Metastasis to the thyroid gland from primary breast cancer presenting as diffuse goiter: A case report and review of literature

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Abstract

BACKGROUND
Metastasis to the thyroid gland (TM) from primary breast cancer is uncommon and usually presents as thyroid nodules; however, diffuse goiter without thyroid nodules is the first sign of TM in rare cases. Skip metastases (SMs) to the lymph nodes in breast cancer, defined as discontiguous higher-level metastases in the absence of lower levels of contiguous metastases, have been reported in the contralateral cervical area of the primary tumor site in rare cases.

CASE SUMMARY
A 49-year-old previously healthy Chinese woman was diagnosed with right lateral invasive ductal carcinoma and underwent neoadjuvant chemotherapy treatment and bilateral mastectomy with axillary lymph node dissection. No malignancy of the left breast or axillary or distant metastases were identified preoperatively. However, enlarged left cervical lymph nodes were detected 36 mo after surgery, and rapidly enlarging thyroid glands without nodules were detected 42 mo after surgery. Fine-needle aspiration cytology was performed on the left cervical lymph nodes and left lobe of the thyroid, which were both revealed to contain metastases from the primary breast cancer. Additionally, the immunostaining profiles changed in the process of metastases. The patient was discharged with the NP (vinorelbine and cisplatin) regimen for subsequent treatment, and stable disease was determined when the curative effect was evaluated.

CONCLUSION
Diffuse goiter may be the first sign of TM, and enlarged lymph nodes in the
A 49-year-old Chinese woman was diagnosed with invasive ductal carcinoma (IDC) of the right breast with a chief complaint of palpable masses and right nipple discharge in October 2015 (Figure 1). The right axillary lymph nodes were also found to contain poorly differentiated metastatic breast carcinoma cells by fine-needle aspiration cytology (FNAC). No mass or enlarged lymph nodes were seen on the left side upon computed tomography (CT) scan or by ultrasound. The patient underwent neoadjuvant chemotherapy, with 3 cycles of the FEC (5-fluorouracil + epirubicin + cyclophosphamide) regimen and 3 cycles of the TG (vinorelbine + cisplatin) regimen (Figure 1). She was evaluated as having achieved partial remission.
Figure 1 Course of disease. FNAC: Fine-needle aspiration cytology.

after finishing chemotherapy. Subsequently, bilateral mastectomy was performed at the request of the patient in April 2016 (Figure 1). Surgical specimens showed T2N3 (12/27) M0 grade 3 IDC with ductal carcinoma in situ on the right side based on hematoxylin and eosin (HE) staining and immunohistochemistry (IHC). Right axillary and intercostal lymph node metastases were also observed microscopically. No carcinoma was found in the left breast or axillary lymph nodes. IHC staining suggested estrogen receptor (ER, strong positive), progesterone receptor (PR, moderate positive) and human epidermal growth factor receptor 2 (HER-2, 2+) positivity, and the monoclonal antibody Ki-67 index was 60%. After surgery, the patient received endocrine therapy with anastrozole and goserelin. Radiation therapy was administered in 25 fractions to the right breast.

In April 2019, the patient presented at the clinic with a cervical mass and intermittent neck discomfort without pain and airway pressure symptoms. CT revealed lymphadenopathy in the left cervical area and posterior mediastinum. Observation and follow-up were recommended. Two months later, the size of the mass had increased. Further investigation was performed by ultrasound, and levels IV and V left cervical nodal disease was confirmed. On CT with contrast, the patient was found to have left cervical and posterior mediastinum lymph node enlargement and suspected right scapula metastasis. No treatment was initiated per the patient’s decision, and she was scheduled to return to the clinic in 3 mo. In October 2019, the patient presented at her outpatient visit with progressive neck swelling that had persisted for 3 mo.

History of past illness
The patient had no history of any previous disease.
**Personal and family history**
The patient had no personal or familial risk factors for thyroid malignancies.

**Physical examination**
On physical examination, a hard fixed palpable nontender left lateral neck mass and enlarged thyroid gland were palpated.

**Laboratory examinations**
Tumor indicators revealed that the carcinoembryonic antigen was elevated at 3.92 μg/L and carbohydrate antigen 15-3 was elevated at 22.30 kU/L. The thyroid function analysis revealed mild hypothyroidism, with a thyroid stimulating hormone level of 5.61 mU/L and a free thyroxine level of 11.62 pmol/L. Blood analysis and inflammatory indicators were normal.

**Imaging examinations**
Multimodality ultrasound was performed to evaluate neck swelling, revealing homogeneous enlargement of the thyroid gland without nodules (measuring 2.5 cm × 5.0 cm × 2.2 cm in the right lobe, 2.5 cm × 5.0 cm × 2.0 cm in the left lobe, and 0.8 cm in the isthmus) and level II-VI left abnormally enlarged cervical lymph nodes (the largest measuring 2.7 cm × 2.8 cm × 2.3 cm with microcalcifications and heterogeneous high enhancement ([Figure 2A](#)). Fine-needle aspiration cytology (FNAC) of the enlarged thyroid and lymph nodes was conducted for diagnosis ([Figure 2B](#)).

**Differential diagnosis**
Hashimoto's thyroiditis, Grave's disease and primary/secondary thyroid malignancy were our initial differential diagnoses to explain the rapid growth of the thyroid gland.

**FINAL DIAGNOSIS**
The patient was ultimately diagnosed with TM from primary breast cancer and SMs to the contralateral cervical lymph nodes ([Figure 3](#)).

**TREATMENT**
Given the suspected bone metastasis and financial issues, the patient was discharged on the NP (vinorelbine and cisplatin) regimen ([Figure 1](#)).

**OUTCOME AND FOLLOW-UP**
To date, after 6 cycles of chemotherapy, the patient has remained clinically stable, and no recurrence at other sites has been detected or confirmed.

**DISCUSSION**
We performed a comprehensive literature search of the PubMed and Medline databases to identify studies of TM metastasis from breast cancer published from 2000 to 2020, and twenty-five articles were found. Detailed information about thyroid metastatic breast cancer was extracted from these articles (Table 1), and only descriptive analyses and literature reviews were found, given the low incidence of TM.

Metastasis to the thyroid gland is rare due to its rich blood supply; however, reports of TM have increased in recent years as a result of more sophisticated diagnostic methods, such as FNAC and proton emission tomography[5,6]. The characteristics of TM from breast cancer are listed in Table 1. We collected information regarding age, sex, histology of the primary tumor, other sites of recurrence, the time interval between primary diagnosis and TM, presentation of TM, treatment of metastasis, response to the treatment and follow-up for 45 women with TM of breast cancer from 2000 to 2020(6-30). The development of TM does not seem to be age-related and mostly occurs in women. The time interval between primary and metastatic disease and the
| Ref.          | Study year | No of patients | Sex | Age | Primary tumor | Other recurrence | Time interval (mo) | Presentation | Treatment | Response | Follow-up (mo) | Ref.          | Study year | No of patients | Sex | Age | Primary tumor | Other recurrence | Time interval (mo) | Presentation | Treatment | Response | Follow-up (mo) |
|--------------|------------|----------------|-----|-----|---------------|------------------|-------------------|--------------|-----------|----------|----------------|--------------|------------|----------------|-----|-----|---------------|------------------|-------------------|--------------|-----------|----------|----------------|
| Wang et al  [8], 2020 | -          | 1              | F   | 58  | Mucinous      | Nil              | 156               | Neck swelling  | Thyroidectomy | Stable   | 9 alive         | Durmo et al [10], 2019 | -          | 1              | F   | 72  | Ductal        | Abnormality of 18F-FDG PET/CT | -               | Abnormality of 18F-FDG PET/CT | -          | -   | -              |
| Pensabene et al [11], 2018 | 2011-2015 | 1              | F   | 64  | Lobular       | Nil              | 6                 | Multinodular goiter | Hemithyroidectomy | Recurrence in bone | 32          | Zhou et al [12], 2017 | 2005-2015 | 8              | F   | 48  | Poorly differentiated | Neck swelling | 84               | Chemotherapy | PR        | 14 alive         | Plonczak et al [13], 2017 | 2004-2017 | 1              | F   | 62  | Ductal        | Lung, bone | 144               | Chemotherapy | CR        | 5 alive          |
|             |            |                |     |     |               |                  |                   |              |           |          |                 | Magers et al [14], 2016 | -          | 1              | F   | 37  | Ductal        | Brain, bone | 72                | Chemotherapy | CR        | 21 alive         |
| Liu et al [15], 2014 | 2007-2009 | 1              | F   | 47  | Ductal        | Nil              | 24                | Enlarged thyroid with diffuse microcalcification | -          | -          | -              | Nguyen et al [16], 2013 | -          | 1              | F   | 67  | Lobular       | Nil              | 48                | Chemotherapy | PR        | 30 alive         |
| Lacka et al [17], 2012 | -          | 1              | F   | 54  | Ductal + lobular | Bone, suprarenal gland | 168              | Multinodular goiter | Total thyroidectomy | -          | 36 alive         | Kolarevic et al [18], 2012 | 2002-2011 | 1              | F   | 54  | Ductal + lobular | Nil              | 84                | Palpable thyroid nodules | Chemotherapy and hemithyroidectomy | PR        | 24 alive         |
| Leboeuf et al [19], 2006 | 1989-2005 | 1              | F   | 59  | Ductal        | Mediastinal, lung, LN, adrenal | 168              | Unpalpable thyroid nodules | Total thyroidectomy | -          | 12            | Skowronska Jorwiek et al [19], 2010 | -          | 2              | F   | 49  | Lobular       | Nil              | 0                 | Palpable thyroid nodules | Total thyroidectomy | -          | -              |
| Peteiro et al [23], 2005 | -          | 1              | F   | 42  | Ductal        | Nil              | 0                 | Palpable thyroid nodules | Hemithyroidectomy | -          | -              | Garrido et al [21], 2006 | 2003-2005 | 1              | F   | 43  | -            | Palpable thyroid nodules | 24              | Palpable thyroid nodules, hoarseness, dysphonia, dysphagia | Total thyroidectomy and chemotherapy | Carcinomatous lymphangitis | -          | -              |
| Cichoń et al [22], 2006 | 1993-2005 | 1              | F   | 50  | -             | Nil              | 120               | Multinodular goiter | Total thyroidectomy | Stable | 24 alive         | Owens et al [24], 2005 | -          | 1              | F   | 64  | Invasive      | Neck swelling and pain | -               |-neck swelling and pain | Chemotherapy | -          | -              |
prognosis of TM varies among the reports. In two patients, TMs were detected synchronously with the diagnosis of the primary cancer[17,21].

As shown in Table 1, TM has various clinical presentations. On physical examination, TM usually appears as a palpable mass or neck swelling, with or without dysphagia, hoarseness, dysphonia, pain and other symptoms, when thyroid metastasis is the first presentation of recurrent disease. In the reports that presented clinical information, most patients (90.1%) had thyroid nodules confirmed with ultrasound or CT, except one patient who had an enlarged thyroid with diffuse calcification[14] and

| Study                  | Year     | Age | Histology | Metastatic Site(s) | Clinical Presentation | Treatment          | Outcome     | Remarks               |
|------------------------|----------|-----|-----------|-------------------|----------------------|-------------------|-------------|----------------------|
| Kim et al[7], 2005     | 1997-2003| 36  | Ductal    | LN, lung          | Palpable thyroid nodules | Chemotherapy      | Stable      | 6 alive              |
|                        | 34       |     | Ductal    | Lung, scalp       | Multinodular goiter   | Chemotherapy      | Stable      | 17 alive             |
|                        | 44       |     | Ductal    | Nil               | Palpable thyroid nodules | Chemotherapy      | Stable      | 4 alive              |
|                        | 55       |     | Ductal    | Lung, parotid gland | Multinodular goiter   | Chemotherapy      | PD          | 26                   |
|                        | 45       |     | Ductal    | Neck LN, lung, bone | Palpable thyroid nodules | Chemotherapy      | Stable      | 8 alive              |
| Wood et al[26], 2004   | 1985-2002| 1   | Invasive  | Nil               | -                    | Total thyroidectomy | Stable      | 36 alive             |
| Mistelou et al[9], 2019| 1998-2013| 3   | Ductal    | Pleura, chest wall, lung, heart, liver | -                   | -                | -           |                      |
|                        | 76       |     | Ductal    | Pleura, bone, chest wall, lung, adrenal | -                   | -                | -           |                      |
|                        | 76       |     | Lobular   | Chest wall, pleura, lung, bone, liver | -                   | -                | -           |                      |
| Ridder et al[28], 2003 |          | 1   | Lobular   | -                   | -                    | Hemithyroidectomy | -           | 19                   |
| Chung et al[30], 2001  | 1995-2000| 6   | Lobular   | -                   | -                    | -                 | -           |                      |
|                        | 61       |     | -         | -                   | -                    | -                 | -           |                      |
|                        | 51       |     | -         | -                   | -                    | -                 | -           |                      |
|                        | 32       |     | -         | -                   | -                    | -                 | -           |                      |
|                        | 22       |     | -         | -                   | -                    | -                 | -           |                      |
|                        | 33       |     | -         | -                   | -                    | -                 | -           |                      |
| Bult et al[31], 2000   |          | 1   | Invasive  | Nil               | Palpable thyroid nodules | Chemotherapy + radiation | No response | 10                   |
| Loo et al [29], 2003   |          | 1   | Ductal    | bone              | Palpable thyroid nodules | Chemotherapy      | Stable      | 24 alive             |
| Gong et al[25], 2005   |          | 1   | Metaplastic| Nil             | Palpable thyroid nodules, hoarseness, dysphasia | - | - | - |
| Jimenez et al[27], 2004|          | 1   | -         | Nil               | Acute thyroiditis     | Total thyroidectomy | Stable      | 7 alive              |
| Current study          | 2015-2020| 1   | Ductal    | neck LN           | Enlarged homogeneous thyroid | Chemotherapy      | Stable      | 6 alive              |

LN: Lymph node.
Figure 2 Ultrasound images of lymph node and thyroid. A: Contrast-enhanced ultrasound of the left cervical lymph node; B: Fine-needle aspiration cytology of the left lobe of the thyroid.

one patient who presented with acute thyroiditis[25]. Only 5 out of 97 patients presented with diffuse goiter out of all primary cancer origins in a study at the Mayo Clinic[1]. Here, we report a rare case of TM presenting as diffuse goiter without thyroid nodules that had metastasized from primary breast carcinoma. This case report provides valuable information for clinicians, indicating that rapidly occurring diffuse goiter without other symptoms may be the first sign of TM in patients with malignant disease.

Thyroid metastasis usually occurs in patients with widespread metastatic disease, and the other sites of metastasis are primarily the bone and lung, according to the data shown in Table 1. Not all previously published studies contained information on other recurrence sites, and in 18 patients (41.9%, Table 1), the thyroid was the first and only site of recurrence. In the studies that contained histological information, primary breast cancer was mostly referred to as "invasive" carcinoma (85.7%), indicating that invasive carcinoma might be the most prevalent type of cancer to result in TM (Table 1). Among those reports, two patients had poorly differentiated adenocarcinoma as the primary disease[11], one patient had medullary carcinoma[11], one had metaplastic carcinoma[23], and one had mucinous carcinoma[7].

Patients with TMs generally have a poor prognosis[31,32]. Therapeutic choices for TM vary among reports, depending on the primary cancer origin, recurrence at other sites and the symptoms caused by TM. Surgical excision is considered the first choice for thyroid metastasis, and it has been reported that thyroidectomy improves the prognosis of patients[33]. Patients with multisite metastases are usually recommended for treatment with chemotherapeutic and endocrine approaches according to studies of metastatic breast cancer, but research on the effects of chemotherapy for thyroid metastasis is limited[34]. Among 30 patients, 16 were treated with chemotherapy, and 75% of them were clinically stable during follow-up (Table 1). It is believed that the biological behavior of primary cancer might be the primary influence on the prognosis of patients with TM[2]. Thus, therapeutic choices for TM patients should be determined individually and with multidisciplinary board discussion.
Another notable fact in this case report is that the patient had SMs in the contralateral cervical area of the primary tumor site, and no malignancy was previously found in the left breast or axillary region. SM to the lymph nodes in breast cancer is an important phenomenon, and it is critical to make the correct choice of surgical resection techniques and chemotherapies. It has been reported that only 6% of SMs occur on the contralateral side of the primary tumor site\(^4\), with SMs accounting for 3.5% to 34.6% of metastatic lymph nodes\(^4,35,36\). Enlarged lymph nodes were detected before diffuse goiter. Aron et al\(^37\) reported that the vast majority of metastases are able to remain dormant for a long period of time, referred to as metastatic dormancy. This suggests that thyroid metastasis probably occurred before the cervical lymph node changes and remained indolent and silent for a long period of time. It remains unknown whether the metastasis to the contralateral cervical lymph nodes originated from the thyroid metastasis or from the breast directly.

The IHC profiles of the patient changed during the process of cancer management. The immunostaining profiles of the core-tissue needle biopsy before NAC were ER (+++), PR (++) and HER-2 (-), which changed to ER (+++), PR (+) and HER-2 (2+) in the surgical pathology results; finally, the cytology of enlarged lymph nodes and thyroid indicated triple negative breast cancer. Several studies have demonstrated that hormone receptor (ER and PR) status changes between initial core-tissue needle biopsy and surgical specimens obtained after chemotherapy and endocrine treatment. Tacca et al\(^38\) reported that the positivity rate of HER-2 decreased from 42.0% to 32.1% after neoadjuvant chemotherapy, which could explain the conversion of HER-2 status between FNAC and surgery pathology results. A Chinese nationwide multicenter study showed that 37.7% of breast cancer patients have hormone receptor conversion in metastatic lesions, and patients with PR conversion had shorter overall survival times than patients whose PR remained positive \((P = 0.016)\)\(^39\). This reveals that IHC profiles may change in the process of metastasis, which offers more information for
making precise individual treatment decisions.

CONCLUSION

Few studies on diffuse goiter without thyroid nodules and SMs in the contralateral cervical area have been published. This report illustrates that rapidly occurring diffuse goiter without thyroid nodules may be the first sign of TM and that enlarged lymph nodes in the contralateral cervical area may indicate SMs of primary breast cancer. This finding raises awareness of these clinical presentations, which would be helpful for the early detection of metastatic breast cancer. In addition, IHC profiles may change during the process of metastasis, which indicates that biomarker testing for metastatic disease may be crucial for clinical decision-making.

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