Colorectal cancer metastasis to the thyroid: A case report and review of the literature

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Abstract. Metastatic thyroid cancer is rare. Here, the case of a patient with colon cancer that metastasized to the thyroid is described. The patient underwent radical rectal cancer surgery in August 2017 and received six cycles of chemotherapy with oxaliplatin and capecitabine postoperatively. On August 4, 2018, the patient was admitted to the hospital due to the discovery of thyroid nodules on ultrasound and carcinoembryonic antigen levels within the normal range. The biopsy from the fine needle aspiration suggested a malignant tumor. The patient underwent radical thyroid cancer surgery. Using intraoperative rapid frozen pathology, medullary carcinoma was diagnosed. Using postoperative routine pathology combined with immunohistochemistry results, thyroid metastasis from colorectal adenocarcinoma was diagnosed. After surgery, the patient regularly visited the outpatient clinic for chemotherapy with capecitabine. As of May 2023, the patient is still alive with no recurrence.

Introduction

Metastatic cancer of the thyroid is uncommon and most commonly originates from the lung, kidney, breast, or esophageal cancers, while colorectal cancer metastasizing to the thyroid is rarer (1,2). Colorectal cancer is one of the three major malignant tumors. According to statistics, colorectal cancer is the second most common cause of cancer-associated death in both men and women (3). Of note, 20% of these cases exhibit metastases at the time of diagnosis (4). The common metastatic sites are the liver, lungs, and brain, while the thyroid is a rare site for tumor metastasis (5). Metastases of colorectal cancer to the thyroid typically arise as a late manifestation, usually subsequent to metastases to the liver, lungs, or other organs (6). The instance where the thyroid serves as the initial metastatic organ is exceedingly rare. Clinical presentations of thyroid metastases are often nonspecific and can easily be misdiagnosed as a primary thyroid disease. Additionally, the diagnostic accuracy of ultrasound-guided fine needle aspiration biopsy remains suboptimal (7). Due to the rarity of thyroid metastasis from colorectal cancer in which the thyroid gland is the initial site of metastasis, there is a lack of sufficient understanding in clinical and pathological diagnosis and treatment.

Here, the case of colon cancer metastasizing to the thyroid gland as the initial site of metastasis, which was misdiagnosed by fine needle aspiration and intraoperative rapid cryopathological diagnosis is described. Despite the presence of a stage IV tumor, this patient survived beyond 5 years following standardized surgery and postoperative chemotherapy. This case should prompt clinicians and pathologists to remain vigilant of thyroid nodules in patients with a history of colorectal cancer, even in the absence of metastases to other commonly affected organs. Timely fine-needle aspiration can assist clinicians in performing early interventions to potentially prolong patient survival. By sharing this experience and reviewing the clinicopathological characteristics of fine needle aspiration of thyroid metastases from colorectal cancer as reported in the literature, this study may assist in improving the diagnostic accuracy of fine needle aspiration pathology and provide clues for other physicians to develop treatment strategies for similar patients in the future.

Case report

The patient, a 54-year-old woman, presented with changes in bowel habits, irregular bowel movements, and daily passage of small amounts of unformed stool for more than 6 months. She then experienced abdominal pain and bloating, and thus sought medical attention. On July 28, 2017, she was admitted to the People's Hospital of Putuo District (Zhoushan, China) and an abdominal computed tomography (CT) scan (Fig. 1A) showed localized intestinal wall thickening accompanied by intestinal obstruction in the colon (at the rectosigmoid junction), suggesting colon cancer. On August 4, 2017, she underwent radical rectal cancer surgery (pathologically diagnosed with

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rectal adenocarcinoma) and received chemotherapy with oxaliplatin and capecitabine on the following dates: September 9, September 29, October 13, November 7, and December 28 in 2017, and January 26 and February 12 in 2018.

On August 4, 2018, a thyroid ultrasound revealed multiple thyroid nodules, suggesting nodular goiter. An echogenic nodule at the lower pole of the left lobe was classified as TI-RADS 4a, indicating the possibility of cancer (Fig. 1B), and fine needle aspiration biopsy was recommended (Supplementary materials and methods). She was admitted to the People's Hospital of Putuo District on August 10, 2018. On August 11, 2018, the biopsy from fine needle aspiration showed densely arranged atypical follicular epithelial cells with occasional nuclear grooves, and cancer could not be completely ruled out (Fig. 1C). Consequently, the patient underwent radical surgery for left-sided thyroid cancer; a nodule ~1x1 cm in size and hard in texture was observed on the ventral surface of the midpole of the thyroid gland (Fig. 1D).

Intraoperative rapid freezing revealed a gray-white and gray-yellow nodule on the thyroid cut surface, which was slightly hard and slightly transparent, and the boundary was not clear. Pathological diagnosis revealed a malignant tumor on the left side of the thyroid, and medullary carcinoma was the primary consideration (tumor size 1.3x1.3 cm), close to the capsule.

Postoperative histopathological examination (hematoxylin-eosin staining, Supplementary materials and methods) showed that the tumor tissue was tubular and sieve-like, tumor cells were columnar, nuclear atypia was obvious, chromatin appeared coarse granular, mitotic figures were easily visible, interstitial fibrous tissue proliferation was observed, and local necrosis was visible, infiltrating the surrounding thyroid tissue (Fig. 2A and B).

Immunohistochemistry (Figs. 2C, S1 and S2) analysis showed the following: CDX-2 (+), TTF-1 (-), TG (-), CK7 (-), CK20 (+), calcitonin (-), CK19 (+), HBME1 (-), galectin-3 (+), CEA (+), Syn (-), CgA (-), EMA (+), ER (-), and Ki-67 (~50% +) (the methodology and reagents used for immunohistochemistry is described in the Supplementary materials and methods). Thus, the patient was diagnosed with metastatic adenocarcinoma from the colon carcinoma.

On January 18, 2019, a chest CT scan showed a nodule of ~0.8 cm with high density in the anterior segment of the right upper lobe, and clear edges (Fig. 3A). The patient underwent resection of the right upper lobe nodule (pathologically diagnosed as lung metastasis from colon adenocarcinoma) and continued to receive outpatient chemotherapy postoperatively.

Follow-up was performed until July 13, 2019. An ultrasound examination discovered a nodule in the left sternocleidomastoid muscle area, and postoperative pathology of the nodule resection showed metastatic adenocarcinoma in the left neck. The patient regularly visited the outpatient clinic for chemotherapy with capecitabine, and as of May 2023, the patient was still alive. Follow-up to the present day did not find obvious metastatic lesions in the liver on CT scans (Fig. 3B). Recently, she was suffering from pain in the neck and was treated with capecitabine and celecoxib.

Ethics approval (approval no. 2023020KYLW) was obtained from the People's hospital of Putuo District and informed consent was obtained from the patient.

Discussion

Clinically, metastatic malignant tumors of the thyroid are relatively rare (8), accounting for only 1.4-3.0% of all malignant thyroid tumors (9,10). However, the proportion of metastatic malignant tumors found in autopsy results is as high as 9.5% (11). With improvements in thyroid tumor diagnostic techniques in recent years, as well as the increase in long-term survival rates of patients with malignant tumors, the detection rate of metastatic malignant tumors of the thyroid has increased. According to reports, metastases to the thyroid often originate from lung cancer, renal cancer, breast cancer, or esophageal cancer, with only a small proportion of cases originating from colorectal cancer (12). Lam and Lo (2) studied the pathological features of patients with secondary tumors of the thyroid over a 26-year period. They revealed that the lung was the most common primary tumor site, followed by the breast and stomach. Balta *et al* (13) reported that the most common sites of origin of metastatic thyroid tumors were the kidney (28.5%), lungs (28.5%), head and neck malignancies (28.5%), and unknown primary tumors (14.5%). Stergianos *et al* (1) indicated that of the 1,939 surgical cases with a histopathologic diagnosis of thyroid malignancy, 31 were diagnosed as metastatic tumors of epithelial neoplasms to the thyroid gland. Due to the rarity of cases of thyroid metastasis from colorectal cancer, there is a lack of sufficient understanding of the clinical and pathological diagnosis and treatment.

The mechanism of thyroid metastasis from colorectal cancer is not yet clear. Manatakis *et al* (14) indicated that the majority of cases of thyroid metastases are the result of combined metastases from other organs, such as the liver and lung, suggesting that hematogenous metastasis is the primary metastatic route. There was a case of colon cancer in the hepatic flexure with thyroid metastasis but no liver or lung metastasis (15). This suggests the possibility of a vertebral venous system pathway for metastasis as proposed by Batson (16); that is, the physiological and pathological characteristics of the vertebral venous system allow the tumor to bypass the portal and pulmonary vein, and vena cava and directly metastasize to the thyroid. In addition to mechanical factors, there may also be changes in the molecular genetics during thyroid metastasis from colorectal cancer. Studies have shown that the degree of KRAS mutations in lung metastases from colorectal cancer is significantly higher than that in primary tumors (17). However, the role of molecular genetic changes in the metastasis of colorectal cancer to the thyroid requires further study.

Willis (18) proposed two hypotheses regarding metastatic malignant tumors of the thyroid in 1931. The first hypothesis was the dynamic hypothesis, which suggests that the thyroid is an organ with an extremely abundant arterial blood supply and that rapid blood flow prevents tumor cells from adhering to the thyroid. The second hypothesis is the chemical hypothesis, which suggests that the high oxygen saturation and high iodine content of the thyroid can inhibit the growth of tumor cells. When there is a concurrent underlying thyroid disease, it may reduce arterial blood flow, leading to a hypoxic environment, or hypothyroidism may create a low iodine state, increasing the likelihood of tumor metastasis to the thyroid (19). Yeo *et al* (20) reported that metastatic cancer lesions only exist within the thyroid tumor (thyroid medullary carcinoma)

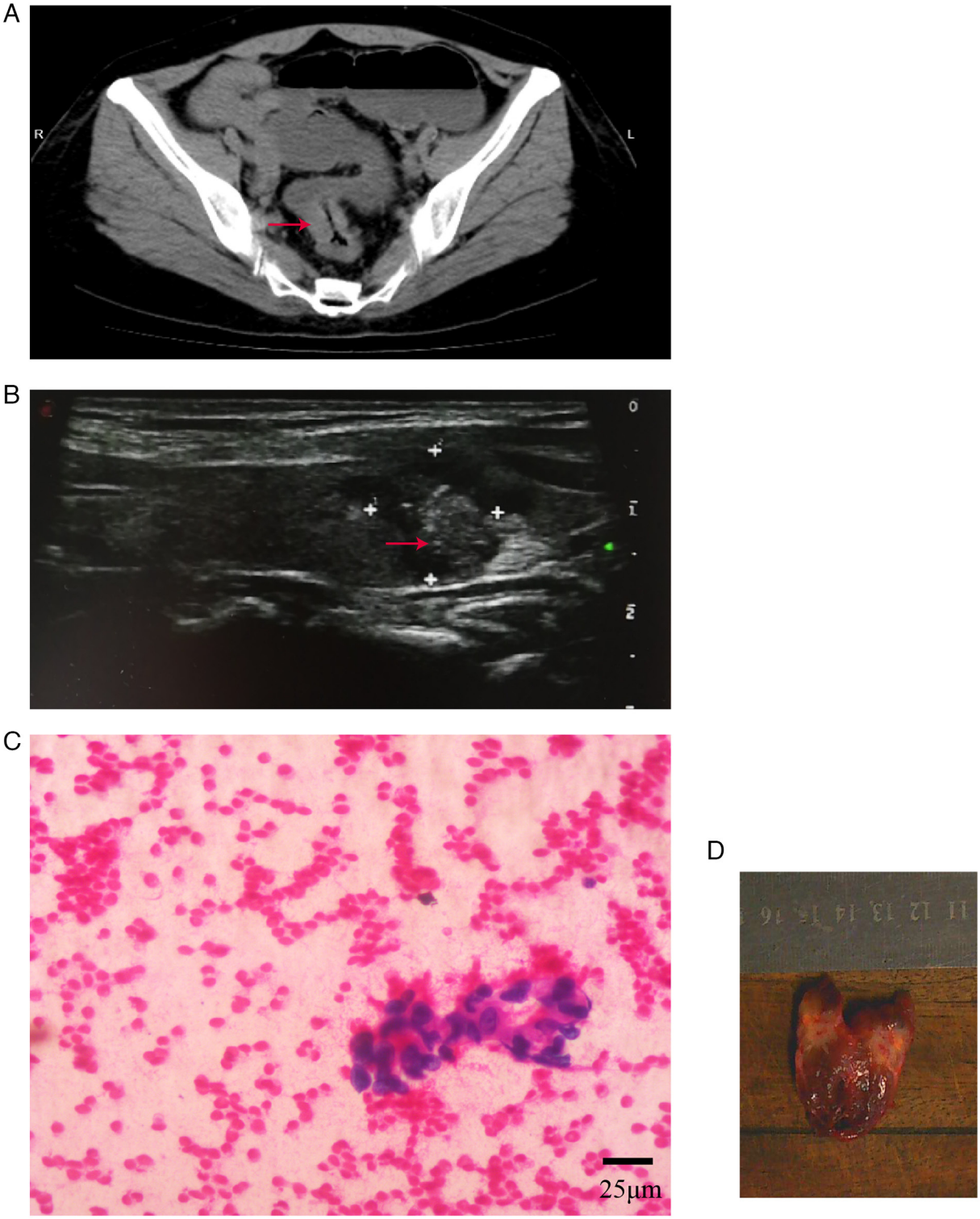

Figure 1. CT scan of colon cancer. (A) Abdominal computed tomography. (B) Thyroid ultrasound revealed a thyroid nodule. (C) Fine needle aspiration biopsy showed clusters of cellular nests exhibiting a microfollicular architecture, nuclear atypia, irregularity, nuclear overlapping, nucleoli, and nuclear grooves that were similar to the features of primary thyroid carcinoma. (D) Macroscopic aspect of the thyroid after excision. Arrows indicate lesion site.

and no significant pathological changes were observed in the surrounding thyroid tissue.

Metastasis of colorectal cancer to the thyroid often presents clinically as a mass in the neck, difficulty breathing, difficulty swallowing, and hoarseness, among other symptoms. It lacks specificity and is easy to misdiagnose as a primary thyroid disease. Ultrasound-guided fine-needle aspiration biopsy of the thyroid is relatively easy to perform and has become an important tool for preoperative pathological diagnosis of thyroid nodules (12,21). Out of 42 patients who underwent thyroid fine-needle aspiration biopsy, positive findings were found in 36 cases (85.7%). However, it is challenging to make the diagnosis of metastatic colorectal adenocarcinoma, with only 13 cases (36.1%) suggesting thyroid metastasis from colorectal

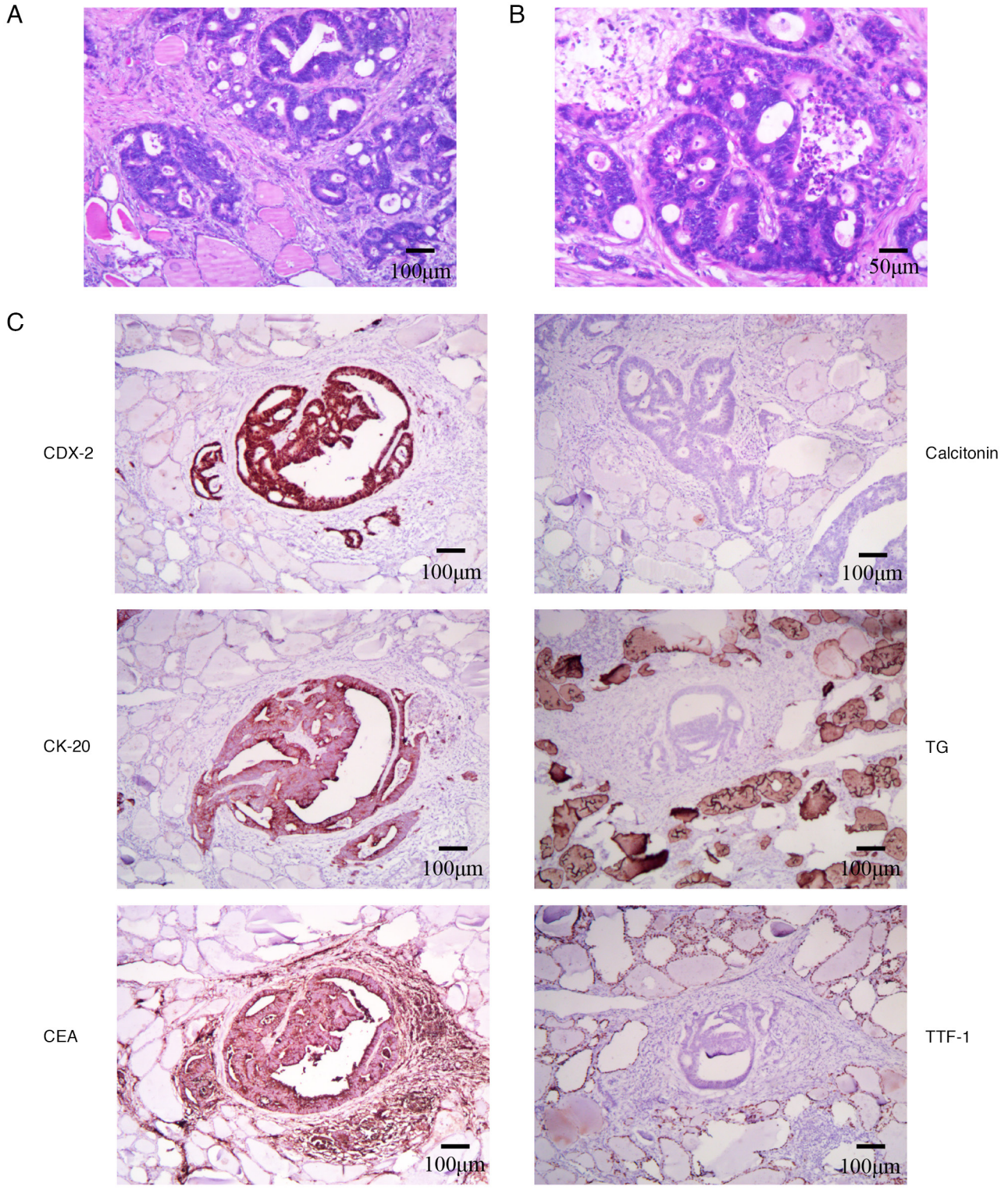

Figure 2. Microscopic sections showed metastatic glands of colon adenocarcinoma infiltrating between thyroid follicles. H&E staining (A) Magnification, x100, scale bar, 100 μm and (B) 200x; scale bar, 50 μm. (C) The metastatic gland showed positivity for CDX2, CK20, and CEA immunoreactivity and negativity for calcitonin, TG and TIF-1. H&E, hematoxylin and eosin.

cancer. There were misdiagnoses of carcinoma of unknown classification (11 cases), primary thyroid papillary carcinoma (5 cases), and thyroid low-undifferentiated carcinoma (3 cases). When primary thyroid carcinoma is also present, the cells of the metastatic cancer may be overlooked as easily identifiable components of a primary thyroid cancer have already been found or the metastatic cancer tissue may not have been biopsied, leading to diagnostic omissions. Of the 42 patients, 4 (3 with concurrent thyroid papillary carcinoma and 1 with concurrent thyroid medullary carcinoma) also had primary thyroid carcinoma, and none of them were correctly diagnosed (6,20,22,23).

The cytological features of thyroid metastases from colorectal cancer via fine-needle aspiration are often atypical columnar cells, vacuolated cells, palisade

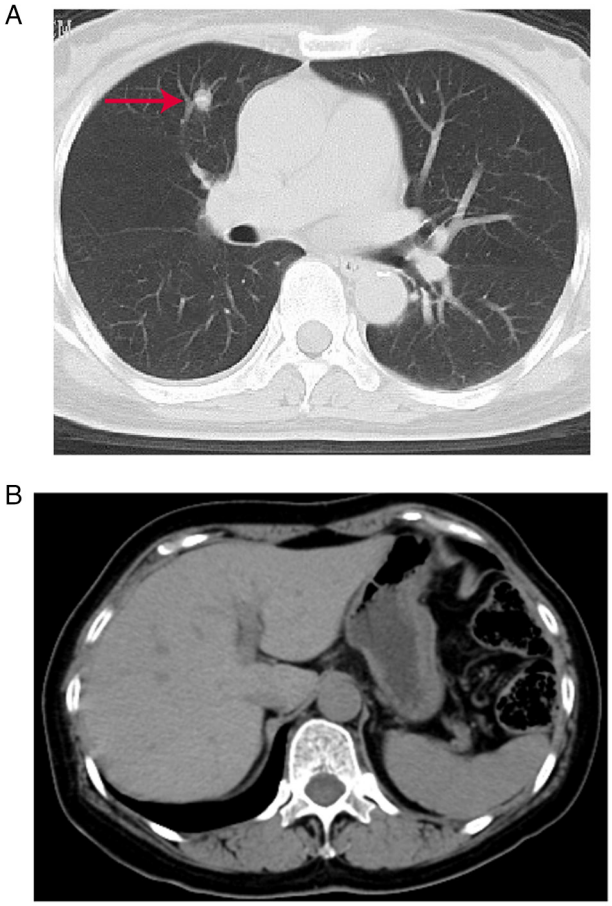

Figure 3. CT scan of the lung and liver. (A) A CT scan showed a mass in the upper region of the right lung (arrow). (B) No metastases were seen on the CT scan of the liver. CT, computed tomography.

arrangement, large, deeply stained nuclei, with an increased nucleoplasmic ratio, obvious nucleoli, and several mitotic figures (24-27). The background is often mass inflammation, fibrosis, and even mucus; in addition, some normal follicular epithelial cells can be seen, which can form small follicular structures with small nuclei and inconspicuous nucleoli (28,29). Moreover, it is very difficult to differentiate metastatic colorectal cancer from primary undifferentiated (anaplastic) thyroid cancer as several cytological features overlap, including obvious nuclear atypia, coarse chromatin, obvious nucleoli, and a large number of mitotic figures (30). However, mucinous background and tall columnar cell clusters are not common in primary undifferentiated thyroid cancer; it is also very similar to the tall cell variant and columnar cell variant of thyroid papillary carcinoma (31,32). The tall cell variant has tall columnar cells, acidophilic cytoplasm, and necrosis can be seen, but nuclear grooves and intranuclear pseudoinclusions are more common (31). The columnar cell type cells often have deep staining, columnar cell pseudolayered arrangement, glandular structures can sometimes be seen, and typical nuclear grooves and intranuclear pseudoinclusions are rare (32). If there are enough cells in the fine-needle aspiration cell sample, immunohistochemical staining of cell paraffin blocks can be performed, as TTF-1, CK7, and thyroglobulin (TG) are positively expressed in primary thyroid cancer. Similarly, positive CK20 and CDX-2 indicate metastatic colorectal cancer (26,28). Typically, a thyroidectomy is required for a definitive diagnosis. In the present case, both fine-needle aspiration diagnosis and intraoperative rapid freezing pathology diagnosis were misdiagnosed. Therefore, for the diagnosis of thyroid metastasis from colorectal cancer, it is necessary to combine clinical data, carefully identify various suspicious cells in fine-needle aspiration cytology, repeat biopsies when necessary, and perform histological diagnoses of postoperative mass tissues (including immunohistochemistry and molecular genetics).

Thyroidectomy remains the conventional treatment for thyroid metastases from colorectal cancer. The outcome of surgical treatment is likely to depend on a variety of factors, including the status of the primary tumor, the patient's own conditions, and the symptoms caused by the thyroid mass. Resection of metastatic colorectal cancer lesions in the thyroid gland can reduce the tumor load, and the likelihood of metastasis to other organs, and symptoms, including hoarseness and dyspnea (33). Russell *et al* (34) reported that total thyroidectomy is recommended for thyroid metastases from colorectal cancer, which can avoid the possibility of re-emerging metastases from the residual thyroid gland. Yamamoto *et al* (35) and Cheung *et al* (36) revealed that patients with thyroid metastases from colorectal cancer are usually treated with previous colon cancer chemotherapy regimens.

In conclusion, an increasing number of thyroid metastases from colorectal cancer have been detected in recent years. In the postoperative management of colorectal cancer, in addition to routine follow-up examinations of the chest and abdomen, attention should also be paid to thyroid examinations. Fine needle aspiration biopsy is an effective measure for the preoperative diagnosis of thyroid nodules. Pathologists should examine a patient's clinical history and comprehensively review the pathological results to improve accuracy. Surgical resection remains an effective treatment method for patients with thyroid metastasis from colorectal cancer. Accurate diagnosis can help patients develop chemotherapy plans with the aim of prolonging survival.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

HL and MZ collected clinical data. YC analyzed the data. HZ analyzed and interpreted the data and wrote the paper. HL and

HZ confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval (approval no. 2023020KYLW) was obtained from the People's hospital of Putuo District and informed consent was obtained from the patient.

Patient consent for publication

The patient consented to the publication of this report.

Competing interests

The authors declare that they have no competing interests.

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