Primary Hyperparathyroidism Masquerading as Immobilization Hypercalcemia: Report of an Illustrative Case

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Abstract. We report a male who exhibited the Landry-Guillain-Barre syndrome and hypercalcemia. He initially exhibited normocalcemia, followed by hypercalcemia which developed during tetraplegia and the recovering phase of the syndrome. The administration of prednisolone, saline, calcitonin, etidronate, and indomethacin failed to normalize the serum calcium level. Since, with mobilization, the serum calcium level gradually became normal, the calcium abnormality was misdiagnosed as immobilization hypercalcemia. However, among 6 different parathyroid hormone (PTH) assays used, including a two-site immunoradiometric assay, only a mid-region specific PTH (mPTH) assay showed high levels in both hypercalcemic and normocalcemic periods, and a high level of mPTH was not suppressed by calcium infusion in the normocalcemic period. Neck exploration disclosed a parathyroid adenoma weighed 100 mg. This case illustrates the hypercalcemia-inducing effect of immobilization on mild type primary hyperparathyroidism. A high level mPTH assay, its unsuppressibility by the calcium infusion test, and ineffectiveness of oral etidronate for hypercalcemia were valuable in differentiating hypercalcemia due to primary hyperparathyroidism from that resulting solely from prolonged immobilization.

Key words: Immobilization, Hyperparathyroidism, Hypercalcemia, Parathyroid hormone assay.

(IMMOBILIZATION is a rare cause of hypercalcemia [1]. It is also speculated to be a factor predisposing to the onset of hyperparathyroidism [2] and cancer associated hypercalcemia [3]. The differential diagnosis of the hypercalcemia induced by immobilization in a patient with underlying hyperparathyroidism from that caused solely by prolonged immobilization may in some cases be difficult [4]. We present the diagnostically difficult case of a patient with small parathyroid adenoma who initially had normocalcemia and then developed hypercalcemia during immobilization due to Landry-Guillain-Barré syndrome. Among 6 different PTH assays including two-site immunoradiometric assay (IRMA), only a mid-region specific assay with a CH9 antibody developed by Slatopolsky et al. [5] showed a high level in this...
A 38-year-old man was admitted on July 31, 1987, with a two-day history of progressive motor weakness and numbness in both lower extremities. There was no significant medical history. Physical examination on admission revealed significant motor weakness in all extremities (grade 0/5- to 1/5), which was more prominent distally, and absent deep tendon reflexes. There was weakness of the facial and trapezius muscles indicating the involvement of the 7th and 11th motor cranial nerves. The cerebrospinal fluid (CSF) on admission contained one leukocyte/mm$^3$ and a protein concentration of 58 mg/dl (normal 20-40 mg/dl). On the 3rd hospital day the CSF contained one leukocyte/mm$^3$ with a protein level of 198 mg/dl and IgG level of 69.3 mg/dl (normal 1.0–1.4 mg/dl). The myelin basic protein level was 4.0 µg/l (normal <4.0 µg/l) and oligoclonal bands were detected in the CSF. A nerve conduction study of the central nerves demonstrated a decrease in motor nerve conduction velocity compatible with demyelination. The serum calcium level was normal at 10.0 mg/dl (normal 8.4–10.4 mg/dl) with a total protein level of 7.4 g/dl, and the inorganic phosphorus level was low at 2.1 mg/dl (normal 2.5–4.3 mg/dl) on admission.

The day after admission, the patient required intubation due to respiratory insufficiency and continued to receive ventilatory assistance for 47 days. During the initial two months in the hospital, he required parenteral nutrition. Thereafter he had a normal diet.

Twelve days after admission, the following values were found: serum calcium, 13.2 mg/dl; inorganic phosphorus, 2.1 mg/dl; chloride, 99 mEq/l; and total protein, 7.6 g/dl. Tests for calcium metabolism were as follows; urinary calcium output, 652 mg/day (normal <200 mg/day); urinary calcium/creatinine ratio, 1.35 (normal 0.06–0.45); C-terminal PTH (PTH-C RIA kit, Immuno Nuclear Corporation, U.S.A.), 0.47 ng/ml (normal 0.20–1.00 ng/ml); N-terminal PTH (Teijin Bioscience Laboratories, Tokyo, Japan), 20 pg/ml (normal 10–30 pg/ml); mid-region PTH with CH9 antibody (mPTH-CH9) (Highly Sensitive PTH kit, Yamasa Co., Ltd., Tokyo, Japan), 624 pg/ml (normal 180–560 pg/ml); mid-region PTH (PTH MM RIA kit, Immuno Nuclear Corporation, U.S.A.), 0.42 ng/ml (normal 0.30–1.00 ng/ml); intact PTH (N-tact kit, Immuno Nuclear Corporation, U.S.A.), 36 pg/ml (normal <120 pg/ml); 25-OH D, 12 ng/ml (normal 10–55 ng/ml); 24, 25 (OH)$_2$ D, 3.1 ng/ml (normal 1.8–3.8 ng/ml); 1,25 (OH)$_2$D, 14 pg/ml (normal 20–76 pg/ml); vitamin A, 699 ng/ml (normal 410–1200 ng/ml); nephrogenous cyclic AMP (NcAMP), 3.2 nmol/dl of GF (normal 0.8–2.8 nmol/dl of GF); and TmPO$_4$/GFR, 2.5 mg/dl (normal 2.3–4.3 mg/dl).

Arterial blood gas analysis during ventilatory assistance showed the following values: pH , 7.44 (normal 7.35–7.45); PaO$_2$, 87.9 mmHg (normal 80–100 mmHg); PaCO$_2$, 45.0 mmHg (normal 35–45 mmHg); HCO$_3$, 30.4 mEq/l (normal 23.2–28.8 mEq/l) with a serum chloride level of 101 mEq/l. Examinations including ultrasonography, computed tomography and thallium-201-technetium-99m parathyroid subtraction scintigraphy did not reveal a parathyroid tumor. The administration of prednisolone, eel calcitonin (elcatonin), oral etidronate, indomethacin, and intravenous saline all failed to normalize the serum calcium level (Fig. 1). The possibility of primary hyperparathyroidism remained, but the patient refused a surgical exploration of the neck. Gradually he recovered his muscle strength and by the 96th day of hospitalization he was able to walk unaided. With mobilization, the levels of calcium and inorganic phosphorus and the urinary calcium/creatinine ratio gradually returned to normal (Fig. 1). The patient was discharged on the 327th hospital day. During hospitalization, the serum calcium level was inversely correlated with the urinary creatinine output ($r=-0.56$, $n=98$, $P<0.001$) and the serum creatinine level ($r=-0.61$, $n=123$, $P<0.001$), indicating that muscle activity was important in the normalization of the serum calcium level.

During the two year follow-up after the patient had become normocalcemic, we observed an intermittent slight increase in the serum calcium level, up to 11.0 mg/dl, with a concomitant lowering of the serum inorganic phosphorus level, down to 2.0 mg/dl. Results of parathyroid function testing performed on June 6, 1990 were as follows; serum calcium, 10.0 mg/dl; inorganic phosphorus, 3.1 mg/dl; urinary calcium output, 259 mg/day; urinary calcium/creatinine ratio, 0.17; C-terminal
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PTH, 0.59 ng/ml; intact PTH (N-tact kit), 60 pg/ml; two-site PTH IRMA (Allegro Intact PTH kit, Nichols Institute, U.S.A.), 28 pg/ml (normal 10–60 pg/ml); mPTH-CH9, 593 pg/ml; 25OH, 26 ng/ml; 24, 25 (OH)2D, 1.80 ng/ml; 1,25(OH)2D, 49 pg/ml; NcAMP, 4.99 nmol/dl of GF; and TmPO4/GFR, 2.7 mg/dl. Ultrasonography, computed tomography, and a thallium-201-technetium-99m parathyroid subtraction scintigram did not reveal a parathyroid tumor. Calcium infusion test (15 mg/kg body weight/4h) demonstrated an unsuppressible mPTH (Fig. 2). The patient finally agreed to undergo a surgical exploration of the neck, performed on June 15, 1990. It revealed a right lower parathyroid adenoma weighed 100 mg (3×4×7 mm), and the excision was performed. Histopathologic examina-
tion showed a chief cell adenoma with surrounding normal parathyroid tissue (Fig. 3). The three other glands were grossly normal, and the results of histopathologic examination of a right upper parathyroid gland biopsy specimen were normal. Eighteen days postoperatively, the following results were obtained: serum calcium, 8.6 mg/dl; inorganic phosphorus, 4.0 mg/dl; total protein, 7.2 g/dl; urinary calcium output, 153 mg/day; urinary calcium/creatinine ratio, 0.18; C-terminal PTH, 0.50 ng/ml; intact-PTH (N-tact PTH kit), less than 25 pg/ml; PTH-IRMA 14 pg/ml; mPTH-CH9, 301 pg/ml; NcAMP, 0 nmol/dl of GF; and TmPO4/GFR, 4.0 mg/dl. A calcium infusion test showed normally suppressible mPTH (Fig. 2).

Discussion

This case illustrates the hypercalcemia-inducing effect of prolonged immobilization on mild type primary hyperparathyroidism. Such immobilization causes an increase in the ratio of bone resorption/formation by decreasing the formation of bone [6–8], presumably resulting from the decrease in piezo-electric stimulation of the osteoblast [9]. While hypercalciuria is commonly observed during immobilization, hypercalcemia is rare, because the factors which induce bone resorption and stimulate renal calcium reabsorption such as PTH are suppressed [10], so that the increase of bone resorption/formation ratio do not reach a level high enough to result in hypercalcemia. Hypercalcemia due to immobilization commonly occurs in patients with high bone turnover such as adolescents and in those with Paget’s disease [1]. In our patient, the sustained resorption of bone and limited calcium excretion due to the autonomous secretion of PTH and the decrease in the formation of bone due to prolonged...
immobilization resulted in the development of hypercalcemia.

The clinical course of our patient, i.e. normalization of the serum calcium and inorganic phosphorus levels with re-mobilization, obscured the presence of primary hyperparathyroidism. However several biochemical data hinted at a diagnosis of primary hyperparathyroidism, such as hypophosphatemia on admission, intermittent mild hypercalcemia and hypophosphatemia present during long follow-up, increased NcAMP, and above all, increased mPTH-CH9 and its unsuppressibility by the calcium infusion test. Our patient’s PTH assay results indicate higher sensitivity in the mid-region PTH assay with CH9 antibody than in the other assays in detecting mild type of hyperparathyroidism. This is in line with the report by Endres et al. [11] in which they said that a research quality mid-region assay provided the greatest sensitivity in measuring high levels of PTH in primary hyperparathyroidism. Recently, Hollenberg and Arnold [12] reported a patient with hyperparathyroidism in whom PTH was quite normal in all 3 assays used, including an IRMA, and proposed it as a novel presentation of primary hyperparathyroidism. However mid-region PTH was not determined in their patient. It is possible that mid-region PTH was high in their patient. The reason why mPTH detected with a PTH MM RIA kit was not high in our patient may be due to the low sensitivity of the kit. The ineffectiveness of oral etidronate, which has been reported to be effective in treating immobilization hypercalcemia [4, 13, 14], may also be important in signalling the presence of hyperparathyroidism.

In summary, this patient illustrates the hypercalcemia inducing effect of prolonged immobilization on the course of mild type primary hyperparathyroidism. In the case of mild type hyperparathyroidism with normocalcemia in a active condition and hypercalcemia during prolonged immobilization, a high level of mPTH-CH9, its unsuppressibility by the calcium infusion in the normocalcemic state, and the ineffectiveness of oral etidronate for controlling hypercalcemia in addition to a careful follow-up may be useful in making the diagnosis.

Acknowledgments

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References