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Severe Hypothyroidism Induced by Thyroid Metastasis of Colon Adenocarcinoma: A Case Report and Review of the Literature

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Abstract. An 85-year-old man who had undergone a right hemicolectomy for colon cancer presented with severe hypothyroidism and hoarseness 21 months after the operation. The serum thyrotropin (TSH) was markedly elevated to 118.14 μIU/mL and serum free thyroxine (fT4) level was markedly suppressed to 0.34 ng/dL. Symptoms of hoarseness and neck swelling were already evident 4 months prior at which time tests for normal thyroid function were performed. The patient was referred due to aggravated pain on his diffusely enlarged hard goiter. An enlarged thyroid with some calcification was noticed in the neck ultrasonography with multiple cervical lymphadenopathies. Core biopsy of the thyroid gland showed invasion of poorly differentiated adenocarcinoma cells. Immunohistochemical studies showed positive staining only for carcinoembryonic antigen (CEA). There were multiple lung parenchymal nodules and adrenal masses at the time of evaluation. The patient was started on palliative chemotherapy with thyroid hormone replacement and gradually became euthyroid. From these findings and the clinical observations, thyroid metastasis with hypothyroidism developing acutely from metastatic colon adenocarcinoma was diagnosed.

Key words: Hypothyroidism, Metastatic thyroid cancer, Colon adenocarcinoma, Immunohistochemical staining, Diagnosis
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FROM a clinical aspect, metastasis to thyroid cancer from other malignancies is uncommon. Metastatic thyroid cancer has histologically been proven in only 1.4% of surgical tissues [1]. When examining for the common physical characteristics of diffused goiter, it is difficult to diagnose metastasis to thyroid cancer from other malignancies unless the physician is familiar with the disease. Frequent primary lesions for metastatic thyroid cancer are kidney, lung, and breast [2, 3]. Only 12 cases of metastasis from colon cancer to the thyroid have been reported since 1936 [4–7]. Currently there are only 5 cases of thyroid dysfunction caused by metastatic cancer infiltration [8–12]. Most of the manifestations were thyrotoxicosis followed by destruction. This case study reports of a patient that presented initially with severe hypothyroidism due to metastasis from a colon adenocarcinoma and who had undergone a right hemicolectomy 21 months earlier. In addition, this paper will discuss a review of the literature.

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Case Report

An 85-year-old male presented with a 4-month history of a painful diffused goiter with hoarseness. This patient was diagnosed 21 months earlier with colon adenocarcinoma in the ascending colon and underwent a right hemicolectomy. The final pathology revealed a moderately differentiated adenocarcinoma extending to the pericolic fat tissue with lymphovascular permeation with 6 positive lymph nodes out of 14. He was

finally diagnosed as Duke C2 stage, and after surgery he was treated with 3 cycles of postoperative adjuvant chemotherapy with 5-fluorouracil and leucovorin. There were no specific problems during the regular follow-ups.

Four months before admission, he developed a diffused goiter with hoarseness and visited a private clinic. The results of the first thyroid function tests were normal (fT_4 was 1.26 ng/dL; TSH was 0.63 uIU/mL). He showed no thyrotoxic symptoms such as weight loss, palpitation or tremor in recent months. The hoarseness and the pain in the neck gradually worsened so he was referred to our institution for evaluation to determine the cause of the neck swelling. He reported overall weakness, fatigue, poor appetite, hoarseness and cervical pain. Although he appeared chronically ill, his mental status was alert. Upon physical examination, the cervical and supraclavicular lymph nodes were extensively enlarged. The thyroid was enlarged as a hard diffused pattern, and severe tenderness was reported without any bruit. During auscultation, the breathing sound was clear without stridor or wheezing, and the heart sound was normal. The abdomen felt soft without any palpable mass. There was no sign of any exophthalmos. Routine blood chemistry including liver function tests and urinalysis were normal (AST 22 IU/L, ALT 15 IU/L, Total bilirubin 0.5 mg/dL). However, the serum carcinoembryonic antigen (CEA) level was elevated to 1710.2 ng/mL, which was within the normal range after the previous chemotherapy. The serum thyrotropin (TSH) was markedly elevated to 118.14 μIU/mL and serum free thyroxine (fT4) level was markedly suppressed to 0.34 ng/dL. Serum thyroglobulin was normal (1.56 ng/mL). Thyrotropin receptor antibody (TRAb) was also within normal range (20.4%) and antimicrosomal and antithyroglobulin antibodies were both negative. I^{131} thyroidal uptake for 24 hours was suppressed to 0.81%. Ultrasonographic findings of the thyroid gland showed a diffused enlargement with heterogeneous echogenicity and dense calcifications (Fig. 1). On the neck and chest computed tomography, the thyroid was enlarged as a diffused pattern without any enhancement and the airway was not compromised (Fig. 2). There were multicentric small subpleural nodules in the lung and several enlarged lymph nodes around the internal jugular veins and aorta. There were 3.8 cm and 2.2 cm sized masses in both adrenal glands. The patient underwent ultrasound-guided core biopsy of the thyroid gland. As shown in Fig. 3, the tumor cells infiltrating the thyroid gland consisted of poorly differentiated adenocarcinomas partially mixed with areas showing glandular structure. Neither desmoplastic change nor inflammatory cell infiltration around the tumor cells was observed and there was similarity to the previous colonic adenocarcinoma. To differentiate primary thyroid cancer and metastatic cancer originating from organs other than the colon, immunohistochemical staining of CEA,

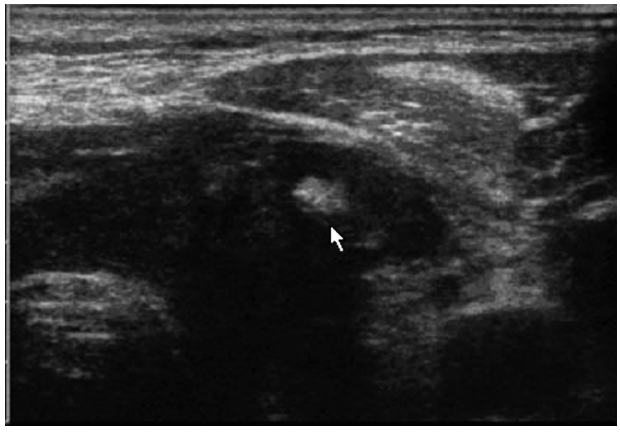

Fig. 1. Neck Ultrasonography
Both thyroid glands are diffusely enlarged with heterogeneous parenchymal echogenicity. Dense calcification is noted in left thyroid gland (arrow). There were multiple variable sized lymph node enlargements in submandibular, jugular chain, and supraclavicular fossa.

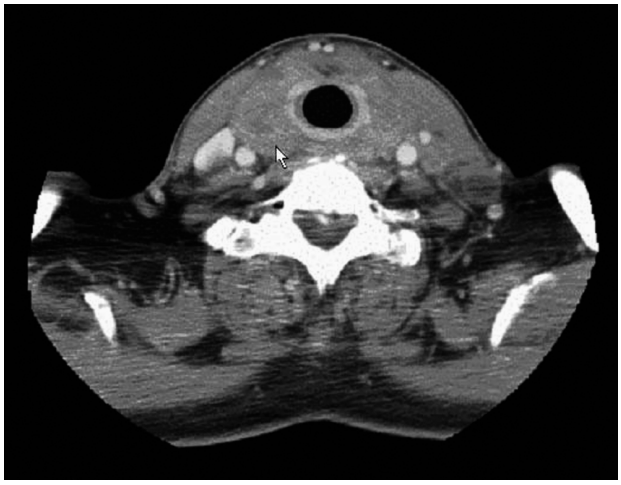

Fig. 2. Neck CT
Diffusely enlarged thyroid gland with internal small low attenuating nodules (arrow) is noted. Multiple lymph node enlargements are seen at bilateral internal jugular chain, supraclavicular fossa.

thyroglobulin, TTF-1, CK20, CK7, calcitonin, and p53 were performed. Most of the tumor cells were strongly and frequently positive for CEA and p53 (Fig. 4), and negative for other markers. With histological findings and the results of immunohistochemical staining, it was considered to be reasonable to diagnose as metastasis to the thyroid from the colonic adenocarcinoma concurrent with distant metastasis in the lung and the adrenal; however, there was no evidence of any liver metastasis.

Initially 100 μg of levothyroxine was started for hypothyroidism. However, 6 weeks after the thyroid hormone replacement, TSH levels did not change, so the dosage was titrated to levothyroxine 225 μg and liothyronin 15 μg. After the TSH was normalized, the patient was treated with a maintenance dose of 100 μg of levothyroxine. The underlying metastatic colon cancer was treated with irrinotecan-based chemotherapy with an oral fluoropyrimidine agent. The CEA level decreased to 74.67 ng/mL after the second cycle of chemotherapy. After the third chemotherapy, follow-up neck CT scans showed that the thyroid gland had also significantly decreased in size. The patient is under follow-up observation with ongoing chemotherapy every 6 weeks.

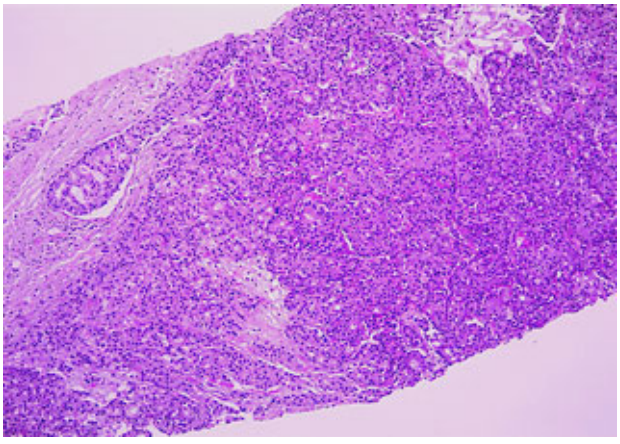

Fig. 3. Histological findings
Thyroid biopsy reveals areas of multinodular and poorly differentiated adenocarcinoma (H&E × 100).

Discussion

Clinically, cancer metastatic to the thyroid gland is considered to be rare. According to a series of autopsies performed to assess malignancies in the thyroid gland originating from other organs, there were many more cases of microscopic metastasis than expected [13, 14]. The incidence of the metastasis rate of primary tumor to the thyroid gland in autopsy studies varies widely according to the investigator, from 1.25% to as high as 24.2% [2, 15]. Breast and lung cancer are known to be the most frequent primary tumors metastasized to the thyroid in the autopsy data [2, 3]. Clinically, renal cell carcinoma has been reported to be a frequent cause of metastasis in the thyroid [16]. Among cancers in the gastrointestinal tract that metastasize to the thyroid, colon cancer has been reported to be extremely rare, appearing in only 4% of autopsy studies [14]. Currently, only 12 cases of colorectal cancer that have metastasized to the thyroid gland have been reported and reviewed [17]. In addition, metastasis in the thyroid is frequently detected after an extended period of time following the diagnosis of a complete cure of tumors in the primary lesion. This

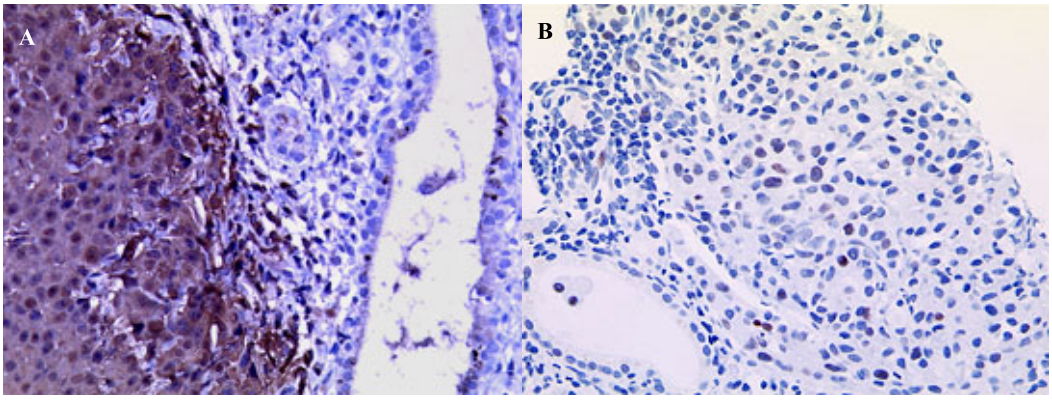

Fig. 4. Histological and immunohistochemical findings of metastatic carcinoma in the thyroid tissue. The metastatic adenocarcinoma area shows (A) strong immunoreactivity to CEA (CEA × 400) and (B) frequent p53 immunoreactivity (p53 × 400).

renders the diagnosis of metastasis in the thyroid more difficult. Out of 43 patients diagnosed with metastatic thyroid cancer, metastasis in the thyroid with no other metastasis was detected in 6 patients (13.9%). Metastatic thyroid cancer was recently detected 10 years after the diagnosis of primary tumors in 12 patients (27.9%) out of 43 cases [16]. Therefore, it is important to consider the possibility of a patient with a previous history of cancer developing a goiter.

There are two types of metastatic pathways to the thyroid, either the hematogenous or the lymphangitic pathway. The "vertebral venous system" was suggested by Batson to explain the direct metastasis of the cancers in the breast, lung, kidney, and gastrointestinal tract [18]. This could explain the absence of any metastasis in the liver (as in this case), which is the most common site of metastasis from the colon carcinoma. The lymphangitic pathway includes direct metastasis to the thyroid gland, especially from lung and breast malignancies.

In cases of metastasis to the thyroid, there exists the possibility of thyroid dysfunction due to thyroid destruction. Recently, only 4 cases were reviewed that developed transient thyrotoxicosis caused by massive metastasis of an extrathyroid tumor, such as breast cancer, lung cancer or pancreatic carcinoma [11]. The term "malignant pseudothyroiditis" has been described in a few cases of primary or secondary thyroid cancer presenting with clinical and often biochemical features of subacute or chronic thyroiditis [19]. However, a single manifestation of severe hypothyroidism due to the direct invasion of colon cancer cells has not yet been reported. There is a possibility that a short episode of thyrotoxicosis may have gone unrecognized since it is known that transient thyrotoxicosis is often followed by a rapidly progressive destructive process in the thyroid gland. A short clinical course is compatible with destructive thyroiditis. There were no significantly notable associated symptoms or biochemical evidences, both of which were checked frequently before the final acute increase in the TSH level. In evaluation of both the histological findings and the immunohistochemical observations, we hypothesize that the tumor cells that metastasized to the thyroid from the colon adenocarcinoma advanced so aggressively that thyroid follicles were destroyed, leading to severe hypothyroidism.

The survival time after the diagnosis of metastatic thyroid cancer varies slightly according to the investigator and is generally known to be from 15 to 24 months [20, 21]. The average survival after the diagnosis of metastatic thyroid carcinoma with thyroid dysfunction was much shorter, *i.e.* 3 to 16 months [11], compared to the cases without any functional change.

The treatment for the metastasis in the thyroid varies according to the characteristic of the primary cancer and can be largely classified to surgical resection, chemotherapy, and radiation therapy. Reports show that patients with renal cell carcinoma who have already undergone nephrectomy with a confirmation of only metastasis in the thyroid, curative resection could be expected by surgery only [22]. By the time metastases are found in the thyroid gland, the tumor has metastasized systemically, and the only therapeutic option is palliation. In the case of thyroid metastasis, since it is accompanied by the risk of airway obstruction, conservation of the airway is necessary in addition to treatment of the primary tumor. Therefore, surgical resection of the thyroid, tracheostomy or local radiation therapy should be considered [16]. Due to a greater systemic spread in patients with metastasis in the thyroid gland [6], as in this case, systemic chemotherapy may be administered first.

In summary, we have presented a case of severe hypothyroidism induced by thyroid metastasis from a colon adenocarcinoma. Although such a metastatic tumor to the thyroid gland causing thyroid dysfunction signifies an advanced systemic disease, it is of clinical importance to make a differential diagnosis between primary thyroid cancer and metastasized tumors involving the thyroid, leading to a completely different therapeutic approach.

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