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CASE REPORT

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Thyroid metastases from cervical carcinoma: unusual implications for clinicians-case report

Qian Yang[1†], Weipeng Yan[1†], Ning Wang[1], Pengfei Xu[2] and Qing Huang[3*]

Abstract

Background Thyroid metastases from uterine cervical carcinoma are exceedingly rare. Imaging examination and pathological detection exert a pivotal function in distinguishing between benign and malignant thyroid tumors, as well as differentiating metastases from primary thyroid cancer.

Case presentation Here, we present two cases of uterine cervical cancer metastasizing to the thyroid gland, confirmed by postoperative histopathology at our hospital. Furthermore, we conduct a comprehensive analysis of the imaging appearances, pathological characteristics, diagnosis, prognosis and treatment of the disease through a review of relevant literature. The two cases do not exhibit specific laboratory indicators, making imaging examinations important auxiliary tools, while pathology remains the gold standard for diagnosis.

Conclusions Although thyroid malignancies predominantly arise as primary tumors, it's crucial to consider the possibility of metastases in patients with a history of cancer. Metastases to the thyroid are relatively uncommon but can occur, particularly in advanced stages of other cancers. Poor outcomes of thyroid metastases from cervical carcinoma have presented significant hurdles for clinicians. Surgical excision of metastatic thyroid cancer may serve as an alternative, offering relief from compression symptoms and prolonging survival to some extent. Further studies are crucially needed to optimize clinical outcomes of the disease.

Keywords Uterine Cervical Neoplasms, Metastases to Thyroid, Characteristics, Prognosis

Background

Cervical cancer is one of the most common gynecological malignancies. It typically metastasizes through local invasion (the most common method), lymph node involvement, or blood spread, with advanced stage potentially leading to metastasis in the lung, liver, or bones. Autopsy literature reports an incidence of thyroid metastasis ranging from 2 to 17% [1]. The most commonly reported primary sites include the lung, breast, malignant melanoma, stomach, and kidney [2–6]. Metastases of cervical cancer to the thyroid are extremely rare, only a few cases have been reported to date in the literature [7–11]. Here, we present two cases of cervical carcinoma metastasizing to the thyroid, confirmed by Computed Tomography (CT), histopathology, and immunohistochemistry.

Case presentation

Patient 1

Patient 1 is a 70-year-old female, who underwent a radical local vulvectomy under general anesthesia in August 2013, for vulvar pruritus and pain. The postoperative histopathology revealed grade 3 vulvar intraepithelial neoplasia. In 2015, ultrasonography indicated an enlarged

†Qian Yang and Weipeng Yan are co-first authors.

*Correspondence:
Qing Huang
326332855@qq.com
[1] Department of Radiology, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[2] Department of Pathology, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[3] Department of Medical Oncology, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

uterus and cervix (92 mm × 68 mm × 90 mm) with hydrometra. Magnetic resonance imaging (MRI) showed a cervical tumor invading the vulva and vagina. Biopsy from the vulva, vagina and cervix confirmed squamous cell carcinoma. The patient refused treatment after the diagnosis. In 2016, the patient again presented with lower abdominal pain, and CT revealed an enlarged uterus and a large amount of hydrometra. Treatment included one cycle of chemotherapy with Paclitaxel and Cisplatin, followed by external image-guided intensity-modulated radiotherapy and concurrent intracavitary brachytherapy from August to October 2016. The Gross tumor volume (GTV) encompassed the lower uterine segment, cervical, vaginal and vulvar, along with two cycles of sensitized chemotherapy with Cisplatin.

In February 2017, a walnut-sized mass was found on her right neck, without pain or swallowing issues. Six months later, she visited our hospital, where a mobile, painless mass measuring 4.0 cm × 3.5 cm with moderate texture was palpable on the right side of her neck. Ultrasonography revealed an enlarged right thyroid lobe containing a poorly defined, irregular-shaped, heterogeneous hypoechogenic mass measuring 4.0 cm × 3.7 cm, with irregular non-echogenic fluid areas. No cervical lymph nodes were detected. Color Doppler flowing imaging (CDFI) showed blood-flow signals in and around the mass. Based on the ultrasonography, the mass was classified as a mixed cystic-solid tumor, categorized as Thyroid imaging reporting and data system (TI-RADS) 5 (Figs. 1A and B). A CT scan of the neck demonstrated an enlarged right thyroid lobe with a quasi-round soft tissue mass (5.4 cm × 3.4 cm) of ill-defined and irregular border and heterogenous density, compressing the adjacent airway (Fig. 1C). Thyroid function tests showed a decreased thyroglobulin (TG) level of 1.09 ng/mL (normal range:1.4–78 ng/dL), with free thyroxine (FT4) and thyroid-stimulating hormone (TSH) levels within normal limits. The patient refused further treatment.

The patient refused fine-needle aspiration cytology (FNAC) examination before surgery. She underwent a total thyroidectomy under general anesthesia to relieve airway compression from the tumor in August 2017. Postoperative pathology demonstrated moderately differentiated squamous cell carcinoma with extensive necrosis in the right lobe of the thyroid (Fig. 1D). Immunohistochemical staining was negative for TG (Fig. 1E) and PAX-8, but positive for P40 (Fig. 1F), P16 (Fig. 1G), TTF-1, and Ki-67 (80%). Based on the immunohistochemical findings and the patient's medical history, a diagnosis of metastatic cervical squamous cell carcinoma to the thyroid gland was established.

Six months after the operation of thyroid metastatic cancer, the patient was diagnosed with dyspnea. An emergency CT scan revealed a soft tissue mass at the right rear of the mediastinal trachea in the lower neck, the trachea was obviously compressed, and the airway was obviously narrowed. The tumor grew rapidly and the disease deteriorated quickly, the patient finally died of respiratory and cardiac arrest.

Patient 2

A 62-year-old woman underwent a colposcopy-guided cervical biopsy because of intermittent vaginal discharges, which confirmed a diagnosis of papillary squamous cell carcinoma of the uterine cervix. The patient was diagnosed with stage IIIB cancer. She received concurrent chemoradiation therapy from December 2015 to January 2016.

In September 2017, an ultrasound conducted during a physical examination revealed a solid, irregular-shaped nodule with an indistinct border and several punctate calcifications, measuring 1.1 cm × 0.8 cm, in the right lobe of the thyroid. CDFI revealed obvious blood-flow signals in and around the nodule. The left lobe of the thyroid gland was inhomogeneous. The TI-RADS score was 5 (Figs. 2A and B). A CT scan revealed several low-density nodules with unclear borders in both thyroid lobes (Fig. 2C) and no metastatic lesions in the lungs and abdomen. Her thyroglobulin (TG) was less than 0.04 ng/mL (normal range: 1.4–78 ng/dL), but the TSH, free triiodothyronine (FT3), and fT4 were all within normal limits.

The patient refused a FNAC examination prior to surgery. The patient underwent a right thyroid lobectomy and partial thyroidectomy of the left lobe in October 2017. Histopathologic analysis of the specimen revealed squamous cell carcinoma with vascular tumor thrombus (Fig. 2D). Immunohistochemical staining was positive for P16, CK5/6, and CK19, but negative for TTF-1 and

(See figure on next page.)

Fig. 1 Metastasis of cervical cancer to the thyroid gland from Case 1. **A** Ultrasonography revealed nonuniform hypoechogenic mass in the right thyroid lobe, with irregular liquid dark areas appearing within it. **B** CDFI displayed blood-flow signals in and around the mass. **C** CT image showed a quasi-round soft tissue mass with uneven density, compressing the adjacent airway. **D** Histology of cervical cancer metastasis to the thyroid gland showed moderately differentiated squamous cell carcinoma with extensive necrosis (hematoxylin–eosin, original magnification × 200). **E** Tumor cells negative for thyroglobulin immunostaining (EnVision, original magnification × 400). **F** Tumor cells strongly positive for P40 (EnVision, original magnification × 400). **G** Tumor cells strongly positive for P16 (EnVision, original magnification × 400)

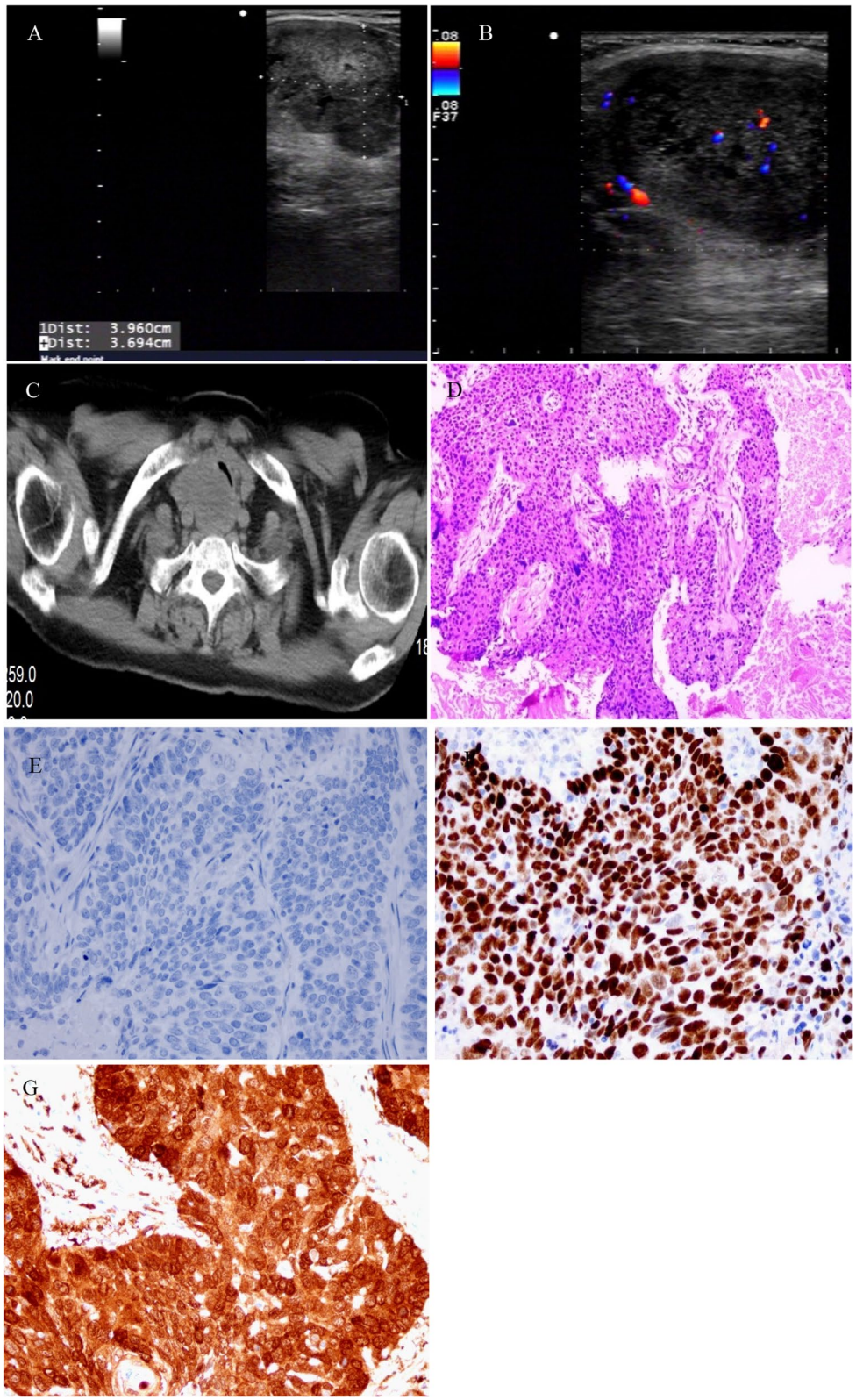

Fig. 1 (See legend on previous page.)

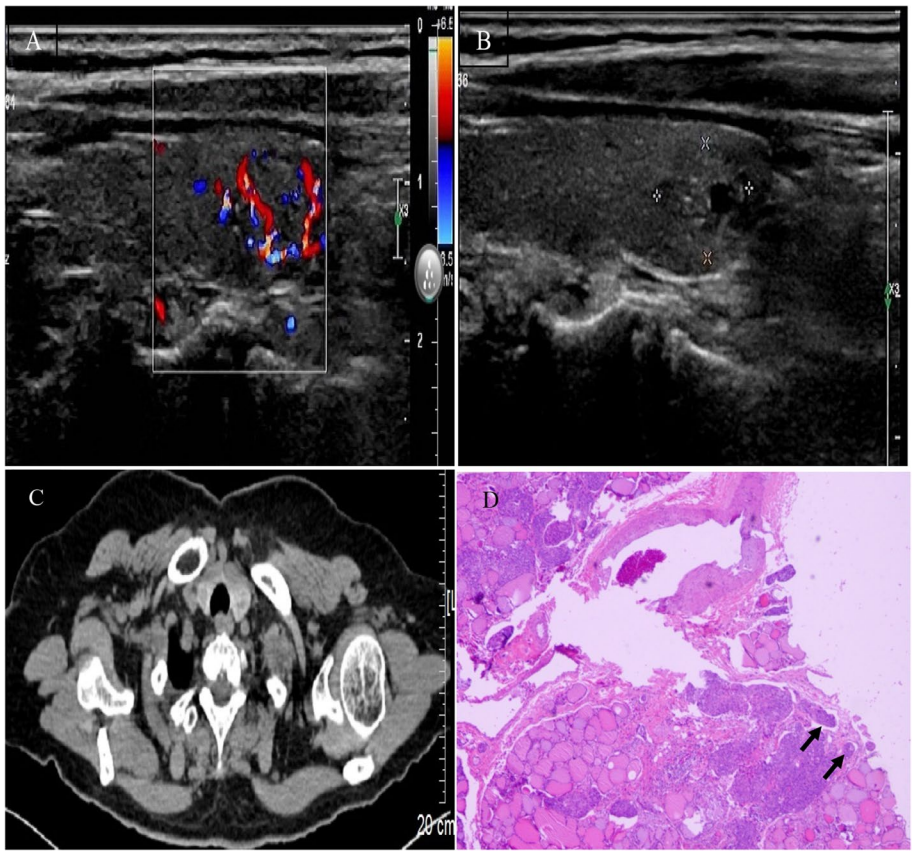

Fig. 2 Metastasis of cervical cancer to the thyroid gland from Case 2. **A** Ultrasonography displayed several hypoechogenic nodules in the right thyroid lobe. **B** CDFI revealed blood-flow signals in and around the nodules. **C** CT showed several low-density nodules with unclear borders in both thyroid lobes. **D** Histology of cervical cancer metastasis to the thyroid gland, demonstrating squamous cell carcinoma with vascular tumor thrombus(black arrow) (hematoxylin–eosin, original magnification × 100)

TG. Based on the patient's medical history, a diagnosis of uterine cervical squamous cell carcinoma metastasized to the thyroid was rendered. Regretfully, more than two years after the operation, the patient developed thoracic vertebra metastasis and died without treatment.

Discussion and conclusion

The main routes of cervical cancer spread include local invasion (the most common), lymphatic dissemination, and hematogenous dissemination (typically spreading to lungs, liver, or bones). Despite its extensive blood supply, the thyroid gland is an uncommon metastatic site for primary neoplasms elsewhere. The mechanism of metastasis from cervical cancer to the thyroid gland remains unclear. The onset is insidious and most patients are asymptomatic [12], leading to frequent cases of missed or misdiagnosed conditions.

It is important to differentiate thyroid metastases from primary thyroid cancer due to their distinct treatment and prognostic implications. Patients with metastatic thyroid cancer do not exhibit specific laboratory indicators compared to those with primary thyroid cancer [13, 14]. Markers such as TSH, FT3, FT4, TG, thyroglobulin antibody, thyroid peroxidase antibody (TPOAb) are either normal or decreased with different degrees in both primary and metastatic cases, resulting in a lacking of specificity. In this report, the preoperative laboratory indexes of two cases were normal, except for decreased thyroglobulin levels. The diagnosis was confirmed postoperatively through histopathology and immunohistochemistry of the specimens. Of note, TG immunostaining is mostly positive in primary thyroid cancer but negative in thyroid metastases [13]. In our study, two cases were negative for TG, but positive for P16 and P40. TG is mainly used for distinguishing between primary and metastatic thyroid cancer, with TG positivity indicating a thyroid origin. In contrast, P16 is highly expressed in high-grade cervical intraepithelial tumors and high-risk HPV infected tumors, playing a crucial role in the detection of cervical cancer. P40 antibody is detected in more than 90% of squamous cell carcinoma. Overall, pathological diagnosis has become

Table 1 Summary of literature review

Study	Study type	Age	Tumor size(cm)	Features	Ultrasound /CT/MRI	Outcome
Cheung AY et al.2000(USA) [7]	Case Reports	57	4	Twelve months later, due to the rapid enlargement of the goiter, which was causing difficulty in swallowing and breathing, the patient underwent an emergency total thyroidectomy	No inspection	Upon completion of a five-week course of radiotherapy, the clinically enlarged cervical nodes showed complete regression. No survival outcomes were reported
Singh R et al.2002(USA) [8]	Case Reports	38	8	One year later, the patient underwent an FNAC examination due to an enlarging neck mass	MRI of the neck showed a large mass on the right side	The patient died six months later despite receiving four cycles of Chemotherapy
Karapanagiotou E et al.2006 [9]	Case Reports	68	9	Four years later, a painless swelling in the region of the thyroid gland and a palpable mass on the right side of the neck prompted a biopsy of the thyroid gland	CT showed a large, irregular mass in the right lateral region of the neck	Overall survival following the diagnosis of thyroid metastasis was sixteen months
Varlı B et al.2019(Greece) [10]	Case Reports	55	3	Five months after her surgery, she experienced a painless enlargement of the thyroid gland, which was causing dyspnea	Ultrasonography was performe, revealing only a multinodular goiter	A total thyroidectomy was performed to relieve her symptoms. No survival outcome was reported
Celik SU et al.2016(Turkey) [11]	Case Reports	56	3.4	The patient had a six-month history of uterine cervical squamous cell carcinoma, with swelling in the neck and severe difficulty in swallowing. She underwent palliative surgery	Ultrasonographic examination of the thyroid revealed bilateral and multiple nodules with both micro- and macrocalcifications	Died five months after the diagnosis of thyroid metastasis

the gold standard in the diagnosis of metastases to the thyroid.

Most thyroid metastases are not easily detected through routine physical examinations or imaging follow-ups after the resection of primary lesion [15]. Therefore, early imaging examinations are essential for detecting metastatic thyroid cancer. The ultrasound and CT manifestations of thyroid metastases can vary and lack specific characteristics. The two cases in this report both showed a solitary mass. CT is useful for determining the size, extent, and number of metastatic thyroid lesions, as well as detecting lymph node metastasis in the neck, which is crucial for assessing tumor progression and the invasion of adjacent tissues. Additionally, as an important auxiliary examination, CT clearly reveals both the primary tumor and any metastatic lesions elsewhere, providing a critical foundation for treatment planning.

Ultrasound is widely used for the early diagnosis of thyroid diseases and plays a crucial role in distinguishing between benign and malignant thyroid nodules. Additionally, ultrasound-guided fine-needle aspiration biopsy is essential for diagnosing metastatic thyroid cancer. Ultrasonography, as a key technical tool for differentiating benign from malignant diseases, can be used to help distinguish thyroid metastases from the following diseases [2, 6, 16, 17]: ① Thyroid adenoma: Ultrasonography typically shows a well-defined, regularly shaped mass that may be surrounded by an envelope or hypoechoic halo. CDFI reveals that peripheral blood flow signals are stronger than those within the mass. ② Nodular goiter: Ultrasonography reveals multiple solid, mixed cystic-solid nodules or masses with varying echoes, often including coarse calcifications and colloid echoes. CDFI shows hypervascularity. ③ Hashimoto's thyroiditis: Ultrasonography shows the thyroid is diffusely enlarged in a reticular pattern. ④Thyroid cancer: Ultrasonography reveals an irregular-shaped, ill-defined, solid hypoechoic mass with calcification and an aspect ratio greater than one. CDFI shows hypervascularity.

As we know, there were only scarce references in the literature regarding thyroid metastases from cervical cancer, with most being case reports (Table 1) [7–11]. Among five patients, three underwent surgical treatment, two had needle biopsies, two underwent ultrasound examination, one underwent CT, and one had an MRI. The imaging findings were described briefly and lacked distinctive features, with each patient undergoing only a single type of examination. Three of the five patients died, consistently with the poor outcomes seen in the two patients from our study, indicating the exceptionally dismal prognosis of the disease. Clinicians should take it seriously and enhance their understanding of this disease. Some studies suggest that early detection and surgical management of metastatic thyroid cancer, especially when the thyroid is the sole site of metastasis, could improve the prognosis [4, 18]. Although there is no established consensus on treatment due to the rarity of the disease, we believe that surgical excision followed by radiation and chemotherapy, particularly in cases involving surrounding tissue invasion, may prolong survival. Further research is urgently needed to explore the underlying mechanisms and guide the field toward effective treatment strategies in the disease. Based on our team's previous research, we have summarized the imaging findings and clinical characteristics of 27 cases with thyroid metastasis [19]. In the future, we will continue to explore the relationship between imaging features (such as lesion size, shape, enhancement patterns, etc.) and survival rates or disease progression of patients, thereby providing data to support the role of imaging examinations in clinical decision-making.

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Authors' contributions
QY and WPY composed the manuscript and literature review. NW and PFX provided figures and pathology review. QY and QH had the acquisition, analysis or interpretation of data for the work, revising it critically for important intellectual content. All authors read and approved the final manuscript.

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Data availability
The original materials present in the study are included in the article. Further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
Our study was approved by the Ethics Committee of Hubei Cancer Hospital. "Clinical trial number: not applicable". Our research was implemented according to the principles in the World Medical Association Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research Involving Subjects (GIOMS, Geneva, 1993).

Consent for publication
As the patients passed away, written informed consent for publication of this manuscript and any identifying images or data was obtained from their next of kin for both patients.

Competing interests
The authors declare no competing interests.

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