Case Report

Cinacalcet is effective in the treatment of hyperparathyroidism secondary to malignant transformation of autotransplanted parathyroid tissue. A case report

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Abstract
Calcimimetics are effective in lowering serum parathyroid hormone (PTH) levels in hyperparathyroidism (HPT). However, they failed to reduce PTH levels in the long term in the setting of primary malignant HPT. A haemodialysis patient suffering from severe longstanding secondary HPT underwent total parathyroidectomy with autotransplantation of parathyroid tissue in her left arm. In the following years, she developed a severe HPT sustained by cancerous transformation of the parathyroid transplanted tissue and resistant both to pharmacological and repeated surgical treatments. The calcimimetic 'cinacalcet' was able to effectively reduce serum PTH levels over a 3-year follow-up and to induce disappearance of the neoplastic lesion on radionuclide imaging. Biochemical control of HPT was associated with a remarkable improvement in cardiac function.

Keywords: cinacalcet; dialysis; hyperparathyroidism; malignant

Background

Autotransplantation of parathyroid tissue following total parathyroidectomy was a surgical technique performed some years ago in patients with severe secondary hyperparathyroidism not responding to medical treatment [1]. It proved effective only in about 30% of the cases [2], and severe secondary hyperparathyroidism due to parathyroid hyperplasia in the transplanted tissue often occurred, which was commonly complicated by malignant transformation of transplanted parathyroid cells [3]. In the last case, therapy with calcitriol i.v. and phosphate-lowering drugs was unavoidably ineffective, leaving the dramatic dilemma whether or not to perform amputation of the arm.

Experimental and clinical studies have repeatedly shown that calcimimetics significantly decrease serum parathyroid hormone (PTH) in both secondary [4] and primary hyperparathyroidism [5] but not in malignant hyperparathyroidism due to primary parathyroid carcinoma [6].

Case report

A 69-year-old woman was on chronic haemodialysis since 1990 for autosomal dominant polycystic kidney disease. Due to poor compliance to diet and medication, she progressively developed severe hyperparathyroidism (serum iPTH steadily over 1000 pg/ml). In 1994 and 1995, two attempts to perform partial parathyroidectomy (PTx) were not effective in lowering serum iPTH levels. In November 1996, the patient underwent total parathyroidectomy with autotransplantation of parathyroid tissue into the muscles of her left forearm. Following surgery, serum iPTH levels sharply fell to normal values and remained stable till 1999 when they went up again.

From 1999 to 2004, serum iPTH remained persistently elevated with iPTH level ≥10 000 pg/ml in the veins draining her left arm (regional iPTH) and ≥800 pg/ml in the veins draining the contralateral arm (systemic iPTH) despite treatment with maximal doses of calcitriol i.v. (3–6 µg/week) and sevelamer (8–10 g/day). Serum phosphorus and calcium values were high as well, with values persistently in the region of 7 and 11 mg/dl, respectively. In the time course, serial echocardiographic examinations showed an increase in left ventricular end-diastolic diameter (LVEDD) with concomitant reduction in ejection fraction (EF) of the left ventricle (from 54 to 59 mm and from 50 to 38%, respectively). Ultrasoundography and radionuclide study (‘99mTc-MIBI’) showed multiple nodular lesions in the left forearm. In 2001 and 2002, three attempts of surgical resection of parathyroid tissue failed to reduce serum iPTH. Histopathological examination showed neoplastic parathyroid tissue infiltrating the radial artery and degenerative changes and intense sclerosis of the muscle fibers.

In September 2004, a new radionuclide study confirmed increased 99mTc-MIBI uptake by a focal area in the left forearm (Figure 1A) and the patient started the oral calcimimetic cinacalcet. A single dose (30 mg) of the drug acutely decreased the iPTH serum levels with nadir values (−26 and −17% of the basal values for ‘sys-
In the following years, cinacalcet was prescribed at a dose of 60 mg/day. During 2005, iPTH serum levels progressively fell to values <100 pg/ml for the ‘systemic’ and about 300 pg/ml for the ‘regional’ iPTH (Table 1). At the end of the first year of calcimimetic therapy, the nodular lesion in the left forearm was not detectable on control radionuclide study (Figure 1B). In 2006 and 2007, iPTH serum levels were 194 ± 76 and 243 ± 140 pg/ml, respectively. These values were consistently lower, on average, than before calcimimetic therapy but with fluctuations due to periods of patient’s poor compliance. Whenever the patient was adherent to the drug, calcimimetic was able to maintain low levels of serum iPTH (Table 1). During the whole follow-up, calcium and phosphate serum values diminished and LVEDD progressively reduced in parallel with increasing EF (Table 1). In the meanwhile, therapy with calcitriol i.v. could be reduced from 4.0 to 1.0 µg/week. Treatment with sevelamer and cardiovascular drugs (calcium channel blocker, angiotensin-converting enzyme inhibitor, beta-blocker) was maintained unchanged both before and during calcimimetic prescription.

**Discussion**

To the best of our knowledge, this is the first report of a successful use of calcimimetics in a carcinoma developed in autotransplanted parathyroid tissue in a haemodialysis patient.

In our patient, prolonged and intensive pharmacological treatment performed according to current guidelines and repeated surgery were not able to achieve any control of hyperparathyroidism. On the contrary, cinacalcet normalized iPTH serum levels in a few months and maintained hormone levels under control in the long run. Calcimimetic controlled but not ‘cured’ HPT as pointed out by the prompt increases of iPTH values whenever the patient stopped the drug. It is interesting to note that the improvement in secondary hyperparathyroidism was associated with a significant improvement of dilated cardiomyopathy.

Data regarding the use of calcimimetics in primary malignant hyperparathyroidism are very scarce. Cinacalcet was able to significantly diminish serum calcium levels in 62% of 29 patients with inoperable parathyroid carcinoma, but the reduction in serum PTH levels was negligible (~4.6%) [7,8]. At variance with these studies, in our patient, cinacalcet was highly effective in reducing serum PTH levels. In the Collins and Silverberg studies [7,8], patients experienced advanced forms of parathyroid carcinoma while carcinoma in our patient was at an early stage. It is tempting to speculate that the density of calcium-sensing receptors on the surface of cancerous cells is inversely related to the tumour life span. Also, the different surrounding milieu (ureaemia in our patient, normal renal function in subjects with primary malignancy)
could have played a role in altering the phenotype of malignant cells, making them more sensitive to the calcimimetic. In our patient, the biochemical improvement was associated with the disappearance of the increased radioisotope uptake from the autotransplanted parathyroid tissue. The prompt increase of iPTH values whenever the patient stopped the drug is consistent with the hypothesis that treatment with cinacalcet only prevented the taking up of 99mTc-MIBI radioisotope. Regrettably, we did not perform sequential echo study to ascertain whether or not cinacalcet also induced a reduction in parathyroid mass as recently demonstrated in patients affected by secondary hyperparathyroidism [9].

During cinacalcet treatment, we observed a remarkable amelioration of dilated cardiomyopathy. We have no data to affirm that this temporal association represents a cause–effect relationship; however, PTH is a well-known inducer of myocardial fibrosis and PTx induces beneficial effects on cardiovascular function [10]. On the other hand, it is hard to attribute the observed amelioration in cardiac function to cardiovascular therapy since it remained unchanged either before or after cinacalcet prescription.

In conclusion, in our patient, cinacalcet was extremely effective in the control of hyperparathyroidism in such a severe clinical setting as malignant transformation of autotransplanted parathyroid tissue. Further studies are needed to clarify the pathophysiological mechanism underlying this clinical observation as well as potential beneficial effects of the drug on the heart.

Conflict of interest statement. None declared.

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Received for publication: 21.2.09; Accepted in revised form: 17.12.09