Exceptional Case

Spontaneous remission of severe hyperparathyroidism with normalization of the reversed whole PTH/intact PTH ratio in a haemodialysis patient

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Introduction

Secondary hyperparathyroidism is one of the most common and serious abnormalities in patients with chronic kidney disease. Despite recent progress in the treatment of hyperparathyroidism, advanced uraemic nodular hyperplasia, or rarely, sporadic primary adenoma accompanied by chronic renal failure is usually resistant to medical treatment and requires parathyroidectomy [1,2]. Spontaneous remission of hyperparathyroidism is a very rare complication, either primary or secondary, especially in patients on dialysis. The aetiology of spontaneous infarction has not been elucidated, but excessive tissue growth may well be one of the most clinically relevant factors, because a large parathyroid gland is susceptible to ischaemic insult [3].

For the management of hyperparathyroidism in chronic kidney disease, second-generation PTH assays, such as intact PTH assay, have been widely used [4]. However, these assays react not only with full-length PTH (1–84), but also with large C-terminal fragments, mostly PTH (7–84). The newly developed third-generation PTH assays, such as whole PTH assay, are more sensitive and specific when measuring bioactive PTH (1–84) [5]; therefore, PTH values obtained with second-generation assay are generally higher than those obtained with third-generation PTH assay [6]. Rare exceptions to this rule, however, have been reported in severe primary or secondary hyperparathyroidism and parathyroid carcinoma [7–10].

We present here a case of a haemodialysis patient with severe hyperparathyroidism, in whom abnormally higher whole PTH levels than intact PTH levels normalized after spontaneous remission due to autoinfarction of the parathyroid gland.

Case

The patient was a 59-year-old male who had been receiving maintenance haemodialysis since April 2005, for end-stage renal disease due to diabetic nephropathy. In August 2005, the patient was found to have a high serum intact PTH level (676 pg/mL, Elecsys PTH; Roche Diagnostics, Mannheim, Germany; normal range, 15–65 pg/mL), and was treated with 15 µg/week of intravenous maxacalcitol (normal dose range, 7.5–30 µg/week). Although the serum intact PTH level effectively decreased to 276 pg/mL, this treatment had to be stopped in December 2005 because of concomitant hypercalcaemia (adjusted serum calcium, 11.8 mg/dL). After discontinuation of intravenous maxacalcitol treatment, the serum intact PTH level progressively increased up to 792 pg/mL in August 2006, and an abnormally high level of whole PTH (1010 pg/mL, whole PTH; Scantibodies Laboratories, Santee, CA, USA; normal range, 5–39 pg/mL) was noted with the same sample. Serum alkaline phosphatase activity also increased progressively up to 813 IU/L (normal range, 75–234 IU/L), indicating high bone turnover. Power Doppler ultrasonography showed a single enlarged parathyroid gland with hypervascularity (Figure 1A), and a hot spot was detected at the same location by ⁹⁹ᵐTc–MIBI (methoxy-isobutyl-isonitrile) scintigraphy (Figure 1B). Enlargement of a single gland and a relatively short haemodialysis vintage until the progression of severe hyperparathyroidism were considered to clinically indicate primary adenoma rather than secondary hyperparathyroidism, and the patient was scheduled for parathyroidectomy.

In November 2006, while awaiting surgery, routine laboratory tests suddenly revealed asymptomatic hypocalcaemia (adjusted serum calcium, 6.5 mg/dL) and hypophosphataemia (serum phosphorus, 2.7 mg/dL). Spontaneous remission of hyperparathyroidism was detected, with the...
Reversed whole PTH/intact PTH ratio

Figure 1. (A) Power Doppler ultrasonography before spontaneous remission. A single enlarged parathyroid gland (23.3 mm × 17.1 mm × 15.3 mm) with hypervascularity was detected. (B) ⁹⁹mTc-MIBI scintigraphy before spontaneous remission. A hot spot was detected in the right inferior parathyroid gland. (C) Three months later, emergency ultrasonography showed a significantly enlarged right parathyroid gland (27.1 mm × 20.5 mm × 22.7 mm) with hypovascular findings, suggesting autoinfarction of the parathyroid gland. (D) After spontaneous remission, the hot spot could not be detected in the right inferior parathyroid gland. (E) Histological findings of the resected parathyroid gland. The capsule was highly thickened, and the centre of the gland was replaced by necrotic debris from autoinfarction. (F) Note the acellular debris from autoinfarction (arrow) with residual subcapsular parathyroid gland (arrowhead). Carcinomatous changes were not evident.

decrease of PTH levels and normalization of the reversed whole PTH/intact PTH ratio (intact PTH, 178 pg/mL; whole PTH, 108 pg/mL). Emergency ultrasonography of the neck showed a significantly enlarged right parathyroid gland with hypovascular findings (Figure 1C), and the hot spot could not be detected by ⁹⁹mTc-MIBI scintigraphy (Figure 1D). Parathyroidectomy was performed 10 days after the spontaneous remission. The histological findings of the resected parathyroid gland revealed acellular debris from autoinfarction (Figure 1E and F). After surgery, the intact and whole PTH levels decreased further to 8 and 2.2 pg/mL, respectively (Figure 2).

Discussion

Abnormally higher third-generation PTH levels than second-generation PTH levels have been reported in a minority of patients with severe hyperparathyroidism and parathyroid carcinoma [7,8]. Recently, we also reported two cases of haemodialysis patients with advanced uraemic nodular hyperplasia, in whom third-generation PTH levels were paradoxically higher than second-generation PTH levels [9,10]. In these patients, the reversed third-generation PTH/second-generation PTH ratio was normalized by surgical parathyroidectomy. HPLC fractionation in the latter case revealed overproduction and secretion of a novel form of PTH with an intact N-terminal, distinct from (1–84) PTH [10]. This N-PTH is detectable by third-generation PTH assays but less well reactive in second-generation PTH assays, presumably due to a modification in the region 15–20 [7,8]. Therefore, reversal of the third-generation PTH/second-generation PTH ratio is considered suggestive of the production of N-PTH. In this case, we observed the reversed whole PTH/intact PTH ratio, which dramatically normalized after spontaneous infarction of the parathyroid gland. We speculated that this phenomenon suggested the overproduction and secretion of N-PTH from the enlarged parathyroid gland, as demonstrated by HPLC analysis in the previous cases [7,8,10].
The specific role of N-PTH variant is unclear; however, relatively high bone turnover in this case and our previous case of severe uraemic hyperplasia [10] and severe hypercalcaemia in other primary hyperparathyroidism patients [7] may indicate the possibility of biological activity of this molecular form. In addition, reversed third-generation PTH/second-generation PTH ratio has previously been reported only in a limited number of patients with severe hyperparathyroidism and parathyroid carcinoma [7–10], suggesting the possible relationships between N-PTH oversecretion and clinically worse parathyroid disease. In our case, it is also possible that the reversed whole PTH/intact PTH ratio had some relevance to its excessive tissue growth, thereby outstripping vascular supply. This case and previous reports may help to confirm that the reversed third-generation PTH/second-generation PTH ratio or the existence of N-PTH could be a marker for the severity of hyperparathyroidism. Such a possibility needs to be examined in future clinical studies.

We report the first case of a haemodialysis patient with severe hyperparathyroidism, in whom an abnormally high whole PTH/intact PTH ratio normalized after spontaneous infarction of the enlarged gland. We speculate that the enlarged gland overproduced and secreted a novel form of N-PTH. Further studies are required to elucidate the relationships between the reversed third-generation PTH/second-generation PTH ratio and severity of hyperparathyroidism.

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References


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