

CASE REPORT

SOLITARY BREAST METASTASIS FROM OESTROGEN RECEPTOR-POSITIVE PULMONARY ADENOCARCINOMA: REPORT OF A CASE WITH A POTENTIAL PITFALL

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Solitary breast metastases are rare and mimic primary breast carcinoma. A 60-year-old female with a history of pulmonary adenocarcinoma presented with a solitary left breast lump suspicious for malignancy on breast imaging. Core-needle biopsy disclosed an adenocarcinoma strongly and diffusely positive for oestrogen receptors. Further immunohistochemistry was consistent with the breast tumour being a solitary metastasis of her pulmonary cancer. Clinicians and pathologists should be aware of the fact that pulmonary adenocarcinomas may sometimes display strong rather than only focal positivity for oestrogen receptors by immunohistochemistry and may mimic breast cancer of no special type.

Key words: breast metastasis, oestrogen receptor, mammary carcinoma of no special type, pulmonary adenocarcinoma.

Introduction

According to the Cancer Facts and Figures publication of the American Cancer Society, the lifetime risk of males and females for developing a malignant tumour is between 1 out of 2 or 3 [1]. Therefore, the risks of having multiple primary tumours in a patient are relatively high. The treatment strategies for stage IV metastatic carcinomas and multiple early stage primary cancers are obviously different. A metastasis to an organ, like the breast, where most malignant tumours are primary cancers, may give rise to misdiagnosis as a primary neoplasm, especially if the metastatic lesion shares features with the morphology of primary carcinomas. We report a case in which oestrogen receptor positivity of the breast metastasis, a common feature of primary breast carcinomas, predisposed for a potential misdiagnosis.

Case report

A 60-year-old cachectic female presented at the Breast Imaging Unit of Bács-Kiskun County

Teaching Hospital in June 2015 for the evaluation of a lump observed two months earlier. A circumscribed, palpable, and mobile mass of 8 mm in greatest dimension was identified in the axillary tail of her left breast (Fig. 1A). Mammography and ultrasound findings were suspicious for malignancy, scored as BI-RADS 4C, and a core-needle biopsy was performed. All tissues described were fixed in neutral buffered formalin, and were embedded in paraffin. The biopsy showed a gland forming adenocarcinoma with desmoplastic reaction and no specific features, simulating breast cancer of no special type (ductal carcinoma) [2], morphologically the most heterogeneous group among breast cancers (Fig. 1B). No associated ductal carcinoma in situ was present. The tumour could have been graded as well-differentiated, Grade I according to the Nottingham grading scheme [3], with scores of tubule formation – 1; nuclear pleomorphism – 3; and high power field area adjusted mitotic count – 1. Routine assessment of oestrogen receptors (ER) and progesterone receptors (PR) as well as human epidermal growth factor receptor-2 (HER2) was done using conventional immunohistochemistry. The

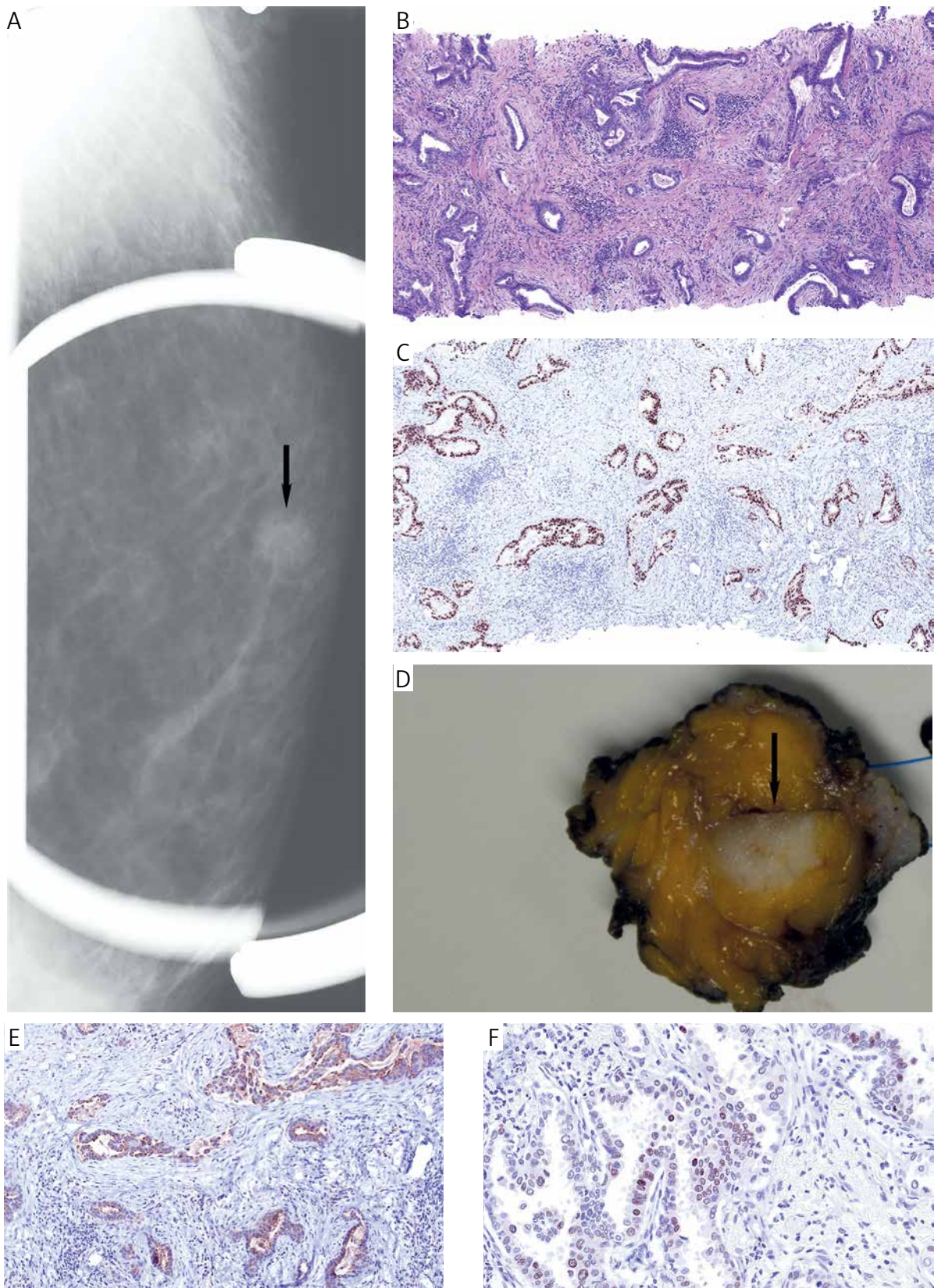


Fig. 1. Morphology of the breast lesion and the primary lung adenocarcinoma. A) Magnification mammographic view of the lesion (arrow) in the axillary tail of the left breast. B) Gland forming adenocarcinoma without features of special types of breast cancer in the core-needle biopsy specimen (haematoxylin and eosin, magnification 10 \times). C) Strong and diffuse positivity for oestrogen receptor with the SP1 antibody (magnification 10 \times). D) Gross view of the relatively circumscribed tumour (arrow) after its removal. E) Diffuse Napsin-A staining of the breast tumour (magnification 20 \times). F) Focal oestrogen receptor positivity of the pulmonary adenocarcinoma with the SP1 antibody (magnification 40 \times)

antibodies used are listed in Table I. The tumour was found to be strongly and diffusely (about 95% of the cells) positive for ER- α using the 6F11 antibody, resulting in an Allred score of 8 [4], and was negative for PR (with one or two cells, and obviously < 1% of the cells staining weakly) and HER2 (no staining at all) [5, 6]. Because the anamnestic data mentioned a lung adenocarcinoma diagnosed previously, a TTF-1 immunostain was also done and resulted in positive staining of many nuclei. The ER staining was repeated with an alternative antibody (SP1) and resulted in a similarly strong and diffuse staining (Fig. 1C). Napsin-A was diffusely and strongly positive with a characteristic granular cytoplasmic pattern (Fig. 1E), whereas GATA-3 and mammaglobin were negative in the tumour. The bronchial biopsy of the lung adenocarcinoma could not be further assessed because it was used for diagnostic and molecular testing, without remnants. The original immunostains obtained (p63-, CK7+, TTF1+) had the same staining profile in the breast needle biopsy specimen. The tumour was diagnosed as a solitary metastasis of a pulmonary adenocarcinoma being unusually strongly and diffusely positive for ER- α . The tumour was excised (Fig. 1D), but the patient refused any further treatment (ALK-EML4 translocation was later tested from this specimen with a Vysis FISH break-apart probe [Abbott Molecular, Des Plaines, Illinois, USA] and was absent from the tumour cells). Multidisciplinary discussion of the case revealed that the patient had a right upper lobectomy for pulmonary adenocarcinoma in September 2003. This was diagnosed as a “bronchioloalveolar carcinoma” at that time. The patient had declined adjuvant systemic treatment. The tumour recurred locally in December 2013 (the mass around the right

main bronchus extending to the distal trachea was interpreted as recurrence), when a course of palliative systemic treatment (four cycles of bevacizumab, paclitaxel, and carboplatinum followed by three of erlotinib) was administered (the biopsy was classified as having a dual wild type after testing for exon 18-21 activating mutations of the epidermal growth factor receptor and mutations in codons 12-13 of K- and N-RAS). The mammography performed as a follow-up of a contralateral microcalcification in August and the positron emission tomography/computed tomography performed in November 2014 did not show the breast lesion, and the patient had no other distant metastasis detected at the time of the diagnostic work-up of the breast lump. The archived lobectomy specimen was retrospectively tested for ER and PR: the lepidic adenocarcinoma displayed ER positivity (about 50% of the cells with a medium average staining intensity – Allred score 6 with the SP1 antibody and weaker, Allred score 4, with the 6F11 antibody) (Fig. 1F) and was also focally positive for PR (about 5% of cells staining, Allred score 4). This proved that the primary tumour was already positive for these steroid hormone receptors.

The metastasis was a proof of progression, and the patient – after a voluntary drug holiday of six months – received further palliative systemic treatment (pemetrexed 12 times). In March 2017, she is alive and receiving vinorelbine as fourth-line treatment in her palliative care. The patient gave written consent for the publication of her case.

Discussion

To the author’s knowledge, this is the first report of a solitary metastasis from an ER-positive pulmo-

Table I. Antibodies used for the immunohistochemistry

ANTIBODY	CLONE	SOURCE	DILUTION	RESULT
ER	6F11	Novocastra (Leica), Newcastle, UK	1 : 40	Diffusely positive
ER	SP1	Ventana Medical Systems, Tucson, AZ	RTU	Diffusely positive
CK7	OV-TL 12/30	Biogenex, Fremont, CA	1 : 200	Diffusely positive
GATA-3	HG3-31	Santa Cruz Biotechnology, Santa Cruz, CA	1 : 50	Negative
GCDFP-15	23A3	Cell Marque, Rocklin, CA	1 : 200	Negative
MGB	1A5	Biocare Medical, Concord, CA	RTU	Negative
Napsin-A	Polyclonal (352A-74)	Cell Marque, Rocklin, CA	1 : 400	Diffusely positive
p63	4A4	Histopathology Kft, Pécs, Hungary	1 : 400	Negative
PR	PGR312	Novocastra (Leica), Newcastle, UK	1 : 200	Negative (<1% weak)
TTF-1	8G7G3/1	Biocare Medical, Concord, CA	1 : 200	Focally positive

ER – oestrogen receptor; CK7 – cytokeratin 7; GATA-3 – GATA binding protein 3; GCDFP-15 – gross cystic disease fluid protein 15; MGB – mammaglobin; PR – progesterone receptor; TTF-1 – thyroid transcription factor 1; RTU – ready-to-use

nary adenocarcinoma to the breast. The recognition of the tumour as a metastatic one partially relied on the knowledge of a coexisting recurrent pulmonary adenocarcinoma, which stimulated the routine prognostic and predictive immunohistochemistry (ER, PR, HER2) panel performed on diagnostic breast core-needle biopsies to be complemented with markers of pulmonary origin (TTF1, Napsin-A). The proper identification of the metastasis as a secondary tumour allowed the omission of systemic treatment used for breast cancers and resulted in a change in the systemic palliative therapy of the lung tumour. The patient has a survival characteristic of oligometastatic disease, which is better than that of patients with advanced metastases [7].

The majority of breast cancers are ER-positive, and ER expression is often considered as evidence in favour of mammary origin. Most recently ER-positivity of lung adenocarcinomas has been reported with a range of 0 to 97% [8, 9]. Positivity is seen especially with SP1 (and with decreasing frequency with 6F11 or 1D5, the latter of which was first reported not to stain lung adenocarcinomas at all [10]); the staining is generally only focal, and has been more common in non-mucinous lepidic adenocarcinomas [8]. According to the described findings, the present tumour could be confidently diagnosed as of pulmonary origin. There were features against a primary breast cancer: no in situ carcinoma was present around the invasive tumour, which was relatively circumscribed like most metastases, but not unlike some breast primaries; except for ER, no markers of primary breast origin (GCDFP-15, mammaglobin, GATA-3) were positive in the tumour. In contrast, markers of pulmonary origin (TTF-1 and Napsin-A) were positive. Neither of these markers are 100% specific and/or sensitive, but the overall pattern is in keeping with a pulmonary origin [11, 12]. Metastases to the breast are rare, and pulmonary adenocarcinomas are uncommon sources of such seeding [13]. Of 12 pulmonary adenocarcinomas metastatic to the breast identified through a PubMed search spanning 20 years, only five were tested for ER, and none were positive [13]. However, an antibody-dependent focal ER positivity should be expected in at least some, if not the majority, of pulmonary adenocarcinomas according to the literature [8, 9, 10], and the reported case suggests that even strong and diffuse positivity may occur. This would add pulmonary adenocarcinomas to cancers of the breast and genital tract (ovarian, tubal, endometrial carcinomas) on the list of tumours expressing ER to be considered as potential sources of ER-positive metastatic tumours.

Pathologists as well as clinicians should be aware of this presentation, and should remember that some lung adenocarcinomas may strongly and diffusely rather than only focally be positive for ER- α with

the 6F11 and SP1 monoclonal antibodies used in this case. To our knowledge this is the first description of a solitary ER-positive breast metastasis from a pulmonary adenocarcinoma.

Conclusions

The reported case highlights that ER positivity may be prominent in some primary or metastatic lung adenocarcinomas. It is recommended to test ER-positive tumours lacking obvious signs of a primary nature, like the one presented here with markers of pulmonary origin, because this may help in avoiding potential diagnostic pitfalls (such as a primary breast cancer in analogy to the present case, or metastatic ER-positive breast or gynaecological cancer in the lung as an extrapolation from this case) and in treating the patients according to the correct diagnosis.

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