An unusual cause of hypercalcaemia in a patient with cystic fibrosis

Sir,

We would like to present an unusual case of hypercalcaemia in a 19 year-old patient with cystic fibrosis (CF). He was homozygous for the ΔF508 mutation and retained excellent lung function with a FEV₁ of 4.47 L (105% predicted) and a FVC of 5.84 (130% predicted). Sputum cultures were persistently negative for Pseudomonas aeruginosa. The patient was pancreatic insufficient and had been prescribed Creon 10000 and vitamin A, D and E supplements. Unfortunately concordance with treatment and out-patient attendance was poor.

At annual assessment the patient’s serum vitamin D level was noted to be 32 nmol L⁻¹ (Sufficiency >75 nmol L⁻¹) while vitamin A and serum adjusted calcium levels were normal. C-Reactive protein was normal at annual assessment. Poor concordance was addressed by the attending physician and he was started on two tablets of Calcichew D3 Forte (Ca²⁺ 12.6 mmol, colecalciferol 10 μg/tablet) and continued on 3 capsules of Vitamin A +D (vitamin A 4000 IU/capsule; vitamin D 10 μg/capsule).

One month after starting Calcichew D3 Forte, a routine blood test revealed asymptomatic hypercalcaemia with serum adjusted calcium level of 2.77 mmol L⁻¹ (Normal range 2.20–2.60 mmol L⁻¹).

The patient was advised to stop taking Calcichew D3 Forte due to concern that the increased calcium intake could have precipitated hypercalcaemia. His concordance with oral medication had also improved.

Shortly after stopping the Calcichew D3 Forte he developed an acute pulmonary exacerbation requiring intravenous antibiotics. The adjusted serum calcium levels were repeated and remained elevated both during and for over 2 months following his admission for intravenous antibiotic treatment.

Further investigations for parathyroid hormone (PTH), serum angiotensin converting enzyme, thyroid stimulating hormone and renal function were normal. Alkaline phosphatase was slightly elevated at 380 IU L⁻¹ (Normal range 220–300 IU L⁻¹). This result was not different from the patient’s previous results and was felt to be a reflection of longstanding CF related liver disease. Fasting vitamin A was elevated at 3.77 μmol L⁻¹ (Normal range 1.05–3.39 μmol L⁻¹) while fasting vitamin D levels remained suboptimal at 23.6 nmol L⁻¹.

In view of the laboratory investigations a diagnosis of hypercalcaemia secondary to hypervitaminosis A was made. The patient’s vitamin A +D supplements were reduced to one capsule and he was recommenced on 2 capsules of Calcichew D3 Forte. Vitamin A levels were in the normal range at 2.28 μmol L⁻¹ 6 months after adjustment of his vitamin A +D supplements and the hypercalcaemia has not reoccurred.

Hypercalcaemia related to hypervitaminosis A is rare but is recognised in patients undergoing haemodialysis [1], receiving enteral feeding [2], consuming large amount of vitamin A supplements [3], prescribed retinol based acne treatment [4,5] and has been described once previously in a patient with CF [6]. Most cases of hypercalcaemia are usually due to chronic ingestion, however hypercalcaemia has been reported after 11 days of ingestion of high amounts of vitamin A [7]. While vitamin A induced hypercalcaemia usually resolves after reducing or stopping vitamin A supplementation, steroid therapy can be helpful in refractory cases [5].

The mechanism by which excess vitamin A induces hypercalcaemia is not well understood and is not thought to be due to the production of excess PTH [8]. The bones of rats fed large quantities of vitamin A show evidence of increased osteoclastic activity and bone resorption [9,10]. More recent work has shown evidence that vitamin A induces loss of bone mass via a mechanism that is independent of the vitamin D endocrine system [11].

The presence of hypervitaminosis A has important potential ramifications for individuals with CF as it is associated with osteoporosis and liver disease. There are several reasons why our young man may have developed hypervitaminosis A. Firstly his concordance had improved significantly and he reported taking regular vitamin A supplements. He had also started taking nutritionally complete sip feeds which provided an additional 2544 IU vitamin A and 13.8 mmol calcium per day. Our patient may have been protected to some extent from hypercalcaemia due to the presence of concurrent hypovitaminosis D. It is important to remember that plasma vitamin A
levels are not necessarily an accurate indicator of status and can be influenced by ongoing inflammation, retinol binding protein levels, plasma zinc and liver disease.

Active inflammation can cause a reduction in serum vitamin A levels; therefore vitamin A monitoring should be carried out at a time of clinical stability and/or alongside a marker of inflammation. Measurement of retinol binding protein and plasma zinc may aid the interpretation of plasma vitamin A level.

This case highlights the importance of regular vitamin A monitoring in patients with CF and the complex interaction between vitamin A, vitamin D and calcium metabolism. Vitamin A deficiency is common in pancreatic insufficient patients who do not receive appropriate supplementation, but hypervitaminosis A can occur and is potentially associated with important complications.

References


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