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Colonic Metastasis from Breast Cancer: A Case Report and Review of the Literature

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Abstract. *Background: Breast cancer often metastasizes to the lungs, bones, liver, and brain, colon metastasis from breast cancer (CMBC) is extremely rare. Case Report: The patient was a 63-year-old female. Mastectomy had been performed for breast cancer (pStage IIB) 15 years earlier at another hospital. Metastasis to the lumbar spine had been detected 4 years prior to referral to us and the patient had undergone hormonal therapy with an aromatase inhibitor. Furthermore, early primary sigmoid colon cancer had been endoscopically resected 2 years before referral. The patient was diagnosed with cancer recurrence in the colon at follow-up examinations performed 2 years after that endoscopic resection. After referral to our hospital, laparoscopic sigmoidectomy was performed. Based on the histopathological examination and immunohistological staining results (positive for cytokeratin 7, GATA-binding protein 3, estrogen receptor and human epidermal growth factor receptor-related 2 (2+); negative for cytokeratin 20, progesterone receptor, E-cadherin, gross cystic disease fluid protein 15 and caudal-related homeobox 2) the final pathological diagnosis was CMBC. Conclusion: Although extremely rare, the possibility of CMBC should be considered in the case of colonic tumors in patients with a history of breast cancer.*

Breast cancer is a common cancer with a yearly worldwide incidence of approximately 2,090,000 new cases and 630,000 deaths (1). The number of patients with breast cancer is increasing; however, its prognosis is better than that of other cancer types due to recent advances in surgical procedures, radiation, chemotherapy, and hormone therapy (2). Breast cancer generally metastasizes to the lungs, bones, liver, and brain, rarely to the gastrointestinal (GI) tract (3). In most cases to the GI, metastasis occurs in the stomach or small intestine, with colonic metastasis from breast cancer (CMBC) being extremely rare. We herein report a case of metastasis to the colon 15 years after mastectomy, with a review of the pertinent literature.

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Key Words: Breast cancer, colon metastasis, distant metastasis, laparoscopic sigmoidectomy.

Case Report

We received a referral for a 63-year-old female patient with a history of right mastectomy for breast cancer (pT2, N1a, M0, pStage IIB) (4) treated 15 years previously at another hospital. She subsequently received adjuvant chemotherapy (cyclophosphamide and fluorouracil) (5) and hormonal therapy (tamoxifen) (6) as adjuvant therapy. Eleven years after that surgery, metastasis to the lumbar spine (L4 and L5) as well as to axillary lymph nodes was detected, for which the patient underwent hormonal therapy with an aromatase inhibitor (7). Thirteen years after surgery, early primary colonic cancer was detected in the sigmoid colon by follow-up positron-emission tomography (PET) and a lower GI endoscope examination, for which endoscopic mucosal resection was performed. The results of a pathological examination confirmed well-differentiated adenocarcinoma with a submucosal depth, although the resection margins were negative. No additional resection of the sigmoid colon was performed because multiple breast cancer metastases under treatment were considered to be a prognostic factor. The patient underwent regular follow-up and received hormonal therapy. Fifteen years after the right mastectomy, PET performed during the follow-up showed an abnormal accumulation in the sigmoid colon, and wall irregularity, thickening and entire circumferential stenosis of the sigmoid colon with the area around the markings of the previous endoscopic mucosal resection being confirmed upon a lower

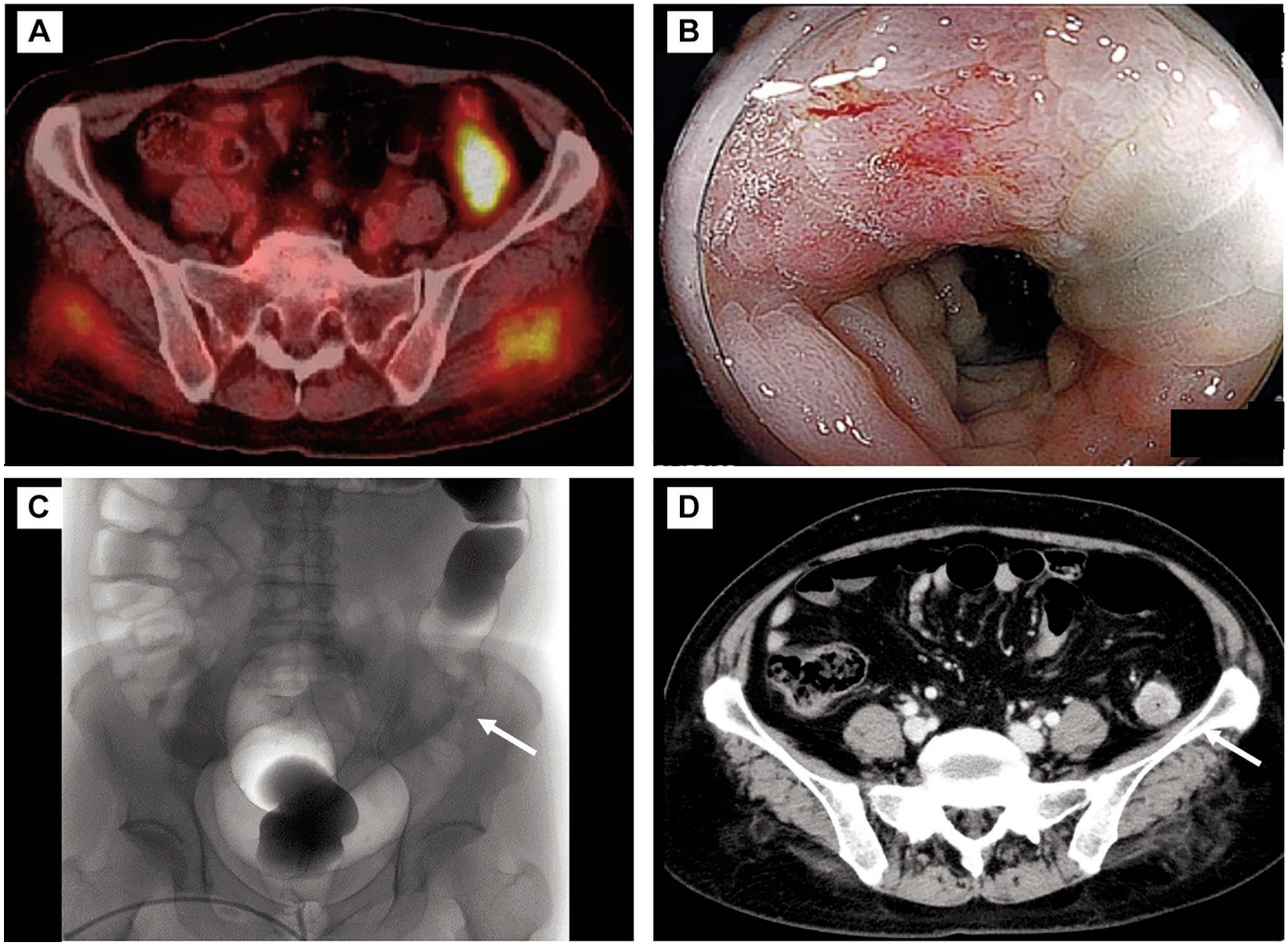

Figure 1. *A: An abnormal accumulation of fluorodeoxyglucose in the sigmoid colon positron-emission tomography–computed tomography. B: Irregularly thickened wall with stenosis on the anal side at the site of endoscopic mucosal resection conducted in 2016. C: Stenosis of the entire circumference (arrow) associated with a 3-cm wall irregularity. D: Wall thickening (arrow) associated with the contrast effect on the sigmoidal colon.*

GI endoscope examination (Figure 1A-C). Computed tomography (CT) of the abdomen revealed thickening around the entire circumference of the wall in the sigmoid colon; however, neither an increased fat concentration nor swelling of the regional lymph nodes was confirmed (Figure 1D). The laboratory data were as follows: Carcinoembryonic antigen: 42.8 ng/ml, and cancer antigen 19-9: 6.8 U/ml. Biopsy identified adenoma; however, no malignant components were found. Based on the results of CT, PET, colonoscopy, elevated carcinoembryonic antigen, and the previous medical history, a comprehensive diagnosis was the relapse of sigmoid colon cancer, and after referral to our hospital, laparoscopic sigmoidectomy was performed.

Surgery was performed in the lithotomy position under general anesthesia and with five ports. An examination of the abdominal cavity revealed no obvious liver or peritoneal metastasis, and a tumor was confirmed on the oral side of the sigmoid colon (Figure 2A). The tumor had partially penetrated the abdominal wall (Figure 2B). Arteries were ligated at the root of the left colic artery and sigmoid artery to preserve blood flow in the superior rectal artery. At the position at which it had partially penetrated the abdominal wall, the tumor was excised together with the abdominal wall. Surgical margins were taken 10 cm from the tumor towards the mouth as well as on the anal side and a specimen was extracted (Figure 2C). The colon was reconstructed by functional end-to-end anastomosis.

According to a histopathological examination, tumor cells were solitary and propagating in a funicular structure. A further histopathological examination showed low adhesion between tumor cells, and cells possessed bright cellular bodies from acidophiles. Nuclei were small and round. Moreover, tumor cells had mainly propagated in the proper muscular layer, subserosa, and part of the submucosa, and there was a small

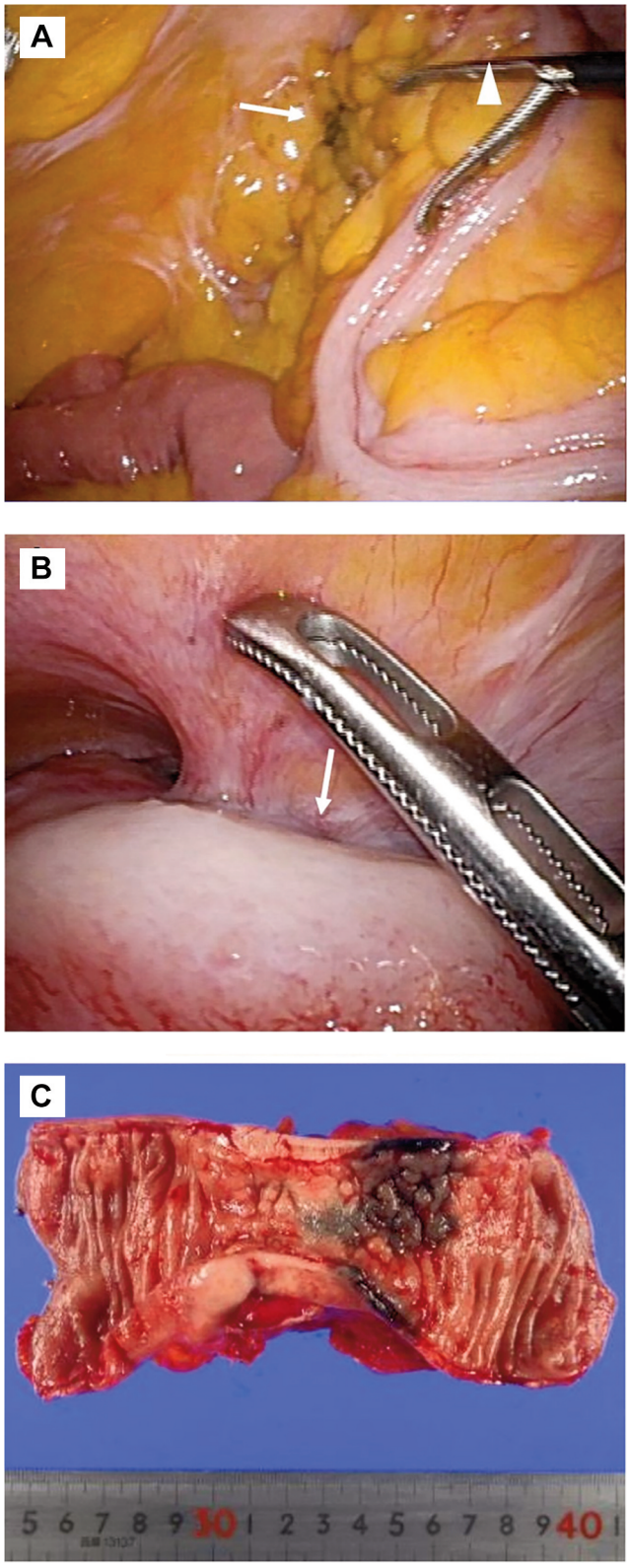

Figure 2. *A: Ink mark on the sigmoid colon (arrow), and tumor (arrow head). B: Tumor penetration into the abdominal wall (arrow). C: Resected specimen.*

amount of penetration into the mucosa. The exposure of tumor cells at the membrane surface was confirmed in some fields (Figure 3A-C). Immunohistochemical staining revealed that tumor cells were positive for cytokeratin 7, GATA-binding protein 3, estrogen receptor and human epidermal growth factor receptor-related 2 (2+); negative for cytokeratin 20, progesterone receptor, E-cadherin, gross cystic disease fluid protein 15 and caudal-related homeobox 2 (Figure 3D-I). Based on morphological and immunostaining results, metastasis infiltrating the lobular carcinoma that had originated from the mammary glands was suspected. Therefore, we examined the excised breast cancer specimen from 15 years earlier, and found that cancer cells were solitary or propagating in a funicular structure with stromal infiltration, as observed in colon tissue; moreover, the nuclei of cells had clear cytoplasm and relatively round structures (Figure 3J). The pathological morphologies of breast cancer tissue and the present resected sigmoid colon specimen were very similar. Breast cancer specimens had been shown to be estrogen receptor- and human epidermal growth factor receptor 2-positive (1+), progesterone receptor-negative, and immunohistochemical staining under the same conditions was negative for E-cadherin (Figure 3K), which was the same as the immunostaining result for the colon specimens. Therefore, the patient was diagnosed with CMBC due to invasive lobular carcinoma (ILC).

The patient had no complications and was immediately discharged from hospital. One month after surgery, chemotherapy was resumed using fulvestrant and abemaciclib (8). Two years after sigmoidectomy, the disease was stable with neither growth of the remaining lesion nor the appearance of new metastatic lesions.

Discussion

Breast cancer is the most prevalent cancer for women and its prevalence has been increasing in recent years (1). Distant metastasis of breast cancer is primarily to the lungs, bones, liver, and brain; however, metastasis to the GI tract is relatively rare (3). CMBC is extremely rare. McLemore (9) *et al*. reported 24 cases among 12,001 patients diagnosed with breast cancer between 1985 and 2000 with subsequent metastasis to the colon.

The tissue form of breast cancer has the highest number of invasive ductal carcinomas (IDCs). ILCs are classified as a special type of breast cancer in Japan, and are relatively rare in Europe and the United States, accounting for between 8% and 14% of all breast cancer cases (10). Common sites of metastasis according to the histological type of breast cancer are the lungs and pleura for IDCs. On the other hand, the most ILCs are metastasis to the internal genitalia, such as the ovaries or uterus, along with the peritoneum, retroperitoneum, adrenal glands, and bone marrow. The rate of metastasis to the GI tract was previously reported to be approximately 1.1% for

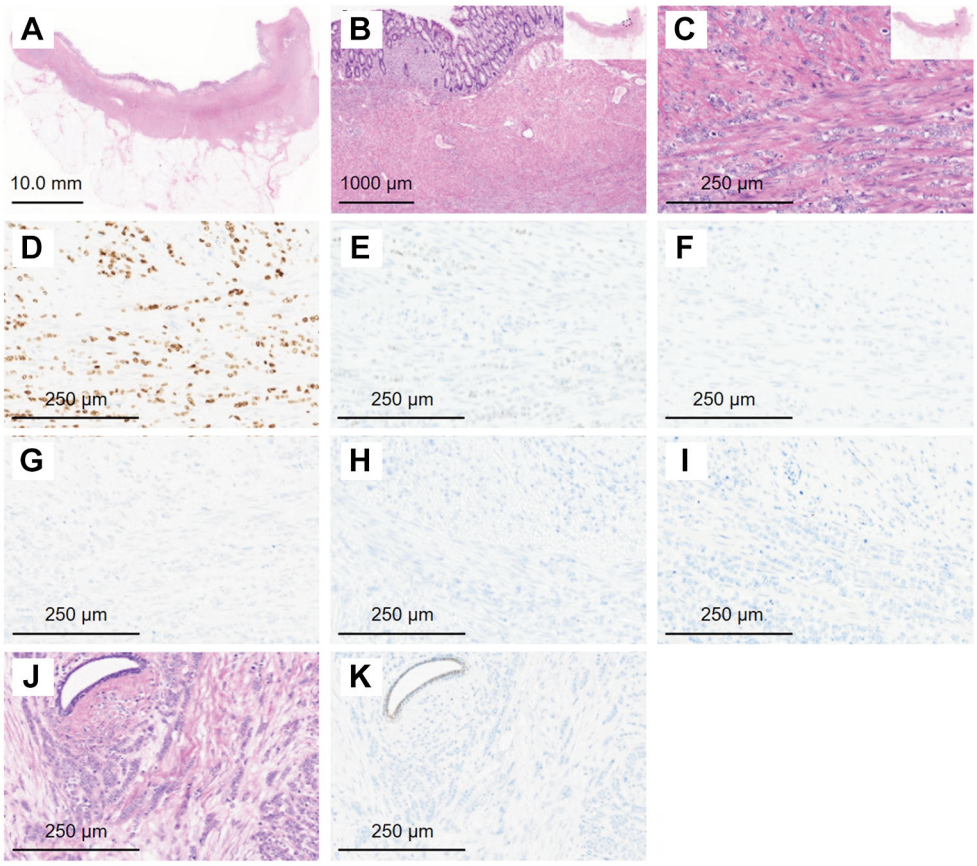

Figure 3. *Histological examination of the resected sigmoid colon specimen. A-C: Hematoxylin and eosin staining as seen under increasing magnification. D-I: Immunohistochemical staining. The results were positive for GATA-binding protein 3 (D) and estrogen receptor (E), and negative for progesterone receptor (F), E-cadherin (G), gross cystic disease fluid protein 15 (H) and caudal-related homeobox 2(I). J: Hematoxylin and eosin staining of the previous primary breast cancer specimen. K: Immunohistochemical staining of previous primary breast cancer specimen showing it was negative for E-cadherin.*

IDCs and 4.5% for ILCs (10). Among breast cancers, ILC frequently metastasizes to the GI tract, and the histological type of primary breast cancer in this case study was also ILC.

Metastasis occurs through hematogenous, lymphogenous, and surgical dissemination pathways. Since no peritoneal nodes or hydroperitonea was confirmed during surgery in the present case, it is unlikely that dissemination had occurred. Previous relapse at the lymph nodes, and venous invasion and lymphatic invasion were pathologically confirmed; therefore, we were unable to establish whether CMBC was hematogenous or lymphogenous.

Chang *et al*. reported that a long period of time was sometimes required for metastasis to the GI tract after breast cancer surgery (11); however, the underlying mechanisms remain unclear. We searched PubMed and, to the best of our knowledge, only 15 cases were reported from 2010, including the present case, for the surgical resection of CMBC 10 years or more after primary breast cancer resection (Table I) (12-25). In these reports, and the present case, a long period of time had elapsed following breast cancer surgery, which made it difficult to diagnose CMBC prior to its resection.

To diagnose CMBC, it is important to make a comprehensive diagnosis based on GI endoscopic imaging and pathological findings by biopsy. In the literature, five cases of CMBC were diagnosed preoperatively (Table I), all of which were diagnosed based on GI endoscopic imaging and pathological findings. The imaging findings of metastatic colon cancer based on the findings of lower GI series examinations are important and classified as convergent, exclusive, or diffuse. Under this classification, breast cancer metastasis is mostly diffuse and characterized by stenosis and hardening, similar to primary diffuse invasive carcinoma. In lower GI endoscopic examinations, the macroscopic appearance of metastatic colon cancer may be different from primary cancer because the mucosal surface may be normal (26). Pathological findings from mucosal biopsies are very valuable findings, but

Table I. *Reported cases of colorectal metastasis from breast cancer (CMBC).*

Year (Ref)	Age, years*	Primary tumor	Time to recurrence in colorectum, years	Preoperative diagnosis	Surgery	Status
2010 (12)	54	IDC	14	CMBC or transverse colon cancer	Right hemicolectomy	10 Months alive
2011 (13)	61	ILC	17	Colitis	Hartmann's resection	ND
2011 (14)	80	ILC	25	Sigmoid colon cancer	Hartmann's resection	Died after 9 Months
2012 (15)	62	ILC	24	Rectal cancer	Low anterior resection	ND
2012 (16)	52	IDC	16	CMBC	Ascending colon partial colectomy	Died after 8 Months
2013 (17)	63	ILC	17	Inconclusive	Hartmann's resection	12 Months alive
2014 (18)	70	ILC	10	Ascending colon cancer	Right hemicolectomy	2 Years alive
2014 (19)	69	ILC	18	Neoplastic perforation	Hartmann's resection	12 Months alive
2015 (20)	63	IDC and ILC	23	CMBC	Right hemicolectomy	ND
2015 (21)	72	ILC	11	CMBC	Sigmoidectomy	2 Years alive
2016 (22)	50	IDC	12	CMBC	Sigmoidectomy	12 Months alive
2016 (23)	75	IDC	10	CMBC or transverse colon cancer	Right hemicolectomy	5 Months alive
2018 (24)	67	ILC	14	CMBC	Right hemicolectomy	7 Months alive
2018 (25)	68	IDC	15	Volvulus	Right hemicolectomy	ND
Current	63	ILC	15	Sigmoid colon cancer	Sigmoidectomy	2 Years alive

IDC: Invasive ductal carcinoma; ILC: invasive lobular carcinoma; ND: not described. *At diagnosis and at the time of colorectal surgery.

may be inadequate for diagnosis if not performed properly because of technical limitations in approaching tumors that penetrate the serous side of the colon. In the present study, a lower GI series examination indicated stenosis, CT confirmed thickening of the wall, and PET showed an abnormal accumulation; however, tumor cells were not confirmed in a biopsy specimen. In the pathological examination after surgery, tumor cells had mainly propagated in the proper muscular layer, subserosa, and part of the submucosa. A small amount of penetration into the mucosa was noted, and the exposure of tumor cells at the mucosal surface was confirmed in a few fields. Therefore, mucosal biopsy prior to surgery was insufficient for a diagnosis in our case. This result confirmed previous findings showing that a diagnosis using endoscopic ultrasound-fine-needle aspiration was effective when a diagnosis was not possible due to an insufficient specimen. Endoscopic ultrasound-fine-needle aspiration may be considered for patients with colonic neoplasm not diagnosed by mucosal biopsy and with a previous history of breast cancer.

The present case was asymptomatic at the time of surgery; however, there were findings of stenosis in the lower GI series examination, and symptoms of stenosis may have appeared in the future. Therefore, even if an accurate diagnosis of CMBC prior to surgery had been made, surgery would still have been required. However, an accurate diagnosis may lead to other treatment strategies, such as radiation, chemotherapy, and sigmoidectomy without lymph node dissection. Therefore, a detailed examination and well-considered treatment strategy need to be carefully decided in cases of colonic tumors in patients with a previous history of breast cancer.

Conclusion

We herein report our encounter of an extremely rare case of breast cancer metastasis to the colon 15 years after mastectomy. CMBC sometimes requires a long period of time to be identified. A detailed examination and well-considered treatment strategy need to be carefully decided in cases of colon tumors with a previous history of breast cancer.

Conflicts of Interest

The Authors declare that they have no conflicts of interest or competing interests.

Authors' Contributions

H. Inoue wrote the article and acquired the images. H. Inoue and T. Arita contributed to the discussion and interpretation for this article. H. Inoue and T. Arita, Y. Kuriu, H. Shimizu and J. Kiuchi were in charge of the treatment, and all Authors determined the treatment plan through preoperative conference. Y. Kuriu and E. Otsuji carried out critical revision. All Authors read and approved the article.

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