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Case report

Pathological complete response in a patient affected by multiple synchronous, breast and lung primary malignancies: a case report and review of the literature

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Key words

Breast cancer • Pulmonary adenocarcinoma • Pathological complete response • Multiple primary malignancies

Summary

A pathological complete response in a patient affected by multiple synchronous, breast and lung primary malignancies is reported. A 63-year-old woman presented with an invasive ductal carcinoma of the breast and a lung adenocarcinoma. After multidisciplinary discussion, the patient underwent pulmonary left lower lobectomy followed by radio-chemotherapy with cisplatin and vinorelbine and started hormone therapy with letrozole. Ten months later, a left mastectomy with axillary lymph nodes dissection was performed. Histologically, a pathological complete response (pCR) was documented.
With a review of the Literature, we discuss the issue of multiple primary malignancies, with its diagnostic and therapeutic implications. In cases of multiple synchronous malignancies it has been highlighted the importance of the choice of the best therapeutic approach for both the malignancies, reducing collateral individual effects.

Introduction

Multiple primary malignancies are an emerging problem in clinical practice. Their incidence is increasing likely due to overall longer lifetime and improvements in early diagnosis, treatments and follow-up for many neoplasms. Furthermore, a priority is the exclusion of a metastasis site rather than a second primary cancer. The distinction of multiple primary malignancies does play a critical role for determining the tumor stage, the correct therapeutic approach and the prognosis of the patients [1].
We describe an uncommon case of a patient affected by a breast carcinoma with a pathological complete response after hormonal therapy and radio-chemotherapy for a synchronous pulmonary adenocarcinoma.
To study in depth this unusual but important issue, a review of the principal and most recent articles is also reported (Tab. I).

Case report

A 63-year-old woman attended to the Mammographic Screening Program, during which a high-density nodule with a diameter of 11 mm and with some microcalcifications has been identified.
Stereotactic core biopsy revealed the presence of a moderate differentiated (G2 sec. Elston-Ellis modification of Bloom-Richardson score) invasive breast carcinoma not otherwise specified (sec. WHO 2012) associated with a focal component of well differentiated (G1) ductal carcinoma in situ of cribriform type.
Immunohistochemical analysis was conducted as described previously [2]. Neoplastic cells showed immunoexpression for estrogens receptor in >95% (ER, RabbitSP1, Thermo Sc. Labvision, Fremont, CA, 1:50), progesterone receptor in 92% (PgR 636, Dako, Carpinteria, CA, USA 1:150) and E-cadherin (NCH-38, Dako, 1:20). The Ki-67 index (MM1, Novocastra, New Castle, UK, 1:50) was 7% and HER2/neu score (CB11, Novocastra, 1:100) was 1 (Fig. 1).
During the staging for breast cancer, a chest X-ray revealed the presence of a nodule with not well-defined margins in the dorsal segments of the left lower lobe,

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Tab. I. This table summarizes the principal and most recent reports about multiple primary malignancies (MPM) from different cancer registries and the characteristics of the paired MPM.

Study	Year	Subjects (n)	MPM (n)	Most frequent first location	Most frequent second location	Most frequent associations	Synchronous (n)	Metachronous (n)	Type of study
Aydiner [4]	2000	26255	271 (1%)	-	-	Lung-head and neck, breast-breast, breast-female genital tract	92 (34%)	179 (66%)	Retrospective
Irimie [5]	2010	-	63	Breast, cervix, ovary and gastrointestinal tract	Breast, lung, colorectal	-	22 (34.9%)	41 (65.1)	Retrospective
Liu [6]	2010	1,351,621	85,676 (6%)	Breast, colorectal, prostate	Squamous cell cancer of the skin, colorectal, breast	Breast-female genital tract, urinary tract and prostate, Hodgkin´s lymphoma and breast cancer	-	-	Retrospective
Gursel [7]	2011	9783	117	Larynx, bladder and breast	Lung, breast, colon	-	47 (40.5%) ¤	69 (59.5%) *	Retrospective
Babacan [8]	2012	-	377	Head and neck, breast, colorectal	Lung, colorectal, breast	Breast-gynecologic cancers, colorectal-breast cancers, breast-colorectal cancers.#	-	-	Retrospective
Hulikal [9]	2012	-	38	Head and neck, breast, gastrointestinal tract	Head and neck, gastrointestinal tract, genitourinary tract	-	13 (35%)	25 (65%)	Retrospective
Arpaci [10]	2013	-	130	Breast, head and neck, colorectal	Lung, breast, colorectal	-	24 (18.4%)	106 (81.6%)	Retrospective
Geryk [11]	2013	1,486,984	290.312 (19.5%)	Cancers of skin, breast, female genital organs ¶	Gastrointestinal tract, respiratory tract, urinary tract, breast	-	-	-	Retrospective

* Among 116 adult patients
¶ Among females

with dimensions of 43x28 mm. This finding was confirmed by subsequent examination with computed tomography (CT).

Moreover, whole body 18-fluorine deoxyglucose positron emission tomography and computed tomography (18F-FDG PET/CT) study showed a left hilar adenopathy. To clarify the primary or metastatic nature of the pulmonary lesion, the patient underwent bronchoscopy with bronchial brushing and fine needle aspiration, but the cytology examination was non-diagnostic. After a multidisciplinary discussion, the patient started hormonal therapy with letrozole and left posterolateral pulmonary needle-biopsies was planned. Frozen section examination of the intraoperative needle-biopsies was consistent with a non-small-cell lung cancer (NSCLC), thus the surgeons proceeded with lower left lobectomy

and regional lymph nodes dissection. On this surgical specimen, the neoplasm was diagnosed as an adenocarcinoma solid predominant, involving the visceral pleura, with metastases to the hilar, peribronchial and aorto-pulmonary window lymph nodes.

Neoplastic cells expressed Cytokeratin 7 (CK7, RN7, Novocastra, New Castle, UK, 1:100) Thyroid transcriptor factor 1 (TTF-1, 8G7G3/1, Dako, Carpinteria, CA, 1:50) and Napsin-A (clone TMU-. Ad02, ARP American Research Products, Belmont, MA, 1:500) (Fig. 1). The morpho-phenotypic profile ruled out the possibility of a lung metastasis from the previously diagnosed breast carcinoma. EGFR gene was wild type and the EML4-ALK translocation, evaluated by fluorescence in situ hybridization, was absent. On the basis of the histologic report and clinical evaluation, the patient underwent 4 cycles of cisplatin and vinorelbine, and radiotherapy (50 Gray in 25 fractions).

The patient had a short follow-up and four months later, the breast carcinoma appeared unchanged by 18F-FDG PET/CT study and ultrasound sonography.

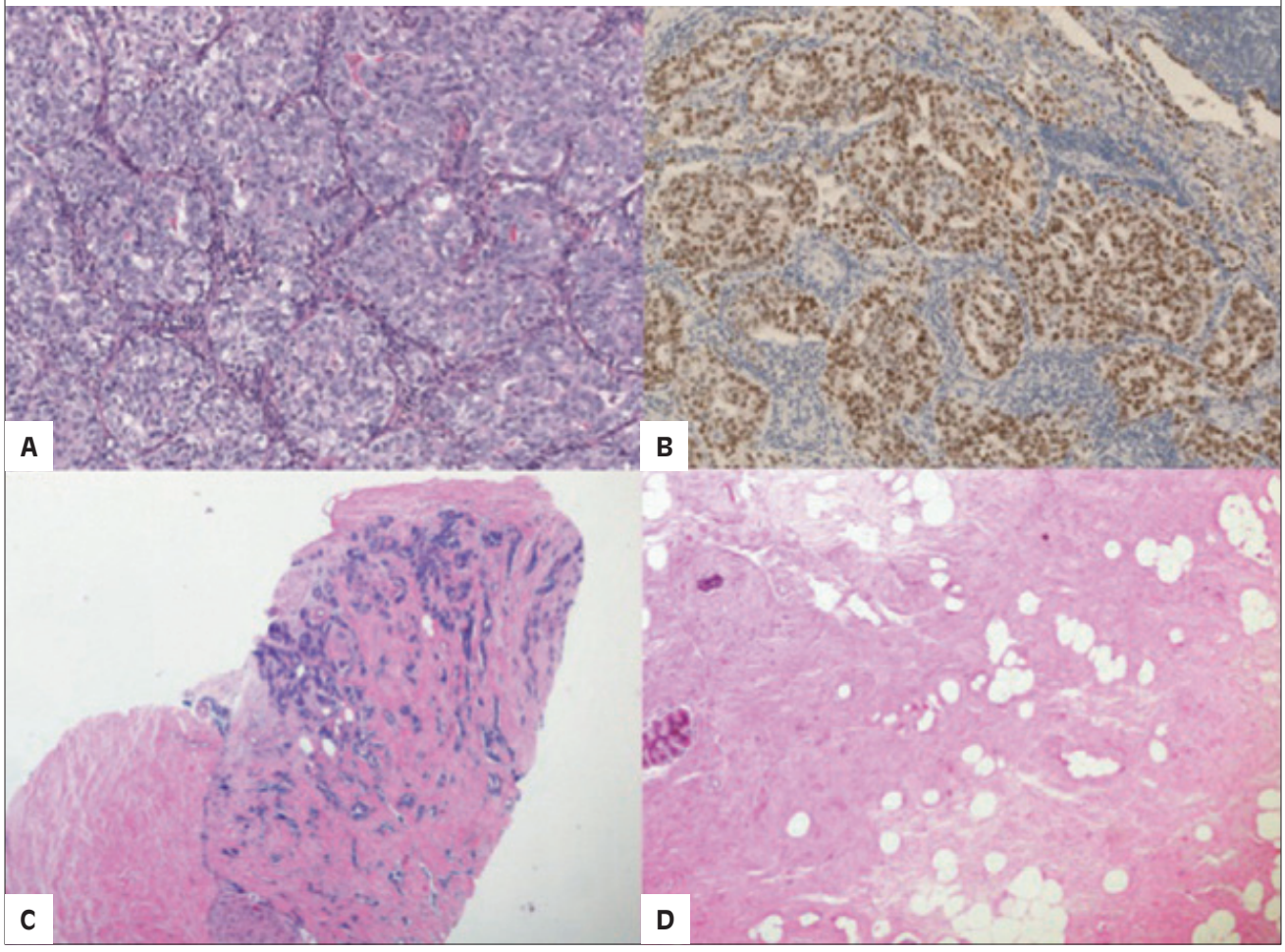
After further five months, the patient was considered suitable for breast surgery. The patient underwent a radical mastectomy with axillary lymph nodes dissection. Grossly, in the upper-outer quadrant a fibro sclerotic area with a central tattoo, 6 cm in diameter, was evident. Surprisingly, in spite of extensive inclusion and sectioning of the whole area, on microscopic examination a pathological complete response (pCR) was retrieved. Neither in situ nor invasive residual tumor was identified on breast specimen. Axillary lymph nodes showed fibrotic regressive phenomena, but there was no evidence of metastatic tumor (Fig. 1).

Discussion

We present a case of co-occurrence of breast carcinoma and pulmonary adenocarcinoma.

Our case was consistent with the definition of synchronous multiple primary malignancies. According to Warren and Gates criteria, MPM are defined as: i) malignant tumors confirmed by histology, ii) topographically distinct without connection with submucosal or intra-

Fig. 1. Pathological findings in the pulmonary adenocarcinoma and the invasive ductal carcinoma of the breast. The pulmonary adenocarcinoma showed a predominant solid pattern (A), and expressed TTF-1 (B). The invasive ductal carcinoma of the breast on the stereotactic core biopsy (C) and the tumor bed completely replaced by fibrosis in the mastectomy specimen (D).



epithelial alterations (skip metastasis), iii) probability of one being the metastasis of the other must be excluded [3]. Synchronous tumors are two or more primary tumors that are diagnosed within 6 months of the first primary tumor.

Among the principal more recent reported series of MPM, breast carcinoma is one of the cancers most frequently associated with other synchronous or metachronous neoplasms in females. One of the associations most frequently described is breast-breast and breast-gynecological cancers (Tab. I) [4-11]. Although the reasons for the increased risk of MPM in patients with breast cancer have not been fully elucidated, several factors have been implicated: genetic (e.g. mutations BRCA1-2), hormonal (e.g. nulliparity), exposure to carcinogens including radio-chemotherapy used in the treatment of the first malignancy [10 12].

In our case the association was synchronous breast and lung cancer. Data from surveillance epidemiology and end results (SEER) cancer registries demonstrated a decreased risk for lung cancer in women affected by breast cancer. This is likely due to a lower rate of tobacco use in this group than in general population [12].

When patients have an extrapulmonary malignancy and a lung nodule, it is crucial and sometimes challenging to establish the nature of both the lesions (eg, metastatic vs primary). In fact, the lung is one of the most frequent sites for primary malignancy as well as one of the most typical locations for metastatic carcinomas, with bones and liver.

An accurate diagnosis is mandatory for its therapeutic and prognostic valence. Pulmonary metastases are usually detected as multiple pulmonary nodules and/or pleural carcinomatosis. However, in the case of detection of a solitary pulmonary nodule in patients with synchronous or previous diagnosis of an extra-pulmonary malignancy, an accurate diagnosis can be very difficult. Zhou et al. found that close to half of the lung nodules in patients with extrapulmonary malignancy was primary lung adenocarcinoma [13].

In some cases, fine needle aspiration cytology and core biopsy followed by the analysis with an appropriate immunohistochemical panel (TTF-1 and Napsin-A, Cytokeratin 7) are useful tools to achieve the correct diagnosis. However, in other cases, such as the presented one, these techniques may be non-diagnostic, and/or the pulmonary nodule cannot be reached by bronchoscopy. Therefore intraoperative frozen section technique can resulted necessary, but also in these cases differential diagnosis between pulmonary adenocarcinoma and metastatic pulmonary tumor could be difficult. Thus, the examination of the resected specimens followed by immunohistochemical analysis represents sometimes the only way to achieve an accurate diagnosis. For cases like these, TTF-1, Napsin-A and CK7 are essential to demonstrate the pulmonary origin of a neoplasm, even if poorly differentiated. In our case, intraoperative frozen section was consistent with a primary NSCLC.

Treatment of synchronous tumors often requires a multidisciplinary approach. The therapeutic decisions depend on histology of the tumors, location, stage and general health conditions of the patient. Surgeons, medical oncologists, radiation oncologists, pulmonary medical specialists, radiologists and pathologists should be the principal members of the multidisciplinary team. This group has a great potential to improve patient care and health.

Currently available data suggest that adding chemotherapy after surgery for NSCLC increase the 5-year survival rate of 4% [14]. Therefore, our patient received 4 cycles of cisplatin and vinorelbine plus radiotherapy after surgery, which is the most recommended association for pulmonary adenocarcinoma. Simultaneously, the patient continued to assume hormone therapy with letrozole for breast cancer.

These chemotherapeutic agents are not usually the first-line drugs, but can be acceptable also for breast carcinoma [15].

In our case after radio-chemotherapy, radical mastectomy and axillary lymph-nodes dissection were carried out. At histologic examination, a pCR was retrieved.

In patients undergoing primary endocrine treatment for breast carcinoma the pCR rate is very low, mostly around 1%, and Orlando et al. reported that 5 out of 26 patients affected by locally advanced breast carcinomas had complete pathological response (20%; 95% CI: 7-41%) after a neoadjuvant regimen containing vinorelbine, cisplatin and 5-fluorouracil as continuous infusion [15].

In our case we cannot determine with certainty which agent has determined a pCR in breast cancer, but it is likely to be a combination of factors: early stage of breast cancer diagnosed during the Mammographic Screening Program, hormonal therapy with letrozole and radio-chemotherapy for lung adenocarcinoma with chemotherapeutic agents that are also effective in breast carcinoma.

In conclusion, synchronous MPM have an increasing incidence and can be encountered during the routinely clinical practice. Because of the lack of guide-lines for diagnosis and treatment of MPM, a case-specific management is often required. Especially when MPM involve organs that are frequently sites of metastases (such as lung and liver) the primary or metastatic nature of the lesions should be investigated.

The choice of treatment should consider the tumor stage of the malignancies and priority should be given to the most advanced cancer. As highlighted by the present case, if possible, chemotherapeutic agents effective in both tumors should be preferred, since they can induce a response in both tumors or at least prevent tumor progression of the second primary tumor.

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