CASE REPORT

Metastasis to the Pancreas From Ductal Carcinoma In Situ of Breast Cancer: A Case Report and Review of Literature

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ABSTRACT

Background • The usual locations of metastatic breast neoplasms include the bones, the liver, the lung, and the brain. Breast cancer rarely metastasizes to the pancreas. However, pancreatic metastasis and primary pancreatic cancer are difficult to differentiate because of their similar clinical features and radiological characteristics.

Case presentation • We report on a 49-year-old woman initially diagnosed with left breast ductal carcinoma in June 2008. The patient was admitted to the hospital with jaundice after 12 years. Computed tomography (CT) scan and magnetic resonance imaging (MRI) revealed a mass in the pancreas head. Histopathology and immunohistochemistry showed ductal carcinoma originating from breast cancer. She underwent pancreatoduodenectomy to relieve jaundice. The patient is still alive with a favorable prognosis.

Conclusions • In this paper, we mainly discuss the clinical characteristics, diagnostic methods, and surgical treatment of pancreatic metastasis. When a pancreatic lesion is detected with a history of breast cancer, the pancreatic metastasis likely originates from breast cancer. (*Altern Ther Health Med.* 2022;28(6):150-155)

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INTRODUCTION

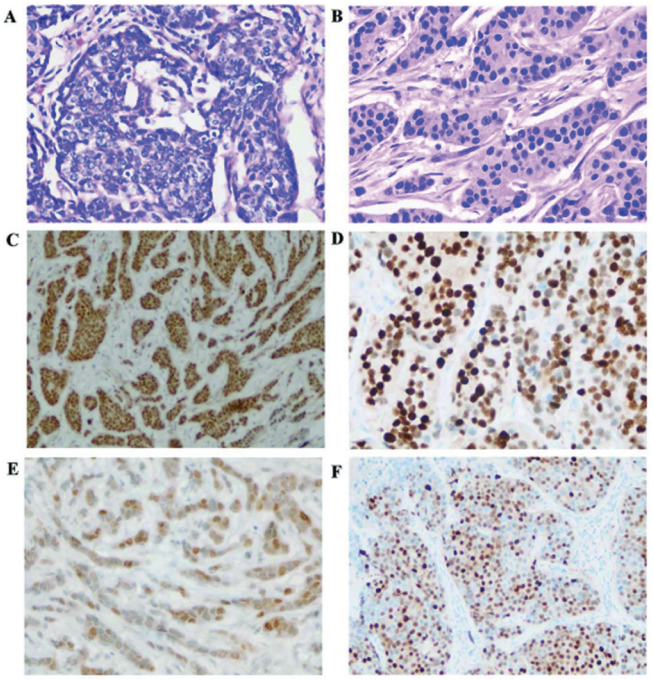
Pancreatic metastasis from other cancer is rare, accounting for approximately 2% of all pancreatic tumors.[1] The prevalence of pancreatic metastasis ranges from 6 to 11% in a large autopsy series.[2] The most common neoplasm metastasizing to the pancreas is renal cell carcinoma, while a metastatic pancreatic tumor from breast cancer is extremely rare.[3,4] Primary pancreatic cancer and metastatic pancreatic cancer from the breast are difficult to distinguish because clinical features and radiological characteristics are similar.[5] A pancreatic biopsy, which can determine the pathological type, is the most accurate diagnostic method. Immunohistochemistry can further identify the source of the metastatic tumor.[4,6,7] Here, we discussed a patient with pancreatic ductal carcinoma from breast cancer after 12 years of primary cancer treatment. We also reviewed the relevant published literature.

Case Report

The reporting of this study conforms to the CARE guidelines.[8] All patients have been de-identified.

A 49-year-old female was originally diagnosed with left breast invasive ductal carcinoma at our hospital in June 2008. Shortly after admission, the patient underwent a modified mastectomy with peripheral lymph node dissection. Pathological examination of the breast mass led to invasive ductal carcinoma diagnosis with a T2N0M0 grade II classification (Figure 1A). The margins of the breast specimens were free of neoplastic infiltration, as were the peripheral lymph nodes. The tumor cells were immunoreactive for hormone receptors, including the progesterone receptor (PR) and estrogen receptor (ER) (Figure 1C and E), and for human epidermal growth factor receptor-2 (HER-2). The patient underwent six courses of chemotherapy, consisting of Cytoxan (CTX), methotrexate (MTX), and fluorouracil (5-FU). The patient was followed up regularly with routine examinations with no disease recurrence. Twelve years after

Figure 1. Histological imaging of the breast ductal carcinoma (A, C, E) and pancreatic metastasis (B, D, F). A and B: Pathological features of the breast and pancreas lesions (H&E, × 200). C and D: ER-positive staining of the carcinoma of the breast and pancreas (× 200). E and F: PR-positive staining of the carcinoma of the breast and pancreas (× 200).



she was first diagnosed with breast cancer, she presented to the Emergency Unit of our hospital with a complaint of 2 days of jaundice. Urgent biochemical tests revealed liver dysfunction, with the level of serum aspartate aminotransferase (AST) at 193 U/l (normal range 8–40 U/l), alanine aminotransferase (ALT) at 78 U/L (5–40 U/l), total bilirubin at 118.9 umol/L (2–19 umol/l), and CA19-9 at 409 U/ml (0–40 U/ml). Later, the patient was admitted to the gastroenterology department. An MRI revealed an irregular mass in the pancreas head and a dilated biliary tract.

The patient underwent hepatobiliary surgery, and the subsequent CT imaging showed that the mass of the head of the pancreas was either a pancreatic tumor or a metastatic tumor (Figure 2). The subsequent chest and bone CT scans did not suggest multiple metastases. A standard pancreatoduodenectomy was performed to palliate obstructive jaundice. Surprisingly, there was a mass of about 1 cm in the transverse mesocolon; it was excised. The pathological results showed that it was a malignant tumor (Figure 3).

The pancreatic mass biopsy revealed a 3.5-cm lesion infiltrating the head of the pancreas and duodenal submucosa; thus, the mass was considered to be pancreatic carcinoma. (Figure 1B) The tumor in the transverse mesocolon was also infiltrated with malignant cells. The surgical specimen margins were not infiltrated by tumor cells, the peripheral lymph nodes were negative for malignancy. However, we did

Figure 2. A contrast-enhanced CT scan shows a 21 × 22 mm mass of low-density, with ill-defined margins and dilated intra- and extra-hepatic bile ducts and pancreatic ducts in the pancreas head.

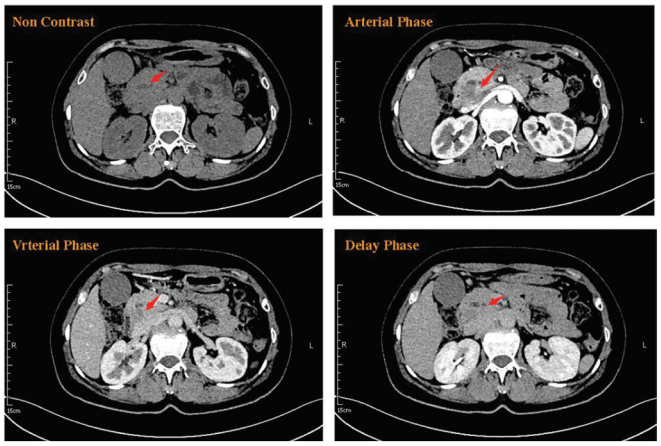


Figure 3. Transverse mesocolic mass: the tumor tissue was observed under light microscope (A: H&E, × 100. B: H&E, × 200)

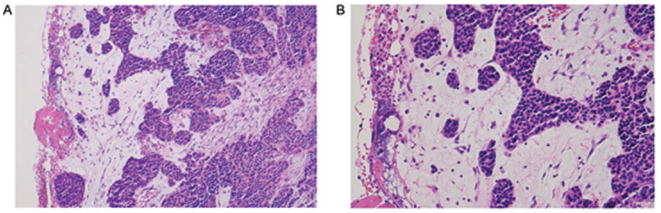
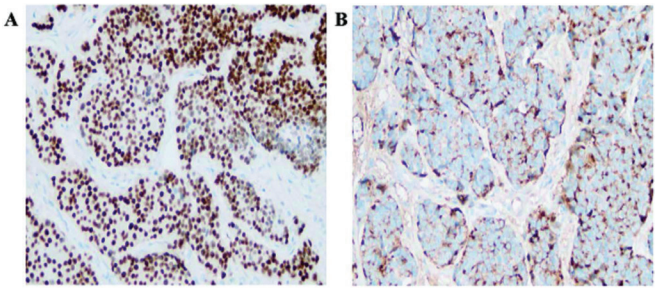


Figure 4. Immunohistochemical imaging of the pancreatic lesions with light microscopy. A: GATA-3 staining of pancreatic metastasis (× 200). A: GCDFP-15 staining of pancreatic metastasis (× 200).



not determine the source of neoplasm. Immunohistochemical examination was used to differentiate the sources of the tumor. The neoplastic cells were shown to be positive for ER, PR (Figure 1D and F), GATA-binding protein 3 (GATA3), GCDFP-15 (Figure 4), HER-2, E-cadherin, cytokeratin-7 (CK7), and CK19; the cells were negative for mammaglobin.

After the patient recovered from the operation, she received serial adjuvant chemotherapy with paclitaxel (PTX) and nedaplatin. Cytotoxic chemotherapy was not prescribed, and there was no indication for radiotherapy. The patient

Table 1 Clinical characteristics of patients with metastases to the pancreas from breast tumor

Author	Age (mouths)	Pancreatic metastases subtype	Disease-free interval (mouths)	sympotoms	Localization of metastases	Features of metastases	Treatment	Overall survival (mouths)	Clinical outcome
Shee[4]	72	Signet-ring cells	144	Jaundice	Head of pancreas	Solitary	Hospice care	NA	Alive
Derouane[5]	51	Ductal	116	Jaundice, weight loss	Head of pancreas, Liver,lung	Widespread	CHT	11	Alive
Zammit[6]	72	Lobular	228	Abdominal pain	Head of pancreas	Solitary	CHT	NA	NA
Amir[7]	34	Phyllodes	21	Acute pancreatitis	Head of pancreas	Solitary	CHT	10	Death
Sun[9]	48	Lobular	14	Abdominal pain	Neck of pancreas	Widespread	Pancreatosplenectomy, CHT	NA	NA
Kliiger[10]	60	Ductal	Synchronous	Diarrhea, weight loss	Head of pancreas, stomach	Widespread	CHT	NA	NA
Apodaca[11]	64	Ductal	24	Pain, weight loss	Tail of pancreas	Solitary	Distal pancreatectomy, CHT	18	Alive
Tunio[12]	44	Ductal	Synchronous	Pain,jaundice	Head of pancreas	Solitary	PD, CHT	NA	Alive
Molino[13]	68	Lobular	Synchronous	Jaundice	Head of pancreas	Solitary	PD,HT	12	Alive
Bednar[14]	75	Lobular	96	Jaundice, pain	Head of pancreas	Solitary	PD	48	Alive
Bednar[14]	57	Phyllods	48	Pain	Head of pancreas, lung	Widespread	CHT	15	Death
Razzetta[15]	51	Lobular	Synchronous	Jaundice, pain, diarrhea	Head of pancreas, bone	Widespread	PD,CHT, mastectomy	5	NA
Bonapast[16]	53	Ductal	24	Jaundice, pain	Head of pancreas	Solitary	PD, CHT	36	Death
Ochoa[17]	60	Lobular	1	Jaundice	Head of pancreas, bone	Widespread	Biliary stent, PD, CHT	2	Alive
Ochoa[17]	55	Ductal	114	Asymptomatic	Tail of pancreas	Solitary	Distal pancreatectomy, splenectomy, CHT	2	Alive
Tohnosu[18]	54	Scirrhous type	52	Asymptomatic	Tail of pancreas	Solitary	Distal pancreatectomy, CHT, HT	5	Alive
Kitamura[19]	55	Ductal	117	Jaundice	Head of pancreas	Solitary	Percutaneous drainage	1	Death
Nomizu[20]	46	Lobular	80	Jaundice	Head of pancreas	Solitary	PD, CHT	18	Alive
Pappo[21]	52	Lobular	24	Jaundice	Pancreas,gallbladder	Widespread	Palliative bypass, HT	16	Alive
Serikawa[22]	50	Phyllods	36	Jaundice	Head of pancreas	Solitary	PD	48	Alive
Sweeney[23]	41	Ductal	60	Pain	Body of pancreas	Solitary	distal pancreatectomy, CHT	NA	Alive
Cil[24]	44	Ductal	48	Asymptomatic	Tail of pancreas	Solitary	CHT	5	Alive
Mullady[25]	66	Lobular	Synchronous	Acute pancreatitis	Head of pancreas	Solitary	CHT	0	Death
Hefferna[26]	36	Ductal	Synchronous	Jaundice, weight loss	Pancreas	Solitary	PD, CHT	10	Alive
Pan[27]	59	Lobular	182	Jaundice	Head of pancreas	Solitary	CHT, HT	21	Alive
Dar[28]	76	Ductal	108	Asymptomatic	Pancreas, liver	Widespread	Palliative bypass	6	Death
Crippa [29]	46	Lobular	60	Jaundice	Head of pancreas	Solitary	PD	22	Alive
Crippa [29]	70	Lobular	36	Jaundice,pain	Head of pancreas	Solitary	PD	38	Alive
Crippa [29]	57	Lobular	84	Jaundice,pain	Head of pancreas	Solitary	PD	26	Death
Haque[30]	85	Lobular	168	Jaundice,pain	Head of pancreas	Solitary	Palliative bypass, CHT	NA	NA
Moussa[31]	53	Ductal	132	Acute pancreatitis	Head of pancreas	Solitary	RH, CHT, HT	50	Alive
Moussa[31]	35	Lobular	45	Abdominal mass	Body of pancreas	Solitary	Total pancreatectomy, CHT	7	Death
Borgne[32]	48	Lobular	Synchronos	Jaundice	Head of pancreas	Solitary	PD,CHT	12	Death
Mountne[33]	57	Lobular	16	Jaunpdice	Head of pancreas	Solitary	Palliative bypass, HT	24	Alive
Mehta[34]	30	Comedo type	36	Jaundice, pruritus	Head of pancreas	Solitary	PD, CHT, HT	27	Alive
Alberto[35]	49	Lobular	43	Jaundice	Head of pancreas	Solitary	PD,HT	72	Alive
Engel[36]	59	Signet-ring cells	46	Pruritus, choluria	Head of pancreas	Solitary	Palliative bypass,CHT	15	Death

Abbreviations: CHT, Chemotherapy; PD, Pancreaticoduodenectomy; HT, Hormonal therapy; RT, radiotherapy; NA, not available.

underwent the second round of chemotherapy and recovered well. There was no evidence of distant metastasis and active disease, as confirmed by CT scan and serum tumor marker tests. As of 14 months after the diagnosis was made, the patient is alive without evidence of distant metastasis.

DISCUSSION

The usual metastatic locations of breast neoplasm are the liver, bone, brain, and lung; however, breast cancer metastastic to the pancreas is extremely rare, with an incidence lower than 3%.[9] In this case, the metastasis route of the lesions (pancreatic head mass and a mass in the mesocolon) were considered as lympho-vascular metastasis. Previous studies showed the major route of spread from breast cancer was into the axillary lymph nodes and from there into the systemic circulation. The arterial blood supply of the pancreas is abundant, mainly from the aorta abdominalis and superior mesenteric artery.[3] In studies of large autopsies of patients who died of breast neoplasms, metastatic pancreatic tumors from breast neoplasm account for approximately 11% to 17% of all gastrointestinal malignancies. Still, gastrointestinal metastasis from breast cancer is uncommon.[2] Analyzing in detail the case series performed by Molino and other recent case reports, we identified 37 cases with pancreas metastasis from breast cancer (Table 1).

In the current case, the only symptom of the patient was jaundice. Clinical characteristics of primary pancreatic cancer, including obstructive jaundice, pain, pruritus, pancreatitis, weight loss, and diarrhea, are similar to those of pancreatic metastasis. However, patients with pancreatic metastasis may be completely asymptomatic. Interestingly, the most common symptom and metastatic sites are jaundice and the pancreas head, respectively, in all the patients with pancreatic metastasis. The head of the mass is more likely to compress the common bile duct than the pancreas' tail or body, causing obstructive jaundice.[4,5] The common histopathological diagnosis is lobular carcinoma. However, our patient was diagnosed with invasive ductal carcinoma. The disease-free interval (DFI) ranges from synchronous to 228 months with a median of 59.5. The DFI of our patient was 144 months. The prognosis of solitary pancreatic metastasis is usually better than that of primary pancreatic carcinoma: the median overall survival of all the cases with reported survival information is 19.4 months. The median overall survival of patients undergoing surgical resection and chemotherapy was 17 months and 21.5 months, respectively, but this difference was not statistically significant. However, previous studies showed that 5 and 2-year survival rates of the patients with breast cancer metastasis to the pancreas were 34.3% ± 15% and 57.1% ± 13%, respectively.

In the current case, the only symptom of the patient was jaundice. Clinical characteristics of primary pancreatic cancer are similar to pancreatic metastasis, including obstructive jaundice, pain, pruritus, pancreatitis, weight loss, and diarrhea. However, it is notable that the patients with pancreatic metastasis may be completely asymptomatic. Interestingly, the most common symptom and metastatic sites are jaundice and pancreatic head in all patients with pancreatic metastasis, respectively. The mass in the pancreas head is more likely to compress the common bile duct than the pancreas' tail (or body), causing obstructive jaundice, as reported by these cases.[4,5] The most common histopathological diagnosis is lobular carcinoma, but our case was invasive ductal carcinoma. The disease-free interval (DFI) ranges from synchronous to 228 months (median 59.5), and the DFI of our patient was 144 months. The prognosis of solitary pancreatic metastasis is usually better than that of primary pancreatic carcinoma, and the median overall survival of all cases with reported survival information here was 19.4 months. However, previous studies showed that 5-year and 2-year survival rates from breast cancer metastasize to the pancreas were 34.3 ±15 and 57.1 ± 13%, respectively .[37]

The symptoms of pancreatic metastasis are nonspecific; they can be identified using imaging examinations, including abdominal ultrasonography (US), CT, and MRI.[17] However, it is challenging to differentiate pancreatic metastasis from primary pancreatic adenocarcinoma. The most important diagnostic method is image-guided fine-needle aspiration, although this test is considered optional.[29,38] In our opinion, if the patient only has isolated pancreatic metastasis with a good clinical condition, a postoperative pathological examination can be performed to avoid a preoperative endoscopic ultrasound (EUS)-guided biopsy. Histopathological results suggest that metastatic pancreatic tumors mimic primary gastrointestinal cancer; thus, immunohistochemistry can help make a more accurate diagnosis.[18] In this case, the CT imaging showed a solitary pancreatic mass, and the systematic workup, i.e., bone and chest scans, ruled out the possibility of other metastatic lesions. Finally, we reached a consensus on the treatment of curative pancreatic resection.

Most pancreatic tumors are found during routine follow-up examinations; the most common examination method is a CT scan.[3,13] In our case, CT scan and MRI imaging revealed a mass in the head of the pancreas with dilated intra- and extra-hepatic bile ducts and pancreatic ducts. CT scans of metastatic pancreatic tumors usually uncover space-occupying masses with focal or irregular margins and sometimes with the dilatation of the biliary tract or the pancreatic duct or both, presenting as hypervascular tumors.[38] However, primary pancreatic cancers are usually relatively hypovascular.[28] Notably, pancreatic metastasis from renal cell carcinoma appears as hypervascular cancers on these images and should be differentiated from the pancreatic endocrine tumors. Moreover, some pancreatic metastases are hypovascular, such as lung cancer, colon cancer, and breast cancer.[27,28,29,31] Also, in the ultrasound examination, the metastatic pancreatic tumors appear as a solid hypoechogenic mass with regular margins; in contrast, primary pancreatic cancer tumors have ill-defined margins.[5] Therefore, CT can be a reliable method to reach a definitive diagnosis.[13]

Positron emission tomography (PET)/CT is a new diagnostic method for pancreatic tumors in recent years.

PET/CT can be used to evaluate the possibility of distant metastases in the advanced stage of breast neoplasm and peripheral lymph nodes metastasis and for the prognosis of malignant tumors.[13] CA19-9 is the most significant tumor marker for pancreatic carcinoma, while CA15-3 is for breast cancer.[16] Our patient had an increased CA19-9 serum level. Although the increase of serum marker CA19-9 can often help differentiate pancreatic carcinoma from pancreatic metastasis, the increase in serum CA19-9 levels is not always significant. On the contrary, levels of serum CA19-9 of patients in published studies were within the normal range.[11,16] In addition, CA19-9 is also elevated in benign diseases such as obstructive jaundice and hepatitis. Endoscopic retrograde cholangiopancreatography (ERCP) has been used to diagnose and treat obstructive jaundice in recent decades.[14] We did not attempt ERCP for the patient and performed a definitive curative pancreatic resection.

A pancreatic biopsy is the most accurate diagnostic method in pancreatic masses.[27] Histopathological examinations enable pathological classification by the structure of neoplastic cells; however, the primary cancer site cannot be defined using this method. The pathological features of pancreatic ductal adenocarcinoma are similar to those of breast carcinoma; thus, immunohistochemistry is a reliable method to determine the origin of the tumor.[4] Twenty-two cases with pancreatic metastasis from breast tumors and reported results of immunohistochemistry were identified in the literature.[4–7,9-25] The positive biomarkers of pancreatic metastasis from breast cancer by immunohistochemistry are summarized in Table 2.

Table 2 Positive biomarkers of pancreatic metastases from breast cancer (n = 22)

Biomarker	Percentage rate
ER	13 (58.8%)
PR	8 (36.4%)
GATA-3	6 (27.3%)
GCDFP-15	4 (18.2%)
CK7	4 (18.2%)
CK19	3 (13.6%)
Mammaglobin	2 (9.1%)
HER-2	2 (9.1%)
CK20	1 (4.5%)
CK17	1 (4.5%)
P120	1 (4.5%)
E-cadherin	1 (4.5%)
Carcinoembryonic antigen	1 (4.5%)

ER is the most sensitive specific marker, followed by PR, GATA3, GCDFP-15, CK7, CK19, and mammaglobin. Most breast neoplasms express hormone receptors associated with better prognosis and lower tumor invasion.[4,9] This phenomenon may explain why our patient's DFI was 12 years. In several reported cases,[9,11,19] pancreatic metastases were negative for hormone receptors in contrast to the ER- or PR-positive primary breast cancers. Several studies have revealed that the loss of ER and PR in breast cancer is common, occurring in approximately 36% of metastatic breast tumors;[4,39] therefore, it cannot be used to rule out the diagnosis. GATA3 is produced in 100% of the hormone receptor-positive breast cancers, maintaining the stability of expression in primary breast cancer and metastatic carcinomas, including tumors with loss of hormone receptors.[9,40] Also, recent studies suggested GATA3 is a more sensitive maker than mammaglobin and GCDFP-15, which is overexpressed in the nucleus of breast tumor cells and the cytoplasm of pancreatic carcinoma cells, respectively.[9,41] Some studies have suggested that MUC5AC is a useful biomarker to distinguish primary and secondary pancreatic cancer.[42]

Surgical indications of pancreatic metastasis have not been defined, and there are no published guidelines on the recommended treatment of these lesions with pancreatic metastasis. Curative resection (R0) has been considered a firstline treatment for patients with solitary pancreatic metastasis.[28] A multi-disciplinary team (MDT), including an oncologist, surgeon, and radiologist, is essential for assessing the resectability. Resectability is determined by the anatomical relationship between the tumors and vessels as well as the surgeon's proficiency.[1]

The skill of a surgeon is an important factor in postoperative complications.[1,29] We proposed performing an operation in large pancreatic centers where experienced surgeons practice. Previously published studies suggested that pancreatic surgery outcomes depend on the location of the tumors. Pancreatoduodenectomy is the first choice of treatment for pancreatic head carcinoma, and pancreatectomy with splenectomy is a common option for carcinomas of the pancreas body and tail.[3,27,29,38] In addition, systematic treatments based on chemotherapy can be a reliable method to relieve symptoms, prolong survival, and improve patients' quality of life with widespread disease.

CONCLUSION

Metastases to the pancreas from breast neoplasm are extremely rare. Early detection of diseases relies on imaging examinations such as US, CT, and MRI. Immunohistochemistry has a key role in distinguishing between metastatic breast tumor and primary adenocarcinoma. Additionally, it is crucial to use a group of biomarkers instead of one or two biomarkers. We recommend preoperative EUS-FNA to obtain the pathological results of the mass. The indications for surgical resection are no distant metastasis, no invasion of celiac trunk, superior mesenteric artery, common hepatic artery and portal vein. Moreover, the treatment should be individualized, and the patient evaluation by a multidisciplinary team should be emphasized. In summary, we believe that when pancreatic lesions are detected in a patient with a history of breast cancer, the pancreatic metastasis likely originates from breast cancer.

AUTHOR CONTRIBUTIONS

YY gathered data and wrote literature review; XSZ made charts and pictures; YKX provided histopathological examination and immunohistochemical staining; XNW and BHX contributed to management and operation of patient; JHZ performed surgery and revised manuscript.

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AVAILABILITY OF DATA AND MATERIALS

Data for this study were obtained from previously published case reports or case series.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed were in accordance with the ethical standards of the ethics committee of the First Affiliated Hospital of Gannan Medical University. The patient signed the informed consent.

CONSENT FOR PUBLICATION

Patients has consented to the publication of the study.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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