Elevated bone resorption markers in a patient with hypercalcemia associated with post-partum thyrotoxicosis and hypoadrenocorticism due to pituitary failure

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ABSTRACT. A 36-yr-old woman began to suffer from headache, anorexia and general fatigue at 35 weeks’ gestation. About 2 or 3 months after the delivery, fever, tachycardia and generalized musculoskeletal disorder appeared. Thereafter, they worsened rapidly, accompanied by a disturbance of consciousness and hypercalcemia. Thyrotoxicosis, due to a post-partum thyroiditis, and glucocorticoid deficiency, due to a pituitary failure, probably associated with lymphocytic hypophysitis, were also observed. All the symptoms and hypercalcemia disappeared after the glucocorticoid replacement therapy and the normalization of thyroid hormone levels. Serum and urinary bone resorption markers, such as urine pyridinoline (U-Pyr), urine deoxypyridinoline (U-DPD), urine amino-terminal telopeptide of type I collagen (U-NTx) and serum carboxy-terminal telopeptide of type I collagen (ICTP), were extremely high at the hypercalcemic state. In this case, they were 10 to 20 times higher than the normal upper limits, and then markedly decreased in a normocalcemic state, thereby showing an extreme acceleration of bone resorption in a state of both thyrotoxicosis and glucocorticoid deficiency. (J. Endocrinol. Invest. 27: 782-787, 2004) ©2004, Editrice Kurtis

INTRODUCTION

Slight or mild hypercalcemia is sometimes found either in adrenal failure or in thyrotoxicosis. However, patients with both adrenal failure and thyrotoxicosis have been reported to show severe hypercalcemia (1-4). Although an extreme increase in calcium release from the bone is suggested to be one of the main reasons of hypercalcemia in this state (3-7), it has so far been difficult to collect clinical evidence. Recently, measurements of sensitive bone turnover markers have been developed: urine pyridinoline (U-Pyr)(8), urine deoxypyridinoline (U-DPD)(8, 9), urine amino-terminal telopeptide of type I collagen (U-NTx)(10), and serum carboxy-terminal telopeptide of type I collagen (ICTP)(11), which are bone collagen breakdown products and used as bone resorption markers. On the other hand, serum procollagen type I carboxy-terminal propeptide (PICP)(12) and serum osteocalcin (OC)(13) are used as bone formation markers. We herein report a case with post-partum thyroiditis and adrenal failure, probably due to lymphocytic hypophysitis, showing severe hypercalcemia, which disappeared in parallel with the normalization of thyrotoxicosis and glucocorticoid deficiency. In this case, serum and urinary bone resorption markers were extremely high in a hypercalcemic state, and then markedly decreased in a normocalcemic state, thus suggesting a co-operative effect of glucocorticoid and thyroid hormone on the coupling of bone resorption and bone formation.

CASE REPORT

In July 1998, a 36-yr-old woman began to suffer from headache, anorexia and general fatigue at 35 weeks’ gestation. On September 6th, she delivered a healthy baby assisted by a suctional method, without peri/post-partum hemorrhage or hypotensive episodes.
After the delivery, lactation was absent and marked fatigue, anorexia, generalized muscle weakness, myalgia and arthralgia appeared and worsened. She became feverish and unable to stand up, and therefore was admitted to a hospital on December 2nd 1998, at which time thyrotoxicosis (free T₃ over 30 pmol/l, free T₄ 82 pmol/l, normal range 3.8-6.6, 12-25, respectively) and hypercalcemia (serum calcium 3.35 mmol/l, normal range 2.20-2.56) were revealed. Although the treatment was started including intravenous saline infusion and nutrition, injection of antibiotics, administration of potassium iodide (KI) and methylmercaptoimidazole (MMI), hypercalcemia was not improved and the symptoms still worsened accompanied by delirium, hallucination and disturbance of consciousness. She was then transferred, under continued saline infusion, to the Department of Medicine and Clinical Science, Kyushu University Hospital, on December 9th.

On a physical examination, her height was 152 cm, weight 46 kg, temperature 39.1 °C, blood pressure 128/76 mmHg, and pulse rate 128/min. She felt uncomfortable and suffered from delirium. No exophthalmos, struma or neck stiffness was observed. Fundoscopy was normal. Dysarthria and dysphagia were noticed. Her extremities were in a semi-bent state and in difficulty to move, while passive stretching of the limbs elicited myalgia and arthralgia.

A routine blood analysis on December 9th revealed hypercalcemia with a serum albumin-corrected (14) calcium level of 3.12 mmol/l. Urinary calcium excretion was increased (3.0 mmol/l). Serum phosphate (1.03 mmol/l), sodium (144 mmol/l), chloride (105 mmol/l), aspartate aminotransferase (AST)(30 U/l), alanine aminotransferase (ALT)(20 IU/l), lactate dehydrogenase (LDH)(395 IU/l), alkaline phosphatase (191 IU/l), and blood urea nitrogen (BUN)(5.3 mmol/l) levels were in the normal range. Serum potassium (3.0 mmol/l), creatinine (35 μmol/l) and total cholesterol levels (1.4 mmol/l) were low. C-reactive protein was slightly positive (0.5 mg/dl), while the number of white blood cells was normal (5300/μmm³).

A hormonal analysis on December 9th showed abnormally high levels of free T₃ (18.9 pmol/l) and free T₄ (51 pmol/l), and low levels of TSH(<0.03 mU/l), cortisol (<3 mmol/l), ACTH (1 pmol/l) and PRL (0.1 μg/l). Both the PTH (<0.5 μg/l) and PTH-related protein PTHrP (<0.2 pmol/l) levels were low. The other hormonal data were as follows: GH 0.9 μg/l, LH 1.66 U/l, FSH 8.9 U/l, estradiol 60.2 pmol/l, and progesterone <0.6 nmol/l. Regarding bone turnover markers, extremely high levels of bone resorption mark-
ers were seen: U-Pyr 701 μmol/molCr (normal range 13-31), high performance liquid chromatography, TSL, USA), U-DPD 84 μmol/molCr (normal range <7, high performance liquid chromatography, TSL, USA), U-NTx 746.8 nmolBCE/mmolCr (normal range 8.3-69.9, enzyme-linked immunosorbent assay, Ostex International, USA), and ICTX 62.0 ng/ml (normal range <4.5, radioimmunoassay, Orion Diagnostica, Finland). In contrast, the bone formation markers showed a mild increase: PICP 220 ng/ml (normal range <160, radioimmunoassay, Orion Diagnostica, Finland) and OC 40 ng/ml (normal range 2.5-13, immunoradiometric assay, Mitsubishi-kagaku Bioclinical Labs., Japan).

In a serologic analysis, anti-thyroglobulin antibody was slightly positive (0.4 U/ml), but other antibodies, including TSH binding inhibitor immunoglobulin (TBI), thyroid stimulating antibody (TSAb), anti-thyroid peroxidase antibody, anti-nuclear antibody (ANA), anti-pituitary antibody and anti-adrenal cortex antibody, were all negative. Magnetic resonance imaging (MRI) of the head showed a mild swelling of the pituitary, in which a small and poorly enhanced irregular region was noticed.

Clinical course (Fig. 1): as ‘thyroid crisis’ was suggested at the admission (day-1), hydrocortisone (100mg/day) and β-blocker were started just after urine and blood sampling, which later revealed the coexistence of thyrotoxicosis and glucocorticoid deficiency due to pituitary failure. The thyroid hormone levels normalized rapidly, and MMI, KI and β-blocker were stopped on December 14th (day-6). The dose of hydrocortisone replacement was gradually decreased and was set at 25 mg/day from December 18th (day-10). All symptoms and hypercalciemia rapidly disappeared in parallel to the improvement in both glucocorticoid deficiency and thyrotoxicosis. Thyroidal radioactive iodine uptake on December 24th (day-16) was low (0.9 %/24h). Stimulating tests, by ACTH-releasing hormone, TSH-releasing hormone, GH-releasing hormone and GnRH, on December 28th (day-20), revealed no response in ACTH and PRL, and impaired responses in TSH, LH, and FSH levels. Hydrocortisone replacement was reduced to 20 mg/day in January 1999, while the thyroid function showed a transient latent hypothroid state and thereafter normalized spontaneously. The bone turnover markers were measured again on January 6th (day-29), when serum calcium level was 2.32 mmol/l, three weeks after the disappearance of hypercalciemia. The bone resorption marker levels were still high but had markedly decreased in comparison to those observed on day 1: U-Pyr 110 μmol/molCr, U-DPD 13 μmol/molCr, U-NTx 82 nmolBCE/mmolCr, and ICTX 8.4 ng/ml (Fig. 2, upper). The bone formation marker levels showed a mild decrease in OC (13 ng/ml) and a mild increase in PICP (233 ng/ml) (Fig. 2, lower). The patient improved and was discharged from the hospital under treatment by hydrocortisone replacement of 20 mg/day alone on January 22nd (day-45). A follow-up MRI, in March 1999, showed a normalization of the swelling in the pituitary gland.

DISCUSSION

The clinical course of this patient is summarized as follows: 1) headache, anorexia and general fatigue appeared at 35 weeks' gestation, 2) lactation was absent, and fever, tachycardia and generalized musculoskeletal disorder appeared and then rapidly worsened accompanied by mental disorder at two-three months after the delivery, 3) severe hypercalciemia, thyrotoxicosis and glucocorticoid deficiency due to pituitary failure were recognized at that time, 4) all the symptoms and hypercalciemia disappeared in parallel to the improvement of thyrotoxicosis and glucocorticoid deficiency, 5) bone resorption markers were extremely high in the hypercalciemic state, and then markedly decreased in a normocalciemic state.

Thyrotoxicosis in this case was diagnosed as 'postpartum thyroiditis' because of its onset time, negative TBI and TSAb, and low thyroidal radioactive iodine uptake. On the other hand, although no histological confirmation was available and anti-pituitary antibody was negative, pituitary failure in this case seemed to be 'lymphocytic hypophysitis', because: 1) its onset was in the third trimester of gestation without any hemorrhagic episode, 2) ACTH secretion was predominantly impaired in comparison to other pituitary hormones, and 3) the MRI findings including transient swelling of the pituitary gland were not incompatible to the lymphocytic hypophysitis. As the demand of glucocorticoid hormone increases markedly in thyrotoxic state (15), the preceding glucocorticoid deficiency, probably experienced by the patient since July 1998, seemed to become very severe after the onset of post-partum thyroiditis from November to December 1998. The musculoskeletal disorder in this case was thought to be myopathy, due to glucocorticoid deficiency (16), which became exacerbated somewhat by hypercalciemia. Furthermore, hypercalciemia itself seemed to be induced by the combination of glucocorticoid deficiency and thyrotoxicosis, because both the PTH and PTHrP levels were low and this hypercalciemia promptly disappeared by the replacement of glucocorticoid and normalization of thyroid hormone levels.
Although hypercalcemia is sometimes recognized in patients with adrenal failure alone or thyrotoxicosis alone, a severe hypercalcemia has been reported in those with a coexistence of adrenal failure and thyrotoxicosis (1-4). On the other hand, it has been reported that thyroidectomy prevented the appearance of hypercalcemia in adrenalectomized dogs (5). These reports suggest that thyroid hormone may play an important role in the pathogenesis of hypercalcemia associated with glucocorticoid deficiency.

Hypercalcemia recognized in hypoadrenalism has been reported to result from the combined effects of a hypovolemia-induced reduction in calcium excretion by the kidney and an increased calcium release from the bone, and the latter has been thought to be the main reason for hypercalcemia in this state (5-7). In our case, also, hypercalcemia was resistant to the rehydration therapy and urinary calcium excretion was increased before the glucocorticoid replacement. The effects of glucocorticoids on bone may be controversial: namely, glucocorticoid excess inhibits bone formation and increases bone resorption, together with the induction of secondary hyperparathyroidism, thus resulting in 'steroid-induced osteoporosis' (17, 18). However, physiological amounts of glucocorticoid are thought to be necessary for the differentiation of osteoblasts (19), and a cytotoxic action of glucocorticoids on osteoclasts has also been observed (20). Furthermore, glucocorticoid deficiency can increase the number of cytokines which promote bone resorption, such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF) (21-23). Therefore, in patients with glucocorticoid deficiency, bone resorption may become predominant, thus leading to the appearance of hypercalcemia.

On the other hand, thyroid hormone is known to stimulate both bone formation and resorption, and thyroid hormone excess dramatically increases bone resorption, thus resulting in osteoporosis and sometimes hypercalcemia which is, however, usually mild (24, 25). Stimulative effects of thyroid hormone on the osteoclast activity have been observed in organ cultures (26-28), and such effects could be inhibited by glucocorticoids (26). However, the detailed mechanism of thyroid hormone action on osteoclasts is still unclear. The presence of nuclear thyroid hormone receptors, not only in osteoblasts but also in osteoclasts, has recently been demonstrated (29), and the existence of plasma membrane-associated thyroid hormone receptors has also been reported in bone cells (30). These findings suggest the possibility that thyroid hormone may therefore directly stimulate osteoclasts. However, in vitro studies using isolated osteoclasts have so far failed to show any direct stimulation by thyroid hormone, as the stimulation required the presence of osteoblasts (31). Thyroid hormone has also been reported to indirectly
stimulate osteoclasts mediated by prostaglandins and cytokines (27, 32). Especially, IL-6, which stimulates osteoclastogenesis and bone resorption, can be produced by osteoblasts (23), and thyroid hormone may up-regulate the stimulatory effect of IL-1 beta on IL-6 production in osteoblasts (33). In this aspect, the inhibitory effect by glucocorticoids on thyroid hormone-induced bone resorption may be partly explained by the suppression of such ILs. In conclusion, the combined effect of an excessive amount of thyroid hormone and glucocorticoid deficiency is hypothesized to cause an extreme acceleration of the bone resorption resulting in severe hypercalcemia. Our case may be the first reported in which extreme elevations of serum and urinary bone resorption markers were confirmed in such a state with hypercalcemia. Further studies are required in both clinical and experimental ways to elucidate the mechanism of actions of thyroid hormone and glucocorticoid on bone.

REFERENCES


