CASE REPORT

'Inflammatory breast cancer' due to metastatic adenocarcinoma of lung

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SUMMARY

A 67-year-old woman with a history of lung adenocarcinoma presented with 3 weeks of redness, pain, swelling and skin changes in her right breast. Her vital signs and physical examination were within physiological limits except for the right breast. She had extensive red streaks radiating from the right nipple with peau d'orange appearance of her overlying skin. Her breast was tender on examination and did not have any associated cervical or axillary lymphadenopathy. Her mammography revealed thickening of the skin, increased parenchymal markings and shrinkage the breast. Multiple skin biopsies demonstrated moderately differentiated lung adenocarcinoma with lymphovascular invasion. The patient made an informed decision to undergo radiotherapy following discussion with her oncologist and breast surgeon. She succumbed to her illness 2 months after the diagnosis of metastasis to her breast.

Medical history

She is a known hypertensive with coronary artery disease status post-percutaneous coronary intervention, COPD on 2 L/min of oxygen by nasal cannula, oesophageal stenosis following radiation therapy, peripheral vascular disease, inflammatory arthritis, depression and degenerative joint disease. Her right breast had multiple episodes of mastitis following the placement of port-a-cath and was being regularly seen by the breast surgeon since mid-2013. She had undergone a mammogram and MRI in early 2014 which showed breast oedema with no other abnormalities. Multiple core biopsies and skin biopsies performed in June 2014 were reported to be normal. Therefore, she was treated for lymphoedema of the right breast with a near total resolution of her breast symptoms.

Her family history was significant for breast cancer in her sibling.

BACKGROUND

Breast cancer is the most common cancer among women and the second leading cause of mortality due to cancer among women. Metastasis to the breast from an extramammary malignancy is rare. The three most important points which help differentiate between primary breast cancers from extramammary metastatic deposits are clinical history, histopathology and immunohistochemistry. The differentiation between a primary breast cancer from metastasis to the breast from an extramammary malignancy is of paramount importance as the prognosis and management of both these conditions are dissimilar. This is the first case report of breast metastasis from lung adenocarcinoma with isolated dermal lymphovascular invasion.

CASE PRESENTATION

A 67-year-old woman with chronic obstructive pulmonary disease (COPD) on 2 L/min of nasal oxygen presented with 3 weeks of increasing redness, rash and pain on her right breast. Three weeks previously she noticed rashes like 'stretch marks' on her right breast which was associated with pain and itching. Over the course of the next 2 weeks, the breast swelling increased, rashes grew and she felt like 'red hot ants marching on her breast'. She decided to seek further medical attention as her symptoms progressed despite being treated with antibiotics for suspicion of acute mastitis. She did not report any fever, nipple discharge or retraction of the nipple.

Oncological history

She was diagnosed to have stage IIIB adenocarcinoma of the right lung with epidermal growth factor

Figure 1 (A) Anterior view of the right breast demonstrating evidence of inflammation. (B) Lateral view of the right breast. (C) Comparison of right and left breast.

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receptor (EGFR) positivity in May 2008. Radiation to the mediastinum with additional weekly taxol and carboplatin combination chemotherapy was administered over a 6-month period. She was then treated with Tarceva (erlotinib) for 6 months but was later discontinued as she developed a skin rash. However, Tarceva was restarted intermittently between 2012 and June 2014 for suspicion of tumour recurrence; it was finally discontinued in July 2014 due to severe dermatopathy.

Physical examination

She was noted to have vital signs within physiological limits while on 2 L/min of oxygen by nasal cannula.

There were extensive red streaks radiating from the right nipple limited by the anterior axillary line and the skin overlying the breast had a peau d'orange appearance (figure 1A–C). The breast was tender to palpation and no palpable breast lumps, cervical or axillary lymphadenopathy were noted. The rest of her systemic examination was at her baseline.

INVESTIGATIONS

Her biochemical laboratory results were within normal limit. Her mammogram revealed an increase in skin thickness consistent with an infiltrative process in the right breast (figure 2).

DIFFERENTIAL DIAGNOSIS

- ▶ Acute mastitis
- ▶ Right lymphoedema with cellulitis
- ▶ Primary breast carcinoma— inflammatory breast cancer

OUTCOME AND FOLLOW-UP

The skin biopsy performed by the breast surgeon confirmed metastatic moderately differentiated adenocarcinoma consistent with lung primary, extensive lymphovascular invasion and positive surgical margins (figure 3A,B). The neoplastic cells stained positive for thyroid transcription factor 1 (TTF-1) (figure 4A), napsin and cytokeratin 7 (CK7) (figure 4B), but were negative for GATA-3 and gross cystic disease fluid protein-15 (GCDPF-15) on immunohistochemical staining.

Figure 2 Mammogram (Cranio-caudal view)—comparison of breasts demonstrating superficial skin thickening on the right.

Figure 3 (A) Skin biopsy viewed under low-power microscope stained with H&E. (B) Skin biopsy viewed under a high-power microscope stained with H&E demonstrating tumour in the dermal lymphatics.

The patient made an informed decision to pursue radiotherapy following discussions with her oncologist and breast surgeon. She completed 15 fractions of radiation to the breast. A positron emission tomography scan following radiotherapy revealed no evidence of metabolically active neoplasm. Sadly, the patient expired 2 months after the diagnosis of breast metastasis.

DISCUSSION

The American Cancer Society has estimated the total incidence of breast cancer in the USA to be 234 190, the most common cause of cancer among women (29%) and the second leading cause of mortality (15%) among women due to cancer.¹ The commonest cause of metastasis to the breast is contralateral primary breast cancer.² Trevithick reported the first case of extramammary breast metastasis in 1903.³ A 0.4–1.3% of all breast cancers have been reported to be metastasis from an extramammary neoplasm; of which, a rare 0.041% are due to lung cancers.^{4–6} The common primary extramammary cancers metastasising to the breast are malignant melanoma, lymphoma, lung, renal cell and ovarian cancers.^{4–6} However, there are variabilities in incidences as reported by Lee *et al*; their study documented gastric carcinomas to be the most common tumours metastasising to the breast. They explained this discordance by the higher rates of gastric carcinoma presenting at their institute.

Figure 4 (A) Skin biopsy section stained with TTF-1 immunostain. (B) Skin biopsy section stained with cytokeratin 7 immunostain.

Since 1992, 20 case reports of breast metastasis from a lung adenocarcinoma have been reported.^{5–25} The largest retrospective study (1907–1999) on breast metastasis from an extramammary malignancy by Georgiannos *et al*⁴ documented 9 of their 60 patients to have lung primary, but none of them were adenocarcinomas. A 77% of patients, according to Lee *et al*,²⁶ had a history of extramammary primary carcinoma and the mean time from diagnosis of the primary cancer to breast metastasis was 13.9 months. A review of literature revealed just 5 of the 20 patients with lung adenocarcinoma to have a synchronous presentation, both metastatic breast deposits and primary lung cancer presenting simultaneously.^{6 22 24 27} The American Joint Committee on Cancer (AJCC) defines inflammatory breast cancer as ‘a clinical–pathological entity characterised by diffuse erythema and oedema (peau d’orange) involving a third or more of the skin of the breast’.²⁸ Only one of the 20 case reports of breast metastasis from lung adenocarcinoma mimicked inflammatory breast cancer as definition by AJCC.¹³

Rapidly growing painless solitary palpable mass is the most common presentation of mammary metastasis. These lumps are usually located superficially in the subcutaneous tissue or adjacent to the breast parenchyma, because of the rich vascular supply. Diffuse skin involvement as in our patient is rarely seen.²⁹ Although redness, pain and discharge are rare presentations for breast metastasis; 5 of 33 patients diagnosed to have breast metastasis from extramammary primaries had inflammatory breast symptoms (redness, pain or oedema) in the 15-year retrospective study by Lee *et al*.²⁶ All 30 patients subjected to radiological imaging were noted to have metastatic lesions; unlike our patient, who had just skin changes on mammography and ultrasound.²⁶ Thirty per cent patients were observed to have more than one lesion.

Metastatic disease to the breast on mammography are commonly well circumscribed sharply defined solitary masses with slightly irregular margins and no microcalcifications. Lee *et al*²⁶ noted microcalcification in 4 of the 30 patients (1 hepatocellular carcinoma, 1 ovarian carcinoma and 2 gastric carcinomas) who had radiological imaging. Typically, metastatic deposits on ultrasound are round to oval shaped well-circumscribed hypoechoic masses without spiculations, calcification or architectural distortion.³⁰

Four histological growth patterns have been identified in metastases to the breast. A circumscribed nodule surrounded by healthy breast tissue is the commonest presentation. Haematological malignancies and malignant melanoma are known to infiltrate around the ducts and lobules. The least common presentations are lymphangitis (as in our patient) and diffuse infiltration.²⁹

Immunohistochemistry is a reliable and widely available tool to approach metastatic malignancies with unknown primary. Keratins, a family of intermediate proteins expressed in epithelial cells are commonly used in confirming epithelial origin, although other tumour types such as mesothelioma and synovial sarcomas also express keratins.³¹ Among the keratin family, CK7 and CK20 are widely used to predict the primary site. The expression patterns of these keratins help to prioritise the possible site of origin; however, the profile is not particularly helpful to suggest a particular anatomic site of origin and additional lineage-specific markers are required. These lineage-specific markers are usually chosen based on patient’s prior history and the morphology of the metastatic tumour. In the current case, the neoplastic cells of the tumour in question stained with CK7 but were CK20 negative. Given the patient’s known history of lung cancer, additional lineage-specific markers were performed to exclude breast or lung as primary sites. These lineage-specific markers in our case included TTF-1 and napsin A for lung adenocarcinoma and GCDFFP-15 and GATA-3 for breast carcinoma. None of these markers are entirely specific to any tumour type and cross-reactivity with other tumour types is frequently seen. For example, GCDFFP-15 is expressed by 60–80% of breast carcinomas; however, it is also expressed in 2–5% of lung adenocarcinomas.³² Clinical history and imaging studies in conjunction with morphology and immunohistochemistry help in pointing the primary site of metastatic disease. The neoplastic cells in the current case stained with CK7, TTF-1, napsin A and were negative for GCDFFP-15 and GATA-3. Given the patient’s known history of lung adenocarcinoma, the morphology of the tumour with the extensive lymphatic spread and the immunoprofile are consistent with metastatic lung adenocarcinoma.

The overall prognosis of patients with metastasis from solid tumours is poor, only a minority of patients survive more than a year.³³ In the study by Lee *et al*,²⁶ the median survival period from the diagnosis of metastasis to death was 13.9 months. There are no clear guidelines on the management of patients with breast metastasis; however, these patients are managed according to their primary malignancy, existing comorbidities and Eastern Cooperative Oncology Group (ECOG) status. Extensive surgery with curative intent is less likely to be successful when performed in cancers in later stages, especially metastatic disease, and is associated with higher mortality and morbidity. Five of the seven patients with breast metastasis from lung adenocarcinoma who underwent surgery had synchronous breast metastasis.^{6 22 24 27} The conventional modalities of treatment for metastatic breast disease are systemic treatment or palliative care (which may involve radiation). Platinum-based chemotherapy was the commonly used modality of

chemotherapy. Newer agents, such as EGFR inhibitor, have been used with limited results. Only one of the 20 patients with breast metastasis from lung adenocarcinoma received radiation therapy.²³ The longest follow-up period among patients with breast metastasis from lung adenocarcinoma was 27 months.¹⁹ In comparison, the 5-year survival rate for patients with inflammatory breast cancer following combination neoadjuvant systemic chemotherapy, surgery and radiation therapy is ~30%.³⁴

The three most important points which help differentiate primary breast cancers from extramammary metastatic deposits are clinical history, histopathology and immunohistochemistry. It is of paramount importance that clinicians differentiate between primary breast cancer from metastatic disease to the breast as the prognosis and management of both these conditions are worlds apart.

Patient's perspective

I had kept all my appointments with my breast surgeon and undergone all the tests she recommended. How did this disease go unnoticed? I thought I had defeated cancer; now I have it in my breast! At least it is the same cancer I have been battling and not a new cancer. The radiotherapy which my breast surgeon recommended is going to be my final try and if that does not work, then come what may. I have lived a very fulfilling life and if my Maker says it's time, it's time.

Learning points

- The commonest cause of metastasis to the breast is contralateral primary breast cancer.
- The three most important points which help differentiate between primary breast cancers from extramammary metastatic deposits are clinical history, histopathology and immunohistochemistry.
- The prognosis of patients with breast metastasis from an extramammary malignancy is poor.
- It is crucial to differentiate between primary breast cancer from extramammary metastasis as the management and prognosis are significantly dissimilar.

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