

## PRIMARY SMALL CELL CARCINOMA OF LUNG WITH METACHRONOUS BREAST METASTASIS

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## PRIMARNI MIKROCELULARNI KARCINOM PLUĆA SA METAHROMOM METASTAZOM U DOJCI

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### ABSTRACT

Breast metastases from an extra-mammary malignancy are rare. Among the lung malignancies that metastasise in the breasts, previous literature has described approximately 30 cases of NSCLC and only a few cases of SCLC. Here, we present a 54-year-old woman with metachronous breast metastasis from pulmonary small cell carcinoma. She presented with a soft tissue mass in the right lung hilum. After bronchoscopy with biopsy, SCLC was verified. The patient was given 4 cycles of etoposide and cisplatin followed by radiation therapy. Seven months after the diagnosis of primary lung cancer, the patient palpated a mass in her right breast. Clinical examination and further diagnostics revealed the suspected malignancy, and a radical mastectomy was performed. Immunohistochemical findings suggested metastatic SCLC in the breast. Differentiation between primary and metastatic cancer in the breast is very important for therapeutic planning.

**Keywords:** small cell lung carcinoma, metachronous metastasis, breast carcinoma

### SAŽETAK

Dojka predstavlja retko mesto ektramamarnih metastaza. Među karcinomima pluća koji su prezentovani sa metastazom u dojci, u literaturi je opisano oko 30 slučajeva NSCLC i samo nekoliko slučajeva SCLC. Mi smo prikazali pacijentkinju starosti 54 godine sa metahronom metastazom sitnoćelijskog karcinoma pluća u dojku. Pacijentkinji je inicijalno dijagnostikovana mekotkivna masa u desnom hilusu pluća. Nakon bronhoskopije i biopsije tumorskog tkiva, postavljena je dijagnoza sitnoćelijskog karcinoma pluća. Pacijentkinja je lečena sa 4 ciklusa hemioterapije po protokolu etopozid i cisplatina, nakon čega je nastavljena radioterapija. Sedam meseci nakon postavljanja dijagnoze primarnog karcinoma pluća, pacijentkinja je napipala čvor u desnoj dojci. Klinički pregled i dodatna dijagnostika su pokazali da se najverovatnije radi o malignom tumouru. Urađena je radikalna mastektomija. Imunohistohemijska analiza je ukazala na metastazu sitnoćelijskog karcinoma u dojku. Diferencijalna dijagnoza između primarnog i metastatskog karcinoma dojke je veoma bitna radi daljeg planiranja terapije.

**Ključne reči:** sitnoćelijski karcinom pluća, metahrone metastaze, karcinom dojke

### ABBREVIATIONS

SCLC: small cell lung carcinoma

NSCLC: non-small cell lung carcinoma

LD: limited disease

### INTRODUCTION

Small cell lung cancer (SCLC) is an aggressive malignancy that comprises 13-15% of all lung cancers (1). At the time of diagnosis, SCLC presents itself as a metastatic disease in 60% of cases. The most common places for metastasis are the liver (35%), brain (47%), bones (25%), adrenal gland (8%) and lungs (12%) (2). Metastasis in the breasts

represents an extremely rare phenomenon, and it occurs in 0,4-1,3% of cases (3). Primary malignancies that usually metastasise in the breasts are melanoma (29,8%), lung carcinoma (16,4%), ovarian and endometrial cancer (12,7%), intestinal carcinoma (9,9%), leukaemia and lymphoma (8,4%), rhabdomyosarcoma (7,3%) and renal cell carci-



**Figure 1.** CT scan of the thorax shows a soft tissue mass in the right lung hilum with dimensions of 24×30 mm.

noma (1,5%) (4). Among lung cancers that metastasise in the breasts, the literature has described approximately 30 cases of NSCLC and only a few cases of SCLC (5-9). Here, we report the case of a 54-year-old woman with breast metastasis from SCLC.

## CASE REPORT

A 54-year-old woman who smoked 20 cigarettes a day for 40 years presented with dyspnoea, orthopnoea, exhaus-

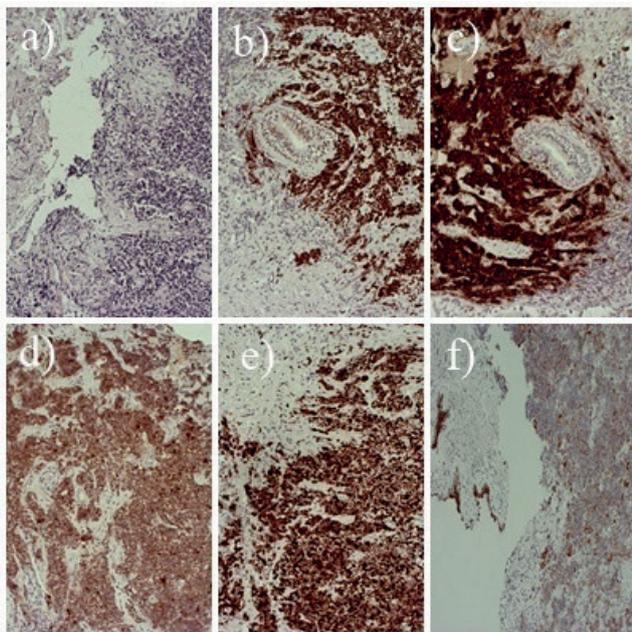
tion, coughing and subfebrile temperature (up to 37,5°C). She had been experiencing these ailments for two months. A computed tomography (CT) scan of the thorax showed a soft tissue mass in the right lung hilum with dimensions of 24×30 mm, without mediastinal lymphadenopathy and without contents in the pleural spaces (Figure 1). The liver, spleen, adrenal glands and other abdominal organs did not exhibit morphological changes. After bronchoscopy with biopsy, SCLC was verified (Figure 2). As the tumour mass was only on one side of the chest and can be treated with a single radiation field, it was staged as limited disease (LD). The patient was given 4 cycles of etoposide and cisplatin followed by radiation therapy.

Seven months after the diagnosis of the primary lung cancer, the patient palpated a mass in her right breast. Clinical examination revealed a change in the lower lateral quadrant of the right breast, approximately 40 mm in size, that was hard, painless and had a fixed base. Breast ultrasound revealed a heterogeneous, lobulated mass that was consistent with malignancy. Considering that the *ex tempore* biopsy showed a malignancy with the impression of primary breast carcinoma, a radical mastectomy was performed. The tumour cells were positive for CD56, chromogranin, synaptophysin, and neuron-specific enolase (NSE) and did not express receptors for oestrogen (ER), progesterone (PR) or *human epidermal growth factor receptor 2* (HER-2). The cells were diffusely positive for thyroid transcription factor-1 (TTF-1) and p53 and focally positive for EMA, cytokeratin 7 (CK7) and CK8, while they were negative for mammaglobin, gross cystic disease fluid protein 15 (GCDPF-15), CK5/6, CK14, CK20, BerEP4, vimentin and p63; the cells also revealed a high proliferation index (Ki67 90%). No evidence of *in situ* carcinoma was observed. The histomorphological image together with the obtained immunophenotype of the cancer cells corresponded to small cell cancer metastasis, which was primarily localised in the lungs (Figure 3).

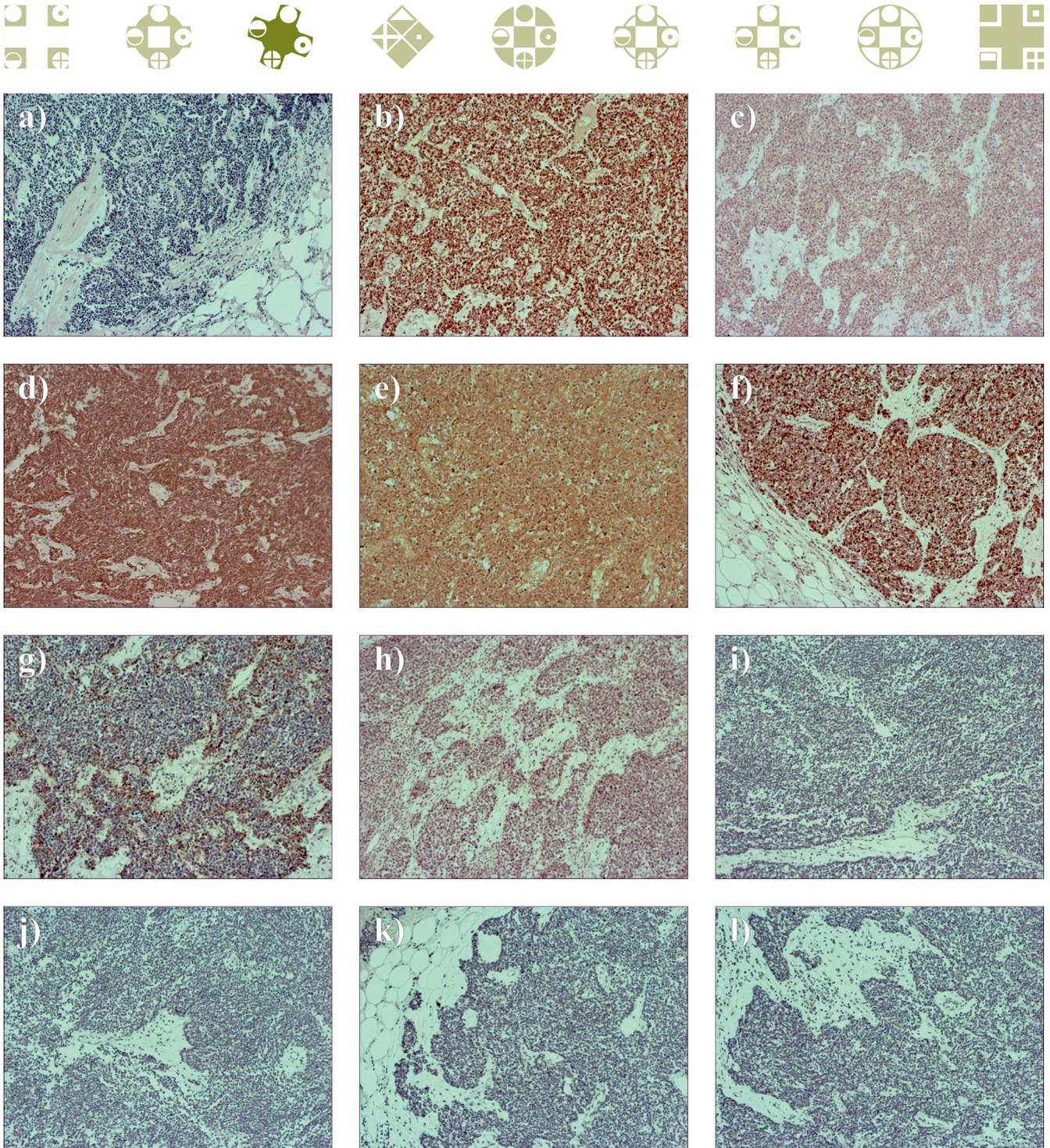
Due to postural instability and headaches, another cranial CT examination was performed one month after the operation. The results of CT demonstrated metastatic changes. Palliative radiotherapy was administered at a dosage 25 Gy in 5 fractions. Because of the poor general health of the patient, further treatment was continued with symptomatic and supportive therapy. The patient died 15 months after the diagnosis of primary lung cancer and three months after the diagnosis of breast metastasis.

## DISCUSSION

In rare cases, the breasts could be a location for metastasis from the contralateral side, while extra-mammary primary neoplasm metastases are exceptionally rare. The reason for this metastasis can be a large surface of fibrous tissue in the breast and a relatively poor blood supply (10). Mirrielees et al. published a systematic review of the literature on breast metastasis from primary lung carci-



**Figure 2.** Primary small cell carcinoma of the lung: a) haematoxylin and eosin staining shows fragments of bronchial mucosa imbued with irregular tumour sheets and ribbon tumour arrangements consisting of easy polymorphic cells, about twice the size of lymphocytes with scant cytoplasm and large hyperchromatic nuclei. Immunohistochemical tumour cells were diffusely positive for b) TTF-1, c) CD56, and d) chromogranin. e) The proliferation index was high; around 90% of the tumour cell nuclei are expressing Ki67. f) CK7 was partially positive.



**Figure 3.** Metastases of small cell lung cancer in the breast: a) haematoxylin and eosin staining of the metastatic breast tumour showed irregular tumour sheets consisting of easy polymorphic cells, about twice the size of lymphocytes with scant cytoplasm and large hyperchromatic nuclei. Immunohistochemical tumour cells were positive for b) TTF-1, c) synaptophysin, d) CK8, and e) NSE. f) The proliferation index was high; around 90% of the tumour cell nuclei are expressing Ki67. g) CK7 was partially positive, while other markers were negative, including h) CK5/6, i) mammaglobin, j) ER, k) PR, and l) HER2.

noma. Thirty-one cases of non-small cell lung carcinoma (NSCLC) were identified with metastases in the breasts, and eight cases of SCLC were identified with metastases in the breasts. Sixty-seven percent of the presented breast metastases of NSCLC patients were metachronous, while in 80% of the primary SCLC cases, breast metastases were synchronous (11).

The influence of oestrogen was indicated as a risk factor for the appearance of breast metastasis, especially in

younger women, which increases vascularisation and loosens the breast stroma. In the literature, breast metastases were described in men who were treated with oestrogen hormonal therapy due to primary prostate carcinoma (12).

Metastasis to the breast occurs either by direct invasion, pleural seeding, haematogenous dissemination or lymphatic spreading. With lymphatic spreading, there is an assumption that the lung cancer cells first metastasise to the ipsilateral axillar lymph nodules, then retrogradely



spread to the intra-mammary lymphatic system, and finally establish breast metastasis (13). Clinically, a breast metastasis is presented as a palpable, quickly growing, well-limited, painless tumour mass whose preferred location is the upper outer quadrant of the breast. Retraction of the skin above the affected part of the breast or the nipple is not a characteristic of the metastasis. A mammogram shows the breast metastasis as a limited mass, while irregular edges, spiculations and micro-calcifications are rarely observed. Breast metastases are localised in subcutaneous tissue unlike primary carcinoma, which develops in the breast glandular parenchyma.

Differential diagnosis between primary and secondary breast carcinoma often presents a challenge, especially in the case of poorly differentiated tumours. Histological detection of an in situ intra-ductal component is of great importance because supports primary breast carcinoma. Metastatic deposits are sharply limited compared to surrounding breast tissue. Elastosis and calcification are characteristics of primary breast carcinoma but rarely of metastases. SCLC cells express neuroendocrine differentiation markers, usually CD56, synaptophysin, NSE or chromogranin. TTF-1 has a role in the regulation of protein expression in the thyroid gland, lungs and diencephalon, and as such represents a specific and sensitive marker for diagnosis of lung adenocarcinoma (14).

TTF-1 was positive in 93% of SCLCs and negative in breast adenocarcinomas (15,16). According to the literature, 2,8% of primary breast carcinomas can show weak or focal expression of TTF-1, and those cases are usually associated with CK5/6 or P-cadherin positivity, grade 3 tumours and the 'triple negative' (ER-, PR- and HER2-negative) phenotype. Napsin A is a sensitive marker for lung adenocarcinoma, which is why the combination of Napsin A and TTF-1 is better for establishing or excluding metastasis in the primary lung carcinoma of the breast compared to using only TTF-1 (17,18).

The 8G7G3/1 clone of TTF-1 is less sensitive but more specific with regard to SPT24, which is why it is recommended for routine use in order to avoid doubts when determining an adequate diagnosis.

Markers that are in favour of primary breast cancer are receptors for ER, PR, GCDFP-15 and mammoglobin. Receptors for ER are expressed in 80% and GCDFP-15 in 45-53% of primary breast carcinomas. Expression of ER in lung carcinoma is low (7,6-14,1%) as well as expression of GCDFP-15 (5,2-15%). Mammoglobin is expressed in 48-72,1% of breast carcinomas and is negative in lung carcinomas (19-22).

The combination of CK7 and CK20 is irreplaceable in a crude differentiation with regard to the origin of cancer. Breast carcinomas are mostly CK7+ and CK20-, while it is less probable that the malignancy is a breast carcinoma if it is CK20+ and CK7- (23).

Breast metastases from non-breast solid malignancies are associated with a poor outcome; the median survival from the time of breast metastasis diagnosis is 10 months. Significantly

better survival was observed in patients who had no evidence of another disease at the time of diagnosis, in patients with neuroendocrine tumours, and in patients who underwent surgical resection for breast metastases (24).

Surgical treatment of the metastatic change in a breast represents an option for the treatment of metachronous metastases, although it is not completely clear if surgical treatment may influence the prognosis of the disease. For patients presenting synchronous lung cancer with breast metastasis, removal of the breast lesion offers no benefit to the patient (11).

In our case, we presented a patient with breast cancer in the T2-N0 clinical stage. Cancer metastases in the breast are extremely rare, and taking into account the high prevalence of primary breast cancer, a palpable tumour mass was considered a new primary breast tumour. Fine-needle aspiration (FNA) cytology and needle core biopsies with immunohistochemical analyses should be the diagnostic procedures of choice in patients with a palpable tumour mass in the breast, especially in those with a previously diagnosed malignant disease, in order to avoid unnecessary radical surgery. If the axillary lymph nodes are not palpable, axillary imaging with ultrasound should be considered, and suspicious nodes should be sampled by FNA or core biopsy. Neoadjuvant chemotherapy with possible surgical resection is a therapeutic option in those patients without distant metastases.

## CONCLUSION

Breast metastases from SCLC represent an extremely rare phenomenon. These metastases mainly occur in the contralateral breast, while in only 0,5% of cases, the metastases result from extra-mammary primary tumours. Since the treatment and prognosis of the diseases are different, it is important that the differentiation be made between primary and metastatic breast carcinoma. Information about previously diagnosed malignancies is of great importance, especially regarding metachronous metastases, in order to carry out the necessary diagnostic procedures so that the most adequate therapeutic modality can be provided to the patient.

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