BMJ Best Practice

Hypercalcaemia of malignancy

Straight to the point of care

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Summary

Hypercalcaemia of malignancy can result from: humoral hypercalcaemia of malignancy (characterised by tumour secretion of parathyroid hormone-related peptide [PTHrP]); local osteolytic hypercalcaemia (characterised by local release of factors, including PTHrP, by bony metastases that promote osteoclast differentiation and function); calcitriol (1,25-dihydroxyvitamin D)-mediated hypercalcaemia (characterised by autonomous production of calcitriol [(1,25-dihydroxyvitamin D)] by lymphoma cells); and ectopic hyperparathyroidism (characterised by tumour production of parathyroid hormone [PTH]), which is very rare.

Pharmacological therapy can transiently improve hypercalcaemia. However, sustained maintenance of normocalcaemia requires eradication of underlying malignancy.

Treatment options include intravenous bisphosphonates, denosumab, calcitonin, glucocorticoids (for calcitriol [1,25-dihydroxyvitamin D]-mediated hypercalcaemia), and calcimimetics (for ectopic PTH production).

Definition

Hypercalcaemia occurs in 20% to 30% of patients with cancer.[1] [2] Cancer represents the most common aetiology of hypercalcaemia in the inpatient setting.[3] It can result from: humoral hypercalcaemia of malignancy (characterised by tumour secretion of parathyroid hormone-related peptide [PTHrP]); local osteolytic hypercalcaemia (characterised by local release of factors, including PTHrP, by bony metastases that promote osteoclast differentiation and function); calcitriol (1,25-dihydroxyvitamin D)-mediated hypercalcaemia (characterised by autonomous production of calcitriol [(1,25-dihydroxyvitamin D)] by lymphoma cells); and ectopic hyperparathyroidism (characterised by tumour production of parathyroid hormone), which is very rare.[4][5]

THEORY

Epidemiology

Hypercalcaemia occurs in 20% to 30% of patients with cancer.[1] [2] Cancer represents the most common aetiology of hypercalcaemia in the inpatient setting.[3] Humoral hypercalcaemia of malignancy (parathyroid hormone-related peptide [PTHrP]-mediated) is believed to account for 80% of cases (however, retrospective studies report elevated serum PTHrP levels in <40% of patients).[1] [14] [15] [16] Tumours associated with humoral hypercalcaemia include squamous cell cancer, renal cancer, ovarian cancer, endometrial cancer, breast cancer, and human T-lymphotrophic virus-associated lymphoma.[1] [2][10] Local osteolytic hypercalcaemia (local production of factors, including PTHrP, by bony metastases that promote osteoclast differentiation and activity) accounts for 20% of cases, with typical tumours including breast cancer, multiple myeloma, and lymphoma.[1] [5] [10] Hypercalcaemia mediated by increased calcitriol (1,25-dihydroxyvitamin D) synthesis or ectopic parathyroid hormone secretion accounts for <1% of cases.[1] [10]

Aetiology

Humoral hypercalcaemia of malignancy is most commonly associated with:[1] [2][10]

- Renal cancer
- Ovarian cancer
- Breast cancer
- Endometrial cancer
- Human T-lymphotrophic virus-associated lymphoma
- Squamous cell carcinoma.

Local osteolytic hypercalcaemia is most commonly associated with:[1][10]

- Breast cancer
- Multiple myeloma.

Calcitriol (1,25-dihydroxyvitamin D)-mediated hypercalcaemia is associated with:[1] [10]

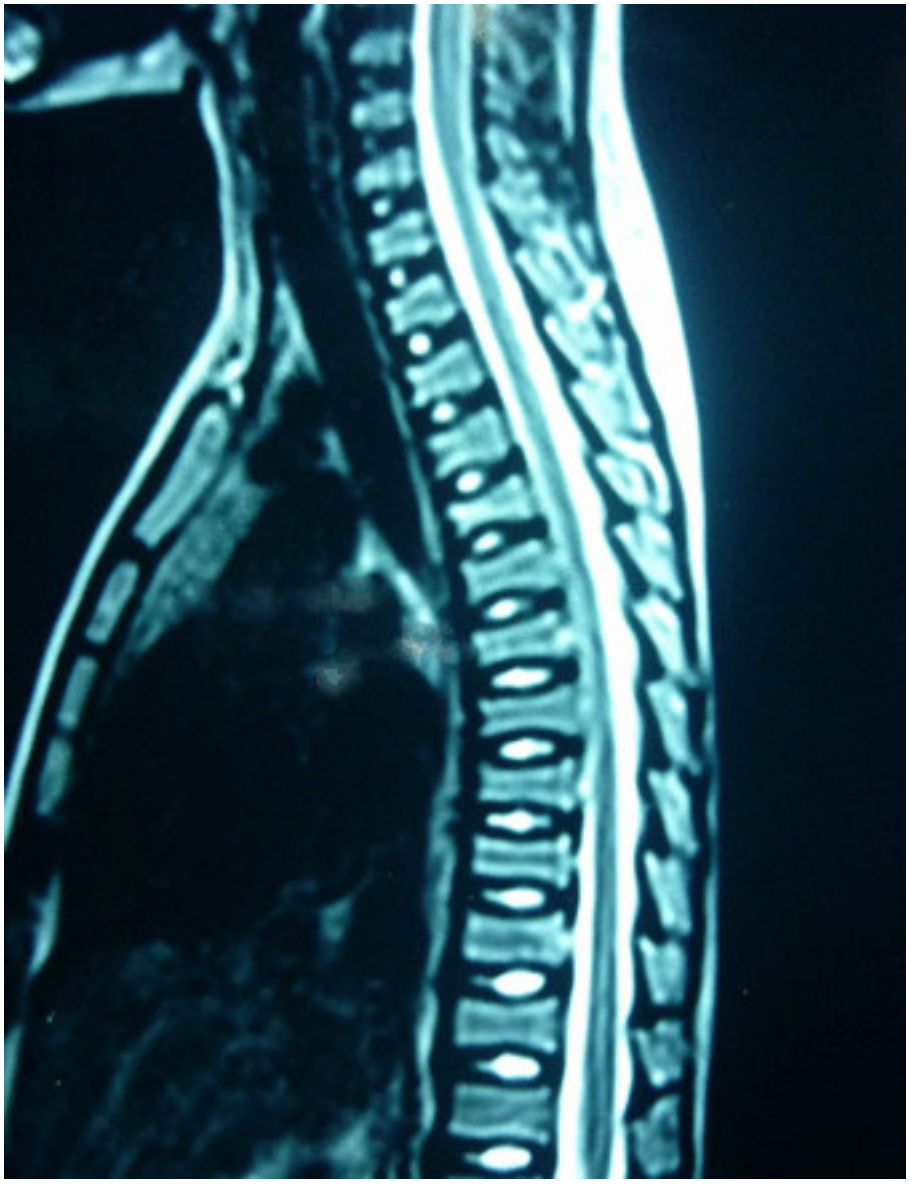
- Lymphomas (of all types)
- Granulomatous disease (such as active sarcoidosis) or tuberculosis.

Ectopic parathyroid hormone secretion by tumours is rare, but has been reported.[1][11] [12]

Pathophysiology

Humoral hypercalcaemia of malignancy: tumour secretion of parathyroid hormone-related peptide (PTHrP) leads to activation of osteoclastic bone resorption and suppression of osteoblastic bone formation. This results in skeletal release of calcium and subsequent hypercalcaemia. PTHrP also acts at the level of the kidney to reduce calcium clearance, as well as to reduce the renal phosphorus threshold, leading to hyperphosphaturia and hypophosphataemia.[1] [2]

Local osteolytic hypercalcaemia: in the setting of malignancy with widespread skeletal involvement, local release of cytokines (e.g., interleukin [IL]-1 and IL-6), chemokines, and PTHrP leads to increased osteoclastic bone resorption, and to increased release of calcium into the serum that overwhelms the kidney's capacity to clear calcium.[5]



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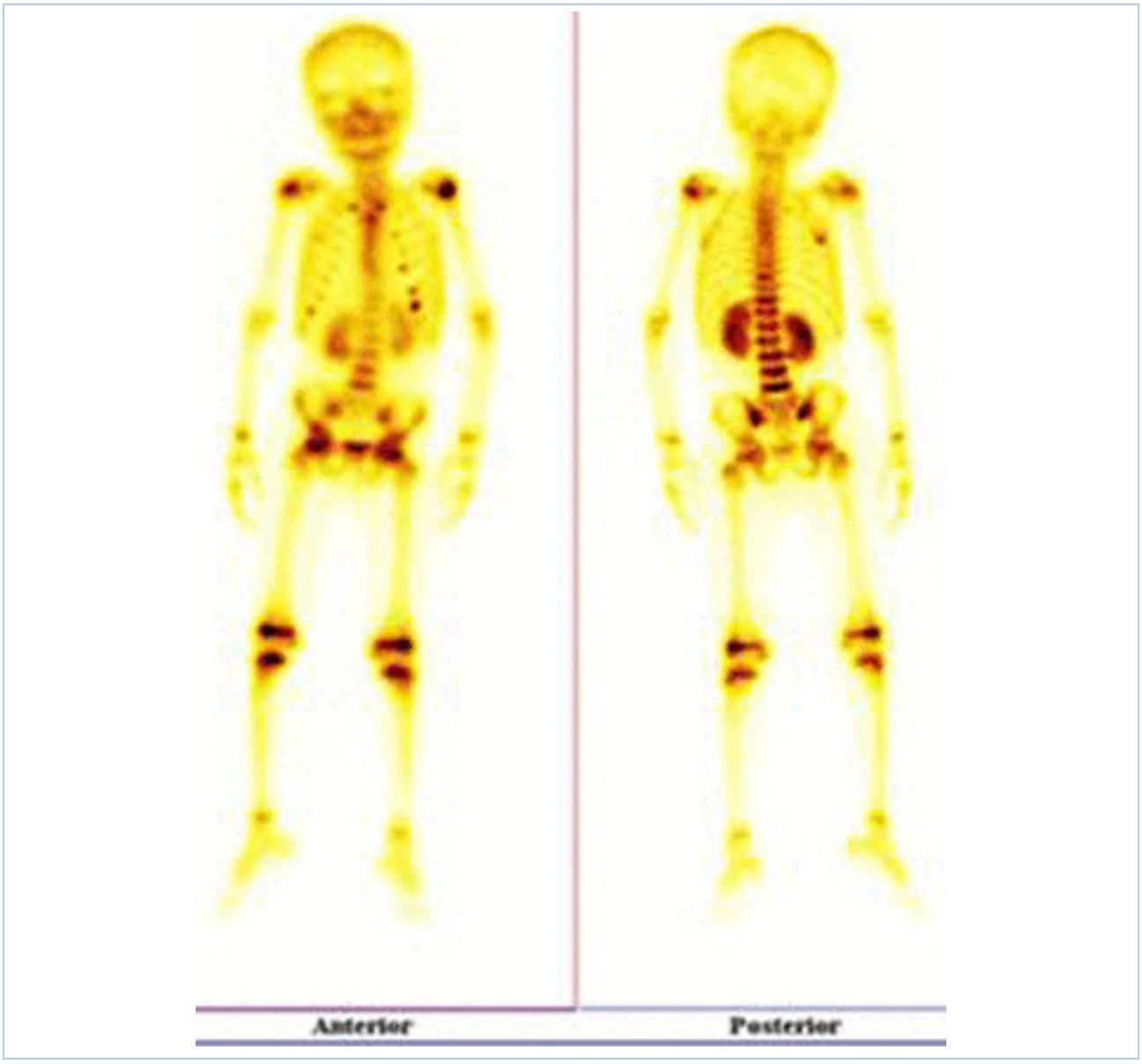

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Calcitriol (1,25-dihydroxyvitamin D)-mediated hypercalcaemia: overexpression of 1-alpha hydroxylase (the enzyme that converts precursor 25-hydroxyvitamin D [25OHD] to calcitriol [(1,25-dihydroxyvitamin D)]) by malignant or adjacent normal cells leads to autonomous production of bioactive vitamin D.[1] [5] Calcitriol (1,25-dihydroxyvitamin D) in turn increases intestinal calcium absorption and subsequent hypercalcaemia. In addition, calcitriol (1,25-dihydroxyvitamin D) may stimulate osteoclast-mediated bone resorption.[5]

Ectopic secretion of authentic parathyroid hormone with subsequent hypercalcaemia has been rarely reported.[1][11] [12]

Classification

Severity

While there is no universally accepted classification of mild, moderate, or severe hypercalcaemia, the following criteria are widely used:[6] [7] [8]

- Mild hypercalcaemia: total calcium of less than 3 mmol/L (<12 mg/dL) or ionised calcium of 1.4 to 2.0 mmol/L (5.6 to 8.0 mg/dL)
- Moderate hypercalcaemia: total calcium of 3.0 to 3.5 mmol/L (12.0 to 13.9 mg/dL) or ionised calcium of 2.5 mmol/L or greater (≥10 mg/dL)
- Severe hypercalcaemia: 3.5 mmol/L or greater (≥14 mg/dL) or ionised calcium of 2.5 to 3.0 mmol/L (10-12 mg/dL).

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) classifies hypercalcaemia of malignancy into four grades premised on corrected serum calcium:[9]

- Grade 1: corrected serum calcium (SCa) of >upper limit of normal* to 2.9 mmol/L (11.5 mg/dL); ionised calcium >upper limit of normal to 1.5 mmol/L (6 mg/dL)
- Grade 2: corrected SCa of >2.9 to 3.1 mmol/L (>11.5 to 12.5 mg/dL); ionised calcium >1.5 to 1.6 mmol/L (>6.0 to 6.4 mg/dL); symptomatic
- Grade 3: corrected SCa of >3.1 to 3.4 mmol/L (>12.5 to 13.5 mg/dL); ionised calcium >1.6 to 1.8 mmol/L (>6.4 to 7.2 mg/dL); hospitalisation indicated
- Grade 4: corrected SCa of >3.4 mmol/L (>13.5 mg/dL); ionized calcium >1.8 mmol/L (>7.2 mg/dL); life-threatening consequences.

*upper limit of normal: serum calcium 2.7 mmol/L (10.8 mg/dL); ionised calcium 1.3 mmol/L (5.3 mg/dL) (values may vary among laboratories)

Causes of hypercalcaemia of malignancy

Humoral hypercalcaemia of malignancy is most commonly associated with:[1][10]

- Renal cancer
- Ovarian cancer
- Breast cancer
- Endometrial cancer
- Human T-lymphotrophic virus-associated lymphoma
- Squamous cell carcinoma.

Local osteolytic hypercalcaemia is most commonly associated with:[1][10]

- Breast cancer
- Multiple myeloma.

Calcitriol (1,25-dihydroxyvitamin D)-mediated hypercalcaemia is associated with:[1] [10]

- Lymphomas (of all types)
- Granulomatous disease (such as active sarcoidosis) or tuberculosis.

Ectopic parathyroid hormone secretion by tumours is rare, but has been reported.[1][11] [12]

THEORY

Case history

Case history #1

A 63-year-old woman is brought in by her family for progressive fatigue and confusion. Past medical history is notable for ovarian cancer. Physical examination reveals dry mucous membranes. Admission labs are significant for an elevated adjusted serum calcium of 3.2 mmol/L (12.8 mg/dL), a low-normal albumin level, a low-normal phosphorus level, and elevated alkaline phosphatase. Hypercalcaemia work-up reveals a suppressed parathyroid hormone, an elevated parathyroid hormone-related peptide (PTHrP), and a low-normal calcitriol (1,25-dihydroxyvitamin D) level.

Other presentations

Hypercalcaemia of malignancy can occur with both solid and liquid tumours. Presenting symptoms are similar to those seen in hypercalcaemia of any aetiology. Symptoms include neuropsychiatric changes (mood disturbance, fatigue, confusion, stupor, and coma), gastrointestinal disturbance (loss of appetite, nausea, constipation), muscle weakness, acute kidney injury, polyuria, polydipsia, and bone pain.[1] [5] [13] Mild hypercalcaemia may be asymptomatic. Severe hypercalcaemia may be associated with hypercalcaemic crisis, with complications such as acute pancreatitis, acute kidney injury, and coma.[10]

Approach

Diagnosis of malignancy-associated hypercalcaemia is based on a history of malignancy, signs/symptoms of hypercalcaemia, presence of hypercalcaemia, and biochemical work-up to determine the underlying aetiology of hypercalcaemia.

History and physical examination

Symptoms of hypercalcaemia include neuropsychiatric changes (e.g., mood disturbance, fatigue, confusion, stupor, and coma), gastrointestinal disturbance (loss of appetite, nausea, constipation), muscle weakness, polyuria, polydipsia, and bone pain.[1] [2] [5] [10] [13] Signs of dehydration associated with hypercalcaemia include poor skin turgor and dry mucous membranes. However, hypercalcaemia may not be associated with any specific physical examination findings.

History to evaluate potential causes of hypercalcaemia unrelated to malignancy should be elicited.[1] [5] These include hyperthyroidism, phaeochromocytoma, adrenal insufficiency, and granulomatous disease. A thorough medication history to evaluate for use of medications that may cause or worsen hypercalcaemia (thiazide diuretics, lithium, calcium, over-the-counter antacids, and large doses of vitamin D) should be undertaken.[1] [5] [10]

Severity of symptoms may correlate with duration and rapidity of onset of hypercalcaemia.[10] It is important to note that malignancy-associated hypercalcaemia is less commonly associated with life-threatening decompensation, but a hypercalcaemic crisis (characterised by oliguria, anuria, somnolence, coma) can occur.

An ECG should be performed to assess for a shortened QT interval and dysrhythmias.

Laboratory evaluation

Biochemical evidence of hypercalcaemia should be demonstrated by measuring total serum calcium and albumin in order to calculate the adjusted serum calcium level. Some sources prefer measurement of serum ionised calcium, if available. Serum ionised calcium should be measured if the albumin level is altered, and if calcium-binding immunoglobulins may be present (e.g., in multiple myeloma).[1]

Parathyroid hormone (PTH)-dependent hypercalcaemia should be ruled out by measuring a serum intact PTH level.[5] Conditions associated with elevated PTH include primary and tertiary hyperparathyroidism, familial hypocalciuric hypercalcaemia, and ectopic hyperparathyroidism.

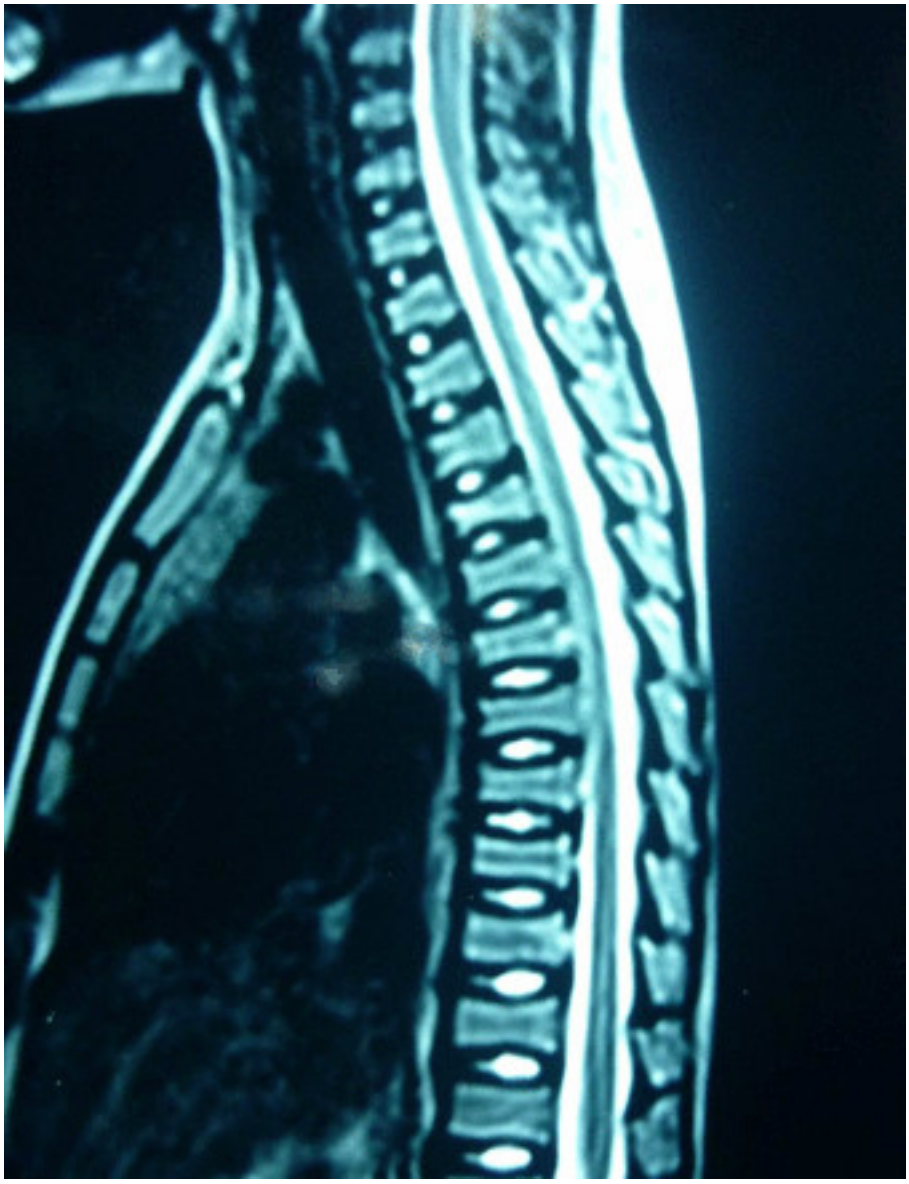
A complete metabolic panel should be ordered to check for hypercalcaemia-induced acute kidney injury. A high bicarbonate level may indicate that malignancy or exogenous calcium excess may be a more likely cause of hypercalcaemia than primary hyperparathyroidism.

The aetiology of non-PTH-dependent hypercalcaemia should be determined. Conditions associated with hypercalcaemia and an appropriately suppressed PTH include malignancy-associated hypercalcaemia, hyperthyroidism, phaeochromocytoma, and adrenal insufficiency.

All laboratory tests should be obtained before treatment is started, as improvement of hypercalcaemia after treatment is initiated may cause difficulty in interpreting test results. The following tests are also recommended:

- Screening for hyperthyroidism, phaeochromocytoma, and adrenal insufficiency, as clinically indicated.
- Serum parathyroid hormone-related peptide (PTHrP). An elevated PTHrP associated with a suppressed PTH and low to low-normal calcitriol (1,25-dihydroxyvitamin D) level represents likely humoral hypercalcaemia of malignancy. PTHrP-mediated hypercalcaemia typically occurs with non-metastatic tumours that may be apparent on examination and initial imaging. Exceptions include small neuro-endocrine tumours.[1]
- Serum phosphorus. In humoral hypercalcaemia of malignancy, PTHrP also acts at the level of the kidney to reduce calcium clearance, as well as to reduce the renal phosphorus threshold, leading to hyperphosphaturia and hypophosphataemia.[1] [5]
- Calcitriol (serum 1,25-dihydroxyvitamin D) level, if lymphoma and/or granulomatous disease are suspected. Calcitriol (1,25-dihydroxyvitamin D)-mediated hypercalcaemia occurs with lymphomas of all kinds and granulomatous disorders.
- Serum 25-hydroxyvitamin D, if intravenous bisphosphonate or subcutaneous denosumab is being considered. Vitamin D deficiency should be corrected prior to administration of bisphosphonates or denosumab to avoid the risk of hypocalcaemia and, possibly, osteonecrosis of the jaw.[17] [18] [19] [20]

If there is a history of malignancy complicated by skeletal involvement, PTHrP and calcitriol (1,25-dihydroxyvitamin D) are found to be normal, and other aetiologies of hypercalcaemia have been eliminated, local osteolytic hypercalcaemia is the most likely diagnosis.



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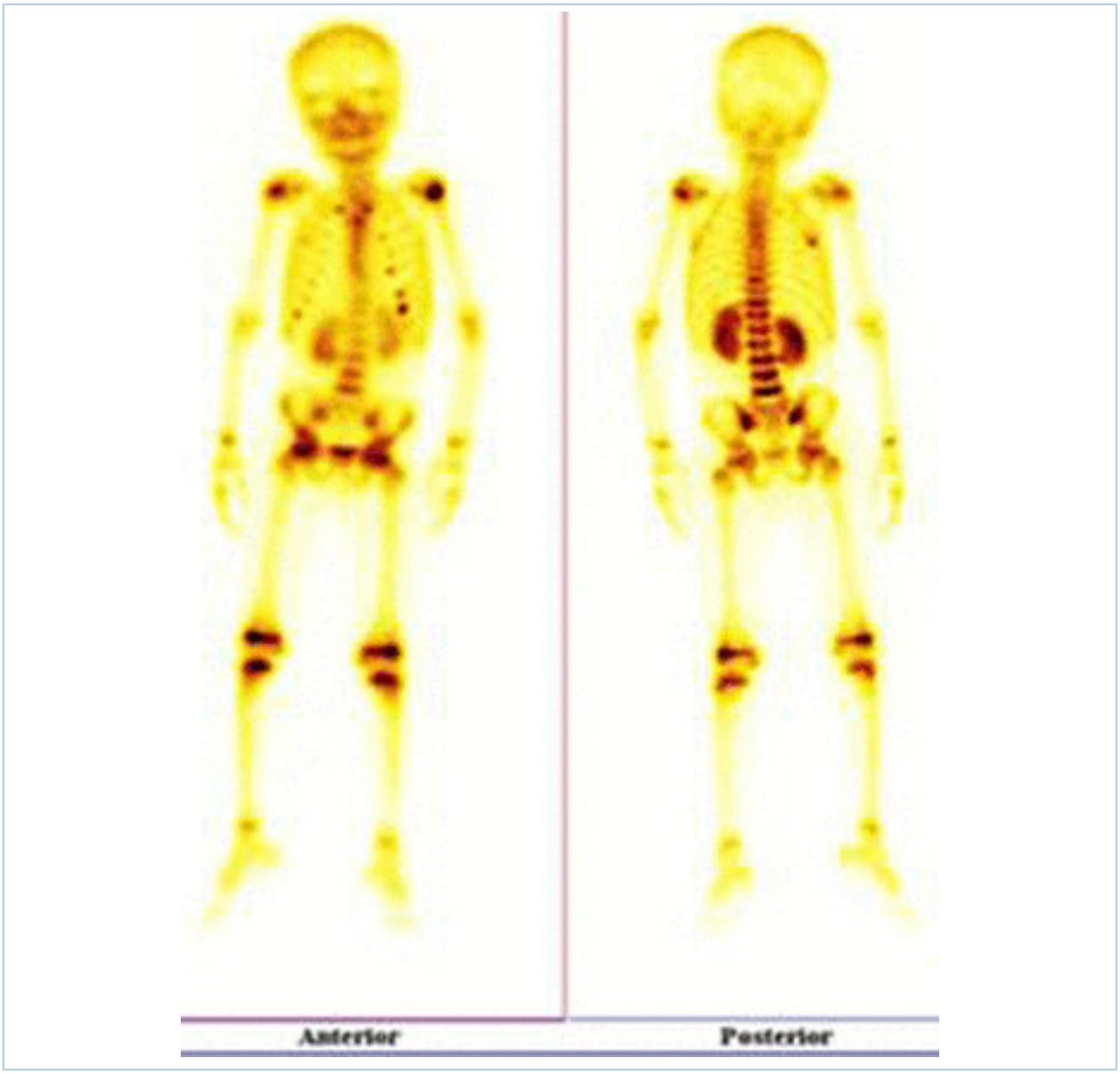

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Radiology evaluation

In order to assess for underlying causes of hypercalcaemia, the following tests should be considered:

- Skeletal survey in patients in whom multiple myeloma, bone metastases, or leukaemia are suspected.
- Chest x-ray to assess for lung cancer, sarcoidosis, or tuberculosis.

Further imaging should be ordered, according to the suspected cancer or condition and the anatomical region involved.

Other tests

An ECG should be performed to look for shortened QT interval or other conduction abnormalities.[2]

History and exam

Key diagnostic factors

presence of risk factors (common)

- Key risk factors include non-metastatic malignancy (humoral hypercalcaemia), metastatic skeletal involvement (local osteolytic hypercalcaemia), and lymphoma (calcitriol [(1,25-dihydroxyvitamin D)]-mediated hypercalcaemia).

history of malignancy (common)

- Hypercalcaemia occurs in 20% to 30% of patients with cancer.[21] [22] Cancer represents the most common aetiology of hypercalcaemia in the inpatient setting.[3] It can result from: humoral hypercalcaemia of malignancy (characterised by tumour secretion of parathyroid hormone-related peptide [PTHrP]); local osteolytic hypercalcaemia (characterised by local release of factors, including PTHrP, by bony metastases that promote osteoclast differentiation and function); calcitriol (1,25-dihydroxyvitamin D)-mediated hypercalcaemia (characterised by autonomous production of calcitriol [(1,25-dihydroxyvitamin D)] by lymphoma cells); and ectopic hyperparathyroidism (characterised by tumour production of parathyroid hormone), which is very rare.[21] [5]

Other diagnostic factors

normal physical exam (common)

- Hypercalcaemia may not be associated with any specific physical examination findings.

poor skin turgor and/or dry mucous membranes (common)

- Signs of dehydration may be apparent on physical examination.

confusion (common)

- Hypercalcaemia may be associated with neuropsychiatric symptoms.

fatigue (common)

- Hypercalcaemia may be associated with neuropsychiatric symptoms.

constipation (common)

- Hypercalcaemia is associated with gastrointestinal symptoms.

loss of appetite (common)

- Hypercalcaemia is associated with gastrointestinal symptoms.

nausea (common)

- Hypercalcaemia is associated with gastrointestinal symptoms.

polyuria (common)

- Hypercalcaemia is associated with increased urinary excretion and dehydration by inducing nephrogenic diabetes insipidus.

polydipsia (common)

- Hypercalcaemia is associated with increased urinary excretion and dehydration.

bone pain (common)

- Hypercalcaemia is associated with bone pain.
- Bone pain may be a feature of metastatic skeletal involvement.

use of hypercalcaemia-inducing medication (common)

- Medications that may cause or worsen hypercalcaemia include thiazide diuretics, lithium, calcium, over-the-counter antacids, and large doses of vitamin D.[21] [5] [23]

stupor (uncommon)

- Hypercalcaemia may be associated with neuropsychiatric symptoms. Stupor is a non-specific symptom that may result from hypercalcaemia, but has numerous toxic/metabolic and neurological aetiologies that need to be considered.

coma (uncommon)

- Hypercalcaemia may be associated with neuropsychiatric symptoms. Coma is a non-specific symptom that may result from hypercalcaemia, but has numerous toxic/metabolic and neurological aetiologies that need to be considered.

Risk factors

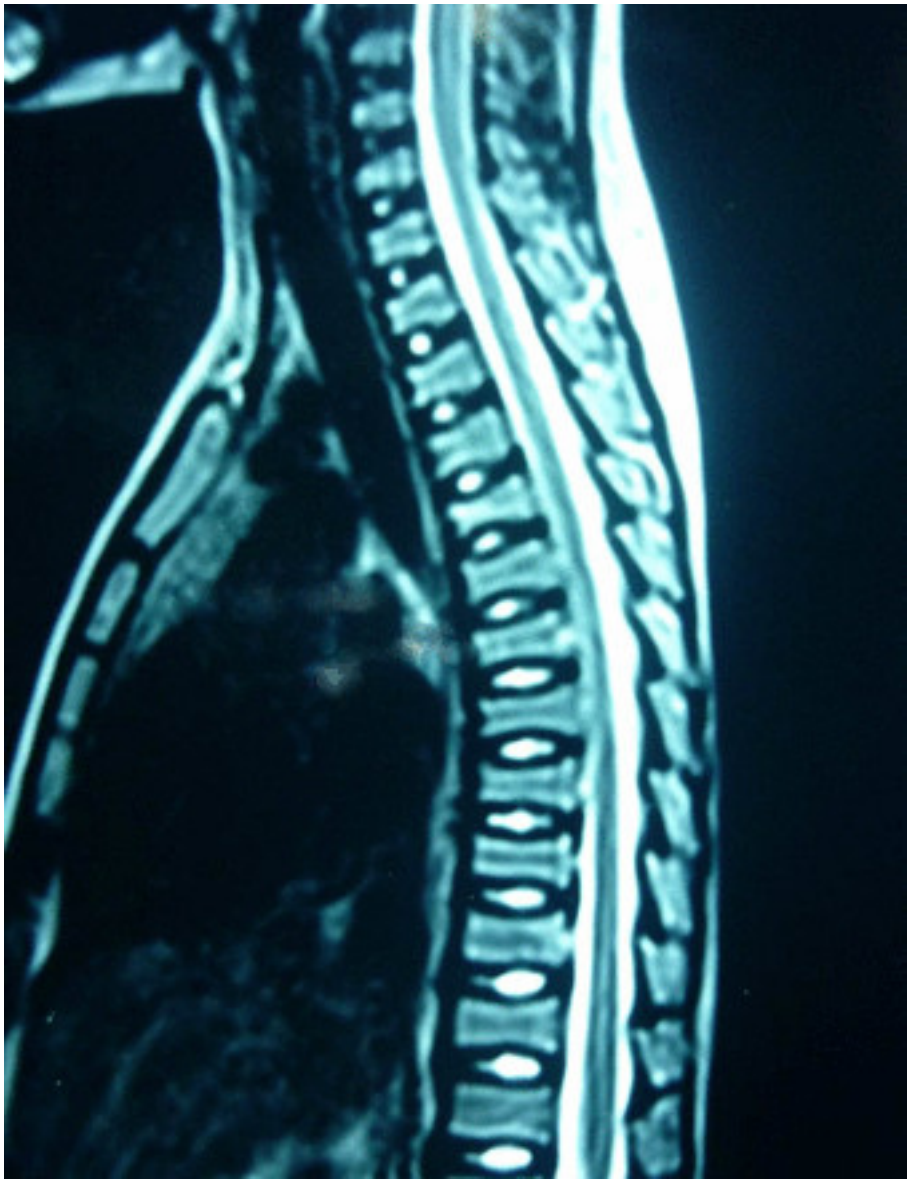
Strong

non-metastatic malignancy

- Humoral hypercalcaemia of malignancy results from tumour secretion of parathyroid hormone-related peptide (PTHrP), and typically occurs with non-metastatic disease.[4] Types of cancer include renal cancer, ovarian cancer, breast cancer, endometrial cancer, and squamous cell carcinoma.[1] [5] [10]

metastatic skeletal involvement

- Local osteolytic hypercalcaemia occurs with disease complicated by widespread skeletal involvement.[1] Types of cancer include breast cancer and multiple myeloma.[1] [5] [10]



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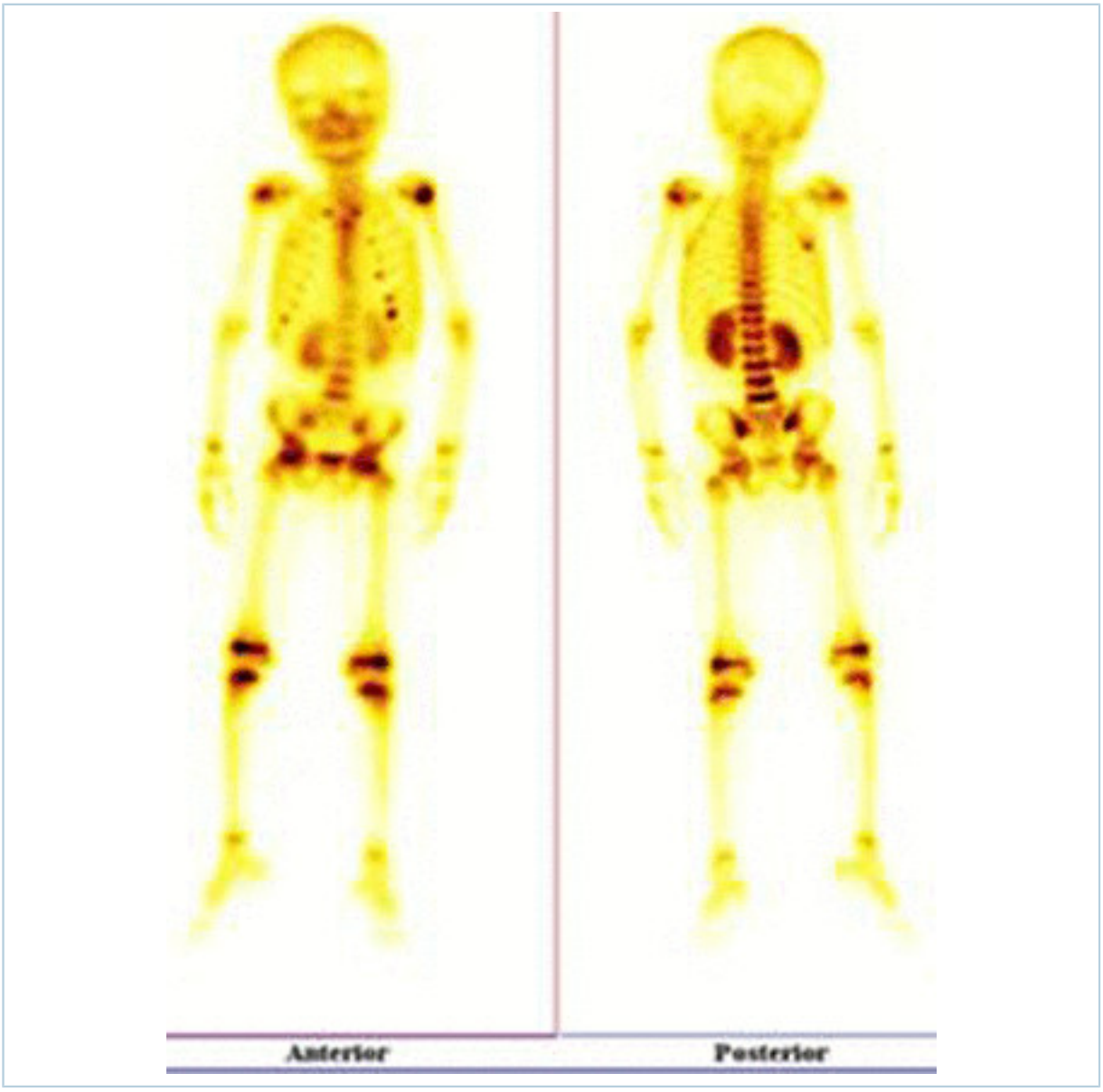

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lymphoma

- Calcitriol (1,25-dihydroxyvitamin D)-mediated hypercalcaemia occurs with lymphomas of all types, including human T-lymphotrophic virus-associated lymphoma.[1] [10]

Investigations

1st test to order

Test	Result
total serum calcium • Hypercalcaemia is defined by an elevated serum calcium level. Total serum calcium measurements are influenced by serum albumin levels, and by calcium-binding immunoglobulins as in multiple myeloma.[1] Serum calcium measurements should ideally be obtained from specimens collected without the use of a tourniquet/ cuff. • May be included in comprehensive metabolic panel.	**elevated**
serum ionised calcium • Some sources prefer measurement of serum ionised calcium to total serum calcium plus serum albumin, if available. Measurement of serum ionised calcium should be considered when factors that affect the accuracy of total serum calcium are present, such as abnormal serum albumin levels, and calcium-binding immunoglobulins as in multiple myeloma.[1] Serum calcium measurements should ideally be obtained from specimens collected without the use of a tourniquet/ cuff.	**elevated**
serum albumin • For SI units (calcium in mmol/L; albumin in g/L), the formula for adjusted serum calcium is (0.02 x [normal albumin - patient's albumin]) + serum calcium. Calculation of albumin-adjusted total calcium is not required when ionised calcium is measured. • The formula for adjusted calcium may not be reliable in all circumstances (such as in critically ill patients). • May be included in comprehensive metabolic panel.	**variable**
comprehensive metabolic panel • May show elevated urea and creatinine in acute kidney injury; elevated bicarbonate level may indicate malignancy or exogenous calcium excess as a cause for hypercalcaemia.	**may show elevated urea or bicarbonate**
resting ECG • A resting ECG should be done to check the QT interval or other conduction abnormalities.	**may show shortened QT interval and dysrhythmias**
serum intact parathyroid hormone • Should be ordered for initial biochemical assessment of hypercalcaemia to distinguish between parathyroid hormone (PTH)-mediated hypercalcaemia and non-PTH-mediated hypercalcaemia. Malignancy-associated hypercalcaemia generally leads to appropriate suppression of PTH secretion by the parathyroid gland. However, co-existing malignancy and primary hyperparathyroidism should be excluded. Rare scenarios in which PTH is inappropriately normal or elevated despite the presence of hypercalcaemia include malignancy-associated hypercalcaemia plus concurrent primary hyperparathyroidism, or patients with PTH-secreting tumours.[1] [5] [24]	**elevated in PTH-mediated hypercalcaemia (e.g., primary hyperparathyroidism, tertiary hyperparathyroidism); suppressed in malignancy-associated hypercalcaemia unless concurrent primary hyperparathyroidism is present or ectopic PTH (rare)**

Test	Result
serum parathyroid hormone-related peptide • Should be ordered if initial PTH level is low or if PTH level is normal to high despite the presence of a known malignancy. Humoral hypercalcaemia of malignancy results from tumour secretion of parathyroid hormone-related peptide (PTHrP). This mechanism accounts for 80% of cases of malignancy-associated hypercalcaemia. An elevated PTHrP in combination with a suppressed PTH confirms the diagnosis. In rare cases, an elevated PTRHrP in combination with an elevated PTH suggests concurrent humoral hypercalcaemia of malignancy plus primary hyperparathyroidism.[1] [5] [10] [11] [24]	**elevated in humoral hypercalcaemia of malignancy (PTHrP-mediated hypercalcaemia)**
serum phosphorus • In humoral hypercalcaemia of malignancy, PTHrP acts at the level of the kidney to reduce calcium clearance, as well as to reduce the renal phosphorus threshold, leading to hyperphosphaturia and hypophosphataemia.[1] [5] • May be included in comprehensive metabolic panel.	**low in humoral hypercalcaemia of malignancy (PTHrP-mediated hypercalcaemia)**
serum calcitriol (1,25-dihydroxyvitamin D) • Should be ordered if initial PTH level is low in the presence of lymphoma and/or granulomatous disease is suspected. Dysregulated production of calcitriol (1,25-dihydroxyvitamin D) can occur in lymphoma cells or neighbouring normal cells.	**elevated in calcitriol (1,25-dihydroxyvitamin D)-mediated hypercalcaemia**
serum 25-hydroxyvitamin D • Serum 25-hydroxyvitamin D should be checked if intravenous administration of bisphosphonate or subcutaneous denosumab is being considered, as vitamin D deficiency needs to be corrected prior to administration to avoid the risk of hypocalcaemia and, possibly, osteonecrosis of the jaw.[17] [18] [19] [20]	**excludes vitamin D deficiency prior to bisphosphonate or denosumab use**

Other tests to consider

Test	Result
skeletal survey • A skeletal survey should be done in patients in whom multiple myeloma, bone metastases, or leukaemia is suspected.	**may show osteopenia, osteolytic lesions, or pathological fractures**
chest x-ray • Hilar and/or paratracheal adenopathy with upper lobe predominant bilateral infiltrates are seen in sarcoidosis. A central mass, hilar lymphadenopathy, or pleural effusion may be seen in lung cancer. May show typical infiltrates, effusions, or cavitation in tuberculosis (TB).	**may show typical findings of lung cancer, TB, or sarcoidosis**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Primary hyperparathyroidism	• No differentiating signs or symptoms.	• Hypercalcaemia associated with elevated parathyroid hormone level and normal or elevated 1,25-dihydroxyvitamin D level.
Hyperthyroidism	• Symptoms include weight loss, palpitations, anxiety, heat intolerance, hyperdefecation, tremor, diaphoresis. • Signs may include a goitre or palpable thyroid nodule(s); stare; lid lag; or exophthalmos (Graves' disease).	• Suppressed thyroid-stimulating hormone and elevated free T4 level.
Adrenal insufficiency	• Symptoms include fatigue, weight loss, anorexia, abdominal pain, muscle aches, lightheadedness, nausea, vomiting, and diarrhoea. • Signs may include orthostatic hypotension, hyperpigmentation of skin creases and buccal mucosa.	• Inadequate response to adrenocorticotrophic hormone stimulation. • Hyponatraemia. • Hypoglycaemia.
Phaeochromocytoma	• Symptoms include episodic headache, sweating, palpitations. • Signs include persistent hypertension, tachycardia.	• Elevated 24-hour urinary or plasma fractionated catecholamines and metanephrines.
Sarcoidosis	• Symptoms include cough, dyspnoea, chronic fatigue, arthralgia, wheezing, photophobia, painful red eye, blurred vision; may be asymptomatic; family history of sarcoidosis. • Signs include rhonchi, lymphadenopathy, erythema nodosum, lupus pernio, conjunctival nodules, facial palsy.	• Chest x-ray may show hilar and/or paratracheal adenopathy with upper lobe predominant bilateral infiltrates. • Serum ACE level may be elevated.
Medication-related hypercalcaemia	• History of use of thiazide diuretics, lithium, calcium supplementation, over-the-counter antacids, or large doses of vitamin D.	• Serum calcium slightly elevated and returns to normal after cessation of the medications.

Condition	Differentiating signs / symptoms	Differentiating tests
Pulmonary tuberculosis	• Cough, fever, anorexia, weight loss, and malaise.	• Chest x-ray: primary disease commonly presents as middle and lower lung zone infiltrates. Ipsilateral adenopathy, atelectasis from airway compression, and pleural effusion can be seen. Reactivation-type (post-primary) pulmonary tuberculosis (TB) usually involves apical and/or posterior segment of right upper lobe, apicoposterior segment of left upper lobe, or superior segment of either lower lobe, with or without cavitation. As disease progresses it spreads to other segments/lobes. • Sputum smear: positive for acid-fast bacilli (AFB).
Extrapulmonary tuberculosis	• Enlarged lymph nodes, pleuritic chest pain, skeletal pain, headache, urinary symptoms, abdominal swelling or pain.	• Chest x-ray: evidence of unrecognised pulmonary TB or evidence of old healed TB (e.g. upper lobe fibrosis) may be present; pleural TB will usually have a small to moderate unilateral pleural effusion. • Sputum smear: positive for AFB. • Analysis of lymph node aspirate; pleural, cerebrospinal, or ascitic fluid; bone films; or urine may show evidence of TB infection.

Criteria

Severity

While there is no universally accepted classification of mild, moderate, or severe hypercalcaemia, the following criteria are widely used:[6] [7] [8]

- Mild hypercalcaemia: total calcium of less than 3 mmol/L (<12 mg/dL) or ionised calcium of 1.4 to 2.0 mmol/L (5.6 to 8.0 mg/dL)
- Moderate hypercalcaemia: total calcium of 3.0 to 3.5 mmol/L (12.0 to 13.9 mg/dL) or ionised calcium of 2.5 mmol/L or greater (≥10 mg/dL)

- Severe hypercalcaemia: 3.5 mmol/L or greater (≥14 mg/dL) or ionised calcium of 2.5 to 3.0 mmol/L (10-12 mg/dL).

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) classifies hypercalcaemia of malignancy into four grades premised on corrected serum calcium:[9]

- Grade 1: corrected serum calcium (SCa) of >upper limit of normal* to 2.9 mmol/L (11.5 mg/dL); ionised calcium >upper limit of normal to 1.5 mmol/L (6 mg/dL)
- Grade 2: corrected SCa of >2.9 to 3.1 mmol/L (>11.5 to 12.5 mg/dL); ionised calcium >1.5 to 1.6 mmol/L (>6.0 to 6.4 mg/dL); symptomatic
- Grade 3: corrected SCa of >3.1 to 3.4 mmol/L (>12.5 to 13.5 mg/dL); ionised calcium >1.6 to 1.8 mmol/L (>6.4 to 7.2 mg/dL); hospitalisation indicated
- Grade 4: corrected SCa of >3.4 mmol/L (>13.5 mg/dL); ionised calcium >1.8 mmol/L (>7.2 mg/dL); life-threatening consequences.

*upper limit of normal: serum calcium 2.7 mmol/L (10.8 mg/dL); ionised calcium 1.3 mmol/L (5.3 mg/dL) (values may vary among laboratories)

Approach

Therapy directed at hypercalcaemia can temporarily restore normocalcaemia. Long-term maintenance of normocalcaemia requires eradication of the underlying malignancy.

While there is no universally accepted classification of mild, moderate, or severe hypercalcaemia, the following criteria are widely used:[6] [7] [8]

- Mild hypercalcaemia: total calcium of less than 3 mmol/L (<12 mg/dL) or ionised calcium of 1.4 to 2.0 mmol/L (5.6 to 8.0 mg/dL)
- Moderate hypercalcaemia: total calcium of 3.0 to 3.5 mmol/L (12.0 to 13.9 mg/dL) or ionised calcium of 2.5 mmol/L or greater (≥10 mg/dL)
- Severe hypercalcaemia: 3.5 mmol/L or greater (≥14 mg/dL) or ionised calcium of 2.5 to 3.0 mmol/L (10 to 12 mg/dL).

Supportive measures and monitoring

For all patients with hypercalcaemia of malignancy, maintain adequate hydration. Ensure that any medications that can worsen hypercalcaemia (e.g., thiazide diuretics, calcitriol [(1,25-dihydroxyvitamin D)], calcium supplementation, antacids, lithium) or worsen symptoms of hypercalcaemia (e.g., sedatives, hypnotics, analgesics) are avoided, if possible.[1] [10]

Patients with mild hypercalcaemia or with moderate hypercalcaemia who are asymptomatic should be monitored, have adequate fluid intake, and receive treatment for the underlying malignancy. Serum calcium should be tested again after 1 week to confirm the diagnosis.[13]

Initiation of treatment

Therapy for hypercalcaemia should be initiated for symptomatic patients with moderate or severe hypercalcaemia (serum calcium concentrations >3.0 mmol/L [>12.0 mg/dL]).[2] [6] If the person has severe hypercalcaemia or severe symptoms, emergency hospital admission should be arranged.[13]

Once the presence of moderate or severe hypercalcaemia has been established, treatment with intravenous normal saline, an antiresorptive agent (intravenous bisphosphonate or denosumab), and calcitonin (for patients with severe hypercalcaemia) can begin immediately.

In cases of hypercalcaemic crisis, urgent initiation of therapy is required to achieve adequate diuresis. Once the results of additional tests are available, further targeted treatment can be started, mainly for calcitriol (1,25-dihydroxyvitamin D)-induced hypercalcaemia. For parathyroid hormone-related peptide (PTHrP)-induced hypercalcaemia, humoral hypercalcaemia, and hypercalcaemia due to metastatic skeletal involvement, no additional specific treatments are available other than treatment of the underlying malignancy.

First-line therapy

- Intravenous normal saline reverses dehydration secondary to hypercalcaemia-induced nephrogenic diabetes insipidus in addition to oral hydration, and promotes calciuresis.[1] An initial bolus of 1-2 L should be administered, followed by 200-500 mL/hour depending on volume status, cardiac function, and kidney function.[6]

- Intravenous bisphosphonates are the most effective agents for treating malignancy-associated hypercalcaemia. Bisphosphonates effectively block osteoclastic bone resorption. Therapy should be instituted immediately upon diagnosis, because response takes 2-3 days.[4] Options include pamidronate disodium or zoledronic acid, which are administered as a single dose.[1] [10] [25] Although one study suggests that zoledronic acid is superior to pamidronate disodium, the evidence overall is unclear and both are acceptable options.[1] [26] Ibandronate is also approved for this indication in the UK. Potential adverse effects associated with intravenous bisphosphonate therapy include transient flu-like syndrome with aches/chills/fever, acute kidney injury, acute osteonecrosis of the jaw, and hypocalcaemia if high-dose bisphosphonates are given to hypercalcaemic patients with critical vitamin D deficiency.[2] [4][5] [26]
- Denosumab (a monoclonal antibody directed against the receptor activator of nuclear factor-KappaB ligand [RANKL]) is also an option for treating hypercalcaemia of malignancy.[6] [20] It reduces osteoclast differentiation and bone resorption. It is easier to administer (subcutaneous injection) than intravenous bisphosphonates and requires less monitoring of renal function. In the US, denosumab is approved for treatment of hypercalcaemia of malignancy refractory to bisphosphonate therapy. Endocrine Society guidelines recommend denosumab as an alternative to first-line bisphosphonate therapy and favour its use in patients with renal impairment.[6] The guidelines also suggest that it may be used in preference to bisphosphonates for patients with moderate hypercalcaemia. However, the recommendation is based on indirect evidence from randomised trials assessing outcomes such as skeletal-related events and hypocalcaemia rather than hypercalcaemia. Potential adverse effects of denosumab include skin infections, acute osteonecrosis of the jaw, and hypocalcaemia in patients with vitamin D deficiency. Rebound hypercalcaemia has been observed in patients taking denosumab. In June 2018, the UK Medicines and Healthcare products Regulatory Agency (MHRA) issued a safety alert following a pooled analysis of four phase 3 studies of denosumab in patients with advanced malignancies involving bone.[27] New primary malignancies were reported more frequently among patients receiving denosumab than those receiving zoledronic acid (cumulative incidence of new primary malignancy at 1 year was 1.1% for denosumab and 0.6% for zoledronic acid). No treatment-related patterns for individual cancers or cancer groupings were identified. It is not known whether there is an increased risk of new primary malignancy when denosumab is prescribed for the treatment of hypercalcaemia of malignancy.
- Measure vitamin D (and correct if deficient) prior to administration of a bisphosphonate or denosumab to avoid the risk of hypocalcaemia.[2] Regular monitoring of calcium levels is also important.

Adjunctive therapies to consider

- Calcitonin interferes with osteoclastic bone resorption and renal tubular reabsorption of calcium.[1] [2] It may effect a more rapid correction of hypercalcaemia than bisphosphonates or denosumab alone.[28] [29] The clinical utility of calcitonin is limited by its transient effect and lack of availability.[1] [10] [28] [29] A combination of calcitonin and a bisphosphonate or denosumab should be used for initial treatment of severe hypercalcaemia.[6] Calcitonin treatment should be limited to 48-72 hours while awaiting the therapeutic effect of bisphosphonate or denosumab therapy.[6] [30] Potential adverse effects include flushing and nausea.[1]
- Furosemide is reserved for managing fluid overload in conjunction with intravenous hydration. Caution should be taken to avoid overdiuresis, which depletes sodium stores relative to calcium, causing intravascular volume depletion and worsening hypercalcaemia.[10]

Recurrent or refractory hypercalcaemia

- If hypercalcaemia is improved with the initial infusion of bisphosphonate, but serum calcium levels begin to increase again, the bisphosphonate infusion may be repeated:[6]
    - in 7 days, and then every 3-4 weeks thereafter (zoledronic acid)
    - every 2-3 weeks (pamidronate).
- Endocrine Society guidelines recommend that denosumab should be used for patients with recurrent or refractory hypercalcaemia on an intravenous bisphosphonate.[6]

Therapy in advanced kidney disease

- Dialysis can be considered in patients who have cancers that are likely to respond to therapy, but in whom renal and cardiac function limits utilisation of intravenous hydration or accepted pharmacological therapy.[1] [31]
- Denosumab may be considered as an adjunct to dialysis.[32] However, patients with severe renal impairment (creatinine clearance <30 mL/minute) or who are receiving dialysis are at increased risk for hypocalcaemia. Regular monitoring of calcium levels is important.

Calcitriol (1,25-dihydroxyvitamin D)-mediated hypercalcaemia

Glucocorticoid therapy may be efficacious in treating calcitriol (1,25-dihydroxyvitamin D)-mediated hypercalcaemia. Endocrine Society guidelines provide advice on dosing and duration of therapy.[6]

An intravenous bisphosphonate or denosumab may be added to glucocorticoid therapy in patients already receiving glucocorticoid therapy who continue to have severe or symptomatic hypercalcaemia.[6]

Ectopic parathyroid hormone production

Removal of primary malignancy/ectopic parathyroid hormone-secreting source can reverse hypercalcaemia.[33]

If surgery is not possible or further management of hypercalcaemia is needed for patients with parathyroid carcinoma, treatment options may include cinacalcet or an intravenous bisphosphonate or denosumab. Endocrine Society guidelines include advice on dosing and duration of therapy, and second-line treatment.[6] See Primary hyperparathyroidism .

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
mild hypercalcaemia or asymptomatic moderate hypercalcaemia		
	1st	**treatment of underlying malignancy + supportive measures + monitoring**
symptomatic moderate or severe hypercalcaemia: without advanced kidney disease		
	1st	**intravenous normal saline**
	plus	**intravenous bisphosphonate or denosumab**
	adjunct	**calcitonin (while awaiting effect of bisphosphonate or denosumab)**
	adjunct	**furosemide**
	plus	**avoidance of exacerbating medications**
	plus	**treatment of underlying malignancy**
with established calcitriol (1,25-dihydroxyvitamin D)-mediated hypercalcaemia	**plus**	**corticosteroid**
symptomatic moderate or severe hypercalcaemia: with advanced kidney disease		
	1st	**renal dialysis ± denosumab**

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

mild hypercalcaemia or asymptomatic moderate hypercalcaemia

1st **treatment of underlying malignancy + supportive measures + monitoring**

» Treatment is based on severity of hypercalcaemia and symptoms. While there is no universally accepted classification of mild, moderate, or severe hypercalcaemia, the following criteria are widely used:[6] [7] [8]

» Mild hypercalcaemia: total calcium of less than 3 mmol/L (<12 mg/dL) or ionised calcium of 1.4 to 2.0 mmol/L (5.6 to 8.0 mg/dL)

» Moderate hypercalcaemia: total calcium of 3.0 to 3.5 mmol/L (12.0 to 13.9 mg/dL) or ionised calcium of 2.5 mmol/L or greater (≥10 mg/dL)

» Severe hypercalcaemia: 3.5 mmol/L or greater (≥14 mg/dL) or ionised calcium of 2.5 to 3.0 mmol/L (10-12 mg/dL).

» Maintain adequate hydration and ensure that any medications that can worsen hypercalcaemia (e.g., thiazide diuretics, calcitriol [(1,25-dihydroxyvitamin D)], calcium supplementation, antacids, lithium) or worsen symptoms of hypercalcaemia (e.g., sedatives, hypnotics, analgesics) are avoided, if possible.[1] [10]

» Patients with mild hypercalcaemia or asymptomatic moderate hypercalcaemia should be monitored, have adequate fluid intake, and receive treatment for the underlying malignancy. Serum calcium should be tested again after 1 week to confirm the diagnosis.[13]

» Therapy for hypercalcaemia should be initiated for symptomatic patients with moderate or severe hypercalcaemia (serum calcium concentration >3.0 mmol/L [>12.0 mg/dL]).[2] [6]

» Long-term maintenance of normocalcaemia requires eradication of the underlying malignancy.

» Serial monitoring of calcium is important.

MANAGEMENT

Acute

symptomatic moderate or severe hypercalcaemia: without advanced kidney disease

1st **intravenous normal saline**

» Treatment is based on severity of hypercalcaemia and symptoms. While there is no universally accepted classification of mild, moderate, or severe hypercalcaemia, the following criteria are widely used:[6] [7] [8]

» Mild hypercalcaemia: total calcium of less than 3 mmol/L (<12 mg/dL) or ionised calcium of 1.4 to 2.0 mmol/L (5.6 to 8.0 mg/dL)

» Moderate hypercalcaemia: total calcium of 3.0 to 3.5 mmol/L (12.0 to 13.9 mg/dL) or ionised calcium of 2.5 mmol/L or greater (≥10 mg/dL)

» Severe hypercalcaemia: 3.5 mmol/L or greater (≥14 mg/dL) or ionised calcium of 2.5 to 3.0 mmol/L (10-12 mg/dL).

» Therapy for hypercalcaemia should be initiated for symptomatic patients with moderate or severe hypercalcaemia (serum calcium concentrations >3.0 mmol/L [>12.0 mg/dL]).[2] [6] If the person has severe hypercalcaemia or severe symptoms, emergency hospital admission should be arranged.[13]

» Once the presence of moderate or severe hypercalcaemia has been established, treatment with intravenous normal saline, an antiresorptive agent (intravenous bisphosphonate or denosumab), and calcitonin (for patients with severe hypercalcaemia) can begin immediately.

» In cases of hypercalcaemic crisis, urgent initiation of therapy is required to achieve adequate diuresis.

» Intravenous normal saline reverses dehydration secondary to hypercalcaemia-induced nephrogenic diabetes insipidus in addition to oral hydration, and promotes calciuresis.[1] An initial bolus of 1-2 L should be administered, followed by 200-500 mL/hour depending on volume status, cardiac function, and kidney function.[6]

plus **intravenous bisphosphonate or denosumab**

Treatment recommended for ALL patients in selected patient group

Primary options

Acute

» pamidronate disodium: 15-60 mg intravenous infusion as a single dose or given over 2-4 days (dose depends on serum calcium level, maximum 90 mg/treatment course)

OR

» zoledronic acid: 4 mg intravenous infusion given over at least 15 minutes; dose may be repeated after 7 days if necessary and then every 3-4 weeks thereafter

Secondary options

» denosumab: consult specialist for guidance on dose

» Intravenous bisphosphonates are the most effective agents for treating malignancy-associated hypercalcaemia. Bisphosphonates effectively block osteoclastic bone resorption. Therapy should be instituted immediately upon diagnosis, because response generally takes 2-3 days.[4] Options include pamidronate disodium and zoledronic acid, which are both administered as a single dose.[1] [10] [25] Although one study suggests that zoledronic acid is superior to pamidronate, the evidence overall is unclear and both are acceptable options.[1] [26]

» If hypercalcaemia is improved with the initial infusion of bisphosphonate, but serum calcium levels begin to increase again, the bisphosphonate infusion may be repeated: in 7 days, and then every 3-4 weeks thereafter (zoledronic acid); every 2-3 weeks (pamidronate).[6]

» Potential adverse effects include transient flu-like syndrome with aches/chills/fever, acute kidney injury, acute osteonecrosis of the jaw, and hypocalcaemia if high-dose bisphosphonates are given to hypercalcaemic patients with critical vitamin D deficiency.[2] [4][5] [26]

» Denosumab (a monoclonal antibody directed against the receptor activator of nuclear factor-KappaB ligand [RANKL]) is also an option for treating hypercalcaemia of malignancy.[6] [20] It reduces osteoclast differentiation and bone resorption. It is easier to administer (subcutaneous injection) than intravenous bisphosphonates and requires less monitoring of renal function. In the US, denosumab is approved for treatment of hypercalcaemia of malignancy refractory to

Acute

bisphosphonate therapy. Endocrine Society guidelines recommend denosumab as an alternative to bisphosphonate therapy and favour its use in patients with renal impairment.[6] The guidelines also suggest that it may be used in preference to bisphosphonates for patients with moderate hypercalcaemia. However, the recommendation is based on indirect evidence from randomised trials assessing outcomes such as skeletal-related events and hypocalcaemia rather than hypercalcaemia. Potential adverse effects of denosumab include skin infections, acute osteonecrosis of the jaw, and hypocalcaemia in patients with vitamin D deficiency. Rebound hypercalcaemia has been observed in patients taking denosumab. Endocrine Society guidelines recommend that denosumab should be used for patients with recurrent or refractory hypercalcaemia on an intravenous bisphosphonate.[6]

» In June 2018, the UK Medicines and Healthcare products Regulatory Agency (MHRA) issued a safety alert following a pooled analysis of four phase 3 studies of denosumab in patients with advanced malignancies involving bone.[27] New primary malignancies were reported more frequently among patients receiving denosumab than those receiving zoledronic acid (cumulative incidence of new primary malignancy at 1 year was 1.1% for denosumab and 0.6% for zoledronic acid). No treatment-related patterns for individual cancers or cancer groupings were identified. It is not known whether there is an increased risk of new primary malignancy when denosumab is prescribed for the treatment of hypercalcaemia of malignancy.

» Measure vitamin D (and correct if deficient) prior to administration of a bisphosphonate or denosumab to avoid the risk of hypocalcaemia. Regular monitoring of calcium levels is also important.

adjunct **calcitonin (while awaiting effect of bisphosphonate or denosumab)**

Treatment recommended for SOME patients in selected patient group

Primary options

» calcitonin-salmon: 4-8 units/kg intramuscularly/subcutaneously every 6-12 hours

» Calcitonin interferes with osteoclastic bone resorption and renal tubular reabsorption of calcium.[1] [2] It may effect a more rapid

Acute

correction of hypercalcaemia than initial treatment with a bisphosphonate or denosumab alone.[28] [29] The clinical utility of calcitonin is limited by its transient effect and availability.[1] [10] [28] [29] A combination of calcitonin and a bisphosphonate or denosumab should be used for initial treatment of severe hypercalcaemia.[6]

» Calcitonin treatment should be limited to 48-72 hours while awaiting the therapeutic effect of bisphosphonate or denosumab therapy.[6] [30] Potential adverse effects include flushing and nausea.[1]

adjunct **furosemide**

Treatment recommended for SOME patients in selected patient group

Primary options

» furosemide: consult specialist for guidance on dose

» Furosemide is a loop diuretic reserved for managing fluid overload in conjunction with intravenous hydration. The initial dose is variable.

» Caution should be taken to avoid overdiuresis, which depletes sodium stores relative to calcium, causing intravascular volume depletion and worsening hypercalcaemia.[10]

plus **avoidance of exacerbating medications**

Treatment recommended for ALL patients in selected patient group

» It is important to avoid medications that can worsen hypercalcaemia (e.g., thiazide diuretics, calcitriol [(1,25-dihydroxyvitamin D)], calcium supplementation, antacids, lithium) and those that may worsen symptoms of hypercalcaemia (e.g., sedatives, hypnotics, analgesics, if possible).[1] [10]

plus **treatment of underlying malignancy**

Treatment recommended for ALL patients in selected patient group

» Long-term maintenance of normocalcaemia requires eradication of the underlying malignancy.

» If hypercalcaemia is secondary to the rare occurrence of ectopic parathyroid hormone secretion by the underlying malignancy, removal of the primary malignancy can reverse hypercalcaemia.[33]

Acute

» If surgery is not possible or further management of hypercalcaemia is needed for patients with parathyroid carcinoma, treatment options may include cinacalcet or an intravenous bisphosphonate or denosumab. Endocrine Society guidelines include advice on dosing and duration of therapy, and second-line treatment.[6] See Primary hyperparathyroidism .

with established calcitriol (1,25-dihydroxyvitamin D)-mediated hypercalcaemia — **plus** — **corticosteroid**

Treatment recommended for ALL patients in selected patient group

Primary options

» prednisolone: 60 mg orally once daily for 10 days; or 10-20 mg orally once daily for 7 days

OR

» hydrocortisone sodium succinate: 200-400 mg/day intravenously for 3-5 days

» Once the results of additional tests are available, further targeted treatment can be started for calcitriol (1,25-dihydroxyvitamin D)-induced hypercalcaemia.

» Glucocorticoid therapy may be efficacious. Endocrine Society guidelines provide advice on dosing and duration of therapy.[1] [6]

symptomatic moderate or severe hypercalcaemia: with advanced kidney disease

1st — **renal dialysis ± denosumab**

Primary options

» denosumab: consult specialist for guidance on dose

» Therapy for hypercalcaemia should be initiated for symptomatic patients with moderate or severe hypercalcaemia (serum calcium concentrations >3.0 mmol/L [>12.0 mg/dL]).[2] [6]

» Dialysis can be considered in patients who have cancers that are likely to respond to therapy, but in whom renal and cardiac function limits utilisation of intravenous hydration or accepted pharmacological therapy.[1] [31]

» Denosumab may be considered as an adjunct to dialysis.[32] However, patients with severe renal impairment (creatinine clearance <30 mL/minute) or who are receiving dialysis are

Acute

at increased risk for hypocalcaemia. Regular monitoring of calcium levels is important.

» In June 2018, the UK Medicines and Healthcare products Regulatory Agency (MHRA) issued a safety alert following a pooled analysis of four phase 3 studies of denosumab in patients with advanced malignancies involving bone.[27] New primary malignancies were reported more frequently among patients receiving denosumab than those receiving zoledronic acid (cumulative incidence of new primary malignancy at 1 year was 1.1% for denosumab and 0.6% for zoledronic acid). No treatment-related patterns for individual cancers or cancer groupings were identified. It is not known whether there is an increased risk of new primary malignancy when denosumab is prescribed for the treatment of hypercalcaemia of malignancy.

Patient discussions

Weight-bearing ambulation and oral hydration should be encouraged. Patients should stop any calcium supplementation that they may be taking. There may need to be discussions about the continued use of medications that are associated with hypercalcaemia (e.g., lithium, thiazide diuretics, calcitriol [(1,25-dihydroxyvitamin D)], and vitamin D), and medications that may impair mental clarity (sedatives, hypnotics, analgesics).

Monitoring

Monitoring

The nadir in serum calcium levels following bisphosphonate administration typically occurs within 7 days. Responses last for 1-4 weeks.[26] Serial monitoring of calcium is, therefore, important. Eradication of underlying malignancy is crucial for continued maintenance of normocalcaemia.

Complications

Complications	Timeframe	Likelihood
bisphosphonate-induced flu-like syndrome	**short term**	**low**
Potential adverse effects associated with intravenous bisphosphonate therapy include transient flu-like syndrome with aches/chills/fever.[36] [35] [37]		
acute kidney injury	**variable**	**low**
Hypercalcaemia can lead to renal vasoconstriction, volume depletion, and a subsequent reversible decrease in glomerular filtration rate. Long-standing hypercalcaemia and hypercalciuria can lead to calcification, degeneration, and renal tubular atrophy/necrosis.[35] In addition, intravenous bisphosphonate therapy can be associated with acute kidney injury.[36] [35] [37]		
coma	**variable**	**low**
Hypercalcaemia is associated with neuropsychiatric symptoms, of which coma is a serious complication.		
acute pancreatitis	**variable**	**low**
Hypercalcaemia may lead to calcium deposition in the pancreatic duct, and to activation of trypsinogen in the pancreatic parenchyma, leading to pancreatitis. Incidence of acute pancreatitis associated with malignancy-associated hypercalcaemia is unknown.[38]		

Prognosis

Intravenous hydration and pharmacological therapy for malignancy-associated hypercalcaemia can provide transient restoration of normocalcaemia. Eradication of underlying malignancy is crucial for permanent reversal of hypercalcaemia.

Humoral hypercalcaemia of malignancy or local osteolytic hypercalcaemia

Intravenous hydration and calcitonin may improve hypercalcaemia within the first 24-48 hours of therapy.[1] [28] [29] Intravenous bisphosphonates are most efficacious and may restore normocalcaemia within 10 days of treatment in the majority of patients.[1] [26] Duration of effect is variable.[26] Sustained resolution of hypercalcaemia requires effective anti-tumour therapy.

FOLLOW UP

Calcitriol (1,25-dihydroxyvitamin D)-mediated hypercalcaemia

Intravenous hydration and calcitonin may transiently improve hypercalcaemia within the first 24-48 hours of therapy.[1] [28] [29] Glucocorticoid therapy requires several days to improve serum calcium levels.[34] Duration of effect has not been extensively studied.

Diagnostic guidelines

United Kingdom

Clinical knowledge summaries: hypercalcaemia (https://cks.nice.org.uk/topics/hypercalcaemia)

Published by: National Institute for Health and Care Excellence **Last published:** 2019

Emergency management of acute hypercalcaemia in adult patients (https://www.endocrinology.org/clinical-practice/clinical-guidance/society-for-endocrinology-guidance)

Published by: Society for Endocrinology **Last published:** 2016

North America

Cancer guidelines: symptom management. Oncologic emergencies (https://www.albertahealthservices.ca/info/cancerguidelines.aspx)

Published by: Alberta Provincial Tumour Council **Last published:** 2022

Treatment guidelines

United Kingdom

Clinical knowledge summaries: hypercalcaemia (https://cks.nice.org.uk/topics/hypercalcaemia)

Published by: National Institute for Health and Care Excellence **Last published:** 2019

Emergency management of acute hypercalcaemia in adult patients (https://www.endocrinology.org/clinical-practice/clinical-guidance/society-for-endocrinology-guidance)

Published by: Society for Endocrinology **Last published:** 2016

North America

Treatment of hypercalcemia of malignancy in adults: an Endocrine Society clinical practice guideline (https://www.endocrine.org/clinical-practice-guidelines/bone-health-and-osteoporosis)

Published by: Endocrine Society **Last published:** 2022

Cancer guidelines: symptom management. Oncologic emergencies (https://www.albertahealthservices.ca/info/cancerguidelines.aspx)

Published by: Alberta Provincial Tumour Council **Last published:** 2022

Oceania

Hypercalcaemia of malignancy (HCM) (https://www.eviq.org.au/clinical-resources/oncological-emergencies/486-hypercalcaemia-of-malignancy-hcm#management)

Published by: Cancer Institute NSW, New South Wales Government, Australia **Last published:** 2019

Key articles

- Cancer Institute NSW. Hypercalcaemia of malignancy (HCM). Jul 2019 [internet publication]. Full text (https://www.eviq.org.au/clinical-resources/oncological-emergencies/486-hypercalcaemia-of-malignancy-hcm)
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- El-Hajj Fuleihan G, Clines GA, Hu MI, et al. Treatment of hypercalcemia of malignancy in adults: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2023 Feb 15;108(3):507-28. Full text (https://academic.oup.com/jcem/article/108/3/507/6916871) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/36545746?tool=bestpractice.bmj.com)
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Images

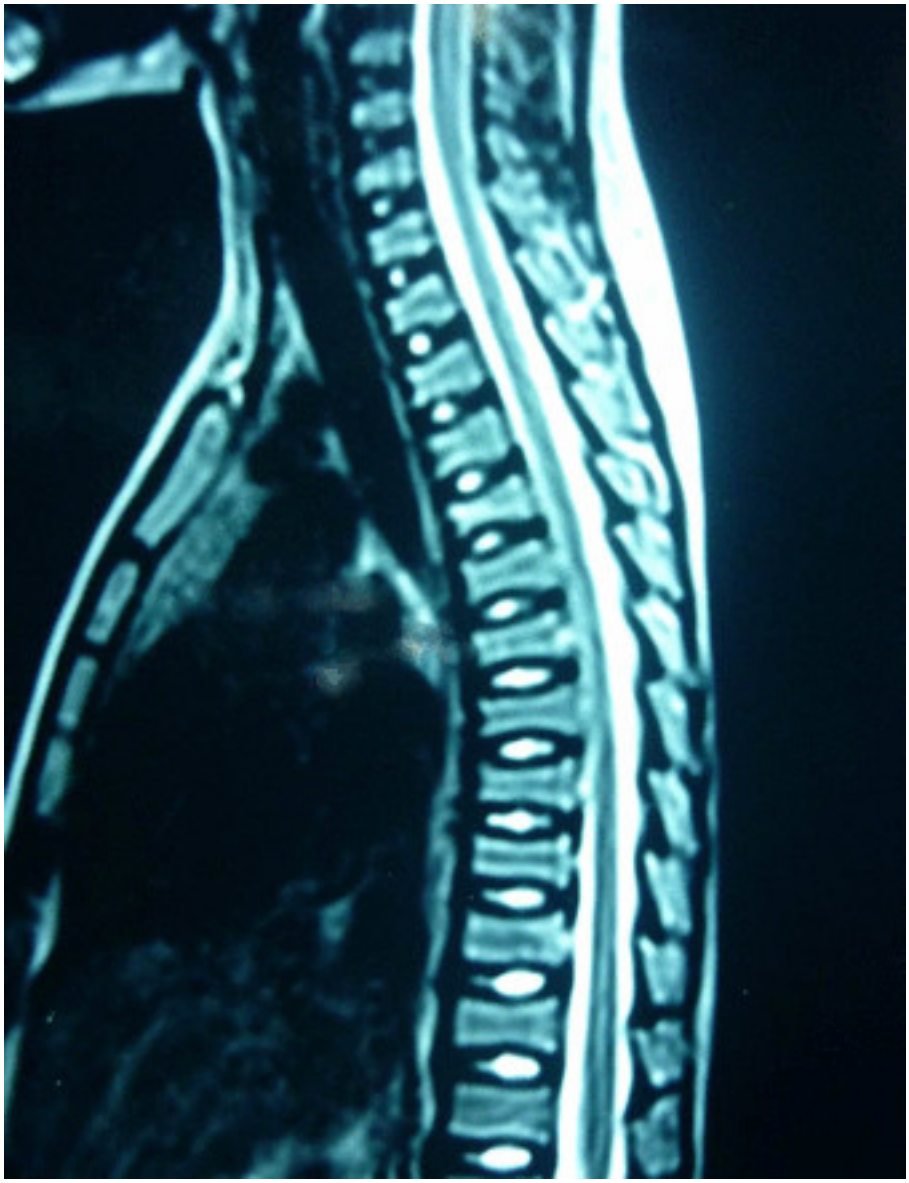

Figure 1: CT chest showing compression fracture of multiple vertebral bodies in a child presenting with acute lymphoblastic leukaemia. Biochemistry showed hypercalcaemia with a suppressed parathyroid hormone level

Sukumar SP, Balachandran K, Sahoo JP, et al. Acute lymphocytic leukaemia presenting as a metabolic bone disease. BMJ Case Reports 2013; doi:10.1136/bcr-2013-008758

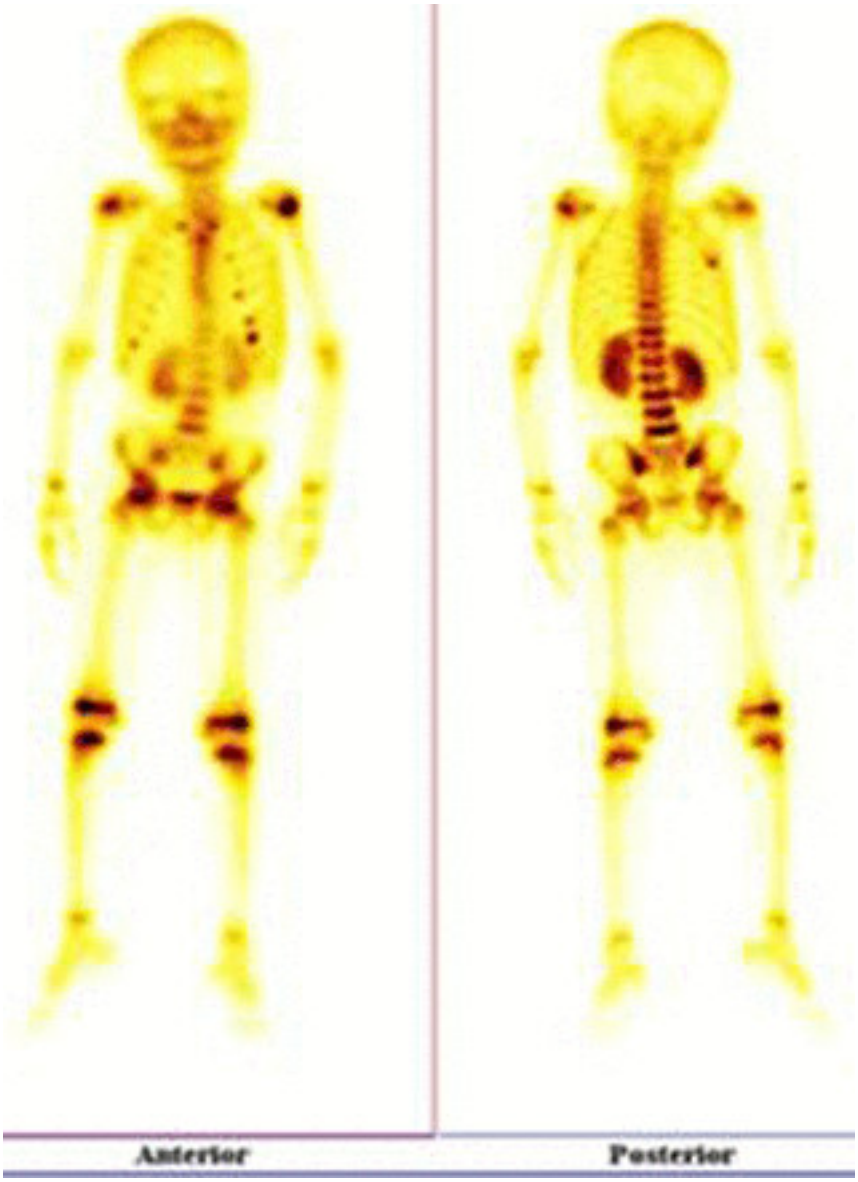

Figure 2: Whole body planar images suggestive of skeletal infiltration in a child with acute lymphoblastic leukaemia showing areas of abnormal increased uptake. Biochemistry showed hypercalcaemia with a suppressed parathyroid hormone level

Sukumar SP, Balachandran K, Sahoo JP, et al. Acute lymphocytic leukaemia presenting as a metabolic bone disease. BMJ Case Reports 2013; doi:10.1136/bcr-2013-008758

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Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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