SECONDARY AND TERTIARY HYPERPARATHYROIDISM IN CHRONIC KIDNEY DISEASE

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In the treatment of secondary hyperparathyroidism of end-stage chronic kidney disease, vitamin D receptor activation and allosteric modulators of the calcium-sensing receptor – inhibit glandular hyperplasia, reduce parathyroid hormone levels, impact on bone turnover and mineral density. But the use of calcimimetic and vitamin D analogs or mimetics did not reduce the need for parathyroidectomy for refractory hyperparathyroidism. The enlarged parathyroid gland and gland nodular transformation became refractory to medical therapy and patient need for parathyroidectomy. Tertiary hyperparathyroidism is a state of excessive secretion of parathyroid hormone after a long period of secondary hyperparathyroidism and renal transplantation.

In this article, we present the case of a Caucasian male with chronic kidney disease (end-stage on chronic hemodialysis and after kidney transplantation) and different forms of hyperparathyroidism (secondary and tertiary). Our case study shows that only a multi-interventional strategy is likely to be more effective treatment in cases of severe and refractory to medical therapy hyperparathyroidism.

KEYWORDS: Case report; secondary hyperparathyroidism; tertiary hyperparathyroidism; cinacalcet; parathyroidectomy; hemodialysis; kidney transplantation

BACKGROUND

Currently, chronic kidney disease (CKD) is considered as a multidisciplinary medical problem rather than just a nephrological condition. Renal replacement therapy (dialysis) and kidney transplantation are considered complementary in the treatment of ESRD (end-stage renal disease). A loss in the number of functioning nephrons in CKD causes a complication cascade, including vitamin D deficiency, hyperphosphatemia, changes in calcium-sensing receptor (CaSR) function in the parathyroid glands (PTG), lower gastrointestinal absorption of calcium, increased synthesis of parathyroid hormone (PTH), hypertrophy and hyperplasia of PTG cells. Such hyperplasia involves PTG cell transformation accompanied by aggressive growth and reduced vitamin D receptor and CaSR expression [1, 2].
Subjected to a timely initiated treatment, secondary hyperparathyroidism (SHPT) in most patients can be controlled by dietary phosphorus restrictions and pharmacotherapy (phosphate-lowering agents, vitamin D oral or parenteral formulations, calcimimetics) [3-5]. However, there is a cohort of patients resistant to the aforementioned therapy despite the achieved success in the conservative treatment of CKD and clear criteria for prescribing and monitoring. Even after successful kidney transplantation these patients still have mineral bone disorder and persistent hyperparathyroidism with a consequent development of tertiary hyperparathyroidism (THPT) accompanied by hypercalcemia and hypophosphatemia. In a large-scale observational retrospective study 18% of patients (108 out of 607 patients) were diagnosed with elevated PTH levels and 8% (47 patients) had hyperparathyroidism with hypercalcemia both within the first year after successful kidney transplantation [6]. Parathyroidectomy is an effective treatment of secondary and tertiary hyperparathyroidism resistant to the drug therapy [7]. A described case report demonstrates the challenges in disease management and the need for timely diagnostics of the mineral bone disorder and its complications in patients with CKD. It is also a relatively rare example of SHPT transition which was successfully treated prior to the kidney transplantation into tertiary hyperparathyroidism (THPT) occurred after the allotransplantation, thus leading to parathyroidectomy.

CASE REPORT

*Patient M.*, born in 1966, with stage 5 CKD on kidney replacement therapy (chronic hemodialysis), sought medical attention at the Endocrinology Research Centre of the Ministry of Healthcare of the Russian Federation in 2009.

At the time of encounter the patient complained about muscle weakness, bone and joint pain, stiffness in body movements, and skin pruritus.

Past medical history shows periodic disease (familial Mediterranean fever) in 1976 and kidney amyloidosis in 1988 according to biopsy. Stage 5 CKD was diagnosed in 2006; the patient was put on kidney replacement therapy (chronic dialysis). Above symptoms began to trouble patient in 2008. After examination the patient was diagnosed with CKD-mineral bone disorder (CKD-MBD): secondary hyperparathyroidism with hyperplasia of the parathyroid glands hyperplasia; upper right: V = 1.08 mm³, lower right: V = 0.04 mm³, upper left: V = 0.3 mm³, lower left: d = 0.6 cm. In 2008 a cadaveric kidney allotransplantation resulted in acute rejection. A tendency for increased calcium-phosphorus product has been observed since 2009.

After the patient encounter the following lab tests were performed:
- PTG ultrasound have revealed signs of four parathyroid glands hyperplasia; upper right: V = 1.08 mm³, lower right: V = 0.04 mm³, upper left: V = 0.3 mm³, lower left: d = 0.6 cm.
- Wrist X-ray showed vascular calcification (3rd stage) and active bone resorption.

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total calcium (mmol/l)</td>
<td>2.53</td>
</tr>
<tr>
<td>Phosphorus (mmol/l)</td>
<td>2.1</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>42</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>816.1</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/l)</td>
<td>496</td>
</tr>
<tr>
<td>Osteocalcin (ng/ml)</td>
<td>over 300</td>
</tr>
<tr>
<td>C-terminal telopeptide (CTx) (ng/ml)</td>
<td>3.1</td>
</tr>
<tr>
<td>25(OH)D (ng/ml)</td>
<td>7.9</td>
</tr>
<tr>
<td>TSH (μIU/mL)</td>
<td>2.1</td>
</tr>
<tr>
<td>Hemoglobin (g/l)</td>
<td>90–105</td>
</tr>
</tbody>
</table>

- Bone densitometry showed a decrease (Z-score) in bone mineral density (BMD) in the lumbar spine (L1-L4) down to -1.1 SD; in the proximal femur (total hip) down to -2.2 SD; in the femoral neck (neck) down to -2.0 SD; in the radial bone (Rad 33%) down to -4.0 SD. Laboratory test results are shown in the table 1.

**Clinical diagnosis:** CKD-MBD (stage 5) as a result of kidney amyloidosis (chronic dialysis since 2006, condition after the kidney transplantation and acute graft rejection in 2008): secondary hyperparathyroidism with hyperplasia of the four parathyroid glands, hyperphosphatemia, vitamin D deficiency, decreased (Z-score) bone mineral density of mixed origin (CKD, hyperparathyroidism) down to -4.0 SD in the radial bone, nail bone subperiosteal resorption in both wrists, extraskeletal calcification.

**COMMENT:** It should be mentioned that patients with stage 3-5D CKD have increased bone fragility due to both decreased bone mineral density and deterioration of bone microarchitecture (with normal and increased mineral density). Taking this information into account and considering pathophysiological differences, the term “osteoporosis” should be used only at early stages of CKD; a consequent decrease in mineral density should be described as “chronic kidney disease-mineral bone disorder with decreased bone mineral density” [8].

The following therapy was recommended, based on the results of the clinical examination:
1. for secondary hyperparathyroidism correction - cinacalcet, 30 mg/day;
2. for hyperphosphatemia relief - strict hypophosphate diet (not more than 800 mg per day) and prolongation of chronic dialysis sessions;
3. for target calcium maintenance according to Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease (KDOQI, 2013) - decrease in calcium concentration in the dialysis solution down to 1.25 mmol/L.

Levels of PTH, serum calcium, serum albumin, and serum phosphorus were checked monthly.

**During follow-up period:**
1. the cinacalcet dose was titrated up to 60 mg per day;
2. to correct vitamin D deficiency Colecalciferol (50,000 IU/week) was added to the therapy after the phosphorus level was back to normal;
3. after vitamin D deficiency has been corrected (36 ng/mL), alfalcaldiol was added to the therapy (1 μg three times a week) in order to correct SHPT, providing normal levels of calcium and phosphorus along with PTH levels over 300 pg/mL (KDOQI, 2003).

**During 6 weeks** of the combination therapy, a positive dynamics of health parameters was observed:

- **Clinical data:** fewer complaints, no skin pruritus.
- **Laboratory data:** PTH level decreased by 60.2%, [Ca] x[Pi] product decreased by 22.03%. Bone-formation (AP, OC) and bone-resorption (CTX) marker levels decreased, vitamin D deficiency was compensated.

**Instrumental methods of examination**

- **Wrist X-Ray** showed a decrease in vascular calcification (to stage 2), and fewer signs of nail bone resorption.
- **Densitometry** showed a prominent positive dynamics: in the L1-L4 up to +5.4%, in total hip up to +6.4%, in neck up to +4.9%, and in Rad 33% up to +9.3%.
- **PTG ultrasound** revealed a reverse in hyperplasia of three (!) PTGs, but an increase in the right upper PTG volume, i.e. V=1.89 mm3 (+75%).

**COMMENT:** Therefore, improvement was achieved during the combination therapy. The dynamics and range of decrease in lab test values generally depend on the PTG during the combination therapy. The dynamics and range of decrease in lab test values generally depend on the PTG during the combination therapy.

**During cinacalcet dose titration a tendency for PTH increase was revealed.**

**COMMENT:** As mentioned earlier, successful kidney transplantation does not always lead to recovery from mineral bone disorder. Some graft recipients demonstrate persistent hyperparathyroidism or tertiary hyperparathyroidism accompanied by hypercalcemia and hypophosphatemia [6]. Development of nodular PTG hyperplasia is a common cause of such hyperparathyroidism. Taking into account the volume of the upper right PTG, a parathyroidectomy was required prior to the kidney transplantation. No specific recommendations for management of patients with THPT after the kidney transplantation are available so far. However, persistent hypercalcemia is an indication for an active therapeutic intervention like in every case of hyperparathyroidism.

**Initial recommendations in this case include:**

1. maximum limitation in the food which contains calcium;
2. correct water schedule;
3. alfalcaldiol withdrawal; 4. cinacalcet 60 mg/day with dose titration.

**On October 11, 2010, parathyroidectomy (the upper right PTG) was performed.**

**Clinical diagnosis:** CKD-MBD (T1) as a result of kidney amyloidosis (chronic dialysis in 2006-2010, condition after the kidney transplantation and acute graft rejection in 2008, condition after the repeated kidney transplantation on May 27, 2010, graft function is satisfactory): tertiary persistent hyperparathyroidism with hyperplasia of the upper right parathyroid gland, hypercalcemia, vitamin D deficiency, osteoporosis of mixed origin (CKD, hyperparathyroidism, steroid-induced) with a loss in bone mineral density down to Z-score -3.4 SD in the radial bone.

**Table 2. Laboratory results on August 2010**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (μmol/l)</td>
<td>69</td>
</tr>
<tr>
<td>GFR (mL/min/1.73m2)</td>
<td>98</td>
</tr>
<tr>
<td>Total calcium (mmol/l)</td>
<td>3.4</td>
</tr>
<tr>
<td>Phosphorus (mmol/l)</td>
<td>0.98</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>39</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>815</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/l)</td>
<td>416</td>
</tr>
<tr>
<td>25(OH)D (ng/ml)</td>
<td>22.7</td>
</tr>
</tbody>
</table>

**COMMENT:** It should be mentioned that the PTH target level corresponds to that in the general population whereas the graft function is adequate. The main aim of cinacalcet treatment is the normalization of calcium-phosphorus metabolism parameters. A decrease in the PTH concentration correlates with the cinacalcet concentration. However, due to nodular PTG hyperplasia and a decrease in CaSR number and sensitivity, along with a decrease in vitamin D receptors number and sensitivity, the gland becomes resistant to the drug therapy [9, 10]. Parathyroidectomy is a treatment of choice in PTG drug resistance.

A suspected nodular transformation of PTG cells led to a decision to perform parathyroidectomy.

**On October 11, 2010, parathyroidectomy (the upper right PTG) was performed.**

PTH levels were monitored during the surgery in order to assess performance of the intervention. Such
procedure is usually carried out in the treatment of primary hyperparathyroidism, however, taking into account similarities between primary and tertiary condition, it can be used in hyperparathyroidism after the kidney transplantation. PTH blood level rapidly decreases after the surgery, if no other hyperplastic PTGs are present. If in 10-15 minutes after parathyroidectomy the PTH level decreased two-fold or more (comparing to the maximum lever prior to the surgery), the second hyperfunctional PTG in the patient is quite unlikely. A rapid PTH level decrease means that the surgery can be finished and there is no need to remove all PTGs [11, 12].

15 Minutes after parathyroidectomy PTH levels decreased more than 50% which evidences an adequate PTG removal.

Histological examination of the PTG revealed nodular hyperplasia in the chief cells.

COMMENT: An active bone tissue recovery takes place after parathyroidectomy accompanied by the hungry bone syndrome (increase in AP versus baseline and marked hypocalcemia). Hypocalcemia can be quite evident in patients with severe renal hyperparathyroid osteodystrophy.

In the postoperative period the patient experienced marked hypocalcemia (clinical and laboratory evidence), so he received high doses of calcium carbonate products (4 g/day) and vitamin D active metabolites (3 μg/day) with gradual dose down-titration until a complete withdrawal (March 2011). Blood calcium, PTH, and AP levels were controlled during the whole period.

COMMENT: The literature sources discuss a functional state of the kidney graft in patients after parathyroidectomy. According to several authors, there is an increase in serum creatinine levels [13], however, other researchers prove otherwise: the surgery has no effects on the creatinine level increase and worsened function [14].

The graft function of our patient was stable and satisfactory, no significant changes in creatinine levels were observed (table 4).

Densitometry showed a decrease in BMD: in the L1-L4 down to -1.0 SD; in the total hip down to -2.2 SD; in the neck down to -2.0 SD; and in the Rad 33% down to -3.2 SD.

Clinical diagnosis: CKD-MBD (T1) as a result of kidney amyloidosis (chronic dialysis in 2006-2010, condition after the kidney transplantation and acute graft rejection in 2008, condition after the repeated kidney transplantation on May 27, 2010, graft function is satisfactory): condition after parathyroidectomy (the right upper PTG) due to persistent hyperparathyroidism, vitamin D deficiency, osteoporosis of mixed origin (CKD, hyperparathyroidism, steroid-induced) with a loss of bone mineral density down to Z-score -3.2 SD in the radial bone.

COMMENT: According to the clinical recommendations on CKD-MBD if the renal graft function is satisfactory, osteoporosis treatment should be started within 12 months after the kidney transplantation. The drug therapy is the same as in general population and depends on the CKD stage [8, 15].

According to the recommendations, both the correction of vitamin D deficiency and anti-osteoporotic therapy were initiated (alendronate, a bisphosphonate drug in tablets). During the follow-up, calcium-phosphorus metabolism parameters (blood and daily urine) and the graft function were within normal ranges.

Densitometry in 2012, 2013, and 2014, showed positive dynamics. According to the bone densitometry in 2014 no decrease in BMD was observed in the lumbar spine, in the proximal femur and in the femoral neck; the only BMD decrease was found in the radial bone (an early stage of osteopenia). Therefore, a decision on a medication-free period has been made, with the next assessment of BMD 1 year apart.

The patient has received only colecalciferol 10,000 IU/week.

After the patient sought medical attention in July 2016, a high PTH level (71 pg/mL), vitamin D deficiency (21.4 ng/mL), and serum creatinine 98 μmol/L with normal levels of calcium and phosphorus in the blood and urine were detected.

Densitometry showed a decrease in BMD: in the total hip down to -1.8 SD; in the neck down to -1.7 SD; in the Rad 33% down to -1.6 SD. No decrease in BMD was observed in the L1-L4.

Vitamin D formulations (both active and inactive forms) and dynamic monitoring were recommended after patient examination.

CONCLUSION

The described case report clearly demonstrates how complicated the management of CKD-MBD patients can be.

The drug therapy (vitamin D and calcimimetic) of SHPT during CKD in dialysis stage provides prominent positive dynamics with the normalization of calcium-phosphorus metabolism parameters, improvement of hyperparathyroid renal osteodystrophy progression, BMD recovery and decrease in bone turnover markers. During the complex treatment a reverse of hyperplasia and/or hypertrophy of three PTGs was observed; the fourth gland, however, increased in volume which was an indirect sign of PTG nodular transformation and monoclonal growth.

### Table 3. Changes in blood calcium and PTH levels during Cinacalcet dose titration

<table>
<thead>
<tr>
<th>Cinacalcet dosage (mg)</th>
<th>PTH (pg/ml)</th>
<th>Blood calcium (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>576</td>
<td>2.9</td>
</tr>
<tr>
<td>120</td>
<td>403</td>
<td>2.68</td>
</tr>
<tr>
<td>180</td>
<td>298</td>
<td>2.54</td>
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<tr>
<td>210</td>
<td>313</td>
<td>2.51</td>
</tr>
<tr>
<td>240</td>
<td>282,4</td>
<td>2.56</td>
</tr>
</tbody>
</table>

### Table 4. Laboratory results on April 2011

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (μmol/l)</td>
<td>71</td>
</tr>
<tr>
<td>Total calcium (mmol/l)</td>
<td>2.21</td>
</tr>
<tr>
<td>Phosphorus (mmol/l)</td>
<td>1.1</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>43</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>34</td>
</tr>
<tr>
<td>25(OH)D (ng/ml)</td>
<td>27.3</td>
</tr>
</tbody>
</table>
Development of hypercalcemia during persistent THPT is relatively rare providing a successful SHPT treatment at the dialysis stage and an adequate function of the kidney graft after its transplantation. Our clinical report is an example of SHPT transition (successfully treated prior to the kidney transplantation) to THPT (after the kidney allotransplantation) which proves the importance of both laboratory tests and PTG volume evaluation before the kidney transplantation. Despite calcemia stabilization and a tendency for PTH level decrease during calcimimetic therapy, a decision to perform parathyroidectomy was made due to suspected PTG nodular hyperplasia which was later confirmed by histology. Marked hypocalcemia was observed at the postoperative period due to the hungry bones syndrome. Normalization of calcium-phosphorus metabolism parameters was observed after the syndrome compensation. Kidney graft function was stable and satisfactory, no significant creatinine level changes or worsened function were observed after parathyroidectomy and during dynamic follow-up. The anti-osteoporotic therapy demonstrated good results in BMD increase.

Despite complicated management of CKD patients with different forms of hyperparathyroidism, a personalized combination approach therefore proves to be successful.

**ADDITIONAL INFORMATION**

**Conflict of interests** Authors declare no explicit and potential conflicts of interests associated with the publication of this article.

**The patient's informed consent** The patient provided his informed consent for the publication of this case report.

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**СПИСОК ЛИТЕРАТУРЫ | REFERENCES**


CASE REPORT

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