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Original Article

Clinicopathological characteristics of tumor-like lesions arising in gastric heterotopic pancreas

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Abstract: Heterotopic pancreas is defined as the presence of pancreatic tissue, outside its usual location, which lacks anatomical and vascular continuity with the pancreas proper. The heterotopic pancreas can accompany various lesions of the pancreas, such as acute pancreatitis, epithelial cyst, pancreatic pseudocyst, and exocrine and endocrine tumors. Tumor-like lesions arising from heterotopic pancreas appear to be rare, and there are only sporadic cases available in the literature. This study analyzed the clinical and pathological characteristics of our single patient and 31 previously reported cases in the literature. Assessment of all 32 cases showed no gender differences and a median age of 57 years. The most common site of tumors occurred in the gastric antrum (14/26). Most of the cases were classified according to the Heinrich classification of heterotopic pancreas. The most frequent Class of heterotopia associated with tumors was Class I (11 cases, 42%), followed by Class III (9 cases, 35%). Our patient presented with a Class III heterotopic pancreas. Most of the tumors associated with heterotopic pancreashave been adenocarcinomas (21/32). Other less common types of pancreatic neoplasia included intraductal papillary mucinous neoplasms (5/32), acinar cell carcinoma (4/32), and neuroendocrine tumors (2/32). With a median follow-up of 18 months, 12 patients (60%) survived and were disease-free, and 5 patients (25%) died of disease. Only 3 patients had recurrence or metastasis after partial tumor resection.

Keywords: Heterotopic pancreas, ectopic pancreas, aberrant pancreas, tumor-like lesion, intraductal papillary mucinous neoplasm, adenocarcinoma

Introduction

Heterotopic pancreas, also called ectopic or aberrant pancreas, is a relatively uncommon lesion occurring at any age and is found in 2% to 15% of all autopsies [1]. Heterotopic pancreases occasionally observed in areas such as the gastrointestinal tract, biliary duct, liver, spleen, and mediastinum. About 25% to 40% of such reported heterotopic cases occur within the stomach and the most frequent location is the greater curvature of the gastric antrum [2]. Most of the lesions occurring in the pancreas have been reported to occur in the ectopic pancreas, these lesions include pancreatitis, pseudocyst, cyst formation, insulinoma, adenoma and malignant tumors. Tumor-like lesions arising within the heterotopic pancreas are quite rare. In the literature, 31 well-documented cases of such lesions have been reported. Here, we present a case of intraductal papillary mucinous neoplasm (IPMN) with severe dysplasia and invasive ductal adenocarcinoma occurring in the gastric heterotopic pancreas and discuss this rare neoplasm based on a review of the literature.

Materials and methods

Assessment of the new case

Data of one case of IPMN with severe dysplasia and invasive ductal adenocarcinoma occurring in the gastric heterotopic pancreas were retrieved from the surgical pathology files of Ningbo Clinical and Pathological Diagnosis Center. A detailed clinical history was obtained from Ningbo No. 2 hospital records. Pathological specimens were treated with routine histological processing, including formalin fixation and paraffin embedding. Tissue blocks were cut into 4-μm-thick slices for hematoxylin and eosin (H&E) staining and immunohistochemical staining. After antigen retrieval (steam ethylene dia-

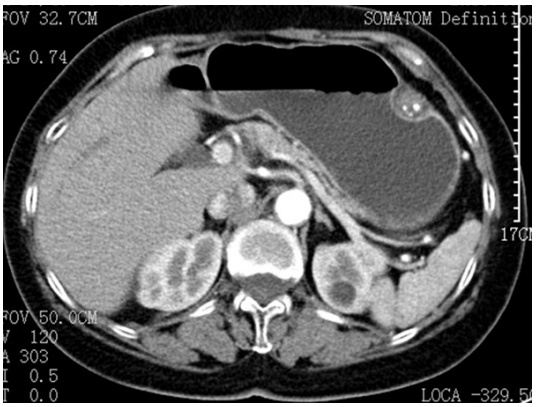

Figure 1. Abdominal Computed tomography showed that gastric wall was locally thickened, with local punctate high density shadow.

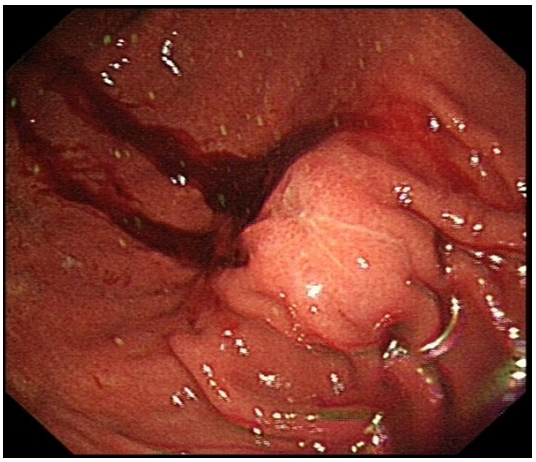

Figure 2. Endoscopic revealed that there was a submucosal protuberance.

minetetraacetic acid), mouse monoclonal antibodies to p53 (clone DO-7, DAKO), Ki-67 (clone MIB-1, DAKO), CK19 (cloneA53-B, MXB), CEA (clone ZC23, MXB), CK7 (clone RN7, ZSGB-BIO), Muc-1 (clone MRQ-17, ZSGB-BIO) and Muc-2 (clone Ccp58, ZSGB-BIO) were applied using standard techniques, with positive and negative controls. Real-time fluorescent quantitative PCR for KRAS and BRAF were performed for our single case using KRAS and BRAF genetic testing kits (AmoyDx, China). Experiments were carried out in accordance with the product specification. The positive control and negative control were performed simultaneously.

Literature review

A review of the literature published in English was performed with MEDLINE search using the

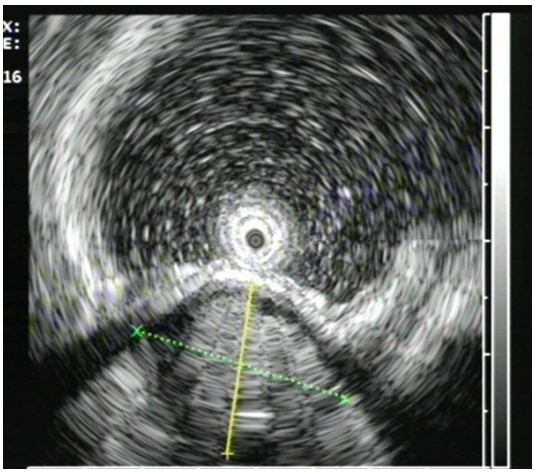

Figure 3. Endoscopic ultrasonography showed a protuberance lesion in the gastric body.

terms “gastric heterotopic pancreas” or “gastric ectopic pancreas” or “gastric aberrant pancreas” combined with “tumor-like lesion” or “carcinoma”. The articles that included cases of IPMN were selected and the references from these articles were also reviewed and the related literature included.

Results

Clinical history of the novel case

The patient was a female aged 63 years. She underwent a medical examination and was found to have a submucosal protuberance in the gastric body for about 1 month. The patient did not have dyspepsia, diarrhea, vomiting, nausea, weight loss or melena. She presented at our hospital on March 13, 2016.

On presentation, the patient had a normal physical examination, including her abdominal examination. Specifically, there was no tenderness, rebound tenderness nor detection of abdominal masses. Her hematological analysis and biochemical values were normal. The viral and tumor markers were negative. Abdominal computed tomography (CT) showed that the gastric wall was locally thickened, with a local punctate high density shadow (**Figure 1**). No other tumor was observed in the pancreas or liver. The patient underwent endoscopy with biopsies. Endoscopy revealed that there was a submucosal protuberance located in the greater curvature of the gastric body, with a presumptive diagnosis of gastrointestinal stromal tumor (GIST) (**Figure 2**). Endoscopic ultrasonog-

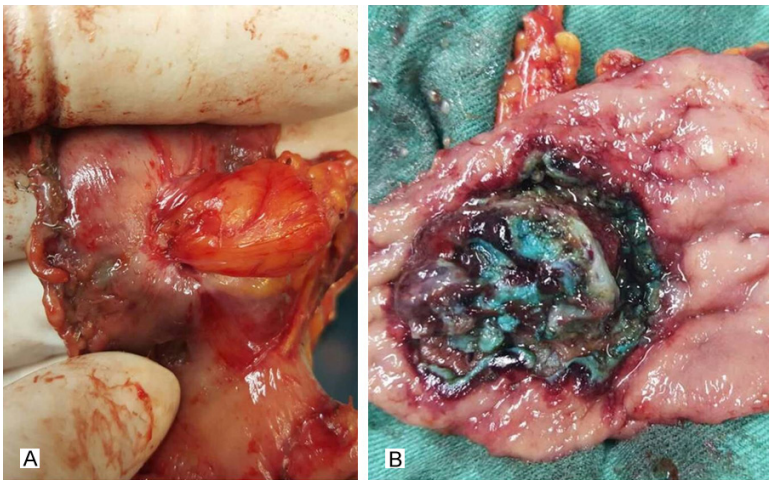

Figure 4. Serosa locally became harden (A) and the mucosa was damaged (B).

raphy also showed a protuberant lesion in the gastric body (**Figure 3**). First, the patient was treated to remove the gross tumor by endoscopic submucosal dissection (ESD), but not successfully. Then, the patient underwent a surgical gastric wedge resection on March 21, 2016. No additional therapy was carried out after the operation. Follow-up for 8 months showed no recurrence or metastasis.

The patient had a past medical history of gallbladder lithalsas, and she had undergone cholecystectomy about 10 years ago. Eighteen months ago, the patient underwent resection of a pure mammary gland and sentinel lymph node biopsy because of high grade ductal carcinoma in situ in the right side of the breast, and was treated with 4 courses of chemotherapy on October 28, November 18, December 8, and December 29, 2014.

Pathological findings of the novel case

Gross examination of the wedge gastrectomy specimen revealed local hardening of the serosa (**Figure 4A**) and damage to the mucosa (**Figure 4B**). The thickness of the gastric wall was 0.8 cm, but the central part was thickened and contained a solid and cystic mass with a size of 3.0×2.0×1.5 cm. The cut surface of the tumor revealed a 1.5-cm white nodule in the cyst. Histological examination showed the cystically dilated ducts contained intraluminal papillae (**Figure 5A**), around a small residual pancreatic duct. The papillary structures were lined by mucinous epithelium with moderate to severe nuclear atypia (**Figure 5B**). Near the serosal surface, there were invasive ductal adenocarcinoma components within the fibrous stroma (**Figure 5C**). In this patient, the type of heterotopic pancreas seemed to be categorized as type III. Immunohistochemistry of the tumor revealed positive results for CK7 (**Figure 5D**), CK19, Muc-1, CEA, and negative results for Muc-2, P53. Ki-67, the proliferation index was 40%. Molecular analysis showed that our patient harbored an activating mutation in KRAS at codon 12 (p.G12D), without any BRAF mutation.

Literature review

A total of 31 cases of tumor-like lesions arising from gastric heterotopic pancreas were retrieved from the literature. Clinical information on these 31 cases, along with the single new case, is detailed in **Table 1**.

There were 17 women and 15 men included in the study. Patients ranged in age from 24 to 86 years (median 57 years). Sixteen patients complained of dyspepsia or epigastric pain, and 2 patients of melena or anemia, while 14 patients had no clinical symptoms. Most cases reported in the literature had occurred in the gastric antrum (14/26, 54%), gastric pylorus (5/26, 19%), the cardia (4/26, 15%), and the gastric body (2/26, 8%), and 1 case in the gastric fundus (1/26, 4%).

Most of the cases were classified according to the Heinrich classification of heterotopic pancreas [23]. In fact, 11 of 26 (42%) cases were categorized as Class I heterotopia, with Class II and Class III occurrence at 23% (6/26) and 35% (9/26) of cases, respectively. The average size of tumors was 3.4 cm, ranging from 0.9 cm to 7.6 cm (median, 2.5 cm).

Most tumors associated with heterotopic pancreas have been identified as adenocarcinomas (21/32), including invasive ductal adeno-

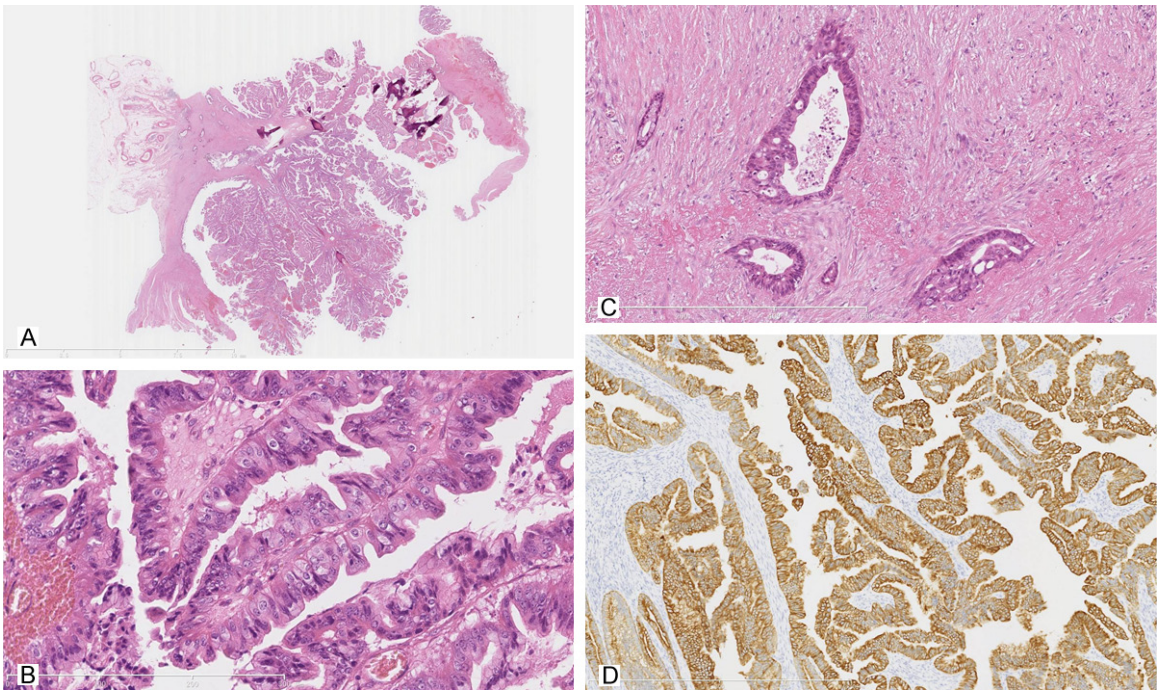

Figure 5. A cystically dilated ducts contained intraluminal papillae (A). Papillary structures were lined by mucinous epithelium with moderate to severe nuclear atypia (B). Invasive ductal adenocarcinoma component within fibrous stroma (C). Immunostains showed that tumor cells were positive for CK7 (D).

carcinoma, IPMN with locally invasive carcinoma, anaplastic adenocarcinoma, mucinous carcinoma and papillary cystadenocarcinoma. Other less common types of pancreatic neoplasia included IPMN with different grade dysplasia (5/32), acinar cell carcinoma (4/32), and neuroendocrine tumors (NET) (2/32).

All patients underwent surgical local tumor excision. Twenty patients had complete follow-up results. The follow-up time ranged from 1 to 132 months (mean, 18 months). At the last follow-up, 5 patients (25%) had died of disease, 3 patients (15%) underwent recurrence or metastasis after initial treatment and 12 patients (60%) were alive with no evidence of disease.

Molecular analyses were reported in 3 cases. One case of IPMN arising from heterotopic pancreas, had negative results for the K-ras mutation, but there were loss-of-heterozygosity (LOH) mutations of 10q and 17q [4]. Analysis of another patient with ductal adenocarcinoma in heterotopic pancreatic parenchyma identified that there was a KRAS mutation at codon 12 [22]. Our patient had an activating mutation in KRAS at codon 12 (p.G12D).

Discussion

Heterotopic pancreas is defined as pancreatic tissue that lacks anatomic and vascular continuity with the main body of the pancreas [24]. Heterotopic pancreas can occur in any part of the digestive tract, including, most commonly, the stomach, duodenum, and jejunum. It is also found in the ileum, gallbladder, mesenteric and omental, transverse colon, liver and spleen [24]. Heterotopic pancreas in the stomach is usually located along the greater curvature of the stomach, often in the gastric antrum [24].

Heterotopic pancreas is most commonly found incidentally. Although most patients are asymptomatic, heterotopic pancreas can occasionally lead to dyspepsia, epigastric heaviness, gastrointestinal obstruction, epigastric pain, obstructive jaundice, and other presentations according to the location of the ectopic tissues. Heterotopic pancreatic tissue can occur with pathological changes including pancreatitis, pancreatic cyst and pancreas exocrine or endocrine tumor.

Tumor-like lesions within the heterotopic pancreas are rare, and there are only sporadic

Table 1. Summary of reported cases of tumor-like lesions arising from gastric heterotopic pancreas

	Age/sex	Symptoms	Location	Tumor size	Heterotopia type	Carcinoma type	Last follow-up (months)	Outcome
1 [3]	66/M	Asymptomatic	Antrum	1.2 cm	I	IPMN	19	AW
2 [4]	44/M	Abdominal bloating and epigastric pain	Antrum	0.9 cm	I	IPMN	NA	NA
3 [5]	60/M	Dyspepsia and epigastric heaviness	cardia	7.5 cm	NA	Adenocarcinoma	48	AW
4 [6]	85/M	Dyspepsia	NA	1.7 cm	I	NET	1	AW
5 [7]	71/F	Melena	Antrum	1.5 cm	II	IPMN with severe dysplasia	NA	NA
6 [8]	77/F	Anemia	Fundus	4.5 cm	NA	Acinar cell carcinoma	1	died
7 [9]	86/F	Asymptomatic	Antrum	5.0 cm	NA	Acinar cell carcinoma	NA	NA
8 [10]	73/M	Epigastralgia	Pylorus	7.6 cm	NA	Acinar cell carcinoma	11 disease 11 months	Metastasis to the liver AD
9 [11]	60/M	Epigastric pain	Antrum	1.7 cm	I	IPMN	NA	NA
10 [12]	56/F	Epigastric pain, periodic nausea and vomiting	Antrum	2.0 cm	III	Carcinoma	6	AW
11 [13]	49/F	Dyspepsia	Cardia	1.3 cm	I	NET	6	AW
12 [14]	74/F	Epigastralgia	Gastric body	4.0 cm	I	Invasive ductal carcinoma	132	AW
13 [1]	52/M	Epigastric pain	Antrum	4.0 cm	III	Adenocarcinoma	9	AW
14 [15]	56/F	Asymptomatic	Antrum	2.5 cm	III	Mucinous carcinoma	48	AW
15 [16]	35/M	Asymptomatic	Antrum	1.7 cm	III	Adenocarcinoma	5	AW
16 [17]	58/F	Vomiting	Antrum	2.5 cm	II	Adenocarcinoma	18	Metastasis to the abdominal wall AD
17 [18]	52/M	Dyspepsia	Antrum	4.0 cm	NA	Acinar cell carcinoma	NA	NA
18 [19]	80/M	Dyspepsia/diarrhea	Antrum	6.0 cm	I	IPMN	NA	NA
19 [20]	42/M	Asymptomatic	NA	NA	III	Ductal adenocarcinoma	NA	NA
20 [21]	73/F	Asymptomatic	NA	NA	III	Ductal adenocarcinoma	NA	NA
21 [21]	48/F	Asymptomatic	NA	NA	III	Ductal adenocarcinoma	NA	NA
22 [2]	60/M	Epigastric pain	Cardia	6.0 cm	I	Ductal adenocarcinoma	3	died
23 [22]	57/F	Asymptomatic	NA	NA	II	Ductal adenocarcinoma	NA	died
24 [23]	55/F	Asymptomatic	Antrum	NA	II	Ductal adenocarcinoma	NA	died
25 [24]	27/F	Epigastric pain	Pylorus	2.5 cm	III	Poorly differentiated adenocarcinoma	24	AW
26 [25]	58/M	Weight loss, epigastric pain and vomiting	Pylorus	1.0 cm	I	Fuctal adenocarcinoma	NA	Recurrent
27 [26]	55/F	Weight loss, epigastric pain and vomiting	Pylorus	6.0 cm	I	Fuctal adenocarcinoma	NA	NA
28 [27]	44/F	Asymptomatic	NA	NA	II	Adenocarcinoma	48	AW
29 [27]	53/M	Asymptomatic	Cardia	NA	II	Adenocarcinoma	NA	died
30 [28]	24/F	Asymptomatic	Pylorus	NA	NA	Anaplastic adenocarcinoma	NA	NA
31 [29]	M	Asymptomatic	Antrum	NA	I	Papillary cystadenocarcinoma	NA	NA
Present	63/F	Asymptomatic	Gastric body	2.4 cm	III	IPMN with invasive cancer	8	AW

AW, alive and well; NA, not available; AD, alive with disease.

cases available in the literature. In our review of the literature, most of the tumors which originated in the heterotopic pancreas occurred in the gastric region [1]. To our knowledge, 31 cases have been reported. The genetic structure, physiological function, and local environment exposure of heterotopic pancreas, are similar to that of the normal pancreas. Pancreatic intraepithelial neoplasia (PanIN) is a precursor to ductal adenocarcinoma. Zhang *et al* [30] considered that duct epithelial cells in heterotopic pancreas had an equal chance of developing carcinoma as those in the orthotopic organ, and suggested that heterotopic pancreas in surgical pathology practice should be examined carefully for the presence of PanIN.

Heterotopic pancreas has been classified into 3 types by Heinrich: Class I is typical pancreatic tissue with acini, ducts and islet cells, Class II shows a large number of acini and few ducts, and Class III shows numerous ducts with few acini or islet cells [23]. Most of the cases in our review were classified according to the Heinrich classification. The most frequent class of heterotopia associated with tumors was Class I (42%), followed by Class III (35%). Our patient had disease that occurred in a Class III heterotopic pancreas. Most of the tumors associated with heterotopic pancreas have been adenocarcinomas, most of which have shown a ductal differentiation. While the follow-up time is short or most of the cases lack follow-up information, the prognosis of heterotopic pancreas carcinoma appears to be similar to that of pancreatic cancer.

The differential diagnosis for ectopic pancreas and their corresponding tumor-like lesions includes carcinoid, GIST, or other mesenchymal tumors, such as leiomyoma or neurofibroma. A central umbilication, which fills with contrast, is a diagnostic feature of ectopic pancreas thought to represent a rudimentary duct. Our patient was initially misdiagnosed as having GIST, and an operation by ESD was not successful. Endoscopic ultrasonography is valuable and safe for the diagnosis of ectopic pancreas in the upper gastrointestinal tract. By endoscopic ultrasonography, the ectopic pancreas is characterized as a submucosal neoplasm with low echo or mixed echo, unclear border, uneven internal echoes, and occasionally mucous membrane and muscularis are affected. Tubulous or cystic anechoic structure in the mass is of more diagnostic value. The depth of lesions revealed by endoscopic ultrasonography can help further treatment.

Studies have found that there is a gradual process from precursor lesions of the pancreas to invasive pancreatic adenocarcinoma, with an activating mutation in codon 12 of KRAS being a common and early event [31]. Only a few studies have examined the molecular changes in tumor-like lesions arising inheterotopic pancreas. One study reported that in 1 case of IPMN arising from the heterotopic pancreas, loss-of-heterozygosity (LOH) mutations of 10q and 17q were identified, without the KRAS mutation [4]. Another case of ductal adenocarcinoma in heterotopic pancreatic parenchyma was evaluated by molecular analysis. A KRAS mutation at codon 12 was identified, which is the most common mutational changes observed in patients with pancreatic carcinoma [22]. Our patient was also found to have the activating mutation in KRAS at codon 12 (p.G12D), which was consistent with studies by Ma *et al* [32].

Because the heterotopic pancreas frequently occurs in the submucosa, apophasis lesions in the submucosa should take into account the possibility of heterotopic pancreas. The patient in the present case had no specific clinical manifestations, and endoscopy only hinted at a submucosal lesion. Because the attending doctor had a lack of understanding of gastric ectopic pancreas and the possibility of tumor, the patient did not have a clear diagnosis preoperatively. There is no consensus on whether cancer arising from the ectopic pancreas should be treated with radical cure postoperative adjuvant chemotherapy. However, we think that appropriate treatment should be given according to the tumor staging.

Disclosure of conflict of interest

None.

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