Case Report

No marked apoptosis of parathyroid cells after intraparathyroid injections of Calcijex—observation in a patient with tertiary hyperparathyroidism after successful renal transplantation

Jerzy Chudek¹, Franciszek Kokot¹, Joanna Witkowicz¹, Henryk Karkoszka¹, Teresa Nieszporek¹, Antoni Podwiński², Andrzej Niemiec² and Gyula Kovacs³

¹Department of Nephrology, Endocrinology and Metabolic Diseases in Katowice and ²Department of Surgery in Bytom, Silesian University Medical School, Poland, and ³Laboratory of Molecular Oncology, Department of Urology, Ruprecht-Karls University, Heidelberg, Germany

Keywords: apoptosis; loss of heterozygosity; tertiary hyperparathyroidism

Introduction

Long-term stimulation of parathyroid cells by hypocalcaemia and hyperphosphataemia are important factors leading to parathyroid enlargement and overactivity in chronic uraemic patients. Theoretically, reversal of this process by enhancement of apoptosis may be expected if the triggering and maintaining causes of hyperparathyroidism are removed. Successful kidney transplantation is a good model for answering the question of whether therapeutic induction of parathyroid cell apoptosis is a fact or remains a dream of nephrologists.

Case

A 50-year-old female with a 6-year history of haemodialysis renal replacement therapy, was referred to our department on the third day after kidney transplantation. For the previous few years she had been treated with alpha-calcidiol due to severe secondary hyperparathyroidism. During this therapy mild hypercalcaemia was periodically observed and the iPTH level was highly elevated (1400 pg/ml).

She received a kidney from a cadaver donor. The initial immunosuppressive treatment consisted of prednisolone, azathioprin and cyclosporin. A week later an episode of acute graft rejection prompted us to intensify the immunosuppressive therapy (steroid bolus). After this treatment, a systematic improvement in renal excretory function was noticed (decrease in serum creatinine to 2 mg/dl). In parallel to the normalization of graft function hypercalcaemia (S-Ca 3.3 mmol/l), hypophosphataemia (S-iP 0.8 mmol/l) and an elevated activity of serum total alkaline phosphatases (2500 nmol/l/s) were observed. The serum iPTH level at that time was 500 pg/ml. Ultrasonography of the neck revealed an enlargement of all four parathyroid glands, which was most marked for the right lower gland (1.6 cm in diameter). The patient decided to delay the proposed surgical procedure as long as possible. Based on the preliminary report of Kitaoka et al. [1] we performed a direct, ultrasonography-guided injection of 1 ml of calcitriol solution in renal excretory function was noticed (decrease in serum creatinine to 2 mg/dl). In parallel to the normalization of graft function hypercalcaemia (S-Ca 3.3 mmol/l), hypophosphataemia (S-iP 0.8 mmol/l) and an elevated activity of serum total alkaline phosphatases (2500 nmol/l/s) were observed. The serum iPTH level at that time was 500 pg/ml. Ultrasonography of the neck revealed an enlargement of all four parathyroid glands, which was most marked for the right lower gland (1.6 cm in diameter). The patient decided to delay the proposed surgical procedure as long as possible. Based on the preliminary report of Kitaoka et al. [1] we performed a direct, ultrasonography-guided injection of 1 ml of calcitriol solution

Correspondence and offprint requests to: Prof. dr hab. n. med. F. Kokot, Department of Nephrology, Endocrinology and Metabolic Diseases, Silesian University School of Medicine, Francuska Str. 20/24, 40-027 Katowice, Poland.

© 2000 European Renal Association–European Dialysis and Transplant Association
(1 μg/ml Calcijex, Abbott GmbH) into the largest parathyroid gland. Calcitriol was injected twice at a 1-month interval. We did not observe any suppression of parathyroid function. Serum calcium even increased up to 3.5 mmol/l and iPTH was between 500 and 700 pg/ml.

Two months after kidney transplantation the patient was referred to the surgical department (on the seventh day after the second intraparathyroid calcitriol injection). Total parathyroidectomy with intramuscular transplantation of the parathyroid tissue into the forearm was performed. Parathyroids were markedly enlarged (size 4–15 mm) with a histological pattern of nodular hyperplasia. After surgery a rapid decrease in serum calcium and iPTH (20 pg/ml) was observed.

Several nodules were found in both lower parathyroid glands. For further genetic analyses we used four nodules from the right lower gland (injected) and one from the left lower one (not injected). No apoptotic fragmentation of DNA was observed in either the injected or uninjected parathyroid gland (Figure 1). The microsatellite analysis for markers localized to chromosome 1p, 1q, 2p, 2q, 3p, 3q, 4p, 5q, 6q, 7p, 8p, 9p, 10q, 11p, 11q, 12q, 13q, 14q, 15q, 16q, 17p, 17q, 20q regions did not show any alteration.

Discussion

The important issue remains unresolved whether it is possible to accelerate the involution of parathyroid hyperplasia by stimulating apoptosis in parathyroid cells. It has been reported that calcitriol may induce apoptosis of parathyroid cells in rats [2]. A substantial regression of parathyroid volume determined ultrasonographically after the intravenous administration of high calcitriol doses could be shown only by some investigators. It was suggested that extreme gland size [3], diminished expression of vitamin D receptors [4] and, probably, a monoclonal pattern of growth in nodular hyperplasia may be the cause of hyporesponsiveness to the calcitriol therapy.

Direct injection of calcitriol into an enlarged parathyroid gland provides the highest possible local concentration of this hormone. In contrast to the report by Kitaoka et al. [1] such treatment was ineffective in our case. Furthermore, we failed to observe apoptotic DNA fragmentation by agarose gel electrophoresis both in the injected and an uninjected parathyroid gland.

In the majority of kidney transplant patients in parallel to the restoration of renal function, normalization of serum calcium and PTH and involution of parathyroid hyperplasia can be noticed, although sometimes not earlier than 1–2 years after successful kidney transplantation. As shown in our case, lack of marked apoptosis of the hyperplastic parathyroid cells after local calcitriol injection is in line with Parfitt’s suggestion [5], that involution due to apoptosis is sometimes too slow to be of clinical relevance.

References


Received for publication: 11.8.99
Accepted in revised form: 20.10.99