CASE REPORT

Malignant Transformation in Gastric Pancreatic Heterotopia A Case Report and Review of the Literature

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ABSTRACT

Context Gastric pancreatic heterotopia is a relatively common incidental finding; however, malignancy arising in this tissue is an extremely rare occurrence, with nonspecific clinical, radiographic, and intraoperative features. We herein report the case of adenocarcinoma arising in ectopic pancreatic tissue of the gastric antrum and review the literature to summarize all recent cases of malignancy arising in gastric pancreatic heterotopia. **Case report** A Forty-five-year-old male presented with six-week history of gastric outlet obstruction found on endoscopy to be secondary to a submucosal mass within the gastric antrum. Pre-operative suspicion of a gastric cancer *vs*. gastrointestinal stromal tumor prompted a subtotal gastrectomy. Recognition of perineural invasion associated with a well-differentiated adenocarcinoma prompted further histological sections to be taken, and a gastric pancreatic heterotopia was identified associated with the malignancy through a transition zone. The diagnosis of malignancy arising in pancreatic heterotopia was made. **Conclusions** Accurate diagnosis of this rare diagnosis remains a challenge and is heavily reliant on histopathological evaluation. The presence of perineural invasion in a gastric adenocarcinoma should prompt suspicion of a non-primary gastric cancer such as a gastric pancreatic heterotopia.

INTRODUCTION

Heterotopia, defined as the presence of pancreatic tissue beyond the natural anatomic boundaries and without vascular or anatomic connection to the native pancreas, is a relatively common incidental finding at autopsy, discovered in approximately 0.6-15% of patients [1]. However, malignancy in these lesions is extremely rare. We herein report the case of adenocarcinoma arising from pancreatic heterotopia in the gastric antrum and review the current available literature to analyze trends of this rare diagnosis.

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CASE REPORT

A Forty-five-year-old male presented with a six week history of early satiety, vomiting, and constipation consistent with gastric outlet obstruction. Upper gastrointestinal endoscopy revealed a submucosal mass with an unremarkable overlying mucosa within the gastric antrum causing obstruction of the gastric outlet.

The differential diagnosis included gastrointestinal stromal tumor (GIST) versus primary gastric malignancy and, as such further imaging was arranged. A helical CT scan with intravenous contrast showed the presence of a well-defined 4.3×2.7×3.4 cm enhancing mass located within the antrum that extended into the first part of the duodenum. The remainder of the abdomen, including the pancreas, was unremarkable aside from multiple mildly enlarged gastric and sub-pyloric lymph nodes **(Figure 1)**.

The presence of such lymphadenopathy was suggestive for malignancy and the patient was planned for a subtotal gastrectomy with anterior jejunostomy. Intraoperatively an antral-based mass measuring 5×4.3×3.5 cm was

identified with normal overlying mucosa and no evidence of hemorrhage, necrosis, or calcification **(Figure 2)**.

Histopathological examination confirmed the presence of a moderately well-differentiated adenocarcinoma that was unusually associated with extensive perineural invasion reminiscent of a pancreatico-biliary type of malignancy **(Figure 3a)**. The overlying mucosa was unremarkable. Additional sections showed the coexisting presence of gastric pancreatic heterotopia composed of well-developed pancreatic acini and ducts (Heinrich type II) in the adjacent muscularis propria of the stomach wall close to the carcinoma **(Figure 3b)** with a well-defined transition between the ectopic pancreatic tissue and the adjacent malignancy, thus supporting the diagnosis of a malignancy arising from pancreatic heterotopia in the gastric antrum.

Postoperatively, the patient had an uneventful recovery and is well at one year follow-up.

LITERATURE REVIEW

A review of the published English literature using the databases PubMed and Google Scholar was conducted with the search terms "heterotopia", "ectopic", "pancreas", "gastric", "stomach", "carcinoma", "malignancy" and "cancer". Fifteen new reports (2003-present) of malignancy in a gastric pancreatic heterotopia were identified in the published literature and are listed in **Table 1** [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14]. A summary of the previously reported cases from 1963 to 2003 were tabulated by Matsuki *et al*. [9]. Some of these cases, such as references 3, 5, 6, 8 and 12, upon scrutiny fall short of the strict criteria proposed by Guillou; however, as these are cases already published in the peer-reviewed literature as malignancy in a pancreatic heterotopia they are included in this review for the sake of completion.

Patient ages ranged from 35 to 86 years (average 60.0 years) and there were equal females (n=7) to males (n=7). The majority of patients presented with abdominal pain (33%), anemia (27%), vomiting (27%), and weight loss (20%). Less common presentations included melena (13%), dyspepsia (13%), and as an incidental finding (13). The most common pre-operative presumptive diagnoses were gastric carcinoma (47%) and GIST (27%). In keeping with the literature, tumors were most frequently located in the antrum (33%), followed by the body and pylorus (20% respectively) and fundus (13%) with isolated cases to the lesser curvature and the esopgagogastric junction. Adenocarcinoma was the most frequent histologic diagnosis (40%), with more recent reports of acinar cell carcinoma, endocrine tumor with acinar differentiation, and endoepithelial (in situ) carcinoma. Outcomes were poor, with 58% of patients developing metastases and/or dying between 1 month and 1.5 years postoperatively.

DISCUSSION

Pancreatic heterotopia or the presence of pancreatic tissue outside of its normal anatomic location ("ectopic pancreas) has been described in 0.6-15% of patients at autopsy [1], with 25-40% occurring in the stomach [13]. Within the stomach, the prepyloric region and greater curvature are the most frequent sites of ectopic pancreas [1, 15]. Approximately three-quarters of lesions are submucosal, and they rarely extend into the muscular or subserosal layers of the stomach [15].

The embryologic origin of ectopic pancreatic tissue within the stomach is largely unknown; however, two

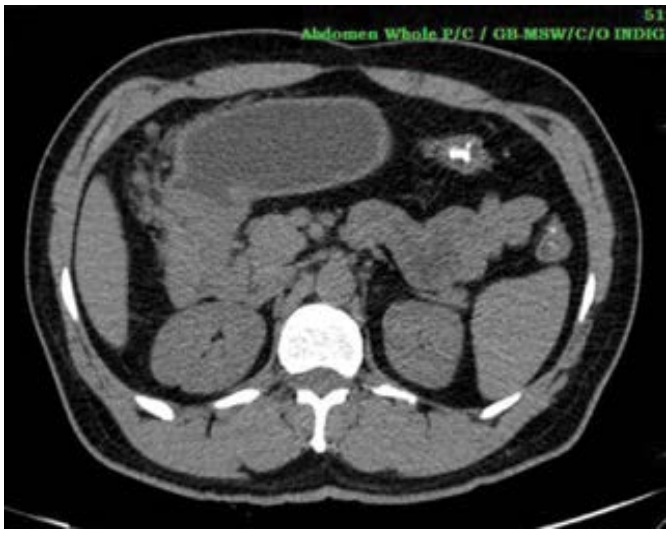

Figure 1. CT scan with contrast demonstrates a well-defined 4.3×2.7×3.4 cm enhancing mass located within the antrum. Adjacent pancreas is unremarkable. Mildly enlarged gastric and sub-pyloric lymph nodes are noted.

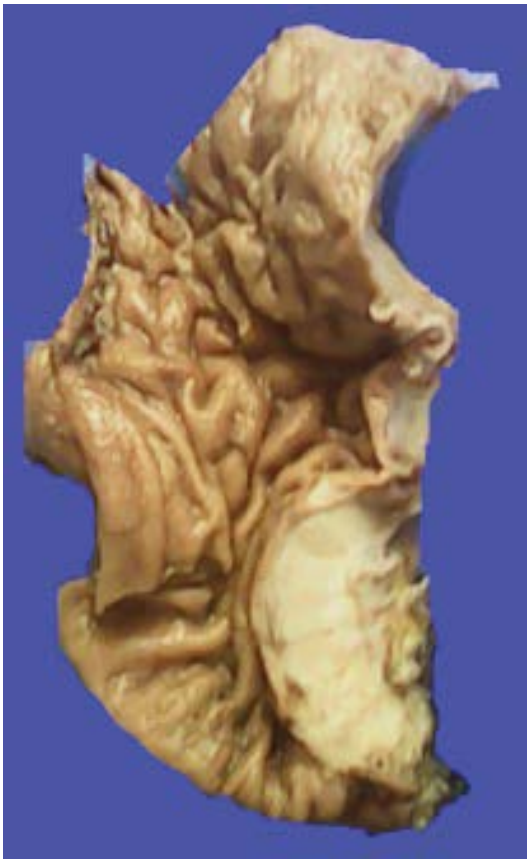

Figure 2. Photograph of the excised specimen demonstrates the presence of a well-defined submucosal mass in the stomach with uninvolved normal overlying mucosa.

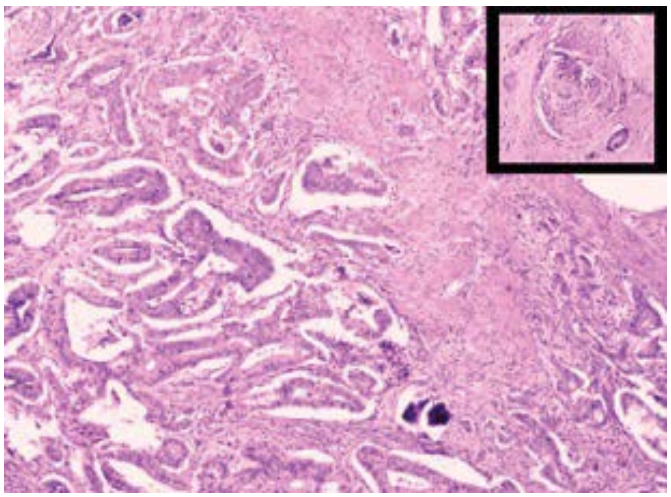

Figure 3a. Photomicrograph of haematoxylin and eosin-stained slide at medium magnification shows the presence of moderately well-differentiated adenocarcinoma in the muscularis propria. The inset at the upper right corner (high magnification) clearly demonstrates perineural invasion.

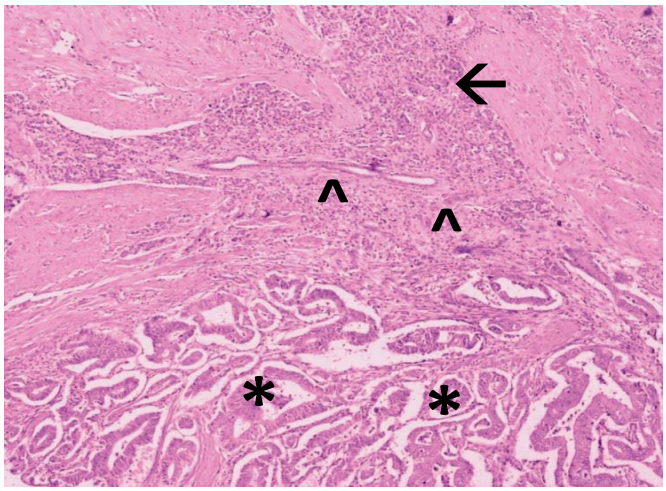

Figure 3b. Photomicrograph of haematoxylin and eosin-stained slide at medium magnification shows the presence of moderately well-differentiated adenocarcinoma (∗) in the muscularis propria coexisting with non-neoplastic pancreatic tissue (←) with a transition zone in between (^). The inset at the upper right corner (high magnification) confirms the presence of pancreatic acini and ducts in keeping with a Heinrich's type II pancreatic heterotopia.

theories –misplacement and metaplastic are proposed. The misplacement theory suggests that during the time in which the normal pancreas develops from duodenal evaginations, one or more evaginations remain in the bowel wall and migrate along with gastrointestinal tract development. The metaplastic theory proposes that pancreatic metaplasia of the multipotent endodermal tissues of the gastric submucosa is responsible for this event [5, 16].

Most cases of gastric heterotopia are asymptomatic and discovered incidentally on imaging, at surgery for another indication, or at autopsy [1, 17]. Among these, lesions measuring less than 2 cm can be followed clinically; however; an increasing size necessitates histopathological evaluation [11, 17]. When symptomatic, patients will typically present with pyloric obstruction, ulceration and bleeding or with symptoms in keeping with pathologic changes as typically seen in the native pancreas including acute/chronic pancreatitis, pseudocyst, or abscess. Constitutional or obstructive symptoms may be in keeping with malignancy and should prompt further investigations and/or intervention. Additionally unusual locations of pancreatic heterotopia such as retroperitoneal-based lesions can masquerade as independent malignant lesions [16].

At endoscopy [EGD], ectopic pancreatic lesions are typically a single firm, round or oval nodule, <4-5 cm in size with a central mucosal depression [15]. Identifying malignancy within these lesions is challenging with EGD due to the intramural location of the mass with delayed involvement of the overlying mucosa, thus typically necessitating submucosal biopsy of the mass with histopathological examination for accurate identification [11]. Additionally, the presence of perineural invasion should raise suspicion for alternative origins as this microscopic finding is uncommon in primary gastric cancer. In the index case, this feature greatly facilitated the accurate identification with the processing of additional histological sections to identify the underlying pancreatic heterotopia in the gastric antrum. In the presence of perigastric lymphadenopathy or changes in the shape/size of any submucosal lesion on imaging surveillance, we recommend urgent surgical intervention as best practice guidelines.

The Heinrich classification divides pancreatic heterotopia into three types: Type I) typical pancreatic tissue with acini, ducts, and islet cells; Type II) Only exocrine components-numerous acini, few ducts, no islet cells; Type III) numerous ducts, few to no acini, no islet cells [13, 16, 18]. Gaspar Fuentes modification adds a Type IV pure endocrine heterotopia containing only islet cells [16, 19].

Malignancy of pancreatic heterotopic tissue is exceedingly rare. Guillou *et al*. proposed the fulfilment of three criteria is necessary to conclude a malignancy has arisen from an ectopic pancreas: 1) the tumor must be within or near the ectopic pancreatic tissue; 2) a direct transition between the pancreatic structures and carcinoma must be present; 3) the non-neoplastic pancreatic tissue must be fully developed and must contain well developed acini and ductal structures [1, 11, 16, 20]. In the index case, as seen in figures 3a and 3b, these three criteria were all fulfilled. Immunohistochemistry may additionally differentiate malignancy arising from a heterotopic pancreas from a gastric primary, with positive immunoreactivity for CA19-9, cytokeratin 19, MUC-1, and insulin supporting a pancreatic origin [21].

Gastric pancreatic heterotopia were last formally reviewed over a decade ago (2005) by Matsuki who reported these lesions are more common in females than males with common symptoms including abdominal pain, epigastric discomfort and vomiting. The majority of patients had an ectopic pancreas localized to the pylorus and antrum [9]. Malignancies reported to arise within pancreatic heterotopia include: adenocarcinoma, papillary

Table 1. A composite table of malignancy arising in gastric pancreatic heterotopia published since 2003.

Ref	Age/Sex	Presentation	Preop Dx	Anatomic Location	Treatment	Pathology	Heinrich	Follow-up
Priyathersini (2016)	45/M	Gastric outlet obstruction	GIST	Antrum	Subtotal gastrectomy with lymphadenectomy	Adenocarcinoma	II	Well at 1 year
Lemaire [2]	60/NR	Dyspepsia	GIST	Lesser curvature	Total gastrectomy, Roux-en-Y, lymph node dissection	Adenocarcinoma	NR	Well at 4 years
Coyne [3]	77/F	Anemia	Gastric carcinoma	Fundus	Partial gastrectomy	Acinar cell carcinoma	NR	Died 1 month
Fukumori [4]	76/F	Incidental finding	GIST	Pylorus	Gastrectomy, lymph node dissection, cholecystectomy	Adenocarcinoma	II	Alive at time of publication
Kusafuka [5]	56/F	Fever	Extragastric mass	Body	Total gastrectomy, splenectomy, Rt hemicolectomy, node dissection	Mixed acinar-endocrine carcinoma	NR	Metastases at 2 months death at 3 months
Ambrosini-Spaltro [6]	52/M	Dyspepsia	Gastric carcinoma	Antrum	Subtotal gastrectomy, Roux-en-Y, omentectomy, lymphadenectomy, cholecystectomy	Acinar cell carcinoma	NR	NR
Papaziogas [7]	56/F	Epigastric pain Vomiting	Gastric carcinoma	Antrum	Distal gastrectomy	Endoepithelial carcinoma (in situ)	III	Well at 6 months
Mizuno [8]	73/M	Epigastralgia	GIST vs. lymphoma	Pylorus	Pancreaticoduodenectomy	Acinar cell carcinoma	NR	Metastases at 65 days
Matsuki [9]	58/F	Vomiting	Gastric carcinoma	Antrum	Partial gastrectomy	Adenocarcinoma	II	Metastases 1.5 years later
Jain [10]	41/F	Abdo pain Weight loss Melena	Acute pancreatitis	Body	Partial gastrectomy Partial omentectomy	Composite glandular & endocrine tumor with pancreatic acinar differentiation	NR	Well 2 years postoperative
	61/M	Anemia	Carcinoid tumor	Fundus	Subtotal gastrectomy			Liver mets 6 months later
	72/M	Melena Anemia	Submucosal gastric mass	Body	Subtotal gastrectomy			Died 4 months later from pneumonia
Song [11]	35/M	Routine medical checkup	GIST	Antrum	Wedge resection	Adenocarcinoma	III	Well at 5 months
Sun [12]	86/F	Anemia	Gastric carcinoma	Antrum	Partial gastrectomy & Billroth II reconstruction	Acinar cell carcinoma	NR	NR
Emerson [13]	52/M	Abdo pain, Emesis, Distention	Gastric carcinoma	Pylorus	50% gastrectomy & vagotomy	Adenocarcinoma	III	NR
Halkik [14]	60/M	Epigastric pain Dysphagia Weight loss	Gastric carcinoma	EG junction	Resection tumor & proximal stomach, biopsy of liver metastases	Adenocarcinoma	I	Death 3 months postoperative

A summary of reported cases of malignancy arising in a gastric pancreatic heterotopia from 1963-2003 is tabulated by Matsuki [9]. NR: not reported

cystadenocarcinoma, acinar carcinoma, and solid and papillary neoplasms [13].

Best practice guidelines for managing malignancy in gastric pancreatic heterotopia are not well-established; they are typically treated the same way as primary gastric carcinoma [11]. As malignancy is often not confirmed preoperatively intraoperative frozen section may facilitate the establishment of a malignant diagnosis. If malignancy is confirmed, wide resection with radical lymph node dissection is recommended [15].

A review of malignancy arising in the pancreas by Emerson and colleagues in 2004 concluded that adenocarcinoma arising in a pancreatic heterotopia may portend an improved prognosis compared with malignancy in the native pancreas, which may be attributed to earlier presentation [13]. The overall clinical course of malignancy in pancreatic heterotopia is however thought to be more similar to primary gastric cancer than primary pancreatic cancer and is solely dependent on the stage of the disease at presentation [17].

CONCLUSIONS

Adenocarcinoma arising in pancreatic heterotopia remains a diagnostic challenge as clinical symptoms and radiographic features are nonspecific, and the rarity of these lesions precludes a high degree of pre-operative suspicion. Such malignant transformation in ectopic pancreas, though rare, should be included in the diagnostic workup of gastric submucosal masses. Accurate diagnosis is heavily reliant on histopathological evaluation of tissue specimens in which the presence of perineural invasion in a gastric adenocarcinoma should prompt suspicion and further investigation of non-primary gastric cancer. Malignancy

within a gastric pancreatic heterotopia behaves similarly to a primary gastric adenocarcinoma and, therefore, similar surgical management is recommended in conjunction with the stage of the disease; however, patients must also be counselled on the improved prognosis for these ectopic pancreatic malignancies in comparison to reported survival data for native pancreatic cancer.

Conflict of Interest

All authors declare having no conflict of interests or financial disclosures.

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