



Appendiceal Metastasis of Breast Cancer and Recurrent Acute Appendicitis: Case Report and Literature Review

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Abstract

Breast cancer is among one of the most common forms of cancer that affects women in Japan, with 94,000 new cases reported annually. The common sites of breast cancer metastasis include the bone, liver, lungs, lymph nodes, and brain, while metastasis to the appendix is extremely rare. Here, we report a case of breast cancer with multiple metastases in the bones, brain and lymph nodes, with concomitant carcinomatous pericarditis in a 54-year-old woman. While undergoing chemotherapy, she experienced recurrent acute appendicitis 5 times over 9 months, which interfered with her chemotherapy schedule. Therefore, a laparoscopic interval appendectomy was performed. The tumor cells from the resected appendix and those of the breast carcinoma were compared immunohistochemically. Both tissues were positive for Estrogen Receptor (ER) and Progesterone Receptor (PR) and negative for epidermal growth factor receptor 2 (HER2). Thus, appendiceal metastasis of breast cancer was pathologically diagnosed. After the appendectomy, her symptoms were alleviated and she was able to maintain her chemotherapy schedule.

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On literature review, we found only 18 reported cases of appendicitis caused by breast cancer metastasis; however, there were no reports of frequent recurrent appendicitis. Although rare, it is necessary to consider the possibility of appendiceal metastasis when a patient with breast cancer presents with frequent recurrent appendicitis.

Keywords: Appendicitis; Breast cancer; ER; HER2; CT

Introduction

In Japan, breast cancer is one of the most common cancers among women, and approximately 94,000 new cases are reported annually. The bone, liver, lungs, lymph nodes and brain are well-known sites for metastasis of breast cancer, whereas metastasis to the gastrointestinal tract or appendix is extremely rare. While reviewing the literature, we identified only 2 and 16 cases of appendiceal metastasis from the Ichu-shi Japanese Centra Revuo Medicina Web and PubMed database, respectively.

We present a case of frequent recurrent acute appendicitis that occurred while undergoing chemotherapy for breast cancer.

Case Presentation

The patient was a 54-year-old woman with recurrent breast cancer combined with subcutaneous, multiple bone, brain, and pericardial metastases. She provided written informed consent to publish her case. Twelve years ago, she underwent left partial mastectomy at another clinic after the diagnosis of ductal carcinoma *in situ* with comedonecrosis. Within a year, the carcinoma recurred and she underwent left mastectomy with axillary dissection. Histologic studies revealed Invasive Ductal Carcinoma (IDC) of size 5.5 cm that had invaded the fatty tissue. The histological grade was assessed as grade 2. Immunohistologically, the tumor cells were positive for Estrogen Receptor (ER) and Progesterone Receptor (PR) and negative for Human Epidermal Growth Factor Receptor 2 (HER2). Metastasis to the axillary lymph nodes was observed in 4/21. After the second surgery,

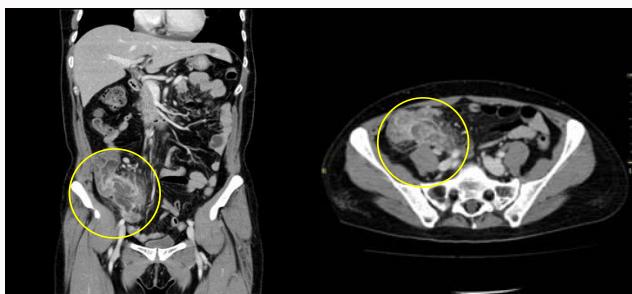


Figure 1A: Acute appendicitis with abscess (circle).



Figure 1B: Acute appendicitis with accompanying wall thickness at the root level (arrow).

Figure 1: Abdominal Computed Tomography (CT) images.

she received adjuvant chemotherapy, endocrine therapy, and post-mastectomy radiation therapy at our breast center. While undergoing adjuvant endocrine therapy, she developed local recurrence of the carcinoma in the subcutaneous tissue of her left breast, which was revealed to be an IDC of size 7 mm; immunohistological findings were as follows: Positive for ER and negative for PR and HER2. Nine years after the first operation, she developed bone metastasis and was started on fulvestrant and denosumab, followed by palbociclib. On account of the bone metastasis, her treatment was changed to medroxyprogesterone acetate; this resulted in brain metastasis and local recurrence of the carcinoma in the subcutaneous tissue of the left breast. After undergoing Gamma Knife radiosurgery for the brain metastasis and local resection of the subcutaneous tissue, she began chemotherapy with capecitabine.

One month later, she complained of lower right abdominal pain, chills, and fever. We performed a Computed Tomography (CT) examination, and acute appendicitis with abdominal abscess and possible perforation was diagnosed (Figure 1). Antibiotic therapy was recommended along with hospitalization owing to the abscess. At almost the same time, new metastases to the mediastinal and hilar lymph nodes, as well as pericardial metastasis, were detected. The appendicitis symptoms were improved by medication; however, 1 month later, it relapsed and was accompanied by increased pericardial infusion, resulting in cardiac tamponade with the following features: Tachycardia, shortness of breath, and right ventricular collapse. Pericardiocentesis was then required. Under cytological examination, the pericardial infusion was diagnosed as carcinomatous pericarditis from breast cancer.

Subsequently, the chemotherapeutic agent was changed from capecitabine to paclitaxel and bevacizumab, and the pericardial infusion was controlled; however, appendicitis recurred twice. Bevacizumab, which may result in bowel perforation, was thought

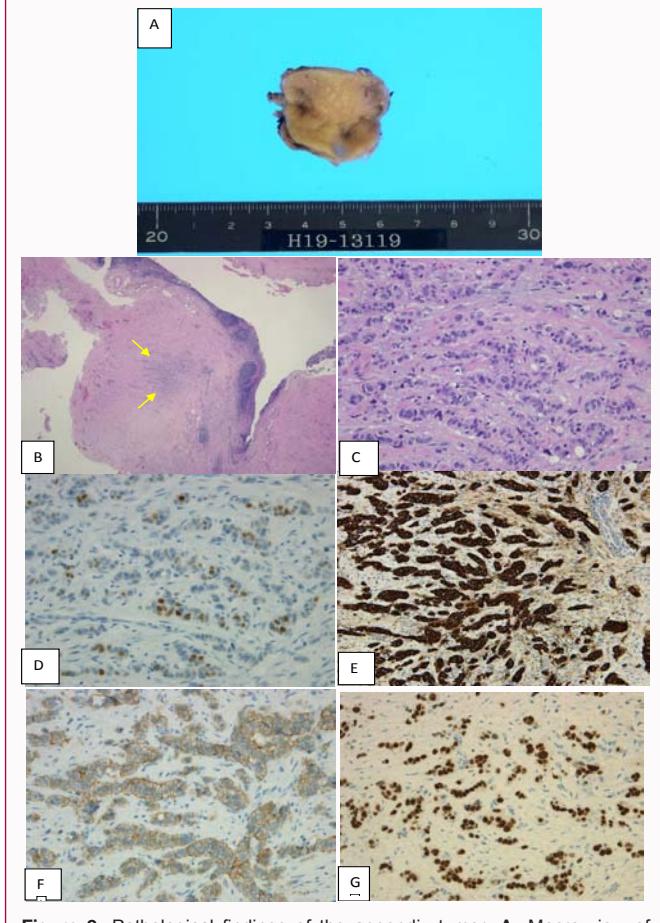


Figure 2: Pathological findings of the appendix tumor. **A:** Macro view of the appendix. **B:** Neoplastic cells observed in the muscularis propria of the appendix (arrows) [Hematoxylin and eosin (HE) stain, 1.25x]. **C:** Neoplastic cells in the muscularis propria [HE stain, 20x]. **D:** 20% of tumor cells were ER-positive [nuclear staining, 20x]. **E:** AE1/AE3-positive [20x]. **F:** E-cadherin-positive [membranous staining, 20x]. **G:** GATA3-positive [20x].

to have exacerbated the appendicitis; therefore, the agent was switched to eribulin. The patient then experienced another episode of appendicitis that interrupted the schedule of intensive dose chemotherapy. Hence, an appendectomy was considered. Because the acute appendicitis episodes recurred 5 times in 9 months, we also considered other diseases, such as appendiceal myxoma, as the cause of appendicitis. At the fifth recurrence, we observed thickening of the appendiceal wall and swelling of the appendix (Figure 1B), and appendiceal tumor was suspected.

Initially, surgery was considered risky considering the carcinomatous pericarditis and administration of bevacizumab. However, the pericardial infusion was still under control, despite changing the anti-cancer agent. Furthermore, 8 weeks had passed since the final administration of bevacizumab and the patient had recovered from the nadir of neutropenia; hence, we performed laparoscopic interval appendectomy.

Intraperitoneal findings revealed no ascites or metastatic dissemination. The appendix was adherent to the small pelvis, right ovary, and right fallopian tube. The adhesion was detachable, but the appendix itself was too fragile to be torn from the root. However, there was no spillage of appendiceal contents, and the amputation stump of the cecum was safely ligated.

Table 1: Details of cases published on breast cancer metastasis to the appendix.

Author/year of study/location	Age (years)	Time after diagnosis (years)	Metastasis except appendix	Perforation	Operation	Pathology
Oldfield, 1946, Leeds UK [7]	40	3	No known metastasis	Yes	Appendectomy	IDC-like
Capper and cheek, 1956, Texas, USA [8]	36	1	Yes (ovaries)	Not mentioned	Appendectomy	IDC-like
Latchis and Canter, 1966, Washington DC USA [9]	45	6	Yes (chest wall, lungs)	Not mentioned	Appendectomy	IDC-like ILC-like
Burney et al. [10], 1974, Connecticut, USA	35	1.3	Yes (brain, liver)	Yes	Appendectomy	Not mentioned
Burney et al. [10], 1974, Connecticut, USA	73	3	Yes (bone, peritoneum)	Yes	Appendectomy	Not mentioned
Sugiya et al. [11], 1988, Osaka, Japan	65	9	Yes (skin, liver, peritoneum, pleura)	Yes	Appendectomy	IDC-like
Solis et al. [12], 1986, New York, USA	60	5	No known metastasis	No	Appendectomy	IDC-like
Halliday, 1987, London, UK [13]	57	0	No known metastasis	No	Right hemicolectomy	Poorly differentiated adenocarcinoma
Maddox. 1990, Cardiff, UK [14]	65	5	Yes	No	Right hemicolectomy	IDC-like
Phillipart et al. [15], 2000, Brussels, Belgium	37	Not mentioned	No known metastasis	Yes	Appendectomy	IDC-like ILC-like
Phillipart et al. [15], 2000, Brussels, Belgium	75	Not mentioned	No known metastasis	No	Right hemicolectomy	IDC-like ILC-like
Varga et al. [16], 2005, Nyíregyháza, Hung.	45	Not mentioned	Not mentioned	Yes	Appendectomy	IDC-like
Pigolkin et al. [17], 2008, Russia	60	1.5	No known metastasis	Not mentioned	Article in Russian	Not mentioned
Dirksen et al. [18], 2010, Pennsylvania, USA	76	Not mentioned	No known metastasis	Yes	Appendectomy	ILC-like
Iwamoto et al. [19], 2014, Tokyo, Japan	58	10	No known metastasis	No	Appendectomy	IDC-like
Tahara et al. [20], 2015, Boston, USA	36	6	Yes (chest wall, peritoneum)	No	Appendectomy	IDC-like
Ng CYD, et al. [21], 2018	59	2	No known metastasis	Yes	Right hemicolectomy	IDC-like
Numan et al. [22], 2019, Kansas, USA	44	3	Yes (bone, lung, ovary)	No	Appendectomy Ileocectomy	ILC-like
The present case	54	13	Yes (bone, brain, pericardial)	No	Appendectomy	IDC-like

IDC: Invasive Ductal Carcinoma; ILC: Invasive Lobular Carcinoma

Table 1 was prepared by modifying the tables in articles cited in the reference list [20,21].

The macro view of the resected appendix, measuring 3.0 cm × 2.9 cm, was atrophic with liquid pooling accompanied by obstruction at the root of the appendix. In the microscopic view (Figure 2A); there were no abnormal findings in the mucosal epithelium. No evidence of scar from perforation was observed. Epithelial neoplastic cells were observed in the muscularis propria in 1 out of 8 slides. Immunohistochemically, the tumor cells were positive for ER, PR, cytokeratin-multi AE1/AE3, GATA3 and E-cadherin, and negative for HER2 (Figure 2B-2G). These findings were similar to that of the mastectomy specimen (IDC, positive for ER and PR and negative for HER2). Thus, the neoplastic cells of the appendix were identified as breast cancer metastases. The patient recovered uneventfully after the operation and was discharged on postoperative day 15.

Discussion

Acute appendicitis induced by appendiceal metastasis is extremely rare. Connor et al. [1] reported in a review of 7,970 appendectomy cases in 16 years, 74 patients (0.9%) with appendiceal tumors were identified: 42 with carcinoid, 12 with benign, and 20 with malignant tumors. Primary malignant tumor of the appendix was found in 0.1% of all appendectomies. Secondary malignant disease was identified in the appendix of 11 patients, most commonly (55%) those with primary colorectal disease, and the most common presentation was appendicitis (49%).

In another review of 7,759 appendectomy cases in Korea in 7 years, 180 cases of appendiceal malignancies were reported, of

which 139 cases (77.2%) were secondary appendiceal tumors [2]. In this report, the ovary was the most common primary site of origin, followed by the colon and stomach [2]. In these two reports, the breast was not mentioned as a primary site for secondary malignant tumor of the appendix.

Regarding secondary tumors of the Gastrointestinal (GI) tract, Washington et al. reviewed 108 autopsy cases over 14 years. They reported that the most common primary tumors at autopsy were from the lung (21 cases), gynecologic organs (18 cases), breast (14 cases), and pancreas (9 cases). In the retrospective study of 73 breast cancer patients with metastasis to the GI tract, peritoneum, or both, the distribution of metastatic disease was as follows: esophagus (8%), stomach (28%), small intestine (19%), and colon and rectum (45%). In this study, the frequency of appendiceal metastasis was not mentioned [3].

IDC and Invasive Lobular Carcinoma (ILC) have different patterns of metastatic spread. ILC frequently causes metastatic disease of the GI tract (2% to 5.7%), in contrast to low GI tract metastasis caused by IDC (0.2% to 0.4%) [4-6]. Despite this, 10 among 16 cases of appendiceal metastatic tumors of breast cancer were originally IDC (Table 1) [7-22].

Appendiceal tumors mostly presented as acute appendicitis (49%), and 9.5% were found incidentally [1]. Appendiceal neoplasms are rare and of many types, and it is difficult to diagnose metastatic tumor as a cause of appendicitis.

The effectiveness of chemotherapy is affected by dose intensity, defined as the amount of drug administered per unit of time, typically reported in mg/m²/week. This patient's chemotherapies were prolonged because of appendicitis recurrence, which resulted in a decreasing level of dose intensity. Initially, surgery was thought to be controversial because of pericardial perfusion. Furthermore, because of the use of bevacizumab, which carries the risk of GI bleeding and perforation as well as delayed wound healing, the operation was postponed. However, it was performed to restore the dose intensity of chemotherapy and was successful systematically.

It is necessary to consider that the adverse effects of chemotherapy, like neutropenia, may worsen acute appendicitis and its other adverse effects on the GI tract may mimic the symptoms of acute appendicitis [23]. Considering this patient had 5 episodes of acute appendicitis within 9 months, the metastatic appendiceal tumor was regarded as the most influential factor for relapsing appendicitis. Nevertheless, the neoplastic cells were localized in only one slice. There remain some possibilities that the healing process was observed in the microscopic views and the effect from appendiceal tumor to appendicitis was limited. However, after the operation, the patient was able to maintain a regular schedule of chemotherapy.

Appendiceal metastasis of breast cancer though rare, should be considered when the patient has a history of breast cancer and recurrent appendicitis.

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