Parathyroidectomy in a hypercalcaemic patient with inappropriately normal plasma parathyroid hormone: an unusual way to arrive at the correct diagnosis

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Case

A 49-year-old Caucasian man presented with a 2-month history of lethargy, nausea, anorexia, weight loss and polyuria. He was cachectic and mildly dehydrated. Laboratory analysis showed: plasma calcium, 3.45 mmol/l (corrected to a reference plasma albumin of 40 g/l using a factor of 0.02 mmol/g albumin); alkaline phosphatase, 160 IU/l (normal range 32–90 IU/l); urea, 17.5 mmol/l; and creatinine, 496 µmol/l. Haemoglobin was 10.5 g/dl (normochromic, normocytic pattern). The following investigations gave normal results: protein electrophoresis of urine and serum, X-rays of chest, hands and skull, and bone scintigraphy. Serum angiotensin converting enzyme (ACE), prostate-specific antigen, alanine aminotransferase and thyroid stimulating hormone were all within normal ranges. Parathyroid hormone (PTH), intact molecule assay, was 4 mg/dl (normal range 3.5–16 mg/dl, depending on plasma calcium).

He was treated initially with intravenous fluids, then frusemide and pamidronate. Plasma calcium fell to 2.66 mmol/l and plasma creatinine to 300 µmol/l. No further therapy was pursued.

At review several weeks later, plasma calcium was 3.03 mmol/l. A technetium-thallium subtraction scintigram was suggestive of generalized parathyroid hyperplasia, although the signal was particularly intense in the region of the left lower gland.

The patient was referred for surgical parathyroidectomy. Four glands were identified, all of which appeared enlarged. Three whole glands plus a section of the fourth gland were removed. Generalized chief cell hyperplasia of all four glands was found on histological analysis.

There was little change in plasma calcium during the peri-operative period and a decision was made to remove the remaining parathyroid tissue. Histological examination again showed hyperplastic change within the gland. More significantly, a granulomatous lesion containing giant cells was noted in sections of an excised lymph node (Figure 1a and b). This was initially considered to be a reaction to a metal clip left in situ after the first operation.

Plasma calcium levels remained high, despite regular oral clodronate, and the patient was referred to our centre. Additional tests suggested a predominantly hepatic source of plasma alkaline phosphatase, and gamma-glutamyl transferase was raised. This information, together with the histopathology report of the lymph node, raised the possibility of sarcoidosis. Granulomata were found in a liver biopsy specimen (Figure 2). Chest X-ray and physical examination remained unremarkable.

The patient was treated with high dose oral steroids. Within weeks, plasma calcium and alkaline phosphatase levels had returned to the normal range. Serum creatinine fell from 300 to 160 µmol/l on correction of the hypercalcaemia.

Discussion

The case serves to illustrate an important point that is relevant to investigation of hypercalcaemia, namely...
Fig. 1. (a) Cervical lymph node showing features characteristic of sarcoidosis, including architectural effacement by demarcated epithelioid granulomas with no necrotizing changes and absence of follicles (H&E, magnification ×12). (b) High magnification showing typical sharply demarcated granulomas with surrounding small lymphocytes (H&E, magnification ×64).
that a plasma PTH level within the normal range (i.e. not suppressed) does not exclude causes other than hyperparathyroidism, and these should be considered prior to surgical exploration of the neck. The converse also applies, in that a normal range PTH (i.e. not elevated) does not exclude hyperparathyroidism[1]. The latter may be explained by the marked variance of PTH values in the ‘normal’ population. An ‘overlap’ with the normal range has been demonstrated in cases of sarcoidosis[2]. Previous work has suggested that ACE measurements are of greater use prior to surgical exploration of the neck. The converse also applies, in that a normal range PTH (i.e. not in monitoring response to treatment[3]). Secondly, useful information may be obtained from measurement of organ-specific isoenzymes of alkaline phosphatase, even when the alanine aminotransferase level is within the normal range. The latter may be explained by the marked variance of PTH values in the ‘normal’ population. An ‘overlap’ with the normal range has been demonstrated in patients with surgically proven hyperparathyroidism[2].

Teaching point

In patients with hypercalcaemia, failure of suppression of PTH secretion should be regarded as an equivocal result, particularly when renal function is impaired. Detailed investigation to exclude pathologies usually associated with PTH suppression is an essential preliminary to surgical exploration of the neck.

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References