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CASE REPORT

The Diagnosis and Management of Severe Hypercalcaemia

A simplified approach - Report of five cases

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تشخيص وعلاج الارتفاع المفرط لمستوى الكالسيوم

بطريقة مبسطة – تقرير 5 حالات

أميمة الشفيع، نيكولاس وود هاوز

الملخص: ارتفاع مستوى الكالسيوم في الدم مشكلة طبية واسعة الانتشار، ويمكن أن يكون عرضا لأمراض عديدة. وارتفاعه بنسبة عالية يمكن أن يسبب حالة طارئة. التشخيص الصحيح مهم لمنع اجراء الفحوص المختبرية غير الضرورية واستئصال الغدة الدريقية بشكل خاطئ. نستعرض هنا حالة خمسة مرضى كانوا يعانون من الارتفاع الشديد في مستوى الكالسيوم بالدم دون تشخيص صحيح لأشهر أو سنوات قبل إحالتهم الى مستشفى جامعة السلطان قابوس. الهدف من هذا البحث هو تأكيد أهمية الفحص الطبي السريري وتقييم فحص الكالسيوم والفوسفات والكرياتنين في الدم ومعرفة نسبة الكالسيوم في البول لمدة 24 ساعة مع مراجعة الصور الشعاعية. كل هذا يساعد في التكهن بوظائف الأعضاء المرضية للاضطراب ويرشدنا إلى عمليات الفحص المطلوبة قبل الحصول على نتائج فحص مستوى الهرمون في الدم.

مفتاح الكلمات: ارتفاع مستوى الكالسيوم بالدم، هرمون الغدة الدريقية، البيبتايد المرتبط بهورمون الغدة الدريقية، 1،25 دايهايدروكسي فيتامين "د"، تقرير حالة، عمان.

ABSTRACT: Hypercalcaemia, a common medical problem, can be a manifestation of various diseases. When severe, it can represent a medical emergency. Correct diagnosis is important to prevent unnecessary investigations and parathyroidectomies. We here present five patients with severe hypercalcaemia, most misdiagnosed for months or years before being referred to Sultan Qaboos University Hospital, Oman. We report how clinical examination, evaluation of fasting serum calcium, phosphate, creatinine and 24-hour urine calcium levels together with a review of their radiographics predicted the pathophysiology of the disorder and guided investigative procedures before hormone assays results were available.

Keywords: Hypercalcaemia; Parathyroid hormone; Parathyroid hormone-related peptide; 1,25 dihydroxy Vitamin D; Case report; Oman

Hypercalcaemia is a common medical problem, can be a manifestation of many diseases and, when severe, can represent a life-threatening medical emergency. Making the correct diagnosis is important to prevent unnecessary investigations and parathyroidectomies. At Sultan Qaboos University Hospital, Oman, we have recently seen five patients with severe hypercalcaemia (calcium ≥3.5 mmol/L), most of whom had been misdiagnosed for months or even years. The clinical examination, evaluation of the fasting serum calcium, phosphate, creatinine and 24-hour urine calcium levels together with a review of their radiographs accurately predicted the pathophysiology of the disorder and successfully guided our investigative procedures well before the results of hormone assays became available.

Case Reports

Details of the five patients together with their presenting serum calcium levels are shown in Table 1. In addition to the well recognised symptoms of a high calcium level, namely constipation, polyuria, polydipsia, nausea and vomiting, they were all anorexic with marked weight loss ranging

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Table 1: Patients' data and brief clinical history

Patient	Age (Yrs)	Calcium (Normal range 2.1-2.5 mmol/L)	Presenting Symptoms / Details
1	23	5.2	Three year history of polyuria, polydipsia, fatiguability, constipation, electrocardiogram abnormality labelled Wolff-Parkinson-White. Renal stone requiring lithotripsy in another hospital. Admitted with confusion, disorientation, marked weight loss (30 kg over previous 6 months), conjunctivitis, calcific keratitis, myopathy, hypotension, oliguria, osteoporosis. Electrocardiogram: remarkable ST depression with T-wave inversion consistent with metabolic electrocardiogram (K 2.3, Mg 0.23)
2	80	4.2	Weakness, weight loss (20 kg in 6 months), myopathy, difficulty in walking
3	45	3.5	Cough, weight loss (12 kg in 6 months), constipation
4	60	4.9	Presented with coma to medical services in neighbouring country, treated with hydration and bisphosphonate. Discharged with diagnosis of hypercalcaemia of unknown aetiology Admitted with confusion, weight loss (10 kg in 6 months)
5	45	4.9	Advanced metastatic breast cancer Admitted with confusion, vomiting, abdominal pain, weight loss (20 kg in 6 months)

from 6–15 kg over 4–8 months, irrespective of the underlying disease. Muscle weakness was profound in patients 1 and 2, and mental confusion was severe in patients 1, 4 and 5.

Some patients had additional clinical problems. Patients 2 and 4 had been successfully treated for hypertension (with atenolol and lisinopril respectively) for more than 5 years and patient 4 also had type 2 diabetes with proteinuria 3.6 mg/24 hours (normal range 0.05–0.1) and a monocloncal gammopathy. Patient 5 had a breast carcinoma, had been treated at another hospital for 2 years and was terminal upon arrival at our hospital.

The biochemistry of the patients at presentation was as follows, with data from the patients' initial fasting sample shown in Table 2. Note the low serum phosphate and normal creatinine levels in patients 1 and 5 and normal phosphate and elevated creatinine levels in patients 2, 3 and 4. The patients' hormone profiles are shown in Table 3. Parathyroid hormone (PTH) levels were dramatically increased in patient 1, but suppressed in the others including patient 5 with metastatic breast cancer. The parathyroid hormone-related peptide (PTH-rP) level was increased in patient 5, but suppressed in all the other patients. Levels of 1,25 dihydroxy vitamin D3 (OH)2D3 were increased in all patients.

Patients' radiographs helped to diagnose the cause of the hypercalcaemia in 4 of the 5 patients. Patient 1 had the classical X-ray findings of primary hyperparathyroidism (HPT) with severe osteoporosis [Figure 1a] and bone mineral density (BMD) of 600 g/cm^2 confirming severe osteoporosis [Figure 1b]. The neck ultrasound, magnetic resonance imaging (MRI) and parathyroid scans confirmed a parathyroid adenoma [Figure 1c]. In

Table 2: Patients bone profile, serum calcium (Ca), phosphorus (Phos), alkaline phosphatase (ALP), creatinine (Crea) and 24-hr urine calcium (24hr UCa), are shown together with their normal ranges (NR).

Patient	Ca NR 2.1–2.5 mmol/L	Phos NR .87–1.45 mmol/L	ALP NR 40–109 U/L	Crea NR 59–104 U/L	24-hr UCa NR 0.5–7.5 mmol/L
1	5.2	0.4	600	98	20
2	4.2	1.88	94	313	5
3	3.5	1.1	101	284	4
4	4.9	1.1	73	333	4.8
5	4.9	0.35	200	90	10

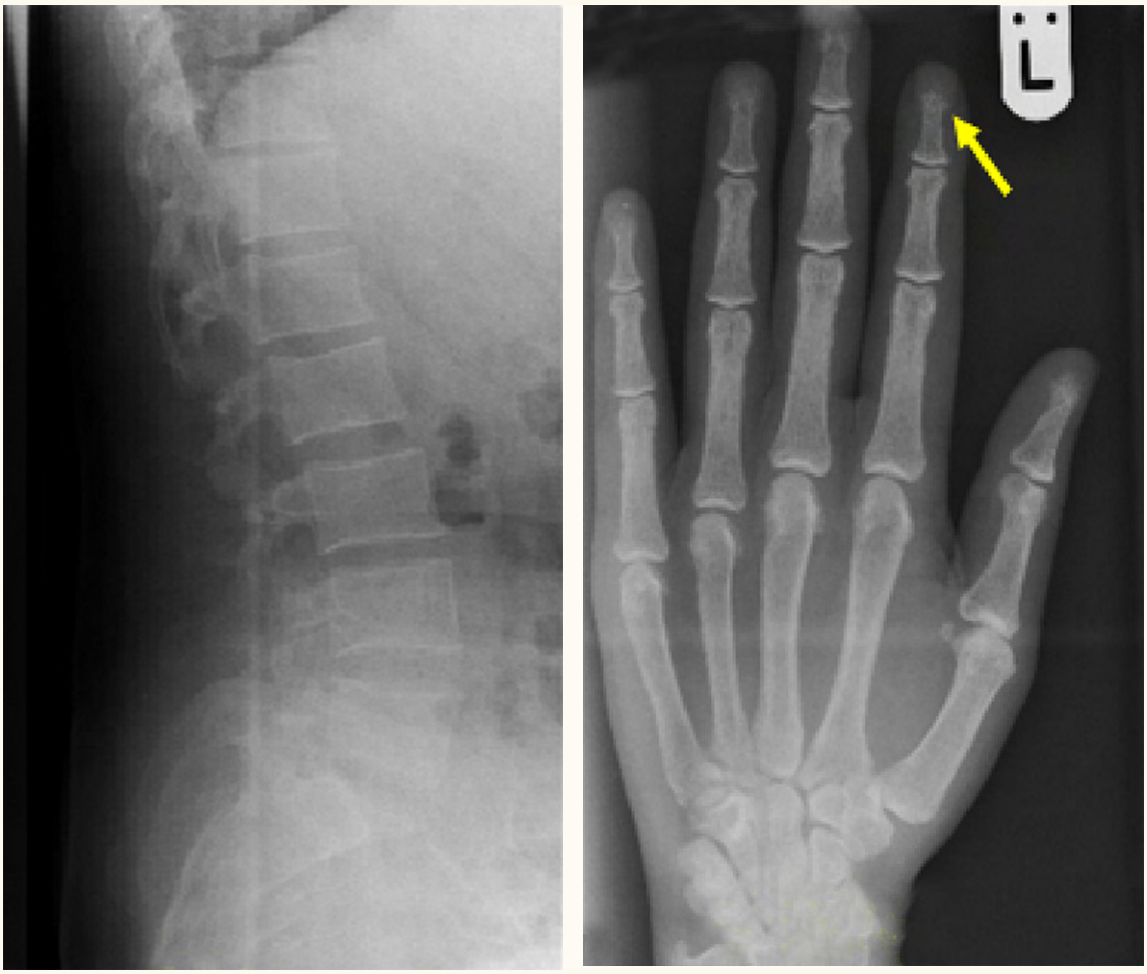

Figure 1a: Patient 1- Spinal film showing osteopenia, and hand X-ray revealing subperiosteal cortical bone erosion

patient 2, the computed tomography (CT) scan revealed a left axillary lymph node which was not palpable clinically [Figure 2a]. He underwent a diagnostic lymph node biopsy. An X-ray and CT scan of the chest of patient 3 showed bilateral hilar lymphadenopathy [Figure 3a], while the chest X-ray of patient 4 was normal. In patient 5, the chest showed metastases to the lung [Figure 5].

Histology confirmed the diagnosis in every patient. Patient 1 had a benign parathyroid adenoma [Figure 1d]. In patient 2, the bone marrow and lymph node biopsy revealed a large β-cell lymphoma [Figure 2b]. In patient 3, with a positive Mantoux test, caseating granulomas were seen on a bronchial biopsy specimen [Figure 3b]. Non-caseating granulomas consistent with sarcoidosis were seen on the renal biopsy in patient 4 [Figure 4], whose Mantoux test was negative. In addition,

Table 3: Patients presenting parathyroid hormone (PTH), parathyroid hormone related peptide (PTH-rP) and 1,25 dihydroxy vitamin D3 (1,25 vit D) levels are indicated with their normal ranges (NR).

Patient	PTH (NR 1.3–.5 pmol/L)	PTH-rP (NR <1.3 pmol/L)	125 Vit D (NR 43–148 pmol/L)
1	268	-	214
2	0.7	1.0	411
3	0.5	1.0	164
4	0.1	0.2	243
5	0.1	10	200

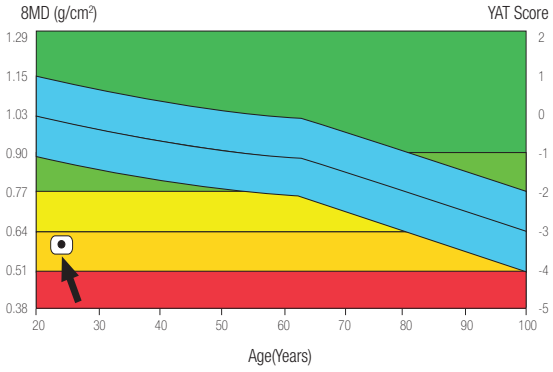

Figure 1b: Patient 1- Bone mineral density scan confirming severe osteoporosis

his bone marrow revealed clusters of plasma cells consistent with myeloma (not shown). The lymph node biopsy in patient 5 confirmed metastatic breast cancer (not shown).

As to the management of the hypercalcaemia, when a patient's serum calcium concentration is ≤3 mmol, then treatment should be aimed solely at managing the underlying disorder. Patients should also be advised to take plenty of oral fluid. If there are symptoms and signs of acute hypercalcaemia as in patients 1, 2, 4 and 5 (Table 1) and serum calcium is >3 mmol, then a series of urgent measures should be instituted as outlined in Table 4.[1] Our patients were treated for their underlying diseases: patient

Table 4: Management of severe hypercalcaemia. Patients with myeloma and some cases with granulomatous disorders will respond to steroid suppression.

Management of Acute Hypercalcaemia
1. Hydration Saline (0.9%) infusion, 2-6 L over 24 hours with K and/or Mg supplementation
2. Inhibition of bone resorption Calcitonin 4 IU/kg to 8 IU/kg q 12 hours sc or IM x 1 to 2 days Bisphosphonate Pamidronate (60 to 90 mg oer 4 hours IV) or Zoledronate (4 mg over 15 min IV)
3. Low calcium diet and avoid sunshine
4. Dialysis (in renal failure)
5. Treat underlying disease

1 with severe hyperparathyroidism, was hydrated aggressively with saline and given calcitonin and bisphosphonate to inhibit bone resorption. His severe electrolyte disturbance was managed with IV potassium and magnesium for 3 weeks until the calcium level had fallen to 3 mmol, and the electrocardiogram (ECG) readings had normalised [Figure 1e]. He then underwent right parathyroidectomy and right hemithyroidectomy. Patient 2 was treated for the large β-cell lymphoma with anti-CD20 antibody (rituximab). Patient 3 was treated for pulmonary tuberculosis (TB) with anti-

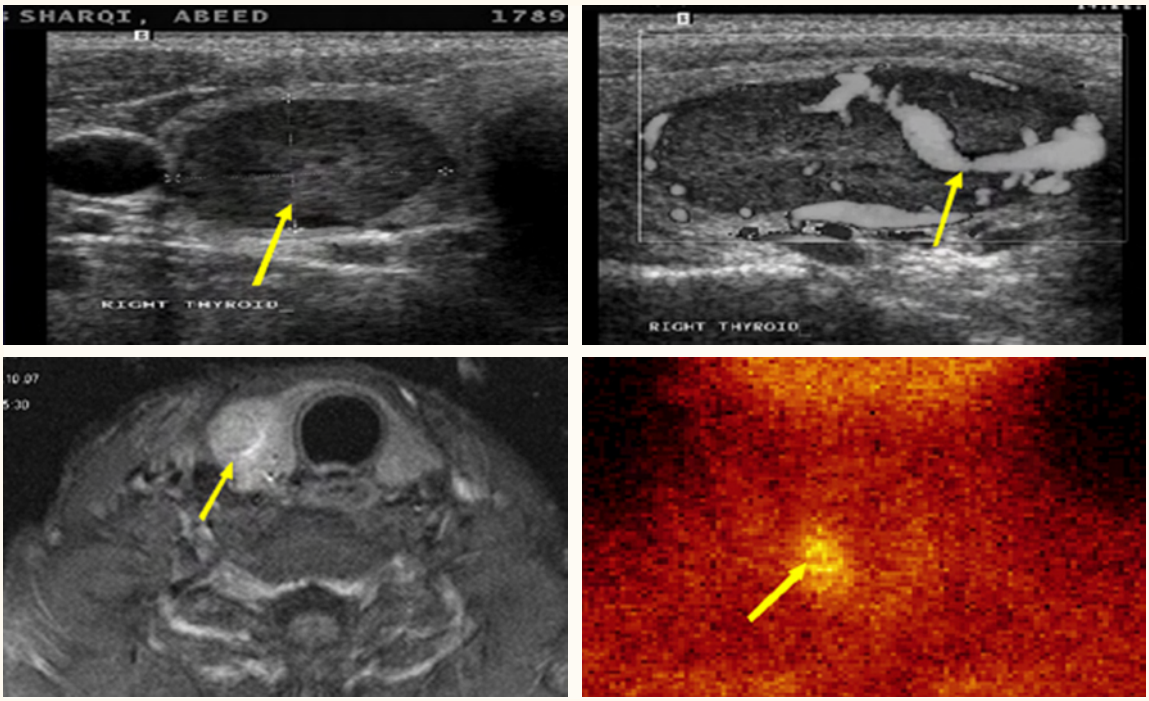

Figure 1c: Patient 1- Ultrasound, magnetic resonance, computer tomography and parathyroid scans showing a 3 x 2 cm vascular adenoma

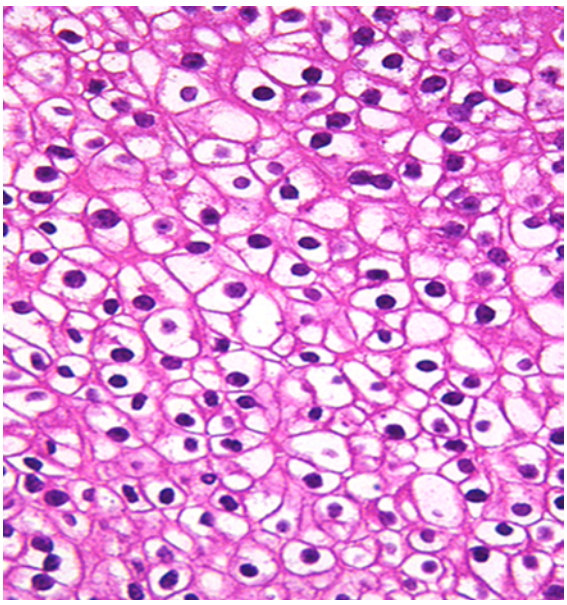

Figure 1d: Patient 1 - Histology reveals an intrathyroidal benign parathyroid adenoma.

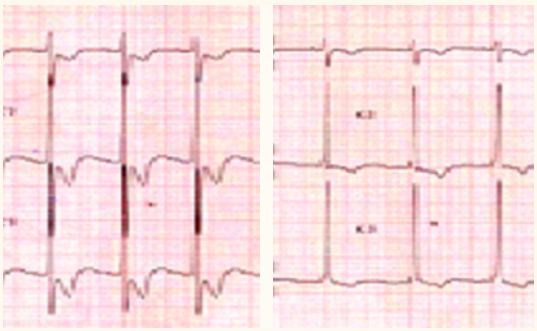

Figure 1e: Patient 1 - Admission ECG revealing severe ST segment depression and T wave inversion and considerable improvement after 3 weeks medical treatment

TB for 9 months. Patient 4 was treated with steroids for sarcoidosis and melphalan for myeloma, while patient 5 received chemotherapy for the breast cancer [Figure 5].

With treatment of the underlying diseases, the serum calcium and 1,25(OH)2 D3 levels and the renal function returned to normal in patients 1, 2, 3 and 4 [Figure 6a, b,& c]. The serum creatinine level was slightly high above the normal range in patient 2 due to his diabetic nephropathy. The serum calcium level returned to normal in patient 5, but she died 6 months later from her advancing metastatic cancer.

As regards parathyroid hormone (PTH) and

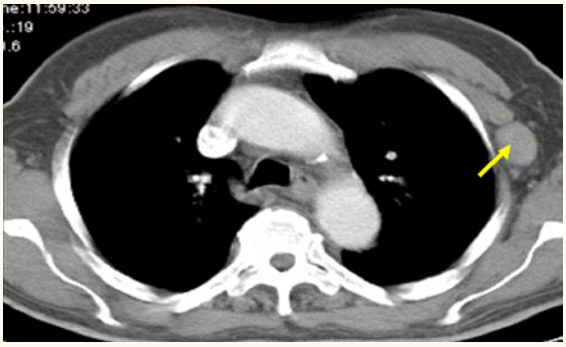

Figure 2a: Patient 2 - Computed tomography chest scan showing a 4 x 2 left axillary node.

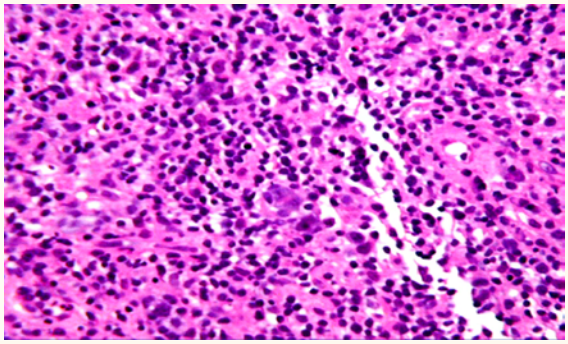

Figure 2b: Patient 2 - Axillary node biopsy revealing a lymphocyte predominant Hodgkin's disease β-cell lymphoma.

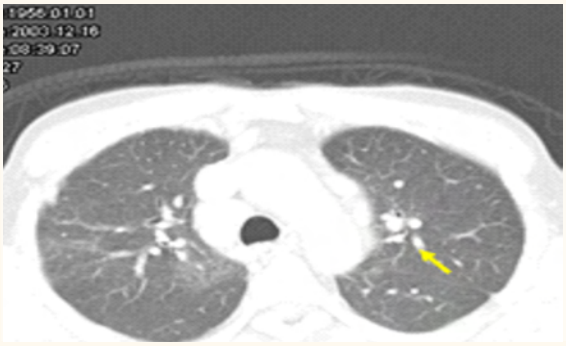

Figure 3a: Patient 3 - Computed tomography chest scan with bilateral hilar lymphadenopathy.

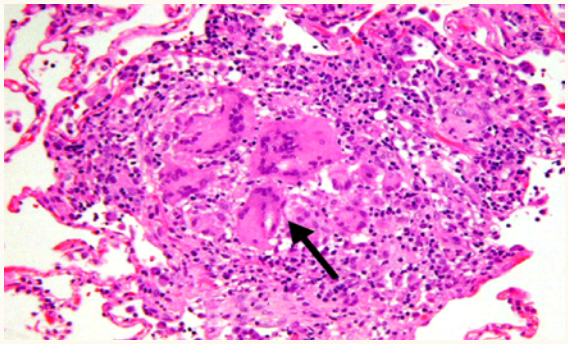

Figure 3b: Patient 3 - Transbronchial biopsy showing a caseating granuloma consistent with tuberculosis.

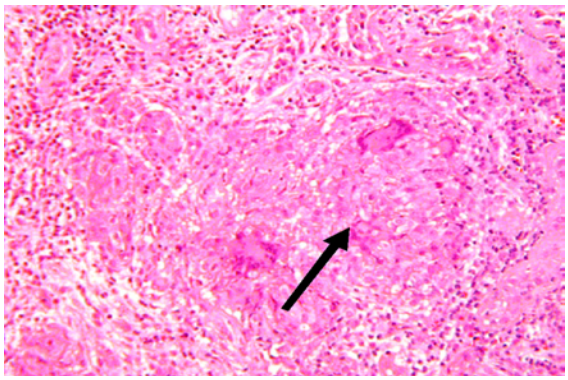

Figure 4: Patient 4 - Renal biopsy showing a non-caseating granuloma consistent with sarcoidosis.

parathyroid hormone related peptide (PTH-rP) excess, the 24-hour urinary calcium values are above normal and increase with rising hormone levels. Low values with normal serum creatinine levels suggest a diagnosis of familial hypocalciuric hypercalcaemia. This disorder results from an inactivating mutation of the calcium receptor (Ca-R) gene causing mild hyperparathyroidism not requiring surgical intervention.[2]

Discussion

The hypercalcaemia observed in these 5 patients was caused by raised circulating levels of 3 different hormones; PTH (patient 1), PTH-rP (patient 5) and $1,25(OH)_2D_3$ (patients 2, 3, and 4). PTH and PTH-rP share the same receptors causing hypercalcaemia and hypophosphataemia in the same way. Both stimulate renal 1α hydroxylase activity and raise circulating $1,25(OH)_2D$ levels thus increasing intestinal calcium absorption.[1,3] This additional load of calcium cannot be excreted as both hormones increase tubular calcium reabsorption. Hypercalcaemia results, but urinary calcium levels are only modestly increased and kidney function spared.[3-5] The net contribution of bone resorption to the hypercalcaemia of PTH/PTH-rP induced disease increases with the circulating hormone level. Bone resorption is relatively unimportant in the majority of patients with mild disease and normal serum alkaline phosphatase levels whereas in patient 1, with severe osteoporosis [Figure 1b] and massively elevated PTH and ALP levels, bone resorption must have been a major additional contributor to his hypercalcaemia. Both hormones also inhibit tubular phosphate reabsorption; urinary

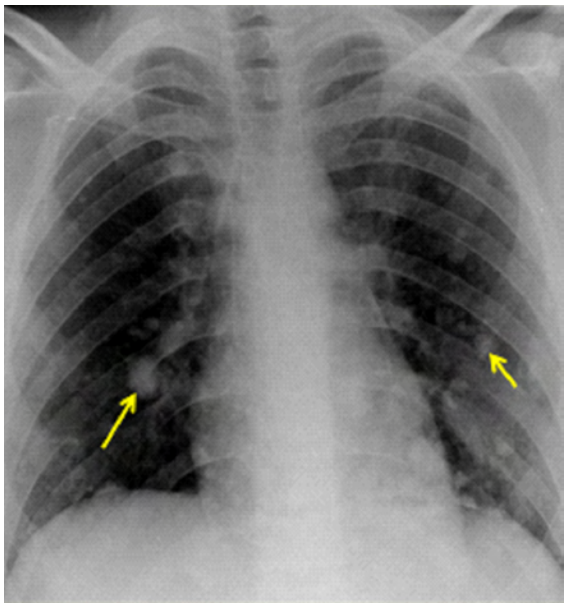

Figure 5: Patient 5 - Chest X-ray revealing bilateral lung metastases.

phosphate levels increase and serum levels decrease most obviously when measured in the fasting state. Examination of the bone profiles illustrates these points; the marked hypercalcaemia seen in patients 1 and 5, with raised PTH and PTH-rP levels respectively, was associated with low serum phosphate, but normal creatinine levels.

The other 3 patients had non-PTH/PTH-rP induced disease. This can occur in two situations; either excessive osteoclastic destruction of bone as occurs in myeloma, or hyperabsorption of intestinal calcium due to elevated circulating $1,25(OH)_2D$ levels.[1,6] In either situation, the body responds as though it is receiving a slow calcium infusion; endogenous PTH levels are suppressed and tubular calcium reabsorption reduced resulting in marked hypercalciuria. Unchecked hypercalciuria is nephrotoxic and results in a progressive fall in glomerular filtration rate (GFR) and rising creatinine levels. Because endogenous PTH levels are suppressed, tubular resorption of phosphate is increased and serum phosphate levels are normal or increased. These features are seen in Table 2 where the hypercalcaemia of patients 2, 3 and 4 was associated with normal phosphate and raised creatinine levels. As their skeletal radiographs were normal, hyperabsorption of calcium, and not increased osteoclastic resorption of bone, was correctly predicted to be the cause of the hypercalcaemia. This was later confirmed by finding raised circulating levels of $1,25(OH)_2D$

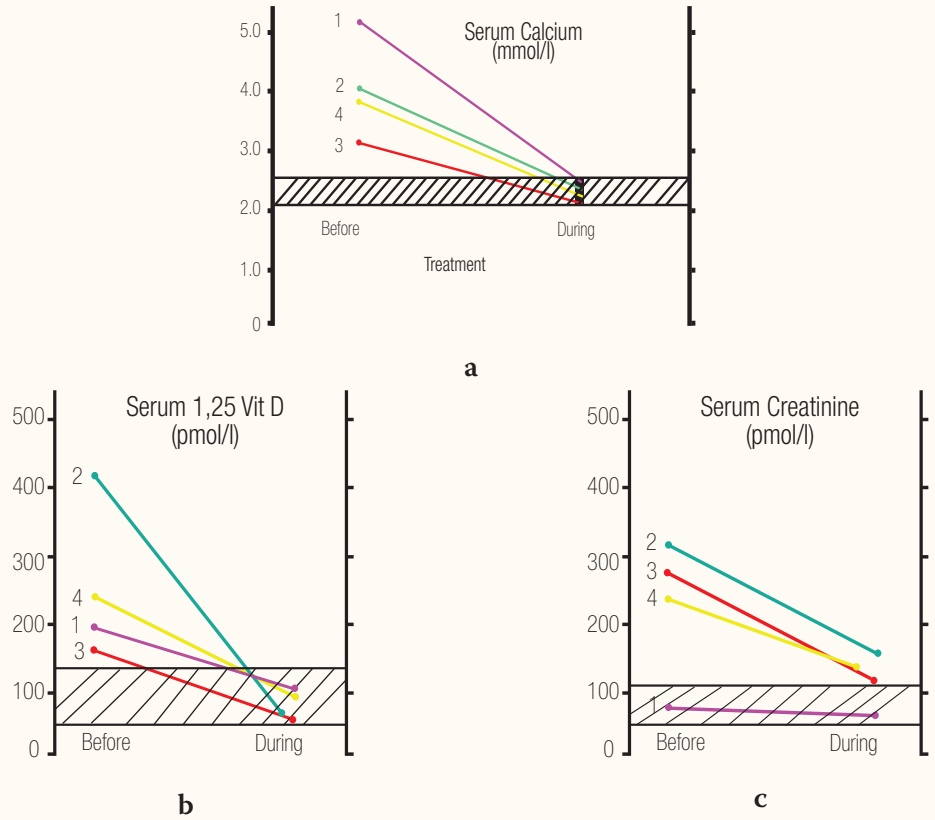

Figure 6a, b & c: Patients 1, 2, 3 & 4 - Response to treatment of the underlying disease. **6a:** Serum calcium; **6b:** Serum 1,25 dihydroxy vitamin D3; **6c:** Serum creatinine

in all 3 patients. Under normal circumstances, macrophages synthesise $1,25(OH)_2D$ from 25OHD. This in turn stimulates the production and secretion of antimicrobial defensins.[7] When macrophages are present in large numbers around inflammatory foci (e.g. tuberculosis[8,9,10] or sarcoidosis[11,12]) or certain lymphomas,[13,14,15] $1,25(OH)_2D$ spills over into the circulation, causing initially hypercalciuria, and later hypercalcaemia as renal function deteriorates and the absorbed calcium load cannot be excreted. At this point, the 24-hour urine calcium levels are often within the 'normal' range [Table 3]. Patient 4 had sarcoidosis and myeloma, but the myeloma was not responsible for the hypercalcaemia[16,17,18] as his haemoglobin and skeletal survey were normal and $1,25OH_2D$ levels elevated.

Conclusion

In the majority of patients, a fasting bone profile and serum creatinine level will distinguish between PTH and non-parathyroid causes of hypercalcaemia. Normal creatinine and low normal or low phosphate levels occur with raised PTH/PTH-rP, whereas raised creatinine and normal or raised phosphate levels are seen in patients with non-parathyroid hypercalcaemia. Twenty-four hour urine calcium levels should be measured in all patients with mild hyperparathyroidism; low values suggest a diagnosis of familial hypocalciuric hypercalcaemia and surgery is not indicated.

Patients with a parathyroid crisis should be treated medically for at least 2 weeks to avoid complications during surgery.

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