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# Primary Hyperparathyroidism: Modern Conception and Clinical Observation

## Abstract

The article is devoted to one of the current medical and social issues — primary hyperparathyroidism, the late diagnosis of which leads to the development of severe complications and an increased risk of premature death. Unlike developed countries, where mild forms of the disease constitute 80% of cases, in the Russian Federation this figure does not exceed 30%, with overt forms accounting for 70%. For the timely detection of the disease, widespread awareness among doctors of various specialties of the diagnosis of parathyroid adenoma is necessary. The article describes the main stages of studying the disease, examines the pathogenesis of the clinical signs of primary hyperparathyroidism, which classic clinical pattern involves changes in the target organs of the parathyroid hormone: bone tissue, urinary system and gastrointestinal tract. Bone tissue disorders are the most common manifestation of hyperparathyroidism and are characterized by increased bone metabolism with a progressive decrease in mineral density. Typical changes in the kidneys include nephrolithiasis and nephrocalcinosis with renal failure. Gastrointestinal signs of hyperparathyroidism are gastric erosion and ulcers and duodenal ulcer, prone to bleeding, and recurrent pancreatitis. Diagnosis of the disease is based on the results of laboratory tests: elevated blood levels of calcium and parathyroid hormone. Normally, parathyroid adenoma is imaged using ultrasound and scintigraphy. The most effective treatment is the removal of parathyroid adenoma. A clinical case of a severe course of the disease is presented, indicating the urgent need to solve the problem of primary hyperparathyroidism.

***Key words:*** *primary hyperparathyroidism, parathyroid adenoma, hypercalcemia*

## Conflict of Interests

The authors declare that this paper, its topic, subject and content do not involve competing interests

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PHPT — primary hyperparathyroidism

*In matters of natural science ... cognition of phenomena is what leads us to examining and finding the cause.*
Galileo Galilei

## Relevance

Primary hyperparathyroidism (PHPT) is an endocrine disease of medical and social significance, which is primarily due to the low level of diagnosis. Its incidence is 1–2 cases per 1,000 people; PHPT is one of the most common endocrine diseases. Untimely detection is the cause of severe disabling complications: osteoporotic fractures, recurrent stone formation in the urinary tract and nephrocalcinosis with renal failure, gastrointestinal bleeding,

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etc., as well as an increased risk of premature death. However, early diagnosis of primary hyperparathyroidism allows to achieve cure [1, 2].

## Background

In 1880, the Swedish researcher Ivar Sandström (1852–1889) first described areas of glandular tissue located on the posterior surface of the thyroid gland in humans. He called these structures parathyroid glands (PS), considering them to be underdeveloped thyroid tissue. Ten years later, in 1890, the French physiologist Eugène Gley (1857–1930), while studying the function of the parathyroid glands in dogs, found that the removal of the thyroid gland together with the parathyroid glands causes tetany in experimental animals. By this time, cases of convulsive syndrome in patients undergoing thyroidectomy had been described, and Gley's discovery shed light on the cause of this complication. In 1905, the Canadian-American researcher William George McCollum (1874–1944) found that post-thyroidectomy tetany is associated with the development of hypocalcemia due to parathyroid gland damage and proved that the latter is an independent endocrine organ that affects calcium metabolism.

In 1925, the Canadian biochemist James Bertram Collip (1892–1965) isolated parathyroid hormone (PTH), and almost 40 years later, in 1963, American scientists Solomon Berson (1918–1972) and Rosalyn Yalow (1921–2011) developed the radioimmune method of parathyroid hormone detection. After another 30 years, in 1993, a calcium receptor was discovered on the surface of parathyroid cells. Thanks to the above discoveries, by the end of the 20th century, the issues of parathyroid function regulation and the pathogenesis of various disorders were elucidated.

The history of primary hyperparathyroidism exploration also began in the last decade of the 19th century. In 1891, the German pathologist Friedrich Daniel von Recklinghausen (1833–1910) reported severe damage to the skeletal system, because of which the bones were easily cut with a knife during pathological examination and the skull was easily squeezed like a rubber ball. The disease was named after the researcher — Recklinghausen's disease of bone (osteitis fibrosis cystica), but its cause remained unknown for several decades. Fifteen years later, in 1906, the Austrian pathologist Jakob Erdheim (1874–1937) diagnosed a parathyroid tumor in a patient with Recklinghausen's disease, the development of which was explained by compensatory organ enlargement in response to bone damage. Based on these ideas, over the next twenty years, this disease was treated with a parathyroid gland extract or transplantation of this organ.

In 1915, Erdheim's compatriot, professor Friedrich Schlagenhaufer, first expressed the opposite opinion that the destruction of the skeleton is a consequence of a parathyroid tumor, the removal of which leads to healing. However, he did not find support. In 1924, at the congress of pathologists, the Russian pathologist Arseniy Rusakov (1885–1953) also proposed the extirpation of a parathyroid tumor for the treatment of osteitis fibrosis cystica, which was again rejected. In 1925, the Austrian surgeon Felix Mandl (1892–1957) removed a parathyroid tumor measuring 25×12×15 mm after unsuccessful treatment of severe Recklinghausen's bone disease using parathyroid transplantants. As a result, blood and urine calcium levels returned to the normal values, the patient's condition quickly improved and within a few days he could walk unassisted. From this moment, Recklinghausen's bone disease was given its current name "primary hyperparathyroidism", indicating the primary nature of the parathyroid gland lesion in relation to parathyroid osteodystrophy, and parathyroidectomy became the primary method of treatment.

During the first decades of the study of the disease, osteitis fibrosis cystica was considered the only specific sign of the disease. In 1934, the American endocrinologist Fuller Albright (1900–1969) first reported that 80% of patients have urinary system disorders: urolithiasis or nephrocalcinosis. In 1946, PHPT was associated with the development of peptic ulcers of the stomach and duodenum. In the 1950s, mental disorders in PHPT were reported, and later an increased risk of cardiovascular disorders (hypertension, left ventricular myocardial hypertrophy, left ventricular diastolic dysfunction, cardiac arrhythmias and conduction disorders), type 2 diabetes mellitus, and dyslipidemia was revealed, but their relationship with PHPT requires further study [3].

Until the second half of the 20th century PHPT was considered a rare disease. In the 1970s, in the United States of America and Western Europe, an automated biochemical analyzer allowed to identify the widespread prevalence of hypercalcemia due to PHPT, which is now regarded as one of the most urgent problems in medicine. According to the results of the study, about 80% of PHPT cases

were clinically apparent and approximately 20% were low-symptomatic. In Europe and USA, thanks to the study of PHPT and active early diagnosis of the disease, by 2004 the situation has changed dramatically: 80% of cases involved a mild course of the disease and 20% — overt forms. Over the past decade, the same ratio of overt and mild forms of PHPT has been achieved in China. In India and Latin America, the situation has not changed over the past 50 years: as before, 80% of cases are severe forms of the disease. The situation in Russia remains extremely unsatisfactory: 70% of diagnosed cases are overt forms and only 30% are mild.

As the experience in developed countries shows, the main approach to solving this problem is the detection of hypercalcemia using screening data. In addition, widespread awareness among physicians of various specialties of the basic physiology and pathophysiology of the parathyroid gland is necessary, the knowledge of which is the key to the timely diagnosis of PHPT [3–6].

## Regulation of Parathyroid Function and Effects of Parathyroid Hormone

The main regulatory factor of the functional state of the parathyroid gland is the blood calcium level, the decrease of which stimulates specific calcium receptors on the surface of parathyroid cells, which almost immediately leads to the release of PTH. The hormone release is regulated by a negative feedback loop: with the achievement of normocalcemia, the effects of PTH are quickly eliminated, due to its short half-life (about 10 minutes). PTH maintains a concentration gradient of extracellular and intracellular calcium: the level of calcium is 1,000 times higher in the extracellular fluid.

The main target organs for PTH are the bones, which are the main calcium pool, as well as the kidneys that regulate its excretion, and the intestines, which facilitate calcium intake into the body.

In bone tissue, PTH stimulates the functional activity of osteoblasts involved in the formation of bone tissue, which is associated with the activation of osteoclasts, which provide bone lysis and calcium release. In the kidneys, PTH enhances calcium reabsorption and phosphate excretion in the distal tubules, the latter contributing to the development of hypophosphatemia and, as a result, mobilization of calcium from bones.

Enhanced intestinal absorption of calcium has a mediated mechanism: under the influence of PTH in the kidneys, 1α-hydroxylase is activated, which catalyzes the formation of calcitriol — the active form of vitamin D. Calcitriol stimulates the formation of a calcium-binding molecule, with the participation of which calcium is absorbed. In accordance with the negative feedback mechanism, vitamin D deficiency contributes to an increase in PTH synthesis with the development of hyperplasia of one or all parathyroid glands. The effect of PTH on bone demineralization and renal regulation of calcium appears immediately, whereas the intestinal effect appears after a longer period. Under the action of PTH, the level of extracellular calcium rises, which is normally 10,000 times higher than the intracellular calcium content [1, 2].

## Causes of Primary Hyperparathyroidism

The majority of cases of PHPT (80–85%) are caused by solitary parathyroid adenoma, 10–15% — by multiple parathyroid hyperplasia, and 1% — by parathyroid cancer. Sporadic PHPT accounts for 90–95% of cases and about 5% is a hereditary variant characterized by multiple parathyroid damage and onset before the age of 40 years.

The cause of the disease is unknown. A triggering factor of parathyroid adenoma is irradiation of the head and neck: at a dose of 1200 rad and higher, the risk increases by more than 50%. It is also assumed that the prevalence of PHPT is associated with vitamin D deficiency.

## Pathogenesis and Symptoms

The classic symptoms of PHPT are disorders of the main target organs of PTH — bone tissue, kidneys and gastrointestinal tract. Bone tissue disorders are the most common sign of hyperparathyroidism. Excessive secretion of parathyroid hormone, which enhances bone metabolism, leads to the predominant proliferation of osteoclasts. As a result, endosteal resorption with the expansion of the medullary canal and thinning of the cortical layer develops. Clinical signs of osteoporosis are bone pain and spontaneous fractures. With the progression of the disease, osteitis fibrosis cystica is observed, which includes the formation of cysts and proliferation of connective tissue. The proliferation of cellular

elements of bone tissue causes the formation of a giant-cell tumor of the bone or epulis, which often develop in the bones of the skull and upper extremities and are characterized by a recurrent course in the absence of treatment for hyperparathyroidism. The decrease in bone mineral density (BMD) of the spine is clinically manifested as pain, which is aggravated by physical exertion, prolonged upright position (standing, sitting), as well as reduced growth in the case of compression fractures. Because of demineralization, teeth become loose and fall out, and filling material does not hold well.

With PHPT, damage to the kidneys is observed in more than 60% of cases and can sometimes be the only sign of the disease. PTH activates calcium reabsorption, therefore the calcium content in the urine may be normal. However, with an increase in the severity of hypercalcemia, the level of calciuria also rises. Hypercalciuria causes damage to the epithelium of the renal tubules and the development of nephrolithiasis, the risk of which with PHPT increases up to 40 times, while stone formation is recurrent. As a result of damage to the renal tubules, their sensitivity to the antidiuretic hormone decreases, which leads to impaired water reabsorption with the development of polyuria and polydipsia. Hypercalcemia and hypercalciuria contribute to the deposition of calcium in the renal parenchyma, which causes the formation of nephrocalcinosis and renal failure, the risk of which with PHPT increases to 6.5 times.

Hypersecretion of the parathyroid hormone and hypercalcemia activate the production of hydrochloric acid and digestive enzymes in the gastrointestinal tract, which triggers damage to the mucous membrane of the digestive tract and damage to the pancreas. Gastric ulcer in 15–27% of cases may be the only sign of hyperparathyroidism. Erosions and ulcers of the stomach and duodenum are characterized by frequent exacerbations, severe pain, resistance to treatment, tendency to bleeding and perforation. Pancreatitis is also characterized by a recurrent course; it may be accompanied by the development of pancreatic calcinosis and pancreatolithiasis.

As the disease progresses and parathyroid hormone synthesis increases, the severity of disorders associated with intracellular calcium deficiency increases, which primarily affects muscle tissue. Fatigue and weakness are observed, especially in the proximal muscles, which experience the greatest functional load, which makes it difficult to sit down, get up, climb stairs, and comb hair. Muscle hypotonia and atrophy is the cause of the "waddling gait" and the development of flat feet. In severe cases, patients can be bedridden. A severe decrease in body weight up to cachexia is also characteristic of severe PHPT. PHPT is characterized by a long history with a gradual progression of clinical symptoms. With prolonged duration of the disease, the development of hypercalcemic crisis is possible, which is a result of a significant increase in the calcium level (more than 3.5 mmol/L) and is associated with a high risk of death. It manifests as multiple organ failure, which mainly includes gastrointestinal (anorexia, nausea, vomiting, abdominal pain, acute pancreatitis), renal (dehydration, oliguria, acute kidney injury, renal colic), cardiovascular (rhythm and conduction disturbances, shortening of the QT interval) and neurological (myalgia, severe weakness, confusion, stupor, coma) disorders. Infectious diseases, fractures, prolonged immobilization, pregnancy, and antacids are triggering factors of the crisis [7–10].

## Classification

Symptomatic (overt) and asymptomatic PHPT are distinguished, which can be represented by hyper- and normocalcemic variants. Overt PHPT is characterized by the presence of "classical" signs, including bone tissue (osteoporosis, low-traumatic fractures and fibrocystic osteitis) and visceral disorders (nephrolithiasis, nephrocalcinosis, decreased concentration and filtration functions of the kidneys, ulcers of the upper gastrointestinal tract, and pancreatitis). Asymptomatic PHPT is characterized by the absence of typical clinical signs and in most cases has a long-term benign course. However, the question of whether asymptomatic PHPT is an independent form of the disease or its initial stage remains open [4].

The most common is the hypercalcemic variant of the disease. In hypercalcemic PHPT, normocalcemia can be transient or persistent, which is regarded as a normalcalcemic variant of the disease.

## Diagnosis

Diagnosis is based on laboratory test results. The main biochemical marker of PHPT is hypercalcemia. The study of blood calcium levels is indicated in the detection of bone system pathology (osteoporosis, low-traumatic fractures, signs of osteitis fibrosa cystica), kidneys (nephrolithiasis, nephrocalcinosis),

gastrointestinal tract (recurrent gastric ulcer or duodenal ulcer, recurrent pancreatitis) as well as in the presence of symptoms of hypercalcemia (polyuria, polydipsia, nausea, vomiting, dehydration).

Blood calcium is presented in two forms: total (or associated with protein), and ionized, accounting for approximately half of total calcium. When the concentration of plasma proteins (blood albumin less than 40 g/L or more than 45 g/L) changes, the measurement of total blood calcium requires adjustment. For this purpose, the formula is used: total plasma calcium (mmol/L) = measured level of total plasma calcium (mmol/L) + 0.02 × (40 — measured plasma albumin level (g/L)) [3].

A combination of hypercalcemia and hypophosphatemia is characteristic of PHPT, which is associated with the multidirectional effect of PTH on these blood components. When hypercalcemia is first detected, retesting is recommended to confirm it. Retesting is also required in cases when the level of calcium is within the reference interval in a patient with clinical signs of PHPT. The second most common cause of hypercalcemia is cancer. However, elevated calcium levels are usually detected at the stage of the disease when the diagnosis of cancer is obvious.

If there is a suspicion of PHPT, blood PTH is studied, the results of which are elevated or high-normal, which reflects the loss of the regulatory role of hypercalcemia on the activity of the parathyroid gland in adenoma. In contrast to PHPT, in paraneoplastic syndromes, hypercalcemia is accompanied by a reduced or low-normal level of PTH.

With the presumptive diagnosis of PHPT, the functional state of the kidneys, one of the main target organs, is assessed. To determine the glomerular filtration rate (GFR) in outpatient practice, the CKD-EPI formula is recommended [4]. With PHPT, the involvement of bone tissue in the pathological process reflects an increased or high-normal level of total alkaline phosphatase, as well as more specific markers of bone metabolism: C-terminal telopeptide of type 1 collagen (resorption) and procollagen type 1 N-terminal propeptide (bone formation). The determination of vitamin D level is recommended for patients with PHPT, the most informative method of assessment of which is a blood test for 25(OH) vitamin D.

With satisfactory renal function (GFR > 60 mL/min/1.73 m$^2$), to verify the diagnosis of PHPT, it is recommended to determine the content of calcium and creatinine in daily urine, which, with GFR < 60 ml/min/1.73 m$^2$, is not informative. Calculation of the calcium/creatinine clearance ratio allows to exclude familial benign hypocalciuric hypercalcemia, the only * disease with laboratory changes similar to PHPT (elevated blood calcium level in combination with elevated or highly normal PTH levels). This is a rare genetic pathology with an autosomal dominant type of inheritance caused by a defect in calcium-sensitive receptors in the parathyroid gland and in the kidneys, which perceive the normal level of hypercalcemia as low. As a result, parathyroid cells secrete an excessive amount of PTH, and the kidneys intensely reabsorb calcium, which leads to a pronounced decrease in the calcium/creatinine clearance ratio below 0.01, whereas with PHPT this index ** is usually above 0.02. In addition, in contrast to PHPT, abnormal laboratory test results in familial benign hypocalciuric hypercalcemia are detected in patients from childhood, as well as in their relatives, and are less severe. The disease has a relatively favorable prognosis and does not require treatment [4].

The normocalcemic form of PHPT is diagnosed with a persistent increase in PTH (in at least two studies with an interval of 3–6 months) in combination with normal blood calcium levels, if secondary hyperparathyroidism is excluded and hypercalciuria is absent. The most common causes of secondary hyperparathyroidism include vitamin D deficiency (25-(OH)-D ≤ 30 ng/mL) and chronic kidney disease with GFR ≤ 60 mL/min/1.73 m$^2$. In addition, secondary hyperparathyroidism can be caused by drugs (bisphosphonates, denosumab, lithium preparations), and diseases of the gastrointestinal tract with malabsorption syndrome and hypercalciuria. For the differential diagnosis of the normocalcemic form of PHPT and secondary hyperparathyroidism, it is recommended to carry out functional tests using vitamin D and a thiazide diuretic.

Vitamin D supplementation in patients with secondary hyperparathyroidism leads to normalization or reduction of PTH at a normal level of blood calcium, while in PHPT hypercalcemia is observed, and the level of PTH remains elevated. Native vitamin D

* Tertiary hyperparathyroidism is also characterized by hypercalcemia and elevated levels of PTH, but it develops in patients with a long-term history of secondary hyperparathyroidism.

** The formula for calculating: Clearance Ca/Cr = $Ca_u$ x $Cr_s$ / $Cr_u$ x $Ca_s$ ($Ca_u$ — urine calcium, $Cr_s$ — serum creatinine, $Cr_u$ – urine creatinine, $Ca_s$ — serum calcium, mmol/L)

supplements (cholecalciferol 50,000 IU per week or 25,000 IU 2 times a week or 7,000 IU daily) are used for 8 weeks until the target level of 25(OH) vitamin D (more than 30 ng/mL) is achieved; or active vitamin D metabolites (calcitriol, alfacalcidol 1 μg per day) are used for 5 days, and with a trend towards a decrease in PTH level and normocalcemia — up to 1 month. Thiazide diuretic increases calcium reabsorption in the kidney, therefore, the use of hydrochlorothiazide (25 mg 2 times a day) for 2 weeks leads to normalization of PTH level in the case of secondary hyperparathyroidism, while in PHPT the level of PTH does not change, and the calcium content in the blood may increase [11].

Topical diagnosis is carried out with the aim of preoperative preparation for selective parathyroidectomy. The first step is ultrasound. According to ultrasound data, parathyroid adenoma can be mistakenly interpreted as a thyroid nodule, which depends on the doctor's experience and knowledge of the disease symptoms. In most cases, functional and topical scintigraphy with 99mTc-methoxyisobutylisonitrile allows to clarify the diagnosis. If this imaging technique is unavailable, computed tomography (CT) of the neck with contrast enhancement, magnetic resonance imaging of the neck and positron emission tomography are recommended, of which multislice CT is preferable [2, 11, 12].

## Principles of Treatment

Parathyroidectomy of the affected parathyroid gland is the only radical treatment method with high efficiency. It is indicated for the overt form of PHPT, as well as in the following cases: 1) The patient is aged below 50 years; 2) the level of blood calcium exceeds the upper limit of the reference interval by more than 0.25 mmol/L (regardless of the symptoms); 3) there are signs of osteoporosis (history of low-trauma fracture and/or radiologically verified fractures of the vertebral bodies; BMD of the radial bone, proximal femur or lumbar spine according to X-ray densitometry: T-score is below –2.5 SD in postmenopausal women and men older than 50 years); 4) there are signs of functional and/or structural kidney disease (GFR below 60 mL/min/1.73 $m^2$, calcium excretion of more than 10 mmol/day, nephrolithiasis/nephrocalcinosis, including asymptomatic forms).

After surgery, most of the clinical symptoms of PHPT regress. In the absence of severe damage to the skeletal system and kidneys, the ability to work is restored.

Conservative treatment is aimed at the correction of hypercalcemia, the prevention of hypercalcemic crises and low-trauma fractures. It can be recommended for patients with asymptomatic PHPT in the absence of indications for surgical treatment, as well as in case of refusal of the patient or contraindications (severe concomitant diseases). The conservative approach involves the dynamic monitoring of the following parameters: calcium levels — 2–4 times a year, creatinine level (with GFR calculation), PTH and daily urinary calcium excretion — once every 6 months, renal ultrasound (CT if necessary) and BMD in three parts of the skeleton — once a year, as well as lateral radiographs of the spine in case of suspected fractures of the vertebral bodies (decreased growth, back pain) and esophagogastroduodenoscopy in the presence of specific complaints [2, 11].

All patients are recommended a diet with moderate amounts of calcium and fluid intake of at least 1.5–2 L per day. Antiresorptive drugs and/or calcimimetic agents are used to correct hypercalcemia and prevent bone loss. The study of the effectiveness of oral bisphosphonates (alendronic acid 10 mg/day for 1–2 years) showed an increase in BMD in the lumbar spine and proximal femur, which is comparable with the results of surgical treatment [11]. Denosumab showed a more pronounced hypocalcemic effect and a greater increase in BMD in the cortical bone compared with bisphosphonates [11]. The use of calcimimetic agents effectively reduces the level of blood calcium to normal values in 80% of cases, but at the same time does not affect the state of bone tissue. The initial dose is 30 mg per day, followed by titration every 2–4 weeks until the level of calcium reaches the upper limit of the normal range. The maximum dose is 90 mg 4 times a day. The results of the study of combination treatment for 1 year (alendronic acid and calcimimetic agent) showed a significant increase in BMD of the lumbar spine and proximal femur, as well as a decrease in blood calcium level [11].

If D-vitamin deficiency is found in patients with PHPT, it is corrected using native vitamin D. If the level of calcium is not higher than 3 mmol/L, replenishment of vitamin D deficiency at the preoperative stage is recommended (no more than 1,000–2,000 IU per day), and if the level of calcium is higher than 3 mmol/L, replenishment is carried out in the early postoperative period [1, 13–17].

## Case Report

A female patient, 37 years old, born in 1979, mother of four children. From 2008, after the first birth, teeth began to loosen, and by 2014 they had completely fallen out. In 2014, after suffering psychoemotional stress, she began to lose weight, and by January 2015 she had lost 7 kg. At the same time, weakness and pain in the lumbar spine appeared, and the patient was treated by a physician with a diagnosis of "chronic vertebrogenic low back pain, severe, with frequent exacerbations."

In March 2015, the patient noted a lower jaw tumor, and was operated at the Republican Clinical Oncology Center (Ufa) with a diagnosis of giant-cell tumor of the lower jaw. After 7 months, in November 2015, giant-cell tumor of the upper jaw was diagnosed and a second operation was performed at the Oncology Center, after which the patient was referred for consultation with an endocrinologist. During the examination, the endocrinologist found a node in the lower pole of the left lobe of the thyroid, measuring 27 × 17 × 48 mm, and diagnosed nodular goiter of the II stage, euthyroidism. In February 2016, the formation in the lower jaw reappeared, and the patient was operated on for the third time for a giant-cell tumor at the Oncology Center. One month after the operation, in March 2016, pain appeared in the right forearm, and an ulnar fracture was detected via X-ray. The patient continued to lose weight, weakness increased. She was again referred for consultation to the Oncology Center. The oncologist recommended a blood test for the content of calcium, phosphate and PTH, which revealed hypercalcemia (ionized calcium — 1.8 mmol/L (1.1–1.35) (hereinafter, the reference interval is indicated in parentheses), low-normal phosphate level (0.84 mmol/L (0.81–1.45)) and elevated PTH (1411.6 pg/mL (12–88)). Based on the results, Recklinghausen's bone disease was diagnosed and treatment at the G. G Kuvatov Republican Clinical Hospital (G.G. Kuvatov RCH) (Ufa) was recommended. The patient was examined there only two months after the recommendation: in April 2016 there was pain and swelling of the right foot, X-ray showed fractures of the metatarsal bones, and a fracture of the right ulnar process occurred in early May. At the end of May 2016, the patient visited an endocrinologist at the G.G. Kuvatov RCH accompanied by a relative. The appearance of the emaciated patient caused suspicion of cancer. Laboratory tests revealed a significant increase in blood calcium levels (ionized calcium — 1.94 mmol/L (1.1–1.35), total calcium — 3.71 mmol/L (2.20–2.65)) in combination with a decrease in phosphate concentration (0.77 mmol/L (0.81–1.45)). The level of alkaline phosphatase was 12 times higher than normal (1545.5 U/L (30–120)), and PTH was almost 20 times higher than the upper limit of the reference interval (1420.1 pg/mL (12–88)). Ultrasound of the thyroid confirmed the presence of a node of the left lobe of the previous size (27.5 × 19 × 48 mm) of somewhat reduced echogenicity with a tendency to retrosternal growth. X-ray densitometry detected osteoporosis (BMD L1-L4 was –3 SD).

Based on the results of the examination, primary hyperparathyroidism was established and scintigraphy was planned. When the patient returned home to the district center, she had an injury of her left leg (fracture of the upper third of left thigh). Open reduction and osteosynthesis were performed at the Central Regional Hospital of Belebey. The traumatologist suspected the oncological genesis of the fracture, but the results of the histological examination excluded malignancy. A week after surgery, the patient was transported to the Department of Endocrinology of the G.G. Kuvatov RCH to clarify the diagnosis and determine further management approach.

Upon admission, the patient complained of severe weakness and thirst. At the time of examination, the patient's weight was 37 kg with a height of 165 cm (BMI was 13.6 kg/m$^2$)). The deformation of the operated leg in a cast was noted, and therefore X-ray examination was performed (a repeated fracture of the left femur was detected, this time in the middle third). In the hospital, scintigraphy was performed, which revealed an extensive area of hyperfixation of the radiopharmaceutical at the level of the middle-lower parts of the left lobe of the thyroid, measuring 35×23 mm, indicating a large parathyroid adenoma. The diagnosis was: primary hyperparathyroidism, parathyroid adenoma. Complications: epulis of the upper and lower jaw (surgery performed in March and November 2015, in February 2016), severe hyperparathyroid osteoporosis (fracture of the right ulnar bone (March 2016), fractures of the metatarsal bones of the right foot (April 2016), fracture of the right ulnar process (May 2016), fracture of the left femur in the upper and middle third (June 2016)), hyperparathyroid myopathy, cachexia.

Initially, the patient was operated on in the Department of Traumatology, and then transferred to the

Department of Vascular Surgery, where, in July 2016, adenoma of the left lower parathyroid gland was removed. Histological examination verified parathyroid adenoma.

Six months after the surgery, the patient noted a significant improvement: no complaints of weakness, 13 kg weight gain (the previous body weight was restored). At the recommendation of the traumatologist, the patient observes low-load movement regimen; for the first six months after the surgery she used a wheelchair, and now uses a cane when walking. The results of the control laboratory test correspond to the normal values (ionized calcium — 1.12 mmol/L (1.1–1.35), total calcium — 2.23 mmol/L (2.2–2.65), PTH — 35.2 pg/mL (12–88), 25-(OH)-D — 35.94 ng/mL (30–100)).

In the described clinical case, the first sign of PHPT in a young woman was tooth problems. In the next 8 years, the progression of the disease caused a predominant lesion of the skeletal system with the development of epulis and severe osteoporosis with multiple fractures, as well as severe myopathy and cachexia. The patient was examined by a number of specialists — general practitioner, dentist, traumatologist, oncologist, and endocrinologist. Nevertheless, the disease was diagnosed at the stage of severe complications. Focal thyroid formation, which was detected in 2015 based on ultrasound results, was interpreted as a thyroid node. This, in particular, was due to the insufficient analysis of the clinical picture. The presented observation indicates the urgent need for attention to PHPT in educational programs, as well as the need to adopt state programs to address the problem of PHPT in Russia. Biochemical screening of the adult population will allow to determine the prevalence of PHPT, to diagnose it at an early stage, to identify the main risk factors for this disease and to develop preventive measures.

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