



# ▶ Malignancy related hypercalcemia

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- ▶ A 38 year's old man with nausea, vomiting and loss of consciousness was admitted to emergency room with initial suspicion of covid-19. But he was transferred to Endocrine section after detection of severe hypercalcemia in his initial LABs.
  - ▶ He had a history of polyuria, polydipsia, constipation and weight loss(10 kg) in 3 last months. He had no fever and night sweating. He complains of painful mass like lesions in his thigh and arm from 40 days ago which was candidate for biopsy and tissue diagnosis.
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- ▶ General  $p^h/_{Ex}$  was unremarkable .
  - ▶ limbs examination revealed a firm none mobile and none tender mass, measured 10\*6\*4cm and a similar mass measured 20\*15cm in right thigh. Which caused hip joint movement limitation.
  - ▶ No dominant peripheral lymphadenopathy was detected.
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- A decorative graphic consisting of several parallel white lines of varying lengths and orientations, located in the bottom right corner of the slide.

<b>CBC</b> <b>Ferittin=259</b> <b>Fe=59</b>	<b>WBC:7000(Lym: %6.2 )</b>	<b>Hb:12.8</b> <b>TIBC=259</b>	<b>Mcv:88</b>	<b>Plt:217000</b>
<b>ESR=20</b>	BS=95, Urea=68 ,Cr=1.7	Na=141, K=4.2	Ca=16.5 iCa =2.1	P=4.2 Mg=1.4
<b>PTH&lt;3</b> <b>Vit D=28</b>	AST=79,ALT=52,ALK=131	Alb=3.8	LDH=3000 Cpk=56	Uric acid =12

# RIGHT THIGH AND ARM MASS LESION BIOPSY REVEALED:

## Gross Description

Received in two containers:

- 1) Labeled as "right thigh lesion" consists of multiple cream colored soft tissues M= 5x3x2 cm  
SOS=6/3 E=10%
- 2) Labeled as "right arm lesion" consists of multiple cream colored soft tissues M= 2x1 cm  
SOS=m/1 E=T

## Diagnosis

- 1) Right thigh lesion; biopsy:  
- Diffuse large B-cell lymphoma with BCl6 expression .
- 2) Right arm lesion; biopsy:  
- Diffuse large B-cell lymphoma.

## Diagnosis

IHC result:

- 1)  
ck=Negative  
CD99=Negative  
CD45=Positive  
BCl2=Negative  
BCl6=Positive  
This IHC result are in favor of diffuse large B-cell lymphoma with BCl6 expression.
- 2)  
CD45=Positive  
CD20=Positive  
CD1a=Negative  
PAX5=Positive  
S100=Negative  
These IHC result are in favor of diffuse large B-cell lymphoma .

The background features a dark blue gradient with several white circular gauges and arrows. One large gauge on the left has numerical markings from 140 to 260. Other gauges are smaller and scattered across the frame, some with arrows indicating clockwise or counter-clockwise movement. The overall aesthetic is technical and scientific.

# APPROACH TO THE HYPERCALCEMIC PATIENT



# INTRODUCTION AND ETIOLOGY

- Hypercalcemia is a **relatively common** clinical problem.
- Among all causes of hypercalcemia, primary **hyperparathyroidism** and **malignancy** are the most common, accounting for greater than 90 percent of cases.
- Therefore, the diagnostic approach to hypercalcemia typically involves distinguishing between the two.
- The many other causes of hypercalcemia occur less frequently but are important to consider in clinical situations when hypercalcemia is not caused by hyperparathyroidism or malignancy.

**TABLE 403-1 Classification of Causes of Hypercalcemia****I. Parathyroid-Related**

- A. Primary hyperparathyroidism
  - 1. Adenoma(s)
  - 2. Multiple endocrine neoplasia
  - 3. Carcinoma
- B. Lithium therapy
- C. Familial hypocalciuric hypercalcemia

**II. Malignancy-Related**

- A. Solid tumor with metastases (breast)
- B. Solid tumor with humoral mediation of hypercalcemia (lung, kidney)
- C. Hematologic malignancies (multiple myeloma, lymphoma, leukemia)

**III. Vitamin D–Related**

- A. Vitamin D intoxication
- B. ↑  $1,25(\text{OH})_2\text{D}$ ; sarcoidosis and other granulomatous diseases
- C. ↑  $1,25(\text{OH})_2\text{D}$ ; impaired  $1,25(\text{OH})_2\text{D}$  metabolism due to 24-hydroxylase deficiency and inactivating mutations in the sodium-dependent phosphate co-transporters


**IV. Associated with High Bone Turnover**

- A. Hyperthyroidism
- B. Immobilization
- C. Thiazides
- D. Vitamin A intoxication
- E. Fat necrosis

**V. Associated with Renal Failure**

- A. Severe secondary hyperparathyroidism
- B. Aluminum intoxication
- C. Milk-alkali syndrome



- The diagnostic approach to the hypercalcemic patient is strongly influenced by the clinical setting
  - Among **outpatients** referred to endocrinologists for evaluation of hypercalcemia, more than 90% are found to have primary hyperparathyroidism.
  - In **ill or hospitalized** patients, malignant disease is the cause in more than 50% of cases.
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# CLINICAL MANIFESTATIONS

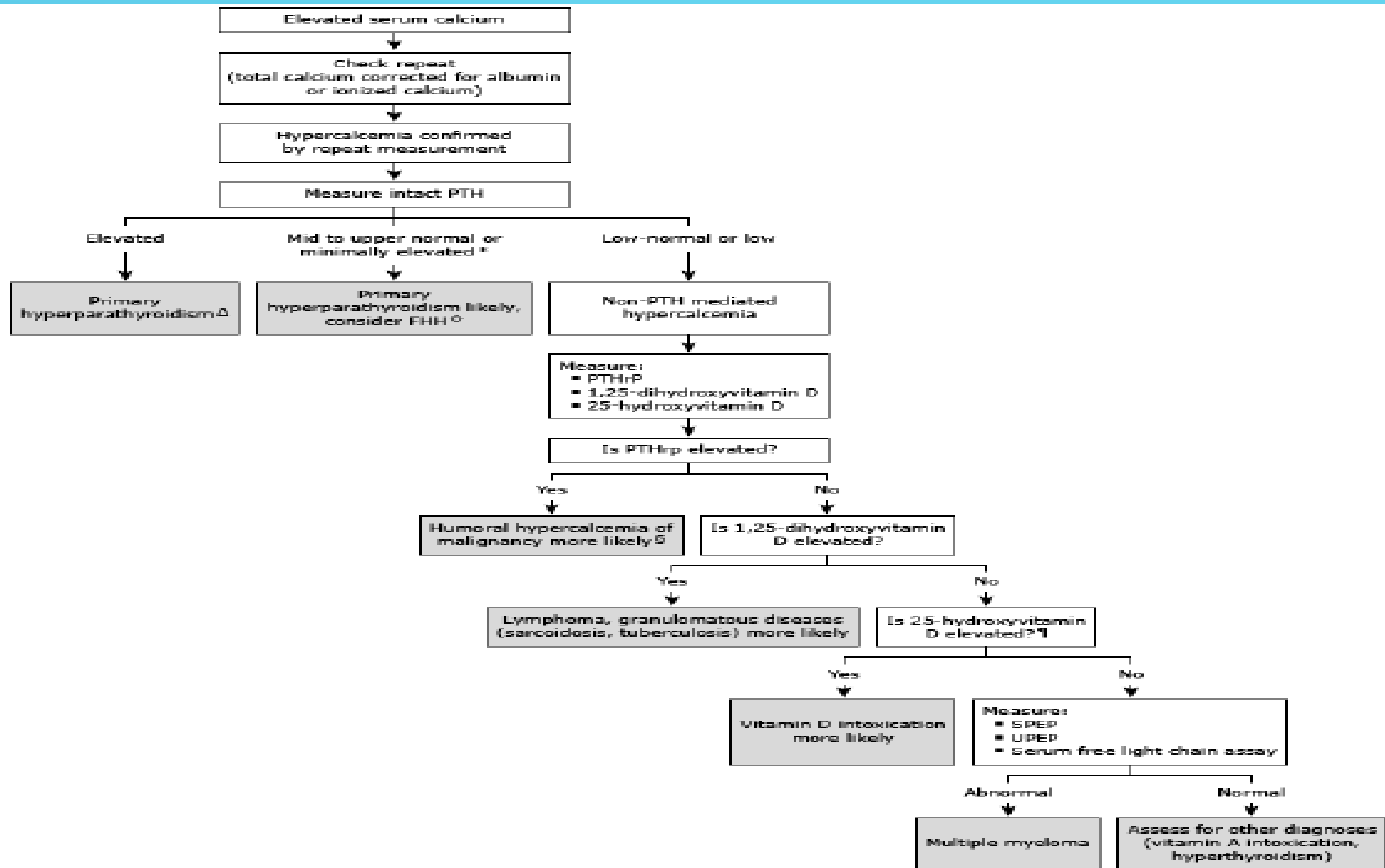
- ▶ The symptoms of hypercalcemia depend upon both **the degree** of hypercalcemia and the **rate of onset of the elevation** in the serum calcium concentration
- ▶ Patients with **mild hypercalcemia (calcium <12 mg/dL)** may be asymptomatic, or they may report nonspecific symptoms, such as constipation, fatigue, and depression
- ▶ A serum calcium of **12 to 14 mg/dL** 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)** there is often progression of these symptoms

# DIAGNOSTIC APPROACH

## ▶ Clinical clues

- 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
- review of diet and medications

- 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.
- it is important to distinguish **hemoconcentration** or rare instances of calcium-binding **paraproteinemia** or **thrombocythemia**-associated hypercalcemia (due to release of intracellular calcium in vitro) from a true increase in serum ionized Calcium
- The **single most important test** in the differential diagnosis of hypercalcemia is the measurement of serum **PTH**, preferably in a two-site assay specific for the intact, biologically active molecule



Elevated serum calcium



Check repeat  
(total calcium corrected for albumin  
or ionized calcium)

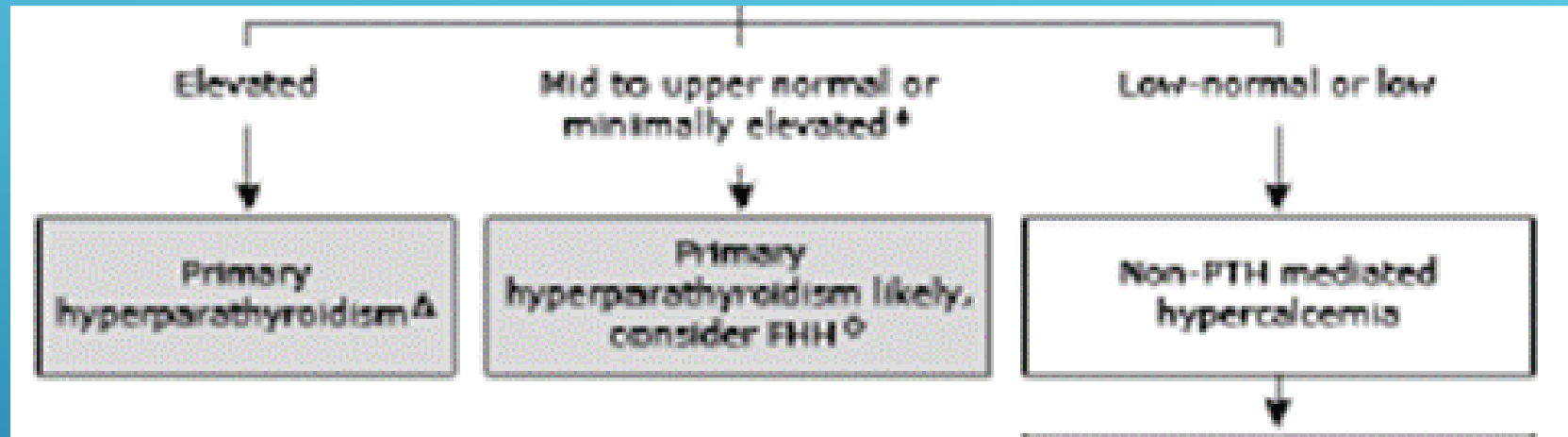


Hypercalcemia confirmed  
by repeat measurement

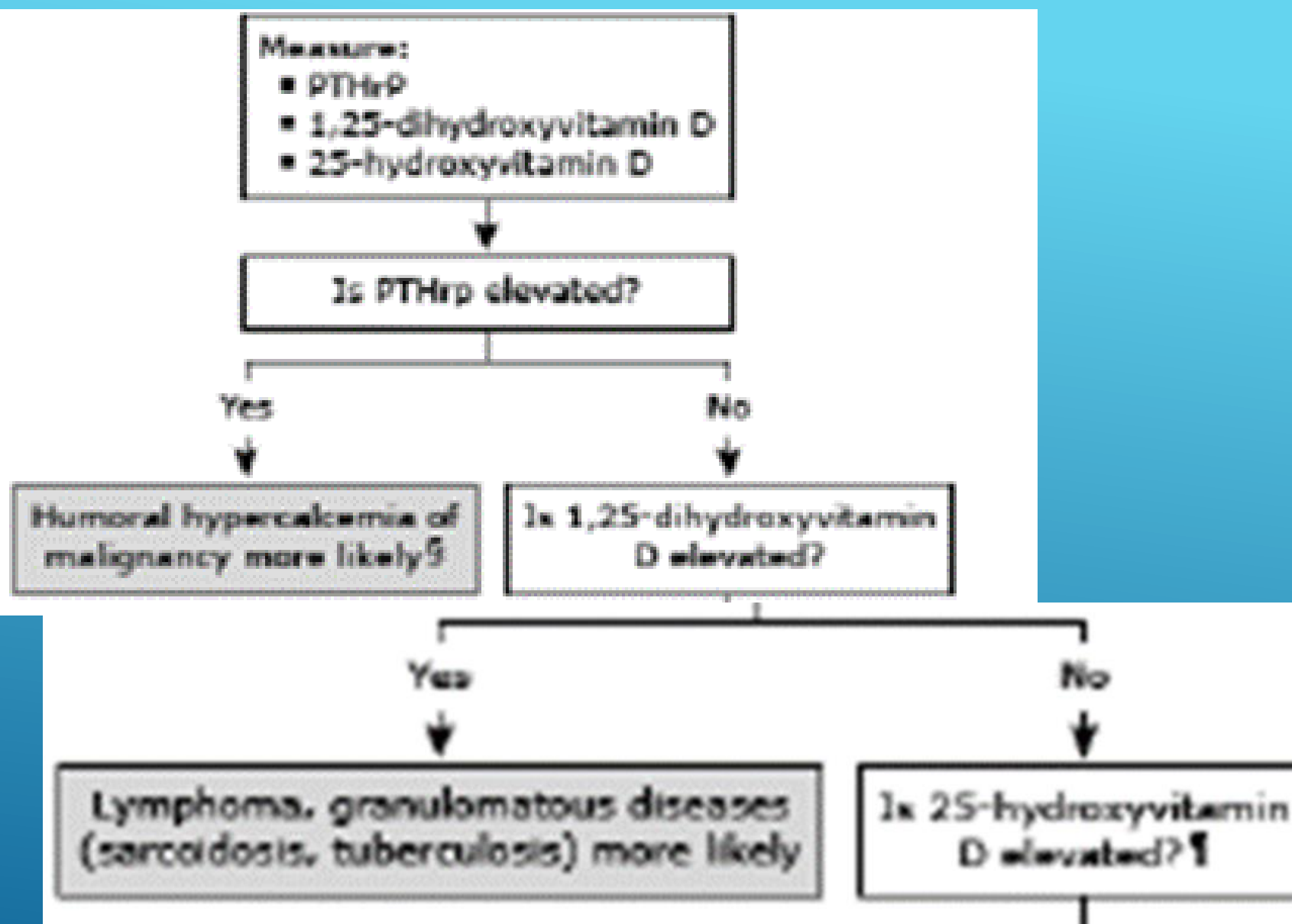


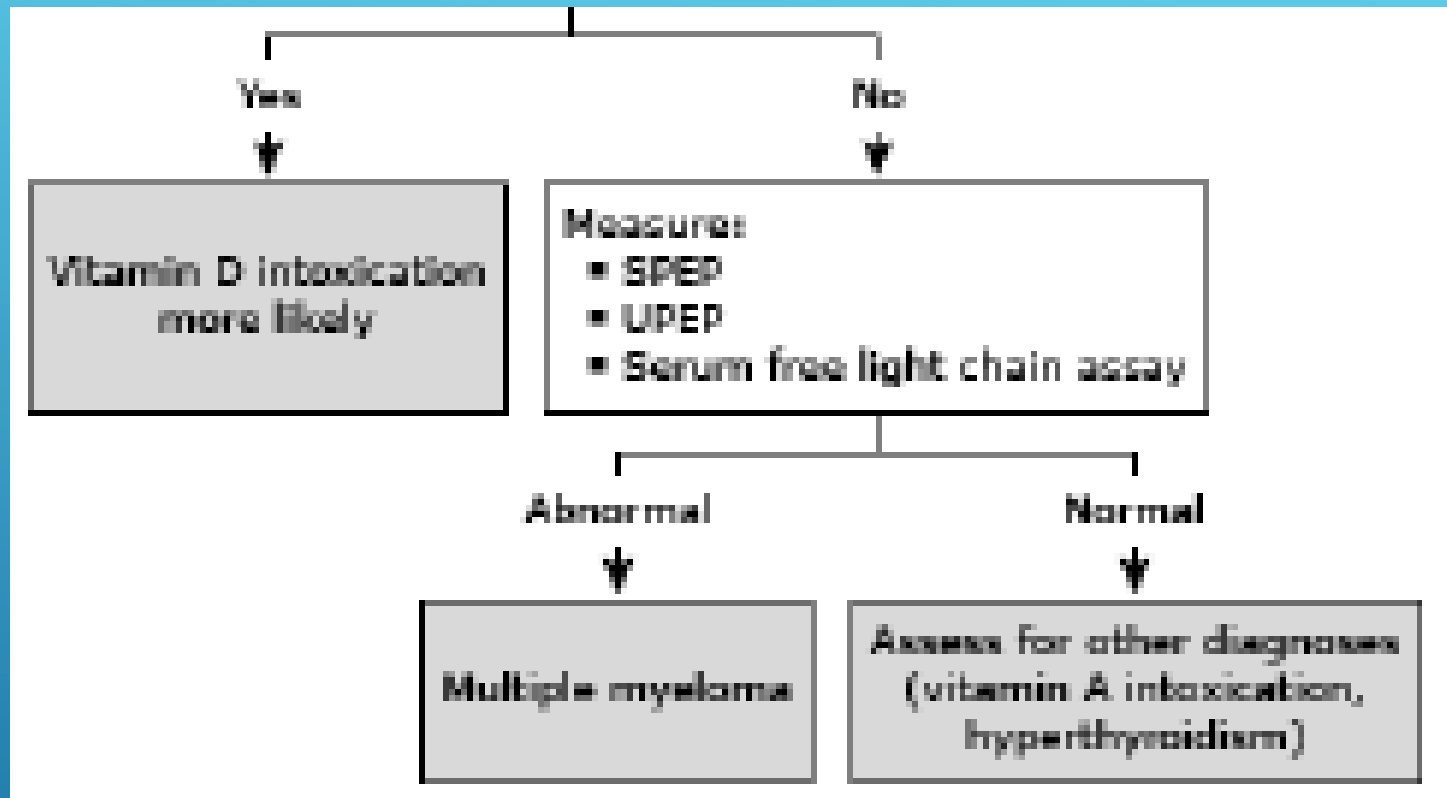
Measure intact PTH












# HYPERCALCEMIA OF MALIGNANCY

- ▶ The diagnosis of malignant hypercalcemia is seldom a subtle one.
- ▶ Most malignancies produce hypercalcemia only when they are **far advanced**
- ▶ Patients with malignant hypercalcemia usually **die 1 to 2 months** after hypercalcemia is discovered
- ▶ Perhaps because of the acuteness of the hypercalcemia and the elderly patient population involved, dramatic changes in mental status, culminating in coma, are relatively common.

- ▶ Although mechanisms in a given patient may be multiple, it is still useful to distinguish hypercalcemia associated with local involvement of bone from that caused by humoral mechanisms.
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# LOCAL OSTEOLYTIC HYPERCALCEMIA

- ▶ Hypercalcemia resulting from tumors invading bone occurs most clearly in **multiple myeloma** and some patients with **breast cancer**
- ▶ **Myeloma cells** and marrow cells associated with myeloma cells secrete numerous cytokines and chemokines capable of stimulating bone resorption, including macrophage inflammatory protein 1 (**MIP1**), **lymphotoxin** (tumor necrosis factor- $\beta$ ), and **interleukins 1 $\beta$ , 3, and 6**. These factors lead to increased expression of RANKL on the surface of marrow stromal cells and stimulation of osteoclast formation and activity.

- ▶ The increased bone resorption not only releases calcium into the circulation but also weakens the bone structurally.
- ▶ The pathogenesis of hypercalcemia in breast cancer is not completely understood
- ▶ Breast cancer cells make a host of cytokines capable of stimulating bone resorption by osteoclasts
- ▶ A majority of breast cancer patients with hypercalcemia have elevated blood levels of PTHrP. This circulating PTHrP, as well as PTHrP produced in bone by metastatic tumor cells, may generate the hypercalcemia
- ▶ Primary breast tumors that stain for PTHrP are more likely to result in bone metastases than are those that do not stain for PTHrP;

# HUMORAL HYPERCALCEMIA OF MALIGNANCY

- ▶ **PTHrP** binds to the PTH/PTHrP receptor and mimics all of the actions of amino-terminal fragments of PTH
- ▶ Blood levels of PTHrP are elevated in most patients with **solid tumors** and hypercalcemia.
- ▶ The tumors most commonly associated with humoral hypercalcemia include **squamous cell cancers of the lung, head and neck, esophagus, cervix, vulva, and skin; breast cancer; renal cell cancer; and bladder cancer**



- ▶ Benign or malignant **pheochromocytomas, islet cell tumors, and carcinoids** can also overproduce PTHrP, causing hypercalcemia
- ▶ The **aggressive T-cell lymphoma associated** with human T-cell lymphotropic virus type 1 (**HTLV1**) infection is the only hematologic malignancy commonly associated with PTHrP overproduction and hypercalcemia
- ▶ It is unlikely that PTHrP is the sole cause of the humoral hypercalcemia of malignancy

- ▶ many **cytokines** produced by tumors can stimulate bone resorption.
- ▶ The actions of these cytokines have been shown to synergize with those of PTHrP
- ▶ in hypercalcemic patients with **non-Hodgkin lymphoma**, blood levels of **1,25(OH)2D3** were found to be higher than otherwise expected
- ▶ Only a **minority** of patients with non-Hodgkin lymphoma have clear elevations of either PTHrP or 1,25(OH)2D3.416
- ▶ *In these hypercalcemic patients, the relative importance of **1,25(OH)2D3, cytokines, PTHrP**, needs to be clarified*

- ▶ Hypercalcemia associated with lymphoma is a relatively common disorder. In our series, the classic pattern **mediated by calcitriol** was observed only in **25%** of the patients; most of them had multifactorial pathogenesis.


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HYPERCALCEMIA IN PATIENTS WITH LYMPHOMA

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- ▶ *Hypercalcemia at diagnosis of diffuse large B-cell lymphoma was found to be strongly correlated with **adverse prognostic factors***
- ▶ **the prevalence of hypercalcemia >10.5 mg/dL at diagnosis of DLBCL was 23%.**

Diffiuse large B cell lymphoma (**DLBCL**) is the most common histologic subtype of non Hodgkin lymphoma (NHL), accounting for approximately **25 percent of adult NHL cases.**

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- ▶ Patients with DLBCL typically present with a rapidly enlarging symptomatic mass, most usually nodal enlargement in the neck or abdomen, or, in the case of primary mediastinal large B cell lymphoma, the mediastinum, but **may present as a mass lesion anywhere in the body.**

The organs most commonly affected are central nervous system, kidneys, lungs, and skin, but virtually any site may be involved.





"Primary cutaneous large B cell lymphoma, leg type")

Diffuse large B cell lymphoma, leg type typically presents as red or bluish (violaceous) nodules or tumors on one or both legs, typically below the knee; 10 to 15 percent will develop outside of the lower extremities.

Systemic "B" symptoms (ie, fever, weight loss, drenching night sweats) are observed in approximately 30 percent of patients, and the serum lactate dehydrogenase (LDH) is elevated in over one-half .

Approximately 60 percent of patients will present with advanced stage DLBCL (usually stage III or IV disease) while 40 percent have more localized disease, usually defined as that which can be contained within one irradiation field

- ▶ The major mechanism by which NHL patients develop hypercalcemia is not mediated by calcitriol or PTHrP. Hypercalcemia is most prevalent in patients with diffuse large B-cell lymphoma of the nongerminial cell subtype. Patients with **calcitriol-mediated hypercalcemia** showed a trend toward **worse outcomes**, suggesting that calcitriol might be a marker of high-grade lymphoma, transformation to such, or a surrogate for more advanced disease.

• 2018 Feb;18(2):e123-e129.

doi: 10.1016/j.clml.2017.12.006. Epub 2017 Dec 30.

## **Mechanisms of Hypercalcemia in Non-Hodgkin Lymphoma and Associated Outcomes: A Retrospective Review**

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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

- ▶ factors affecting the differentiation of both osteoblasts and osteoclasts involved in the pathogenesis of hypercalcemia and bone lesions of lymphoma. This was similar to that of multiple myeloma in which bone lesions and hypercalcemia are frequently observed.

**ASE REPORT**

**PUBLISHED: 09 APRIL 2010**

**MULTIPLE BONE LESIONS AND HYPERCALCEMIA PRESENTED IN DIFFUSE LARGE B CELL LYMPHOMA: MIMICKING MULTIPLE MYELOMA?**





Thank You

