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Puzzling hypercalcaemia: sarcoidosis without lung involvement

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In a patient with unexplained hypercalcaemia, sarcoidosis is a possibility even if there is no overt pulmonary disease.

CASE HISTORY

A Caucasoid woman of 68 was seen after three weeks of confusion, polydipsia, anorexia, general malaise and weight loss. A life-long smoker of ten cigarettes a day, she had no medical history of note. On examination she was cachectic and dehydrated. Nothing else was found—in particular, no rashes, lymphadenopathy, or respiratory or neurological signs. Routine investigations revealed a lymphopenia of $0.6 \times 10^9/L$ (full blood count otherwise normal), erythrocyte sedimentation rate 34 mm/h, normal serum electrolytes with mild renal impairment (urea 12.1 mmol/L, creatinine 164 $\mu\text{mol/L}$) and hypercalcaemia with a corrected serum total calcium of 3.56 mmol/L and phosphate 1.3 mmol/L; alkaline phosphatase was 165 IU/L, alanine aminotransferase 44 IU/L, gammaglutamyltransferase 81 IU/L, and albumin 30 g/L. Her chest radiograph was normal.

The initial clinical diagnosis was hypercalcaemia secondary to malignant disease. Further testing revealed a normal mammogram, a normal parathyroid hormone (PTH) of 25 ng/L (normal range 10–65), parathyroid-related peptide (PTHrP) 1.0 pmol/L (0.1–1.8) and 25-hydroxyvitamin-D 68 nmol/L (20–100) but a raised

1,25-dihydroxyvitamin-D of 144 pmol/L (20–120). Serum protein electrophoresis was normal and urine examination was negative for Bence Jones protein. After rehydration with intravenous colloid her renal function returned to normal over four weeks. However, she remained symptomatic with a serum calcium concentration of greater than 3.7 mmol/L. She was treated with four intravenous doses of pamidronate (30 mg, 60 mg, 90 mg, 30 mg) over eight weeks, during which her calcium peaked at 4.2 mmol/L (Figure 1).

Abdominal CT revealed minimal dilatation of the left hepatic ducts and portahepatic lymphadenopathy. A CT-guided biopsy of these nodes showed non-caseating granulomata. She had a grade zero Heaf test. High-resolution CT of the chest revealed bullous emphysema in the apices but no radiological pulmonary features suggestive of sarcoidosis; however, her serum angiotensin converting enzyme (sACE) was raised at 211 IU/L (27–82).

Sarcoidosis was diagnosed and she was treated with oral prednisolone 40 mg daily. Symptoms quickly resolved; serum calcium became normal within two weeks and sACE within two months. Twenty months after discharge she was taking 5 mg prednisolone daily and symptom-free; her serum calcium was normal (2.55 mmol/L).

COMMENT

Hypercalcaemia, although seen in 10–20% of patients with sarcoidosis, is rare in the absence of pulmonary involvement.¹ A search of EMBASE and Medline yielded only ten such cases. The present case illustrates the difficulty of distinguishing between causes of hypercalcaemia. Though not a diagnostic marker of sarcoidosis, a high ACE is a useful pointer.²

The mechanism of hypercalcaemia in sarcoidosis is not fully understood. Calcium homeostasis is controlled mainly by levels of vitamin-D, PTH and calcitonin. 1,25-dihydroxycholecalciferol (1,25(OH)₂D₃), the most active form of vitamin-D, is ultimately formed in the kidney following 1 α -hydroxylation of 25-hydroxycholecalciferol (25[OH]₂D₃) by the enzyme 1 α -hydroxylase. 1,25(OH)₂D₃ acts to increase gastrointestinal absorption of calcium and phosphate whilst also stimulating osteoclast-mediated bone resorption.³ Studies showing increased circulating concentrations of 1,25(OH)₂D₃ in patients with sarcoidosis and hypercalcaemia led to the hypothesis that the cause was related to abnormal vitamin-D metabolism. One theory suggests that increased 1,25(OH)₂D₃ synthesis is caused by activated pulmonary macrophages in granulomatous tissue.¹ This is validated by studies showing generation of 1,25(OH)₂D₃ from homogenates of alveolar macrophages from patients with sarcoidosis.⁴ Furthermore, an increase in 1 α -hydroxylase mRNA expression has been

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Figure 1 Serum calcium and angiotensin converting enzyme (ACE) concentration and the effect of prednisolone. ■ Serum calcium concentration (mmol/L); ♦ serum ACE (IU/L)

reported in alveolar cells obtained from patients with sarcoidosis, with a correlation between expression and disease activity.⁴

If the above theories are correct, hypercalcaemia should not occur in the absence of chest disease. In cases such as ours three possible explanations have been offered. First, the granulomatous tissue responsible for $1,25(\text{OH})_2\text{D}_3$ production might be below the limits of standard radiographic resolution.¹ Secondly, the excess $1,25(\text{OH})_2\text{D}_3$ might originate from extrapulmonary sarcoid granulomatous tissue. Thirdly, hypercalcaemia might be explained by production of PTHrP. PTHrP acts on $1,25(\text{OH})_2\text{D}_3$ in a similar manner to PTH but is regulated by tumour necrosis factor- α and interleukin-6.³ PTHrP can be found in sarcoid tissue specimens and lymph node homogenates from patients with sarcoidosis^{3,4} and high concentrations have been reported in some patients with sarcoid. The PTHrP was normal in our patient. Finally, there is the possibility that increased $1,25(\text{OH})_2\text{D}_3$ production may not be the sole cause of hypercalcaemia since $1,25(\text{OH})_2\text{D}_3$ is not always raised in these patients.⁴

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A diabetic breast lump

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Organs commonly affected by diabetes mellitus include retina, kidneys and peripheral nerves. Involvement of the breast is unusual.

CASE HISTORY

A man of 47 sought advice because of below-knee numbness and brief loss of consciousness after a fall from a bicycle. Non-insulin-dependent (type 2) diabetes had been diagnosed 4 years earlier and he was being treated with glibenclamide and metformin. He was also hypertensive.

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