Case Report Thyroid neuroendocrine cancer accompanied with multiple papillary thyroid carcinomas: a case report

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Abstract: Neuroendocrine tumors (NETs) are neoplasms that arise from the cells of endocrine and nervous systems. Most of them are found in the gastrointestinal tract; however, some cases of NETs have been detected in the thyroid gland, especially the malignant NETs. In this paper, we have reported a case of NET in the thyroid gland; the tumor was accompanied with multiple papillary thyroid cancers. The patient had also developed cervical lymphatic metastasis. Before performing the operation, the lesions were detected by ultrasound examination. However, the pathological results of this case were unexpected. The patient was subjected to FNA examination. Thereafter, we performed total thyroidectomy and cervical lymph node dissection. The diagnosis was confirmed by pathological examinations. PET-CT was also performed after the operation to rule out the occurrence of secondary endocrine cancers.

Keywords: Neuroendocrine cancers, thyroid, papillary thyroid carcinomas

Introduction

Thyroid cancer is very commonly encountered in clinical practice. In general, papillary thyroid cancer is detected in most cases [1], accounting for about 75-85% of thyroid malignancies. Although the incidence of papillary thyroid is very high, the prognosis of patients is not very poor [2]. Lymphatic and distant metastasis are usually detected in patients with multiple lesions, or in patients diagnosed with other malignant tumors; many young children also develop lymphatic and distant metastasis [3]. A high frequency ultrasound is generally used for differentiating malignant nodules from benign ones in the thyroid gland [4].

Neuroendocrine tumors (NETs) are neoplasms that arise from the endocrine and nervous systems. Most NETs are benign, while some are malignant. They are most commonly encountered in the intestine, where they are often known as carcinoid tumors, but they can also occur in the pancreas, lungs, and the remaining organs of the human body [5, 6]. In this paper, we have reported a case of NET; the tumor was detected in the thyroid gland, and it was accompanied by multiple papillary thyroid carcinomas.

Case report

A 54-year-old woman was admitted to our hospital as she had developed a slowly growing mass in her neck. About a month ago, she had accidentally found the cervical mass but she did not experience any pain. There was no hoarseness in her voice: she also did not experience any difficulties in breathing or swallowing. She did not show any signs of hypermetabolism or temperature change. Physical examinations revealed a mass in the right upper neck. The mass was located under the jaw, next to the mastoid process; it was 5.0 cm × 3.0 cm × 3.0 cm in size. As this mass was oval and smooth, we thought it was a swollen lymph node. Therefore, we performed an ultrasound scan to examine the swollen mass. We did not detect any swelling in the thyroid gland through the ultrasound scan; physical examination also did not reveal any masses in the thyroid gland.



Figure 1. The ultrasonic image of the nodule in the middle of the right lobe. It was further diagnosed as papillary cancer by FNA.



Figure 2. An ultrasonic image of the nodule located in the upper pole of the right lobe. It was confirmed as neuroendocrine cancer.



Figure 3. The swollen lymph node in level II of the right neck, measuring $4.9 \text{ cm} \times 2.3 \text{ cm}$.



Figure 4. The pathological image of neuroendocrine cancer (HE stained, $200 \times$).

A cervical ultrasound was also performed on the same day. In this scan, we detected two small hypoechoic nodules in the upper part of the left lobe and the middle part of the right lobe. In the upper part of the left lobe, the nodule was 0.24 cm × 0.34 cm in size. In the middle part of the right lobe, the nodule was 0.63 × 0.71 cm in size (Figure 1). Both these nodules were blurry in appearance as they did not have a clear capsule. The shape of the nodules was irregular; their length was greater than their width. Another solid hypoechoic nodule, measuring 1.0 cm × 0.9 cm in size, was detected in the upper pole of the right lobe (see Figure 2). However, it had a clear boundary and was regular in shape. Furthermore, we also detected several swollen lymph nodes in level II of the right neck. The biggest lymph node was 4.9 cm × 2.3 cm in size (see Figure 3). The lymph nodes were heterogeneous and solid; these lymph nodes had clear boundaries. An enhanced cervical CT examination was also performed. Thus, we detected several low-density areas of nodules; the biggest nodule was 1.4 cm × 0.7 cm in size; it was located in the upper pole of the right lobe. Several heterogeneous soft tissues of nodules were enhanced in the oropharynx, which was located in the right parapharyngeal space; the biggest nodule was 4.3 cm × 2.7 cm × 2.3 cm. No positive results were detected while performing chest radiography or laryngoscope examination. The results of the laboratory tests and the reference ranges were listed as follows: TSH: 3.46 uIU/mI (0.27-4.2), FT3: 4.44 pmol/L (3.1-6.8),

A rare case of neuroendocrine carcinoma in thyroid gland



Figure 5. A-F: The immunohistochemical results of the nodule: Tg (-), CgA (+), MaxVison Syn (+), MaxVisonTTF-1 (+), MaxVisonCalcition (-), MaxVisonKi-67: 40%+.

FT4: 16.24 pmol/L (12.0-22.0), TG-Ab: 73.36 IU/ml (< 115.0), TPO-Ab: 27.09 IU/ml (< 35.0). The levels of parathyroid hormone, carcino-embryonic antigen, and calcitonin were normal.

Fine needle aspiration (FNA) biopsy was performed on the nodule located in the middle of the right lobe; thyroid papillary cancer was detected in the biopsy, so the swollen lymph nodes were considered to be metastatic in nature. Subsequently, we also performed total thyroidectomy and cervical lymph node dissection. During the operation, we excised several lymph nodes surrounding the right jugular vein; the biggest lymph node was 5.0 cm × 3.0 cm in size. Frost pathological examination of the lymph nodes indicated that the carcinoma was poorly differentiated. A similar nodule was found in the upper pole of the right lobe of the thyroid. It had many necrotic cells, and signs of fission were detected in the pathological images (see Figure 4). The immunohistochemical results of the nodule were as follows: Tg (-), CgA (+), Syn (+), Calcition (-), Ki-67 (+, 40%), TTF (+), HBME-1 (+) (see Figure 5). Thus, we confirmed that the patient had developed neuroendocrine cancer in the thyroid gland. Another four micro papillary carcinomas were detected in the rest of the thyroid gland; two papillary carcinomas were found in the right lobe (measuring 0.2 cm and 0.7 cm in length and width, respectively) and the other two papillary carcinomas were found in the left lobe (both measuring 0.2 cm in length). The immunohistochemical results of the four nodules were as follows: Tg (+), CgA (-), Syn (-), Ki-67 (+, < 5%), HBME-1 (+).

In order to determine whether neuroendocrine carcinoma had developed in other parts of the patient's body, we performed positron emission tomography-computed tomography (PET-CT) scanning of the patient. The results of the scan were negative. So, the final diagnosis of this patient was primary neuroendocrine cancer accompanied with multiple thyroid papillary cancers and cervical lymph node metastasis. The patient was prescribed an oral tablet of sinistral thyroxine to inhibit the function of the thyroid gland, and 1131 radiotherapy treatment was provided to the patient. Six months after the operation, no positive findings were detected during the follow-up.

Discussion

NETs arise from neuroendocrine cells, which are widely distributed in many tissues of the body. The functions of neuroendocrine cells are similar to those of neurological and endocrinal cells. So, NETs can also develop in many other organs of the human body [7]. The incidence of NETs is quite low; according to the reports of Jan Maarten, about 25 cases of NETs are detected in a population of 1000,000 [8]. Most of the NETs (about 76%) are found in the gastrointestinal tract, lung, and bronchus [2, 9]. Although there are many kinds of NETs, they are treated as a group of tissues, because the cells of these neoplasms share common features, such as similar appearance and special secretory granules. Moreover, they often produce biogenic amines and polypeptide hormones [10]. Malignant neuroendocrine tumors, also known as neuroendocrine carcinomas (NEC), are divided into three types according to the extent of their differentiation. The well differentiated NECs are also called carcinoids, while the moderately differentiated NECs are called atypical carcinoids. Furthermore, the poorly differentiated NECs are called small cell carcinomas.

In very rare cases, we have detected NETs in the thyroid glands. The origin of these tumors has been associated with various kinds of cells, including the parafollicular cells, paraganglion cells, and parathyroid gland [11]. According to their origin in the thyroid gland, NETs are divided into six groups: parafollicular tumors, paraganglion tumors, complex tumors originating from both follicular and parafollicular cells, parathyroid tumors, secondary NETs, and NECs. Compared with NETs, NECs are found in extremely rare cases. After searching the database of our hospital, we found that only this case was finally diagnosed with NECs out of a total of 12100 patients, who had undergone surgical treatment from December, 2009 to April, 2015.

Most of the patients with NETs were older than 65 years [8]. In the early phase, the hormone produced by the tumor was very low. As a result, very few of these patients showed symptoms related to NETs. In this case, the patient was admitted at our hospital because she had developed a slowly growing mass in the neck. Using various diagnostic techniques, we confirmed that swollen mass actually consisted of several swollen lymph nodes.

The diagnosis of thyroid NECs includes the following two aspects: 1) The tumor arises from the thyroid gland; 2) The tumor fulfills the criteria of diagnosing NECs. Before performing the operation, it is very difficult to make a correct diagnosis of thyroid NCEs. Most of the cases are diagnosed on the basis of immunohistochemical examinations. NECs are found to be positive in NSE, CgA, and Syn. The expression of Ki-67 is associated with the differentiation of NECs. In this case, the NECs were poorly differentiated, because the expression of Ki-67 was higher than 40%; however, in papillary thyroid cancer tissues, the expression of Ki-67 was lower than 5%. In pathological images, poorly differentiated NECs have small cells; these cells have a deeply stained, round nucleus. For example, consider the case of "small blue cell

tumors": these tumors contain uniform cells. which have a round to oval shaped nucleus and a scanty cytoplasm consisting of pink granules. There can be anaplasia, mitotic activity, and necrosis in these tumor cells. High power examination exhibits bland cytopathology. Electron microscopy can identify secretory granules, which are vital to make a correct diagnosis of the case. In this case, the patient underwent PET-CT examination after the surgery. No other tumors were detected in this scan. Although the tumor tested negative in Tg, it was positive in TTF-1, CgA, and Syn. So, it was finally confirmed that the patient had developed NECs in the thyroid gland. Two similar cases were reported by Eusebi V in 1992 [12].

Medullary thyroid cancer (MTC) is a form of thyroid carcinoma that originates in the parafollicular cells (C cells), which produce the hormone calcitonin. Medullary tumors are the most commonly seen thyroid NETs; they are the third most common type of thyroid cancers. They make up about 3% of all thyroid cancer cases [13]. We have also come across cases in which MTCs tested negative for calcitonin [14]; however, most of these cases have a family history of hyperplasia in the parafollicular cells. In this case, the tumor tested negative for calcitonin; but we also did not detect a hyperplasia of parafollicular cells.

Secondary thyroid NECs originates from the tissues of thyroid gland. We performed a thorough literature search to determine the incidence of secondary thyroid NECs; only 9 cases were reported until February, 2012 [15-23]. Most cases of secondary thyroid NEC originated from the larynx and long tissue [23]. Cytologically and pathologically, secondary NETs are similar to those of MTCs [16, 20, 21]. However, secondary NETs are negative in calcitonin and CEA, while MTCs are positive. In this case, when the patient underwent PET-CT examination after the surgery, no other NETs were found. So, we propose that the patient had developed primary NEC in the thyroid gland.

Surgery is the conventional treatment in cases diagnosed with poorly differentiated thyroid NECs. The invasiveness of such NECs is very strong, especially tumors that test negative for calcitonin [24]. In our case, the prognosis of the patient was unfavorable, as there was metastasis of the cervical lymph nodes. Moreover, the patient had developed a poorly differentiated tumor. Both the metastatic lymph nodes and the poorly differentiated tumor are insensitive to chemoradiotherapy.

Disclosure of conflict of interest

None.

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