

# BREAST AND OVARIAN CARCINOMA IN THE SAME PATIENT, METASTASIS OR DUAL PRIMARIES?

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## ABSTRACT

Metastases to breast from extramammary primaries are very rare events. These lesions differ from primary breast carcinomas and they are known to have poor prognosis. Discrimination between metastatic tumors and primary breast carcinomas are usually done by clinical and pathological evaluation including immunohistochemistry. Here we report an unusual case of ovarian epithelial carcinoma which was initially diagnosed as to give metastasis to breast 17 months later than the first diagnosis of ovarian carcinoma. Clonality evaluation revealed that breast and ovarian tumors were metachronous dual primaries. [Turk J Cancer 2007;37(1):27-30]

## KEY WORDS:

Ovarian carcinoma, breast carcinoma, metastasis, clonality

## INTRODUCTION

The breast is an uncommon site for tumor metastasis. There are only 37 cases that have been reported as ovarian cancer metastasizing to breast in the English literature (1-8). The frequency of breast metastasis of ovarian carcinoma varies from 0.5 to 1.2% in the clinical setting (9-11). These ovarian cancers are widespread ones and they have poor prognosis with breast metastasis.

Hereby we suggest that accurate differentiation of metastatic from primary tumors is important because the treatment and prognosis differ significantly. Using immunohistochemical staining solely –as it is done in daily practice- to support the histological findings may not be helpful and sometimes may cause false diagnosis and an ineffective treatment strategy.

The question that needs to be addressed for the correct diagnosis of lesion is, to what extent are breast and ovarian tumors of the same patient different at the genetic level? Microsatellite markers were used to decipher the genetic status of the tumors, based on patterns of loss of heterozygosity (LOH). Microsatellites are repeat sequences of either mono/di or tri bases that occur throughout the genome, and that over the course of evolution, have become highly polymorphic. LOH relies on a given microsatellite to be

heterozygous, which enables loss of an allele to be identified when it is reduced homozygosity. Thus, if tumor samples from different locations show different LOH pattern in different genetic loci, then it can be shown that they are different genetically.

This case report is also a self criticism that we made to lighten both pathologists and gynecologic oncologists.

## CASE REPORT

A 50-years-old woman was admitted to an urban hospital with the complaint of abdominal distention and pain. Laparotomy was done and biopsies were taken. Pathologic examination of the specimens was reported as serous papillary adenocarcinoma of the ovary. Patient was then referred to our clinic. Physical examination revealed a right adnexial mass of nearly 8 centimeters in diameter. Computed tomographic scans of abdomen and pelvis showed a semisolid mass of 65 mm in diameter originating from right ovary and CA-125 assay was found as 16317 U/ml. Staging laparotomy was done. There were papillomatous tumoral lesions derived from both ovaries, omentum was infiltrated and also there was a tumoral mass nearly 2 cm in diameter over the rectum. Optimal debulking together with pelvic and paraaortic lymph node dissection was carried out.

The diagnosis of serous papillary cystadenocarcinoma, Grade II and Stage III C was established. Adjuvant chemotherapy was planned and initiated in June 2000, with six course of intravenous paclitaxel ( $175\text{mg}/\text{m}^2$ ), carboplatin ( $\text{AUC}=6$ ) and epirubicin ( $60\text{ mg}/\text{m}^2$ ) once in every 3 weeks. Patient was completely asymptomatic during and after six cycles of chemotherapy. Clinical evaluation and diagnostic tests were all in normal ranges after the chemotherapy ended and a second look laparotomy (SLL) was planned according to our clinic's policy. There were no grossly visible tumors at SLL. Pathological evaluation reported microscopic tumoral lesions in the biopsies taken from intestinal adhesions. Three courses of the same chemotherapy regimen were given to the patient after SLL. CA-125 values and clinical examinations were all normal during this time period. Patient was followed up for one year and there was no abnormality and then was admitted to outpatient clinic of our hospital with the complaint of mammarian mass: CA-125 was 92.8 U/ml. Bilateral mammography was done and a smooth surfaced mass of 17 x 16 mm in left breast

was diagnosed, this diagnosis was also confirmed with breast ultrasonography. Mass was extirpated and pathologic evaluation together with immunohistochemistry showed that it was a papillary adenocarcinoma of ovarian origin (Tumor was positively stained for CA-125, ck7 and estrogen receptor while it was negative for c-erb-B2, CK20 and Progesterone receptor). A third-line chemotherapy regimen consisting of weekly paclitaxel was administered. Patient's laboratory and clinical findings were in normal ranges during that chemotherapy regimen which lasted for six weeks. At the end of this regimen patient complained from another mass in her right breast and breast ultrasonography was done. A heterogenic solid lesion of 33 mm in diameter was diagnosed. This lesion was evaluated clinically and was decided as another metastasis of her primary ovarian tumor. Lesion was extirpated and pathologic evaluation showed no malignancy with the diagnosis of fibrocystic disease of the breast. Weekly paclitaxel was continued for 30 weeks and the patient was accepted as stable disease. Another tumoral lesion in the right breast and a different lesion 5.5 cm in diameter in the right thoracic front wall were diagnosed after this time period. Mass in the right breast was extirpated and pathologic evaluation was resulted as metastasis of the primary ovarian tumor with similar abovementioned immunohistochemical findings. Patient was decided to receive chemotherapy because of systemic involvement and received 3 courses of topotecan ( $1.25\text{ mg}/\text{m}^2/\text{day}$ ) 5 days in every 3 weeks. Just after this regimen bilateral mass in the breast was diagnosed by ultrasonography and bilateral simple mastectomy was carried out. Pathologic evaluation was reported as papillary adenocarcinoma and these tumors were still believed as metastasis of primary ovarian carcinoma.

After this atypical progression of the disease a clonality analysis was requested from Queen Mary University, Barts and the London Gynecologic Oncology Research Center, London. Patient's paraffin blocks of ovarian primary and tumor extirpated from breast were sent to London and clonality analysis was performed. Patient was informed verbally and her permission for further analysis was taken.

## CLONALITY ANALYSIS

QIAamp DNA mini kit was used to extract the DNA from microdissected formalin fixed paraffin embedded breast and ovarian tumor samples and neighboring non-

neoplastic tissue of the same patient (Qiagen, London, UK). The protocol was followed as described in the manual.

The DNA samples were PCR amplified for 15 microsatellite markers for 9 different loci on chromosomes 2, 9, 10, 11, 17 and 22 (D2S2241; D2S2275 and D2S2299 on 2q23; D2S2345; D2S306 and D2S354 on 2q24; D9S1821 and D9S1881 on 9q33; D10S187 on 10q24; D11S902 on 11p14; D11S922 on 11pter; D17S520 and D17S132 on 17q12; CACNLB1 on 17q21; D22S156 on 22p11) using fluorochrome labelled markers. PCR reactions were performed in a 15 ml volume that contained 5 ml of the DNA; 1x Promega PCR buffer, 200 mM of each dNTP, 20 ng of each primer, 1 unit of Amplitaq Gold DNA polymerase and 3 or 4 mM MgCL2 (all reagents from Perkin Elmer) (95 °C for 15 minutes followed by 35 cycles of amplification -annealing temperature varied for each primer from 58 °C to 65 °C for 45 seconds- and a final extension step at 72 °C for 10 minutes. For each primer set, a PCR negative control consisting of PCR reaction mix, in which template DNA was replaced with DNase/Rnase free water was employed. Amplified products were pooled; diluted, size standard ladder (Rox) and formamide was added and then was genotyped using ABI prism 3700 automated genotyper (Applied Biosystems). The data was then analysed using the ABI prism Genotyper 3.7 NT software.

There was loss of lower allele in ovarian tumor on chromosome 2q23 (D2S2275) while breast tumor retained heterozygosity on the same locus. On the other hand, on chromosome 22p11 (D22S156); upper allele of breast tumor was lost while it was retained in ovarian tumor (Figure 1A and B). Other loci examined were either uninformative, normal or were showing similar LOH pattern in breast and ovarian samples.

Although LOH may also reflect the inactivation of tumor suppressor genes in different steps of tumorigenesis and a variety of LOH patterns may be found due to the genetic instability, LOH pattern concordance in two different populations supports common clonal origin (12). On the other hand, because the lower allele was lost on 2q23 in the ovarian tumor DNA sample but still retained in the breast tumor, it is unlikely that the breast tumor is a metastasis of the ovarian tumor as the lost allele is nearly impossible to be repaired in tumor progression steps. As the upper allele was lost on 22p11 in

the breast tumor DNA sample but retained in the ovarian tumor, it is again unlikely that the ovarian tumor is a metastasis of the breast tumor. Although it may be possible that breast tumor may be metastasis from ovary according to the LOH finding at 22p11, the LOH pattern at 2q23 excludes this probability. In summary, existence of different LOH patterns in two different populations in two different chromosome loci while the other organ retaining homozygosity was the clue for this particular case to reveal difference in genetic fingerprint. Based on this result, it was concluded that both tumors are dual primaries.

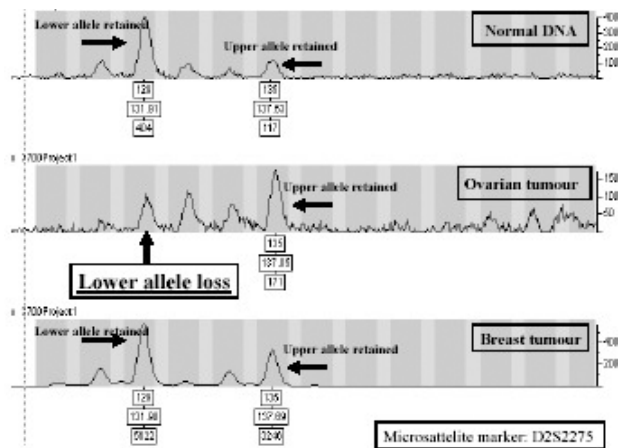


Figure 1A. Clonality analysis results: Upper allele

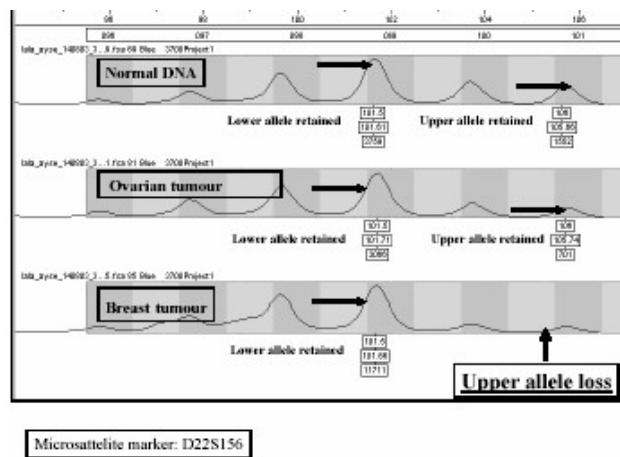


Figure 1B. Clonality analysis results: Lower allele

## DISCUSSION

Breast tumors of extramammary origin are very rare. Frequently seen primary tumors metastasizing to breast are usually of hematological origin and melanoma (9,11, 13-17). There are only 37 cases of ovarian cancer metastatic to breast in the English literature, reported beginning from 1907 (18).

All of these metastases occur by two distinct routes; lymphatic and blood borne (16). Among the extramammary malignancies ovarian epithelial cancers are extremely rare (1,19). In an autopsy study of Abrams (10), only 3% of ovarian cancers with breast metastasis was reported. Usual metastatic routes of ovarian carcinoma are transperitoneal shedding and lymphatic dissemination through the pelvic and paraaortic lymphatics. In contrast to primary tumors of breast, metastatic tumors are usually superficial, mobile, smooth surfaced, and sharp edged. There are no skin sign of underlying tumor. Ovarian cancer metastasis occurs at a mean time of two years after initial diagnosis (19-21). Patients who had metastatic lesions of ovarian primaries have a survival time between 13 days and >3.5 years (1,14,19,20,22).

Discriminating between metastatic or primary breast tumors by Hematoxylin&Eosin may be impossible. Most of the cases in the literature report the immunohistochemical evaluation as a major and reliable method for pa-

thologists to make the discrimination between the two. Whatever the diagnostic method is; histomorphology alone or together with immunohistochemistry, the final decision is of great importance because therapeutic strategies extremely differ from each other in metastatic and primary breast tumors. False diagnosis may result in over or false treatment. False diagnosis as metastatic tumor originating from ovarian primaries may lead to adjuvant systemic chemotherapy while the breast surgery may be limited to the extirpation of the metastatic tumor in that circumstances. Treatment strategy will be of course different if it is diagnosed as a metachronous tumor arising as a primary breast carcinoma in an ovarian cancer patient as it will include axillary lymphadenectomy and adjuvant radiotherapy when needed. We suggest that evaluation of clonality must also be done in patients that immunohistochemical staining seems to support the diagnosis as it is in our case.

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