

Receptor conversion and vocal cord paralysis in a patient with breast cancer

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SUMMARY

Receptor conversion in breast cancer occurs in up to 32% of patients, resulting in ineffective therapy in the absence of corresponding biomarkers. We report a case of a middle-aged woman who presented with a 2-month history of hoarseness. Laryngoscopy demonstrated right vocal cord paralysis. Whole body positron emission tomography-CT (PET-CT) scan showed a hypermetabolic cervical lymph node, worrisome for metastasis. Biopsy of the cervical lymph node was consistent with metastatic carcinoma of the breast (GATA3 and mammaglobin positive, oestrogen receptor (OR)-positive, progesterone receptor-negative and human epidermal growth factor receptor 2 (HER2)-positive). She underwent targeted therapy with ado-trastuzumab emtansine every 3 weeks. Repeat PET-CT scan after 6 months showed stable disease. Reassessment of receptor status in metastatic breast cancer is encouraged to rule out receptor conversion. There is significant cross-talk between OR and HER2 signalling pathways, leading to treatment resistance. Close collaboration and teamwork among various subspecialties facilitate prompt management of patients with suspected metastatic breast cancer.

BACKGROUND

Breast cancer is the most common cancer and the leading cause of cancer-related mortality among women worldwide.¹ The landscape of breast cancer treatment has vastly improved over the past decade due to early detection, timely surgery and the introduction of targeted therapies. Despite these advances, nearly one-third of women diagnosed with early stage breast cancer will develop metastasis.² The prognosis for patients with metastatic breast cancer remains dismal, with a 5-year survival rate of only 22%.³

Therapeutic options for patients with metastatic disease include chemotherapy, human epidermal growth factor receptor 2 (HER-2)-directed therapy and hormonal agents. The choice of which systemic therapy to use depends on the oestrogen receptor (OR), progesterone receptor (PR) and HER2 expression status of their tumour.⁴ Intriguingly, differential expression of OR/PR and HER-2 between primary tumour and metastasis occurs in up to 32% of patients, resulting in ineffective therapy in the absence of corresponding biomarkers.⁵ This change of hormone receptor or HER2 expression between the primary malignancy and the consequent metastasis characterises the phenomenon of receptor conversion. Therefore, prompt reassessment of these biomarkers at the time of disease progression

can help optimise treatment decisions. Performing a biopsy on metastatic sites is integral to confirm tumour origin and determine receptor status.

We report a case of a patient with breast cancer who developed gradual hoarseness of voice, highlighting the importance of performing a biopsy on suspected metastatic sites to ascertain receptor status and subsequently guide therapeutic decision-making.

CASE PRESENTATION

A middle-aged woman presented to the oncology clinic with a 2-month history of gradual hoarseness of voice. There was no associated cough nor difficulty of breathing. Seven years ago, she was diagnosed with stage 1B (T1N1M0) moderately differentiated invasive ductal carcinoma of the left breast, positive for OR, PR and negative for HER2 overexpression. She underwent left breast lumpectomy with axillary lymph node dissection. Oncotype DX and BRCA1/BRCA2 testings were not performed. She received adjuvant chemotherapy with six cycles of doxorubicin, cyclophosphamide and docetaxel. This was followed by radiation therapy and institution of daily letrozole. Unfortunately, she was only able to take letrozole for less than 1 year due to development of osteoporosis. Annual mammogram since then showed no recurrence of breast cancer. She has no other comorbidities. She has one first-degree and one second-degree relative diagnosed with breast cancer at the ages of 50 and 46. Physical examination revealed neither palpable breast masses nor lymph nodes.

INVESTIGATIONS

Nasopharyngeal laryngoscopy was performed by an otolaryngologist, showing persistent glottic gap during phonation with an immobile right vocal fold at the paramedian position. Edematous arytenoid and interarytenoid mucosa were noted. Findings were consistent with right vocal cord paralysis (figures 1 and 2).

Given the history of breast cancer in the patient, whole body positron emission tomography-CT (PET-CT) scan was done, which revealed hypermetabolic right level four cervical lymph node measuring 0.6 cm (Standard Uptake Value (SUV) 3.2) and hypermetabolic right paraaortic (SUV 6.3) and right paratracheal (SUV 5.2) lymph nodes, measuring 0.8 and 0.9 cm respectively, worrisome for metastasis (figure 3). No other hypermetabolic foci were seen.



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Figure 1 Laryngoscopy showing a persistent glottic gap during phonation.

Excision biopsy of the right cervical lymph node confirmed tumour cells consistent with metastatic carcinoma. Immunohistochemistry showed that tumour cells were positive for GATA3 and mammoglobin, supporting the diagnosis of a breast primary. Breast panel of the excised cervical lymph node revealed OR positive (80% of invasive tumour cells), PR negative and HER2 positive (3+, strong complete membranous staining in 80% of invasive tumour cells). Subsequent metastatic workup was unremarkable.

TREATMENT

Given the involvement of non-contiguous lymph nodes, she was managed as a case of OR positive, HER2 positive metastatic breast cancer. She was not amenable to chemotherapy and preferred treatment with the least possible side effects. Due to the relative resistance to hormonal therapy of HER2-positive breast cancers, the medical oncologist started her on targeted therapy with ado-trastuzumab emtansine (TDM-1) every 3 weeks.



Figure 2 Laryngoscopy revealing an immobile right vocal fold at the paramedian position.

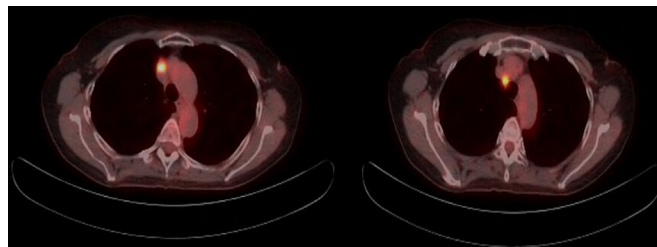


Figure 3 PET/CT scan findings include a hypermetabolic right level four cervical lymph node, measuring 6 mm (SUV 3.2), and right paratracheal lymph nodes (SUV 5.2), measuring 8 and 9 mm, respectively. PET/CT, positron emission tomography/CT. Standard uptake value (SUV) is a semiquantitative method of determining metabolic activity in a region of interest in PET/CT scan.

OUTCOME AND FOLLOW-UP

On subsequent follow-up consultations over the past 3 months, no side effects were noted and there were no limitations to activities of daily living. There was no improvement in her hoarseness of voice, but she was otherwise asymptomatic. After her third session of TDM-1, she underwent repeat PET-CT scan to assess the status of lymph node metastasis. PET/CT scan showed stable size of enlarged prevascular lymph node measuring 1.5×1.3 cm and right upper paratracheal lymph node measuring 0.9×0.8 cm (figure 4).

DISCUSSION

The development of vocal cord paralysis in a patient with breast cancer is a relatively rare occurrence. To the best of our knowledge, there are only two published studies that dealt with vocal cord paralysis in patients with breast cancer. The first study is an old case series of 37 patients with breast cancer who developed vocal cord paralysis.⁶ In the study, the left vocal cord was more commonly affected than the right, with vocal cord paralysis arising as a result of compression of the vagus or recurrent laryngeal nerves by nodal metastasis in the neck or mediastinum.⁶ The most common site of first recurrence was cervical lymph node involvement. Survival outcomes were deemed poor in patients who developed vocal cord paralysis. Meanwhile, another study discussed the development of vocal cord paralysis in a patient with breast cancer and the use of calcium hydroxyapatite gel as local treatment for vocal cord paralysis.⁷ Neither study discussed the principles of diagnostic assessment and treatment of breast cancer in these patients.

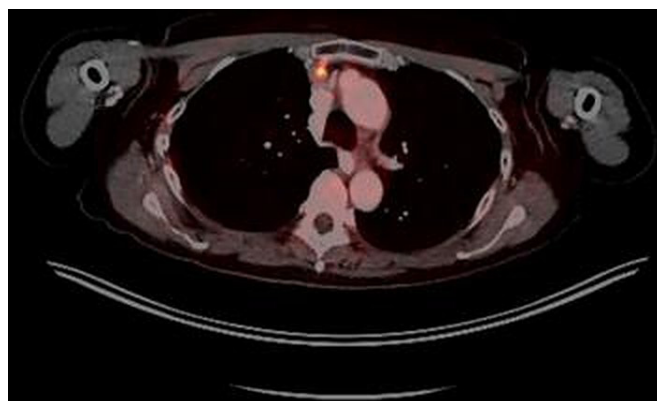


Figure 4 Interval PET/CT scan exhibiting stable size of lymph nodes. PET/CT, positron emission tomography/CT.

Receptor conversion arises as an adaptive mechanism of breast cancer to systemic therapy. Abnormal regulation of signalling pathways emerges in the course of breast cancer development and is controlled predominantly by overactive OR or HER2 signalling pathways.⁸ Bidirectional crosstalk between the two major pathways enable cancer cells to develop resistance against hormonal agents, targeted agents or chemotherapy. Blocking one pathway provokes the tumour to amplify and upregulate alternative signalling pathways, resulting in cancer progression, recurrence or metastasis.⁸ Therefore, inhibition of OR activity through the use of aromatase inhibitors or tamoxifen can enhance HER2 signalling, allowing for continued tumour growth and development.⁸ Interestingly, development of high expression of HER2 among patients with OR-positive breast cancer confers relative resistance to hormonal therapy.⁸

The incidence of receptor conversion varies widely depending on receptor type. A recent meta-analysis showed that pooled positive to negative conversion rates for OR, PR and HER2 were 22.5%, 49.5% and 21.3%, respectively.⁵ On the other hand, negative to positive conversion rates for OR, PR and HER2 were 21.5%, 15.9% and 9.5%, respectively.⁵ Receptor conversion is a relatively rare phenomenon, especially in patients with previously HER2-negative disease who become HER2-positive.

HER2-positive breast cancer is a heterogeneous disease, as they are subdivided into OR-positive and OR-negative tumours. These distinct subgroups of HER2-positive tumours demonstrate unique patterns of growth and response to HER2 directed therapy. Specifically, patients with HER2-positive, OR-positive tumours are less likely than HER2-positive, OR-negative tumours to respond to dual HER2 blockade with trastuzumab and pertuzumab or treatment with the intracellular tyrosine kinase inhibitor lapatinib.⁹ In terms of the progesterone receptor, tumours that are OR-positive, PR-negative have been shown to exhibit more aggressive clinical features and poor survival outcomes when compared with OR-positive, PR-positive tumours.⁹ PR-negative tumours express increased levels of HER2, indicating that the loss of PR expression in OR-positive tumours can signify activation of the HER2 signalling pathway.⁹ The California Cancer Registry demonstrated that the survival outcomes of OR-positive, PR-positive, HER2-positive tumours exceeded that of OR-positive, PR-negative, HER2-positive tumours, substantiating the pivotal role of PR-expression in HER2-positive breast cancer.¹⁰ As such, the difference in receptor expression has distinct ramifications for treatment decision-making and patient prognosis.⁹

Guidelines developed by the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology and European Society of Medical Oncology concur that repeat biopsy from an accessible site is crucial in patients with suspected disease recurrence.^{11–13} Repeat biopsy assists in verification of disease recurrence and provides information on gain or loss in OR, PR and HER2 expression.¹¹

In terms of therapeutic options for patients with OR-positive, HER2-positive breast cancer, NCCN recommends systemic treatment with pertuzumab, trastuzumab and a taxane based on the CLEOPATRA clinical trial.¹¹ An alternative treatment option supported by NCCN is the use of TDM-1, an antibody–drug conjugate that stably links the HER2-targeted agent trastuzumab to the cytotoxic activity of the microtubule inhibitory agent DM1.¹¹ The MARIANNE phase III trial compared the use of TDM-1 with or without pertuzumab vis-à-vis trastuzumab plus a taxane as first line therapy in locally advanced and metastatic HER2-positive patients with breast cancer.¹¹ The study revealed that progression-free survival for TDM-1 alone was

equivalent to trastuzumab plus a taxane.¹¹ Grades 3–5 adverse events were less in the TDM-1 arm, with improved quality of life reported.¹¹ Given that our patient wanted to be started on a regimen that had the least side effects, the oncologist decided to initiate TDM-1. The role of endocrine therapy in OR-positive, HER2-positive disease remains controversial.¹¹ Thus far, there have been no published clinical trial results that have directly compared HER2-targeted therapy plus endocrine therapy versus HER2-targeted therapy plus chemotherapy.

This case highlights the importance of close collaboration and team work among various subspecialties to enable prompt diagnosis and treatment of patients with suspected metastatic breast cancer. Through cooperation with otolaryngology, interventional radiology and pathology departments, we were able to detect disease recurrence and facilitate optimal management of the tumour.

Patient's perspective

It is been 7 years since I have been diagnosed with breast cancer. These past few years, I felt confident that I had conquered cancer. I got complacent, neglecting to follow-up with my medical oncologist. My world was rocked again when I suddenly lost my voice. I started to get worried when my voice did not improve after 2 months. I decided to see an otolaryngologist and underwent a fiberoptic laryngoscopy. I was terrified when the doctor told me that my right vocal cord was paralysed. The otolaryngologist could not explain the finding. I consulted a medical oncologist who advised me to undergo a PET/CT scan. It was through the PET/CT scan that I learnt that I had three lymph nodes suspicious of cancer. I scheduled an appointment with a general surgeon who excised the lymph node located in my neck. The biopsy revealed that my breast cancer has transformed to a different type! At first, I was afraid of starting chemotherapy again, because of the side effects I experienced 7 years ago. Fortunately, my medical oncologist reassured me that there were available treatment options with less side effects. Since I wanted to be able to do my daily chores at home, I decided to start HER2-targeted treatment. It has been 3 months since I have been started on therapy, and I feel great! I am grateful for my doctors for guiding me through this difficult time. I have learnt the importance of following up with my medical oncologist. We should always be vigilant because this dreaded disease can strike back at any time.

Learning points

- ▶ Reassessment of receptor status in metastatic breast cancer is encouraged due to the possibility of receptor conversion.
- ▶ There is significant cross-talk between oestrogen receptor and human epidermal growth factor receptor 2 signalling pathways, resulting in treatment resistance.
- ▶ Close collaboration and teamwork among various subspecialties facilitate prompt diagnosis and treatment of patients with suspected metastatic breast cancer.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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