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## Thyroid metastasis from breast cancer presenting with enlarged lateral cervical lymph nodes: A case report

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## Abstract

### BACKGROUND

Secondary malignancy of the thyroid occurs infrequently and mainly originates from malignant tumors of the kidney, gastrointestinal tract, lungs, breast, and skin. The correct diagnosis is important but difficult. Importantly, there are major differences in the treatment of primary and metastatic thyroid cancer, which has a significant impact on prognosis and survival. Therefore, how to diagnose thyroid metastasis (TM) correctly before surgery is a major concern for surgeons.

### CASE SUMMARY

We report a 38-year-old woman who presented with palpable cervical lymph nodes after breast cancer (BC) surgery 2 years ago. Ultrasonography and computed tomography revealed thyroid nodules with irregular margins and enlarged cervical lymph nodes. Biopsy was performed for the right largest cervical lymph node, and immunohistochemical analysis revealed negativity for thyroglobulin, estrogen receptor, and progesterone receptor and positive for human epidermal growth factor receptor 2. The diagnosis was TM from BC with cervical lymph node metastasis. Total thyroidectomy with bilateral central and lateral neck lymph node dissection was performed. After a 5-mo follow-up, no recurrence or novel distant metastasis was identified.

### CONCLUSION

TM from BC is a rare secondary malignancy. Broad differential diagnosis by biopsy and immunohistochemical analysis needs to be considered.

**Key words:** Secondary malignancy; Thyroid; Breast cancer; Metastasis; Case report

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**Core tip:** Thyroid metastasis from breast cancer is a rare secondary malignancy. The correct diagnosis before surgery is important but difficult. Importantly, there are major differences in the treatment of primary and metastatic thyroid cancer, which has a significant impact on prognosis and survival. Because of its low incidence, thyroid metastasis from breast cancer is easily overlooked and misdiagnosed. Broad differential diagnosis by biopsy and immunohistochemical analysis needs to be considered.

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## INTRODUCTION

Although the thyroid gland is highly vascularized, secondary malignancy, which metastasizes to the thyroid, occurs infrequently, accounting for only 1%-3% of thyroid cancers<sup>[1,2]</sup>. However, reports suggest that thyroid metastases (TM) are possibly more common than primary thyroid carcinoma (TC) by autopsy series<sup>[3]</sup>. Usually, secondary malignancy of the thyroid gland originates from renal cell carcinoma, followed by malignant tumors of the gastrointestinal tract, lungs, breast, and skin<sup>[4,5]</sup>. More importantly, these cases are diagnostically challenging. There are major differences in the treatment of primary and metastatic thyroid cancer, which has a significant impact on prognosis and survival. Therefore, determining a correct diagnosis before surgery is a major concern for surgeons. In addition, patients with metastatic breast cancer (BC) to the thyroid usually present with symptoms of a new or enlarging thyroid nodule<sup>[6]</sup>. TM from BC presenting with enlarged lateral cervical lymph nodes is rare. Here, we report a case of bilateral thyroid and bilateral cervical lymph node metastasis from left invasive ductal carcinoma along with a brief literature review of similar cases. A literature search was performed with key words (thyroid cancer, breast cancer, and metastasis) for studies regarding TM from BC until December 2019.

## CASE PRESENTATION

### Chief complaints

A 38-year-old woman was admitted to our clinic in July 2019 for bilateral cervical palpable lymph nodes.

### History of the present illness

The patient was euthyroid, and there were no high metabolic symptoms, such as heat, sweating, and hand shaking, during the course of the disease. Biopsy was carried out in another hospital for the right enlarged cervical lymph node. Immunohistochemical analysis revealed negativity for thyroglobulin (TG), estrogen receptor (ER), and progesterone receptor (PR) and positive for human epidermal growth factor receptor 2 (Her-2). There was no obvious bone metastasis in the whole-body bone scan.

### History of past illness

In March 2017, she was diagnosed with left breast invasive ductal carcinoma with Paget's disease and treated by mastectomy and axillary lymph node dissection followed by chemotherapy and radiotherapy. The patient underwent chemotherapy (docetaxel and capecitabine) and Herceptin targeted therapy for another 12 mo.

### Personal and family history

The patient had no significant personal or family history.

### Imaging examinations

Ultrasonography (US) revealed solid, hypoechoic thyroid nodules with irregular margins and multiple enlarged lymph nodes (Figure 1). Computed tomography (CT) showed multiple bilateral lymph nodes with diameters ranging from 0.4 cm to 1.2 cm.

Contrast-enhanced CT showed homogenous enhancement (Figure 2).

## FINAL DIAGNOSIS

TM from BC with cervical lymph node metastasis.

## TREATMENT

Total thyroidectomy and bilateral central and lateral neck lymph node dissection were performed for this patient. Postoperative pathology showed extensive intravascular infiltration and nerve infiltration of breast invasive ductal carcinoma in the bilateral thyroid tissue, accompanied by interstitial fibrous tissue hyperplasia, scattered necrosis, and calcification (Figure 3). The positive status of cervical lymph nodes was: Central lymph nodes (3/3), the left lateral neck from level II-IV lymph nodes (7/12), and the right lateral neck from level II-IV lymph nodes (14/14). The results of immunohistochemistry indicated the following: ER (-), Her-2 (3+), PR (-), GATA3 (+), PAX-8 (-), and TTF-1 (-) (Figure 4).

## OUTCOME AND FOLLOW-UP

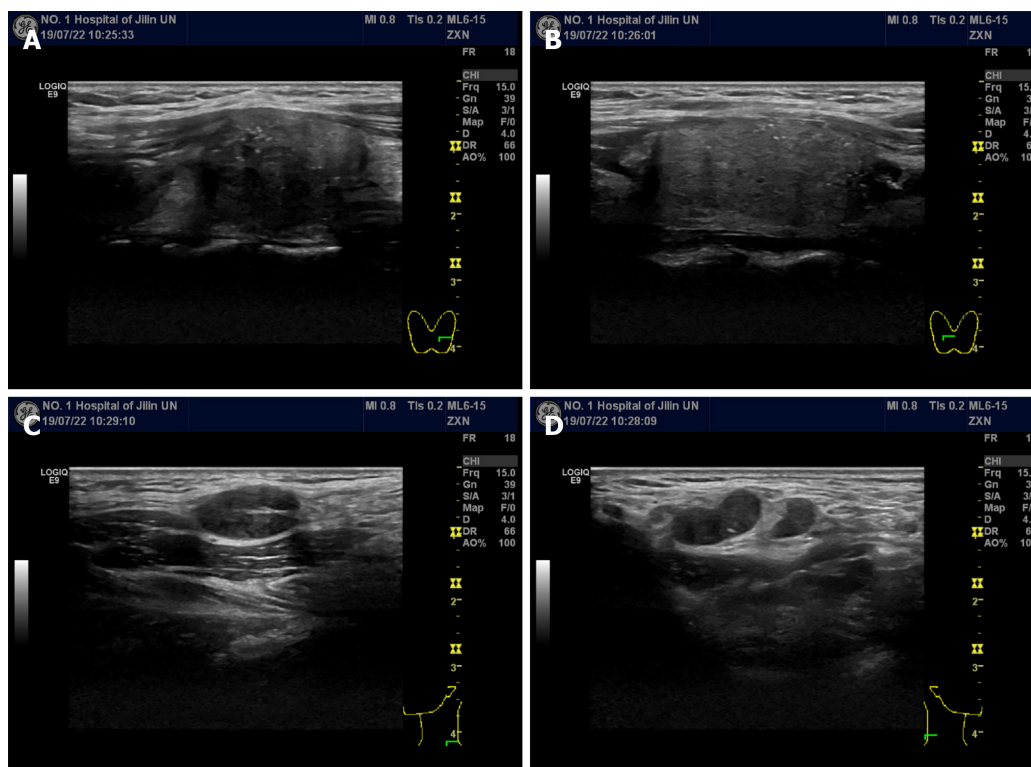
One month after surgery, the patient was admitted to the Oncology Department of our hospital for postoperative examination. Breast ultrasound examination was performed, indicating that the right breast mass was BI-RADS 3. Currently, no recurrence or novel distant metastasis was identified after a 5-mo follow-up.

## DISCUSSION

TM is uncommon, and breast-derived TM is relatively rare. We searched PubMed until December 2019 and identified 15 reports about metastases to the thyroid from BC (Table 1)<sup>[1,4,6-18]</sup>. According to this literature review and analysis, some preliminary conclusions can be made as follows: (1) The occurrence of TC may have no correlation with age, and all reported cases were female; (2) among BC, invasive ductal carcinoma is a more common histopathological type that metastasizes to the thyroid than others, such as invasive lobular carcinoma and metaplastic breast carcinoma; (3) the interval time from BC diagnosis to TC ranges from 6 months to 288 mo. Therefore, for patients with thyroid nodules or cervical lymph nodes who have a history of malignant breast tumors, regardless of the course of the disease, the possibility of metastatic cancer should be considered; and (4) preoperative biopsy and immunohistochemical analysis can assist in the diagnosis of TM and primary malignancy.

TM has no difference in symptoms from primary thyroid cancer, and the physical examination is usually normal. TMs from renal cell carcinoma are usually symptomatic, such as neck masses, dysphagia, and hoarseness, while lung cancer and BC usually have no symptoms and are mostly found by US<sup>[19]</sup>. In this case, the patient with TM from BC initially presented with enlarged cervical lymph nodes, which has not been reported before to our knowledge. Therefore, preoperative diagnosis of TM from BC is difficult and easy to misdiagnose. It can be identified by the following points: (1) Medical history: For patients with a medical history of thyroid nodules or enlarged cervical lymph nodes with BC, the possibility of metastatic cancer should be considered; (2) Imaging findings: Imaging, like US, magnetic resonance spectroscopy, diffusion magnetic resonance, and perfusion CT, provides useful information such as diffuse calcification or invasion of surrounding tissues for assessing the nature of the nodules or lymph nodes<sup>[20-22]</sup>. However, it is difficult to determine the source of malignancy; (3) Findings of biopsy and immunohistochemical staining: The accuracy of US-guided biopsy for diagnosis of TM is reported to be 90.8% to 91.2%<sup>[7]</sup>. However, some thyroid metastatic carcinomas can still have similar morphological features to those of primary thyroid cancer by biopsy, including papillary, follicular, and myeloid structures. On these occasions, immunohistochemical staining, such as for TG, calcitonin, GATA3, PAX8, and thyroid transcription factor-1 (TTF-1), is helpful for distinguishing between primary thyroid cancer and TM. TG is the only specific marker for malignant tumors of thyroid origin and can confirm the nonmedullary carcinoma of the thyroid containing a follicular structure<sup>[16]</sup>. Calcitonin is generally considered to be the most important specific marker for parafollicular cells (C cells)

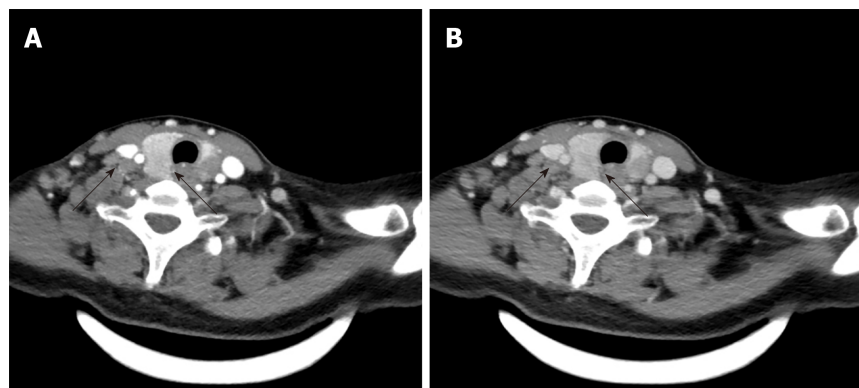




**Figure 1 Ultrasonography of the thyroid and lateral neck.** A and B: Left (A) and right (B) thyroid lobes; solid, hypoechoic thyroid nodules with irregular margins could be observed; C and D: Left (C) and right (D) lateral neck; enlarged metastatic lateral lymph nodes could be observed.

and is considered to be an essential condition for diagnosing medullary carcinoma of C cell origin<sup>[19]</sup>. TTF-1 regulates the transcription of specific genes in thyroid follicular cells and activates the transcription of *Tg* and thyroid peroxidase genes in thyroid cancer cells<sup>[15]</sup>. However, TTF-1 has no specificity because it can also be found in lung cancer, and PAX8 can also be found in kidney cancer and gynecological tumors<sup>[8]</sup>. GATA3, ER, PR, and HER-2 are markers for BC, and the positive staining for E-cadherin supports the catheter phenotype<sup>[8]</sup>. BC with ER positivity often metastasizes to the thyroid gland and parathyroid glands, while PR positivity tends to metastasize to the myocardium, gastrointestinal tract, or urinary tract epithelium<sup>[9]</sup>. However, in this case, the BC exhibited strong positivity for Her-2 and negativity for ER and PR. According to this case, the intraoperative pathology can only suggest a diagnosis of malignant tumors, and the source was confirmed by paraffin sectioning and immunohistochemistry; and (4) positron emission tomography-computed tomography findings: If there is a history of malignant tumors, it should be actively explored. Small lesions can be found, and the general condition of patients can be assessed. This patient refused to perform this test because it was too expensive. Based on these characteristics, we can develop a simple diagnostic flow chart for patients who underwent thyroid tumor biopsy and immunohistochemical staining (Figure 5) that can aid in the diagnosis of patients with suspected TC with a history of BC.

The impact of distant metastasis to the thyroid from BC on prognosis is still unknown. Although TM is a late-stage manifestation of malignant tumors, some patients can achieve relatively satisfactory results in prolonging survival if they can be detected early and treated by surgery-based comprehensive methods<sup>[17]</sup>. Zhou *et al*<sup>[7]</sup> found that thyroidectomy is feasible in patients with only TM after the treatment of primary tumors. Chemotherapy or endocrine therapy may be more effective in patients with extensive systemic metastases, such as lungs and bones. Thyroidectomy and cervical lymph node dissection are often used, followed by radiotherapy and chemotherapy<sup>[3]</sup>. Metastatic thyroid cancer patients are often accompanied by distant metastasis in other parts of the body, so the specific treatment strategy should be based on the original pathological type and location of the lesions<sup>[7]</sup>. Because of the limited number of BC patients with TM, the findings in our article may not represent all BC patients with TM. To assess the value of treatment strategy in improving the outcome of patients, studies with a large number of patients and long-term follow-up are warranted.



**Figure 2** Computed tomography of the thyroid and lateral neck showed thyroid nodules and multiple lateral lymph nodes with homogenous enhancement. A: Arterial phase; B: Venous phase.

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## CONCLUSION

TM from BC is a rare secondary malignancy. Broad differential diagnosis by biopsy and immunohistochemical analysis needs to be considered.

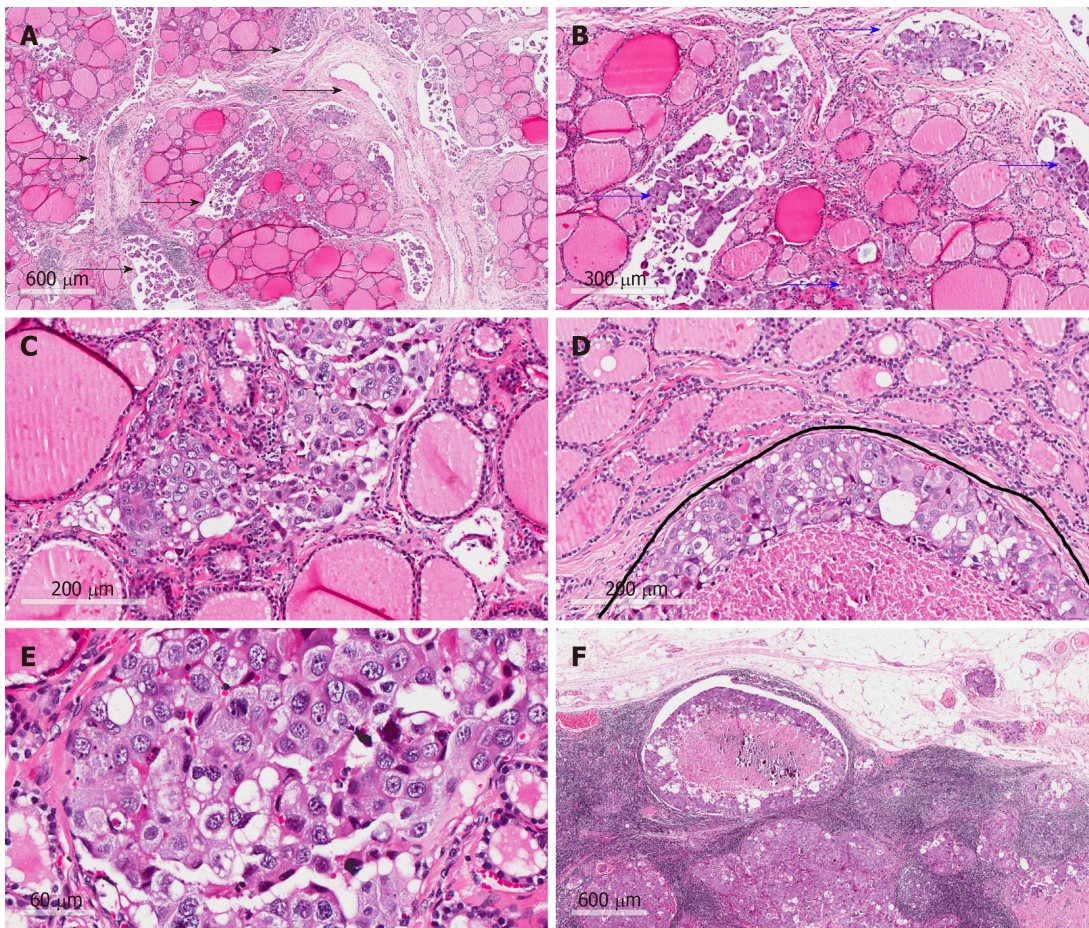
Table 1 Reports of metastatic breast carcinoma involving the thyroid gland

Ref.	No of cases	Age (yr)	Type of BC	Location of BC	Location of TC	Time for metastasis (mo)	Metastases elsewhere	Immunohistochemistry	Treatment
Inic <i>et al</i> <sup>[1]</sup>	1	28	Lobular	Right	Bilateral	60	Lymph nodes in right lateral neck	Mammaglobin (+), GCDFP-15 (+), ER (+), PR (+), Tg (-), TTF-1 (-), CK7 (-) HER2 (-)	TT, right CLND and LLND
Liu <i>et al</i> <sup>[4]</sup>	1	47	Invasive ductal	Bilateral	Right	48	Bilateral cervical lymph nodes	ER (+), PR (+), HER2 (+)	Apatinib
Gong <i>et al</i> <sup>[6]</sup>	1	57	Metaplastic	Right	Left	24	NA	NA	NA
Zhou <i>et al</i> <sup>[7]</sup>	8	55.37	NA	Right (n = 5); left (n = 1); bilateral (n = 2)	NA	6 to 121	Chest wall (n = 2); supraclavicular nodes (n = 2); lung (n = 2); axilla nodes (n = 2); cervical and mediastinal lymph node (n = 2)	TG (-) and TTF-1 (-)	TT or lobectomy or chemotherapy
Ghias <i>et al</i> <sup>[8]</sup>	1	67	Invasive ductal	NA	Bilateral	24	Brain	AE1/AE3 (+), ER (+), GATA3 (+), E-cadherin (+), CK7 (-), CK20 (-), GCDFP/mammaglobin (-), TTF-1 (-), Tg (-), CT (-), synaptophysin (-)	Lobectomy
Yang <i>et al</i> <sup>[9]</sup>	1	51	Invasive ductal	Left	Left	288	Cervical lymph nodes	ER (+), PR (-)	TT with a selective LLND and postoperative chemotherapy
Owens <i>et al</i> <sup>[10]</sup>	1	64	Infiltrating mammary	NA	Left	60	Subcutaneous mass in the right shoulder and liver	HER2 (+)	No surgery
Magers <i>et al</i> <sup>[11]</sup>	1	37	Ductal breast	NA	Right lobe and isthmus	72	Bone and brain	GATA-3 (+), ER (+), PAX-8 (-), TTF-1 (-)	NA
Durmo <i>et al</i> <sup>[12]</sup>	1	72	Invasive ductal	NA	Left	NA	The third lumbar vertebrae and left iliac bone	NA	NA
Yang <i>et al</i> <sup>[13]</sup>	1	45	Infiltrating ductal	Right	Bilateral	36	Bilateral cervical lymph nodes	ER (+), PR (+), CerB-2 (+), TTF-1 (-), Tg (-)	Bilateral subtotal thyroidectomy and lymphadenectomy
Zeng <i>et al</i> <sup>[14]</sup>	1	49	Inflammatory	Right	NA	7	Lymph nodes in right lateral neck	CA15-3 (+), Her2 (+++), GCDFP-15 (-), TG (-), TTF-1 (-), ER (-), PR (-)	TT, CLND, LLND and postoperative RAI and chemotherapy

Lacka <i>et al</i> <sup>[15]</sup>	1	54	Ductal-lobular mammary	Left	Bilateral	168	Skeletal supraclavicular lymph nodes, liver, and right lung	CKMNF 116 (+), CK7 (++), CEA (+), MGB2 (++), ER (+), PR (+), HER2 (+), CK20 (-), TG (-), TTF1 (-), CT (-), chromogranin (-)	TT and bilateral CLND and LLND with chemotherapy
Bourcier <i>et al</i> <sup>[16]</sup>	1	54	Invasive lobular	NA	left	0	Left supraclavicular and cervical lymph nodes	TG (-), TTF-1 (-), E-cadherin (-), HER-2 (-), AE1/AE3(+) ER (+), PR (+), CDX2 (+), PAX8 (+), GATA3(+)	TT and CLND
Pensabene <i>et al</i> <sup>[17]</sup>	1	64	Invasive lobular	Left	left	18	Bone	Cytokeratin-19 (+) ER (+) tireoglobulin (-), e-cadherin (-), cytokeratin-7 (-)	Lobectomy
Plonczak <i>et al</i> <sup>[18]</sup>	1	62	Invasive ductal	Bilateral	NA	144	Lung and bone, both lateral cervical lymph nodes	CEA (+), GATA3 (+), GCDFFP-15 (+), CK7 (+), TG (-), TTF-1 (-), CK20 (-), PR (-), HER-2 (-)	TT and CLND

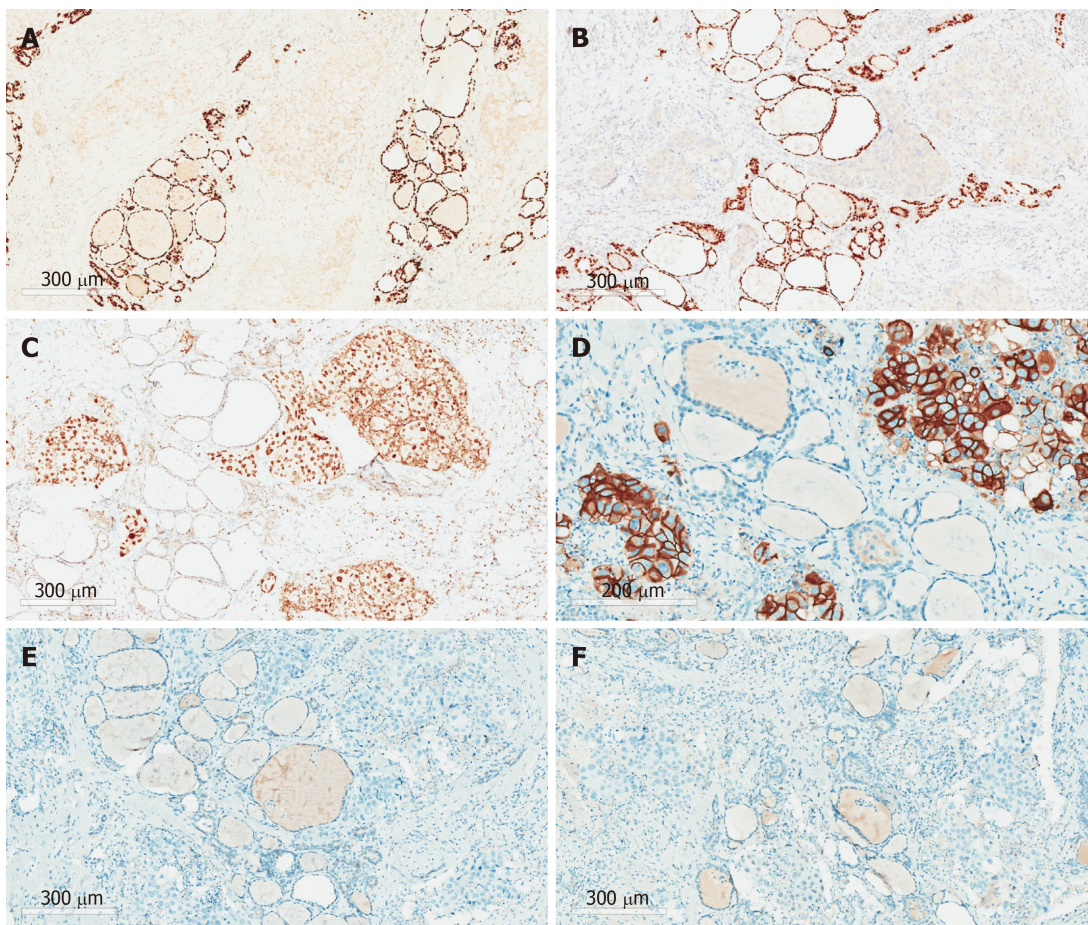
BC: Breast cancer; TC: Thyroid cancer; NA: Not available; TT: Total thyroidectomy; CLND: Central lymph node dissection; LLND: Lateral lymph node dissection; RAI: Radioactive ablation; TG: Thyroglobulin; ER: Estrogen receptor; PR: Progesterone receptor; Her-2: Human epidermal growth factor receptor 2; TTF-1: Thyroid transcription factor-1; CT: Calcitonin; CEA: Carcinoembryonic antigen; NA: Not available.



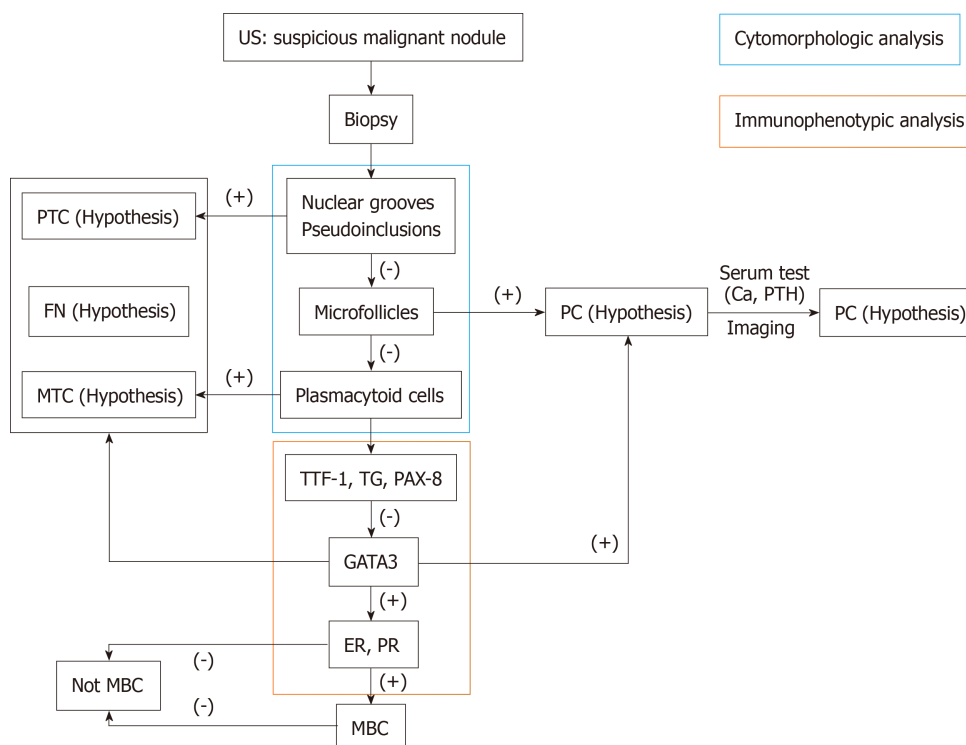


**Figure 3 Hematoxylin-eosin staining.** A: Malignant tumor tissue between follicles (arrows; magnification, 40 ×); B: Malignant tumor tissue in vascular space (arrows; magnification, 100 ×); C: Atypia tumor cells without nuclear features of papillary thyroid carcinoma (magnification, 200 ×); D: Infiltrating tumor cells in the mesenchyme of the thyroid (under the curve; magnification, 200 ×); E: Atypia of tumor cells without nuclear features of papillary thyroid carcinoma (magnification, 400 ×); F: Malignant tumor tissue in lymph nodes (magnification, 40 ×).





**Figure 4** Immunohistochemical staining. A: TTF-1 (-); B: PAX8 (-); C: GATA3 (+); D: HER-2 (3+); E: ER (-); F: PR (-). (Magnification, 200 × for D and 100 × for the rest).



**Figure 5** Diagnostic algorithm for thyroid cancer patients with a history of breast cancer. US: Ultrasonography; PTC: Papillary thyroid carcinoma; FN: Follicular neoplasm; MTC: Medullary thyroid carcinoma; PC: Parathyroid carcinoma; MBC: Metastatic breast cancer.



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