



## CASE REPORT

# Malignant transformation of heterotopic pancreas as middle esophagus adenocarcinoma—A rare case report and comprehensive literature review

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## Abstract

Heterotopic pancreas is a rare congenital abnormality that occurs during the growth and development process. It can be found in any part of the digestive tract, but the most common sites are the stomach, duodenum, and jejunum. Malignant transformation especially in the esophagus is rare. Here, we aim to report an unusual case of mid-esophageal adenocarcinoma that originated from a heterotopic pancreas.

## KEYWORDS

esophagus, heterotopic pancreas, malignant transformation

## INTRODUCTION

Heterotopic pancreas refers to pancreatic tissue found outside its normal location which has no anatomical or vascular relationship with the normal pancreas.<sup>1</sup> It is a congenital malformation that can occur in any part of the digestive tract with the most common sites being the stomach, duodenum, and jejunum.<sup>2,3</sup> It is typically asymptomatic and the lesion is normally discovered incidentally during an unrelated surgery, imaging, or even at autopsy. A few patients may present with nonspecific symptoms such as abdominal pain, dyspepsia, obstruction, bleeding, and inflammation depending on

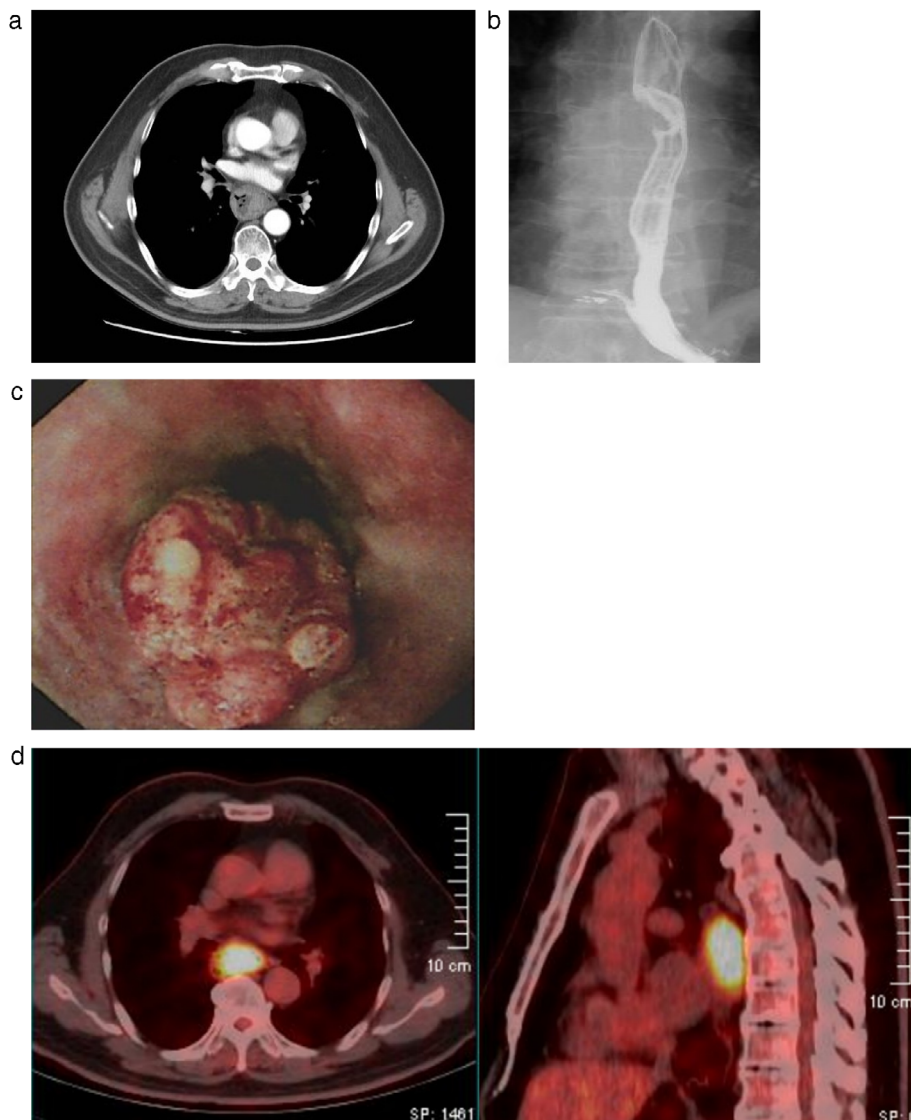
the site of the lesion. Malignant transformations especially those involving the esophagus are rare.<sup>4</sup> Here, we report an unusual case of mid-esophageal adenocarcinoma that originated from a heterotopic pancreas.

## Case report

A 60-year-old gentleman presented to our hospital with a history of epigastric discomfort for 1 month, with no symptoms of dysphagia, heartburn, acid reflux, abdominal distention, diarrhea, or weight loss. Physical examination did not

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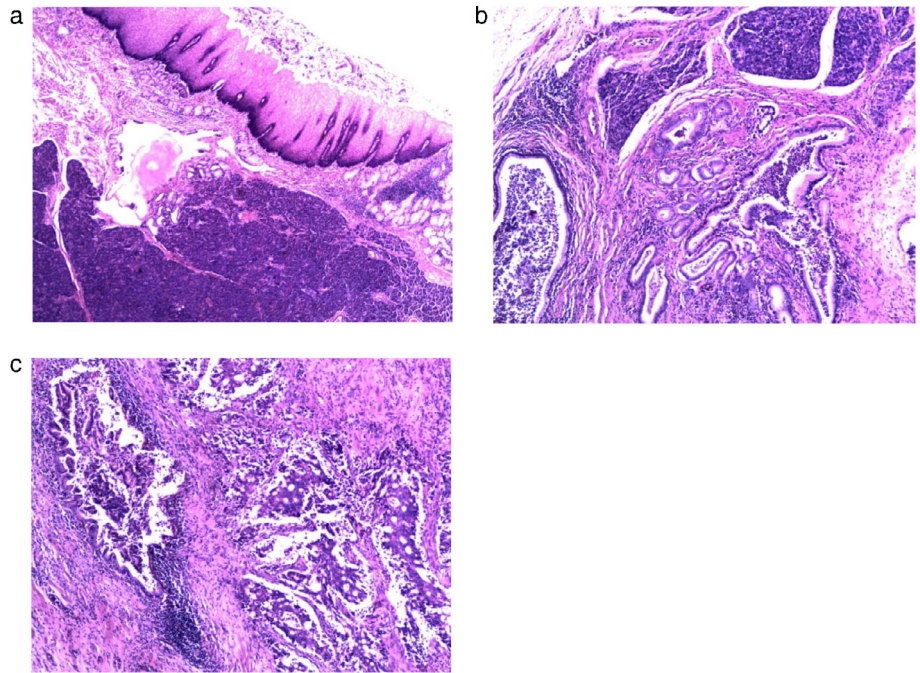


**FIGURE 1** (a) Contrast-enhanced chest computed tomography demonstrates thickening of the middle esophageal wall. (b) Barium swallow shows a filling defect of the middle esophagus. (c) Endoscopy reveals a 4.0 cm mid-esophageal mass. (d) PET/CT image shows a mid-esophageal soft tissue mass with high FDG uptake without lymph node involvement

reveal any abnormalities. Routine hematological, biochemical, and tumor marker (CEA, CA 19-9, CA 72.4, CA 125) tests were within the normal range. Esophagogastroduodenoscopy demonstrated a submucosal cauliflower-like mass with a diameter of 3 cm at the middle esophagus causing luminal stenosis. Biopsy revealed a poorly differentiated adenocarcinoma. Contrast-enhanced computed tomography (CT) demonstrated a  $3.3 \times 3.0$  cm tumor at the right-side wall of the mid-esophagus without any adjacent pleural invasion. Positron emission tomography (PET) revealed a mid-esophageal soft tissue mass with high fluorodeoxyglucose (FDG) uptake without regional lymph node involvement or distant metastases. The patient was diagnosed with mid-esophageal adenocarcinoma that was clinically staged as cT3N0M0 according to the eighth TNM staging system (Figure 1). A minimal McKeown esophagectomy was performed and a mid-esophageal tumor measuring  $3.0 \times 3.0$  cm that did not infiltrate through the adventitia was identified. A  $4.0 \times 2.0$  cm diverticulum was found adjacent to the tumor. The postoperative recovery of

the patient was unremarkable. Histopathological examination showed characteristic moderately differentiated adenocarcinoma with cribriform structure, heterotopic pancreas composed of lobular acini, and hyperplastic ductal glands scattered in the submucosa and mucosa muscularis of the esophagus (Heinrich's type I). Lymph-vascular invasion, or neural infiltration was not identified and all resected lymph nodes were negative. Immunohistochemistry tests were as follows: *BRCA* ( $+<25\%$ ), *C-met* (2+), *EGFR* (3+), *ERCC-1* ( $+50-75\%$ ), *HER2* (0), *Ki-67* ( $+50-75\%$ ), *CK7* (partly +), *CK20* (+), *CDX-2* (+), *TP63* (-), *CA 19-9* (partly +), *CEA* (+), *TP53* (-), *P16* (-), and *CyclinD1* (-) (Figure 2). The patient did not receive adjuvant therapy post-operatively, but had regular follow-up at the outpatient department. Unfortunately, he had mediastinal lymph node recurrence and lung metastasis 37 months after the operation and received adjuvant cisplatin-based chemotherapy for recurrence. The patient did not respond well to chemotherapy and the tumor subsequently slowly progressed. The patient died 20 months after recurrence.

**FIGURE 2** (a) Ectopic pancreas with lobular structure highlighted in the submucosa and mucosa muscularis of the esophagus ( $\times 40$  magnification). (b) Ectopic pancreas with lobular acini and hyperplastic ductal glands ( $\times 100$  magnification). (c) Right-sided moderately differentiated adenocarcinoma with cribriform structure. On the left side, a ductal gland was identified with pancreatic intraepithelial neoplasia 1 (PanIN-1) changes next to the carcinomatous glands, which indicates that this adenocarcinoma originated from the pancreatic duct ( $\times 100$  magnification)



**TABLE 1** Heinrich's classification of heterotopic pancreas

Type	Histopathological characteristics
Type I	Typical pancreatic tissue with ducts, acini, and islet cells
Type II	Numerous acini, few ducts, and no islet cells
Type III	Numerous ducts, few to no acini, and no islet cells
Type IV	Endocrine islets without exocrine pancreatic tissue

**DISCUSSION**

Heterotopic pancreas, also known as an aberrant or ectopic pancreas (EP), is described as pancreatic tissue in an abnormal location without any anatomic, vascular, or neural continuity with the normal pancreas. It is more predominant in men than women and typically is not discovered until the fifth to sixth decade of life. Only a few cases are diagnosed

**TABLE 2** Esophageal ectopic pancreas cases in the literature

Case	Sex	Age	Presentation	Location	Treatment	Pathology	Heinrich's type	Follow-up results
1	M	43	Hematemesis	Distal	Thoracotomy	EP	I	Asymptomatic
2	M	25	Vomiting	Middle	Ivor Lewis esophagectomy	EP	N/A	The intramural esophageal cyst was enucleated by right thoracotomy
3	M	60	Dysphagia, epigastric pain	EGJ	Tumor resection by left thoracotomy and proximal stomach resection	Adenocarcinoma	N/A	Initially asymptomatic, but died 3 months postoperatively
4	F	47	Epigastric pain	EGJ	Ivor Lewis esophagectomy	EP	I	N/A
5	M	45	Dysphagia	EGJ	Sweet esophagectomy	Anaplastic carcinoma	N/A	Survived over 3 years with no recurrence
6	F	24	Nausea and vomiting, fever, and chills	EGJ	Esophageal enucleation	EP	I	Asymptomatic at 1 year
7	M	52	Episodic dysphagia	EGJ	Dietary adjustment	EP	N/A	Asymptomatic
8	F	41	Dysphagia, epigastric pain	EGJ	Gastrectomy with Roux-en-Y esophagojejunostomy	EP	I	N/A
9	F	26	Epigastric pain, nausea	EGJ	Laparoscopic excision	EP	I	Asymptomatic at 2 months

(Continues)

TABLE 2 (Continued)

Case	Sex	Age	Presentation	Location	Treatment	Pathology	Heinrich's type	Follow-up results
10	M	63	Asymptomatic	Middle	Conservative management	EP	II	Asymptomatic for 5 years
11	F	14	Periumbilical abdominal pain	Distal	Conservative management	EP	II	N/A
12	F	58	Dysphagia	EGJ	Ivor Lewis esophagectomy	Intraductal papillary mucinous neoplasm	N/A	Asymptomatic at 3 months
13	M	25	Epigastric pain	EGJ	VATS resection	EP	N/A	Asymptomatic at 2 months
14	F	73	Epigastric pain, heartburn, nausea, vomiting	EGJ	Endoscopic resection	EP	I	N/A
15	M	34	Dysphagia	Distal	Left thoracotomy	EP	I	Asymptomatic at 3 months
16	M	70	Heartburn, nausea, abdominal bloating	Distal	Endoscopic resection	EP	I	N/A

in children.<sup>5</sup> There are several theories regarding the development of heterotopic pancreas: (i) the dislocation theory states that during foregut rotation, the original pancreatic components are separated, deposited, and develop ectopically, thus gradually forming mature pancreatic tissue. (ii) The metaplasia theory posits that heterotopic pancreas originates from the endoderm of the pancreatic metaplasia region and then migrates to the submucosa during embryogenesis. (iii) In the totipotent cell theory, the totipotent endodermal cells lining the gut differentiate into pancreatic tissue.<sup>6</sup>

Patients with a heterotopic pancreas are usually asymptomatic and it is only occasionally found during routine imaging or endoscopy, after surgery, or even at autopsy. Therefore, the true incidence is hard to estimate. The reported incidence ranges from 0.55% to 13.7% on autopsy and 0.2% during upper abdominal surgery.<sup>2,7</sup> A few patients may present with various nonspecific symptoms such as abdominal pain, nausea, dysphagia, dyspepsia, bleeding, and obstruction depending on the site of the lesion.

Because there are no specific clinical manifestations or imaging signs, accurate diagnosis is usually difficult. In many cases, the correct diagnosis cannot be determined until the resected specimen is examined by histopathology. Most lesions are solitary, with a diameter of less than 3 cm. Typical endoscopic findings show a submucosal mass covered by normal mucosa with an intraluminal growth pattern. In some endoscopic cases, central umbilication can be found, but the exact diagnosis is not easy without a biopsy. These lesions are frequently misdiagnosed as gastrointestinal stromal tumors (GIST) or leiomyomas before a complete resection is performed. Endoscopic ultrasonography may exhibit an intermediate echogram between the echo dense submucosa and hyperechoic muscularis propria layer. The

lesions appear to be hypoechoic to the submucosa and isoechoic to the muscularis propria.<sup>1</sup> CT images usually show oval submucosal masses with unclear boundaries and lobular morphology. Lesions exhibiting enhancement greater than or the same as those of the orthotopic pancreas are dominated by acini, whereas lesions with less enhancement are dominated by ducts and hypertrophied muscle.<sup>7</sup>

The heterotopic pancreas is classified into three Heinrich types. The first and most common type is composed of all the elements of normal pancreatic tissue, including acini, ducts, and islet cells. The second and third histological types are dominated by either acini or ducts. In 1973, Gaspar-Fuentes modified this classification system and added a fourth histological type which is composed of only endocrine islet cells without exocrine pancreatic tissue (Table 1).<sup>8</sup> Malignant transformations of the heterotopic pancreas are rare events, with a reported incidence rate of 0.7% to 1.8%. It is even more rare for lesions located at the esophagus. Only three cases of malignant transformations of the heterotopic pancreas at the esophagus have been reported in the literature (Table 2).<sup>3,5,9–23</sup>

There is no standardized guideline for the management of heterotopic pancreas, but treatment depends on the patient's clinical symptoms and the location of the lesion. For asymptomatic patients or those with small lesions, regular observation, or medication is appropriate. For symptomatic patients, or those with the possibility of a malignant transformation, endoscopic or surgical resection should be carried out. Resection is the gold standard of management for a definitive diagnosis.

#### CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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