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GCM2 mutation in primary hyperparathyroidism - A Case Report

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Abstract

Primary hyperparathyroidism is a common endocrine disorder. It is characterised by elevated parathyroid hormone (PTH) level causing hypercalcemia. 90-95% of cases have a spontaneous cause, with the remaining 5-10% having a genetic basis. On routine examination, a 47-year-old patient was found to have hypercalcemia, vitamin D deficiency, normal PTH levels and no hypercalciuria. Despite vitamin supplementation, calcemia remained unchanged. Single photon emission computed tomography (SPECT) examination detected possible adenomas in the lower parathyroids regions, and ultrasound revealed an adenoma of the lower left parathyroid gland and hypertrophy of the lower right parathyroid gland. The atypical clinical presentation - young age, inadequate normal PTH levels and the location of the lesions within the two parathyroid glands suggested genetic testing, which confirmed the presence of a genetic mutation - the GCM2 variant. Treatment included exploration of the parathyroid area using fluorescence. Both lower parathyroid glands were dissected. PTH monitoring showed a decrease in baseline levels of more than 50% after surgery. One month after surgery, PTH and calcium levels remained normal. Primary hyperparathyroidism is usually asymptomatic, detected when laboratory tests are performed for another cause. Symptoms include nephrolithiasis, bone and joint pain, osteoporosis, arrhythmias and fatigue. The typical patient has high PTH levels and hypercalcemia, but not every case will be schematic. High serum calcium levels do not always result in increased PTH levels and an in-depth diagnosis is required. The GCM2 mutation, detected in the patient presented here, may occur in familial isolated hyperparathyroidism. Correct diagnosis and treatment is crucial not only for the patient, as it significantly improves their quality of life, but also for their family members, who may also have a genetic mutation and be unaware of the disorder developing in their body.

Keywords: Primary Hyperparathyroidism; parathyroid hormone; parathyroidectomy; Endocrine System Diseases

Introduction:

Primary hyperparathyroidism (PHPT) is a common disease characterised by an autonomous parathyroid hormone (PTH) secretion, classically resulting in hypercalcemia and high PTH level (1). The criteria for diagnosing the disease, along with subsequent scientific research in the field, have evolved over time. Depending on the cause of the pathology, we can observe a spectrum ranging from inappropriately high or even normal PTH level in the setting of high-normal or even normal calcium (2).

90-95% of cases of PHPT are sporadic, while the rest has a genetic cause (3). Among them single adenomas are responsible for 80-85% of cases, double adenomas occur with a frequency of 4%, the remaining 10-15% of cases are hyperplasias involving all four glands (3). Parathyroid cancer is a very rare cause of PTHP, reported in 1% of all patients (4). Regarding the genetic background of the disorder we can distinguish patients with familial hyperparathyroidism which represents 5% of all PTHP patients (4). Inherited PHPT may be may be part of a syndrome, such as in multiple endocrine neoplasia types 1, 2, and 4 (MEN1, 2, 4) and the hyperparathyroidism jaw-tumor syndrome (HPT-JT). It may also be nonsyndromic, which is also referred to as familial, isolated primary hyperparathyroidism (FIHP) (5). In 2016 germline activating mutations in the the glial cells missing 2 (GCM2) gene were associated with familial PHPT (1) and sporadic parathyroid tumors (1,6,7) or adenomas (8).

The classical symptoms of PHPT include nephrolithiasis, nephrocalcinosis (9), subperiosteal resorption, osteoporosis, osteopenia and pathologic fractures (10), neuromuscular symptoms such as muscle weakness, drowsiness and depression. Hypercalcemia affect also gastrointestinal and cardiovascular system (9). Currently, the majority of PHPT cases in many developed countries have become subtle or asymptomatic (9), with only about 20% of individuals presenting with nephrolithiasis or osteoporosis (11). Individuals are more often diagnosed today through routine blood testing done for other purposes. Although patients often do not present the classic symptoms, PHPT is associated with many non-specific complaints such as depression, anxiety, memory loss, fatigue, sleep problems, bone pains, myalgia, gastroesophageal reflux disease, and decreased concentration (3).

Case Report:

47-year old male with myotonic dystrophy was admitted for incidentally discovered asymptomatic PHPT into Department of General, Endocrine and Metabolic Surgery. He did not have other additional personal medical burdens. Hypercalcemia with calcium level of 2,80 mmol/L was discovered accidentally through a blood test and further laboratory investigations were performed. They revealed vitamin D deficiency (28 nmol/L), inappropriately normal PTH level (5,80 pmol/L) and unelevated level of calcium in urine (163 mg/dl/24h). Despite vitamin D supplementation an increase in vitamin D level to 91 nmol/L, calcium levels remained at 2,88 mmol/L. Subtraction parathyroid scintigraphy showed a region of hyperfixation in the medial part of the right and left mediolobar regions. Single photon emission computed tomography (SPECT) scan demonstrated two possible adenomas in the area of left and right inferior parathyroid glands. Given the result of the scintigraphy and SPECT study, which suggested the presence of pathological glands and the overall clinical picture, the decision to expand the diagnosis and perform an ultrasound scan was made. It showed enlarged thyroid gland with a right lobe estimated at 14,7 cm^3, isthmic thickness 4,5 mm and left lobe 8,3 cm^3. The thyroid was described as multinodular, with multiple cysts and nodules visualized in both lobes, classified as EU-TIRADS 2/3 (European thyroid image reporting and data system). Study of the parathyroid areas revealed an adenoma of the left inferior parathyroid gland measuring 13 mm x 3,9 mm x 7,33 mm and hyperplasia of the right inferior parathyroid gland measuring 9,7 mm x 2,8 mm x 7,2 mm, without abnormal vascularization. Atypical clinical picture and localization of pathological glands suggested performing a next-generation sequencing (NGS) genetic testing, which confirmed a presence of a GCM2-exon 5 variant 1181 A>C p.Tyr394Ser mutation, previously associated with the pathogenesis of the disease. A simultaneous assessment of the condition of other body systems was performed. An ECG was performed, which showed no abnormalities associated with hypercalcemia. A renal ultrasound also showed no pathology in this area. DXA (dual x-ray absorptiometry) scan was performed revealing mildly reduced bonemineral density with femoral T-score: -1,5 SD and lumbal vertebrae T-score: -0.8 SD.

Test	Result
Vitamin D level	28 nmol/L
PTH level	5.80 pmol/L
Calcium level	2.80 mmol/L
Urinary calcium	163 mg/dl/24h
ECG	Normal
Ultrasound of the abdomen	No abnormalities
DXA	Mildly reduced bone mineral density

Table 1. Pre-operative workup findings

Having regard to the whole clinical picture a decision was made that surgical bilateral exploration was required. The fact that surgical procedure required general anaesthesia and an initial anesthesia consultation to evaluate the assess operability was taken into consideration. It also remained to be seen what protocol should be envisaged for the different types of anesthetic products in relation to his primer disease - myotonic dystrophy. The patient was consulted to evaluate vocal cord mobility prior to surgical removal of bilateral parathyroid adenomas. Nasofiberoscopy showed hypomobility of the left vocal cord due to compression of the parathyroid adenoma, which could not be eliminated, but the context of Steinert's disease did not allow for a definitive diagnosis. The patient underwent a bilateral exploration of parathyroid glands with a use of Fluoptics - fluorescence imaging. Both inferior parathyroid glands were dissected out and analyzed histopathologically. The pathology result received a month later showed a parathyroid adenoma on the left inferior parathyroid gland measuring 600 mg (25x8x6 mm) and on the right inferior parathyroid gland 300 mg (8x6x4 mm) (parathyroid within normal limits). The adenoma was well-bounded, finely encapsulated of acinar architecture. Cells oxyphilic, nonomorphic, not atypical were found. No mitosis was detected. The adenoma was not lobulated by fibrous trabeculae, its capsule was not invaded. There was no adipose lobule within the nodule. Healthy parathyroid margin was reported. Postoperative genetic test confirmed the presence of the GCM2-exon 5 variant. PTH level monitoring was conducted during the operation showing a decrease of more than 50% of an initial level after the surgery (Table 2.). Calcemia and PTH levels were normalized postoperatively.

	Time	PTH level (pmol/L)
pre-operative	11:35	6,9
beginning of the surgery	12:10	16,6
pre-excision	13:04	22,3
post-excision (+5min)	13:09	14,7
post-excision (+35min)	13:40	7,1
post-excision (+45min)	13:50	5,9
postoperative (1 h post-surgery)	15:00	4,3
Postoperative (2 h post-surgery)	16:00	4,6

Table 2. PTH monitoring

The patient was advised to consult with the operating physician within a week of the procedure. It was recommended to check calcemia, PTH levels and vitamin D levels one month after the surgery. In the follow-up analysis, all results were normal - vitamin D 81 nmol/L, PTH - 4,2 pmol/L and calcemia - 2,51 mmol/L. Another follow-up blood test in 5 months was recommended as well as remaining under endocrinologists supervision. Due to the absence of a family history of parathyroid disease, it was recommended to consider diagnosis among the patient's relatives.

Discussion and Conclusions:

PHPT is mostly asymptomatic and discovered during a routine checkup. Symptoms may include nephrolithiasis or urolithiasis, kidney failure, bone pain, osteoporosis, arrhythmia, constipation, tiredness. The first step in diagnosing PHPH should be thorough blood and urine tests. Typical patient has a high level of parathyroid hormone and hypercalcemia. As in presented case, it may occur that high serum calcium level is not associated with increased levels of PTH and further diagnostics must be performed. Determination of PTH concentrations alone does not provide a complete explanation of the causes of the resulting disorders. As in our patient's situation, the entire calcium-phosphate metabolism should be assessed - total albumin-corrected calcium concentration, PTH concentration, phosphate concentration,

alkaline phosphatase activity, vitamin D level, general urine examination, urinary calcium and phosphate excretion. Vitamin D deficiency, hypophosphatemia and no hypercalciuria were detected in additional examinations of the patient. Despite vitamin supplementation, calcemia remained unchanged.

The patient should also be examined for systemic complications associated with hypercalcemia. Electrocardiography, imaging studies such as neck and abdominal ultrasound or scintigraphy are recommended, Positron Emission Tomography/Computerised Tomography (PET/CT) or Positron Emission Tomography/Magnetic Resonance Imaging (PET/MR) are also to be considered. Also frequently performed examinations include review radiographs and bone radiographs, as well as bone densitometry or ophthalmological examination. In our patient's case SPECT examination detected possible adenomas in the lower parathyroid region, and ultrasound revealed an adenoma of the lower left parathyroid gland and hypertrophy of the lower right parathyroid gland. An electrocardiography examination (ECG) did not reveal any arrhythmias or other abnormalities associated with hypercalcemia. An ultrasound examination did not show any pathology in the abdominal cavity. DXA (dual x-ray absorptiometry) scan was performer revealing mildly reduced bonemineral density. Attention should be paid to the patient's burdens and previous comorbidities (12). Family history should also be taken to check for the possibility of hereditary forms of PHPT, particularly MEN types 1 and 2A (12). If there is a family history of PHPT, especially in patients younger than 50 years of age, genetic testing for should be considered (3). The described patient, as mentioned above, did not present any symptoms related to hyperparathyroidism. His family history was also non-burdened. Atypical clinical features (young age, normal PTH, bilateral involvement) prompted genetic testing, which revealed a germline mutation in the GCM2 gene (p.Tyr394Ser).

GCM2 encodes a transcription factor whose expression is largely restricted to the parathyroid gland and subsequent PTH expression (13). It is located on human chromosome 6p24.2 and encodes a 506 aa transcription factor (1). GCM2 mutations can cause hypoparathyroidism or hyperparathyroidism (1). Most likely, one of the functions of GCM2 in parathyroid cells is to activate PTH (1) Patients who have the mentioned mutation are more likely to have multiglandular disease (14). Among the referred group, parathyroid cancer is more probable (14). Patients with the mutation have a lower chance of pharmacological cure of hyperparathyroidism and have to be reoperated with greater frequency than others (14).

It is important to remember that not every single patient will fit in to a well-known pattern. As in presented case, sometimes we might have some unexpected results and we should not hesitate to find their reason. Unusual symptoms or the complete absence of symptoms can make it much more difficult and delay a proper diagnosis. It is crucial for the health of patients to recognize disorders early, so as to protect them from developing negative consequences. Pathology of one organ, in this case the parathyroid glands, is linked through metabolic processes to most organs and systems functioning in the human body. Early detection of disease is particularly important for the treatment of cancer. As described in the article, patients burdened with GCM-2 mutations have a higher risk of developing them (14). In the case of inherited diseases, attention to all members of the patient's family is incredibly important. Self-awareness about genetic predisposition can allow for faster implementation of preventive measures and specialty care at an earlier stage.

Disclosure

Author's contribution

Conceptualization: Zuzanna Chmielowiec and Magdalena Pach; Methodology: Agnieszka Fugas and Natalia Wierzejska; Software: Karolina Smykiewicz; Check: Zuzanna Chmielowiec and Agnieszka Fugas; Formal analysis: Mariola Dziedzic and Aneta Michalczewska; Investigation: Magdalena Pach and Natalia Wierzejska; Resources: Justyna Dobrzańska; Data curation: Karolina Smykiewicz; Writing - rough preparation: Mariola Dziedzic and Alicja Partyka; Writing - review and editing: Zuzanna Chmielowiec, Agnieszka Nowak and Justyna Dobrzańska; Visualization: Alicja Partyka; Supervision: Natalia Wierzejska; Project administration: Aneta Michalczewska and Agnieszka Nowak; Receiving funding - no specific funding.

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Institutional Review Board Statement

Not applicable. The study was conducted in accordance with the Declaration of Helsinki. In accordance with the law in force in the Republic of Poland, case report retrospective studies do not require the opinion of consent of the Board of Bioethics Committee, as they are not a

medical experiment in which human organisms would be interfered with. For this reason, we did not seek the consent of the Commission. What is more, the results of the study did not affect the management of patients at any stage, so the above-mentioned procedure was followed.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflict of interest

The authors deny any conflict of interest.

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