DOI: 10.20514/2226-6704-2025-15-6-443-451
УДК [616-008.9-06:616.447-006.6]-07
EDN: CKMHFO

В.Н. Ларина, Е.В. Кудина, Д.С. Амирян, Е.Н. Шерегова, К.А. Замятин, Л.А. Корсаева

Кафедра поликлинической терапии лечебного факультета ФГАОУ ВО «РНИМУ им. Н.И. Пирогова Минздрава России», Москва, Россия

НЕСВОЕВРЕМЕННОСТЬ ДИАГНОСТИКИ РАКА ПАРАЩИТОВИДНОЙ ЖЕЛЕЗЫ НА ФОНЕ ДЛИТЕЛЬНО СУЩЕСТВУЮЩЕЙ ГИПЕРКАЛЬЦИЕМИИ

V.N. Larina, E.V. Kudina, D.S. Amirian, E.N. Sheregova, K.A. Zamyatin, L.A. Korsaeva

Department of Outpatient Medicine, Pirogov Russian National Research Medical University, Moscow, Russia

Untimeliness of Diagnosis of Parathyroid Cancer on The Background of Long-Term Hypercalcemia

Резюме

Гиперкальциемия представляет собой нарушение минерального обмена, возникающее, как правило, в результате повышения функции паращитовидных желез с развитием гиперпаратиреоза. Данное состояние могут спровоцировать различные факторы, например, развитие доброкачественной гиперплазии паращитовидных желез, облучение, употребление определенных лекарственных препаратов, снижение уровня кальция в организме, патология со стороны почек, а также нарушение функции паращитовидных желез и другие. Сложность диагностики данной патологии обусловлена как редкой встречаемостью, так и отсутствием патогномоничной симптоматики. Клинические проявления гиперкальциемии многообразны и проявляются патологией желудочно-кишечного тракта, нервной системы, а также развитием мочекаменной болезни и остеопорозом. Важность своевременного диагностирования гиперкальциемии обусловлена не только необходимостью улучшить качество жизни пациента и предотвратить развитие осложнений, но и возможностью раннего выявления наиболее грозной причины гиперпаратиреоза — рака паращитовидных желез. В статье обсуждается история болезни пациента 46 лет, отражающая позднюю диагностику гиперкальциемии и развитие рака паращитовидной железы, несмотря на длительно существующие клинические проявления гиперкальциемии и стойкие отклонения лабораторных показателей с повышением уровня щелочной фосфатазы; свободного и ионизированного кальция. Сделан акцент на проявлениях гиперкальциемии, которые должны были насторожить врачей и направить диагностический поиск в правильное русло. Подчеркивается важность тщательного сбора анамнеза и интерпретации каждого клинического проявления.

Ключевые слова: *гиперкальциемия злокачественных новообразований, паратиреоидный гормон, паращитовидные железы, кальций*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

Пациент дал согласие на опубликование данных лабораторных и инструментальных исследований в статье «НЕСВОЕВРЕМЕННОСТЬ ДИАГНОСТИКИ РАКА ПАРАЩИТОВИДНОЙ ЖЕЛЕЗЫ НА ФОНЕ ДЛИТЕЛЬНО СУЩЕСТВУЮЩЕЙ ГИПЕРКАЛЬЦИЕМИИ» для журнала «Архивъ внутренней медицины», подписав информированное согласие

Статья получена 27.05.2024 г.
Одобрена рецензентом 29.05.2025 г.
Принята к публикации 08.07.2025 г.

Для цитирования: Ларина В.Н., Кудина Е.В., Амирян Д.С. и др. НЕСВОЕВРЕМЕННОСТЬ ДИАГНОСТИКИ РАКА ПАРАЩИТОВИДНОЙ ЖЕЛЕЗЫ НА ФОНЕ ДЛИТЕЛЬНО СУЩЕСТВУЮЩЕЙ ГИПЕРКАЛЬЦИЕМИИ. Архивъ внутренней медицины. 2025; 15(6): 443-451. DOI: 10.20514/2226-6704-2025-15-6-443-451. EDN: CKMHFO

Abstract

Hypercalcemia is a disorder of mineral metabolism that typically arises due to increased parathyroid gland function, leading to hyperparathyroidism. This condition can be triggered by various factors, such as the development of benign parathyroid hyperplasia, radiation exposure, the use of certain medications, decreased calcium levels in the body, renal pathology, impaired parathyroid gland function, and others. The complexity of diagnosing this condition is attributed to its rare occurrence and the absence of pathognomonic symptoms. The clinical manifestations of hypercalcemia are diverse and include gastrointestinal and nervous system disorders, as well as the development of urolithiasis and osteoporosis. The importance of timely diagnosis of hypercalcemia lies not only in the need to improve the patient's quality of life and prevent complications but also in the early detection of the most severe cause of hyperparathyroidism—parathyroid cancer. This article discusses the case history of a 46-year-old patient, illustrating the delayed diagnosis of hypercalcemia and the development of parathyroid cancer despite long-standing clinical manifestations of hypercalcemia and persistent laboratory abnormalities, including elevated levels of alkaline phosphatase, free and ionized calcium. The clinical case analysis emphasizes the manifestations of hypercalcemia that should have alerted clinicians and guided the diagnostic process in the right direction. The importance of thorough history-taking and the interpretation of each clinical manifestation is underscored.

Key words: *hypercalcemia of malignant neoplasms, parathyroid hormone, parathyroid glands, calcium*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article « Untimeliness of Diagnosis of Parathyroid Cancer on The Background of Long-Term Hypercalcemia» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

Article received on 27.05.2024
Reviewer approved 29.05.2025
Accepted for publication on 08.07.2025

For citation: Larina V.N., Kudina E.V., Amirian D.S. et al. Untimeliness of Diagnosis of Parathyroid Cancer on The Background of Long-Term Hypercalcemia. The Russian Archives of Internal Medicine. 2025; 15(6): 443-451. DOI: 10.20514/2226-6704-2025-15-6-443-451. EDN: CKMHFO

IL — Interleukin, PTHrP — parathyroid hormone-related protein, HCM — hypercalcemia of malignancy, M — malignancy, PTH — parathyroid hormone, PTG — parathyroid gland, US — ultrasound diagnosis, ALP — alkaline phosphatase

Introduction

Parathyroid gland (PTG) cancer is a rare sporadic or hereditary endocrine malignancy (M) encountered in <1 % of primary hyperparathyroidism cases, characterized by the impaired calcium-phosphorus metabolism, affecting other organs and systems [1, 2].

Hypercalcemia is detected in approximately 1 % of the global population, and in 90 % cases it is associated with Ms [3, 4].

Hypercalcemia of malignancy (HCM) is a condition accompanied by enhanced mortality, which is the most common metabolic complication of malignancies [5].

In tumors hypercalcemia is most likely associated with the increased bone resorption and calcium release with subsequent hypercalcemia-induced renal injury [6].

Hypercalcemia is confirmed with calcium levels over 10.5 mg/dL and is a relatively common issue, which always reflects the underlying disease [3, 6].

Mechanisms of hypercalcemia

Four main hypercalcemia mechanisms have been described:

1. Excessive synthesis of extrarenal 1,25[OH]2D.
2. Humoral HCM.
3. Local osteolytic hypercalcemia with the secretion of other humoral factors associated with increased calcium levels in blood.
4. Ectopic PTH production.

Primary hyperparathyroidism.

In 80 % cases, primary hyperparathyroidism emerges due to the benign hyperplasia (adenoma) of a single parathyroid gland, in 20 % — due to that of two-three glands, while four glands are affected in rare situations. This leads to excessive PTH secretion. This condition in <1 % cases is associated with the PTG cancer both in males and females.

Secondary hyperparathyroidism.

This condition develops if such pathologies as hypocalcemia or chronic kidney disease provoke the increased PTH secretion by parathyroid glands.

Tertiary hyperparathyroidism.

The function of parathyroid glands transforms to the autonomous PTH production which is independent of exogenous stimulation is called tertiary hyperparathyroidism.

Clinical manifestations

HCM symptoms emerge with the total calcium levels over 3.0 mmol/L and are non-specific; however, their manifestations directly depend on the disease severity, calcium levels, presence or absence of bony metastases [5].

Depending on calcium levels, hypercalcemia is divided into:

- mild, with serum calcium levels <10.5-12 mg/dL [3 mmol/L];
- moderate, with Ca levels 12.1–14 mg/dL [3–3.5 mmol/L];
- severe, with Ca levels >14 mg/dL [>3.5 mmol/L] [4, 5, 7].

Cardiovascular clinical manifestations of hypercalcemia depend not just on calcium levels in blood, but also on concomitant diseases. If calcium levels increase to 3.2–3.4 mmol/L, automatism may decrease, while ventricular systole may shorten.

With calcium levels over 3.3 mmol/L, QT interval shortens; atrioventricular block may develop at levels of 3.3–4.0 mmol/L; the risk of sudden cardiac death increases with levels over 4.0 mmol/L. Ventricular fibrillation, bradyarrhythmia, hypertension may develop in patients.

Psychoneurological disorders include fatigue, malaise, apathy, hyporeflexia, muscle weakness with paresis and paralysis, headache, seizures, perception and behavior disorders, signs of subcortical edema, sopor, coma. As neurological disorders progress, polyuria and polydipsia lead to dehydration, renal failure, progressive urolithiasis with nephrocalcinosis and nephrolithiasis.

Such dyspeptic signs as nausea, vomiting, constipation, may lead to anorexia, peptic ulcer disease, or bowel obstruction. Non-specific manifestations also include skin itching and ossalgia [2, 6].

Diagnosis

During the primary examination, the serum calcium level (total physiologically inactive transporter-bound calcium and active ionized calcium) is determined. However, increased calcium levels require repeated confirmation, clarifying the total and ionized calcium levels. In this case one has to account factors that affect the interpretation of results, including serum albumin and blood pH. If the albumin level is abnormal, the serum calcium level should be adjusted using the following equation:

$$\text{Corrected calcium} = \text{total calcium} + [0.8 \times (4.0 - \text{albumin})].$$

PTH and PTHrP are measured subsequently — their levels do not increase simultaneously, except if more than one cause can be detected. Hypophosphatemia, hyperchloremia, and mild metabolic alkalosis are possible with high PTH levels against the background of hypercalcemia. If PTHrP levels decrease, 1.25-dihydroxyvitamin D levels are measured. Hypercalcemia with the detected low PTH, PTHrP, and 1.25[OH]2D levels along with bony metastases may be considered a cause of HCM.

Imaging methods are not mandatory in primary hyperthyroidism, however they provide information about the location of gland lesions for further surgical interventions. Densitometry is also used to assess the mineral bone density.

Parathyroid cancer

The incidence of PTG cancer does not depend on the gender, unlike primary hyperthyroidism, where the female-to-male ratio of the disease incidence is 3–4:1; no ethnic predisposition has also been described. The disease onset is approximately at the age of 50 (as of the diagnosis) [8–10].

Clinical manifestations

PTG cancer in the majority of cases is represented by the functioning tumor with typical hypercalcemia signs. In PTGMs, the most common symptoms include bony and renal ones: polyuria, polydipsia, urolithiasis manifestations (renal colics), ossalgia, pathological fractures [8, 11].

In very rare situations PTG cancer may manifest with the non-functioning tumor, normocalcemia, and a palpable neck lesion, which is often detected late due to diagnostic difficulties. This tumor type tends to metastasize to various locations, including cervical lymph nodes, bones, liver, and lungs [8].

Diagnosis

Due to dehydration and nephrolithiasis and/or nephrocalcinosis against the background of hypercalcemia and increased serum PTH levels, the glomerular filtration rate decreases.

In outpatient practice, the biochemistry panel is feasible to detect increased alkaline phosphatase levels (determining the severity of skeletal lesions) and human chorionic gonadotropin levels, especially its hyperglycosylated isoform [9, 11].

The ultrasound (US) is primarily arranged to diagnose PTG cancer — this can reveal large-sized lesions (>3.0 cm), irregular homogeneity with decreased echogenicity, signs of degeneration (cystic cavities, calcifications, irregular borders). US is also used to exclude the lymph node lesions (with subsequent biopsy if necessary).

Contrast-enhanced computed tomography is arranged to clarify the location of lesions.

Magnetic resonance imaging helps to assess the condition of soft tissues in the neck for the possible diagnosis of ectopic glands and to determine the relations to the surrounding structures.

The enhanced glucose metabolism is typical in malignant cells due to a large amount of transporter proteins. Thus, positron emission tomography with fluorodeoxyglucose is used as a highly informative method that can easily evaluate primary tumors; however, micrometastatic lesions sized <6 mm may be missed. The PTG tumor aggression is associated with the standardized uptake values [8, 11].

[99mTc]-technetium scan is arranged to determine the primary location of the malignancy and to detect metastatic lesions. However, such scans are not very informative in the differential diagnosis of benign and malignant neoplasms [11, 12].

Signs of PTGMs with atypical cytological and architectural features include cellular nests in the fibrous septum, significant tissue fibrosis, tumor cells detected in the tumor capsule or suspected invasion, cytological atypia manifesting with mitotic activity >5/10 mm^2 or Ki-67 proliferation index >5 % [8, 9, 11, 12].

The molecular-genetic testing (along with immunohistochemistry) is recommended in patients with the verified PTG cancer to exclude germinal mutations in the CDC73 gene [13].

Despite the sufficient diagnostic investigations for PTGMs, one should note that primary care physicians do not often provide adequate cancer alertness due to such factors as overwork, shortage of staff, limited visit time.

The clinical case described below presents a 46-year-old patient followed up by the general practitioner since 2014; it specifically demonstrates the importance of checking and thoroughly analyzing all clinical and laboratory manifestations of a specific disease, which is especially important in the diagnosis of diseases rarely occurring in the regular practice of the general practitioner.

In January 2017, the patient attended the general practitioner complaining of epigastric pain, abdominal bloating, heartburn, dark stools for 2 months during the administration of bismuth tripotassium dicitrate. Gastroscopy was arranged: superficial gastritis with moderate bulbitis was detected. Based on the patient's words, the duodenal ulcer was diagnosed; however, no documents confirming the diagnosis were provided. Colonoscopy confirmed the hypertonic dyskinesia, while no organic diseases were detected. Hepatobiliary US: hepatomegaly, signs of fatty liver. Blood tests demonstrated moderately elevated transaminases (ALT 79 U/L, AST 81 U/L (N <40 U/L)), hypercholesterolemia (total cholesterol 7.1 mmol/L; N 3.4–6 mmol/L), elevated ESR (77 mm/h; N 1–30 mm/h). The patient was counseled by the gastroenterologist. Diagnosis: chronic superficial gastritis, chronic duodenitis (exacerbation), steatohepatitis, irritable bowel syndrome without diarrhea. Diet, proton pump inhibitors, enzyme preparations, and probiotics were recommended.

While collecting history, the gastroenterologist noted urolithiasis, which was diagnosed earlier, but not clarified in the general practitioner examination.

In 2018 the patient was hospitalized three times (in January, April, and May) due to recurrent renal colics.

The medical chart contained the renal US investigation dated May 2021: no pathology detected.

In December 2018, a routine fracture (due to fist-fighting) was confirmed, followed by a 3-week immobilization.

On May 30, 2019, the patient visited the general practitioner complaining of tremor in the left leg, stiffness, and worsening vision, progressing within six months. The neurologist counseling was recommended.

On June 6, 2019, the patient was counseled by the neurologist. While collecting history, the patient noted that tremor started at the age of 20 and developed during excitation, although it worsened within the preceding years. Weakness, memory lapse also emerged and progressed. After examination, the following preliminary diagnosis was established: "Unspecified extrapyramid and motor disorder. Episyndrome". A 2-month cycle of gopantenic acid and ethylmethylhydroxypyridine succinate treatment was administered. The patient was referred to the Center of Extrapyramidal Diseases of S.P. Botkin CCH; however, the counseling was not arranged due to personal patient circumstances.

When the patient returned to the general practitioner, the following abnormalities were detected in the biochemistry panel (total and ionized Ca — 3.2/1.43 mmol/L (N 2.2–2,65/0.9–1.38 mmol/L); phosphorus — 0,72 mmol/L (N 0.87–1.45 mmol/L); alkaline phosphatase (ALP) — 405 U/L (N 30–120 U/L); glucose — 8 mmol/L). The patient was referred to the endocrinologist.

Visiting the endocrinologist on September 6, the patient complained of a glomus sensation in the throat, frequent urination, burning sensation in feet. The preliminary diagnosis of impaired glucose tolerance was established, however upon subsequent follow-up the glucose level was not elevated, and HbA1c level was

within normal limits (5.3 %). The diagnosis of impaired glucose tolerance was not confirmed, no additional investigations were arranged.

The patient was also counseled again by the neurologist with extra examinations. Electroencephalography demonstrated altered bioelectrical brain activity of irritative origin. The patient was again referred to the Center of Extrapyramidal Diseases of S.P. Botkin CCH.

Subsequently the patient was followed up personally by a private neurologist, and based on word, Parkinson's disease was diagnosed, however no documental confirmations were presented.

In 2020 the patient did not visit the polyclinics.

He visited the general practitioner on April 29, 2021 complaining of dizziness, frequent headaches. The examination revealed persistent hypertension, and essential hypertension was diagnosed; amlodipine 5 mg was administered as hypotensive treatment. The patient was subjected to regular monitoring.

During such monitoring, biochemistry panels revealed persistent elevation of ALP levels, moderate (no negative changes) elevation of transaminase levels, mild elevation of gamma-glutamyl transferase levels, gradually increasing creatinine levels.

In August 2023, the patient visited the general practitioner complaining of neck and leg pain, myalgias worsening after physical exertion, numbness in arms, weakness, morning stiffness, hand tremor. Laboratory tests revealed decreased vitamin D (6.44 ng/mL; N 30–70 ng/mL) and inorganic phosphorus levels (0.81 mmol/L; N 0.87–1.45 mmol/L), increased creatinine (127 μmol/L; N 61–120 μmol/L, glomerular filtration rate 57 mL/min/1.73 m^2), ionized Ca (1,49 mmol/L), total Ca (3.24 mmol/L), PTH levels (58.21 mmol/L; N 1.48–7.63 mmol/L). The patient was referred to TG and PTG US followed by the endocrinologist counseling with suspected hyperparathyroidism. TG and PTG US demonstrated focal lesions: almost the whole left lobe was represented by an hypoechoic nodule sized 52x30 mm with a non-uniform structure and a fluid component (14 mm), with a significant blood flow of mixed type; regional lymph nodes were normal. Conclusion: right lobe — TI-RADS1; left lobe — TI-RADS4 (node over 1 cm in size). Based on the data obtained, the endocrinologist established the diagnosis: "Hyperparathyroidism (not otherwise specified). Grade 2 multinodular goiter". With the preliminary diagnosis "Thyroid neoplasm of undetermined or unknown origin. Cytology signs suspicious of Ms", the patient was referred to the oncologist.

To determine the mineral bone density, X-ray densitometry was conducted: T-test = -2.7 standard deviations at the level of L1-L4 vertebrae (i.e. osteoporosis); T-test = -1.7 standard deviations at the level of right and left femoral necks (i.e. osteopenia).

It should be noted that body weight (92 kg) and height (178 cm) did not change during the whole follow-up period. No gait disorders were observed as well.

In September 2023, the patient underwent an outpatient fine-needle aspiration biopsy (FNAB), with the result of nuclear atypia (Grade III. The Bethesda System for Reporting Thyroid Cytopathology). In October, after the repeated FNAB of the nodule in the left thyroid gland lobe, the oncologist established the diagnosis "Thyroid neoplasm of undetermined or unknown origin", which was followed by the videoassisted minimally invasive thyroidectomy, nerve-sparing cervical lymph node dissection (Level VI). The following main diagnosis was established: "Thyroid gland M. Papillary thyroid cancer, Grade 1a, Stage 1. Neoplastic process stage 1, clinical group IIa". The histology of the surgical material confirmed the focus of the malignant clear-cell malignancy with focal doubtful vascular invasion and invasion into structures of displaced PTG lobules.

After receiving the histology results of both lobes of the excised thyroid gland (Left lobe sized 5.3x4x3 cm. Its section demonstrated total substitution with a dense-elastic grayish nodule, containing a cystic cavity 1.5 cm in diameter), the following main diagnosis was established: "Clear-cell carcinoma of the left parathyroid gland. Condition after surgery on October 10, 2023". During the postoperative period, the patient's general condition significantly improved (weakness and tremor decreased; paresthesia and dyspeptic signs disappeared). The calcium level normalized soon after the surgery. Normocalcemia has been preserved for a year after the surgery.

The patient history steps from the emergence of first symptoms until the diagnosis and surgery are presented in the Figure 1.

Currently the patient is monitored by the oncologist and endocrinologist. Diagnosis: postoperative hypothyroidism, hypoparathyroidism. Accounting for no metastatic tumor spread and its complete surgical removal, the favorable clinical outcome is highly possible in our patient; however, untimely hypercalcemia detection could lead to a partially irreversible pathology (mainly neurological), which could significantly worsen the quality of life. The patient is subject to lifelong follow-up with regular medical examinations to prevent complications, detect recurrencies and disease progression, and to correct the treatment timely.

Discussion

Hypercalcemia is a rather rare pathology in the outpatient physician practice, which leads to its late detection due to low physician awareness. The complexity of diagnosing this mineral disorder is associated with the absence of pathognomonic signs and variable clinical

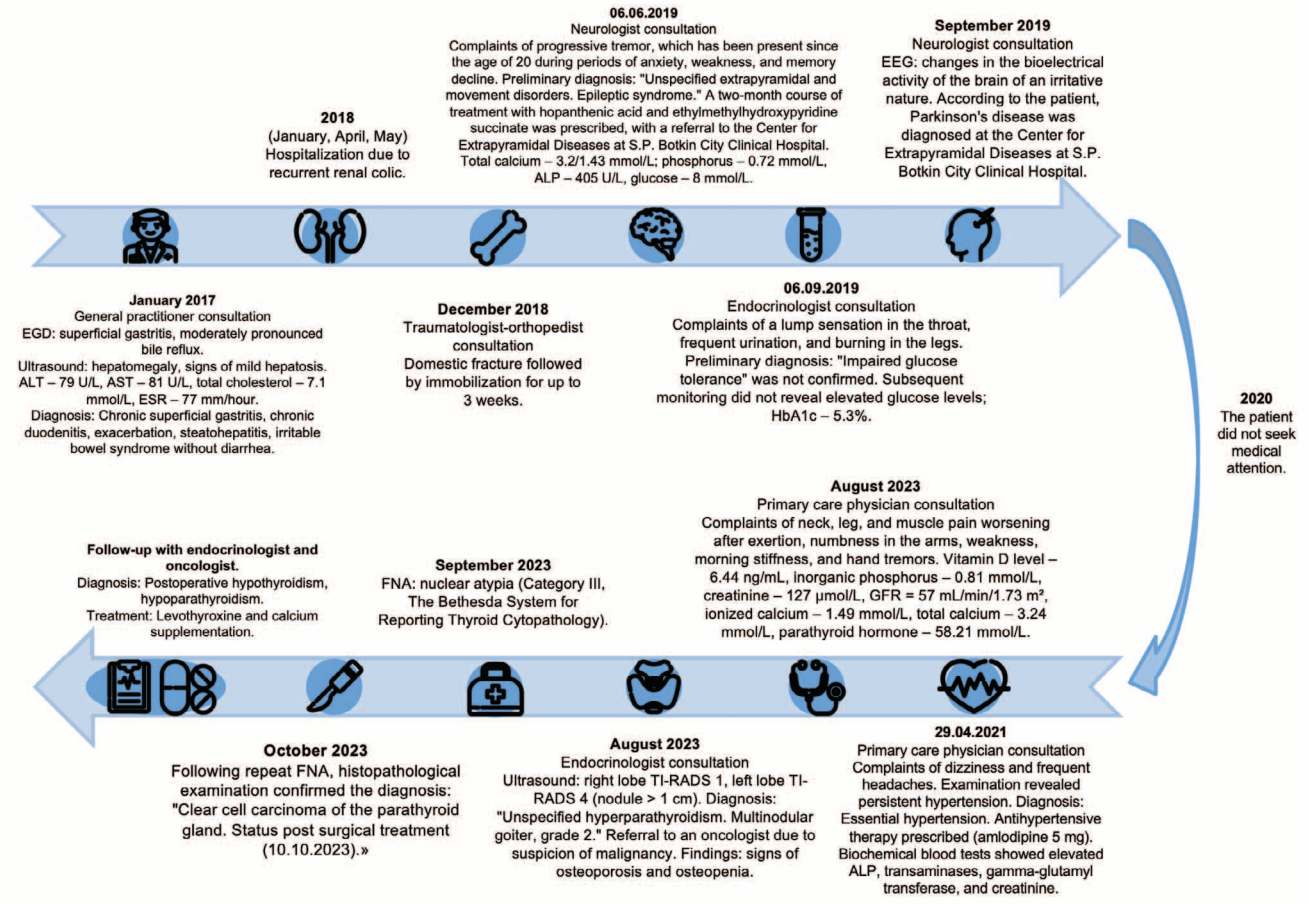

Figure 1. *Timeline of clinical follow-up in a patient with parathyroid carcinoma.*

manifestations, with each potentially representing a separate disease. Such patients may be followed by various physicians with such diagnoses as "Urolithiasis", "Chronic gastritis/Peptic ulcer disease", "Essential tremor", which was demonstrated in the clinical case above.

Parathyroid malignancies are the most rare cause of hypercalcemia; thus, the description of such cases is very interesting for practicing physicians. Although this disease is slowly progressive, the diagnosis in the majority of patients is not established for a long time, which leads to metastases (25 % cases) and severe hyperparathyroidism. Case histories of 15 patients that underwent surgeries due to PTGMs were analyzed by specialists of the National Medical Research Center of Radiology, Ministry of Health of Russia. Metastases were detected at the time of surgery in 3 patients, severe osseous form of hyperparathyroidism — in 6 patients, nephrolithiasis — in 9 patients, thus demonstrating late diagnosis of this disease [14].

PTG tumors may develop as part of various syndromes. Multiple endocrine neoplasia (MEN) syndrome is an example — this emerges due to genetic mutations. PTG hyperplasia or adenomas are reported most frequently. PTG malignancies in this syndrome are very rare, which explains their late detection. Due to this, a description of 2 clinical cases of PTG carcinomas in patients with the MEN syndrome is of a significant interest [15].

The diagnosis of PTG tumors developing against the background of a pre-existing secondary hyperparathyroidism may be challenging. Cases of PTGMs have been reported in patients with secondary hyperparathyroidism against the background of a long-standing CKD C4 [16, 17].

Intrathyroid PTG lesions form another serious diagnostic issue, requiring thorough assessment of calcium and PTH levels [18].

Our patient had a combination of several pathologies, with each of those potentially caused by the calcium metabolism disorders. Prolonged dyspeptic disorders not eliminated by treatment, frequently relapsing renal colics, low-energy fractures, tremor may be manifestations of specific diseases themselves; however, their combination should alert the physician, forming the basis for targeted examination with the purpose of detecting hypercalcemia.

Progressive elevation of ALP levels over several years is significant — this was interpreted as a manifestation of steatohepatitis by physicians. However, one should remember that elevated ALP levels may be a sign of not just cholestasis, but osteoporosis as well, which requires additional examinations. Persistently elevated ALP levels against the background of GGT levels in the reference range more likely suggests osteoporosis rather than cholestasis [9, 11].

In 2019 the following laboratory deviations were detected in a patient: Ca (total) — 3.2 mmol/L, Ca (ionized) — 1.43 mmol/L, P — 0.72 mmol/L, ALP — 405 U/L (with tremor worsening). However, these laboratory alterations were left unnoticed by physicians: the calcium level was not monitored, PTG examinations were not arranged. Meanwhile, neither the general practitioner nor the endocrinologist stressed out hypercalcemia, with the latter one assessing the patient due to the detected hyperglycemia.

Thus, the diagnosis of hypercalcemia could be established quite early, as the alerting combination of clinical manifestations emerged already in 2018, while increased total and ionized calcium levels were reported in 2019. At that moment, the following tests were necessary: serum PTH levels, PTG examination (US and technetium [99mTc]/sestamibi scan), densitometry for bone density evaluation [14].

While analyzing this clinical case, one should pay attention of primary care physicians to the importance of correct interpretation and formulation of clinical diagnoses. In 2021, the patient was diagnosed with essential hypertension. However, he already had long-standing urolithiasis. Thus, hypertension should have been evaluated as a secondary (symptomatic) one. The patient with urolithiasis should also have his chronic kidney disease noted with the stage, especially when in 2023 the glomerular filtration rate decreased to 57 mL/min/1.73 m^2 (corresponding to CKD C3) — that required the mandatory administration of nephroprotective agents (renin-angiotensin-aldosterone system blockers). Thus, the patient should have his hypotensive treatment corrected with the addition of an angiotensin-converting enzyme inhibitor to amlodipine.

Using the clinical case above as an example, one can define several important points for the algorithm of diagnosing the disease without clear pathognomonic symptoms.

1. Each clinical manifestation should be assessed not just as a sign of a specific disease, but also as a part of a common pathological process.
2. Every laboratory deviation should be analyzed, with clarifying investigations and further follow-up arranged.
3. The patient should be counseled by specialists (even with consilium) with the atypical disease course, if the treatment administered has no effect. An independent literature search and continuous medical self-education form an inseparable part of a smart patient management.

Conclusion

This clinical case represents an example of a complex and long path to the diagnosis “Parathyroid gland cancer. Secondary parathyroidism”, while its uniqueness lies in the prolonged course of an undiagnosed hypercalcemia along with a slowly developing PTGM. The discussed case demonstrates the necessary comprehensive evaluation of all patient pathologies, analysis of associations of various diseases (not related at first glance), and thorough attention to all deviations detected during the physical, laboratory, and instrumental patient examinations.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Ларина В.Н.: разработка концепции и дизайна рукописи, анализ и интерпретации данных, редактирование текста, проверка критически важного интеллектуального содержания, окончательное утверждение рукописи для публикации, ответственная за все аспекты работы

Кудина Е.В.: анализ и интерпретации данных, проверка критически важного интеллектуального содержания, окончательное утверждение рукописи для публикации, подготовка текста рукописи, ответственная за все аспекты работы

Амирян Д.С.: обзор публикаций по теме статьи, интерпретация данных, подготовка текста рукописи, работа с литературой, ответственная за все аспекты работы

Шерегова Е.Н.: обзор публикаций по теме статьи, сбор, анализ и интерпретация данных, организационное и ресурсное обеспечение публикации, ответственный за все аспекты работы, итоговые выводы, окончательное утверждение рукописи для публикации

Замятин К.А.: сбор, анализ и интерпретация данных, ответственный за все аспекты работы, окончательное утверждение рукописи для публикации

Корсаева Л.А.: сбор, анализ и интерпретация данных, ресурсное обеспечение публикации, ответственный за все аспекты работы, окончательное утверждение рукописи для публикации

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Larina V.N.: development of the concept and design of the manuscript, analysis and interpretation of data, editing the text, checking for critical intellectual content, final approval of the manuscript for publication, responsible for all aspects of the work

Kudina E.V.: analysis and interpretation of data, checking for critical intellectual content, final approval of the manuscript for publication, preparation of the manuscript text, responsible for all aspects of the work

Amiryan D.S.: review of publications on the topic of the article, data interpretation, preparation of the manuscript text, work with the literature, responsible for all aspects of the work

Sheregova E.N.: review of publications on the topic of the article, collection, analysis and interpretation of data, organizational and resource support for publication, responsible for all aspects of the work, final conclusions, final approval of the manuscript for publication
Zamyatin K.A.: collection, analysis and interpretation of data, responsible for all aspects of the work, final approval of the manuscript for publication
Korsayeva L.A.: collection, analysis and interpretation of data, resource support for publication, responsible for all aspects of the work, final approval manuscripts for publication

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Информация об авторах

Ларина Вера Николаевна — доктор медицинских наук, профессор, заведующий кафедрой поликлинической терапии лечебного факультета ФГАОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» Минздрава России (Пироговский Университет), Москва, email: larinav@mail.ru, ORCID ID: https://orcid.org/0000-0001-7825-5597
Кудина Екатерина Владимировна — кандидат медицинских наук, доцент, доцент кафедры поликлинической терапии лечебного фа-

культета ФГАОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» Минздрава России (Пироговский Университет), Москва, email: e-kudina@mail.ru, ORCID ID: https://orcid.org/0000-0002-9547-078X

Амирян Диана Севаковна — студент ФГАОУ ВО ФГАОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» Минздрава России (Пироговский Университет), Москва, email: diasha.am1234@gmail.com, ORCID ID: https://orcid.org/0000-0001-5005-1461

Шерегова Елена Николаевна — кандидат медицинских наук, доцент кафедры поликлинической терапии лечебного факультета ФГАОУ ВО ФГАОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» Минздрава России, (Пироговский Университет), Москва, email: esheregova@list.ru, ORCID ID: https://orcid.org/0000-0001-9991-546X

Замятин Кирилл Александрович — аспирант кафедры поликлинической терапии лечебного факультета ФГАОУ ВО «Российский национальный исследовательский медицинский университет им. Н.И. Пирогова» Минздрава России, (Пироговский Университет), Москва, email: kazamiatin@gmail.com, ORCID ID: https://orcid.org/0000-0001-6271-228X

Корсаева Людмила Алексеевна — врач общей практики, ДКЦ № 1, филиал 4, ДЗМ, Москва, email: Korsaevala@gmail.com, ORCID ID: https://orcid.org/0009-0004-2565-5039

Information about the authors

Vera N. Larina — M.D., professor, Department of Outpatient Medicine, Pirogov Russian National Research Medical University, Moscow, email: larinav@mail.ru, ORCID ID: https://orcid.org/0000-0001-7825-5597

Ekaterina V. Kudina — M.D., associate professor, Department of Outpatient Medicine, Pirogov Russian National Research Medical University, Moscow, email: e-kudina@mail.ru, ORCID ID: https://orcid.org/0000-0002-9547-078X

Diana S. Amirian — student of Pirogov Russian National Research Medical University, Moscow, email: diasha.am1234@gmail.com, ORCID ID: https://orcid.org/0000-0001-5005-1461

Elena N. Sheregova — associate professor, Department of Outpatient Medicine, Pirogov Russian National Research Medical University, Moscow, email: esheregova@list.ru, ORCID ID: https://orcid.org/0000-0001-9991-546X

Kirill A. Zamyatin — graduate student, Department of Outpatient Medicine, Pirogov Russian National Research Medical University, Moscow, email: kazamiatin@gmail.com, ORCID ID: https://orcid.org/0000-0001-6271-228X

Lyudmila A. Korsaeva — general doctor, DCC № 1, branch 4, Moscow Department of Health, Moscow, email: Korsaevala@gmail.com, ORCID ID: https://orcid.org/0009-0004-2565-5039

Автор, ответственный за переписку / Corresponding author