

Case Report

Postoperative peritoneal inflammatory granuloma mimicking peritoneal metastasis in a patient with breast cancer: a case report

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Received August 8, 2023; Accepted September 22, 2023; Epub October 15, 2023; Published October 30, 2023

Abstract: Peritoneal metastasis from breast cancer is a relatively rare life-threatening condition. The gold standard for diagnosing peritoneal metastasis is a direct peritoneal biopsy. In this report, we describe an interesting case of peritoneal inflammation mimicking peritoneal metastasis in a patient with breast cancer, as confirmed by laparoscopic peritoneal biopsy. A 45-year-old woman with a history of right breast cancer presented with a peritoneal wall mass seen on an abdominal computed tomography (CT) in routine follow-up. She underwent right skin-sparing mastectomy with sentinel lymph node biopsy with direct to implant reconstruction 6 years prior and underwent right salpingo-oophorectomy 2 years before. Positron emission tomography-computed tomography (PET-CT) and abdominopelvic CT showed multiple enhancing nodules in small bowel mesentery and right peritoneal wall with a small amount of ascites, which led to a strong suspicion of peritoneal metastasis. After a multidisciplinary conference, the possibility of peritoneal seeding became doubtful. Laparoscopic biopsy was performed, and peritoneal wall mass biopsy was subsequently performed. Pathologic results showed no evidence of peritoneal metastasis of breast cancer. The peritoneal biopsy specimen revealed postoperative fibrosis and inflammation with some meal content. Although rare in breast cancer, peritoneal metastasis can produce a devastating outcome if left undiagnosed. Despite the imaging findings strongly suggesting metastasis, biopsy confirmation for the suspected lesion was necessary. This not only verifies true metastasis but also determines the treatment options available for the patient and thus unnecessary treatment can be avoided.

Keywords: Breast carcinoma, peritoneal inflammation, peritoneal metastasis, acute peritonitis, laparoscopic biopsy

Introduction

Breast cancer is the most common malignancy found in women worldwide, and in Korea, it is the second most common cancer among women [1]. Although the incidence of locally advanced breast cancer has decreased and early breast cancer cases have increased, the incidence of metastatic breast cancer has not changed. Additionally, although there are advancements in multimodal therapies including intensive local treatment, chemotherapy,

endocrine therapy, and targeted therapy, these have not produced significant changes in the prognosis of patients with breast cancer accompanied by distant metastasis [2].

The common sites of breast cancer metastasis are the bone, lung, liver, and brain, while metastasis to the peritoneal cavity is relatively rare. The reported incidence rates are 0.7-2.7% [3, 4]. Usually, peritoneal metastasis affects patients with gastrointestinal and gynecologic malignancies [5]. Most peritoneal metastasis

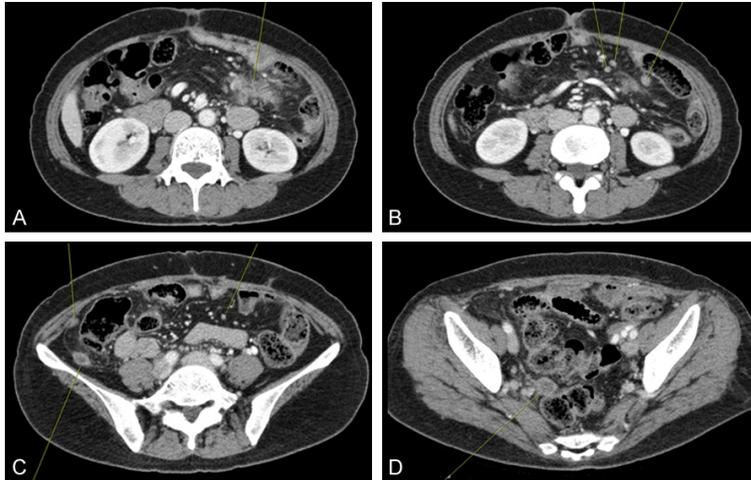


Figure 1. Abdomen pelvis computed tomography findings (A-D) showed multiple enhancing nodules in the small bowel mesentery and the right peritoneal wall with a minimal amount of ascites and a suspicious rim-enhancing nodular lesion in the right salpingo-oophorectomy site. That was suggestive of peritoneal metastasis.

from breast cancer is associated with metastases in other organs, and single metastasis to the peritoneal cavity from breast cancer is uncommon [3]. It is reported that the peritoneal metastasis from breast cancer is developed late and this late onset may be associated with true delayed metastasis or late metastasis detection [3-6]. This might not be associated with any specific symptom, and imaging modalities including computed tomography (CT) are limited in their ability to visualize localized peritoneal metastasis since they have low sensitivity for small-volume disease. Additionally, positron emission tomography-computed tomography (PET-CT) has a high rate of false positives in detecting peritoneal metastasis associated with tissue inflammation following diverse medical and surgical approaches [6]. The gold standard in diagnosing peritoneal metastasis is direct peritoneal visualization, either by laparotomy or laparoscopy. The peritoneal metastasis from breast cancer shows a dismal prognosis, and early accurate detection is critical to avoid a life-threatening condition [3, 4].

In this report, we describe an interesting case of peritoneal inflammation with granulomas mimicking peritoneal metastasis in a patient with breast cancer, as diagnosed with laparoscopic peritoneal biopsy. The publication of this report was approved by the Institutional Review Board of the Chungbuk National Uni-

versity Hospital, Republic of Korea. The patient provided informed consent for her treatment and agreed to the publication of the figures and data in this report.

Case report

A 45-year-old woman with a history of right breast cancer at the age of 40 years presented with a peritoneal wall and omental mass on CT image in routine follow-up. The CT scans of the abdomen and pelvis showed newly appeared multiple enhancing nodules in the small bowel mesentery and the right peritoneal wall with a minimal amount of ascites and a suspicious rim-

enhancing nodular lesion in the right salpingo-oophorectomy site. This was suggestive of peritoneal metastasis (**Figure 1**). A PET-CT showed multiple hypermetabolic nodular lesions in the left upper quadrant of the abdominal mesentery, wall of the descending colon, right paracolic gutter, right pelvic cavity, and cul de sac ($SUV_{max} = 8.4$), suggesting peritoneal seeding. No gross hypermetabolic lesion was noted in both breasts and axillae. Chest CT scan and bone scan also showed no evidence of abnormality suggesting breast cancer recurrence (**Figure 2**).

The patient underwent right skin-sparing mastectomy with sentinel lymph node biopsy with direct to implant reconstruction 68 months before the consultation. The tumor was diagnosed as a well-differentiated invasive lobular carcinoma, measuring 5.5 cm in diameter (**Figure 3A**). On immunohistochemistry, the tumor tested positive for the estrogen receptor (2+, 95%) and progesterone receptor (2+, 75%) and negative for C-erb-B2. The Ki67 proliferation index was 10%. Out of 5 sentinel lymph nodes sampled, one was revealed to have a 3 mm macrometastasis on permanent pathology. According to the eighth edition of the American Joint Committee on Cancer (AJCC) staging system, the tumor was pathologic stage IIIA (pT3pN1snM0). She underwent adjuvant chemotherapy consisting of 4 cycles of adria-

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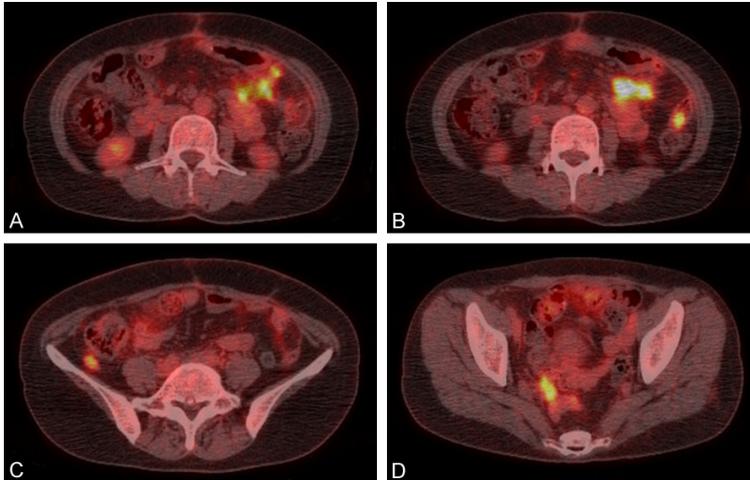


Figure 2. Positron emission tomography-computed tomography findings (A-D) showed multiple hypermetabolic nodular lesions in the left upper quadrant abdominal mesentery, wall of the descending colon, right paracolic gutter, right pelvic cavity, and cul de sac ($SUV_{max} = 8.4$), suggesting peritoneal seeding.

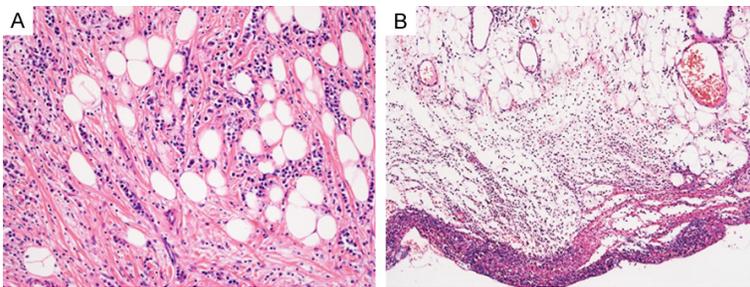


Figure 3. Primary breast cancer was diagnosed as a well-differentiated invasive lobular carcinoma (A, H&E, $\times 200$). Small bowel segmental resection revealed small bowel with chronic active inflammation, erosion, and serositis without a definite mass suggesting metastasis of breast cancer (B, H&E, $\times 100$).

mycin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) and 4 cycles of docetaxel (75 mg/m^2), sequentially. Additionally, she underwent adjuvant radiotherapy consisting of 50 Gy in 28 fractions. The patient has been treated with tamoxifen as adjuvant endocrine therapy and is currently has been taking tamoxifen 20 mg daily for 58 months.

Upon regular gynecologic exam, she developed a right ovarian mass detected on abdominopelvic CT scan and underwent right salpingo-oophorectomy 2 years before the consultation. The lesion was diagnosed as mucinous cystadenoma on final pathology. During a routine follow-up study performed after 6 months, she

did not show any abnormalities suggesting recurrence or metastasis from breast cancer.

She had a history of emergency laparotomy 3 months before a consultation at a different hospital. She developed acute abdominal pain for which she visited the emergency room and was diagnosed to have generalized peritonitis with pneumoperitoneum suggestive of bowel perforation. She underwent emergency laparotomy and small bowel resection and anastomosis. After the operation, she was discharged 2 weeks after surgery due to a prolonged postoperative intestinal obstruction. On physical examination, there was no evidence of abdominal distension and palpable mass with only the anterior midline incision scar being visible. There was no evidence of palpable abnormality on the bilateral breast and axilla. Levels of tumor markers were within normal limits, as follows: carcinoembryonic antigen (CEA), 1.39 ng/ml (normal, $<5.0 \text{ ng/ml}$); carbohydrate antigen (CA) 15-3, 6.4 U/ml (normal, $<28.0 \text{ U/ml}$); CA 125, 24.9 U/ml (normal, $<35.0 \text{ U/ml}$); CA 19-9, 8.61 U/ml (normal, $<35.0 \text{ U/ml}$).

Previous hospital operative records described the lesion as a perforation of the ileum with a large amount of peritoneal spillage, with an indefinite small bowel mass as surgical findings. Operative procedures described that 20 cm of distal small bowel was resected and anastomosed layer by layer.

We referred the resected small bowel specimen block and slide to the pathologic department for review. Slide review of the outside surgical specimen including the small bowel segmental resection was diagnosed as small bowel

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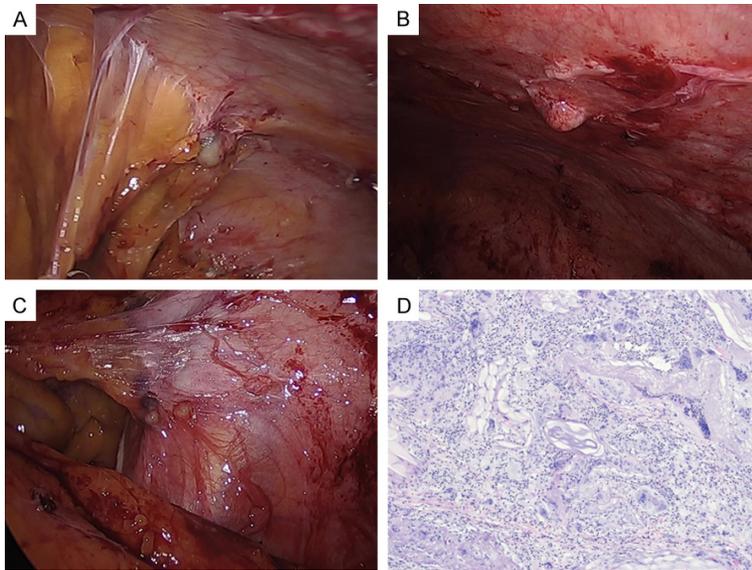


Figure 4. Laparoscopic operative findings (A-C) showed multiple peritoneal wall masses along the right pelvic cavity and peritoneal wall. Omental biopsy showed only foreign body granuloma without definite tumor cells suggesting metastatic or primary malignancy (D, H&E, $\times 100$).

in chronic active inflammation with erosion and perforation, with an indefinite mass suggestive of breast cancer metastasis (**Figure 3B**). The results of immunohistochemistry also showed Pan-CK-negative and GATA3-negative findings.

After a multidisciplinary oncology team meeting, we decided to perform a laparoscopic peritoneal biopsy to ensure accurate diagnosis and to confirm peritoneal metastasis. Laparoscopic surgery was performed by a colorectal surgeon with the patient under general anesthesia, and surgical findings revealed multiple peritoneal wall masses along the right pelvic cavity and peritoneal wall. Additionally, multiple conglomerated masses were seen along the right oophorectomy site and around the small bowel (**Figure 4A-C**). Multiple laparoscopic excisional biopsies were performed for the pelvic masses near the right paracolic gutter, ovary, and omental mass. Intraoperative frozen biopsy revealed chronic inflammation with foreign body granuloma and without malignancy. The postoperative course was uncomplicated and the patient was discharged 3 days after the operation without any complications.

Permanent pathologic results of the peritoneal and omental mass revealed foreign body granuloma with some meal contents. There was no evidence of tumor cells suggesting metastatic

or primary malignancy. Rather, it was suggestive of postoperative inflammatory granuloma associated with small bowel contents relating to a previous small bowel perforation (**Figure 4D**).

After confirming the absence of peritoneal metastasis, she was scheduled for a routine follow-up study for the detection of possible breast cancer recurrence. Since she was still premenopausal at the time and was considered a high-risk patient with stage IIIA as an initial stage, we discussed extended endocrine therapy with tamoxifen up to 10 years. The patient restarted treatment with adjuvant endocrine therapy with tamoxifen 20 mg daily. She is doing

well and is currently on endocrine therapy, with no evidence of breast cancer recurrence.

Discussion

Peritoneal carcinomatosis is diagnosed frequently in several gastrointestinal and gynecological malignancies [5, 7]. It was shown to significantly decrease overall survival, and the occurrence of peritoneal carcinomatosis was traditionally regarded as a terminal condition. The understanding of the biology and the pathways of dissemination of tumors with intraperitoneal spread and the understanding of the protective function of the peritoneal barrier against tumor seeding, the concept of peritoneal carcinomatosis has been changed to locoregional disease in the absence of other systemic metastasis in patients with several gastrointestinal and gynecological malignancies [7]. Accordingly, multimodal treatment including aggressive cytoreductive surgery (CRS), hyperthermic intraperitoneal chemotherapy (HIPEC), and systemic chemotherapy have been proposed and are considered as promising methods to improve loco-regional control of the disease and ultimately to increase survival, especially in patients with colorectal, gastric, and epithelial ovarian cancer [8, 9]. Many studies have reported improved survival outcomes through aggressive locoregion-

al therapy in colorectal and gastric cancer patients with peritoneal carcinomatosis [10, 11].

Metastasis to the peritoneal cavity is relatively rare in breast cancer patients and reported incidence rates are 0.7-2.7% [3, 4]. Breast cancer is the main extra-abdominal primary cause of peritoneal metastasis and it may spread to the mesentery through embolic hematogenous spread. Typically, these tumors involve the antimesenteric margins of the small bowel producing mural nodules with the potential to lead to bowel obstruction or intussusception [5, 7]. According to the results of retrospective analysis of 3096 invasive breast cancer patients, among 9.33% of patients who developed distant metastasis, patients with peritoneal metastasis had the worst survival, comparable with that of brain metastasis [3]. Peritoneal carcinomatosis was an independent risk factor for reduced survival in comparison with other metastatic sites in the study (HR 1.70, 95% CI 1.00-2.90). Another report showed that the median survival of patients with peritoneal metastasis was only 1.56 months (range 0.2-27 months), while the median survival after all distant metastasis was 20.5 months (0.1-125 months) [4]. Patients with metachronous metastases had significantly poorer survival than patients with synchronous metastases [3]. In breast cancer patients with peritoneal metastasis, CRS and HIPEC demonstrated encouraging results in small cohorts. Recently, a preliminary study about aggressive local therapy including CRS and HIPEC for 4 patients with peritoneal metastasis from breast cancer has been reported. Following CRS and HIPEC, the quality of life of each patient was improved and all 4 patients survived for 31, 28, 16, and 52 months, respectively, without disease progression. The 4 cases provide evidence that an integrated therapy of CRS and HIPEC is a promising strategy that could improve the outcomes of patients with breast cancer and peritoneal carcinomatosis [12]. Larger and more robust studies are needed to determine their impact on breast cancer-specific survival.

Regarding the risk factors for peritoneal metastasis among patients affected by breast cancer, high-grade tumor, lobular invasive histology, and advanced TNM stage were reported as

a significant independent predictive factor [3]. Some authors reported that breast cancer patients with mutated *BRCA* genes have a higher prevalence of peritoneal carcinomatosis. This may be interpreted as a new primary malignancy from the ovary, fallopian tube, or peritoneum, which *BRCA*-mutated patients are also predisposed to [13]. Among the patients with abdominal carcinomatosis in women with a history of breast cancer, 74.7% of cases were associated with primary ovary or peritoneal cancer, and only 25.3% of peritoneal metastasis derived from previous breast cancer [14]. Early breast cancer stage and the absence of previous recurrence were predictive of primary ovarian and peritoneal cancer. In our case, the patient was young, had advanced breast cancer, had never experienced a recurrence, and had a surgical history of oophorectomy for an ovarian tumor. Thus, we considered the possibility of abdominal carcinomatosis from the breast or ovary, and there is a need for active histological confirmation. Most peritoneal metastasis from breast cancer is associated with metastases in other organs, and single metastasis to the peritoneal cavity from breast cancer is uncommon [3]. It is reported that the peritoneal metastasis from breast cancer develops late and this late onset may be associated with true delayed metastasis or late metastasis detection [3-6]. In addition to vague and nonspecific abdominal symptomatology, the lack of accurate imaging tests such as CT or PET-CT may also be a cause of late diagnosis. An important tenant of peritoneal carcinomatosis is that any imaging modality may underestimate the true volume and burden of peritoneal carcinomatosis. Typical CT findings of peritoneal metastasis include multifocal discrete nodules to infiltrative masses in the peritoneal cavity, omental haziness, ascites, and peritoneal thickening, nodularity, and enhancement. The frequent locations are dependent on position including peritoneal reflection of the pelvis, lower small bowel mesentery, sigmoid mesocolon, right paracolic gutter, right subphrenic space, and omentum [15]. The diagnostic accuracy of CT for the detection of peritoneal carcinomatosis and the detection of peritoneal implants has improved due to the improvement of CT modality and imaging [15-17]. However, the efficacy of CT for the detection of peritoneal metastasis could be compromised by the small size of tumor

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implants and CT has an important size limit for lesion detection especially in some critical sites like the small bowel walls [15-17]. Sensitivity for CT detection of tumor nodules less than 0.5 cm and 1 cm is reported to be 11% and 25-50%, respectively [18]. The combination of ^{18}F -FDG PET/CT can allow for improvement in the anatomical localization of intra- and extra-pelvic structures. The location of these structures are related with ^{18}F -FDG uptake and thus, can provide more reliable data regarding the nature of the pathological findings. The sensitivity and specificity were reported as 87% and 92%, respectively, in a previous meta-analysis [19]. However, PET-CT has a high rate of false positivity due to tissue inflammation, as well as a high rate of false negatives because of metabolic inactivity of dormant neoplastic cells after chemotherapy [6]. Although it is an exceedingly rare condition and there are many diagnostic difficulties, peritoneal metastasis in breast cancer is a very poor prognostic condition. The diagnostic role of matrix metalloproteinase (MMP)-2 expression and elevated CEA in ascites had been investigated [20]. Confirmatory histological biopsy under exploratory laparotomy or diagnostic laparoscopy must be performed in the presence of suspicious lesions. Diagnostic laparoscopy (DL) allows the surgeon to calculate the extent of disease and assess tumor burden, with less operative time, less morbidity, and mortality compared to laparotomy. DL has demonstrated multiple strengths: evaluation of small bowel mesentery; thorough assessment of the omental bursa, pelvic cavity, diaphragm, and abdominal wall; and allowing peritoneal washings and biopsies if needed to determine the course of treatment. Its areas of inherent weakness pertain to the evaluation of the thickness of diaphragmatic lesions and evaluation of pancreatic or lesser sac involvement; however, with the use of intraoperative laparoscopic ultrasound, these challenges may be overcome [21]. Immunohistochemical (IHC) analysis of peritoneal lesions helps exclude the differential diagnosis. IHC analysis for estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (HER2) on distant metastases demonstrated diagnostic accuracy and is strongly recommended. Staining of gross cystic disease fluid protein 15 (GCDFP-15), regulated by the androgen receptor, was traditionally used for differential diag-

nosis of mammary origin carcinoma. However, it shows relatively low sensitivity (55%-76%) for detecting breast-origin cancer. Recently, GATA binding protein 3 (GATA3) is widely known as mammary cancer and urothelial cancer marker. GATA3, a member of a zinc finger transcription factor family, is crucial for the differentiation of many tissues and an extremely sensitive marker for breast and urothelial carcinomas. GATA3 expression shows 100% positivity in involving breast lobular carcinoma and 96% positivity in breast ductal carcinoma [22]. In the present case, resected small bowel specimen was diagnosed as only chronic active inflammation with erosion and perforation. Pan-CK and GATA3 staining in small bowel showed all negative findings, consistent with no evidence of mammary origin. Additionally, permanent pathologic results of peritoneal mass showed only foreign body granuloma with meal contents. It was suggestive of postoperative inflammatory granuloma associated with small bowel content due to the previous small bowel perforation. After active DL and biopsy, we can conclude that there was no evidence of peritoneal metastasis. The patient was satisfied with the outcome of the treatment and can undergo follow-up tests with confidence. A limitation of this study is that it is not possible to specify the cause of small bowel perforation because this was an emergency surgery conducted at a different secondary hospital and the operative findings could not be fully discussed at the time of the surgery. If there was enough communication for the surgical findings at the time of abdominal surgery, the surgeons could have considered the possibility of diffuse spillage of bowel content associated with bowel perforation and resulting in a peritoneal mass forming a granuloma. However, considering that the patient was young with advanced stage breast cancer patient at the time of diagnosis, that peritoneal metastasis of breast cancer is rare but possible, and the prognosis is very poor, active diagnostic biopsy is thought to be a good approach to confirm the absence of metastasis instead of observation and follow-up using CT or PET-CT imaging.

In conclusion, peritoneal metastasis is a rare condition with many diagnostic difficulties in breast cancer and may result in a very poor prognosis. Surgeons must keep in mind the possibility of peritoneal metastasis in suspect-

ed cases, and an aggressive diagnostic approach including DL and active pathologic analysis with IHC studies should be performed to ensure accurate diagnosis and timely active treatment.

Disclosure of conflict of interest

None.

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