NON-FUNCTIONING PARATHYROID GLAND CARCINOMA: CASE REPORT

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SUMMARY – Parathyroid gland carcinoma is a rare malignancy. The tumor is mostly functioning, causing severe hyperparathyroidism, with high serum calcium level and severe bone disease. Non-functioning parathyroid carcinomas are extremely rare. We report on a 60-year-old male patient admitted to ENT Department due to a large neck tumor mass compressing the thyroid and trachea. Preoperatively, thyroid hormone, parathyroid hormone (PTH) and calcium serum levels were normal. The following immunohistochemical markers (DAKO, Denmark) were used: bcl-2; CD-10; Chromogranin-A; Cyclin-D1; EMA; Ki-67; Mdm-2; p-53; PGP-9,5; RCC; Synaptophysin; Thyroglobulin; and TTF-1. Immunohistochemical analysis indicated the diagnosis of a primary parathyroid gland carcinoma. Tumor cells showed diffusely positive immunohistochemical staining with chromogranin-A and PGP-9,5, positive staining of variable intensity with synaptophysin, and weakly positive reaction with EMA. Also, the cytoplasm of tumor cells was diffusely positively stained with bcl-2, while the nuclei showed positive reaction with p-53 oncogene and TTF-1. The remaining markers (CD-10, cyclin-D1, Ki-67, Mdm-2, RCC and thyroglobulin) were negative. Four years after the surgery, the patient died from renal carcinoma pulmonary metastases and liver cirrhosis complications. In conclusion, non-functioning parathyroid gland carcinoma is a very rare disease. Detailed immunohistochemical analysis is needed to distinguish it from other thyroid and parathyroid neoplasms and metastatic carcinoma. Surgical treatment is presently the best mode of therapy.

Key words: Parathyroid neoplasms – diagnosis; Parathyroid neoplasms – pathology; Non-functioning parathyroid neoplasms

Introduction

Parathyroid carcinoma is a rare malignancy of the parathyroid gland. It usually occurs in patients older than 30, equally in male and female. There is no known geographical variation in its prevalence. In most cases, the etiology of disease is unknown. It may be associated with genetic disease, hyperparathyroidism, jaw tumor syndrome, and with a history of neck irradiation. Parathyroid carcinoma is a slow-growing tumor, has a tendency of local recurrence, and metastasizes late. These tumors are mostly functioning, causing severe hyperparathyroidism with high serum calcium level, severe bone disease and renal stones. The onset and symptoms of hyperparathyroidism are usually more severe than those that are associated with a benign disease. Palpable mass in the neck is seen in approximately 50% of patients. At present, surgical resection is the only effective treatment option. The reported overall 5-year survival rate ranges from 50% to 75%. A significant number of patients die from recurrent disease 5 years or longer after the initial treatment. Only 30% of patients have a long-term cure rate. We report on a 60-year-old male patient admitted to the Ear Nose and Throat Department due to a large...
neck tumor mass, which was compressing the thyroid and trachea. After thorough clinical observation, the neck tumor was surgically removed. Pathologic finding pointed to the diagnosis of primary parathyroid gland carcinoma.

Case Report

A 60-year-old male patient was admitted to the ENT Department for a clinically palpable large tumor on the left side of the neck. Routine laboratory findings: thyroid hormone, thyroid-stimulating hormone, parathyroid hormone, calcium, phosphates, alkaline phosphatase, and urine were within the reference values (data not shown). No previous thyroid abnormalities or other concomitant diseases were present. However, the patient had previously been treated at Urology Department for renal cell carcinoma, which had been surgically removed. It was well differentiated, composed of alveolar nests of clear cells (Fig. 1). The tumor was limited to the upper pole of the kidney, with a 5-cm diameter. There were no metastatic deposits in the aortal and interaortocaval lymph nodes. Radiological findings (computed tomography) revealed dislocation of the larynx and trachea by an expanding tumor mass attached to the left lobe of the thyroid gland. The tumor spread superiorly from the upper corn of the thyroid cartilage and inferiorly to the upper mediastinum and the aortic arch, measuring 6×6×10 cm in diameter. The trachea was severely compressed to the right, while the lumen was limited to the size of 12 mm (Fig. 2). The tumor was surgically removed together with resection of the left thyroid lobe, with preservation of the recurrent laryngeal nerve and the contralateral thyroid lobe. Lymphadenectomy of the central compartment of the neck was also performed. On pathologic analysis, macroscopic appearance showed the extremely large, brown-reddish to grey in color, partially necrotic tumor with broad areas of hemorrhage and fibrosis. Microscopically, tumor tissue showed a trabecular and alveolar pattern of predominantly watermelon cells with nuclei like seeds and numerous mitotic figures, separated by thick fibrous bands. A minor number of cells had bright basophilic cytoplasm and smaller round nuclei.
with finely dispersed chromatin and nucleoli. The tumor was significantly vascularized with broad areas of hemorrhage and hemosiderin deposits. Tumor capsule was infiltrated with clusters of atypical cells, adherent to normal thyroid gland. There were no metastatic deposits present in the lymph nodes. On immunohistochemical analysis, tumor cells showed diffusely positive reaction with chromogranin-A, p-53 oncogene, and thyroid transcription factor-1 (TTF-1) (Fig. 3). Cyclin-D1, antigen Ki-67, murine double minute 2 protein (Mdm2), and thyroglobulin protein were all negative. There was strongly positive expression of protein gene product 9,5 (PGP-9,5) (Fig. 4). Due to the lack of immunostaining markers, parathormone staining was not performed. To exclude the metastases of the simultaneous renal cell carcinoma, the immunostaining for renal cell carcinoma (RCC) was also performed and showed no positivity. The postoperative period was uneventful. Parathyroid hormone and calcium serum levels were within the reference values. Four years following the surgery, the patient died due to the renal cell carcinoma pulmonary metastases (metastatic nests showed intensively positive immunohistochemical expression of markers characteristic of RCC) and hepatic cirrhosis complications.

Discussion

Parathyroid carcinomas account for less than 1% of primary hyperparathyroidism cases. The majority (95%) of parathyroid carcinomas are functioning and secrete parathyroid hormone. Non-functioning parathyroid gland carcinoma is extremely rare. Multiple endocrine neoplasia syndrome type 1 (MEN 1), although rarely affected by carcinomas, has been associated with parathyroid carcinoma. In the present case, the tumor presented as a palpable neck mass severely compressing adjacent anatomic structures, i.e. trachea and larynx. The patient’s pre- and postoperative serum calcium and parathyroid hormone levels were normal, suggesting a non-functioning form of the parathyroid gland tumor. Macroscopically, parathyroid carcinoma can be described as a grayish, hard lobulated tumor surrounded by a dense fibrotic capsule. Its adherence and invasion of the surrounding structures is an important sign of malignancy. The possible criteria have been suggested for diagnosing malignancy, which were also seen in the present case: thick fibrous bands, areas of necrosis and hemorrhage, hemosiderin deposits, pleomorphic nuclei with numerous pathologic mitoses, invasion of the capsule and adhesion for the left thyroid globe. Others consider that cellular atypia, nuclear pleomorphism and macronucleoli are signs of malignancy. Cryns et al.6 were the first to report that immunohistochemical reaction with monoclonal antibody against retinoblastoma (Rb) protein is commonly absent in parathyroid carcinomas and almost always present in adenomas. Rb protein is a cell-cycle regulator that blocks transformation from the G1 (resting) in the S (synthesis) cellular cycle phase, and directly reacts with cyclin-D1. Cyclin-D1 was found to be positive in a small percentage of normal parathyroid tissues (<6%) and may be used as the additional technique in distinguishing between benign and malignant parathyroid tumors. In the present case, cyclin-D1 was found to be negative. On the contrary, Dotzenrath et al.8 and Kytola et al.9 report that Rb protein cannot be used in differentiation between benign and malignant parathyroid tumors. They obtained much stronger reaction in carcinomatous cells stained with Ki-67 proliferation marker. Furthermore, Abbona et al. found statistically significant differences between adenomas and carcinomas using Ki-67 proliferation marker. Today, it is considered that only Ki-67 and p-27 proteins are efficient markers to distinguish adenoma and carcinoma, whereas others such as p-53 and bcl-2 are not reliable. Stojadinovic et al. report that a multiple-marker phenotype including
p-27, bcl-2, Ki-67 and Mdm-2 was useful in defining a subset of benign tumors but that carcinoma displayed a complex range of multi-marker phenotypes, some of which were not specific. In the present case, the Ki-67 protein, Mdm-2, RCC (thus excluding metastases of simultaneous RCC) and thyroglobulin protein (thus excluding thyroid tumors) were all negative. Due to the lack of the specific gold-standard histopathologic criteria in recognition of parathyroid carcinomas, up to 86% of cases are not initially recognized and receive inadequate surgical resection, or the diagnosis is made after disease relapse, thus limiting treatment options. Furthermore, about 20% of patients with apparently sporadic carcinoma may be manifesting a form of hyperparathyroidism-jaw tumor syndrome, i.e. a hereditary multitumor syndrome characterized by HRPT2 gene mutations. This gene has recently been identified as a tumor suppressor gene in parathyroid carcinoma, encoding a novel protein product named parafibromin. Tan et al. suggest that the loss of parafibromin immunoreactivity could distinguish parathyroid carcinoma from benign pathologies of primary hyperparathyroidism.

Another novel gene associated with the parathyroid tumor carcinogenesis is the UCHL1 protein gene product 9,5 (PGP-9,5). It is expressed in neuronal and neuroendocrine tissues, as well as during embryonic development in the parathyroid glands of the rat. Positive diffuse staining for PGP-9,5 has a 78% sensitivity and 100% specificity for parathyroid malignancies. In the present case, the tumor showed high positive expression for PGP-9,5 that confirmed the diagnosis of parathyroid gland carcinoma. With the use of these two highly sensitive and specific markers, hyperparathyroidism tumors are classified in categories with high risk malignancy and atypical adenomas. High-risk carcinomas are positive for parafibromin and PGP-9,5, whereas low-risk ones are positive for PGP-9,5 but negative for parafibromin. Atypical tumors which are parafibromin positive and PGP-9,5 negative should be classified as atypical adenomas and treated with simple surgical excision.

Conclusion
Non-functioning parathyroid carcinoma is extremely rare. These tumors are associated with normocalcemia and normal serum parathyroid hormone level. They need to be distinguished from other functioning parathyroid and metastatic carcinoma in order to be properly treated. Immunohistologic pathologic analysis can be a valuable method in the diagnosis of parathyroid carcinoma. Surgical removal remains the best possible treatment option.

References


Sažetak

NEFUNKCIONALNI KARCINOM PARATIROIDNE ŽLIJEZDE: PRIKAZ SLUČAJA

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Karcinom paratiroidne žlijezde je rijedak maligni tumor. Tumor je najčešće hormonski aktivan i uzrokuje teški oblik hiperparatiroidizma s visokom serumskom razinom kalcija, poremećajima koštane gustoće i bubrežnim kamencima. Ne-funkcionalni paratiroidni karcinom je iznimno rijedak. Prikazuje se slučaj 60-godišnjeg bolesnika koji je primljen na Odjel otorinolaringologije zbog velikog tumora vrata koji je komprimirao grkljan i dušnik. Prijeoperacijski su serumske vrijednosti hormona štitnjače, paratiroidnog hormona i kalcija bile unutar referentnih vrijednosti. Korišteni su slijedeći imunohistokemijski biljezi: (DAKO, Danska): bcl-2; CD-10; Chromogranin-A; Cyclin-D1; Ki-67; Mdm-2; p-53; RCC; Synaptophysin; Thyroglobulin i TTF-1. Imunohistokemijskom analizom tumora postavljena je dijagnoza primarnog karcinoma paratiroidne žlijezde. Tumorske stanice su pokazale difuznu pozitivnu imunoreakciju s kromograninom i PGP-9,5, pozitivnu reakciju različitog intenziteta sa sinaptofizinom, te slabo pozitivnu reakciju na EMA. U citoplazmi je nađena umjereno pozitivna reakcija na bcl-2, a jezgre su bile pozitivne na p-53 i TTF-1, dok su ostali biljezi bili nereaktivni. Četiri godine nakon operacije bolesnik je umro od posljedica plućnih metastaza karcinoma bubrega i dekompenzirane jetrene ciroze. U zaključku, nefunkcionalni karcinom paratiroidne žlijezde je vrlo rijedak i težak za dijagnosticiranje. Detaljnim imunohistokemijskim metodama potrebno ga je diferencirati od ostalih tumora štitne i paratiroidne žlijezde i metastatskog karcinoma. Kirurško liječenje danas predstavlja optimalan oblik terapije.

Ključne riječi: Paratiroidni tumori – dijagnostika; Paratiroidni tumori – patologija; Nefunkcionalni paratiroidni tumori