OLGU SUNUMU CASE REPORT

Prolonged Elevation of Parathyroid Hormone in Normocalcemic Patient After Parathyroidectomy for Primary Hyperparathyroidism: Association with Vitamin D: Case Report

Primer Hiperparatiroidi Nedeniyle Yapılan Paratiroidektomi Sonrası Normokalsemik Hastada Uzamış Paratiroid Hormon Yüksekliği: Vitamin D ile İlişkisi

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ABSTRACT We present a case report of normocalcemic patient with a prolonged elevation of parathyroid hormone (PTH)and low levels of 1,25(OH)2D3 after parathyroidectomy. A 48-year-old man presented with a 3-month history of fatigue. Clinical findings and radiological examinations revealed an ectopic parathyroid adenoma. After parathyroidectomy, he was normocalcemic but he had a low level of serum 1,25(OH)2D3 and urinary excretion of nephrogenous cyclic adenosine monophosphate (NcAMP) regardless of his persistently elevated PTH. Calcium and vitamin D replacement were initiated. Both PTH and 1,25(OH)2D3 gradually normalized within the 19 months after parathyroidectomy. In conclusion, several conditions may account for this secondary hyperparathyroidism (sHPT) in this patient including low levels of preoperative vitamin D, impaired renal function, bone remineralization and a large adenoma. In addition, postoperative renal resistance to PTH may be related to long lasting pimary hyperparathyroidism (pHPT) and sHPT.

Key Words: Hyperparathyroidism, primary; surgery

ÖZET Paratiroidektomi sonrası uzamış paratiroid hormon (PTH) yüksekliği ve düşük düzeyde 1,25(OH)2D3 olan normokalsemik olguyu sunduk. 48 yaşında erkek hasta 3 aydır süren yorgunluk şikayeti ile başvurdu. Klinik bulgular ve görüntüleme ektopik adenom ile uyumluydu. Paratiroidektomi sonrası hasta normokalsemikti ancak serum 1,25(OH)2D3 düzeyi ve idrarda nefrojen siklik adenozin monofosfat (NcAMP) atılım düzeyi uzamış PTH yüksekliğine rağmen düşüktü. Kalsiyum ve D vitamini replasmanı başlandı. Paratiroidektomi sonrası 19 ay içerisinde PTH ve 1,25(OH)2D3 aşamalı olarak normale döndü. Sonuç olarak, bu olguda sekonder hiperparatiroidizmden (sHPT) sorumlu birçok neden olabilir. Bunlar preoperatif vitamin D düzeyinin düşük olması, bozulmuş renal fonksiyon, kemik remineralizasyonu ve büyük adenom varlığı. Ayrıca postoperatif dönemde PTH'ya renal direncin de uzun süreliprimer hiperparatiroidizm (pHPT) ve sHPT ile ilişkisi olabileceği düşünüldü.

Anahtar Kelimeler: Hiperparatiroidizm, primer, cerrahi

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Parathyroidectomy is successful in the majority of patients with pHPT. However, prolonged elevations of PTH in normocalcemic patients have been reported. The pathogenesis has not been yet fully understood.[1-4] We reported a normocalcemic patient with a low level of serum 1,25(OH)2D3 and urinary excretion of NcAMP value regardless of his persistently elevated PTH after parathyroidectomy. Biochemical findings grad-

ually normalized within 19 months. This case was reported to revise the causes of prolonged elevation of serum PTH in normocalcemic patient after parathyroidectomy.

CLINICAL PRESENTATION

A 48 year-old man presented to our hospital with a 3 month history of fatigue and weakness. He was unable to walk because of weakness for 3 weeks. He and his family did not have a history of any disease. Physical examination was normal. Biochemical findings on admission were hypercalcemia, hypophosphatemia, elevation of serum PTH and total alkaline phosphatase activity (ALP), and normal levels of serum 25OHD3 and 1,25(OH)2D3 (Table 1). Radiographic manifestations were subperiostal resorptions and brown tumor in his hands and osteoporotic appearance in the lateral vertebra and pelvic x-ray. Bone mineral density (BMD) by dualenergy x-ray absorptiometry (DXA) demonstrated a marked reduction in bone mass with T-scores in the osteoporotic range at the lumbar spine, hip and distal radius. Abdominal ultrasonography (USG) was normal. Sestamibi parathyroid scintigraphy suggested abnormal uptake in the upper mediastinum just behind the manibrum sterni. Thyroid USG and computed tomography (CT) of the neck and mediastinum showed a mass with a diameter of 24 x 21mm at the entrance of the mediastinum in the paratracheal region of the thorax. He subsequently underwent an exploration of this ectopic parathyroid mass. Pathology reported a benign parathyroid adenoma. Hypocalcemia had not occurred after parathyroidectomy. He was discharged with calcium (1000 mg elementer calcium) and (800 IU) vitamin D replacement. He had no complaint within the first month but we observed that elevation of serum PTH was persistent despite the normocalcemia. Parathyroid adenoma was not present in the scintigraphy, USG, and CT examinations. Moreover, he had a low level of serum 1,25(OH)2D3 with low values of urinary excretion of NcAMP and P regardless of his persistently elevated PTH. These biochemical findings gradually improved within the 19 months after the parathyroidectomy (Table 1). The values of BMD at the lumbar spine increased by 12% (0.75-0.96 g/cm^2) with the T-score improving to above the osteoporotic range (-2.7 to -1.5). The total hip BMD increased by 11% (0.79-0.98 g/cm^2; T-score, -1.8 to -0.3).

Serum 25OHD3 concentration was measured by competitive protein-binding assay involving the use of high-performance liquid chromatography purification. The serum 1,25-(OH)2D3 concentration was evaluated by receptor-binding assay. Urinary excretion of NcAMP was assessed by radioimmunoassay.

TABLO 1: Biochemical values of the patient in the pre- and postoperative period.

	Reference interval	Preoperative (on admission)	Postoperative (1 month)	(6 months)	(19 months)
Serum calcium (mg/dL)	8.5-10.4	14	8.7	9.2	9
Serum phosphorous (mg/dL)	2.5-4.2	1.8	3.4	4.8	2.7
Serum magnesium (mg/dL)	1.8-3	2	2	2.2	2.1
Serum alkaline phosphatase (IU/L)	80-140	170	155	129	110
Serum creatinine (mg/dL)	0.6-1.2	1.4	1.2	1.1	1.1
PTH (pg/mL)	10-55	1440	851	270	52
25OHD3 (ng/mL)	10-72	32	42	47	40
1,25(OH)2D3 (pg/mL)	24-65	52	23	36	56
24-hour urinary calcium (mg/d)	10-300	680	290	200	220
Tubuler reabsorption test phosphorus (%)	79-94	56	67	64	81
Nephrogenous cyclic adenosine monophosphate NcAMP (nmol/100 mL GF)	1.4-5.0	5.9	1.2	1.9	4

DISCUSSION

Prolonged elevation of serum PTH levels in normocalcemic patients were observed to occur after apparently curative parathyroidectomy for pHPT, ranging from 16% to 40%.[1-4] The pathogenesis of this condition has not been elucidated yet. Some explained this phenomenon as an adaptive process and attributed elevated serum PTH to a response to physiological changes. This postoperative sHPT frequently improves during the following several months.[2,3,5,6]

Our patient seemed to have postoperative sHPT, due to more severe parathyroid disease manifested by higher preoperative PTH levels (1440 mg/dL), and increased bone turnover as suggested by increased serum ALP and decreased serum P levels. Several conditions may account for this, including low level of preoperative vitamin D, impaired renal function, secondary response to bone remineralization and large mass.[2-4,5-7] Vitamin D deficiency was a major factor significantly inducing elevated serum PTH. When the level of 25OHD3 falls below 20 ng/mL, PTH level reaches the upper limit of the reference value (55 pg/mL).[8] The patient had a normal level of 25OHD3 (32 ng/mL) and 1,25(OH)2D3 (59 pg/mL) in the preoperative period in winter. Second possible cause may be 'hungry bone syndrome' (HBS) because of the risk factors in the preoperative period including a large parathyroid adenoma, presence of bone involvement, hypercalcemia, and elevation of serum PTH and ALP. Patients with HBS had a lower serum calcium level (≤7.4 mg/dL), which resolved in the majority of the patients within eight weeks and only in 17% of the patients within one year postoperatively.[4,5] The presence of normocalcaemia (8.7 m/dL) in this case may not have excluded the phenomenon of hungry bones, because substantial increase in BMD was observed within the two years. Prolonged severe hypercalcemia (14 mg/dL) and impaired creatinine clerance (88 mL/mn/1.73) in the preoperative period may be another possible cause in this case. Renal insufficiency was reported to be associated with increased PTH levels even at early stages.[2,9] A high preoperative PTH level (1440 pg/mL) in this patient may also induced the sHPT.[1,3-5]

All of these observations suggest that many adaptive causes may be responsible for the postoperative elevation of PTH in this case. In addition, we observed a gradual increase in serum 1,25(OH)2D3 and in urinary excretion of NcAMP while the serum PTH reached normal values within the 19 months after surgery. Conversely, an increase in serum PTH would be expected to lead to an increase in 1,25(OH)2D3 and NcAMP. Substrate deficiency was unlikely to contribute to the low levels of 1,25(OH)2D3 because of the adequate levels of 25OHD3 in the perioperative period. Furthermore, 25OHD3 replacement was also given to the patient, but serum 1,25-(OH)2D3 levels did not increase to normal levels. Another explanation of this condition may be renal resistance to PTH according to the long lasting pHPT and sHPT in the perioperative period. Prolonged increases in circulating PTH before surgery were reported to induce the downregulation of peripheral PTH receptors.[5] Tomlinson et al. showed that the NcAMP response to PTH was blunted in patients with long lasting pHPT and sHPT.[10] Serum calcium, 1,25(OH)2D3, and NcAMP did not seem to increase after PTH infusion in another study.[8]

We initiated oral calcium supplementation in our patient. We did not observe hypercalciuria. Normocalcemia may be related with the low levels of 1,25(OH)2D3, which led to the decrease in calcium absorption by the gastrointestinal tract. These data supported the PTH resistance at the level of proximal tubules in the nephron. Although a recent study reported this, it did not correlate it with vitamin D profile.[6] Another recent study showed that significantly lower 1,25(OH)2D3 levels reflected the downregulation of PTH receptors or the enzyme involved in 1-α hydroxylation of 25OHD3 to 1,25(OH)2D3 in patients with a greater mass of parathyroid tissue excised.[3] Findings were similar to those in our patient.

It was recently reported that vitamin D deficiency in the preoperative period was an important

factor inducing the elevation of PTH according to the mechanism of renal resistance to PTH in the postoperative period.[7]

CONCLUSION

We reported a normocalcemic patient with a low level of serum 1,25(OH)2D3 and urinary excretion of NcAMP value regardless of his persistently elevated PTH after parathyroidectomy. Biochemical findings gradually normalized within 19 months. Although prolonged elevations of serum PTH in normocalcemic patients after surgery are frequently normalized within a few months, they sometimes persist for more than a few years. Several conditions may account for this sHPT in this patient including low levels of preoperative vitamin D, impaired renal function, bone remineralization and a large adenoma. In addition, postoperative renal resistance to PTH may be related to long lasting pHPT and sHPT. Prolonged elevation of circulating PTH before surgery may have induced the downregulation of the PTH receptors or 1-α hydroxylation enzyme in the kidney. For this reason, calcitrol replacement should be recommended in the postoperative period for those patients with renal resistance to the PTH. Therefore, patients should be evaluated in the preoperative period for the predictors of postoperative sHPT. This approach may minimize the occurrence of prolonged elevation of PTH.

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