

Discuss the differential diagnosis and management of a 50 year old woman who presents with a serum calcium concentration of 3.8 mmol/L

#### **Hypercalcaemia - definition**

- Mild 2.6-2.9 mmol/L
- Moderate 3.0-3.4 mmol/L
- Severe >3.5 mmol/L

#### **Differential diagnosis**

- Common causes - 1° hyperparathyroidism (PHPTH) and malignancy.
- Search for other causes when these are ruled out.

#### **1. PTH mediated hypercalcaemia**

##### **Hyperparathyroidism**

- In PHPTH, hypercalcaemia often mild and patients asymptomatic BUT if highly symptomatic usually an indication of advanced disease.
- Mild PHPTH may abruptly worsen leading to severe hypercalcaemic crisis.
- PHPTH more common in women (F 1:500 and M 1:2000)
- Causes are single adenoma (85%) or hyperplasia (15%)
- Tertiary hyperparathyroidism refers to hypercalcaemia caused by autonomous secretion of PTH following long term hyperstimulation and should be obvious from history/clinical exam.
- Ectopic PTH production v. rare

#### **2. Non-PTH mediated hypercalcaemia**

##### **Malignancy**

- Local, osteolytic. (20%) Bony mets common and extensive eg breast cancer, multiple myeloma and lymphoma
- Humoral (80%). Bony mets minimal or absent. Causal agent PTHrP eg squamous cell carcinoma (cervix, lung, head and neck), renal and ovarian carcinomas.
- Concomitant PHPTH can occur with malignancy (6% of patients in one series with malignancy also had PHPTH).

#### **3. Rarer causes of hypercalcaemia**

- Only consider when malignancy and PHPTH have been ruled out.
- For example:
  - FHH
  - Sarcoidosis
  - Vitamin D excess
  - Severe thyrotoxicosis
  - Addison's disease
  - Contributing factors
    - Drugs eg thiazides, lithium
    - (exogenous calcium intake)

#### **History/Symptoms/physical examination**

- Tumours presenting with hypercalcaemia are generally large and clinically obvious except for NE tumours eg islet tumours, phaeo.
- Symptoms are related to severity of hypercalcaemia and rate of change. eg rapid increase in serum calcium to moderate levels can produce marked neurological impairment while chronic severe hypercalcaemia may only cause minimal neurological impairment.

#### **History/Symptoms/physical examination (cont'd)**

- Symptoms often vague and non specific eg weakness, fatigue, poor concentration and may overlap symptoms of underlying disorder eg in malignancy.
- Classic symptoms are:
  - Bones : painful due to bone re-modelling
  - Stones: in longstanding hypercalcaemia (eg PHPTH)
  - Groans: Abdominal pain, anorexia, nausea, pancreatitis
  - Moans: depression, confusion, coma
- ECG changes, arrhythmias in severe hypercalcaemia

### Laboratory investigations

- Renal function and eGFR
- PTH most important
  - Suppressed in hypercalcaemia of malignancy (unless also PHPTH)
  - Inappropriately normal or high in PHPTH
  - In FHH, PTH usually only borderline or moderately raised and serum calcium rarely above 3 mmol/L

### Other investigations

- Depends on cause eg protein elect in multiple myeloma
- If PHPTH and malignancy ruled out, commence other investigations but degree of hypercalcaemia makes some other causes unlikely
  - FHH – calcium/creatinine clearance ratio
  - Sarcoidosis – ACE or rarely 1,25 diOH vit D
  - Vit D excess – Vit D
  - Thyrotoxicosis – TFT
  - Adrenal impairment - 9 am cortisol, synacthen test

### Imaging

- Malignancy: Diagnosis/staging, bony lesions
- PHPTH: hyperplasia/location of adenoma but false +ve/-ve

### Management

- Immediate treatment to lower serum calcium
  - Rehydration – often severely dehydrated due to nephrogenic DI
  - Bisphosphonates take 2-4 days for response. If contraindicated or ineffective, may use steroids or calcitonin depending on underlying cause but response often small and transient
  - Loop diuretics – sometimes used when GFR improves to increase renal water/calcium excretion but only used if re-hydrated.
  - Dialysis required if renal failure as aggressive rehydration is contraindicated.
- Longer term treatment for underlying cause of hypercalcaemia
  - Calcimimetic agents
  - Parathyroidectomy/medical management in PHPTH
  - Appropriate treatment for malignant condition.