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Original Scientific Paper

PARATHYROID CARCINOMA: ULTRASONOGRAPHIC AND CLINICAL EXPERIENCE

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SUMMARY – Parathyroid cancer is an extremely rare malignancy that usually leads to hyperparathyroidism. The aim of this report is to present clinical and ultrasonographic features of tumors in six patients (5 females; mean age 53.2 years) treated for parathyroid carcinoma at the Department of Nuclear Medicine during 20 years. Most patients presented with hypercalcemia, and one of them had a previous history of long-term secondary hyperparathyroidism and was treated with hemodialysis. All patients had significantly reduced bone density, and two of them presented with typical 'brown' tumors involving long bones of lower extremities. After initial treatment, all patients except for the youngest female patient were in long-term remission with normal serum calcium and parathyroid hormone levels. Preoperative imaging procedures such as ultrasound with targeted fine needle-aspiration biopsy and Tc99m-sestamibi scan helped determine the location and extent of the disease, but definitive diagnosis was made after the surgery. Parathyroid cancer is a rare form of malignant tumor that is difficult to diagnose preoperatively due to similar clinical features with benign causes of hyperparathyroidism such as hyperplasia and adenomas, especially atypical ones that require regular follow-up. Complete surgical resection provides the best chance of cure, although metastatic disease is possible.

Key words: *Parathyroid carcinoma; Atypical parathyroid adenoma; Hyperparathyroidism; Neck ultrasound*

Introduction

Parathyroid cancer is an uncommon malignancy usually presented with high levels of calcium and parathyroid hormone (PTH) in the blood and is responsible for less than 1% of hyperparathyroidism cases. Tumors occur with equal frequency in women and men[1,2]. The majority of carcinomas are sporadic, but rare forms of genetic hyperparathyroidism-jaw tumor syndrome (HPT-JT) with mutations in the *HRPT2* gene have also been reported[3,4]. The etiology of cancer remains unknown; it could be associated with a history of neck irradiation. Some authors suggest long-term secondary hyperparathyroidism as a provoking factor of the disease[5]. The disease could be clinically mistaken for benign causes of hyperparathyroidism, particularly parathyroid adenomas, because of similar biochemical and echographic findings indicative of benign pathology that could be a potential pitfall which may delay the diagnosis. Suspicious sonographic features include irregular shape, heterogeneous echostructure with cystic portions, and intranodal calcification in large-size

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nodes, which may provide preoperative evidence for those forms of malignancy[6,7]. Parathyroid cancers are usually slow-growing tumors with a tendency to recur locally; in most cases, metastases occur late and most commonly involved are cervical and upper mediastinal lymph nodes and the lung. Early surgery is the most important factor for optimal outcome[6-8].

The purpose of the current report is to present the clinical, imaging and histopathologic features found in patients with these extremely rare forms of malignant tumor.

Patients and Methods

The report includes six patients with parathyroid cancer treated at the Department of Nuclear Medicine during the period of 20 years (from 1998 to 2018); their medical and ultrasound records, as well as biochemical, cytologic and histologic findings were retrospectively analyzed and presented. All patients except for one initially presented with hypercalcemia. Upon correction of the serum calcium level with improvement of the general state, they were referred to parathyroid resection surgery with subsequent histology. Pathologic criteria considered suspicious of parathyroid carcinoma were capsular and vascular invasion, as well as involvement of the surrounding structures and presence of metastases.

Preoperative ultrasound followed by ultrasound guided fine-needle aspiration biopsy (US-FNAB) was performed in all patients. The shape, echogenicity, size and location of enlarged glands were reported with linear 7.5- and 10-MHz probes, and then US-FNAB by a free-hand technique was performed. Each biochemically or cytologically proven parathyroid gland was confirmed histologically after surgical removal. Demographic and clinical data, as well as biochemical parameters (blood calcium, phosphate, and PTH levels) were determined and retrospectively analyzed using available medical records. Combinations of several imaging tests (ultrasound, computed tomography (CT), single photon emission computed tomography-computed tomography (SPECT/CT), technetium-99m sestamibi (Tc-99m-MIBI) scintigraphy, positron emission tomography-computed tomography (PET-CT), magnetic resonance imaging (MRI)) were sometimes used to determine tumor size, location and relationship with surrounding structures. The imaging material and histopathologic features of such cancers were also presented. In case of suspected recurrent disease, repeated excision and biopsy was performed.

All the procedures applied were part of routine diagnostic and therapeutic protocols that have been approved by national health institutions. Signed informed consent for imaging and using data for further research was obtained from all individual participants included in the study.

Results

Six patients (5 women; mean age 53.2 years; range 30-63 years) were diagnosed to have parathyroid carcinoma between 1998 and 2018 (mean follow-up 6.3 years; range 2-10 years). The patients had no previous history of familial hyperparathyroidism or other endocrine disorders but two of them had a previous history of surgery for atypical adenoma of the parathyroid gland (one female patient one year and another one four years prior to the diagnosis of parathyroid cancer). These two patients preoperatively had enlarged parathyroid glands with some atypical cytologic features; however, there were not enough criteria for malignancy in final histologic specimens. None of the patients had a history of previous neck radiation. Most of the patients except for one male patient exhibited symptomatology of hypercalcemia at presentation with high serum calcium and PTH levels. A common reason for referring patients for neck ultrasound (except for hypercalcemia) was thickening of the neck in the area of thyroid gland. Two patients had a previous history of multinodular goiter, but in another two patients, total thyroidectomy was suggested at the same time because of cytologic suspicion of thyroid cancer, which was also confirmed by definitive histopathologic findings. In all cases, multiple endocrine neoplasia was excluded.

Demographic data, biochemical values, as well as echographic features of the tumor are shown in Table 1. All patients had a significantly reduced bone density in the form of osteoporosis; three of them had bone fractures before initial diagnosis and two patients had bone changes in terms of *osteitis fibrosa cystica* known as typical 'brown' tumors involving long bones of the extremities (Fig. 1). Nephrolithiasis was present in 4 of 6 patients and among them, one patient had a previous history of long-term secondary hyperparathyroidism due to renal insufficiency and had been treated with dialysis for 10 years prior to diagnosis.

Ultrasound showed enlarged parathyroid gland in all cases, but in one male patient it was located inside

Table 1. Clinical, biochemical, and diagnostic data with follow-up of patients

Patient	Sex	Age	Disease history	Involvement	Side	Size (cm)	Ca (mmol/L)	PTH (pmol/L)	ECHO	Relapse	Follow-up (yr)
1	F	56	APA	B	L	3.0	2.71	17.7	lob, hypo, cyst, pd	No	8
2	F	62	MNG	B	L	5.0	3.26	122.7	lob, iso, pd	No	10
3	F	63	MNG,TC	B,K	L	4.3	4.00	23.5	lob, iso, cyst, pd	No	6
4	F	30	APA	B,K,LN,L	R	2.1	3.30	36.0	hypo, pd	Yes	10
5	F	54	RI,FEO,TC	B,K	L	2.2	3.30	15.0	lob, hypo, cyst, pd	No	2
6	M	54	NE	B,K	R	1.5	NA	NA	hypo, wd, intra	No	2

F-female, M-male
Disease history-comorbidity (NE-not existing, MNG-multinodular goiter, APA-atypical parathyroid adenoma, RI- renal insufficiency, FEO-pheochromocytoma, TC-thyroid cancer)
Involvement (B-bone, K-kidney, LN-lymph nodes, L-lung)
Tm side (L-left, R-right)
Initial Ca level (ref. range 2.14-2.53 mmol/L), PTH level (ref. range 1-6 pmol/L), NA-not available
ECHO-ultrasound finding (LOB-lobulated, ISO-isoechogenic, HYPO-hypoechogenic, CYST-cystic changes, WD-well-defined border, PD-poorly-defined border, INTRA-intrathyroid located)

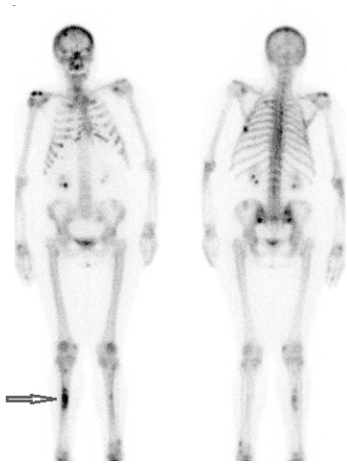

Fig. 1. Bone lesion known as 'brown' tumor showing focal intensive uptake in right lower leg (tibia) of a patient with parathyroid carcinoma.

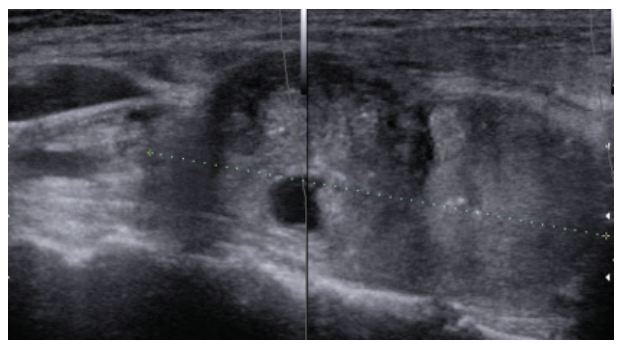

Fig. 2. Ultrasonographic appearance of parathyroid carcinoma demonstrating inhomogeneous, lobulated, isoechogenic structure with cystic changes.

the thyroid gland, and cytology in his case indicated the presence of malignant cells, primarily possible papillary thyroid cancer, but definitive histopathology indicated that it was parathyroid carcinoma. Due to intra-thyroid position and no symptoms of marked hypercalcemia, preoperative calcium and PTH data on that patient are missing. In many other cases, ultrasound revealed enlarged nodule located on the posterior side of the thyroid lobe (4 of them at the left side) that presented as a large heterogeneous mass, with the mean diameter of approximately 3 cm (range 1.5-5 cm), lobulated (4 of them), and with irregular shape (Fig. 2). Cystic changes were present in 3 cases (Fig. 3). However, in two cases (according to previous history), initial histopathologic findings described atypical parathyroid adenoma, presented as a hypoechoic, well-limited node, but later in follow-up, the diagnosis of parathyroid carcinoma was established (Fig. 4a, b).

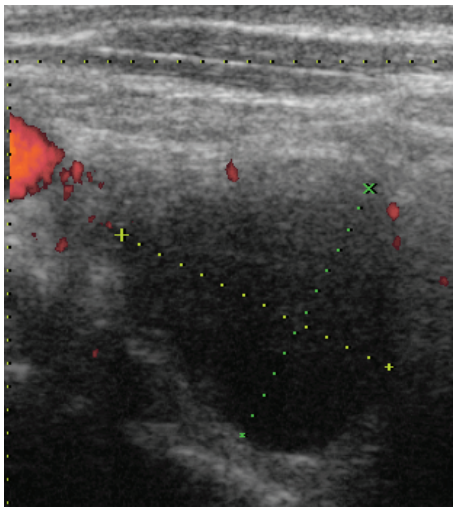

Fig. 3. Cystically changed parathyroid carcinoma.

Cytologic findings of US-FNAB revealed proliferation of parathyroid tissue cells in five patients with positive findings in immunocytochemistry. However, in only two cases the cells in the aspirate indicated pronounced anisonucleosis with atypia, and cytologic diagnosis of suspected parathyroid tumor was made. PTH was high (more than 150 pmol/L) in all aspirates. However, in most cases, definitive diagnosis of cancer was made on the basis of histopathologic findings.

Other preoperative imaging techniques such as Tc-99m sestamibi planar and SPECT/CT scan were performed in three patients before surgery and showed intensive focal uptake of the radiopharmaceutical at the site of enlarged gland, which is also commonly seen in benign parathyroid adenoma. At the time of diagnosis, the mean calcium level was higher than normal (mean 3.31, range 1.71-4.00; reference range 2.14-2.53 mmol/L), and so was the mean PTH level (mean 43, range 15-122.7; normal range 1-6.0 pmol/L). Patients underwent surgery after correction of calcium levels and improvement of the general condition using intravenous saline infusion, diuretics and bisphosphonates (pamidronate), if necessary.

Most patients (5 of 6) experienced long-term remission after surgery, their calcium and PTH blood levels restored back to normal with no signs of recurrence during the follow-up of 2 to 10 years. Among patients, disease recurred in one youngest female who had two subsequent pregnancies and deliveries after establishing the diagnosis. During the first pregnancy, the patient had severe nausea and fatigue, but hypercalcemia and hyperparathyroidism were diagnosed in the postpartum period. Shortly after childbirth, her newborn baby developed neonatal convulsions with laboratory tests that showed severe prolonged hypocalcemia, so the mother's calcium was checked. The mother's level of calcium was high and she was referred to ultrasound study. In her case, Doppler ultrasound of the neck recognized an enlarged lower-right parathyroid gland, initially described as a well-defined, not highly vascularized hypoechoic mass closed to the thyroid, with a homogeneous echo pattern measuring 2.1x1.5x1.5 cm, PTH in aspirate was high and Tc-99m sestamibi planar scan showed an area of increased

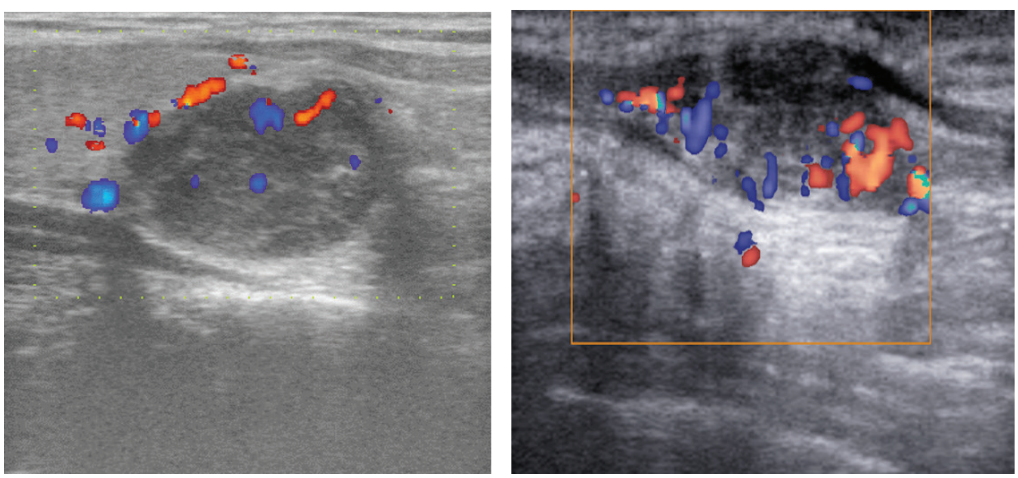

Fig. 4. (a) Echographic presentation of surgically resected and histologically proven atypical parathyroid adenoma; (b) echographic presentation of parathyroid carcinoma in the same patient one year later (as a sign of recurrent disease).

uptake on the right side of the neck as additional evidence for hyperfunctioning parathyroid tissue. US-FNAB showed epithelial cells with pronounced anisonucleosis and non-sharply defined cytoplasmic borders with many naked nuclei. Two months after delivery, the patient underwent surgical removal of the described parathyroid gland. The pathologic report noted parathyroid tissue composed of main and oxyphilic cells with no significant remodeling of the stroma cells or polymorphism; mitotic figures were not observed but there were some cells infiltrating the capsule without breaking through it. There was no invasion of tumor cells into blood vessels or invasion of the surrounding fat tissue, so definitive pathologic diagnosis was atypical adenoma of the parathyroid gland. The patient was repeatedly followed-up after surgery, she was normocalcemic and became pregnant again. The time interval between the two pregnancies was 15 months. During the second pregnancy, calcium levels were normal, and the patient had no nausea or sickness, and the second baby had no convulsions or hypocalcemia after birth, unlike the first one. However, after the second delivery (one year after initial surgery), while lactating, the mother's calcium level increased again, and other laboratory results suggested recurrence of hyperparathyroidism. At that time, ultrasound revealed a solitary mass in the area of the previous surgery with an enlarged lymph node in the pretracheal region. US-FNAB described naked nuclei and malignant cells with pronounced macronucleosis and intranuclear inclusions, leading to a diagnosis of carcinoma of the parathyroid gland, which was subsequently confirmed histologically and the pretracheal node was confirmed as lymph node metastasis. In the following years, the patient was operated on several times due to a recurrent metastatic disease in regional lymph nodes and lungs.

Due to reduced bone mineral density calcium supplements, active metabolites of vitamin D and in some cases bisphosphonate preparations were administered postoperatively. Brown tumors did not require additional surgical treatment.

Discussion

Parathyroid carcinoma is a rare cause of hyperparathyroidism and it accounts for a very small percentage of all head and neck carcinomas. The exact etiology of the tumor is unknown; some studies suggest that radiation to the neck area can cause cancer, although most tumors are sporadic. Also, there are theories of genetic causes of parathyroid carcinoma[9]. Inactivation of the retinoblastoma tumor suppressor (*RB*) gene is common in parathyroid carcinoma and is likely to be an important contributor to its molecular pathogenesis[10]. Few cases of parathyroid carcinoma associated with MEN-1 and less with MEN-2A have been reported in the literature[11]. According to the literature, the risk of developing cancer is increased in autosomal dominant familial hyperparathyroidism and in HPT-JT syndrome with ossifying fibromas of the jaw, which are caused by mutations in the *CDC73* gene[12]. The patients presented in this work had no previous history of familial hyperparathyroidism, other endocrine disorders, or neck irradiation. One female patient had a history of chronic renal disease; medical history data of this 54-year-old patient revealed that she had previous surgery for pheochromocytoma of the left adrenal gland. In her case, ultrasound revealed enlargement of all 4 parathyroid glands due to long-term dialysis, but suspicion of MEN syndrome was not confirmed. Chronic renal failure which leads to secondary hyperparathyroidism and then to parathyroid carcinoma has also been mentioned in other works. The association of hyperplasia, adenoma and carcinoma could be explained by initial hyperplasia of the parathyroid glands due to renal insufficiency, with subsequent transformation into adenomas of which some could become cancerous[13,14]. Berland *et al*. have reported the first case of parathyroid carcinoma developing in a patient on hemodialysis[15]. Since then, many other cases in patients on hemodialysis have been reported in the literature[16]. No preoperative features are known to distinguish patients with parathyroid carcinoma from those with parathyroid hyperplasia. Interestingly, their clinical course may be less aggressive due to the effect of renal insufficiency on lowering serum calcium levels[13,17].

The normal parathyroid gland contains chief cells, oxyphil cells, water-clear cells, and adipose tissue. The majority of parathyroid carcinomas arise from the chief cells. Parathyroid carcinomas are frequently described as a lobulated, firmly shaped mass[14]. Macroscopically, parathyroid carcinomas were not significantly larger than parathyroid adenomas or hyperplastic parathyroid glands[18]. Histopathologic findings of parathyroid carcinoma are not certain. Sometimes, it is difficult to differentiate tumors from degenerative changes, but immunohistochemical markers are beneficial. Among many other markers, global loss of calcium sensing

receptor (CASR) and parafibromin staining, as well as mutations in the *HRPT2/CDC73* gene could be useful in determining potential malignancy[19]. The best predictors of malignancy are the presence of invasion of the fibrotic capsule and nuclear atypia[20]. In our study, two patients had a previous history of surgery in which the histopathologic finding indicated an atypical parathyroid adenoma without sufficient criteria for malignant changes. Later follow-up revealed that it probably was parathyroid cancer. Atypical parathyroid adenomas represent intermediate forms of parathyroid neoplasms of uncertain malignant potential that show some atypical histologic features and are difficult to distinguish from parathyroid carcinoma[21]. These difficulties in making an accurate diagnosis could sometimes lead to underestimation or overestimation in the treatment of those two entities. The overall rate of recurrence of atypical parathyroid adenomas is 3% and is higher in familial than in sporadic cases[21]. Due to the previously mentioned facts, the importance of postoperative follow-up of patients with a diagnosis of atypical adenoma is emphasized[21,22]. Bearing in mind this fact, and in accordance with our clinical experience with two patients previously operated on due to atypical parathyroid adenoma, regular ultrasound examination, as well as monitoring of blood calcium, phosphorus and PTH levels in the postoperative period are absolutely necessary in order to detect possible tumor recurrence earlier.

The most commonly used imaging methods before surgery for primary hyperparathyroidism are high-resolution ultrasonography with doppler imaging, Tc-99m-MIBI scintigraphy and CT. Ultrasonography cannot completely assess the retroesophageal, retrotracheal and mediastinal areas. US and Tc-99m-MIBI, each having its value, are complementary examinations and are both characterized by high specificity and a positive predictive value. If used simultaneously, the positive predictive value ranges from 85% to 90% for primary hyperparathyroidism[23]. Imaging methods allow determining the location, size and extent of the formation, but they are not useful in the assessment of malignant potential. Some retrospective studies compared the ultrasound features of parathyroid adenomas and parathyroid cancers. The malignant lesions are generally heterogeneous, larger and lobular, while the adenomas are homogeneous, smaller and smoother[1,24,25]. Lobulated echographic appearance with non-homogeneous echotexture of hypervascular solid hypoechoic mass located immediately posteriorly to the thyroid gland infiltrating the surrounding tissues with enlarged lymph nodes is often associated with parathyroid cancer[6,24]. Differential diagnosis between parathyroid carcinoma and atypical parathyroid adenoma is difficult and it is advisable to inform the surgeon about the inhomogeneity of the structure with possible infiltration of surrounding structures suggesting parathyroid cancer[22]. In our study, parathyroid cancers were echographically presented as a large lobulated, heterogeneous echostructure with irregular shape (in 5 of 6 patients) situated behind the lobes, and exhibited cystic changes and intranodular calcifications in half of the cases. According to the literature, most parathyroid tumors are solid, but a few of them can be cystic or partly cystic. In a cohort of 907 patients with benign and atypical parathyroid adenomas, Hu *et al*. found an incidence of 4% of cystic parathyroid adenomas, based on ultrasound. The authors defined parathyroid lesion as cystic when the cystic areas occupied more than 50% of the estimated volume of the parathyroid gland. Interestingly, atypical adenomas (n=56) were more common among cystic rather than solid lesions. The overall data from the literature report a frequency of 30% of cystic atypical parathyroid adenomas based on imaging and/or pathology. Close follow-up is necessary in patients with cystic parathyroid adenomas, which account for a substantial proportion of atypical adenoma cases[26]. Of course, preoperative imaging is helpful for tumor localization, but in the evaluation of primary parathyroid tumors it cannot reliably distinguish benign from malignant disease. In those cases, US-FNAB may be helpful in identifying suspected cells and can assist the surgeon in selecting the extension of the procedure in case of suspected malignancy, although surgery is required in any case (either benign parathyroid adenoma or malignancy). Cytologic findings of US-FNAB revealed proliferation of parathyroid tissue cells in the majority of our patients (in 5 patients, except for one intrathyroid-located parathyroid gland). In only two patients, the presence of marked cell atypia raised suspicion of a parathyroid tumor. However, in most cases, definitive diagnosis of cancer was made only on the basis of histopathologic findings. On the other hand, some authors advocate FNAB should be avoided in suspected malignant changes because of disruption of the neoplastic capsule and the possibility of tumor seeding along the needle track and local relapse[27,28]. In

addition, some authors do not recommend fine-needle aspiration cytology due to the high probability of false-negative results, which may influence surgical approach incorrectly[2,27,28]. However, in patients with metastatic tumors, when seeding is of less concern, FNAB of the lesion is useful to identify parathyroid tissue in an aberrant location, either revealing parathyroid cells or by determination of PTH in the aspirate that confirms PTH-secreting tissue[29].

In patients who are suspected to have parathyroid carcinoma, the useful diagnostic methods before surgery (when sestamibi scan is negative) are CT scan or MRI of the neck, mediastinum and chest, as well as possible PET/CT F-18 choline scanning for detecting local extent of primary tumor with possible mediastinal lymph node metastases and to determine the relationship with blood vessels and surrounding structures[1,6,29].

Laboratory criteria for distinguishing parathyroid adenomas from cancers are not specific. According to the literature, the average blood calcium values in cancer patients are higher than those with parathyroid adenomas, and so are PTH levels, so hypercalcemia is usually more severe in patients with parathyroid carcinoma. PTH levels in parathyroid carcinoma are frequently two to ten times the normal values, whereas PTH levels in benign causes of primary hyperparathyroidism are commonly twice the normal value. Other laboratory features include hypophosphatemia, hypercalciuria, and hyperphosphaturia[13]. Nephrolithiasis, nephrocalcinosis and impaired kidney function are found in 32%-80% of patients with parathyroid carcinoma compared with less than 20% in benign primary hyperparathyroidism[2,14]. Parathyroid hormone increases osteoclastic activity in the bones, so bone loss occurs. One of the possible complications of hyperparathyroidism are fibrotic, cystic changes of the bones called 'brown' tumors, which are also known as osteoclastomas or *osteitis fibrosa cystica*. These are bone lesions caused by increased osteoclast activity and are not real tumors as the term 'tumor' suggests, but could mimic it. Brown tumors are benign lesions that usually involve long bones of extremities, ribs, pelvis, but also maxillary and mandibular region, skull and spine, and are much more often a complication of serious secondary hyperparathyroidism or parathyroid cancer than primary hyperparathyroidism due to benign causes. Brown tumors may cause swelling, pain, pathologic fracture and thus simulate malignant changes that cause difficulties in differential diagnosis[30]. Non-functioning parathyroid carcinoma without hypercalcemia and with normal PTH value is a rare entity[31]. Furthermore, only a few cases of intrathyroidally located parathyroid carcinoma have been reported in the literature[32]. In the case of the patient presented in this paper, the diagnosis of parathyroid cancer was made postoperatively. Preoperative cytology indicated the presence of malignant cells, primarily possible papillary thyroid cancer. However, definitive histopathologic finding indicated that it was parathyroid cancer. Due to intrathyroid position without symptoms of severe hypercalcemia, preoperative data on calcium and PTH values of that patient were missing, but subsequent history data suggested hyperparathyroidism preoperatively since the patient had metatarsal bone fracture and nephrolithiasis at the time of diagnosis.

Untreated parathyroid carcinoma usually leads to severe hyperparathyroidism with hypercalcemia, bone pain, osteoporosis, fractures, nephrolithiasis, or other kidney damage. Risk factors associated with shorter survival include large tumor size, older age at the time of diagnosis, and male gender. Early surgery is the most important factor for optimal outcome. Most studies recommend complete removal of the tumor with microscopically unaffected edges without violating the capsule, removal of the thyroid lobe on the same side, and removal of all areas of local adherence and affected structures. If metastases to regional lymph nodes are present, neck dissection is also performed. The postoperative management must include careful monitoring of serum calcium levels, especially ionized[14]. In most cases, parathyroid cancer grows slowly and metastasizes late. Local recurrence and metastases to cervical lymph nodes (30%) appear most often, but distal, hematogenous metastases involve the lungs (20%-40%), and liver in approximately 10% of cases[14]. Furthermore, parathyroid cancers occur rarely in pregnancy, with the risk to both the mother and the child that is directly related to calcium levels[33]. This report includes the case of a young woman with metastatic parathyroid cancer and two subsequent pregnancies who was initially referred to Nuclear Medicine Department for thyroid ultrasound with symptoms of hypercalcemia and diffuse goiter[34]. Among all patients, only this patient had persistent disease with multiple recurrences of the disease and pronounced hypercalcemia. Maternal hypercalcemia could induce profound fetal parathyroid gland suppression leading to severe

neonatal hypocalcemia, which also occurred in our case after first delivery due to unrecognized hypercalcemia in pregnancy, which was probably masked by hyperemesis in pregnancy[33,34]. Based on our experience, we emphasize the importance of early detection and effective treatment of hypercalcemia in pregnancy, which leads to an optimal outcome of pregnancy and childbirth for both mother and child. Hypercalcemia is treated by adequate hydration with isotonic sodium chloride solution, loop diuretics, and pamidronate. There are no official guidelines for the treatment of hyperparathyroidism in pregnancy or the treatment of parathyroid carcinoma. The options are conservative approach or surgery. Both approaches carry a risk of side effects, although the risk imposed by elevated calcium levels appears to be greatest. If surgery is an option, it should be performed in the third trimester of pregnancy.

Generally, patients with parathyroid cancer usually have markedly elevated calcium and PTH levels, so it is important to lower calcium levels in order to avoid complications. Hypercalcemia is treated with saline infusions to restore fluid volume with increased urinary calcium excretion with diuretics. Bisphosphonates are also used to inhibit osteoclast-mediated bone resorption. According to therapeutic strategy, parathyroid cancers are generally not sensitive to radiation, and experience with chemotherapy is limited due to the rarity of those forms of malignancy. Most patients die from metabolic complications due to severe hypercalcemia rather than disease extension. Prognosis for patients with parathyroid cancers is variable. Most important is early recognition and complete resection at the time of initial surgery, but the prognosis for widely disseminated parathyroid carcinoma is poor. Some case reports have provided evidence that immunotherapy may help in prolonged control of hypercalcemia unresponsive to conventional treatments[2,8,14,35,36].

Conclusion

Parathyroid carcinoma is an extremely rare form of endocrine tumor that biochemically looks similar to benign hyperparathyroidism caused by parathyroid adenoma and sometimes could be clinically mistaken. Imaging techniques help localize the disease, but they are not useful in the assessment of malignancy potential. Sonographic features such as enlarged parathyroid glands with heterogeneous echostructure, irregular shape, cystic changes, and intranodular calcifications may provide preoperative evidence for those forms of parathyroid malignancy and should not be overlooked. Due to the overlap in biochemical and imaging findings and difficulties in setting appropriate histologic analysis which may lead to the underestimation or overestimation of the treatment in all cases of doubtful histopathologic findings, especially for atypical parathyroid adenoma, many authors emphasize the importance of adequate postoperative ultrasound monitoring, as well as monitoring of serum calcium, phosphorus and PTH levels. Early recognition and complete resection at the time of initial surgery carries the best prognosis.

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Sažetak

KARCINOM PARATIREOIDNE ŽLIJEZDE: ULTRAZVUČNA I KLINIČKA OBILJEŽJA

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Karcinom paratireoidne žlijezde je iznimno rijedak tumor koji obično dovodi do hiperparatireoidizma. Svrha izvješća je prikaz kliničkih i ultrazvučnih karakteristika tumora u 6 bolesnika s ovim karcinomom (5 žena, prosječne dobi 53,2 godine) praćenih i liječenih tijekom 20 godina u Kliničkom zavodu za nuklearnu medicinu. Većina bolesnika se kod otkrivanja bolesti prezentirala izraženom hiperkalcemijom, a anamnestički je jedna bolesnica imala sekundarni hiperparatireoidizam u sklopu bubrežne bolesti i prethodno je liječena višegodišnjom hemodijalizom. Svi bolesnici su imali denzitometrijski značajno sniženu gustoću kostiju, a dvoje se prezentiralo tipičnim „smeđim" tumorima dugih kostiju donjih ekstremiteta. Nakon provedenog inicijalnog postupka liječenja svi bolesnici osim najmlađe bolesnice su u dugotrajnoj remisiji s urednim vijednostima kalcija i paratireoidnog hormona u serumu. Prijeoperacijski dijagnostički postupci poput ultrazvuka s ciljanom citološkom punkcijom i scintigrafije Tc99m-sestamibijem pomažu u utvrđivanju lokalizacije i proširenosti bolesti, no konačna dijagnoza je u većini slučajeva postavljena tek nakon operacijskog zahvata na temelju patohistološkog nalaza. Karcinom paratireoidne žlijezde je rijedak oblik malignog tumora koji je teško dijagnosticirati prijeoperacijski zbog sličnih kliničkih obilježja s benignim uzrocima hiperparatireoidizma poput hiperplazije i adenoma, osobito atipičnog koji zahtijeva redovito praćenje. Potpuna kirurška resekcija pruža najbolje izglede za izlječenje, iako je moguća i metastatska bolest.

Ključne riječi: *Karcinom paratireoidne žlijezde; Atipični adenom paratireoidne žlijezde; Ultrazvuk vrata; Hiperparatireoidizam*