Breast Metastasis 56 Months before the Diagnosis of Primary Ovarian Cancer: A Case Study

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Abstract. *Background: Breast metastasis of ovarian cancer is rare. A patient with a breast tumor which turned out to be a metastasis as the first clinical manifestation of a primary ovarian cancer diagnosed 56 months later is described. Case Report: A 72-year-old patient presented with a palpable mass in the right breast. Lumpectomy was performed and primary breast cancer was excluded. Histology confirmed a poorly differentiated adenocarcinoma. However, further examination showed no evidence of extramammary primary malignancy. Fifty-six months later, a multicystic pelvic lesion with irregular septa was found. Laparotomy showed a tumor of the right adnexa. The final pathology confirmed the diagnosis of a primary serous ovarian carcinoma. The paraffin blocks of both tumors were reevaluated and showed that the cytological atypia and the immunohistochemical profiles [cytokeratin (CK) 5/6, CK 17, gross cystic disease fluid protein (GCDFP)-15 / BRST-2, estrogen- and progesterone receptor, cancer antigen (CA)125, Wilms tumor (WT-1), tumorsuppressor gene p53, MIB-1 (proliferation marker)] were similar in both the breast and the ovarian specimens. Conclusion: To our knowledge, this is the first report of a breast metastasis preceding the diagnosis of primary ovarian cancer by several years.*

Breast metastasis from primary ovarian cancer is rare but is occasionally found after the diagnosis of the primary tumor. The incidence of breast metastasis from primary ovarian/peritoneal carcinomas accounts for 0.03% to 0.6% of all breast malignancies (1). Autopsy studies have reported breast metastasis in 1-3% of patients with ovarian cancer (2-4). A 72-year-old patient with breast metastasis as the first clinical manifestation of a primary ovarian cancer, which was diagnosed 56 months later, is described.

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Case Report

A 72-year-old patient presented with a 2.5 cm palpable mass in the lower inner quadrant of the right breast and a lumpectomy was performed. The final histopathology showed lymph node structures infiltrated by a poorly differentiated carcinoma with an unusual infiltrative pattern. The neoplastic epithelial cells were arranged in diffusely scattered nodules and small sheets. This infiltration pattern was inconsistent with lymphatic spread *via* lymphatic channels and sinusoidal infiltration. Staining for estrogen and progesterone receptors was negative. Thus, a primary tumor of the breast was virtually excluded. The final diagnosis was of a lymph node metastasis of a poorly differentiated carcinoma possibly arising from the breast, but more probably of extramammary origin. Clinical tumor investigations showed no evidence of extramammary or mammary primary malignancy by mammography, computed tomography of the abdomen and the thorax, chest x-ray and gynecological examination including vaginal sonography. At that time, the only suspicious parameter was an increased preoperative cancer antigen (CA)-125 level of 76 U/ml (normal range up to 35 U/ml).

The patient was followed up closely. Fifty-six months after the removal of the metastasis in the right breast, the patient presented with diarrhea and lower abdominal pain. Abdominal sonography and subsequent computed tomography showed a multicystic pelvic lesion with irregular septa. The CA-125 level was 181 U/ml. Laparotomy showed the colon sigmoideum and ileum adherent to an 8-cm inflammatory tumor of the right adnexa. Frozen section histology showed a serous carcinoma. The left adnexa appeared normal, as did the other intraperitoneal organs. A total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and partial ileum resection were performed. The final pathology confirmed a poorly differentiated primary serous carcinoma of the right ovary with infiltration of the right fallopian tube. The uterus, the left adnexa and the omentum majus were free of tumor. The postoperative course was uneventful. Adjuvant chemotherapy with carboplatin was initiated. Eighty-four months after the initial diagnosis of breast metastasis and 28 months after the

diagnosis of the ovarian primary, the patient developed subileus symptoms and was found to have extensive lymph node metastasis and peritoneal carcinomatosis as well as liver and pulmonary metastasis. The patient died one month later from progressive disease.

To clarify the origin of the lymph node metastasis in the breast removed 56 months before the detection of the ovarian primary, the paraffin blocks of the breast lesion and the ovarian lesion were reevaluated using various antibodies. Standardized automated procedures based on an indirect streptavidin-biotin method (Ventana Medical System, Tucson, AZ, USA and Dako, Glostrup, Denmark) were carried out.

The histomorphology of both tumors was similar regarding cytological atypia, which showed high nuclear pleomorphism and many mitoses. However, their growth patterns were different. The breast metastasis showed a predominantly solid-nodular growth pattern (Figure 1 M1), whereas the primary ovarian tumor, beneath solid sheets with slit-like spaces, also contained small foci with a typical papillary growth pattern (Figure 1 O1). The latter finally led to the diagnosis of a primary serous ovarian cancer. In all the slides evaluated, the tumors showed the same immunohistochemical profile: nearly all the tumor cells showed positive reactions for cytokeratins (CK) 5/6, which in general is not the case in invasive breast cancer, but is in ovarian cancer. CA 125 was also positive in both specimens (Figure 1 M2 and O2), thus confirming the correlation between the tumor growth and the serological test. Although CA125 may be elevated in several malignancies including breast cancer and thus is not exclusively specific, it is a very reliable marker for ovarian cancer. The breast metastasis and the ovarian tumor were non-reactive for estrogen- and progesterone receptors, whereas positivity can be expected in more than 80% of primary breast carcinomas. Finally, gross cystic disease fluid protein-15 (GCDFP-15/BRST-2) showed negative immunoreactions. GCDFP-15 is positive in most invasive breast carcinomas (5, 6). Additionally, CK17, which can be positive in papillary breast carcinomas but which is negative in serous papillary carcinomas, showed a negative reaction. Wilms tumor 1 (WT-1) reactivity was found in nearly all the tumor cells. WT-1 is immunoreactive in primary serous carcinoma of the fallopian tube, ovary, endometrium and peritoneum (6-8). The summarized immunoprofile of both tumors strongly supported the histomorphological diagnosis of primary ovarian serous cancer.

The p53 and MIB-1 (proliferation marker) immuno-reactions were compared to evaluate the relationship between the two locations. Eighty percent of the nuclei were reactive for p53 (Figure 1 M3 and O3), which is involved in transcription regulation. Seventy percent of the nuclei were reactive for MIB-1 in the breast metastasis and in the ovarian cancer.

Discussion

The existence of a breast metastasis and primary ovarian cancer at the time of initial presentation is extremely rare (9, 10). To our knowledge, this is the first report of a breast metastasis preceding the diagnosis of primary ovarian cancer by several years.

The main route of spread of ovarian cancer is intraperitoneal, whereas extraperitoneal seeding usually implies advanced disease (11). Isolated distant spread, such as breast involvement, is very uncommon in ovarian cancer patients.

The breast is an extremely rare site of metastatic ovarian disease and occurs in 0.5%-1.3% of cases only (12). In 1907, Sitzenfrey (13) first described an ovarian cancer metastatic to the breast. Laifer *et al.* (14) observed breast metastases from ovarian cancer after an average of two years following the initial diagnosis and these were usually associated with disseminated disease.

The prognosis of patients with ovarian cancer who develop breast metastasis is poor (15). Survival has been reported to be between 13 days and 3.5 years (16), with most of these patients surviving less than 6 months. Recine *et al.* (1) described a survival range between 2 and 31 months after the development of metastatic disease to the breast or axillary lymph nodes. Nevertheless, our patient survived 85 months after the diagnosis of breast metastasis.

In our case, the unusual infiltrative pattern in the lymph node metastasis in the breast suggested hematogenic tumor spread, which would be consistent with the unusual localization of this metastasis. The affinity of the serous carcinoma cells for the germinal centres of the lymph nodes may have led to this unusual growth pattern.

The recognition and distinction between primary and metastatic tumors of the breast is of great clinical importance, since treatment and prognosis differ significantly. The comparison of morphological features between the primary and metastatic tumors as well as the use of immunhistochemical studies are essential for the establishment of the correct diagnosis (1, 9).

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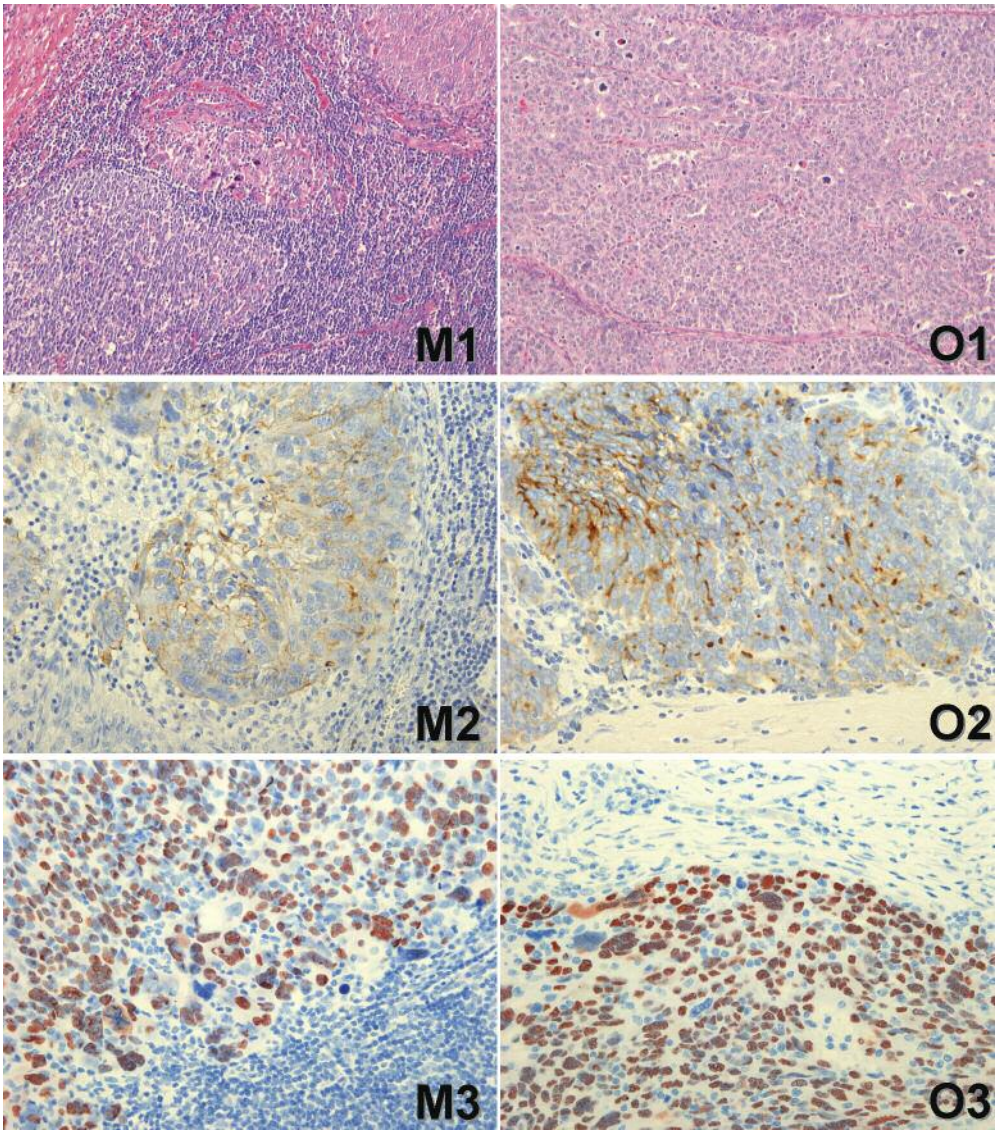

Figure 1. *Intramammary lymph node metastasis (M) and primary poorly differentiated serous carcinoma, (O). M1: Hematoxylin and eosin stained section showing metastatic foci of a poorly differentiated carcinoma surrounded by lymphocytes, in the lower left a residual germinal center is seen. O1: Primary ovarian cancer showing mostly a solid growth pattern with slit-like spaces, typical of poorly differentiated serous carcinoma and high nuclear pleomorphism (original magnification of M1 and O1 ×200). M2 and O2: CA-125 immunohistochemically stained sections showing positive reactions in both (Diamino-benzidine, stained, original magnification ×400). M3 and O3: p53 immunohistochemistry showing high nuclear positivity in both (3-amino-9-ethylcarbazole, stained original magnification ×400).*

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