

NOTE

Synchronous Occurrence of a Follicular, Papillary and Medullary Thyroid Carcinoma in a Recurrent Goiter

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Abstract. The simultaneous occurrence of different types of thyroid carcinoma in a single patient is an unusual event. We report the case of a 52-year-old man with the history of two previous thyroid operations for benign goiters, who developed a recurrent goiter. The patient was referred to our department for thyroidectomy. In the pathohistological examination the specimen showed a 5 cm follicular carcinoma and a 0.3 cm papillary microcarcinoma in the right lobe as well as a 1.5 cm medullary carcinoma in the left lobe. All tumors were clearly separated from each other, representing the pure entity of each type. Postoperatively, *RET* germline mutation was ruled out by sequence analysis of peripheral blood leucocytes. Postoperative I-131-radioiodine scan showed multiple lung and liver metastases, while calcitonin was negative. There is no known common cause of these three different tumor types and they developed most independently from each other. The personal history of our patient was interesting in two aspects: (1) he suffered a period of severe staphylococcal sepsis with temporal immunosuppression and (2) he worked for long years as a coremaker in a foundry. This work represented possible long term exposure to inhalative carcinogenous toxins like hydrazine, which caused thyroid parafollicular cell adenomas in an animal model.

Key words: Papillary carcinoma, Follicular carcinoma, Medullary carcinoma

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THE incidence of differentiated thyroid cancer (DTC) varies from 0.5 to 10 new cases per 100,000 population per year worldwide [1]. Established risk factors for DTC are external radiation, female gender and age [2, 3]. Up to 30% of all papillary cancers seen in a thyroid surgeon's practice are microcarcinomas [4]. The biological significance of these small tumors is still being debated [5, 6], since the incidence of occult thyroid cancer in autopsy studies is much higher and reaches from 3 to 36% [7].

Medullary thyroid carcinoma (MTC) arising from the parafollicular C-cells represents 3–10% of all thyroid cancers. About 75% of them are sporadic, and

about 25% are *RET*-germline mutation associated [2].

Papillary thyroid carcinoma shows multifocal growth in up to 29% of cases [8, 9]. Nevertheless, the occurrence of multiple thyroid cancers of different origin in one individual patient is a rare event [10–14], while the synchronous occurrence of three different tumor types is extremely rare. Up to now, only one case report with a constellation of three different cancer entities has ever been published [15]. We present another patient with synchronous follicular, papillary and medullary thyroid cancer, which had developed in a recurrent goiter.

Case Report

A 52-year-old male Portuguese patient was admitted to our hospital for recurrent goiter. He lived in Germany for 28 years and worked as a coremaker in a

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foundry. He was a smoker from 16 to 24 years of age and had low alcohol consumption. His family history was free of any endocrine or non-endocrine malignant tumors. His personal history included surgery for nasal polyps, anal fistula and appendicitis. Since 13 years old he was suffering from chronic obstructive pulmonary disease. An outstanding event of the patient's past medical history was a septic shock caused by staphylococcal infection with temporary paraparesis and pulmonary embolism 10 years ago. There was no history of neck or whole body irradiation. The patient had two previous thyroid operations in other facilities: First, an enucleation of two thyroid nodules in 1986 and, second, resection of two thyroid nodules in the right and in the left lobe in 1996. Histology was benign in both operations. Paraffin embedded tissue for comparison was not available.

Despite regular medication of L-thyroxine 150 µg/d, the right thyroid lobe grew within one year (2003) to double the size. The patient had no specific complaints.

A routine ultrasound examination of the neck revealed a right thyroid lobe with a volume of greater than 40 ml. It contained multiple echo-homogeneous and echo-complex nodules. The left thyroid lobe had a volume of 5 ml, containing echo-complex as well as cystic nodules. There were small lymph nodes on the right side up to a size of 5 × 8 × 9 mm and no detectable lymph nodes on the left side. A thyroid scan showed a suppressed nuclide uptake in the right lobe. Calcitonin was not measured preoperatively. Fine needle aspiration biopsy was not performed. Chest X-ray study was normal. Electrocardiogram showed no signs of cardiac disease.

Right hemithyroidectomy was performed. Frozen section showed a follicular tumor with a diameter of 5 cm without clear signs of malignant growth. Postoperative histology identified this tumor to be a follicular carcinoma (Fig. 1). Distinct from this a 0.3 cm papillary microcarcinoma was found (Fig. 2). Five days later, a second operation with removal of the remaining thyroid gland on the left side and modified radical neck dissection on the right side was performed.

Surprisingly, the histology of the left lobe showed multiple focuses of medullary thyroid carcinoma with a maximum diameter of 1.5 cm (Fig. 3).

The resected lymph nodes from the right side showed no signs of infiltration by malignant cells.

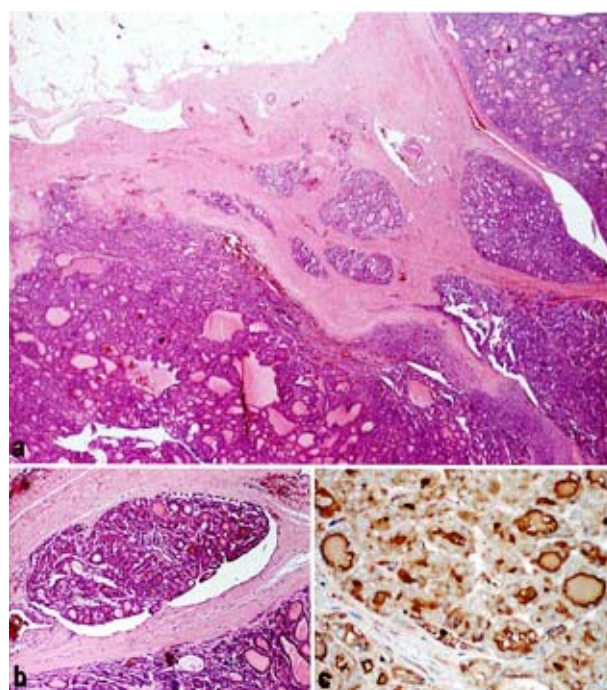


Fig. 1. Follicular carcinoma. (a) Follicular carcinoma of the thyroid with a broad fibrous capsule and an infiltrative growth beyond the capsule adjacent to adipose tissue. (b) Blood vessel invasion into a dilated vein of the tumor capsule. (c) Immunohistochemistry demonstrating strong thyroglobulin expression of the tumor cells.

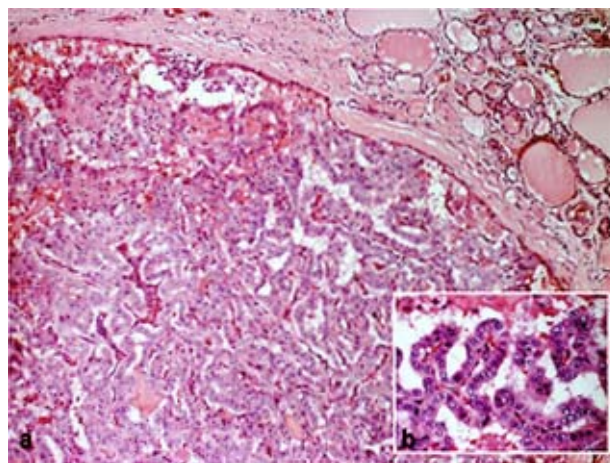


Fig. 2. Papillary carcinoma. (a) Encapsulated papillary carcinoma of the thyroid with a predominant papillary growth pattern adjacent to follicles of a goiter. (b) Typical papillae with ground-glass appearance of the nuclei.

Postoperative pentagastrin-stimulated calcitonin was negative, indicating biochemical cure from the medullary carcinoma. Sequence analysis of the RET-

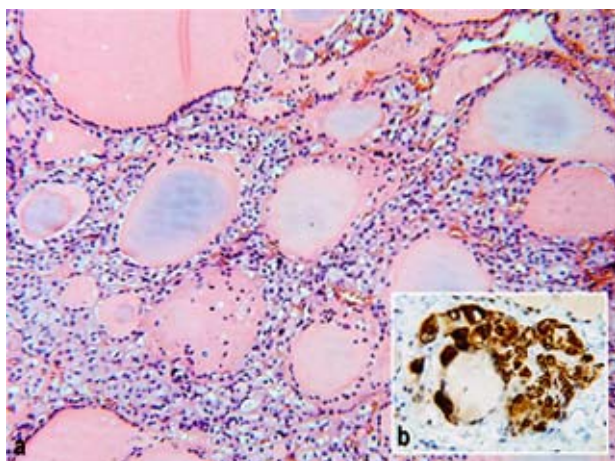


Fig. 3. Medullary carcinoma. (a) Infiltration of tumor cells with small round nuclei between non-neoplastic follicles of a goiter. (b) Immunohistochemistry demonstrating strong calcitonin expression of the tumor cells.

protooncogene from peripheral blood leucocytes showed no mutation in exons 10, 11, 13, 14, 15 and 16.

Radioiodine therapy was performed. Unfortunately 6 weeks after surgery, iodine-131 scan showed multiple liver and lung metastases, which were not seen in the preoperative routine X-ray of the chest. Therefore 3 months later a high dose iodine-131 therapy with a cumulative activity of 10,500 MBq was performed. After that therapy, the multiple lung and liver focuses were regressive compared with the first scan. Thyroglobulin decreased from 2280 ng/ml to 23.3 ng/ml. The next scan control is planned for 6 months later.

Discussion

The combination of three different types of thyroid cancer has been reported only once. In 1992 Gonzalez-Campora *et al.* [15] reported a 27-year-old woman with the combination of a 3 cm follicular carcinoma, a 0.4 cm medullary carcinoma and a papillary microcarcinoma. All three carcinomas were separated from each other. This finding is very similar to our case. Both cases present the focal isolation of all three cancers within one thyroid. There is no hint for intra-thyroidal metastatic spread, since each of the tumors in our patient displays the pure and characteristic pattern of the distinct entity (see Figs. 1–3).

In contrast to these cases the coexistence of various degrees of differentiation in different areas within one

bulky thyroid cancer is rather frequent. Specifically in iodine-deficient areas, dedifferentiation patterns of PTC resembling FTC may account for the major part of the tumor. In this regard, thyroid tumors with mixed histologic characteristics have been described. The most interesting case was described by Parker *et al.* in 1985 [16]: A 51-year-old man showed a composite tumor with mixed pattern of a medullary, papillary, follicular and undifferentiated carcinoma in the thyroid gland and a lymphatic spread of all four tumor types to the regional lymph nodes.

Several genes and genetic alterations which are involved in the tumorigenesis of each type of thyroid cancer have been identified. Activating somatic *Ras*-mutations in follicular thyroid cancer [17], somatic rearrangements of *RET/PTC* as well as *TRK* and *BRAF*-mutations in papillary thyroid cancer [18–20]. *p53*-missense mutations in radiation-induced papillary thyroid cancer were found [21]. Germline *RET* missense mutations are found in the majority of hereditary MTC [22, 23]. Today, there is no common mutation known to be involved in the pathogenesis of all three tumor types. Thus the most likely explanation for the findings in our patient is a mere coincidence.

But two events and aspects in our patient's history may be worth mentioning: First, 10 years ago the patient suffered a severe septic shock caused by staphylococcal infection with temporary paraparesis, a condition which is highly associated with immunosuppression. Second, he worked for long years as a coremaker in a foundry. A coremaker makes sand cores used in molds to form holes or hollows in metal castings. During these work processes, he may have been exposed for a long term to any cancerogenic agents, especially those which are inhalative. In this regard, the coincidence of the thyroid cancers with the history of nasal polyps in our patient may be of special interest. Vernot *et al.* [24] showed that long term exposure to hydrazine (N_2H_4) can induce benign nasal adenomatous polyps, colon neoplasms and thyroid parafollicular cell adenomas in hamsters. Hydrazine is used as a material for several industrial working processes. Hydrazine itself is normally not used in the working area of a coremaker, but some other similar substances are employed, *i.e.* isocyanates and alkylamines in connection with a cold hardening process called "cold-box-process". In a warm hardening processes — generally called "hot-box-process" — hexamethylenetetramine as a promoter for amine gener-

ation (functions as catalyst) by thermal degradation is used. The thermal degradation products are not well studied but it is suggested that inhaltive toxins of the amine and nitrile type which can cause cancers may be generated unintentionally [25–27]. The nasal polyps and chronic obstructive pulmonary disease of our patient may be a hint for a chronic inflammatory reaction caused by long term exposure with inhalative toxic

substances.

There is another instructive aspect in the presented case. Our patient had two partial thyroid resections in the past and presented with re-recurrent goiter. We emphasize complete thyroidectomy or at least hemithyroidectomy in all cases of recurrent goiter to avoid third operations which would increase the risk of recurrent nerve palsy or permanent hypoparathyroidism.

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