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# Parathyroid carcinoma as a preoperative diagnostic dilemma – a case report and review of the literature*

## Rak przytarczycy jako przedoperacyjny dylemat diagnostyczny – opis przypadku i przegląd piśmiennictwa

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**ABSTRACT**

**Introduction**: Parathyroid carcinoma is the least common endocrine-related malignancy and accounts for less than 1% of all cases of primary hyperparathyroidism. In comparison to benign parathyroid adenoma, the clinical signs (including the presence of a tumour with regional or distant nodal involvement), biochemical abnormalities and metabolic activity are usually more expressed in parathyroid carcinoma. In the presented case report, there were no typical signs and symptoms suggesting the preoperative diagnosis of parathyroid carcinoma.

**Case report**: The case was a 52-year-old woman with a history of recurrent renal stones, moderate hypertension, increased total and ionized calcium, low phosphorus, and increased intact parathyroid hormone. The clinical picture and imaging techniques (ultrasonography and SPECT/CT scintigraphy) suggested parathyroid adenoma. However, histological examination of the removed tumour revealed parathyroid carcinoma. Reoperation showed no regional lymph nodes involvement. After 12 months, normalisation of biochemical parameters and reduction of blood pressure from moderate grade to mild hypertension grade was achieved.

**Conclusions**: 1. In patients with parathyroid carcinoma-associated hyperparathyroidism, successful surgical treatment not only restores serum calcium, phosphorus and parathyroid hormone levels, but may also improve blood pressure control. 2. Parathyroid carcinoma may demonstrate faint metabolic activity in the SPECT/CT study, and its biochemical secretion of parathyroid hormone may be placed in ranges more characteristic for benign parathyroid pathology.

**Keywords:** parathyroid neoplasms; primary hyperparathyroidism; radionuclide imaging; ultrasonography; surgery; blood pressure.

**ABSTRAKT**

**Wstęp**: Rak przytarczycy jest jednym z rzadziej występujących nowotworów układu endokrynnego i odpowiada za mniej niż 1% wszystkich przypadków pierwotnej nadczynności przytarczyc. W porównaniu do zmian łagodnych, objawy kliniczne (m.in. obecność guza z zajęciem okolicznych węzłów chłonnych lub odległych przerzutów), parametry biochemiczne i aktywność metaboliczna raka przytarczycy są z reguły bardziej widoczne. W przedstawionym przypadku nie było objawów, które uzasadniałyby przedoperacyjne rozpoznanie raka przytarczycy.

**Opis przypadku**: Przedstawiono przypadek 52-letniej pacjentki z nawrotowa kamicą nerkową, umiarkowanym nadciśnieniem tętniczym, podwyższonym stężeniem wapnia całkowitego i zjonizowanego, niskim stężeniem potasu i podwyższonym poziomym kompletnego parathormonu. Obraz kliniczny i badania obrazowe (badanie ultrasonograficzne, scyntygrafia SPECT/CT) wskazywały na gruczolaka przytarczycy, jednakże za pomocą badania histopatologicznego usuniętej zmiany wykazano raka przytarczycy. Podczas reoperacji nie stwierdzono zajęcia okolicznych węzłów chłonnych. Uzyskano normalizację parametrów biochemicznych i redukcję nadciśnienia tętniczego z umiarkowanego do łagodnego stopnia podczas rocznej obserwacji chorej.

**Wnioski**: 1. U pacjentów z pierwotną nadczynnością przytarczyc spowodowaną rakiem przytarczycy skuteczne leczenie operacyjne nie tylko doprowadza do normalizacji stężenia wapnia, fosforanów i parathormonu, ale również może poprawić skuteczność leczenia nadciśnienia tętniczego. 2. Rak przytarczycy może uwidocznić się jako ognisko o śladowej aktywności metabolicznej w badaniu SPECT/CT i równocześnie wykazywać sekrecję parathormonu w zakresie wartości bardziej charakterystycznych dla łagodnej patologii przytarczyc.

**Słowa kluczowe**: nowotwory przytarczyc; pierwotna nadczynność przytarczyc; nuklearne obrazowanie; ultrasonografia; chirurgia; nadciśnienie tętnicze.

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## INTRODUCTION

Parathyroid carcinoma (PC) is a very rare, slow-growing, invasive cancer of parenchymal cells. It is the least common endocrine-related malignancy and accounts for less than 1% of all cases of primary hyperparathyroidism [1, 2, 3, 4]. It has been suggested that a palpable neck mass of average size exceeding 3 cm, nodal involvement, a high degree of elevation of parathyroid hormone (PTH) and severe hypercalcemia may be more predictive for PC than parathyroid adenoma, but in clinical practice a wide overlap between benign and malignant tumours has been demonstrated [1].

Preoperative parathyroid scintigraphy is a leading diagnostic imaging method. Nowadays, hybrid SPECT/CT imaging helps surgeons to locate the abnormal parathyroid gland. Generally, technetium-99m methoxyisobutylisonitrile ($^{99m}$Tc-Sestamibi) is employed as an oncophilic tracer depicting the metabolic activity of a tumour. The retention of the tracer is observed in the vast majority of abnormal parathyroid glands, including cancers. The prolonged presence of $^{99m}$Tc-Sestamibi is demonstrated in a one tracer-two phases study ("wash-out" protocol) [5, 6, 7, 8].

The next important method of localization is ultrasonography, due to its accessibility, low costs and lack of exposure to ionising radiation [9]. Nuclear magnetic resonance (NMR) is used as a second-line technique, with a reported sensitivity of 80% achieved with 1.5 T magnets. Better visualisation has been obtained with the 3.0 T NMR magnet [10]. Positron emission tomography (PET) was reported as an alternative to $^{99m}$Tc-Sestamibi-SPECT/CT. Two tracers have been used: 2-deoxy-2-[fluorine-18]fluoro-D-glucose ($^{18}$F-FDG), $^{11}$C-methionine and $^{18}$Fluorocholine integrated with computed tomography ($^{18}$F-FDG PET/CT or $^{11}$C-methionine PET/CT). The sensitivity per patient is 100%, but calculated per adenoma it is 88.9% [9]. This option has emerged as a powerful imaging tool for the detection of various lesions with increased metabolic activity. Due to costs and limited availability, this method is used in cases with a negative $^{99m}$Tc-Sestamibi scan [11, 12].

The only method of PC treatment remains parathyreoidectomy with lymphadenectomy of the affected side. Successful treatment results in biochemical and clinical improvements [13, 14]. Additionally, in the presented case, a significant reduction of hypertension from moderate to mild grade was achieved in a one-year follow-up.

## CASE REPORT

The patient was a 52-year-old woman with type 2 diabetes who was referred to the hospital due to unstable grade 2 hypertension treated with ramipril 5 mg/day (Polpril; Polpharma, Poland), indapamide 1.5 mg/day (Indapen; Polpharma, Poland), and betaxolol 5 mg/day (Beto ZK; Sandoz, Switzerland). The past medical history included surgery in 2005 and 2010 due to recurrent renal stone disease. Physical examination showed only moderate obesity with body mass index of 31.2 kg/m$^2$. There was no palpable neck mass.

Laboratory testing revealed increased total (3.38 mmol/L; normal range 2.25–2.75 mmol/L) and ionized calcium (1.88 mmol/L; normal range 1.05–1.35 mmol/L), low phosphorus (0.50 mmol/L; normal range 0.87–1.45 mmol/L) and high intact PTH levels (258.2 pg/mL; normal range 15–65 pg/mL). Total alkaline phosphatase activity was normal (84 IU/L; normal range 35–104 IU/L). Bone mineral density measured in the lumbar spine and total femur was within the normal range. High-resolution ultrasonography showed a solid, homogenous and hypoechogenic mass measuring 15×14 mm located inferior to the lower pole of the left thyroid lobe (Fig. 1). Doppler imaging showed a subtle peripheral hyperperfusion of the lesion. To confirm the suspicion of primary hyperparathyroidism, planar and SPECT/CT parathyroid scintigraphy was performed. Planar and SPECT/CT parathyroid scintigraphy performed with $^{99m}$Tc-Sestamibi in a "wash-out" protocol showed a lesion with only slightly increased activity in the early phase, located postero-inferior to the lower pole of the left thyroid lobe. The lesion showed total "wash-out" and was invisible in the delayed phase of the study (Fig. 2–4).

With the initial diagnosis of parathyroid adenoma, the patient was referred to our surgical unit, where the lower left parathyroid gland was removed. The postoperative PTH level decreased to 57.4 pg/mL. Calcium and phosphorus levels also normalized. However, histological examination of the surgical specimen revealed a greyish tumour measuring 23×17×6 mm, composed of parathyroid cells. The tumour showed capsular invasion and vascular invasion within the vessels of the fibrous tumour capsule, associated with moderate cellular atypia. The

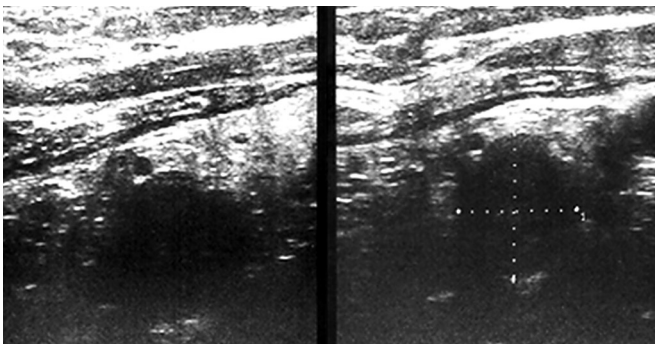

**FIGURE 1.** Ultrasound examination showing a solid, homogeneous and hypoechoic tumour (white dotted cross)

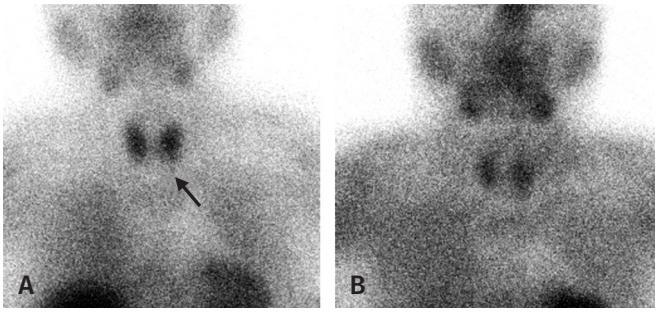


**FIGURE 2.** Planar images in early (A) and late (B) phases. Slightly increased pathologic metabolic activity below the lower pole of the left thyroid lobe (black arrow) in the early phase. Negative image in a delayed planar study

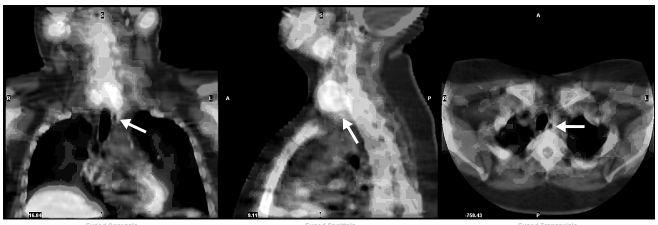

**FIGURE 3.** Early phase of cervico-thoracic SPECT/CT performed 10 minutes after injection depicts a left tracheoesophageal groove lesion of faint metabolic activity in coronal, sagittal and axial planes (white arrows)

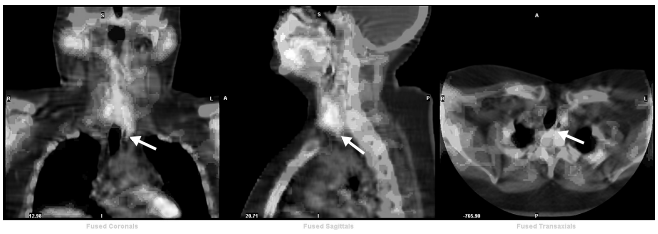

**FIGURE 4.** Delayed phase of cervico-thoracic SPECT/CT performed 90 minutes after injection in coronal, sagittal and axial planes. The lesion washes out and becomes nearly invisible (white arrows)

mitotic activity index was three mitotic figures per ten high-power fields, and the proliferation activity index (Ki-67 expression), expressed as the percentage of immunopositive nuclear area using morphometric image analysis, was below 1%. An immunohistochemical analyses detected the expression of PTH and was negative for calcitonin and thyroglobulin.

Based on these findings, ipsilateral thyroid lobectomy was performed. The cervical lymph nodes were not involved, and histological examination of the removed thyroid lobe was negative. One year after reoperation, a follow-up parathyroid planar and SPECT/CT scan with $^{99m}$Tc-MIBI and peptide receptor scintigraphy with somatostatin analogue $^{99m}$Tc-Tektrotyd; (Polatom, Poland) showed no abnormalities. Serum levels of PTH, calcium and phosphorus remained within normal ranges.

Diabetes was well controlled within the observational period, and the glycated haemoglobin level was stable, ranging from 37 mmol/mol before the first operation to 39 mmol/mol one year after reoperation (recommended range: below 53 mmol/mol). Interestingly, hypertension decreased to grade 1 (mild) and was well controlled with only two antihypertensive medications given in minimal doses, of ramipril (2.5 mg/day; Polpril; Polpharma, Poland) and nebivolol (2.5 mg/day; Nedal; Polfa, Poland). The mean blood pressure values in 24-h ambulatory blood pressure monitoring were 113/71 mm Hg.

Written informed consent was obtained from the patient for the publication of this case report and all accompanying images.

## DISCUSSION

In patients with clinical signs of primary hyperparathyroidism, preoperative differentiation between PC and parathyroid adenoma is impossible. This may hinder proper treatment because the surgical strategies for these conditions differ substantially. In general, the clinical manifestation of the disease is usually more advanced in PC than in benign adenoma [1, 4, 5, 15, 16]. Patients with PC often have a palpable neck mass, with an average tumour size of 3.3 cm, markedly elevated PTH (10-fold to 15-fold higher than the normal range) and total calcium levels (above 3.5 mmol/L), laryngeal nerve palsy, peptic ulcer disease, as well as nodal, skeletal and renal involvement [1, 16]. Among this typical cluster of abnormalities, our case had only moderate hypertension and a history of renal involvement (recurrent urolithiasis). The PTH level was only four-fold higher than the upper normal limit. Serum calcium, although resistant to standard treatment, was below 3.5 mmol/L. Moreover, no palpable neck mass was found, and tumour size was relatively moderate, which together suggested a benign rather than malignant disease.

At the time of presentation, our case had moderate hypertension. An association between calcium level and elevated blood pressure is plausible because calcium may increase vascular resistance by a direct effect on vascular smooth muscle cells, and on the renin-angiotensin system and renal vasoconstriction, leading to kidney dysfunction, as well as by interaction with other cations such as sodium, potassium and magnesium [17]. However, it is unclear whether the hypertension in the presented case was associated with carcinoma-induced hypercalcemia or was a component of metabolic syndrome in addition to co-existing type 2 diabetes and obesity. Interestingly, blood pressure decreased after surgical removal of the parathyroid gland and the subsequent normalization of serum calcium concentration, suggesting the contribution of calcium level to the pathogenesis of hypertension in this case. Although the association between hypertension and hyperparathyroidism has been well established, to our best knowledge this is the first report demonstrating an improvement of blood pressure control after surgical treatment of PC [13, 14].

In primary hyperparathyroidism, ultrasonography, planar and SPECT/CT with $^{99m}$Tc-MIBI, PET offer excellent sensitivity and a high positive predictive value [18]. Imaging techniques have been widely used for initial diagnosis and to detect the recurrence of PC. In this case the first clue, and a guide to seek for parathyroid abnormality, was ultrasonography. Parathyroid carcinoma presented as a hypofunctional lesion only in the early phase of the study on scintigraphy. This is not concordant with the literature [19, 20, 21]. Recently, another case report with a negative $^{99m}$Tc-MIBI scan but positive $^{18}$F-FDG-PET scan was presented. The authors experienced problems with localisation of the lesion but clinical and laboratory findings were concordant with the literature [22]. In our case those elements of differential diagnosis were not typical for PC.

Another diagnostic option which may be useful in the localization of distant metastases is $^{18}$F-FDG PET scanning [18, 23, 24]. Using this technique, several imaging signs have been proposed to raise the suspicion of PC [11, 12, 16, 18, 23, 25]. The PC diagnosis confirms the histopathological evaluation. It has been assumed that the mitotic index of more than five figures per ten high power fields suggests PC. Immunohistochemistry using anti-PTH antibodies has not been demonstrated to be useful

in the diagnosis of PC [26]. Nevertheless, a proliferation index evaluated by the Ki-67 antibody higher than 5% is associated with a higher suspicion of malignancy and the risk of recurrence [27]. In the presented case, the mitotic index and proliferation index were three figures per ten high-power fields and 1%, respectively.

A probable explanation for low uptake of oncophilic tracer might be the increased activity of protein transporters, which resulted in a quick wash-out of $^{99m}$Tc-MIBI from the lesion. The rate of $^{99m}$Tc-MIBI efflux is related to the expression of the *ABCB1* gene since the tracer is a substrate for P-glycoprotein which is encoded by this gene [28]. As PC is a rare disease any additional observation may contribute to updating knowledge. However, they are not PC-specific, and therefore, in the majority of cases, clinical suspicion of the disease results from severe clinical symptoms and markedly elevated PTH and calcium levels.

## CONCLUSIONS

1. In patients with PC-associated hyperparathyroidism, successful surgical treatment not only restores serum calcium, phosphorus and PTH levels, but may also improve blood pressure control.
2. Parathyroid carcinoma may demonstrate faint metabolic activity in the SPECT/CT study, and its biochemical secretion of PTH may be placed in ranges more characteristic for benign parathyroid pathology.

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