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Case Report

Occult breast cancer with pleural metastasis ☆

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ABSTRACT

Carcinoma of unknown primary (CUP) is defined as histologically confirmed metastases from an undetectable malignant primary site. A subgroup of CUP, known as occult breast cancer (OBC), is a biopsy-proven metastatic breast cancer without an original breast tumor. It remains a diagnostic and therapeutic enigma as there is no consensus on the diagnostic and treatment approaches for the patients with OBC. This case report is a unique presentation of OBC, emphasizing the importance of identifying OBC patients in the early stages. A dedicated team of experts and a more definitive approach to diagnosis and treatment of OBC are essential to prevent delays in the whole process.

Introduction

Carcinoma of unknown primary (CUP) is defined as histologically-proven metastasis from an undetectable malignant primary site, after a comprehensive clinical and radiological work-up. The "CUP syndrome" is described as a neoplastic spread from an unknown primary site to multiple organs [1]. This type of disease, which accounts for 3%-5% of all cancer diagnoses, indicates a poor prognosis with a 5-year survival rate of 10% [2].

Occult breast cancer (OBC), a subset of CUP, is a biopsy-proven metastatic breast cancer, without an identifiable primary breast tumor [1]. It is a rare clinical entity, as fewer than 1 in every 100 breast cancers have an unidentifiable primary malignant site. The first manifestation of an OBC is commonly metastasis to the axillary and cervical lymph nodes [1,3]. The diagnosis and treatment of OBC is a clinical challenge, as it requires a thorough physical exam and dedicated radiodiagnostic tests (eg, mammogram, breast ultrasound, MRI and FDG PET CT), and pathologic and immunohistochemical studies [4]. A lack of expertise and an integrated system to rapidly detect OBC patients in the early stages are among the existing issues in clinical practice [5].

It is reported that in 75% of the cases where traditional breast imaging (mammogram and breast ultrasound) has failed to demonstrate a primary breast origin, an MRI was able to detect a primary breast lesion [6].

Histological and immunohistochemical examinations play an important role in the context of OBC, as not only do they aid

Abbreviations: OBC, Occult Breast Cancer; CUP, Carcinoma of Unknown Primary.

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in identifying the tissue of origin, but they can also determine whether systemic and hormone therapy is applicable, based on hormone sensitivity (eg, ER positive breast cancer) [7].

Mastectomy, whole breast radiation and systemic hormone therapy have been used as therapeutic approaches towards OBC [1,8].

Here, we discuss a case of an OBC presented with axillary and cervical lymph nodes involvement, and pleural metastasis. To the best of our knowledge, this is the first case of OBC with metastasis to pleura. The case raises awareness of OBC, and highlights the value of establishing a dedicated team of experts to quickly identify these patients in the early stages.

Case report

A 50-year-old, previously fit-and-well lady with a family history of breast cancer, presented to the hospital with severe left upper arm swelling, pain, and limited range of motion, which had started 3 days earlier. Clinical examination revealed left upper arm lymphedema, and left supraclavicular and axillary lymphadenopathy.

Based on her strong family history of breast cancer, she was called for annual screening mammogram from the age of 47- 50, and all her breast screening mammograms were unremarkable, including her most recent one, which she had 4 months prior to presenting.

Investigations

At the time of the presentation, a Doppler ultrasound of the left upper extremity was performed. It ruled out deep venous thrombosis (DVT), but detected multiple pathologic lymph nodes with irregular margins in the left supraclavicular fossa and the left axilla. (Fig. 1). A CT of the thorax, abdomen & pelvis with contrast was then performed for further investigation, in which multiple pathologic nodes were detected again in the left axilla and supraclavicular fossa with no evidence of any suspicious breast lesion (Figs. 2A, and B).

Given the left axillary and supraclavicular lymphadenopathy and family history of breast cancer, the patient was referred to the breast one-stop clinic for further imaging and pathological nodes core needle biopsy. On her visit to the clinic, an initial mammogram was done, which showed scattered areas of fibroglandular density (BIRADS-B). Bilateral round calcifications were detected bilaterally, which appeared benign findings. No evidence of suspicious microcalcification, architectural distortion, skin thickening/tethering or asymmetrical density was seen. Therefore, mammogram reported as normal (Fig. 3). A left axillary ultrasound-guided needle core biopsy was then performed, which confirmed spread from a breast primary adenocarcinoma grade 2 (LB5) on histology.

The immunohistochemical profile came back positive for CK8-18, MNF 16, CK7, mammaglobin, and GATA3, and negative for CLA, S100, CK 20, TTF, CA125, CEA, and GCDFP. Therapeutic markers were also positive for Her2 and negative for progesterone and estrogen. Taking account of the morphology, the features were consistent with primary carcinoma of the breast. Following a breast multidisciplinary team (MDT) evaluation, the patient underwent dynamic contrast-enhanced breast MRI which did not demonstrate any suspicious lesions in either breast; however, in addition to the previously identified lymphadenopathies, a new infraclavicular

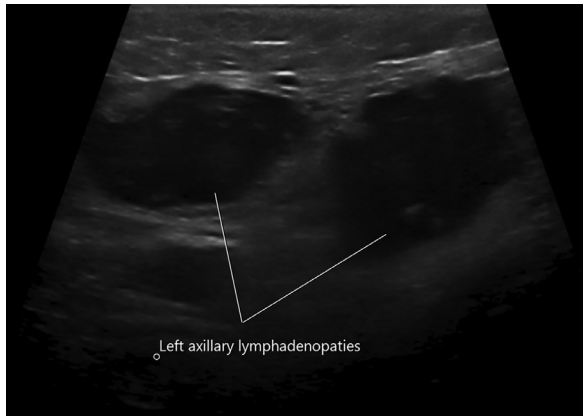

Fig. 1 – Left Axilla US Scan; Multiple pathologic lymph nodes with irregular margins and complete loss of central fatty hilum and maximum short axis of 16 mm. The cortical outline is not well visualized, suggestive of some degree of tumor replacement (A5). All of the lymph nodes exhibited hypervascularity on color Doppler flow (not shown).

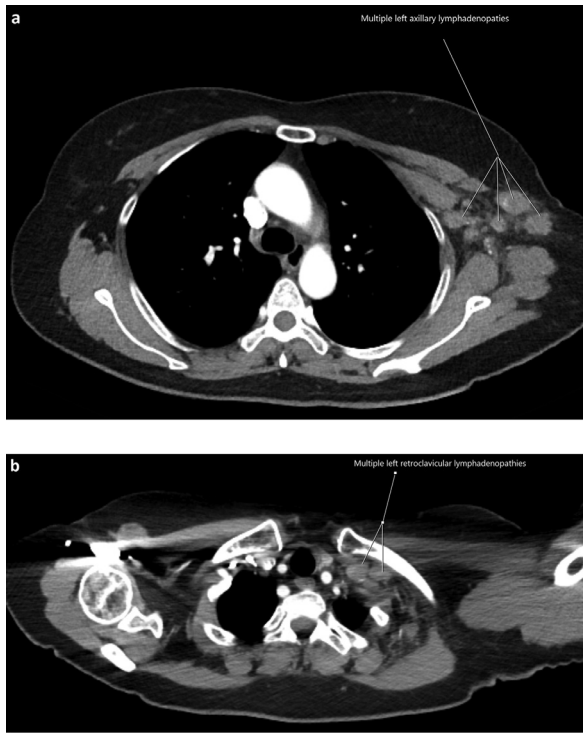

Fig. 2 – CT thorax with contrast. Multiple enlarged pathologic left axillary nodes (A) and multiple left retroclavicular lymphadenopathies (B). The largest lymph node measured 21 x 15 mm (not shown). No suspicious breast pathology.

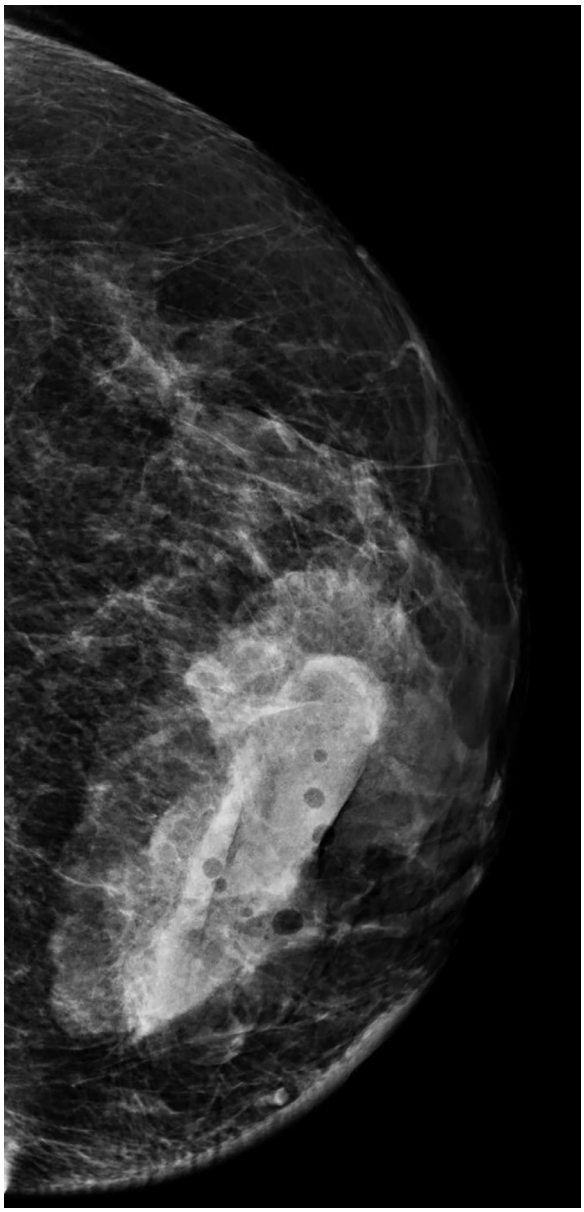

Fig. 3 – Left breast mammogram (CC view) shows BIRADS B density. A foci of benign calcification is detected. No suspicious microcalcification, asymmetrical density or architectural distortion (M2).

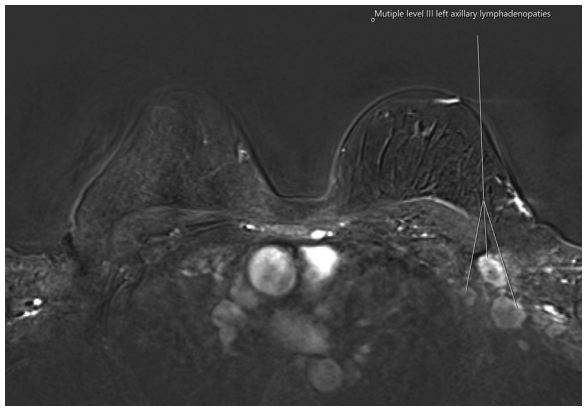

Fig. 4 – Breast MRI; Technique: Axial T1, T2, STIR, I/V dynamic images with subtraction, diffusion-weighted and T1 delayed postcontrast imaging. No suspicious abnormal enhancement is detected in either breast (both breasts MRI 1), Left multiple level III enlarged axillary nodes and left supra and infraclavicular nodes with irregular spiculated margins (MRI 6).

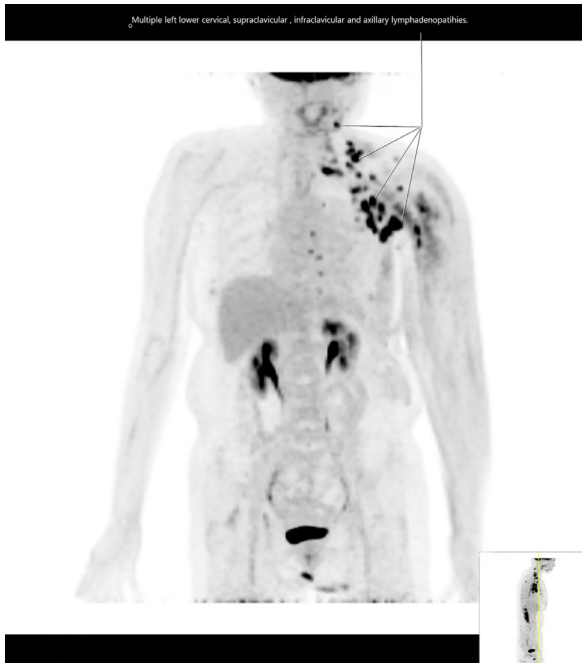

Fig. 5 – NM bone scan whole body. No osteoblastic skeletal metastasis demonstrated. Multiple left supra and infra clavicular, axillary and cervical lymphadenopathies were detected.

enlarged lymph node was detected, indicating progressive disease (Fig. 4).

A month after the initial presentation, because no obvious breast abnormality was detected on mammogram, US or MRI despite the axillary node biopsy showing breast primary, the MDT decided on further imaging with a whole body PET CT and scintigraphy scan to distinguish any abnormal uptake on the breast or other probable sites for metastasis.

On the whole body planar bone scintigraphy (Fig. 5), no osteoblastic skeletal metastasis was detected, and the whole body FDG PET scan showed progression of the adenopathies, along with a new left-sided pleural effusion with focal uptake representing possible pleural disease (Figs. 6A and B), for which, an ultrasound-guided pleural aspiration was performed, and the cytology confirmed the presence of breast cancer cells.

The findings were reviewed at the MDT discussion, and due to the distant metastasis of the OBC to the pleura, surgery was

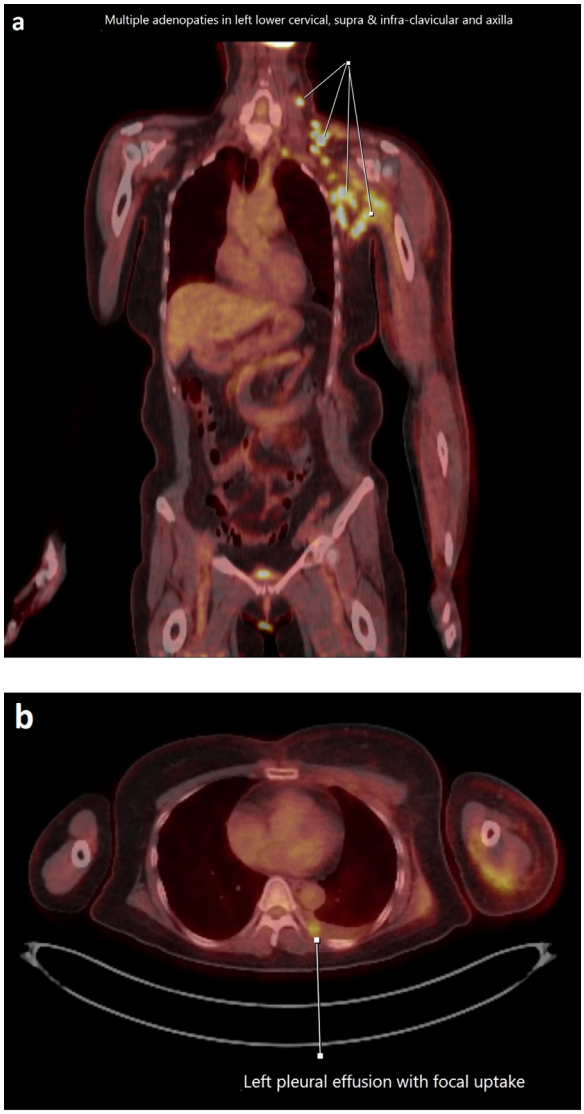

Fig. 6 – NM Whole body PET-FDG. Injected activity 177 MBq. No convincing breast primary. Extensive left axillary adenopathy extending to the lower cervical, subpectoral and the left internal mammary chain (A). New effusion with focal uptake (SUV 10.8) representing possible pleural disease (B).

not deemed suitable and the patient was, therefore, referred for palliative chemotherapy.

Differential diagnosis

Potential diagnoses for axillary lymphadenopathy include infection in an immunocompromised patient, granulomatous diseases (eg, sarcoidosis), and metastatic diseases, such as lung cancer, ovarian cancer, gastric cancer, melanoma and breast cancer [9]. In our case, metastatic breast cancer was eventually confirmed following the lymph node core needle biopsy.

Outcome and follow-up

The patient has so far received 2 out of 6 cycles of palliative chemotherapy with Docotaxel, Herceptin and Pertuzumab. She is coping with chemotherapy with no significant side effects apart from a sore throat. The left arm lymphedema and pain have improved remarkably, and she has regained almost the full range of motion of the left shoulder. Following cycle 6 she will have a reassessment CT scan, as well as an echocardiogram.

Discussion

We reported a case of OBC with metastases to the axillary lymph nodes and pleura in a female. We believe this is the first case of OBC with metastasis to the pleura.

Several studies have reported OBCs with isolated axillary lymphadenopathy, most of which underwent curative treatment with excellent outcomes, including modified radical mastectomy, lumpectomy, axillary lymph node dissection, adjuvant radiation therapy and chemotherapy [10,11]. Barbieri et al. discussed a case of OBC where the patient initially presented with metastasis to the parietal skin. Metastases to the cervical lymph nodes and spinal bones occurred later. Their patient underwent surgery, radiotherapy, and hormone and biological therapy. Five years after the initial presentation, the patient was asymptomatic despite the disseminated disease [1].

In 2015, Ahmed et al., reported an OBC patient with possible leptomeningeal carcinomatosis, who successfully underwent neoadjuvant chemotherapy and BCT[1] [11].

The National Institute for Health and Clinical Excellence (NICE) released its latest guideline on CUP diagnosis and treatment on July 2, 2010 (reviewed in March 2017 with no changes), stating that over 10,000 instances of CUP are reported each year in England and Wales, making it the fourth most common cause of cancer death. According to NICE, patients with CUP are “disadvantaged in many ways.” The guideline lists various issues that impede CUP identification and therapy, such as lack of referral guidelines, no system to quickly identify patients and guarantee early specialist involvement, ambiguity regarding the best diagnostic and therapeutic approach, inadequate specialist expertise, lack of a team structure dedicated to care for the new cases of CUP, and inappropriate referral to site-specific cancer teams [5]. Obviously, the existing barriers to rapidly identifying and treating new cases of CUP result in delayed diagnosis and therapy. The disease progression (eg, distant metastasis to the pleura, as in our case) can alter the management and change a curative intervention to a less favorable palliative approach. In our case, there was a 1-

[1] BCT: Breast conserving therapy, which consists of axillary lymph node dissect on and whole breast radiotherapy. In our case, the patient was initially planned for a mastectomy; however, due to metastasis to the pleura, which occurred later, she was eventually deemed not suitable for any invasive intervention and, therefore, was referred for palliative chemotherapy.

month interval between the first clinical presentation and the referral to the breast clinic and the beginning of the diagnostic work-up. The initial plan after the negative MRI was mastectomy. However, the new pleural metastasis seen on the PET CT changed the management plan to palliative chemotherapy. Lack of an expert team to detect this case of CUP in the early stage and to arrange an urgent referral, led to a cancer spread.

Physicians should remain alert to OBC in patients with a strong family history of breast cancer. It is noteworthy that according to NICE [5], using an 18F-FDG PET-CT early in the management of CUP, might reduce the number of imaging tests required to reach a diagnosis. However, further research is required to confirm this.

Conclusion

Currently, no infrastructure is in place to rapidly identify the CUP patients with OBC to ensure an urgent referral. Moreover, there is no consensus on the appropriate diagnostic tests and treatment for OBC. All of the above can lead to delays in diagnosis and therapy. A designated team of experts and a more definitive method for identifying and treating OBC are required. We encourage clinicians to be vigilant about OBC in patients with a family history of breast cancer and negative initial breast imaging.

Learning points

Physicians should have a strong suspicion of OBC in a patient with a strong family history of breast cancer, and undetectable primary breast lesion on initial imaging tests (breast ultrasound and mammogram)

Delay in diagnosis and treatment of OBC can lead to distant metastasis, which can change a curative therapy to a less desirable palliative approach.

An integrated system and a team of clinical experts are essential to ensure the early diagnosis of OBC.

Patient consent

Written, informed consent for publication of their case was obtained from the patient. The patient has seen the images and text about them, has read the article, and is legally entitled to give this consent.

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