

[CASE REPORT]

Delayed and Synchronous Recurrence of Breast Cancer Metastases in Multiple Organs

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Abstract:

The most common sites of breast cancer metastasis include the lymph nodes, bones, lungs, liver, and brain. Gastrointestinal tract metastasis is rarely seen, and hypopharyngeal metastasis is extremely rare. We herein report a case of late distant recurrence of breast cancer and synchronous metastasis to the hypopharynx, stomach, ileum, bones, and lymph nodes almost 24 years after surgery. To our knowledge, this is the first case of synchronous metastasis to the hypopharynx, gastrointestinal tract, and other organs, especially after a long interval following primary mastectomy.

Key words: breast cancer, gastrointestinal tract, hypopharynx, immunohistochemistry, metastasis, late recurrence

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Introduction

Breast cancer is one of the most frequently diagnosed cancers among women (1). The most common sites of breast cancer metastasis include the lymph nodes, bones, lungs, liver, and brain. Gastrointestinal (GI) tract metastasis is rarely seen (2, 3), and hypopharyngeal metastasis is extremely rare. Late metastasis or recurrence of breast cancers after more than five years has not been uncommon in previous reports (4, 5). However, multiple organ recurrence synchronously after more than 20 years appears to be very rare (6).

We herein report a case of late distant recurrence of breast cancer and synchronous metastasis to the hypopharynx, stomach, ileum, bones, skin, and lymph nodes, almost 24 years after surgery. To our knowledge, this is the first case of synchronous metastasis to the hypopharynx, GI tract, and other organs, especially after a long interval following primary mastectomy. In addition, we conducted a literature analysis of the endoscopic images of gastric metastasis reported in Japan.

Case Report

A 69-year-old woman was referred to our hospital with a skin rash in the cervical region without subjective symptoms (Fig. 1A). She had a history of bilateral breast cancer that had been surgically resected 24 years previously at another hospital. Unfortunately, information regarding the histological type of the resected specimen was inaccessible. Laboratory data showed the following values: peripheral white blood cell count, 7,860/ μ L; hemoglobin, 13.4 g/dL; platelet, 8.6×10^4 / μ L; total protein, 7.4 g/dL; albumin, 3.7 g/dL; aspartate transaminase, 58 U/L; alanine aminotransferase, 31 U/L; alkaline phosphatase, 638 U/L; C-reactive protein, 0.74 mg/dL; carcinoembryonic antigen, 15.4 ng/mL, carbohydrate antigen 19-9, 34 U/mL; and carbohydrate antigen 15-3, 61.1 U/mL. Contrast-enhanced computed tomography (CT) revealed swelling in the supraclavicular, axillary, and para-aortic lymph nodes (Fig. 1B). Bone scintigraphy showed the diffuse accumulation of ^{99m}Tc-hydroxymethylene diphosphate in the spine, ribs, sternum, pelvic bone, and skull (Fig. 1C). Esophagogastroduodenoscopy revealed a semi-pedunculated lesion in the left piriform sinus of the hypopharynx (Fig. 2A) and multiple, reddish, mildly elevated

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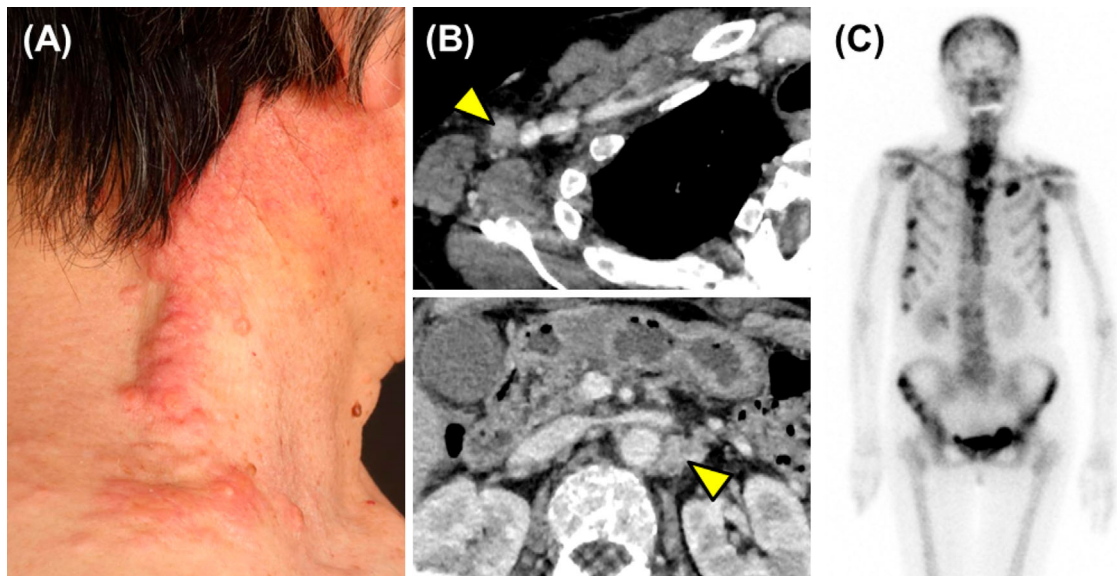


Figure 1. The skin rash in the cervical region of the patient (A). Contrast-enhanced computed tomography shows swelling in multiple lymph nodes (B). Bone scintigraphy shows a diffuse accumulation of ^{99m}Tc -hydroxymethylene diphosphate in the spine, ribs, sternum, pelvic bone, and skull (C).

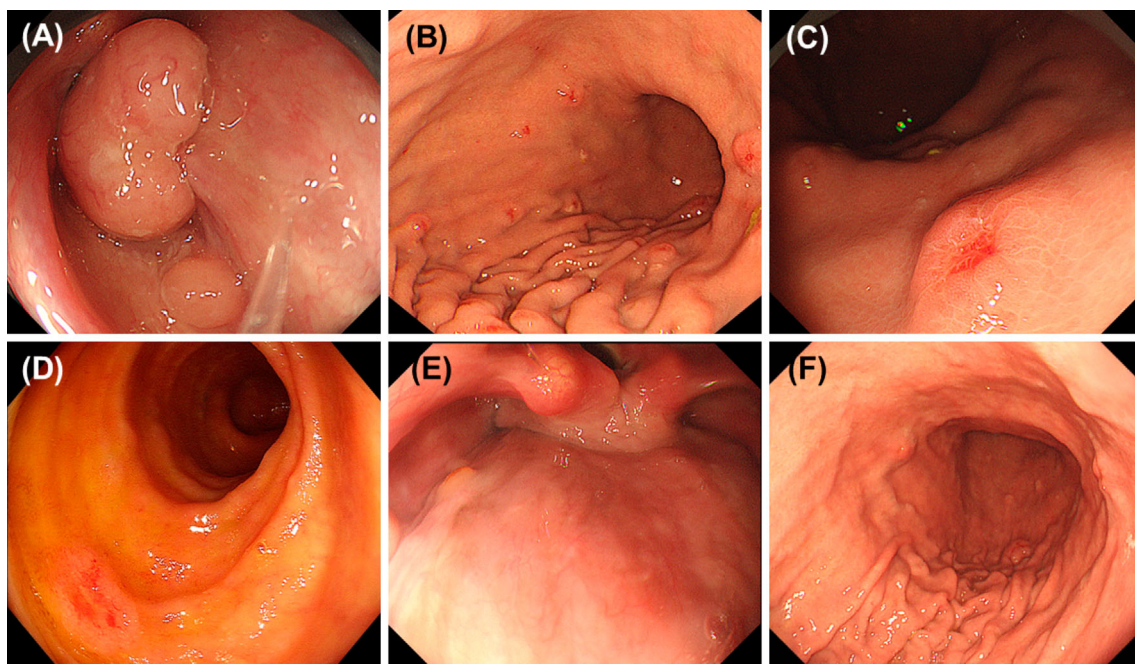


Figure 2. Esophagogastroduodenoscopy reveals a semi-pedunculated lesion in the left piriform sinus of the hypopharynx (A), as well as multiple, reddish, punctate lesions with mild elevation in the gastric body (B, C). Colonoscopy shows a reddish elevated lesion in the terminal ileum (D). The tumors in the hypopharynx and gastric body appear to have disappeared or shrunk after chemotherapy (E, F).

punctate lesions in the gastric body (Fig. 2B, C). Colonoscopy revealed a reddish elevated lesion in the terminal ileum (Fig. 2D).

A histopathological analysis of a biopsy specimen derived from the hypopharyngeal lesion revealed a poorly differentiated adenocarcinoma under normal squamous epithelium [hematoxylin and eosin (H & E) staining; Fig. 3A, $\times 200$; Fig. 3B, $\times 400$]. The gastric biopsy specimen showed dif-

fuse and solid carcinoma cells in the lamina propria without glandular formation under the normal superficial epithelium and a poorly differentiated adenocarcinoma with signet-ring cell morphology (H & E staining; Fig. 3C, $\times 200$; Fig. 3D, $\times 400$). The biopsy specimen derived from the terminal ileum as well as from the hypopharynx and stomach showed similar findings (H & E staining; Fig. 3E, $\times 200$). An immunohistochemical (IHC) analysis of the biopsy specimen de-

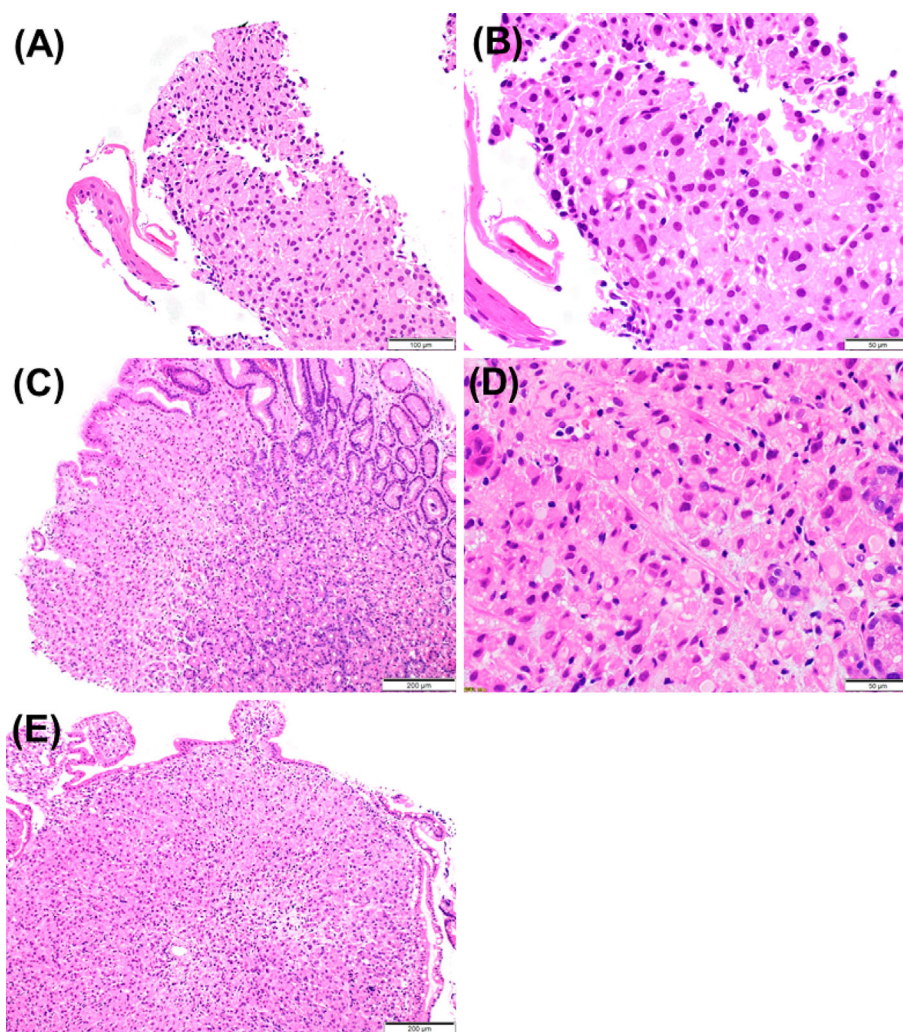


Figure 3. A histopathological analysis of a biopsy specimen derived from the hypopharyngeal lesion revealed a poorly differentiated adenocarcinoma [Hematoxylin and Eosin (H&E) staining; A, ×200; B, ×400]. The gastric biopsy specimen also showed a poorly differentiated adenocarcinoma with signet-ring cell morphology (H&E staining; C, ×200; D, ×400). The biopsy specimen derived from the terminal ileum also showed similar findings (H&E staining; E, ×200).

rived from the hypopharynx, stomach, and terminal ileum revealed that it was strongly positive for gross cystic disease fluid protein-15 (GCDFP-15) but negative for E-cadherin, estrogen receptor (ER), and progesterone receptor (PR) (Fig. 4). The staining pattern was similar among tissue samples. Since these pathological findings were compatible with those of lobular carcinoma, a diagnosis of delayed distant metastases from breast cancer was made; however, no comparison with the histological diagnosis of the primary cancer was possible.

The patient underwent chemotherapy with paclitaxel plus bevacizumab as triple-negative breast cancer with negativity for ER, PR, and human epidermal growth factor receptor 2. The tumors disappeared or decreased in size in the hypopharynx and gastric body following chemotherapy (Fig. 2E, F). However, the patient showed a gradual weakening in her activities of daily living, making it difficult to continue chemotherapy, and she died approximately seven months after the metastases were diagnosed.

Discussion

The most common metastatic sites of breast cancer are the local and distant lymph nodes, bones, lungs, liver, and brain (7). GI tract metastasis is rarely observed. A landmark study by Borst and Ingold found only 17 (0.26%) cases of metastasis to the GI tract among 2,604 cases of breast cancer metastases (2). McLemore et al. also reported a low rate (0.34%) of GI tract metastasis from breast cancer, with the common sites of GI metastasis being the colon and rectum (45%), stomach (28%), small intestine (19%), and esophagus (8%) (3). Furthermore, breast cancer metastasis to the hypopharynx is extremely rare. Only two cases have been previously reported. One was an autopsy case (8), and the other was a case of metastasis to the hypopharynx and cervical lymph nodes almost 24 years after the patient underwent mastectomy and chemotherapy to treat the primary breast cancer (9). In the latter case, laryngoscopy revealed a

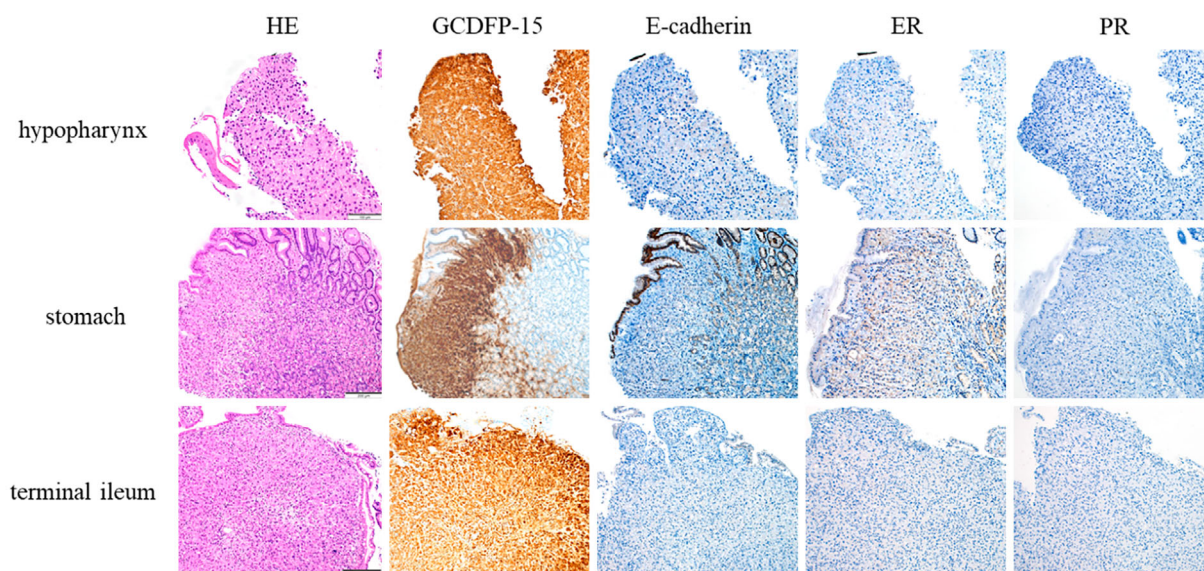


Figure 4. An immunohistochemical (IHC) analysis of the biopsy specimen derived from the hypopharynx, stomach, and terminal ileum revealed that it was strongly positive for gross cystic disease fluid protein-15 (GCDFP-15) but negative for E-cadherin, estrogen receptor (ER), and progesterone receptor (PR).

Table. Summary of 72 Cases of Gastric Metastases from Breast Cancers.

Endoscopic finding	Histological type				
	Invasive lobular carcinoma	Invasive ductal carcinoma	Others	Unknown	
Multiple IIC/varioliiform erosion	13 (18%)	14 (19%)	0 (0%)	2 (2.8%)	29 (40%)
Linitis plastica	20 (28%)	4 (5.5%)	1 (1.4%)	1 (1.4%)	26 (36%)
Others	4 (5.6%)	10 (14%)	1 (1.4%)	2 (2.8%)	17 (24%)
	37 (51%)	28 (39%)	2 (2.8%)	5 (7.0%)	72
Median age, years (range)=55 (30-86)					
Median interval of diagnosis of gastric metastasis, years (range)=3.4 (0-25)					
The numbers of gastric metastasis for every 5-year time interval from the diagnosis of breast cancer.		Synchronous		19	
		≤5 years		29	
		5-10 years		16	
		>10 years		7	
		Unknown		1	

tumor in the post-cricoid area of the hypopharynx, appearing as an elevated lesion resembling a submucosal tumor. To our knowledge, the case reported herein is the first record of synchronous metastasis to the hypopharynx, GI tract, and other organs, especially after a long interval following primary mastectomy.

Gastric metastases from breast cancer often present with endoscopic findings different from those of normal metastatic gastric tumors, such as linitis plastica and multiple IIC/varioliiform erosions. Linitis plastica may be difficult to distinguish from type 4 gastric cancer (10). Table summarizes the endoscopic findings and histological types of 72 cases of gastric metastases from breast cancer (including the present case) reported in Japan from 1990 to 2019. An endoscopic analysis revealed that the tumors were mostly multiple IIC/varioliiform erosions or linitis plastica, and the most com-

mon histological type was invasive lobular carcinoma (2, 10). The incidence of multiple IIC/varioliiform erosions was similar between invasive lobular carcinoma and invasive ductal carcinoma (18% and 19.4%, respectively). The finding of linitis plastica was more common in invasive lobular carcinoma than in invasive ductal carcinoma. In contrast, the endoscopic features of invasive ductal carcinoma tended to show more varied findings, such as multiple IIC/varioliiform erosions and one other item in the endoscopic findings noted in Table, besides simply linitis plastica.

Gastric metastasis from breast cancer is often confused with primary gastric cancer because of the similarities in the endoscopic and pathological findings (11, 12); therefore, the final diagnosis depends on a detailed IHC analysis. IHC staining for ER and PR appears useful for distinguishing metastasis from breast cancer. However, it is noteworthy that

ER and PR positivity has been reported in 32% and 12% of primary gastric cancer cases, respectively (13). GCDFP-15 staining is also helpful in diagnosing whether a case is a metastatic tumor from breast cancer or a primary gastric cancer (14) as GCDFP-15 is a sensitive (45-76%) and specific (91.8-100%) marker. In our case, the diagnosis was confirmed using GCDFP-15 staining, as IHC staining for the hormone receptors yielded negative results. Furthermore, this patient was diagnosed with invasive lobular carcinoma because the IHC analysis of E-cadherin was negative. In cases such as ours of late recurrence after a long interval following the primary treatment, information on the histological type of primary cancer might be inaccessible, thereby necessitating detailed IHC analyses.

Positive GCDFP-15 findings are also seen in cancers of the salivary glands and apocrine glands of the skin. Cancers of salivary glands were ruled out by a physical examination and CT findings in the present patient. According to a previous report (15), cancers of the apocrine glands of the skin are very rare and they tend to occur most frequently in the axilla. Therefore, these were excluded for the above reasons in addition to the present patient's history of breast cancer.

Most patients with breast cancer develop metastatic disease within five years after the resection of the primary tumor (16). The same is true for gastric metastasis, which had a median diagnostic interval of 3.4 years, as shown in Table. However, the numbers of gastric metastases encountered within 5-10 years and over 10 years from the diagnosis of breast cancer were 16 and 7, respectively. In our case, recurrence occurred 24 years after resection of the primary tumor. Delayed recurrence is well explained by the concept of tumor dormancy (17). We must never forget that patients diagnosed with breast cancer remain at risk of recurrence even after successful surgery and adjuvant therapy.

This case has two important limitations. First, we were unable to obtain the medical records of the primary breast cancer from the hospital where the surgery had been performed for the patient 24 years ago. Therefore, the histopathological diagnosis of the primary breast cancer is unknown. However, we diagnosed the patient with multiple synchronous metastases of breast cancer for the following reasons: 1) similar images of biopsy specimens among each tissue, 2) positive staining for GCDFP-15, and 3) exclusion of other primary cancers. Second, we undertook a literature search, as shown in Table, involving only Japanese literature. As these reports are often single case reports, the evaluation was limited.

Invasive lobular breast carcinoma occasionally metastasizes to the GI tract. However, synchronous metastatic lesions from breast cancer in the hypopharynx, stomach, ileum, and other organs are extremely rare, especially after a long interval following primary mastectomy. Therefore, clinicians must be aware that breast cancer has a prolonged

course and has the potential for delayed systemic metastasis.

The authors state that they have no Conflict of Interest (COI).

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