

Case report

Simultaneous occurrence of papillary and medullary thyroid carcinoma in a 25-year-old female patient: a case study

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Summary

Introduction. This study presents a rare case of a patient with simultaneously present papillary and medullary thyroid carcinomas.

Case report. A 25-year-old female patient with a simultaneous occurrence of papillary and medullary thyroid carcinoma and a positive family history of benign thyroid illness was presented. Our patient presented with non-specific symptoms, which led her to consult her family physician. The patient had undergone a complete thyroidectomy only three weeks after her first doctor's appointment since her family physician quickly and correctly presumed thyroid disease. The patient had two operations. During the first surgery, a total thyroidectomy was performed, and 19 regional lymph nodes were removed, two of which were positive for papillary and two for medullary carcinoma. Histopathological examination revealed papillary carcinoma in the left lobe and medullary carcinoma in the right lobe of the thyroid gland. Following the aforementioned surgery, the papillary carcinoma was treated with radioactive iodine, while the medullary carcinoma was treated surgically. Given the high calcitonin levels after thyroidectomy, a several months later new surgery was performed to remove the lymph nodes of the neck (four of nine lymph nodes were positive for medullary carcinoma). RET proto-oncogene test results were negative. The patient had no known risk factors for the development of a malignant disease.

Conclusion. The patient is feeling well two years after diagnosis and complete thyroidectomy, while on her regular checkups, no metastases have been found.

Key words: papillary thyroid carcinoma, medullary thyroid carcinoma, simultaneously present

Introduction

Neoplasms of the thyroid gland can originate from any type of cells found in the thyroid gland, including follicular cells, C-cells (which produce calcitonin), lymphocytes, and stromal and visceral elements [1, 2]. Papillary thyroid carcinoma (PTC) is the most common type, accounting for approximately 84% of all malignant thyroid carcinomas. PTC has a relatively favorable prognosis and a high survival rate. Medullary thyroid carcinoma (MTC) is an uncommon type, accounting for approximately 4% to 10% of all cases. MTC is a rare neuroendocrine tumor originating

from parafollicular cells, which produce calcitonin. The literature reports that, at the time of diagnosis, metastases in local lymphatic nodes are found in approximately half of patients and remote metastases in 15% of patients [3, 4].

The number of patients with malignant thyroid carcinoma is increasing either because of a rise in the incidence of the disease or better diagnostics. Approximately 44,000 new cases of thyroid carcinoma are diagnosed in the United States of America annually, with a 98.5% 5-year survival rate. It was estimated that 43,720 new cases would be diagnosed in 2023 [1].

In recent decades, the incidence of PTC has been on the rise, while the number of patients with MTC in the same period did not increase and remained at the same level. The use of high-resolution ultrasound devices as well as the puncture of found thyroid nodules with fine needles for aspiration with cytological findings improved the diagnosis of malignant tumors of the thyroid gland [5].

Some of the authors believe that the stable incidence of MTC is the result of the existence of the same risk factors, of which the role of genetic risk factors and gene mutations on the RET (REarranged during Transfection) proto-oncogene is emphasized [6, 7].

In cases of simultaneous occurrence of MTC and PTC, tumors can be located in one lobe or are located in separate lobes, which increases the probability of independent tumor origins [8].

PTC is more common in the general population, but gene mutations of the RET pro-oncogene are present in only 20–40% of cases, while genetic mutations are responsible for 30–50% of MTC cases [9, 10].

RET (Rearranged during transfection) proto-oncogenes were discovered in 1985 and were quickly associated with papillary thyroid carcinoma. For many years, this genetic mutation was thought to be associated only with PTC, but further research has shown that RET/PTC rearrangements can also be found in other tumors. A few years after the discovery of this mutation, additional research has shown that

this mutation can be found in both hereditary and sporadic forms of medullary thyroid carcinoma (MTC). Identification of RET mutations is important for early diagnosis of hereditary MTC and prognosis of sporadic MTC, while RET/PTC mutations have great importance in the management of patients with PTC [11].

This study describes the case of a young patient with simultaneously present PTC and MTC, which developed as separate carcinomas in the left and right lobes of the thyroid gland.

Case Report

A 25-year-old female patient visited her family physician complaining that she was always tired, without energy, anxious, in a depressive mood, and got tired quickly. She also complained of throat tightness and chest pain. Since she was not feeling well, she had already undergone laboratory testing, including a complete blood count (CBC), free triiodothyronine (fT3), free thyroxine (fT4), and thyroid-stimulating hormone (TSH), all of which were within reference values. Regardless of normal hormone levels, the patient was sent for an ultrasound of the thyroid gland due to a suspicion of thyroid disease. The ultrasound revealed a right lobe size of 44x16x14 mm and a left lobe size of 42x15x13 mm. A 7x6 mm hypoechogenic nodule was found in the upper half of the right lobe, and a 6x5 mm hypoechogenic nodule with microcalcifications was found in the lower half of the left lobe. Suspicious enlarged lymph nodes were located on the right side of the neck, in the lower jugular chain, right behind the jugular vein.

The preoperative thyroglobulin test (thyroglobulin - TG) was normal (25.36 ng/mL), while the 82.84 pg/mL calcitonin level was significantly elevated. Total thyroidectomy was suggested and performed.

Histopathology of the node in the left lobe showed the follicular subtype of papillary carcinoma with lymph-node metastasis.

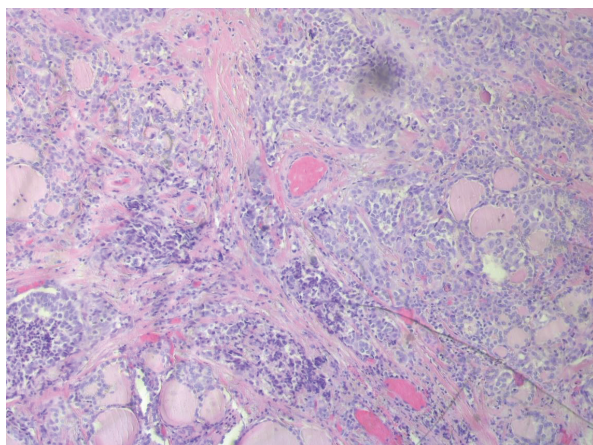


Figure 1. Medullary carcinoma, HE 10x - right lobe

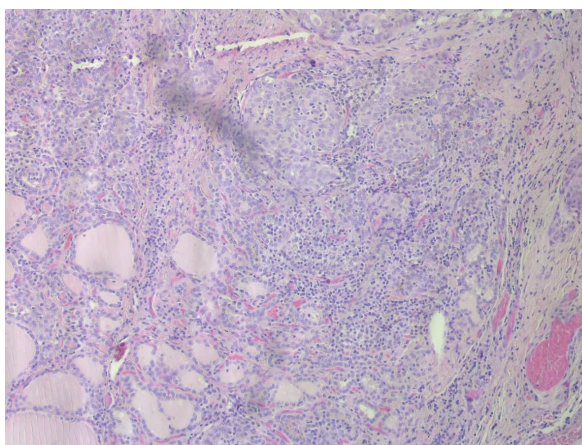


Figure 2. Papillary carcinoma, follicular type, HE 10x - left lobe

Histopathology of the node in the right lobe was diagnosed as MTC based on the histological pattern and immunohistochemistry results (calcitonin +, synaptophysin +, thyroglobulin +). Nineteen regional lymph nodes were removed during surgery, and tumor tissue was found in four lymph nodes (two lymph nodes were positive for papillary and two for medullary carcinoma).

Radioactive iodine therapy (3.7 GBq of I-131) was administered for the treatment of papillary carcinoma, which the patient tolerated well.

Considering the patient's young age and that she was suffering from a rare condition of two simultaneously present malignant carcinomas, the patient was sent to undergo a test for the RET proto-oncogene, which did not show an increased risk of developing malignant diseases that were incorporated in this test. The patient was testing on PreSENTIA Pan-Cancer Panel on hereditary cancer (Hereditary cancer panels for Personalized Risk Assessment) which can identify genetic variants on 19 hereditary cancer panels and up to 62 genes include testing on thyroid cancer.

The patient was monitored after surgery and radioactive iodine therapy. Her postoperative calcitonin levels were continuously elevated, with values of 3.43 pg/mL, 21.60 pg/mL and 33.43 pg/mL. Several months after total thyroidectomy ultrasound examination

showed enlargement of the lymph nodes on the right side of the neck in groups II, III, IV, and V. A new surgery was performed, and nine lymph nodes were removed. Malignant cells of medullary carcinoma were found on the capsules of four removed nodes, but no extranodal extension (ENE) was observed. Immunohistochemistry revealed very high calcitonin levels (+++).

After surgery and removal of suspicious lymph nodes, a repeat ultrasound examination and CT scan were performed. The findings showed the condition after thyroidectomy and no suspicious enlargement of local lymph nodes was observed. The calcitonin level dropped after the removal of the cervical lymph nodes, so that the last measured values of serum calcitonin were 3.55 pg/mL and 3.41 pg/mL. During the complete monitoring of the course of the disease, laboratory values of thyroglobulin (Tg) were also monitored, which after the end of the surgical treatment were within the normal range (0.87 ng/mL). The values of carcinoembryonic antigen (CEA) were also measured, and the last measured value of this tumor marker was 1.4 ng/mL.

The patient felt well 24 months after surgery. During her regular checkups, no local or remote metastases were found, and calcitonin levels were normal.

Discussion

This case report describes the young patient presenting with both PTC and MTC simultaneously. Our patient presented with non-specific symptoms, which led her to consult her family physician. However, other authors [12] state that the disease was often asymptomatic and was only revealed during physical examination or by accident during diagnostic procedures. Other authors report cases of patients with concurrent PTC/MTC in whom the disease was diagnosed due to thyroid enlargement or the appearance of a nodule in the neck [13].

Most authors state that they performed a fine-needle aspiration biopsy with cytological findings before surgery, as this is the best method for diagnosing thyroid nodules with a high degree of sensitivity and specificity [14, 15]. In our patient's case, no puncture was performed. Based on the ultrasound findings and the pathological appearance of the thyroid nodule, a decision was made to perform an urgent total thyroidectomy with extirpation of regional lymph nodes. Malignant thyroid disease was confirmed postoperatively based on histopathological findings.

In the case of our patient, there were close family members with benign thyroid diseases (benign nodules, Hashimoto's thyroiditis), but no one had malignant disease. So, our patient has a positive family history of benign thyroid illness. This is the observation mirrored in case studies reported by other researchers [16]. The other authors report an association between Hashimoto's thyroiditis and thyroid cancer. It is believed that 25% of papillary thyroid carcinomas occur in patients with Hashimoto's thyroiditis, which is explained by the presence of the same biomarkers, gene mutations, and immunological mechanisms. However, the mechanism of the simultaneous occurrence of PTC and MTC has not yet been elucidated [16]. Our patient did not have Hashimoto's thyroiditis, and the development of PTC could not be fully attributed to the aforementioned mechanisms.

The RET proto-oncogene genetic test in our patient showed a negative result. The results of other studies have shown a significant impact of gene mutations on the development of PTC and MTC. The one research has shown a PTC/MTC prevalence of only 0.7% within a sample of 690 cases of malignant thyroid carcinomas. Research studying the influence of genetic mutations on the occurrence of PTC and MTC showed that there was an influence of genetic mutations on the occurrence of PTC and MTC, but did not prove the influence of genetic mutations on the simultaneous occurrence of PTC/MTC [17, 18].

After total thyroidectomy, the patient had elevated serum calcitonin levels for several months, which indicated the presence of metastases of medullary carcinoma. Continuous ultrasound monitoring was performed, and several months after total thyroidectomy, suspicious lymph nodes were observed in the neck, which required a new operation. Pathohistological findings of the removed lymph nodes proved the presence of metastases. The importance of monitoring calcitonin levels has been demonstrated in our case, but also in reports of other cases [19, 20] where the importance of monitoring serum calcitonin levels for the earliest possible identification of metastases has been demonstrated. In our case, after surgical removal of metastatic lymph nodes, there was a sudden drop in calcitonin levels, which has also been shown by other authors [21].

Our case involves the patient 25 years old, whereas other research [21] indicates that simultaneous development of PTC/MTC is most common among middle-aged individuals, with an age range of 49.5 to 64 years, excluding young patients with a positive family history.

The available literature indicates that this disease is more frequent in female patients (60–100%), which is consistent with our patient's sex. However, some studies have also reported a higher prevalence of male patients or an equal prevalence of male and female patients [17, 22].

Family physicians play an important role in establishing a suspicion of a more severe thyroid disease as early as possible and in referring the patient for additional diagnostics. However, this is usually difficult because patients are usually asymptomatic or have non-specific symptoms. Early diagnosis of the disease is crucial for therapy, improving the prognosis, and increasing the chance of patient survival.

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Ethical approval. This article does not contain any studies with human participants performed by any of the authors.

Conclusion

The simultaneous occurrence of PTC and MTC is rare, although its prevalence has been mildly increasing during recent decades, either due to an increasing number of patients with malignant thyroid carcinomas or better diagnostics.

The role of gene mutations in the development of PTC/MTC has been proven, but not in all cases, which indicates the importance of further research in clarifying the origin of these malignant tumors.

Conflicts of interest. The authors declare no conflict of interest.

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Istovremena pojava papilarnog i medularnog karcinoma štitne žlijezde kod 25-godišnje pacijentkinje: prikaz slučaja

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Uvod. U ovom radu prikazan je rijedak slučaj pacijentkinje sa istovremenom pojavom papilarnog i medularnog karcinoma štitne žlijezde.

Prikaz slučaja. Prikazana je pacijentkinja stara 25 godina sa istovremenom pojavom papilarnog i medularnog karcinoma štitne žlijezde i pozitivnom porodičnom anamnezom benigne bolesti štitne žlijezde. Pacijentkinja se javila svom porodičnom ljekaru zbog nespecifičnih simptoma. Zahvaljujući brzo postavljenoj sumnji na oboljenje štitne žlijezde od strane porodičnog ljekara, totalna tireoidektomija je urađena već tri nedjelje nakon prvog pregleda. Pacijentkinja je podvrgnuta dvjema hirurškim intervencijama. Tokom prve operacije izvršena je totalna tireoidektomija uz uklanjanje 19 regionalnih limfnih čvorova, od kojih su dva bila pozitivna na papilarni, a dva na medularni karcinom. Histopatološkim pregledom utvrđeno je prisustvo papilarnog karcinoma u lijevom režnju i medularnog karcinoma u desnom režnju štitne žlijezde.

Nakon navedene operacije, papilarni karcinom liječen je terapijom radioaktivnim jodom, dok je medularni karcinom liječen hirurški. Zbog perzistentno povišenih vrijednosti kalcitonina nakon tireoidektomije, nekoliko mjeseci kasnije urađena je nova operacija sa ciljem uklanjanja limfnih čvorova vrata, pri čemu su četiri od devet uklonjenih limfnih čvorova bila pozitivna na medularni karcinom. Rezultati testiranja na RET protoonkogen bili su negativni. Kod pacijentkinje nisu identifikovani poznati faktori rizika za razvoj malignog oboljenja.

Zaključak. Dvije godine nakon postavljanja dijagnoze i izvršene totalne tireoidektomije pacijentkinja se osjeća dobro, a tokom redovnih kontrolnih pregleda nisu utvrđeni znaci metastatske bolesti.

Ključne riječi: papilarni karcinom štitne žlijezde, medularni karcinom štitne žlijezde, istovremena pojava