

Case Report

Surgery for pancreatic metastasis of neuroendocrine carcinoma of the breast: a case report

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Abstract: A 55-year-old woman underwent a left muscle-preserving mastectomy and axillar lymph node dissection for breast cancer in 1999. Pathological examination of the resected breast revealed an invasive ductal carcinoma that was estrogen receptor-positive, progesterone receptor-positive, and T2N0M0. Postoperatively, she was administered oral doxifluridine and tamoxifen as adjuvant therapy. Follow-up examinations revealed a mass on the frontal bone 6 years after the surgery. Mass enucleation was performed, and the mass was diagnosed as a metastasis of breast cancer to the skull. Postoperatively, she was treated with anastrozole and zoledronic acid. She presented with dark urine, clay-colored stools, and vomiting 9 years and 6 months after the mastectomy. Examination revealed a tumor of the lower bile duct with obstructive jaundice. Cytological examination of the bile indicated Class V. A pancreaticoduodenectomy was performed with a preoperative diagnosis of lower common bile duct carcinoma. Pathological examination of the resected material revealed a neuroendocrine carcinoma, similar to the primary breast cancer. This was diagnosed as a pancreatic metastasis of a neuroendocrine carcinoma of the breast. Following disease progression due to multiple bone metastases, she was treated with capecitabine and denosumab after several hormonal therapies. The patient is currently surviving, 7 years and 10 months after the pancreaticoduodenectomy. Patients with metastatic breast cancer typically receive systemic therapy. However, surgical resection is worth considering for pancreatic metastases from breast cancer under certain circumstances.

Keywords: Breast cancer, neuroendocrine carcinoma, pancreatic metastasis

Background

Neuroendocrine carcinoma (NEC) of the breast is relatively rare, comprising only approximately 2%-5% of all breast carcinomas [1]. Pancreatic metastasis was reported in 13% of 707 autopsies of breast cancer patients [2]. The standard treatment for pancreatic metastases of breast cancer is pharmacotherapy, with few reports on surgery and prognosis.

We reported a case in which a pancreaticoduodenectomy was performed with a preoperative diagnosis of a lower common bile duct carcinoma. Postoperatively, 9 years and 6 months after mastectomy, the tumor was diagnosed as a pancreatic metastasis of breast cancer.

Case presentation

A 55-year-old woman visited a local doctor because of dark urine, clay-colored stools, and vomiting in February 2009.

In August 1999, the patient had undergone a left muscle-preserving mastectomy and axillary dissection for cancer of the left breast. Pathological examination of the resected breast revealed an invasive ductal carcinoma. The tumor measured 31 mm × 31 mm, and there were no metastatic lymph nodes (0/19). The tumor was estrogen receptor (ER)+ and progesterone receptor (PgR)+. Postoperatively, the patient received adjuvant therapy with doxifluridine for 2 years and tamoxifen for 5 years.

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Table 1. Laboratory study on admission

WBC	6150	/ μ l	ChE	315	U/L
RBC	4.0×10^6	/ μ l	CPK	56	U/L
Hb	12.3	g/dl	AMY	317	U/L
Ht	38.4	%	LYP	282	U/L
Plt	33.6×10^4	/ μ l	UA	4.2	mg/dl
TP	7.5	g/dl	BUN	17	mg/dl
ALB	4.2	g/dl	Cr	0.62	mg/dl
T-Bil	3.0	mg/dl	Na	139	mEq/l
D-Bil	1.9	mg/dl	K	4.0	mEq/l
AST	549	U/L	Cl	102	mEq/l
ALT	784	U/L	Ca	9.3	mg/dl
LDH	358	U/L	P	3.6	mg/dl
ALP	3817	U/L	CRP	0.3	mg/dl
LAP	633	U/L	FBS	104	mg/dl
γ GTP	1271	U/L	CEA	0.8	ng/dl
			CA19-9	4.1	U/ml

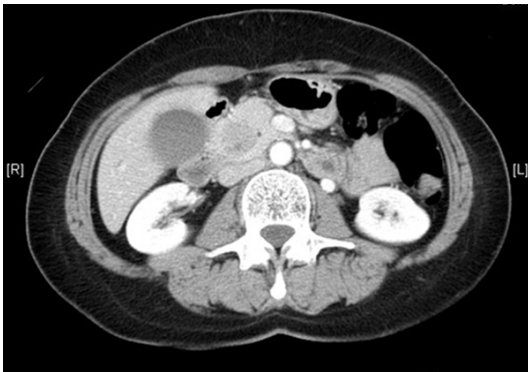


Figure 1. Abdominal enhanced computed tomography. There was a round mass with no enhancement, 30 mm \times 30 mm, with relatively clear boundaries in the pancreatic head.

In September 2005, follow-up bone scintigraphy showed a concentration on the frontal bone. Brain magnetic resonance imaging confirmed a mass on the frontal bone. Mass enucleation was performed, and the mass was diagnosed as a breast cancer metastasis to the skull. Postoperatively, the patient was treated with anastrozole and zoledronic acid.

In February 2009, the patient (now 55 years old) presented with dark urine, clay-colored stools, and vomiting. She was diagnosed with obstructive jaundice, and abdominal enhanced computed tomography (CT) showed a tumor of the lower bile duct. She was referred to our hospital for further examination and treatment.



Figure 2. Endoscopic retrograde cholangiopancreatography (ERCP). There was a round defect, 10 mm in diameter, in the lower bile duct, and the upper bile duct of the defect was dilated. ERCP showed stenosis on the pancreatic duct of the pancreatic head.

She had mild jaundice in the ocular conjunctiva and no other abnormal findings were observed. Total bilirubin level was elevated (3.0 mg/dl, with conjugated bilirubin level of 1.9 mg/dl), and liver and pancreas enzymes were at high levels. CEA and CA19-9 levels were within the normal range (**Table 1**).

Abdominal ultrasonography showed an isochoic mass of 40 mm \times 40 mm in the pancreatic mass of 40 mm \times 40 mm in the pancreatic head, the common bile duct was dilated to 11 mm, and the pancreatic duct was dilated to 3 mm (after biliary stent placement). Enhanced CT (**Figure 1**) demonstrated a round mass, 30 mm \times 30 mm, with relatively clear boundaries in the pancreatic head without enhancement. Bilateral intrahepatic bile ducts were dilated. There were no lymph node metastases, ascites, or other organ metastases, except to the bone. Endoscopic retrograde cholangiopancreatography (ERCP) (**Figure 2**) revealed a round defect, 10 mm in diameter, in the intrapancreatic bile duct, and the upper bile duct of the defect was dilated. ERCP showed stenosis on the pancreatic duct of the pancreatic head. Endoscopic retrograde and endoscopic nasobiliary drainages were performed. The bile cytological examination revealed Class V, and the tumor was suspected to be an adenocarcinoma.

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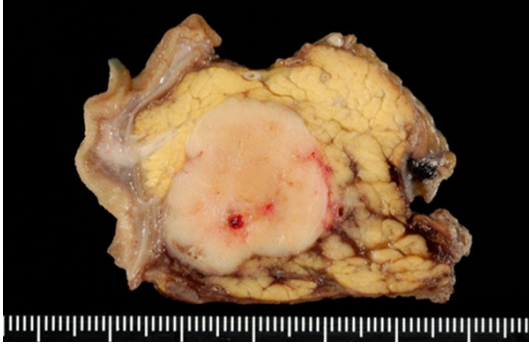


Figure 3. The resected specimen. The tumor was a light tan, solid, 35 mm × 24 mm × 21 mm mass in the pancreatic head.

The preoperative diagnosis was carcinoma of the lower common bile duct. Although the patient had breast cancer with bone metastasis, there were no metastases in other organs and no disease progression. Her general condition was good. The pancreaticoduodenectomy was performed because her prognosis was defined by the cholangiocarcinoma rather than by the metastatic breast cancer.

There were no ascites, and peritoneal lavage cytology was Class I. There was no liver metastasis or peritoneal dissemination. The tumor was located in the pancreatic head and did not invade the peripancreatic tissue, artery, or portal vein. Analyses of intraoperative frozen sections from the pancreatic duct stump and the bile duct stump confirmed the absence of malignancy in both stumps. The patient underwent a standard pancreaticoduodenectomy with reconstruction (modified Child method) and lymph node dissection. The operation took 8 h and 45 min, and the total blood loss was 837 ml.

The resected tumor specimen (**Figure 3**) was a light tan, solid, 35 mm × 24 mm × 21 mm mass in the pancreatic head. Pathological examination of the tumor showed solid, nested, and trabecular growth patterns with necrosis. There was common bile duct invasion and vascular invasion without lymphatic and neural invasions, or lymph node metastasis (0/52). The specimen displayed pancreatic neuroendocrine neoplasm-like histology, which was very similar to that of the patient's primary breast cancer (**Figure 4A, 5A**). Immunohistochemical staining

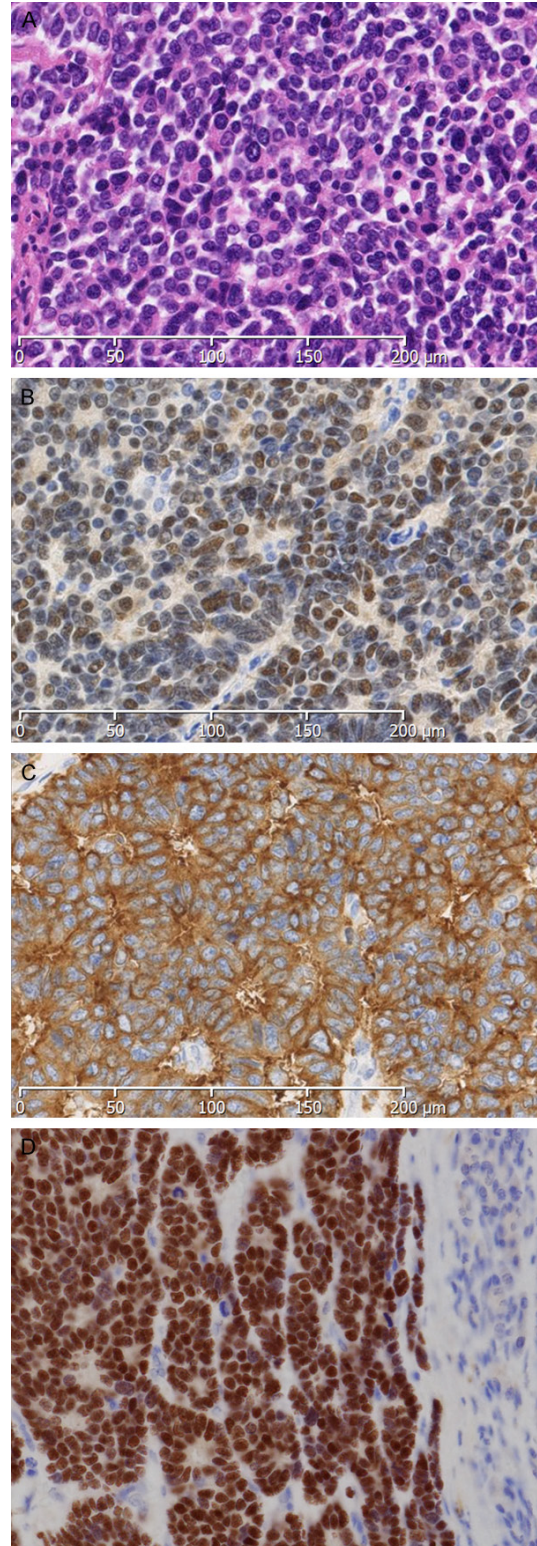


Figure 4. Immunohistochemical findings of the pancreatic tumor. A. Hematoxylin and eosin (× 20). B. Synaptophysin (× 20). C. GATA3 (× 20). D. Estrogen receptor (× 20).

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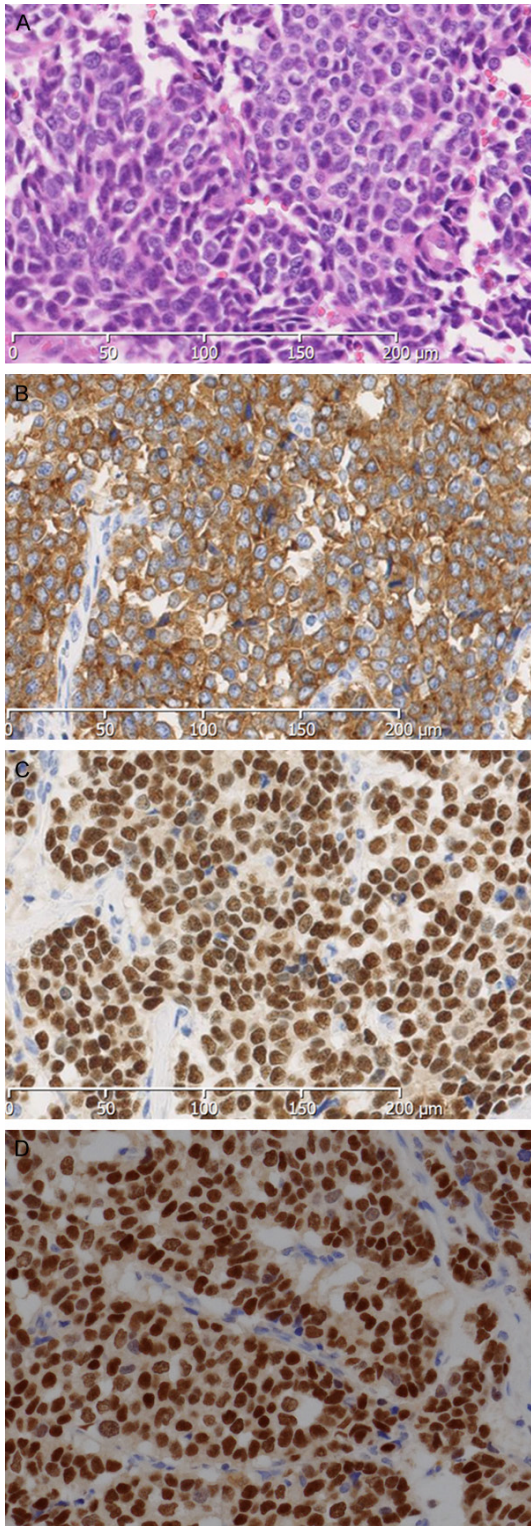


Figure 5. Immunohistochemical findings of the primary breast cancer. A. Hematoxylin and eosin ($\times 20$). B. Synaptophysin ($\times 20$). C. GATA3 ($\times 20$). D. Estrogen receptor ($\times 20$).

was positive for the expression of synaptophysin, CK7, and GATA3 (**Figure 5B, 5C**). The tumor

was negative for chromogranin, CD56, CK20, CDX2, and GCDFF-15. These results were the same as those for the patient's breast cancer and metastatic skull tumor (**Figure 4B, 4C**). The pancreatic tumor, breast cancer, and skull tumor were all ER+, PgR+, and HER2- (**Figure 4D, 5D**). Based on these immunohistochemical findings, the pancreatic tumor was diagnosed as an NEC metastasis of the breast cancer.

Only a grade-A (International Study Group of Pancreatic Surgery) pancreatic fistula was observed, and the patient was discharged from the hospital 26 days after surgery in good health. Because she was newly diagnosed with pubic bone metastasis, she stopped taking anastrozole. Letrozole was administered and zoledronic acid was continued. As the bone metastasis progressed, exemestane, fulvestrant, and then tamoxifen were administered. The patient stopped taking zoledronic acid and denosumab was administered. Capecitabine and denosumab were administered for 5 years and 2 months after the pancreaticoduodenectomy. The patient continues to survive, 7 years and 10 months after surgery, with no visceral metastases.

Discussion

Primary NEC of the breast are rare tumors, constituting approximately 2%-5% of all breast cancers [1]. They were first described by Feyrter et al in 1963 as breast cancers showing carcinoid growth patterns [3].

NEC is diagnosed by Grimelius staining, presence of tumor cells expressing neuroendocrine markers, such as synaptophysin or chromogranin A, and neuroendocrine granules in the cytoplasm visualized by electron microscopy.

Previous studies have suggested that the prognosis for NEC of the breast was similar to [4-6] or better [7-9] than that for non-NEC of the breast. However, Zhang Y et al and Wei B et al reported worse outcomes for NEC of the breast than that for typical breast cancer, with frequent local recurrence [10, 11] and systemic metastasis [11].

In the present case, the primary breast cancer was initially diagnosed as an invasive ductal carcinoma. Immunohistochemical staining allowed further diagnosis of the breast cancer as having NEC. The pancreatic tumor was also diagnosed as NEC based on staining positive

for synaptophysin and negative for chromogranin.

To confirm that the pancreatic tumor was a metastasis from the breast cancer rather than a primary pancreatic tumor, immunohistochemical staining was used. Arnason et al reported no case of pancreatic neuroendocrine tumors (NET) with strong nuclear expression of ER in 40 pancreatic NET cases [12]. NET of the pancreas is likely to be diagnosed as a pancreatic metastasis of NEC of the breast if it shows ER expression and there is NEC of the breast. Recently, immunohistochemistry for GATA3 has been used in surgical pathology to support a breast or urothelial origin in carcinoma [13, 14]. In the present case, the pancreatic tumor was diagnosed as a metastasis of NEC of the breast based on staining positive for ER and GATA3.

Sperti et al reported 19 patients undergoing surgery for pancreatic metastasis of breast cancer. All but one of these patients underwent a pancreaticoduodenectomy because the pre-operative diagnosis was a primary pancreatic tumor [15]. The median survival of patients with recurrent disease was 26 months after pancreatic surgery. Two patients continue to survive more than 5 years post-surgery.

If pancreatic metastasis had not been diagnosed in our case, the patient would have received chemotherapy after biliary stenting. Because pancreaticoduodenectomy made the correct diagnosis possible, cholangitis after biliary stenting and unnecessary chemotherapy was avoidable, and she obtained a good quality of life. If surgical resection is performed at a high-volume regional medical center, it is worth considering pancreatic metastasis of NEC of the breast to achieve a good prognosis and quality of life.

Conclusions

In conclusion, we report a rare case of pancreatic metastasis of NEC of the breast. In this case, the patient has survived for a long term following pancreaticoduodenectomy. Patients with metastatic breast cancer typically receive systemic therapy. However, in certain circumstances, surgical resection is worth considering for pancreatic metastasis of NEC of the breast.

Declaration of conflict of interest

None.

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