extended storage. Boiling extraction represents a false-economy and leads invariably to frustration as laboratory staff have to repeat the extraction, usually by employing a commercial kit. □

LC was supported by the European Social Fund.

References

1 Millar BC, Xu J, Moore JE, Earle JA. A simple and sensitive method to extract bacterial, yeast and fungal DNA from blood culture material. *J Microbiol Methods* 2000; **42**: 139-47.
2 De Vos D, Lim A Jr, Pirnay JP *et al*. Direct detection and identification of *Pseudomonas aeruginosa* in clinical samples such as skin biopsy specimens and expectorations by multiplex PCR based on two outer membrane lipoprotein genes, *opr*I and *opr*L. J Clin Microbiol 1997; 35: 1295-9.
3 Wilson IG. Inhibition and facilitation of nucleic acid amplification. *Appl Environ Microbiol* 1997; **63**: 3741-51.
4 Wilson IG, Cooper JE, Gilmour A. Some factors inhibiting amplification of the *Staphylococcus aureus* enterotoxin C1 gene (sec+) by PCR. *Int J Food Microbiol* 1994; **22**: 55-62.

Hyperparathyroidism – pitfalls in management

SIMON CONROY and WASSIF S WASSIF
Department of Health Care for the Elderly and Department of Chemical Pathology, Bedford Hospital, UK

Parathyroid cancer is uncommon and easy to miss, and the limited studies available suggest the need for family screening and radical surgery. Medical options include chemotherapy, immunotherapy and bone protection with bisphosphonates, calcium and vitamin D or hormone therapy. The following case history illustrates some of the problems encountered.

A 77-year-old lady with a background of hypertension (controlled on methyl-dopa and bendrofluazide) was referred as an emergency with severe hypercalcaemia. Physical examination revealed significant dehydration. Initial investigations showed normal renal function but a corrected serum calcium of 3.96 mmol/L.[1] Emergency management consisted of intravenous rehydration and a standard infusion of disodium pamidronate (90 mg). Bendrofluazide treatment was stopped.

Serial serum calcium measurements are shown in figure 1. The intact serum parathyroid hormone level was markedly elevated at 533 pg/mL (reference range 10-50 pg/mL), 24-hour urinary calcium was elevated at 8.2 mmol/L (2.5-7.5 mmol/L), and a diagnosis of primary hyperparathyroidism was established.

Correspondence to: Dr Simon Conroy
Department of Medicine, Bedford Hospital, Brittania Road, Bedford MK42 9DJ.
Email: spcon@msn.com

Despite initial response to rehydration, calcium levels remained high and began to rise further one month after the initial pamidronate infusion (Figure 1). Bone scan was normal and X-rays of the patient's hands showed degenerative changes only. A parathyroid subtraction scan showed increased uptake at the right upper pole of the thyroid, which was measured on ultrasonography as 2.0 x 1.7 x 1.8 cm, and a smaller area of uptake at the left lower pole. Following preoperative vocal cord assessment, which was normal, a parathyroidectomy was carried out, during which both masses were excised.

Histopathological examination of the right upper mass revealed a parathyroid nodule (2.5 cm diameter) with a follicular growth pattern. The nodule was surrounded by a thickened capsule and strands of fibrous connective tissue that extended into the parathyroid tissue, dividing it into bands. The capsule showed extensive haemorrhage and haemosiderin deposition, and the parathyroid parenchyma contained focal areas of calcification. Although there was minimal pleiomorphism and no frank vascular invasion, infiltration of the capsule by parathyroid tissue was seen. These features were suggestive, but not diagnostic, of parathyroid carcinoma. The nodule removed from the left lower pole proved to be a normal parathyroid gland.

Corrected calcium was 2.6 mmol/L on the first post-operative day, and this level fell gradually over consecutive days to 2.16 mmol/L and then stabilised. A subsequent dual emission X-ray absorbiometry (DEXA) scan showed decreased right hip bone mineral density (BMD) compared to the mean of the young adult female population (T score: 2.4 SD) and that of the age/gender matched control (Z score: 0.7). Lumbar spine values were normal. The patient was discharged to her home, symptom-free. On follow-up, three months after initial presentation, she remained well, with a calcium level of 2.36 mmol/L and PTH of 44 pg/mL. She continues to be monitored to check for evidence of recurrence.

Parathyroid carcinoma is rare and an uncommon cause of hypercalcaemia. It usually presents in the fourth decade of life. Clinical pointers include severe hypercalcaemia (>3.5 mmol/L), a palpable mass and unilateral vocal chord paresis,[2] but not all malignant parathyroid tumours are functional. Histopathological diagnosis in isolation can be difficult but markers include a solid growth pattern, extensive fibrosis, necrosis, nuclear atypia and mitotic figures. Sandelin *et al* reported a series of parathyroid carcinomas in which an initial benign diagnosis was give in 50% of cases.[3] The presence of DNA aneuploidy has been shown to correlated with adverse histological features and a worse prognosis.[4,5] The retinoblastoma tumour suppressor gene is found in some malignant tumours and may be of diagnostic and prognostic value.[6]

Diagnosis of parathyroid carcinoma has implications both for the individual and for family members, as there may be an associated hereditary syndrome (MEN1, MEN2A, hyperparathyroidism-jaw tumour syndrome or familial isolated hyperparathyroidism) in approximately 10% of cases.[7,8]

Experience in the management of parathyroid malignancy is limited as it is an uncommon condition, but it is a very slow-growing tumour and radical surgery can be curative, even in what appears to be invasive disease. Such surgery needs to be extensive and include resection of the ipsilateral

thyroid and include block resection for locally infiltrating cancers.[9-11] In the presence of more than one adenoma or multiple areas of hyperplasia, even where there is no clear evidence of carcinoma, subtotal resection of the ipsilateral thyroid has been advocated in cases of recurrent parathyroid tumour.[12] As yet, the role of radiotherapy remains to be fully established, but chemotherapy may be employed in metastatic disease.[13]

Hypercalcaemia associated with parathyroid tumours can be difficult to control, although the successful use of bisphosphonates in the preoperative phase has been reported,[14] as has the use of gallium nitrate[15] and immunotherapy.[16]

Bone protection is of prime importance in over-active PTH production, as it has long-term detrimental effects on bone density. Apart from definitive surgery, medical therapy to protect bone is worth considering, and benefit may be achieved with bisphosphonates and hormone replacement therapy in post-menopausal women.[17,18]

As indicated above, long-term follow-up of parathyroid tumours is essential, as recurrence can occur up to 30 years later. The most sensitive monitoring test for this purpose is serum calcium.[19] □

KEY POINTS

- A high degree of suspicion is required to identify potential parathyroid carcinomas, with clinical pointers including severe hypercalcaemia, palpable mass and unilateral vocal chord paresis
- Radical surgery can be curative, even in apparent advanced disease
- Bone protection may be achieved through the use of bisphosphonates or hormone therapy
- Long-term survival is common, but late relapse can occur up to 30 years later
- Serum calcium is the best monitoring test

We are indebted to several colleagues at Bedford Hospital for their input in this case.

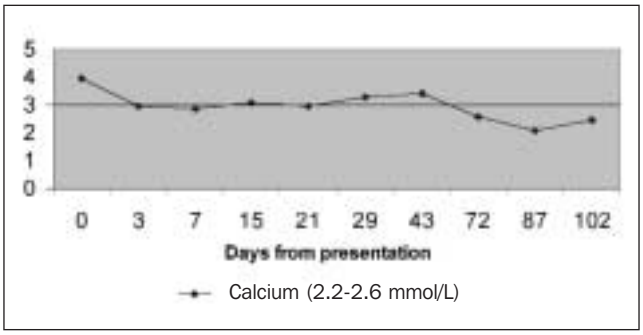

Fig.1. Serial serum corrected calcium before and after parathyroidectomy (day 45).

References

1 Correcting the calcium (Editorial). *BMJ* 1977; **1**: 598.
2 Vetto JT, Brennan MF, Woodruf J *et al*. Parathyroid carcinoma: diagnosis and clinical history. *Surgery* 1993; **114**(5): 882-92.
3 Sandelin K, Tullgren O, Farnebo LO. Clinical course of metastatic parathyroid cancer. *World J Surg* 1994; **18**(4): 594-9.
4 August DA, Flynn SD, Jones MA *et al*. Parathyroid carcinoma: the relationship of nuclear DNA content to clinical outcome. *Surgery* 1993; **113**(3): 290-6.
5 Bondeson L, Sandelin K, Grimelius L *et al*. Histopathological variables and DNA cytometry in parathyroid carcinoma. *Am J Surg Pathol* 1993; **17**(8): 820-9.
6 Cryns VL, Thor A, Xu HJ *et al*. Loss of the retinoblastoma tumor-suppressor gene in parathyroid carcinoma. *New Engl J Med* 1994; **330**(11): 757-61.
7 Wassif WS, Moniz CF, Freidman E *et al*. Familial isolated hyperparathyroidism: a distinct genetic entity with an increased risk of parathyroid cancer. *J Clin Endocrinol Metab* 1993; **77**: 1485-9.
8 Wassif WS, Farnebo F, Tean The B *et al*. Genetic studies of a family with hereditary hyperparathyroidism-jaw-tumour syndrome. *Clin Endocrinol* 1999; **50**: 191-6.
9 Van Heerdan JA, Weiland LH, ReMine WH *et al*. Cancer of the parathyroid glands. *Arch Surg* 1979; **114**(4): 475-8.
10 Sandelin K, Auer G, Bondeson L *et al*. Prognostic factors in parathyroid cancer: a review of 95 cases. *World J Surg* 1992; **16**(4): 724-31.
11 Obara T, Fujimoto Y. Diagnosis and treatment of patients with parathyroid carcinoma: an update and review. *World J Surg* 1991; **15**(6): 738-44.
12 Clark OH, Way LW, Hunt TK. Recurrent hyperparathyroidism. *Ann Surg* 1976 ; **184**(4) : 391-9.
13 Calandra DB, Chejfec G, Foy BK *et al*. Parathyroid carcinoma: biochemical and pathologic response to DTIC. *Surgery* 1984; **96**(6): 1132-7.
14 Jansson S, Tisell LE, Lindstedt G *et al*. Disodium pamidronate in the preoperative treatment of hypercalcemia in patients with primary hyperparathyroidism. *Surgery* 1991; **110**(3): 480-6.
15 Warrell RP, Israel R, Frisone M *et al*. Gallium nitrate for acute treatment of cancer-related hypercalcemia: a randomized, double-blind comparison to calcitonin. *Ann Intern Med* 1988; **108**(5): 669-74.
16 Stevenson GT. Immunotherapy of non-metastatic complication of malignant disease. *Lancet* 1999; **353**(9150): 340.
17 McDermott MT, Perloff JJ, Kidd GS. Effects of mild asymptomatic primary hyperparathyroidism on bone mass in women with and without oestrogen therapy. *J Bone Miner Res* 1994; **9**(4): 509-14.
18 Diamond T, Ng A, Levy S *et al*. Oestrogen therapy may be an alternative to parathyroid surgery for the treatment of osteoporosis in elderly postmenopausal women presenting with primary hyperparathyroidism: a preliminary report. *Osteoporos Int* 1996; **4**: 329-33.
19 Hansen CP, Pedersen ML, Christensen L. Diagnosis, treatment and outcome of parathyroid cancer: a report of eight patients. *Eur J Surg* 1991; **157**: 517-20.