

Metastatic carcinoma of the thyroid gland: a study of 18 cases during a nine years' period

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Abstract: Metastasis to the thyroid gland is extremely rare. The aim of this study is to investigate the clinical and pathological features of metastatic carcinomas of the thyroid. The clinical data of 18 patients with thyroid metastatic carcinoma were obtained from the Affiliated Hospital of Qingdao University ranging from January 2010 to January 2019. All clinical records were carefully reviewed, and follow-up was made by telephone. There were 9 males and 9 females in this group. In descending order, the primary lesions were lung adenocarcinoma (6 cases), small-cell lung cancer (5 cases), breast cancer (3 cases), and esophageal squamous cell carcinoma (2 cases), hypopharyngeal cancer (1 case), gingival cancer (1 case). The thyroid metastasis was presented as the main complaint in 3 patients. The interval from the diagnosis of primary tumor to metastasis ranged from 4 months to 16 years. Thyroid metastatic carcinoma is rare, and the present study is one of the largest case series to date. Our study indicates that lung cancer and breast cancer are the two common types of thyroid metastases in China.

Keywords: Metastatic carcinoma; Thyroid; Pathology; Immunohistochemistry

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1. Introduction

Metastatic cancer to the thyroid is rare. It accounts for about 2 % of all thyroid malignant tumors[1]. The earliest description of metastasis to the thyroid gland is attributed to Virchow, who described a metastatic testicular tumor in 1871[2]. The detection rate of metastatic cancer in thyroidectomy specimens is about 0.13%, and about 2.3-7.5% in fine needle aspiration cytology specimens[1,3]. According to literatures reports, lung cancer and kidney cancer are the two common primary tumors, and followed by colorectal cancer and breast cancer[1,4]. However, the gastrointestinal cancer is the most common tumor type of thyroid metastases in China[5-7]. In some patients, it is difficult to make an accurate diagnosis for the metastasis interval long. Due to its rarity, there are few reports on the metastasis to the thyroid gland. In this study, we have retrospectively reviewed 18 cases of metastatic cancer to the thyroid gland in one institution. The incidence of thyroid disease in Qingdao was high, and there was more than 2000 patients who accepted thyroidectomy in our institution[8]. To the best of our knowledge, the present report is one of the largest case series to date in China.

2. Materials and Methods

The clinical data of 18 patients with thyroid metastatic carcinoma were collected from the Affiliated Hospital of Qingdao University ranging from January 2010 to January 2019. A total of 13679 thyroid

malignancies was diagnosed during this period, including 13661 cases of primary malignancies (accounting for 99.9%) and 18 metastases (0.1%). The most common primary malignancy was papillary thyroid carcinoma (13246, 96.96%), and followed by medullary carcinoma (173, 1.27%), follicular carcinoma (139, 1.02%), undifferentiated (anaplastic) carcinoma (50, 0.37%), poorly differentiated carcinoma (23, 0.17%), lymphoma (17, 0.12%, including 15 cases of diffuse large B-cell lymphoma and 2 cases of mucosa-associated marginal zone B-cell lymphoma), squamous cell carcinoma (7, 0.05%), and 6 cases of thyroid carcinoma with thymus-liked differentiation (0.04%) (Figure 1).

The cases meeting the following criteria were diagnosed as metastasis: (1) a definite medical history of primary malignancies in other locations; (2) pathology examination did not support a primary thyroid cancer; (3) excluded direct invasion of malignancies in surrounding organs. Immunohistochemistry was performed to further investigate the primary location when necessary. All primary antibodies were purchased from Roche.

3. Results

3.1. Clinical findings

There were 9 males and 9 females in this group. The age ranged from 34 to 73 years with an average of 57.6 years. In descending order, the primary lesion was lung adenocarcinoma (6 cases), small cell lung cancer (5 cases), breast cancer (3 cases), and esophageal

squamous cell carcinoma (2 cases), hypopharyngeal cancer (1 case), gingival cancer (1 case) (Figure 2).

Table 1. Clinical characteristics of 18 patients with thyroid metastasis

Case	Gender	Age	Time interval	Primary site	Other sites	Treatment	Survival time
1	Male	69	24 months	Small cell lung cancer	Cervical lymph node	Surgery	24 months
2	male	67	12 months	Small cell lung cancer	Cervical lymph node	Surgery	13 months
3	female	53	12 months	Small cell lung cancer	Cervical lymph node	Not available	Not available
4	female	59	simultaneous	Small cell lung cancer	Cervical lymph node	Chemotherapy	20 months
5	male	58	31 months	Small cell lung cancer	Bone, lymph node	radiotherapy	17 months
6	female	61	First symptom	Lung adenocarcinoma	Cervical lymph node	Surgery	22 months
7	female	57	10 months	Lung adenocarcinoma	Cervical lymph node	Chemotherapy	12 months (Survive)
8	male	65	First symptom	Lung adenocarcinoma	Cervical lymph node	Chemotherapy	12 months (Survive)
9	female	54	First symptom	Lung adenocarcinoma	brain	Chemotherapy	18 months
10	male	64	Not available	Lung adenocarcinoma	bone	Not available	Not available
11	male	42	4 months	Lung adenocarcinoma	Cervical lymph node	Chemotherapy	36 months
12	female	62	16 years	Breast cancer	Cervical lymph node	Surgery	12 months (Survive)
13	female	34	simultaneous	Breast cancer	Lung, bone	Surgery	15 months (Survive)
14	female	60	Not available	Breast cancer	Cervical lymph node	Not available	Not available
15	male	58	10 months	Esophageal cancer	Cervical lymph node	Untreated	6 months
16	male	73	7 years	Esophageal cancer	Lung	radiotherapy	10 months
17	male	46	21 months	hypopharyngeal carcinoma	Not have	Surgery	Not available
18	female	39	76 months	gingival cancer	Not have	Chemotherapy	Not available

The thyroid metastases can be manifested as neck masses (13 patients, with or without hoarseness and swallowing difficulty) or apparent thyroid nodules (5 patients). Among the 18 patients, the thyroid nodules were presented as the first symptom in 3 patients, for whom the thyroid lesion was observed earlier than the primary tumor. The primary tumor and the thyroid lesion were identified simultaneously in 2 patients, and a definite diagnosis of malignancy ahead of the thyroid metastasis was presented in 11 patients. In addition, the detailed information was not appear in 2 patients.

In the 11 cases mentioned above, the thyroid metastasis occurred after operation with a time interval of 4 months to 16 years. The longest interval is 16 years in a patient with breast cancer.

We found that the thyroid metastasis often arose later

than other organs, and often accompanied with the cervical lymph nodes metastasis. Among the 18 patients with the thyroid metastasis, 15 suffered with other organs or lymph nodes metastasis when the thyroid metastasis was found, and only 3 had the thyroid metastasis without other metastatic lesions (Table 1).

The patients were treated by several strategies. Six patients received surgical resection, 6 patients received chemotherapy after diagnosis, and 2 patients received radioactive seed implantation treatment. One patient gave up further treatment. In addition, the detailed information was not available in 3 patients. A total of 16 patients were obtained follow-up by telephone (follow-up was lost in other 2 patients), in whom 10 passed away during a period ranging 2 to 26 months. Of the remaining 6 patients, 2 patients had no

postoperative recurrence, 1 patient had bone metastases, 1 patient had brain metastases, and 2 patients were uneventful after chemotherapy (Figure 3).

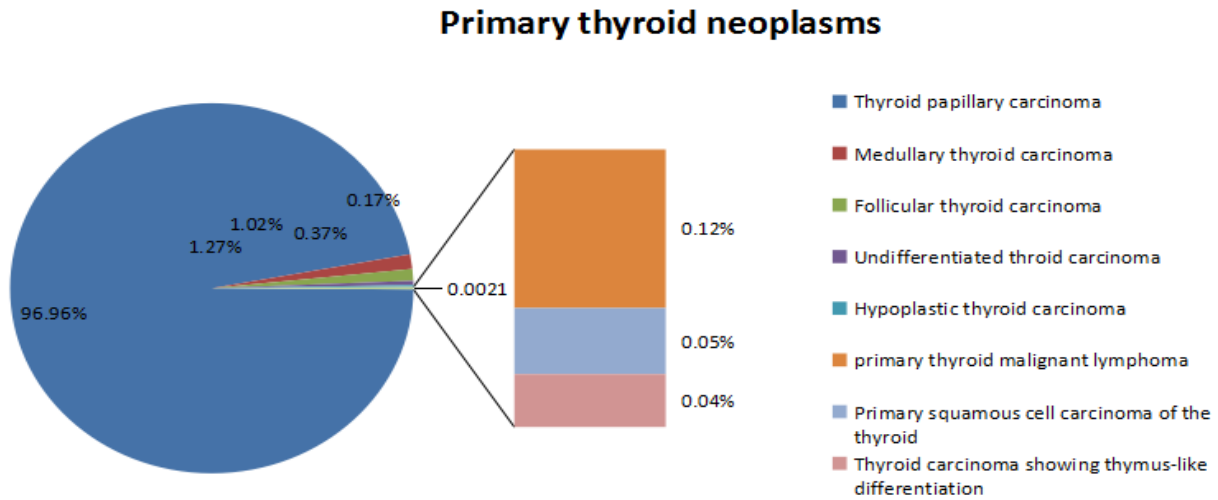


Figure 1. The constitution diagram of primary thyroid malignancies. The most common primary malignancy was papillary thyroid carcinoma (13246 cases, 96.96%), and followed by medullary carcinoma (173 cases, 1.27%), follicular carcinoma (139 cases, 1.02%), undifferentiated (anaplastic) carcinoma (50 cases, 0.37%), poorly differentiated carcinoma (23 cases, 0.17%), lymphoma (17 cases, 0.12%), squamous cell carcinoma (7 cases, 0.05%), and 6 cases of thyroid carcinoma with thymus-liked differentiation (0.04%).

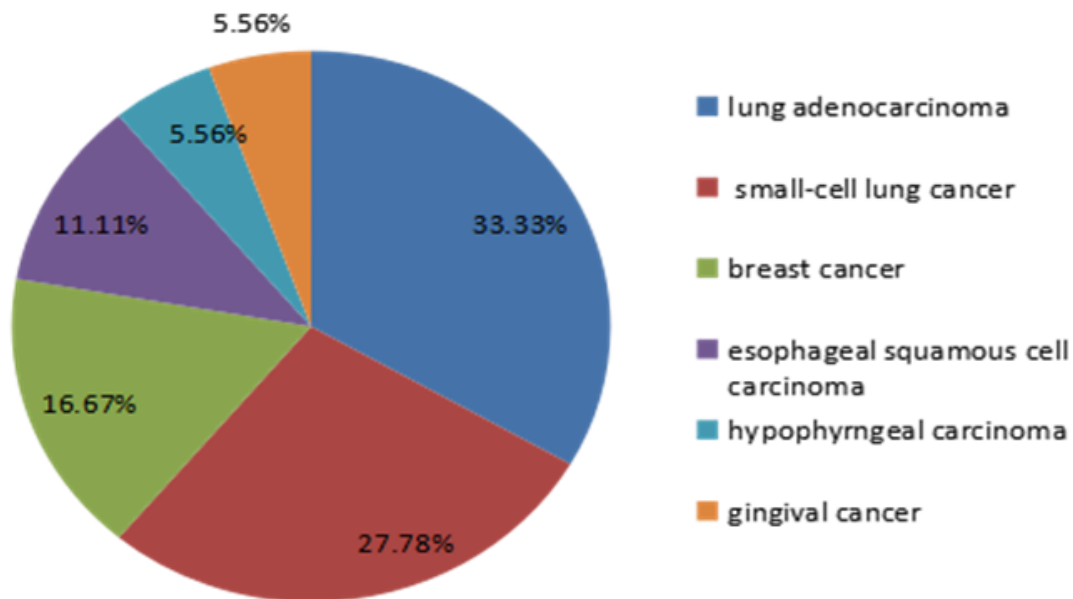


Figure 2. The constitution diagram of metastatic thyroid cancer. The primary lesion was lung adenocarcinoma (6 cases, 33.33%), small cell lung cancer (5 cases, 27.78%), breast cancer (3 cases, 16.67%), and esophageal squamous cell carcinoma (2 cases, 11.11%), hypopharyngeal carcinoma (1 case, 5.56%), gingival cancer (1 case, 5.56%).

3.2. Histopathology

In this series, there were 6 cases of surgical resection samples, 11 cases of biopsy samples, and 1 case of fine needle aspiration (FNA) samples. We found that among the 9 cases of metastatic breast cancer and lung adenocarcinoma, 8 cases presented growth patterns of

papillary or micro-papillary structures, and 1 case presented a growth pattern of glandular tubular (Figure 4, 5, 6). Compared with the primary thyroid papillary carcinoma, the metastatic cancer exhibited multiple nodules rather than a single nodule, and the papilla lacked the nucleus features of papillary thyroid carcinoma: the nucleus were rounder with a small

apparent nucleolus. The metastasis formed by small cell lung cancer and esophageal squamous cell cancer presented a growth pattern of solid flake. In addition, immunohistochemistry was used to make a differential diagnosis. The useful panel for breast cancer included GATA-3, ER, PR, and TTF-1. The metastatic breast cancer was usually positive for GATA-3, ER, and PR, while negative for TTF-1.

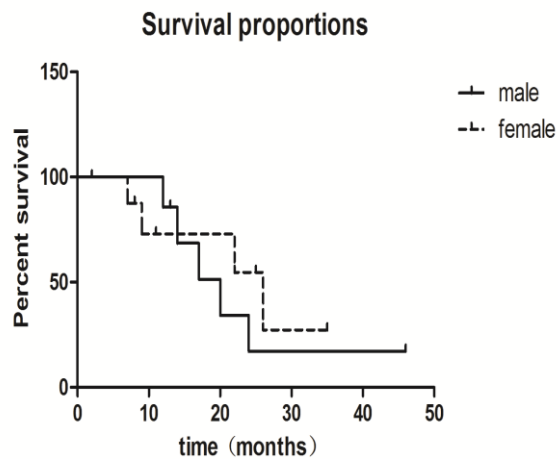


Figure 3. Thyroid metastasis survival curve. The median survival of male is 20 months, and the median survival of female is 26 months. Log-rank (Mantel-Cox) Test P value 0.5822. It can be considered that the difference in the survival rate between males and females is meaningless.

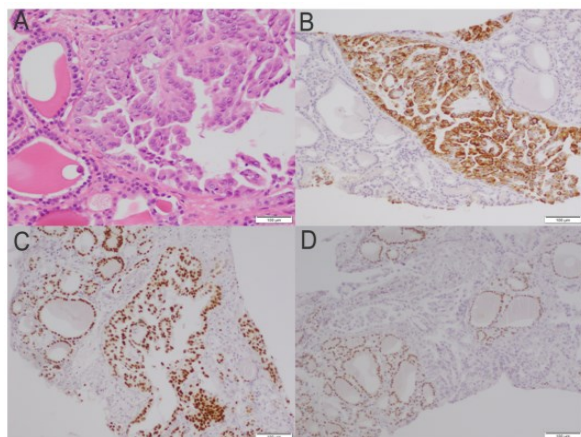


Figure 4. The histopathology features of metastatic lung adenocarcinoma (Case 6). A, The tumor was mainly composed of papillary structures, but the cell nucleus did not have prominent longitudinal grooves and nuclear pseudoinclusions. B, C, D, the tumor cells were positive for CK7 (B) and TTF-1 (C), but negative for PAX-8 (D).

The metastatic lung adenocarcinoma might have overlapping immunohistochemical markers with primary thyroid cancer, such as TTF-1 and CK7. The accurate diagnosis should be taken into account the

morphological features and the clinical medical history. Other metastatic cancers, such as small cell carcinoma and squamous cell carcinoma, were rather uncommon in thyroid, which made the differential diagnosis relatively difficult. Interestingly, we found the primary squamous cell carcinoma of thyroid was often well-differentiated, while the metastatic cancer was poorly differentiated.

In this series, our study found that the thyroid tissue was often accompanied by nodular goiter changes. Hashimoto's thyroiditis or primary thyroid cancer was not found.

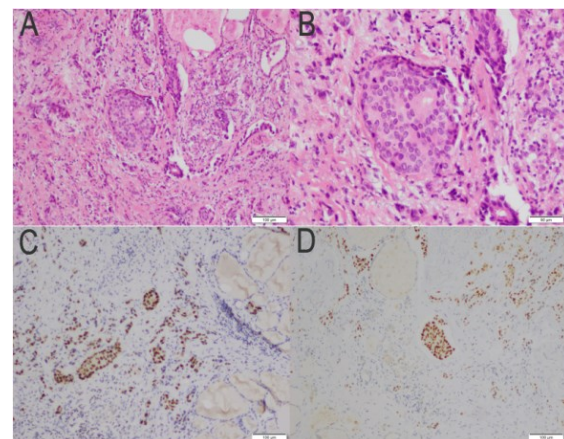


Figure 5. The histopathology features of metastatic breast cancer (Case 3). A, B, The tumor was mainly composed of papillary and micro-papillary structures, but the prominent longitudinal grooves and nuclear pseudoinclusions were not apparent. (H&E stainings, A, 100x, B, 400x); C, D, the tumor cells were positive for GATA-3 (C), and ER (D).

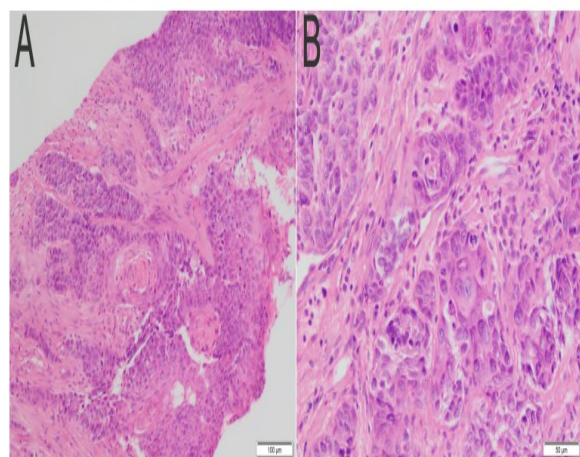


Figure 6. The histopathology features of metastatic esophageal squamous cell carcinoma (Case 2). This is a biopsy sample from patient who has a history of esophageal squamous cell carcinoma. The squamous carcinoma was embedded in a large amount of proliferative connective tissues. We did not find the thyroid follicular structure. (H&E stainings, A, 100x, B, 400x).

4. Discussion

Metastasis to the thyroid gland from other sites is rare, and it is rather difficult to make an accurate clinical and imaging diagnosis. Owing to its rarity, it is often considered as a primary thyroid cancer. In addition, thyroid metastases are usually asymptomatic, and only a few patients have clinical symptoms. Most scholars believe that the malignancies in other locations hardly underwent thyroid metastases. The reasons are as follows: (1) although normal thyroid tissue is rich in the blood circulation, but it lacks the filtration function, cancer cells are not easy to stay; (2) high iodine and high oxygen environment in the thyroid gland can inhibit cancer cell growth[9]. In theory, the thyroid metastasis may be originated from the malignancies in any parts. Our results suggested that metastatic lung cancer accounted for the highest proportion of thyroid metastases, and followed by breast and esophageal cancer. However, other reports in western countries showed that the most common primary lesion of thyroid metastasis is kidney cancer or lung cancer[10,11]. A review published by Chung et al. in 2012 summarized all 374 cases of thyroid metastatic cancer reported in PubMed since 2000, which suggested that the common primary lesion of thyroid metastases were kidney cancer, colorectal cancer, lung cancer and breast cancer[12]. The primary cancer type was varied according to the different populations. In north America, the metastatic renal cell carcinoma and breast cancer were the two most common cancer types[10,13], while the metastatic lung cancer was most common in Europe[1]. Metastatic lung cancer and digestive tract cancer were common in Asia[6,14]. In consistent with other reports in china, we found that lung cancer, breast cancer, and esophageal cancer have a higher proportion of thyroid metastases, which might be related to the high incidence of these tumors in recent years. However, there was no renal cancer metastasis in our series. In the same period, there were 2935 cases of renal cell carcinoma in our institution, in which 122 cases were metastatic renal cell carcinoma (4.2%). The two commonest metastatic sites were lung (52) and bone (30). Anyway, this result suggests that the thyroid gland is not a preferable metastatic site for renal cell carcinoma.

According to previous reports, the average metastatic time of metastatic breast cancer is 131 months, which may be related to the relatively better treatment effect for breast cancer[10]. Due to the aggressive treatment, some tumor cells are "stationary" in the target organs for a long time, and recurrence occurs only when the conditions changed. In addition to breast cancer, it has been reported that renal cell carcinoma, colon cancer, and cervical cancer can all have thyroid metastasis time of more than 15 years[14]. A literature review on large samples showed that colorectal cancer, kidney cancer, and breast cancer are the three malignancies that suffered the longest metastatic-free interval[12,15]. The

interval of thyroid metastasis in lung small cell carcinoma is relatively short ranging 0 to 31 months in this series.

According to previous studies, thyroid metastatic cancer can occur in either normal or abnormal thyroid gland. Approximately 44.2% of metastatic cancer occur in abnormal thyroid tissues, including follicular adenoma, nodular goiter, thyroid carcinoma, and Hashimoto's thyroiditis[12]. However, our study showed that the thyroid tissue was often accompanied by nodular goiter changes. Hashimoto's thyroiditis or primary thyroid cancer was not found. For the metastatic cancer, we found that papillary structures appeared in both metastatic lung adenocarcinoma and breast cancer, which may resemble papillary thyroid carcinoma in some areas. It is worth noting that micro-papillary structure may occur in both lung adenocarcinoma and breast cancer. This structure is morphologically characterized by independent small nipples lacking axial structure. In addition, the nucleus does not have the characteristics of thyroid papillary carcinoma. Furthermore, immunohistochemistry is essential when the differential diagnosis is difficult. For example, thyroid papillary carcinoma was usually positive for TTF-1, PAX-8, and Thyroid Globin; thyroid medullary carcinoma was positive for Calcitonin. Breast cancer was positive for GATA-3, ER, and PR. Lung adenocarcinoma was positive for CK7, TTF-1, and Napsin A. Small cell lung cancer was positive for CD56, Synapsin, and Chromogranin A. Squamous cell carcinoma was positive for CK5/6 and p40.

It is important to distinguish metastatic thyroid cancer from the primary thyroid cancer, which is important for future treatment and prognosis. Thyroid metastatic carcinoma is common in the elderly and women. The average age of this group of patients is 57.6 years old. Clinically, the symptoms of primary thyroid cancer and metastatic thyroid cancer are not much different, which is characterized by the cervical thyroid mass, hoarseness, and swallow difficulty. The imaging examination was also not specific. When there is an exact clinical history, the possibility of metastatic cancer must be considered.

5. Conclusion

In this study we described the clinical and pathological features of 18 cases of thyroid metastasis. This was one of the reports with the largest number of cases in China. We found that the primary site is different from Western countries, which might be related to the spectrum of tumors in our population. Our research will provide a valuable reference for the diagnosis of thyroid disease.

Data Availability

The data used to support the findings of this study are

included within the article.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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