



Occult Breast Cancer: A Diagnostic Dilemma. Case Report and Literature Review

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Abstract

Background: Occult breast cancer, or histologically-proven breast cancers without an identifiable primary breast cancer, is a rare disease. It remains challenging for clinicians to diagnose and treat it as there are currently no standardized diagnostic or treatment approach to patients with occult breast cancers.

Patient Description: We report a case of a 59-year-old female with dyspnea and increased oxygen requirements, who on further investigation was found to have pulmonary lymphangitic carcinomatosis, axillary and supraclavicular lymphadenopathy, which was ultimately diagnosed as hormone positive occult breast cancer. She responded well to palliative hormone therapy and returned to baseline functional status and to breathing on room air.

Conclusion: This case is a unique and unusual presentation of breast cancer that highlights the importance of recognizing that primary malignancies of unknown origin do exist. In this case, the patient was fortunate enough both to have her malignancy discovered early based on symptoms of metastasis and to have hormone positive disease that is more responsive to palliative endocrine therapies. However, there needs to be a clearer approach to diagnosing and treating occult breast cancers.

Introduction

Occult Breast Cancer (OBC), defined as histologically-proven breast cancer detected outside of the breast without an obvious primary breast tumor, remains a diagnostic and therapeutic challenge for many oncologists. Fortunately, OBC is a rare entity, accounting for only 0.1% to 0.8% of newly diagnosed breast cancers [1].

We present a case of occult breast cancer in a patient who presented with shortness of breath and hypoxemia requiring oxygen supplementation, approaching but ultimately avoiding intubation. The patient was found to have pulmonary lymphangitic carcinomatosis with axillary and supraclavicular lymphadenopathy. Biopsy of the supraclavicular lymph node revealed hormone receptor positive, HER2 negative invasive ductal adenocarcinoma without any primary breast mass. She was ultimately treated as OBC with hormone therapy alone. Interestingly, four years later she continues to show response to therapy, without clinical evidence of disease, despite her initially predicted poor prognosis.

Case Presentation

A 59-year-old female immigrant from Guatemala presented to the hospital with two months of progressively worsening cough and shortness of breath. CT angiogram of the chest showed abnormalities of the lung field, concerning for atypical infection versus lymphangitic carcinomatosis of unknown primary. PET-CT confirmed these lung findings, but also revealed right axillary and supraclavicular lymphadenopathy.

She underwent biopsy of the right supraclavicular lymph node that was consistent with adenocarcinoma, concerning for breast cancer primary that was ER positive, PR positive, HER-2 negative, CK7 negative, and GATA3 positive. Tumor markers were checked at the time and she was found to have an elevated CA-125 at 116 units/ml (normal levels below 35 units/ml). Given the critical presentation and the need for oxygen, she underwent bronchoscopy and bronchoalveolar lavage. Interestingly that showed mycobacterium avium complex infection as well, for which she was started on Clarithromycin, Ethambutol, and Rifabutin. During that hospitalization, her ECOG performance status was a 3, and given her poor prognosis and inability to tolerate chemotherapy

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the patient was considering palliative care approach and eventually hospice.

She was ultimately discharged from the hospital with home oxygen and oncology follow up. Given that no primary mass was identified in the initial staging imaging, patient had an MRI of the breasts as well as a mammogram that interestingly enough were both normal. She was started on an Aromatase Inhibitor (AI) as she was postmenopausal and within the first few weeks she had significant response on imaging, as well as clinically, with discontinuation of oxygen use and decreasing of her CA-125. After discussing different treatment options, mastectomy was deferred based on the fact that she had spread to the lungs and no obvious primary on presentation.

She completed the course of antibiotics for her mycobacterial infection and continued to show improvement with hormone therapy for years after diagnosis. She had to transition from the non-steroidal AI anastrozole to exemestane due to arthralgias. After three years being on treatment with antiestrogen therapy, a staging CT chest showed some evidence of progression along with rising CA 125, and thus, she was transitioned to the novel combination of the antiestrogen Fulvestrant and the CDK4/6 inhibitor Palbociclib. She has been on this combination for one year, and is doing well, except the expected side effects of neutropenia. Her ECOG performance status has returned from a 3 to a 0, she is off home oxygen and her initially suspected poor prognosis was surprisingly invalidated.

Discussion

Occult breast cancers can be a diagnostic enigma to oncologists, and warrant comprehensive immunohistochemical staining of the tissue that is biopsied, clinical breast examination and mammography or breast MRI to support the diagnosis of a breast primary. When the clinical exam, mammogram and breast MRI do not show evidence of a primary breast malignancy, the diagnosis tends to be favored based on histologic patterns from the tissue of interest. Positive staining for CK7, ER, PR, mammaglobin, and GATA3 favors the diagnosis of breast cancer, which aside from the negative CK7, was consistent for our patient. HER-2 immunostaining, though it lacks specificity and is only over-expressed in about 18% to 20% of all breast cancers, remains a routine component of the comprehensive tissue staining for OBC, given that there exists effective targeted treatment of HER-2 positive OBC [2,3].

Given the rare nature of OBC, there is no standardized treatment approach. Per the NCCN guidelines, treatment for OBT or Tx Node positive breast cancers, which is considered stage III by 8th edition of American Joint Committee on Cancer (AJCC) guidelines, include mastectomy with Axillary Lymph Node Dissections (ALND) with or without post-mastectomy radiation or simply ALND with radiation [4]. Furthermore, according to the American Society of Breast Surgeons, mastectomy is the most common treatment for OBC (47%), followed by breast radiation (37%) [5]. However, in this case report, the patient not only had metastasis to the lymph nodes but also had pulmonary involvement and poor performance status, and thus, was considered stage IV at diagnosis, in which case, the treatment is the same as for non-OBC metastatic breast cancer.

Moreover, Ping et al. [6] compared the demographics and cancer characteristics between OBC and non-OBC and found that OBC patients were significantly older than those with non-OBC, and estrogen receptor positive rates in OBC were lower, which would typically portend poorer prognosis. By retrospectively analyzing

93 OBC cases and 1576 non-OBC cases between the years of 1980 and 2005, the authors found that the median age for OBC and non-OBC patients was 54 and 48, respectively, which was proven to be statistically significant. There was significantly lower ER positivity, which was 46.2% of OBC cases compared to 56.6% of non-OBC cases; however, there were no significant differences in PR positivity. Furthermore, the authors compared OBC and non-OBC stages I, II, and III and found that the 5- and 10- year survival rates for OBC was comparable to stage III non-OBC cases at about 51% and 43% for 5- and 10- year survivals, respectively. Additionally, Wang et al. [6,7] compared PR positive and PR negative OBC patients and found that the former had statistically significant better overall survival and lower recurrence rates, suggesting that progesterone positivity is an important prognostic feature for OBC.

Regardless of the similar prognosis between OBC and stage III non-OBC disease, this patient presented as stage IV metastatic breast cancer at the time of diagnosis, and the data is currently lacking whether there is a difference in overall survival and progression free survival for patients with metastatic occult breast cancer versus metastatic non-occult breast cancer. Typically, patients with metastatic lymphangitic pulmonary disease tend to have shorter progression free disease and overall survival however a significant cofounder in her case was the fact that she had an underlying infection that compromised her respiratory status at presentation [8].

Serum tumor markers commonly associated with breast cancer include CA 15-3, CA 27.29 and CEA, and these serve prognostic value to clinicians when monitoring response to treatment in patients with metastatic disease. However, interestingly, this patient had an elevated CA-125 on presentation, which is most commonly associated with ovarian cancer, though elevated levels have been seen in 84% of cases of metastatic breast cancer [9]. Additionally, studies have shown that an increased CA-125 is associated with metastasis to the lungs or pleura and is related to poor prognosis [10].

Fortunately, this patient had hormone positive OBC that responded to the standard first line treatments for stage IV hormone positive HER-2 negative breast cancers, which are the Aromatase Inhibitors (AI). AIs have proven to have increased overall survival and more tolerability compared to other hormone therapies, particularly in post-menopausal women [11]. However, her disease eventually progressed despite the first line AI, and she was transitioned to one of the second line therapies, which include combination anti-estrogen Fulvestrant and CDK4/6 inhibitor Palbociclib.

CDK4/6 inhibition in combination with anti-estrogen therapy has shown promising results for patients with hormone positive metastatic breast cancer and is becoming recognized as a first line alternative to AI alone. According to the Paloma II trial, a phase 3 study comparing Palbociclib and Letrozole to Letrozole and placebo, there was a statistically significant difference in the median progression-free survival, of 24.8 months and 14.5 months, respectively [12]. Moreover, the results from the study were remarkable, nearly doubling the duration of progression-free survival for metastatic breast cancer. Additionally, the phase III MONALEESA-3 trial comparing patients with advanced hormone positive breast cancer on Fulvestrant and Ribociclib, another CDK4/6 inhibitor, to Fulvestrant alone, reported a median progression-free survival of 20.5 months and 12.8 months, respectively, representing over 40% reduction in the risk of disease progression, which shows in our patient's impressive response to the treatment regimen [13].

Conclusion

In conclusion, the rare entity of OBC still has much research to be done in order to develop standardized diagnostic and treatment approaches that can be used for our patients. Fortunately, this patient's pulmonary symptoms from her MAC infection and possibly from her pulmonary metastasis, led to an earlier diagnosis of OBC. While advanced at the time of diagnosis, her hormone positive disease was a favorable prognostic feature, and she was responsive to palliative endocrine therapy, impressively able to regain her baseline prior-to-cancer functional status.

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