Hypercalcemia of Malignancy

Hypercalcemia is the most common life-threatening metabolic disorder associated with malignancy. Often seen in patients with known metastatic cancer.

10-30% of patients with cancer suffer from one or more episodes of hypercalcemia. (less common in paediatric cancer patients)

SYMPTOMS:

Stones

Renal stones —> AKI

2. Polyuria, polydipsia (nephrogenic DI) —> free water loss —-> dehydration —-> eventual oliguria

Abdominal Groans/Moans

INITIALLY: Anorexia and Constipation
PROGRESSES TO : Nausea and Vomiting
CAN CAUSE: Peptic ulcers and acute pancreatitis

Bones

Bone related complications (often seen in cancer related and hyperparathyroidism related high Ca): osteoporosis, osteomalacia, arthritis.

Cancer related - pathological fractures

Psychiatric overtones

INITIALLY: Fatigue, difficulties in memory and concentration
PROGRESSES TO: Drowsiness, delirium and coma

Thrones

Constipation and Polyuria

AND CARDIAC

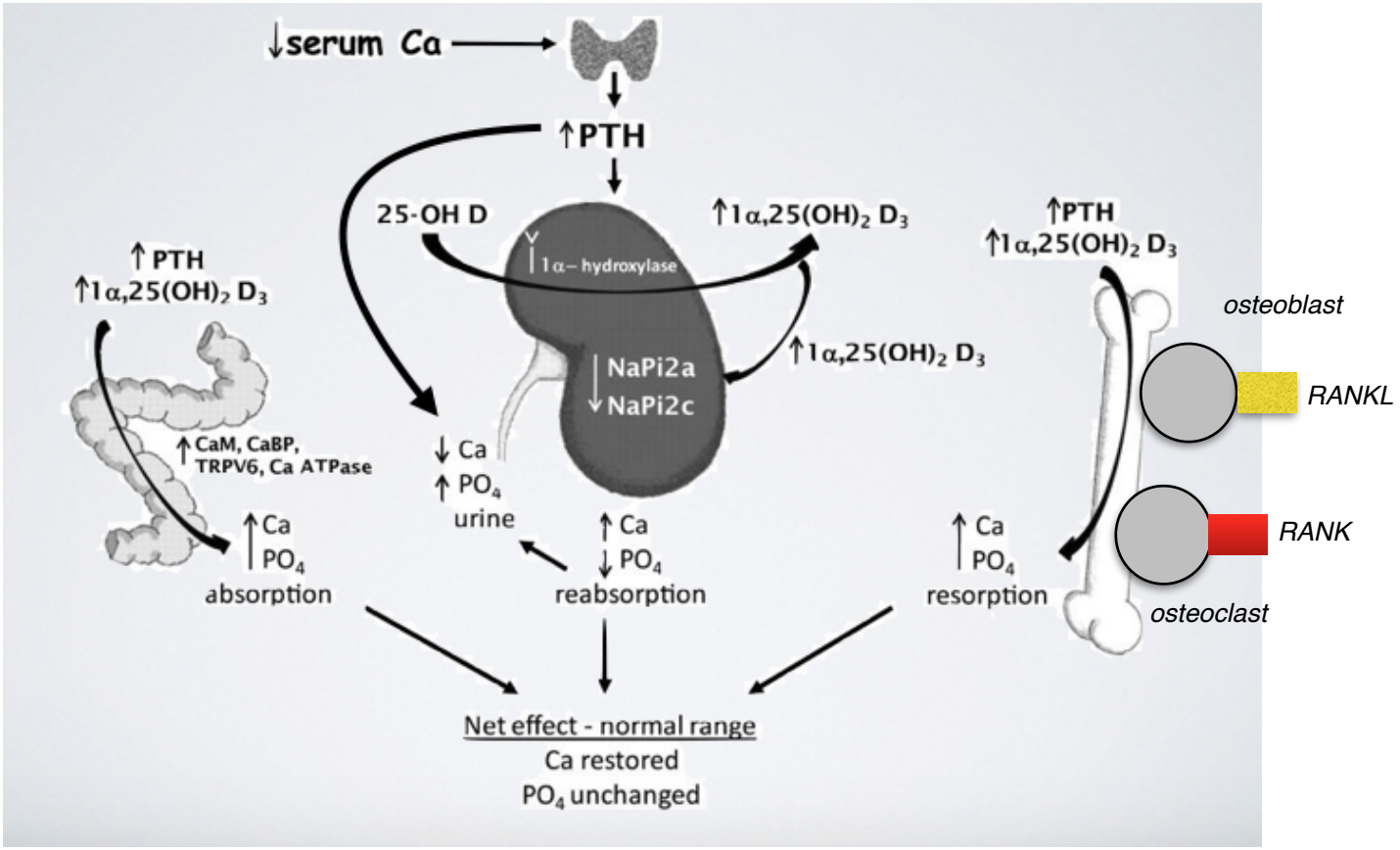
Initially QTc shortening. PROGRESSES to ST elevation, bradyarrythmia, heart block, eventual cardiac arrest

Which Cancers?

Patients with Stage 4 disease more likely to have hypercalcemia.

Lung, Multiple Myeloma, Breast cancer most common causes.

NORMAL PHYSIOLOGY

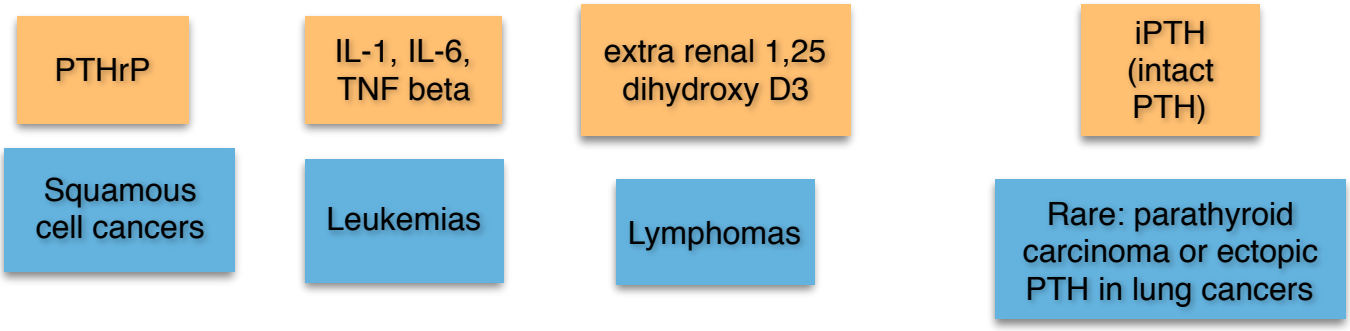


Hypercalcemia:
Defined as >2.6 mmol/L . Severe Hypercalcemia >/= 3.5 mmol/L

Corrected ionised calcium = 0.02 (40 - serum albumin) + Calcium in mmol/L (if serum albumin is
less than 40g/L, corrected levels are HIGHER than reported baseline)

MECHANISMS OF CANCER ASSOCIATED HYPECALCEMIA:

1. HHM (Humoral Hypercalcemia of Malignancy).



BY FAR: Most commonly mediated through a PTH related protein (PTHrP) secreted by tumour cells.

Most common mechanism seen with Squamous cell cancers (Lung, H&N, vulva, cervix)
PTHrP is ALSO secreted by normal tissue and has autocrine and paracrine functions is healthy humans
PTHrP acts like PTH and increases Calcium levels BUT unlike primary hyperparathyroidism or rare cancer syndromes with excess endogenous or iPTH production…

Excess PTHrP	**Excess PTH or iPTH (intact PTH)**
Inhibition of new bone formation	Stimulation of new bone formation
Low 1.25 dihydroxy Vit D	Excess of 1,25 dihydroxy Vit D
Hypochloremic alkalosis	Associated with hyperchloremic acidosis (impaired renal tubule function)

Humoral mediation of hypercalcemia in cancer can also occur via different mediators produced by cancer cells as detailed above. Interleukins directly act on bone causing osteoclastic bone resorption. Excess activation of Vit D to dihydroxy form can occur in Hodgkins lymphoma (ALSO Sarcoidosis), while rarely cancers are associated with excess iPTH production.

2. OTHER CAUSES OF HYPERCALCEMIA IN CANCER

1. Direct osteolytic activity by bony metastases (myeloma, breast cancer)
2. Immobilisation Related
3. Drug Related - Vit D supplementation, Calcium supplements, Retinoids (excess Vit A), Thiazides, Lithium

INVESTIGATION OF HYPERCALCEMIA

HIGH CALCIUM in a patient

Check Albumin (corrected levels)

KNOWN CANCER

- Check U&E, Phosphate and ECG
- Review Drug list
- Check radiology: ? Known bony mets

- PTH and PTHrP levels
- 25 hydroxy Vit D and 1,25 dihydroxy D3 levels

NOT KNOWN CANCER

- Check U&E, Phosphate and ECG
- Review Drug list

- Check TFT (thyrotoxicosis mediated high Calcium)
- Check CXR - sarcoid?
- Check PTH level, 25 hydroxy Vit D and 1.25 hydroxy Vit D levels
- THINK IS THIS CANCER?:

Consider myeloma screen
Consider bony imaging +/- cross sectional imaging

CLINICAL REASONING FOR Confirmation of DIAGNOSIS:

E.g. Known Cancer and High Calcium

If PTHrP high then likely cause of humoral hypercalcemia in cancer.
What will the other tests look like?
High PTHrP —-> High Ca, Low phosphate —-> inhibition of iPTH (low PTH levels) ——> low activated Vit D levels.

TREATMENT

1. **IV hydration**
2. **Bisphosphonates** (Zolendronic acid is 3rd generation bisphosphonate and 100 x more potent than pamidronate). Takes 2 days for ONSET of action. Median duration of action of zolendronic acid is 32 days. (Trials studying 4mg zolendronate and 8mg zolendronate showed normalisation of Calcium in 88% and 87% of patients by Day 10 compared to normalisation in 70% of patients with 90mg of pamidronate)
3. **Calcitonin** - Subcutaneous. Can be used in severe, symptomatic hypercalemia. quick action within 4 hours. Needs to be dosed ever 6 hours. Tolerance or tachyphylaxis within 48 hours and no longer effective (short term solution)
4. **Denosumab** ; Antibody to RANKL (on osteoblasts). Prevent osteoclast activation and bone resorption. Can be used in **bisphosphonate refractory hypercalcemia**. (Defined as corrected calcium levels do NOT decrease to <2.9mmol/L despite bisphosphonate treatment more than or equal to 7 days ago (but less than 30 days ago)). Thus can be trialled second line, if Calcium levels still high 1 week after adequate bisphosphonate dosing.
5. **Steroids/Prednisolone:** Usually dosed at 40-60mg Prednisolone for 5-7 days. Useful in lymphoma/myeloma/bony mets related hypercalcemia. Inhibits production of local inflammatory cytokines that contribute to hypercalcemia. Also inhibits 1 alpha hydroxylase that activates 25 OH Vit D to 1.25 dihydroxy Vit D.

References:

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