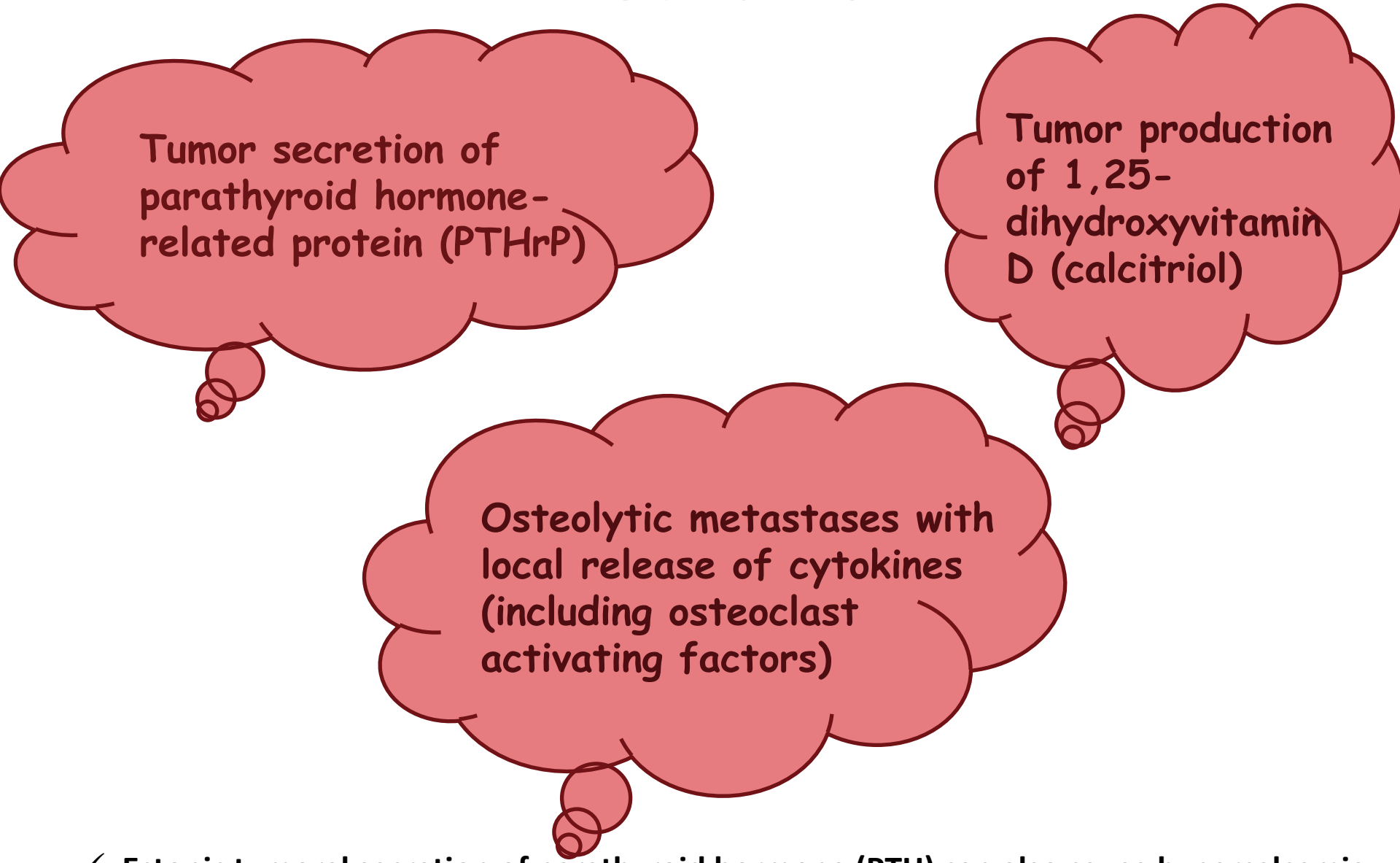
- Started a hemodialysis due to uremia and hypercalcemia, IV Antibiotics
- Stepwise approach to find out the cause of hypercalcemia .
- Due to persistence of hypercalcemia, other therapeutic options were added.



Hypercalcemia of malignancy

- Hypercalcemia is relatively common in patients with cancer,
- It is the most common cause of hypercalcemia in the **inpatient** setting.
- It occurs in patients with both solid tumors and hematologic malignancies.
- The most common cancers associated with hypercalcemia in the United States are **breast, renal, and lung cancer and multiple myeloma** .
- Malignancy is usually evident clinically by the time it causes hypercalcemia, and patients with hypercalcemia of malignancy often have a poor prognosis ☹

Mechanism



- ✓ **Ectopic tumoral secretion of parathyroid hormone (PTH) can also cause hypercalcemia, but it is rare.**

PTHrp

- The most common cause of hypercalcemia in patients with **nonmetastatic solid tumors** and in some patients with **non-Hodgkin lymphoma** is secretion of parathyroid hormone (PTH)-related protein (PTHrP);
- this condition, also called humoral hypercalcemia of malignancy **(HHM),** accounts for up to **80 percent** of patients with hypercalcemia of malignancy .
- Patients with HHM most often have **squamous cell carcinomas (lung, head, and neck) or renal, bladder, breast**, or **ovarian carcinomas**

- **LAB**

✓ **Elevated serum PTHrP**
✓ **Very low or suppressed serum intact PTH (secretion of endogenous PTH is suppressed by PTHrP-mediated hypercalcemia)**
✓ **Normal to low serum 1,25-dihydroxyvitamin D**

Osteolytic Metastasis

- Osteolytic metastases account for approximately **20 percent** of cases of hypercalcemia of malignancy .
- Induction of local osteolysis by tumor cells is common with some solid tumors that are metastatic to bone and with **multiple myeloma, but it is less common with lymphoma and leukemia**

- **LAB:**

- **Low or suppressed serum intact PTH**
- **Low or low-normal serum 1,25-dihydroxyvitamin D**
- **Low or low-normal serum PTHrP (although tumor metastases in bone may secrete PTHrP locally, it is not usually measurable in a serum assay)**
- **Extensive skeletal metastases or marrow infiltration**

1,25-dihydroxyvitamin D

- Increased production of 1,25-dihydroxyvitamin D (calcitriol) is the cause of almost all cases of hypercalcemia in **Hodgkin lymphoma** and approximately one-third of cases in non-Hodgkin lymphoma.

- Hypercalcemia should suppress the release of PTH and therefore production of calcitriol

- The lack of suppression of 1,25-dihydroxyvitamin D production in lymphoma is due to PTH-independent extrarenal production of 1,25-dihydroxyvitamin D from 25-hydroxyvitamin D by malignant lymphocytes, macrophages, or both.

- **LAB:**
- **low or suppressed serum intact PTH**
- **elevated 1,25-dihydroxyvitamin D**

- ***Was it necessary to check PTH in this patient?***

➢ There appears to be a higher incidence of primary hyperparathyroidism in patients with malignancy than in the general population .Thus, it is reasonable to order an intact PTH assay as part of the routine evaluation for hypercalcemia, even in a patient with known malignant disease.

Therapeutic challenges

- **Could we start hydration and diuretic therapy for this patient?**
- **Is there a difference in choosing dialysis fluid?**
- **What should we do for treating persistent hypercalcemia despite dialysis?**
- **Are we allowed to use calcitunin or bisphosphonates in this patient?**




Thanks!