Diffuse Thyroid Enlargement Following Metastasis of Lung Adenocarcinoma

Takaaki Murakami¹, Masato Taki², Takuo Nambu¹, Tomoko Wakasa³, Tomoko Kato¹, Yuki Matsuda¹, Shin Yonemitsu¹, Seiji Muro¹ and Shogo Oki¹

Abstract

A 55-year-old man presented with a rapidly enlarging thyroid. He had been diagnosed with lung adenocarcinoma nine months earlier. Computed tomography (CT) and ultrasound (US) detected reticular cord-like structures, but no nodules, in the thyroid. A fine-needle aspiration biopsy (FNAB) of the thyroid revealed thyroglobulin-negative adenocarcinoma cells, thus establishing the diagnosis of diffuse thyroid metastases of lung cancer. Moreover, the fluid demonstrated milky chyliform effusion. This case suggests that the presence of reticular cord-like structures on US and CT may be a key imaging finding for the clinical diagnosis of diffuse thyroid metastases and that chyliform effusion may contribute to rapid goiter formation.

Key words: thyroid metastases, secondary thyroid tumor, lung cancer, diffuse goiter, chyliform effusion, fine-needle aspiration biopsy


Introduction

It is important for physicians to consider that the thyroid may be a site of metastases in patients with a history of malignancy, although metastases of non-thyroid malignancies to the thyroid gland are reportedly rare due to the rapid arterial flow, high oxygen saturation and iodine content of the thyroid gland (1, 2). Recent autopsy studies have shown that metastasis to the thyroid is relatively common, with a prevalence of 1.9-24% (3, 4). However, clinically apparent thyroid metastases remain relatively uncommon, with a prevalence of 1.4-3% of all patients who undergo thyroid surgery (1) and those with an underdiagnosis of thyroid metastasis in the clinical setting.

Most cases of thyroid metastasis involve the formation of solitary or multiple nodules, as diffuse thyroid metastasis without nodules is rare (5). However, the pathophysiology of thyroid metastases both with and without the formation of diffuse nodules remains unclear. On the other hand, in the clinical setting, diffuse thyroid involvement is most common in patients with autoimmune thyroid diseases, such as Hashimoto’s thyroiditis and Graves’ disease (6). Therefore, it is clinically important to distinguish diffuse thyroid metastases from autoimmune thyroid diseases in cases involving diffuse goiters and subsequently diagnose thyroid metastases accurately.

We herein describe the case of a 55-year-old man who presented with the rapid onset of diffuse enlargement of the thyroid gland without detectable nodule formation in which we arrived at a diagnosis of diffuse thyroid metastases of lung adenocarcinoma.

Case Report

A 55-year-old man was referred to our hospital for an evaluation of mediastinal nodules. The patient’s family history revealed that his father had been diagnosed with colon cancer and his mother had a history of primary thyroid cancer. The patient also had a history of smoking 30 cigarettes per day for 35 years, although there was no history of tuberculosis or hyperlipidemia. Computed tomography (CT) showed enlarged mediastinal lymph nodes and cardiac effusion, without thyroid enlargement or tumor formation in the

¹Department of Diabetes and Endocrinology, Osaka Red Cross Hospital, Japan, ²Department of Respiratory Medicine, Osaka Red Cross Hospital, Japan and ³Department of Laboratory Medicine, Nara Hospital Kinki University Faculty of Medicine, Japan

Received for publication July 24, 2014; Accepted for publication September 1, 2014

Correspondence to Dr. Takaaki Murakami, t.murakami@osaka-med.jrc.or.jp
Lungs or thyroid. 18F-fluorodeoxyglucose positron emission tomography/CT showed an increased uptake in the mediastinal, supraclavicular and right hilar lymph nodes and pericardium; however, no significant uptake was observed in the lungs or thyroid. Pericardial drainage and endobronchial ultrasound-guided transbronchial needle aspiration of the mediastinal lymph nodes and bronchial washing revealed adenocarcinoma, which was subsequently found to be positive for thyroid transcription factor-1 and cytokeratin 7 and negative for cytokeratin 20 on immunostaining (Fig. 1a, b). Therefore, the patient was diagnosed with mediastinal lung adenocarcinoma. The clinical stage was considered to be TXN3M1a (stage IV) lung cancer according to the 7th International Union Against Cancer tumor-node-metastasis staging system. Although he received treatment with several chemotherapy regimens (pemetrexed + carboplatin + bevacizumab as first-line therapy, pemetrexed + bevacizumab as second-line therapy, docetaxel as third-line therapy), the disease progressed. A follow-up CT scan obtained seven months after the diagnosis of lung cancer showed no enlargement of the thyroid gland or nodules (Fig. 2a). However, he subsequently presented with diffuse nodule development and rapid enlargement of the thyroid with dyspnea and was referred to an endocrinologist nine months after the initial diagnosis of lung adenocarcinoma.

Upon presentation, the patient was alert and oriented with the following clinical findings: height, 170.5 cm; weight, 67.0 kg; temperature, 36.6°C; heart rate, 72 beats per min; peripheral blood oxygen saturation, 95% (room air); and blood pressure, 130/80 mmHg. A physical examination revealed a painless, smooth, elastic, hard, diffusely enlarged thyroid gland and enlarged bilateral supraclavicular lymph nodes. No signs of tremors, ophthalmopathy, edema or xanthoma were observed.

The laboratory test results are presented in Table. Thyroid function tests showed normal serum thyroid-stimulating hormone (TSH) (1.84 μIU/mL; normal range, 0.541-4.261 μIU/mL) and free triiodothyronine (F-T3) levels (3.06 pg/mL; normal range, 2.39-4.06 pg/mL), although the free thyroxine (F-T4) level was slightly elevated (1.75 ng/dL; normal range, 0.71-1.52 ng/dL). Meanwhile, the serum thyroglobulin (Tg) level was within the normal range (8.5 ng/mL; normal range, 0-32.7 ng/mL), while the serum amyloid A level was moderately elevated (62.7 μg/mL; normal range, 0-8 μg/mL). Antithyroid autoantibodies were negative. The serum procalcitonin level was only mildly elevated (0.12 ng/mL; normal range, 0-0.05 ng/mL), whereas the serum carcinoembryonic antigen (CEA, 6.7 ng/mL; normal range, 0-5 ng/mL), sialyl-Lewis X (180 U/mL; normal range, 0-38 U/mL) and cytokeratin 19 fragment (CYFRA, 50 ng/mL; normal...
The enlargement of the thyroid and bilateral supraclavicular structures with a density indicating fat content (29 Hounsfield units). The rapid enlargement of the thyroid and the patient’s history of malignancy, an ultrasound-guided fine-needle aspiration biopsy (FNAB) of the cord-like structures in the bilateral thyroid lobes was performed, which revealed a milky, low-viscosity fluid (Fig. 5). An immunohistochemical analysis of the fluid disclosed thyroglobulin-negative adenocarcinoma cells that morphologically resembled those observed on bronchial washing (Fig. 1c, d). Microscopically, adenocarcinoma cells were dominant in the fluid, while the content of the thyroid cells was negligible. There were no pathological findings indicative of infection, lymphocytic thyroiditis, amyloid deposition or fatty infiltration. Therefore, a diagnosis of diffuse thyroid metastases of lung adenocarcinoma was established. The laboratory results of the supernatant fluid showed triglyceride and total cholesterol levels of 130 mg/dL and 1,030 mg/dL, respectively, and agarose gel electrophoresis of the fluid demonstrated percentages of beta-, prebeta- and alpha-lipoproteins of 66% (normal range, 30-55%), 5% (normal range, 8-29%) and 19% (normal range, 29-50%), respectively. The percentage of the fraction between the origin and beta-lipoprotein, which indicates the presence of chylomicrons, was 10%.

As the fourth-line treatment, we started treatment with systemic chemotherapy with carboplatin (area under the curve, 5; intravenous administration on day 1) plus oral S-1 (60 mg/m² on days 1-14) every four weeks and repeated this cycle for up to eight weeks. On a gross examination, the diffuse goiter was found to have immediately reduced in size; however, progressive disease developed thereafter, and the thyroid again became enlarged. A CT scan obtained three months after referral showed a diffusely enlarged thyroid gland without nodule development and obscured cord-like structures (Fig. 2c). Thyroid function tests revealed normal TSH (2.24 μIU/mL) and F-T4 (1.46 ng/dL) levels, with a slightly reduced F-T3 level (2.29 pg/mL) and a serum Tg content within the normal range (11.6 ng/mL). The patient subsequently died four months after referral, and an autopsy was not permitted.

**Discussion**

Secondary thyroid tumors are clinically uncommon due to the fast arterial flow through the thyroid, which prevents adhesion of malignant cells, as well as the high oxygen saturation and iodine content of the thyroid, both of which inhibit the growth of malignant cells (1). Various non-thyroid malignancies have been reported as primary origins of metastasis to the thyroid (1). Although thyroid metastases is often associated with a poor prognosis because the patient usually has metastatic disease elsewhere at the time of presentation, thyroid metastases may continue to be underdiagnosed in the clinical setting (7). Moreover, considerable efforts should be made to arrive at a definitive clinical diagnosis, as surgical resection or radiotherapy and/or chemotherapy may be of value in specific situations (4). Metastasis to the thyroid is classified into solitary, multiple and diffuse types. As previously documented, diffuse metastases are rare, and few cases have been re-
Figure 3. Thyroid ultrasonography revealed a diffuse goiter, without nodules, and reticular hypoechoic cord-like structures. (a) Right lobe, (b) left lobe. (c) Color Doppler ultrasonography visualized no blood flow signals in the structures.

As mentioned in the case presentation, the current patient exhibited the unique finding of thyroid enlargement on ultrasonography and CT (Fig. 2b, 3). In addition, thyroid ultrasound revealed hypoechoic reticular cord-like structures that resembled blood vessels in the thyroid, although color Doppler ultrasonography showed no signals of blood flow through these structures. There are a limited number of reports describing the ultrasonographic findings of diffuse thyroid metastases, although some reports (6, 11) have documented similar ultrasonographic findings of hypoechoic cord-like structures associated with these lesions. In addition, the ultrasonographic features of Hashimoto’s thyroiditis include a heterogeneously hypoechoic thyroid, without an increased vascular flow, exhibiting an irregular margin and multiple hypoechoic micronodules without hypoechoic lines (6). In the present case, ultrasonography revealed relatively smooth margins and the absence of hypoechoic micronodules in addition to negative results for thyroid autoantibodies. Moreover, the cytological analysis of the FNAB
specimen obtained from our patient did not support a diagnosis of autoimmune thyroid disease. Hence, the presence of imaging findings of hypoechoic reticular cord-like structures may be key for making a clinical diagnosis of diffuse thyroid metastases (6). In addition to the ultrasonographic findings noted in this case, contrast-enhanced CT showed reticular cord-like structures. Therefore, in association with ultrasound, CT examinations may provide valuable information for arriving at a definitive diagnosis, although previous studies (6, 8, 11) did not mention CT findings.

One past study reported the high diagnostic accuracy of FNAB for detecting secondary thyroid tumors, particularly those in cases of lung cancer metastasis (1, 7). The current case was confirmed to involve diffuse metastases to the thyroid based on the findings of adenocarcinoma cells in the thyroid FNAB specimen. In addition, neither ultrasonography, CT nor MRI showed nodules in the thyroid during the course of the disease. Taken together, MRI, particularly SPIR, and FNAB are useful for making the differential diagnosis of rapid enlargement of the thyroid (12).

The pathophysiology of diffuse goiter formation in patients with diffuse thyroid metastases remains unclear. However, cervical lymph node metastasis was evident in this case. Furthermore, laboratory examinations of the supernatant fluid obtained via FNAB revealed the unique finding of an enriched triglyceride and cholesterol content, in which the triglyceride level exceeded 110 mg/dL, sufficient to meet the criteria for chylous effusion (13). Taken together with enriched triglyceride fluid, retrograde lymphatic dissemination and lymphostasis, rather than hematogenous metastasis, may contribute to goiter formation (8). Moreover, the level of total cholesterol in the patient’s fluid was significantly elevated, with a ratio of triglycerides to cholesterol of <1.0, suggesting chyliform effusion (14). Although the serum lipid profile was not available in the current case, the significantly high level of cholesterol in the fluid, in addition to the absence of xanthoma and the patient’s past history, excluded the possibility of severe hypercholesterolemia, possibly due to the local collection of cholesterol in the thyroid. According to a widely accepted theory of pleural effusion, the increase in the cholesterol level observed in chyliform effusion is derived from the effects of destroyed cells (15). Although it remains controversial as to whether these criteria, which are usually used for pleural effusion, should be applied to thyroid specimens, there are currently no criteria regarding thyroid effusion characterized by a high cholesterol level. Hence, chyliform effusion, which contains dominantly enriched cholesterol fluid, may originate from aggressive tumor spread in cases of diffuse thyroid metastasis. As shown in pleural effusion studies, the increased cholesterol content in chyliform effusion resulting from tumor cell destruction may increase the osmotic pressure, thus inducing further diffuse thyroid enlargement (15).

In summary, we herein reported a case of diffuse thyroid metastasis of lung adenocarcinoma to the mediastinal lymph nodes in which the patient demonstrated chyliform effusion in the thyroid. FNAB is useful for confirming the clinical
diagnosis of diffuse thyroid metastases, and the detection of reticular cord-like structures on ultrasonography and CT may be a key imaging finding in such cases.

The authors state that they have no Conflict of Interest (COI).

References


© 2015 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imonline/index.html