

Case Report

An Extremely Rare Case of Thyroid Metastasis from Advanced Gastric Cancer

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Keywords

Gastric cancer · Thyroid gland metastasis · CEA · TTF-1

Abstract

Metastases to the thyroid area are extremely rare in cancer, more specifically, in gastric cancer, where intraperitoneal metastases are absent. Herein, we describe a case of a 41-year-old man who had advanced gastric cancer with metastasis to the right thyroid area, which was found 6 years after curative surgery. The patient presented with multiple enlarged right cervical lymph nodes and a right thyroid mass of 1.2 cm. We assumed that the patient had primary thyroid cancer as he had no signs of other metastases. We performed fine-needle cytology under ultrasonography on the thyroid nodule. However, with a positive carcinoembryonic antigen and a negative thyroid transcription factor 1 immunohistochemical staining results, the patient was diagnosed with metastatic adenocarcinoma that was of gastric origin. Subsequently, the patient was treated with radiotherapy and chemotherapy. This report aimed to raise the concern that gastric cancer may cause metastasis to the peri-thyroid area, involving the thyroid, parathyroid, and regional lymph nodes.

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Introduction

Approximately 60% of the patients who have undergone surgery for gastric cancer relapse within 2 years. The most common sites of recurrence are the liver, peritoneum, and locoregional lymph nodes [1]. The brain, breast, bone, and skin are unusual distant metastasis sites occurring from gastric cancer [2]. Metastasis in the thyroid as a result of gastric cancer is extremely rare and has mainly been reported in case reports [3].

The incidence of metastasis to the thyroid gland during autopsy varies from 1.25% to 24% [3]. The most frequently reported origins of thyroid metastasis are the kidneys, lungs, and breasts, while esophageal and colon cancers are the two most frequently reported gastrointestinal sources of metastasis to the thyroid [3].

Herein, we report a rare case of gastric cancer with metastasis to the thyroid gland, perithyroid, and cervical lymph nodes, without peritoneal metastasis 6 years after curative radical total gastrectomy. We also speculate what treatment options we have in this era of targeted treatment of the human epidermal growth factor receptor-2 (HER2) and other molecules regarding the tumor-associated macrophages and inflammatory microenvironment in gastric cancer [4–6].

Case Report/Case Presentation

A 41-year-old man visited our hospital in July 2007 to evaluate an asymptomatic right neck mass that he had noticed 3 months previously. He had a medical history of advanced gastric cancer for which he underwent radical total gastrectomy and adjuvant chemotherapy. His initial esophagogastroduodenoscopy in May 2001 revealed ulceration with nodular masses in the cardia portion without the involvement of the gastroesophageal junction. After a total gastrectomy, the pathological diagnosis was subserosa invasion (T3) and regional lymph node metastases (23/49, N3b) with no metastasis (M0). The adenocarcinoma had moderate to poor differentiation, whereas Lauren's classification revealed that it was an intestinal type. Postoperatively, the patient received adjuvant chemotherapy with mitomycin (bolus 10 mg/m² on day 1 and 22) and fluorouracil (24-h 2,600 mg/m² preceded by a 2-h 500 mg/m² folinic acid) for 6 weeks followed by a 2-week rest period for 2 years. He had no chemotherapy toxicities and did not need dose reduction. For the following 6 years, the patient visited our hospital for regular follow-up, which showed no evidence of recurrence. However, on the sixth year of follow-up, a physical examination revealed a palpable mass in the right cervical area and thyroid. Additional blood tests revealed carcinoembryonic antigen (CEA) of 1.9 ng/mL (reference range: 0–5 ng/mL), carbohydrate antigen 19-9 of 10.7 U/mL (reference range: 0–37 U/mL), thyroid-stimulating hormone of 3.2 mIU/L (reference range: 0.5–5.0 mIU/L), free thyroxine of 1.2 ng/dL (reference range: 0.7–1.9 ng/dL), and antithyroglobulin of 35 IU/mL (reference range: <116 IU/mL).

A neck computed tomography (CT) scan (shown in Fig. 1a, b) revealed a heterogeneous nodule of 1.2 cm next to the right thyroid gland and the enlargement of multiple lymph nodes, with the largest long axis diameter being 3.5 cm. Additional chest, abdomen, and pelvic CT, and brain magnetic resonance imaging results showed no other signs of cancer. Assuming thyroid cancer, fine-needle aspiration cytology under ultrasonography (US) was performed on the thyroid nodule. Hematoxylin and eosin staining and immunohistochemistry (IHC) staining were performed (shown in Fig. 2a). The results were positive for CEA and negative for thyroid-transcription factor 1 (TTF-1) (shown in Fig. 2b, c) confirming the nodule's gastric origin. Thus, the patient was confirmed to have metastatic gastric cancer that recurred 6 years after surgery and adjuvant chemotherapy treatment.

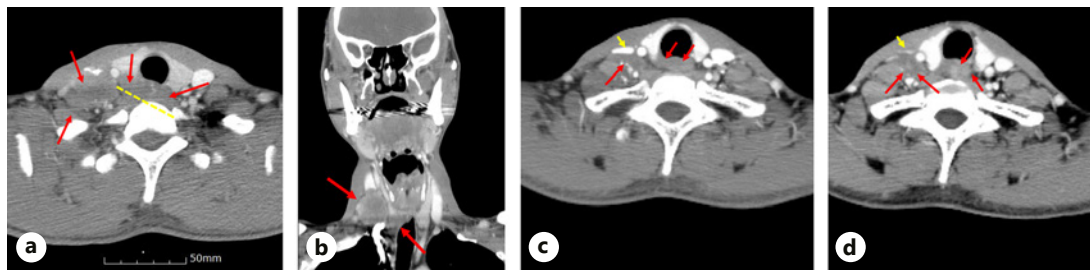


Fig. 1. Computerized tomography (CT) images show a heterogenous 35-mm (yellow dash line, long axis) mass in the right thyroid area and another mass involving the right sternocleidomastoid muscle in the axial view (a), a thyroid mass and another mass in the right sternocleidomastoid muscle in coronary view, with the red arrows indicating the masses (b). c CT image 3 months after palliative cervical radiotherapy where there is a mass reduction in the right and left thyroid areas and the right peri-thyroid area. The reduction of the peri-thyroid mass can be observed by the decompression of the internal jugular vein (RIJV). d CT image 6 months after the treatment, the contralateral thyroid lymph node increased and the peri-thyroid mass increased to compress the RIJV. The metastatic mass is indicated by red arrows, and the RIJV is indicated by yellow arrows.

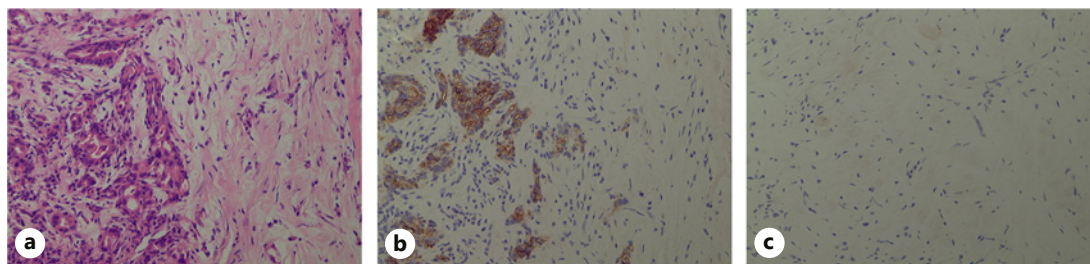


Fig. 2. Biopsy of the right thyroid mass involving the right sternocleidomastoid muscle, hematoxylin and eosin showing glandular shapes with exuberant stromal desmoplastic reaction without follicles (a), Immunohistochemistry (IHC) staining with (carcinoembryonic antigen) with positive results (b), IHC staining with thyroid transcription factor-1 (TTF-1), with negative results (c).

After the metastatic gastric cancer diagnosis, he received palliative cervical radiotherapy (total of 65 Gy on 35 fractionations in 7 weeks) and had no complications during and after radiotherapy. After 3 months of treatment, a follow-up neck CT showed that there was a mass reduction in the thyroid area and right peri-thyroid area: the mass invading the thyroid vanished, while the peri-thyroid mass reduction can be observed by the decompression of the right internal jugular vein (RIJV) (shown in Fig. 1c). However, 6 months after the commencement of the treatment, the contralateral thyroid lymph node increased, and the peri-thyroid mass increased to compress the RIJV (shown in Fig. 1d). He received first-line palliative chemotherapy with docetaxel (75 mg/m² on day 1), cisplatin (75 mg/m² on day 2), and fluorouracil (1,200 mg/m² preceded by leucovorin of 200 mg/m² on day 3) on a 21-day cycle. He had no chemotherapy toxicities, leading to dose reduction or chemotherapy delay for 3 months. During this time, the lymph nodes remained stable. However, the patient developed a new pleural effusion where thoracentesis and cell cytology showed exudate with inflammatory cells with an adenosine deaminase level of 320 U/L (reference: <40 U/L), and the sputum acid-fast bacillus stain was positive, which indicated tuberculosis. After the treatment with isoniazid, ethambutol, rifampin, and pyrazinamide for 2 months and isoniazid,

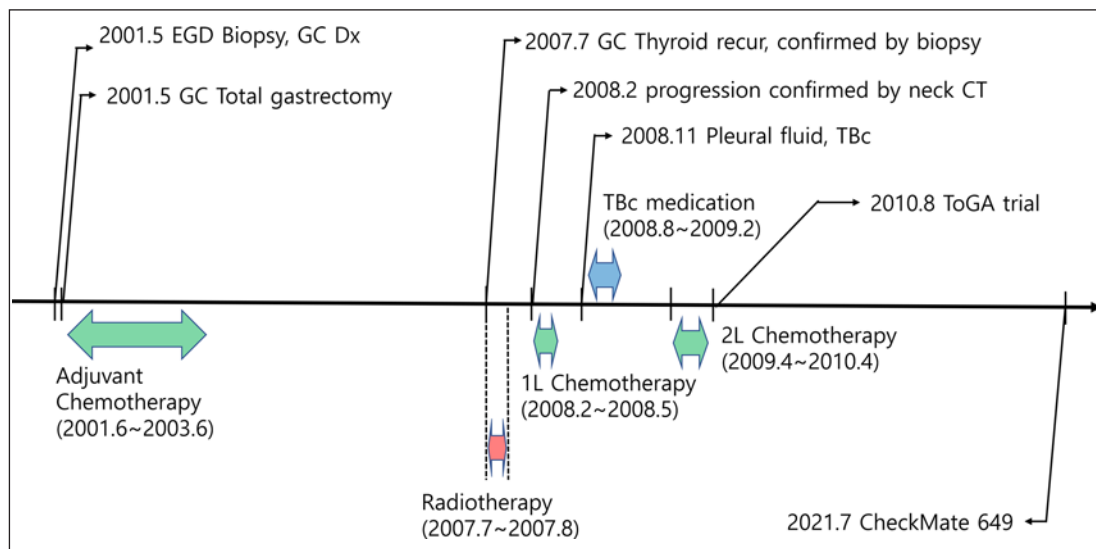


Fig. 3. The timeline of the treatment. The patient was diagnosed with gastric cancer (GC) in May 2001, by esophagogastroduodenoscopy (EGD). He underwent total gastrectomy surgery and 2 years of adjuvant chemotherapy. Six years later, he had a thyroid mass, which was confirmed by a biopsy in July 2007. Afterward, he had 7 weeks of radiotherapy treatment, and approximately 6 months later, in February 2008, progression was confirmed by neck computerized tomography (CT). He had 3 months of first-line chemotherapy until pleural fluid was noticed, caused by tuberculosis (TBc). After standard TBc treatment and resting for 2 months, he had a second-line treatment S-1 for a year. Pivotal trials considering targeted treatment of human epidermal growth factor receptor-2 with cisplatin such as the ToGA, and immune checkpoint inhibitors with cisplatin such as CheckMate 649 are included.

ethambutol, and rifampin regimen for 4 months, the patient was administered second-line S-1 chemotherapy (tegafur/gimeracil/oteracil, 50 mg twice daily for 28 consecutive days followed by 14 days without treatment) for 1 year. During this time, the disease remained stable. The patient stopped follow-up 1 year after the S-1 treatment. The timeline of the treatment is illustrated in Figure 3.

Discussion/Conclusion

The thyroid gland is generally considered a very rare site of metastatic disease in the clinical setting, where hypotheses have been proposed by Willis [7]. First, the rapid and abundant blood supply inhibits tumor implantation, known as the “flushing” action. Second, high oxygenation and colloids with rich iodine inhibit tumor progression because malignant cells prefer anaerobic metabolism. Therefore, while thyroid metastasis is uncommon, the clinical results of thyroid metastasis are reported to be dismal. McCabe et al. [8] reported that metastases to the thyroid were associated with poor prognosis with no long-term survivors and mean overall survival of 12 months (range 6–38 months).

Metastasis to the thyroid from gastric cancer is extremely rare and is mainly reported in case reports [3]. Renal-cell carcinoma is the most common metastatic tumor of the thyroid, accounting for 12–34% of all secondary thyroid tumors [9]. Thyroid metastasis from gastric neoplasms, including carcinomas and sarcomas, is rare, and several cases have been previously reported [3]. Wu et al. [2] reported that gastric cancer metastases were poorly differentiated adenocarcinomas or signet-ring carcinomas, and the interval from the

initial diagnosis to metastasis ranged from 3 to 70 months, with the majority of survival being less than 6 months.

The diagnosis of thyroid nodules is mainly performed using US or contrast-enhanced CT, which combines CT and US to improve the detection rate. Fine-needle aspiration cytology is used for final diagnosis. This can assist in differentiating between benign and malignant diseases. When a tumor is malignant, IHC staining is performed to distinguish between primary thyroid cancer and metastatic thyroid cancer. The most frequently used IHC markers are TTF-1, caudal-type homeobox-2, cytokeratin (CK) 7, and CK20 [10, 11]. Primary thyroid cancer is typically TG, TTF-1, and galectin-3 positive, whereas metastatic cancer is typically negative for these markers [12, 13]. In addition, caudal-type homeobox-2, CK7, and CK20 are expressed in the gastrointestinal epithelium and are widely used in the diagnosis of metastatic carcinomas of the gastrointestinal tract [14]. In our case report, the IHC staining result was negative for TTF-1 and galectin-3 and positive for CEA, which confirmed the tumor's gastric origin.

There are several limitations to our clinical case report. This patient was diagnosed with gastric cancer, had undergone a total gastrectomy in 2001, and had metastasized to the thyroid in 2007. Targeted therapy for HER2 with trastuzumab was not approved in Korea before the ToGA trial was published in August 2010 [4]. Thus, we had no information on the HER2 status of the patient. Therefore, the patient had not been treated with systemic chemotherapy containing cisplatin with trastuzumab if he had HER2 positive for his initial metastasis, and as CheckMate 649 was not published before July 2021, a combination of immune-checkpoint inhibitor (ICI) nivolumab and a cisplatin-containing regimen was not considered in the first-line setting (Fig. 3) [15]. However, if the patient had thyroid recur on this day, we would have considered trastuzumab or ICI combined with cisplatin and may have considered novel agents targeting HER2, such as trastuzumab deruxtecan in the second-recurrence setting if he had HER2 positive status [5]. If he was HER2 negative, first, we would have considered clinical trials that target molecules in tumor-associated macrophages such as emactuzumab or cabiralizumab, which target the colony-stimulating factor 1 receptor [6]. Second, as there was no consensus on local recurrent metastasis in the thyroid, surgical resection was not considered. Several reports have shown that a thyroidectomy has no survival benefit for rapidly growing tumors [8, 14]. As the prognosis is very poor for gastric cancer with distant metastasis, with or without synchronous or metachronous peri-thyroid metastasis, surgery was not considered, and alternative radiotherapy treatment was considered without chemotherapy as concurrent chemoradiotherapy is not approved and reimbursed by the health policy of Korea. However, we believe that this multimodal treatment led to an increased overall survival of at least 2 years compared to the pre-existing treatment. Nevertheless, we do not deny that thyroid metastatic surgery followed by chemotherapy or radiotherapy may have further increased the patient's survival.

In conclusion, thyroid, peri-thyroid, and regional cervical lymph node metastases from gastric cancer are very rare and have a poor prognosis with or without other distant metastases. If the neck is palpable after gastric cancer surgery, metastasis should be suspected with multimodal treatment, as this may increase overall survival.

Statement of Ethics

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. This study was approved and monitored by the IRB of the Inje University Seoul Paik Hospital, Korea (IRB no. PAIK 2022-06-007).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Woo Yong Lee contributed to diagnoses, data curation, and data organization. Byung Woo Yoon contributed to the writing of the manuscript. Woo Yong Lee and Byung Woo Yoon contributed to the conceptualization of the manuscript. All the authors have reviewed and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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