

[CASE REPORT]

Normocalcemic Primary Hyperparathyroidism Presenting with Muscle Weakness and Body Pain

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Abstract:

We herein report a 39-year-old woman who had aggravated body pain, waddling gait, and fatigability for the past 2 years. A neurological examination showed hyperreflexia and proximal muscle weakness. The serum calcium level was normal (10.1 mg/dL). However, serum alkaline phosphatase (3,855 IU/l) and parathyroid hormone (1,008 pg/mL) levels were remarkably high. Cervical ultrasonography revealed parathyroid goiter. The patient was diagnosed with hyperparathyroidism. Her muscle weakness and pain improved within three months after parathyroidectomy. Our findings suggest that clinicians should consider hyperparathyroidism as a differential diagnosis in patients with proximal muscle weakness, even if the serum calcium level is normal.

Key words: normocalcemic hyperparathyroidism, muscle weakness, body pain, alkaline phosphatase

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Introduction

Primary hyperparathyroidism (PHPT) often disguises itself as other diseases. It is known to be accompanied by various symptoms, including myopathy-like symptoms, such as muscle weakness and fatigability (1-4); motor neuron disease-like symptoms, such as hyperreflexia, pyramidal signs and bulbar signs (5-8); and rheumatic disease-associated symptoms, such as arthralgia and muscle pain (9-12). PHPT with neuromuscular symptoms has mainly been diagnosed based on hypercalcemia in past cases (4, 6-8, 10). However, a few cases of hyperparathyroidism have shown muscular symptoms with normal serum calcium levels, and the underlying pathological mechanism has not yet been elucidated (1, 5).

We herein report a case of PHPT due to parathyroid adenoma that began with muscle weakness and whole-body pain with normal serum calcium and abnormally high alkaline phosphatase (ALP) levels. The relation between muscle symptoms and parathyroid hormone (PTH) in this case was discussed.

Case Report

A 39-year-old woman presented with muscle weakness and body pain. Approximately two years ago, she had had pain in the right forearm, right wrist joint, and back. Approximately one year ago, she had felt transient weakness in her left leg. Half a year ago, she had had pain from the neck to the shoulder and difficulty raising both her arms as well as climbing the stairs. She started walking with a waddling gait. She also experienced pain at the side of her chest, arms, knees, and heels. She consulted at a nearby hospital. However, she was judged to need a more detailed examination and was thus admitted to our hospital.

A physical examination revealed knocking pain in her lower back and ribs. She also had arthralgia in the knees, wrists, ankles, and elbows. The thyroid gland and lymph nodes in the cervical spine were not palpable. Her weight (60.3 kg) and body mass index (22.6) were within normal ranges. A neurological examination showed weakness of her grip strength (right hand: 19 kg, left hand: 11 kg), and manual muscle testing (0-5 grade) indicated a decreasing grade

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Figure. Bone scintigraphy ($^{99m}\text{Tc-MDP}$). The diffuse and uniform accumulation of radioisotopes involves the extremities of limbs with a different pattern from that of malignant tumors, suggesting abnormal bone metabolism diseases, such as hyperparathyroidism.

of muscle power in the neck muscle (5- grade), iliopsoas (4+ grade), and gluteus (4+ grade). However, there was no muscle atrophy. Both Gowers' sign and Trendelenburg's sign were observed. The tendon reflexes of the limbs were hyperactive. She walked with a waddling gait, and her tandem gait was shaky. She could not stand up from the chair on her own, and she could not walk for more than 50 meters because of fatigue. Sensory disturbance, extrapyramidal symptoms, and coordination disorder were not detected.

A blood examination revealed that the hematological values, hepatic and renal functions, clotting times, thyroid function, C-reactive protein, and creatine kinase (CK) (47 U/L) were within the normal ranges. The serum acetylcholine receptor antibody was negative. The serum calcium level was also in the normal range (9.9 mg/dL, normal: 8.8-10.1 mg/dL). However, the ALP level was extremely high (3,855 IU/L, normal: 100-325 IU/L). The level of bone-specific ALP isoenzyme was elevated (85%, normal: 25-59%), suggesting multiple myeloma, bone metastasis of malignant tumor, or metabolic bone disease.

Nerve conduction study results were normal, and a repeti-

tive nerve stimulation test did not show waning. Electromyography showed myogenic changes in the proximal muscle of the extremities. Computed tomography (CT) of the skeletal muscle revealed no wasting or fatty degeneration. Bone scintigraphy showed diffuse radioactive accumulation involving the distal extremities, a typical finding of metabolic bone diseases (Figure). Abdominal CT revealed multiple calcified lesions in the pancreas. The bone density of her lumbar vertebrae was decreased (dual-energy X-ray absorptiometry T score: -3.8). The serum intact-PTH level was markedly elevated (1,008 pg/mL, normal: 10-65 pg/mL). Ultrasound of the neck showed a hypoechoic mass in the right thyroid, and whole-body ^{99m}Tc myocardial perfusion imaging (MIBI) scintigraphy revealed radioactive accumulation in the right upper parathyroid. The elevated serum parathyroid level, ultrasound findings, and MIBI scintigraphy results confirmed the diagnosis of PHPT.

Common complications of PHPT, such as urinary calculus, gastrointestinal ulceration, or depression, were not seen in this patient. Other differential diagnoses of muscle weakness, such as myopathies and myositis, myasthenia gravis, and motor neuron diseases, were deemed unlikely in this patient because of the normal serum CK level, lack of any abnormal findings on skeletal muscle CT, lack of waning on repetitive stimulation tests, and absence of neurological changes on electromyography.

For asymptomatic PHPT, the National Institute of Health criteria for parathyroidectomy state that osteoporosis with a T-score of ≤ -2.5 at any site is an indication of parathyroidectomy. The decrease in the lumbar bone density with a T-score of -3.8 was compatible with this criterion. Pathologically, chief cell-like tumor cells with vacuolated cytoplasm showed dense proliferation. The nuclei were not atypical, and no mitosis or invasion was found. This patient was diagnosed with hyperparathyroidism due to parathyroid adenoma.

The patient was referred for parathyroidectomy. At the operation, a 30×15-mm parathyroid adenoma was removed. Subsequently, calcium was given intravenously and orally to treat postoperative hypocalcemia. The serum calcium level dropped to 7.6 mg/dL during the postoperative period. She developed mild Chvostek sign during the postoperative period. However, she did not experience any other subjective symptoms, such as tetany, numbness, or hyperventilation.

One week after the operation, her pain in the heels while walking was reduced, and she became able to stand up from a chair on her own. Her grip strength and fatigability also improved. She was discharged from the hospital 27 days after the operation. Three months later, she was able to do squats and go down the stairs without holding the handrail. One year later, her fatiguability had disappeared, and she stopped taking calcium supplements. She has since fully recovered and returned to work.

Discussion

PHPT with neuromuscular symptoms and pain has been found to be associated with a high serum calcium level (6, 7, 10, 11, 13). For instance, in a survey by El-Sayed et al. (1), 9 of 83 patients with unexplained gradual progressive weakness with normal or mildly elevated CK levels had PHPT (9/83; 10.8%); the serum calcium levels were elevated in 7 patients (77.8%) and normal in 2 patients (22.2%), the the serum ALP level in was elevated in 4 patients. Notably, the ALP levels in the present case were much higher than in those previous patients (65-397 IU/L). In addition, reported cases of normocalcemic PHPT (NPHPT) with neuromuscular symptoms are very rare, and only one case with symptoms similar to those of motor neuron diseases has been described (5). Therefore, there may be overlooked cases that were left undiagnosed. In the present case, the serum calcium level was normal (9.9 mg/dL, normal: 8.8-10.1 mg/dL), but the serum ALP level was markedly elevated (1,348 mg IU/L). Because PHPT cannot be excluded even if the serum calcium level is normal, the PTH level in the blood should be carefully examined, and some imaging examinations should be performed during the differential diagnosis. Our findings suggest that an elevated serum ALP level might be a useful diagnostic marker for PHPT, although it does not correlate with the severity of neuromuscular symptoms (1).

Excessive levels of PTH play a primary role in neuromuscular symptoms in PHPT, and the effect of hypercalcemia is secondary. There are two main mechanisms underlying the muscle weakness and fatigability due to PHPT: energy metabolism disorder (14, 15) and catabolism of skeletal muscle (16) resulting in muscle atrophy (5-8). Smogorzewski et al. proved the first mechanism (14), showing that PTH interferes with the oxidation of long-chain fatty acid by blocking the transformation of free carnitine to acylcarnitine through the inhibition of carnitine palmitoyltransferase activity (carnitine cycle dysfunction). As a result, the acylcarnitine supply into mitochondria is impaired, and energy production is decreased. The second mechanism, involving the promotion of catabolism by PTH, is related to the inhibition of the synthesis of proteins, amino acids, and nucleic acids, which eventually leads to muscle atrophy (5-8, 16). In the present case, energy metabolism disorder was suspected as the underlying mechanism for several reasons. First, the serum acylcarnitine level was low (4.4 $\mu\text{mol/L}$, normal: 6-23 $\mu\text{mol/L}$), indicating the inhibition of carnitine palmitoyltransferase. Second, the drastic recovery of muscle strength after the operation is typically associated with weakness due to metabolic disorders. Third, musculoskeletal CT showed no muscle atrophy. PHPT is also accompanied by pyramidal signs. Since such signs were seen in our normocalcemic case, we suspect that excessive PHT directly caused pyramidal tract disorder without hypercalcemia. However, there is no existing research concerning the mechanism, and the etiology re-

mains to be elucidated.

Pain in various parts of the body is common in PHPT patients (9-13), and such cases are often diagnosed as rheumatic diseases, such as fibromyalgia (12, 13), rheumatoid arthritis (10), and polymyalgia rheumatica (9). PHPT is accompanied by muscle pain and arthralgia in the knees, wrists, shoulders, heels, and hip joints, as well as bone pain, chest pain, neck pain, and back pain (9). The types of pain experienced in PHPT are also varied, and there have been reports of arthralgia, muscle pain, and bone pain as a complications of osteoporosis (9, 17). In our case, the patient complained of arthralgia in the wrists, elbows, knees, and heels, bone pain in the back and side of the chest, and shoulder and neck pain. The distribution of pain is consistent with that in previous reports (9). Given these findings, hyperparathyroidism should be considered in cases of pain in multiple areas with muscle weakness.

There are several limitations to concerning pathomechanism of muscle weakness in our case. First, the carnitine cycle dysfunction in PHPT is suspected, however it has not been verified, as acylcarnitine is not measured routinely in cases of PHPT. Ota et al. measured the serum acylcarnitine in their PHPT case (18) with dropped head syndrome. However, the findings were normal in their case, and they were unable to prove carnitine cycle dysfunction. The further accumulation of acylcarnitine values in PHPT with muscle weakness is required. Second, the intact PTH level was exceptionally high (1,008 pg/mL) compared with a previous report of NPHPT and PHPT. However, the etiology behind the elevated value is unclear. In a survey on NPHPT by Schini et al. (19), the intact-PTH level did not differ significantly between NPHPT (normal: 10-65 pg/mL; 95% confidence interval: 86.9-123.9 pg/mL) and PHPT (95% confidence interval: 89.0-112.4 pg/mL). El-Sayed et al. reported (1) that the intact-PTH level in PHPT with muscle weakness was higher than that in normal PHPT (range: 117-1,038 pg/mL, 95% confidence interval: 296.6-489.2 pg/mL). Since excess PTH directly causes muscle weakness through metabolic disorder, the intact-PTH level may correlate with muscle weakness severity. Further studies are needed to clarify the pathology of NPHPT with an exceptional high intact-PTH level.

We diagnosed a case of normocalcemic PHPT with high serum ALP levels that began with proximal muscle weakness and whole-body pain. The symptoms resolved relatively quickly after the removal of the parathyroid adenoma. Our findings suggest that clinicians should consider the possibility of hyperparathyroidism in cases of myopathy with a normal serum calcium level.

The authors state that they have no Conflict of Interest (COI).

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