〈Case Report〉

Jejunal heterotopic pancreas containing high-grade pancreatic intraepithelial neoplasia (PanIN-3): case report and literature review

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ABSTRACT We here report a rare surgical case of heterotopic pancreas in the jejunum that contained high-grade pancreatic intraepithelial neoplasm (PanIN-3). When a sixty-four-year old man had a surgery for transverse colon cancer in our hospital, a subserosal mass was coincidentally found in the jejunum and was resected for pathological determination. The mass was Heinrich type-I heterotopic pancreas that contained irregular dilation of pancreatic ducts with moderate to severe atypia, so-called PanIN-3. It is reported that heterotopic pancreas can be found at approximately 0.5% of laparotomy, mostly without specific preoperative symptoms. Most of its pathological characteristics are benign, whereas, there are a few reports of its malignant cases. PanIN-containing heterotopic pancreas is very rare in the literature. However, its malignant alteration is thought to arise through PanIN or intraductal papillary mucinous neoplasm (IPMN) as the carcinogenesis of orthotopic pancreas.

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INTRODUCTION

Heterotopic pancreas is a congenital anomaly defined as the presence of pancreatic tissue outside its normal location without anatomic, neural or vascular connection to the orthotopic pancreas[1)]. Heterotopic pancreas is found in 0.5% of laparotomies, mostly without any specific preoperative symptoms, and in up to 13% of autopsies[2, 3)]. Most of its pathological characteristics are benign, with few reports of malignant cases[4－6)]. Similar to carcinogenesis in the orthotopic pancreas[7, 8)], malignant alteration in heterotopic pancreas is also thought to arise through pancreatic intraepithelial neoplasia (PanIN) or

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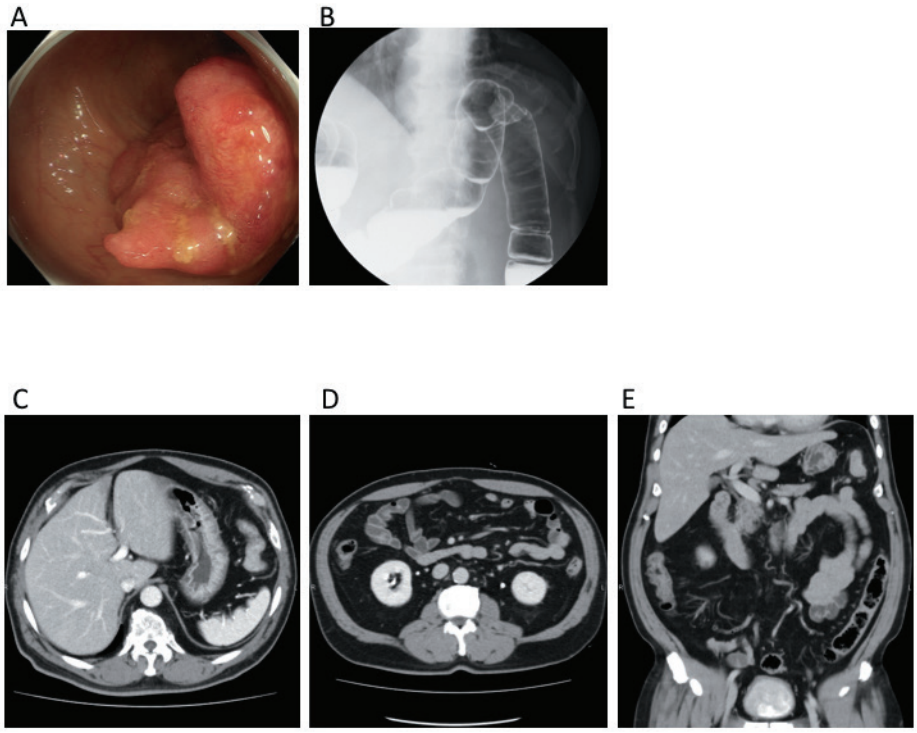

Fig. 1. Preoperative images
Preoperative image assessments did not show any intestinal tumors other than the transverse colon cancer.

intraductal papillary mucinous neoplasm (IPMN), though PanIN-containing heterotopic pancreas is very rare in the literature[8-10]. We report here on a rare surgical case of heterotopic pancreas in the jejunum that contained high-grade PanIN (PanIN-3).

CASE REPORT

A sixty-four-year old man taking various regular medications for hypertension, dyslipidemia, hyperuricemia, diabetes, and constipation was positive for fecal occult blood during a routine medical checkup but had no symptoms. At the time, he was no history of hospitalization or any remarkable family history. A colonoscopy and a barium enema examination revealed an advanced cancer in the transverse colon (Fig. 1A, B). Representative laboratory data are shown in Table 1, and preoperative radiological examinations showed no apparent intestinal mass other than the colon tumor, nor any metastatic lesions (Fig. 1C-E). During the laparoscopy-assisted colectomy for the colon cancer, laparoscopic observation coincidentally found a subserosal mass 2.5 cm in diameter in the jejunum (Fig. 2A). When a small-incision laparotomy was made for colonic anastomosis, the jejunal mass was resected and

Table 1. Results of preoperative blood examination

WBC	*9270*	*/μL*	*H*	TP	8.1	g/dL	
RBC	4.87	x 10^6/μL		Glu	116	mg/dL	
Hgb	15.7	g/dL		T.Bil	0.6	mg/dL	
Hct	44.0	%		ALP	261	U/L	
PLT	21.0	x 10^4/μL		LD	169	U/L	
PT	10.8	sec		ALB	4.7	g/dL	
APTT	*37.4*	*sec*	*H*	*ALT*	*49*	*U/L*	*H*
HBs-Ag	(-)			AST	25	U/L	
HCV-Ab	(-)			*Cre*	*1.19*	*mg/dL*	*H*
HbA1c	6.4	%		UN	13	mg/dL	
Na	139	mmol/L		*CRP*	*0.23*	*mg/dL*	*H*
K	4.0	mmol/L		CEA	1.7	ng/mL	
Cl	103	mmol/L		*CA19-9*	*37.4*	*U/mL*	*H*

H indicates that the value exceeded its upper limits of normal.

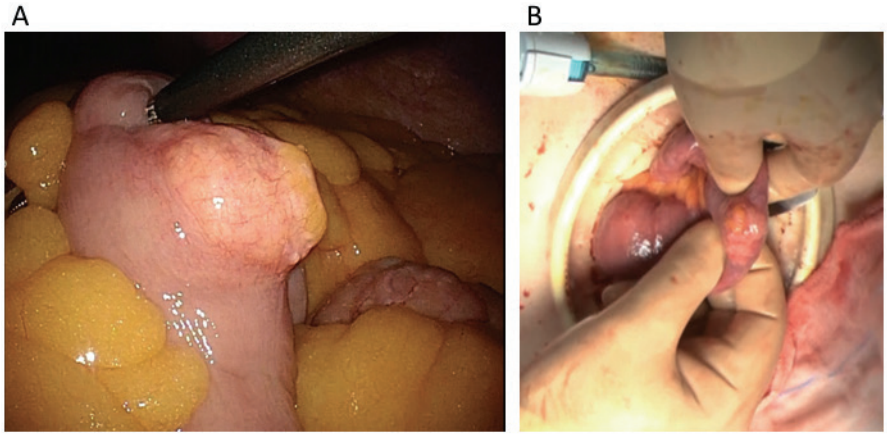

Fig. 2. Representative pictures of intraoperative findings
(A) Laparoscopic observation coincidentally found a subserosal mass in the jejunum.
(B) The jejunal mass was resected when a small-incision laparotomy was made for colonic anastomosis.

pathological examination (Figs. 2B, 3A, B) revealed that the mass contained acini, ducts, and islets of Langerhans, similar to those seen in orthotopic normal pancreas tissue, equivalent of type-I heterotopic pancreas of Heinrich's classification (Fig. 3C). No apparent inflammatory change was observed in the tissue. Furthermore, this aberrant pancreas contained moderate to severe irregular dilation of the pancreatic ducts that were classified as PanIN-2 to PanIN-3 (Fig. 3D, E). The patient was discharged with no post-operative complications and no apparent malignant alteration in the orthotopic pancreas. He is currently under regular outpatient observations without recurrence for more than 3 years.

DISCUSSION

Heterotopic pancreas is variously referred to as ectopic, aberrant or accessory pancreas in the literature[1]. Heterotopic pancreas is most commonly found in the upper gastrointestinal tract, especially in the stomach, duodenum and proximal jejunum[1]. All pathologic conditions that can possibly develop in the normal pancreas have been observed in heterotopic pancreases, such as acute and chronic pancreatitis, pseudocystic changes, IPMN, intraepithelial lesions and pancreatic neuroendocrine tumors[1, 4]. Malignant transformation, however, is exceedingly rare[2, 4]. According to Cazacu *et al*, malignant heterotopic pancreas was commonly located in the stomach (35.2%), and arose within Heinrich's type I heterotopia[4]. More than 80% of cases had clinical symptoms such as abdominal pain, nausea/vomiting, dyspepsia and weight loss. In comparison with reported data for orthotopic pancreatic cancer, malignant heterotopic pancreas appeared to show improved prognosis[4]. In the reported rare cases of PanIN lesions in the heterotopic pancreas, the premalignant changes seemed to occur with approximately the same incidence as in the orthotopic pancreas[11]. Malignant transformation in heterotopic pancreas is also thought to occur in the same fashion of that in orthotopic pancreas, which arises from its precursor lesions, such as PanIN and IPMN. Accumulation of genetic alterations is observed during carcinogenesis of heterotopic pancreas as well as that of orthotopic one. Zhang *et al*. demonstrated that alterations of p53, p16, and cyclin D1 were observed in most of PanIN-2 and PanIN-3 lesions accompanied by K-ras

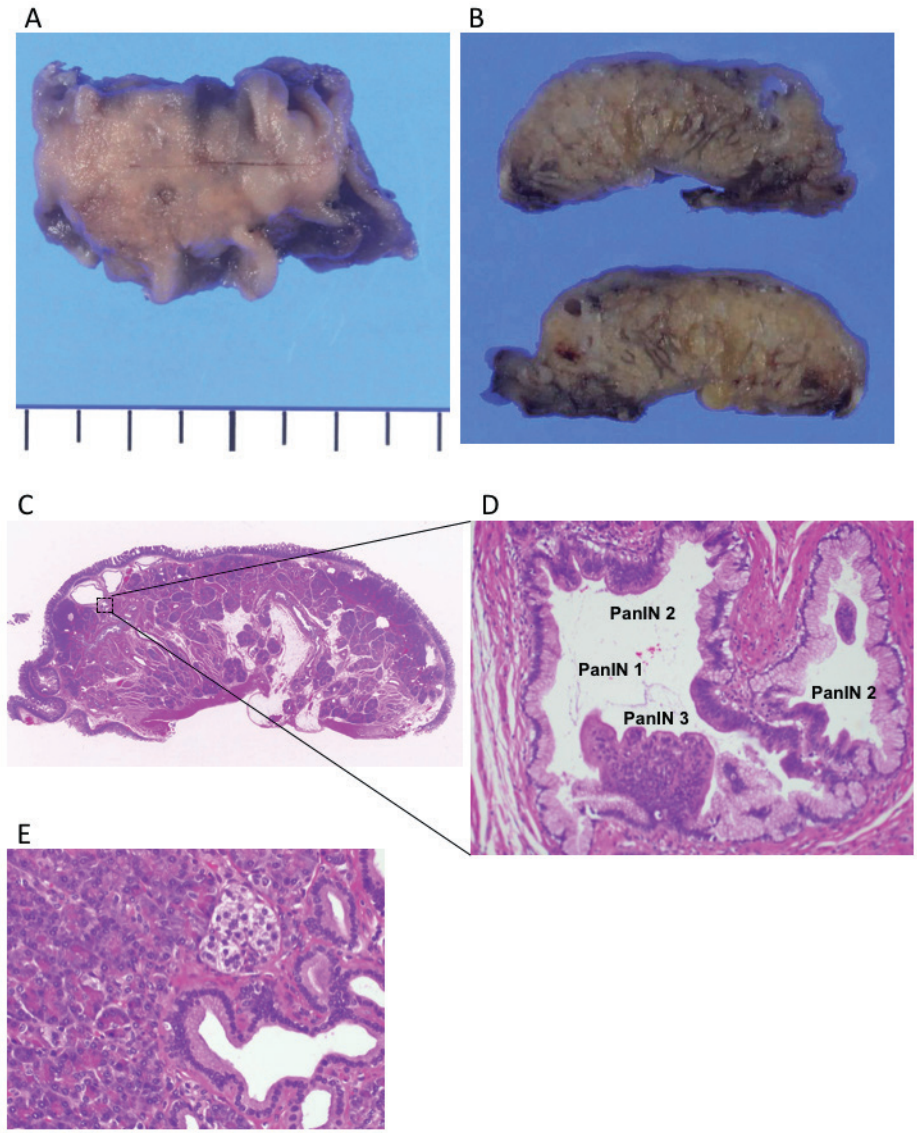

Fig. 3. Macroscopic and microscopic observations of resected tissues
The jejunal mass was 36 × 20 × 12 mm (A and B) and was Heinrich type-I ectopic pancreas. This aberrant pancreas contained irregular dilation of the pancreatic ducts with moderate to severe atypia (PanIN2-3) (C-E).

mutation[8].

Thus far, including this case, just eighty-eight cases of PanIN in heterotopic pancreas have been reported in 10 articles[7–16], with only 6 of those 88 cases having high-grade PanIN (PanIN-3) (Table 2). In the majority of cases the lesions were located in the stomach or duodenum, whereas only 16 cases had lesions in the jejunum, as in the case in this report. Interestingly, there were two cases in the omentum and a case in Meckel's diverticulum[15, 16]. Most of the PanIN cases arose from heterotopic pancreases with a Heinrich's classification of type I or type II, both of which contain a certain amount of duct structure[4, 12, 16].

It is difficult to diagnose malignant and

Table 2. Summary of literatures about aberrant pancreas with PanIN

Case	Year	Location	Heinrich's classification	PanIN grade
Zhang et al. (8 cases)	2007	Stomach: 1, Duodenum: 5, NA: 2	I/II/III/NA = 3/3/0/2	-1/-2/-3 = 3/4/1
Sadeghi *et al*.	2008	stomach	(III)	PanIN-2
Lee *et al*.	2013	stomach	(III)	PanIN-3
Niino *et al*.	2014	jejunum	I	PanIN-3
Macedo *et al*.	2014	jejunum	NA	PanIN-2
Ulrych *et al*.	2015	esophagus	I	PanIN-2
Ma *et al*. (5 cases)	2016	Stomach: 3, Small intestine: 1, Meckel's diverticulum: 1	I/II = 1/4	-1/-2/-3 = 3/2/0
Cornea *et al*.	2017	jejunum	I	PanIN-2
Jun *et al*. (68 cases)	2017	Stomach: 35, Duodenum: 18, Jejunum: 13, omentum: 2	NA	-1/-2/-3 = 58/9/1
Safadi *et al*.	2018	duodenum	NA	PanIN-3
Our case		jejunum	I	PanIN-3

premalignant ductal lesions in heterotopic pancreases preoperatively, thus their surgical excision is mandatory[10]. Considering the difficulty of distinguishing a heterotopic pancreas from other gastrointestinal submucosal malignancies, it is reasonable to choose surgical resection for unusual intraperitoneal masses due to the possibility that it may be a tumorigenic heterotopic pancreas. On the other hand, we must always keep in mind that such unusual intraperitoneal masses can be just benign tissues like heterotopic pancreas, which is not necessarily removed. We should carefully determine its surgical indication based upon the pros and cons of its removal, which may affect patients' perioperative condition or may invite a potential risk of intestinal repair, in addition to getting informed consent from patients. Based upon this idea, careful assessment of preoperative images and intraoperative observations are both quite important.

CONCLUSION

A heterotopic pancreas does not always need to be removed, although it is often difficult to distinguish from other tumors by preoperative image examinations or even by intraoperative inspection. The surgical indication should be carefully considered on the basis of possible malignant alteration.

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CONFLICT OF INTEREST STATEMENT

No author of this manuscript has any conflicts of interest to be disclosed.

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