CASE REPORT

Pancreatic Heterotopia: Masquerading as Malignancy - A 15-Year Single Institutional Surgicalpathology Review

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ABSTRACT

Context Pancreatic heterotopia, the presence of pancreatic tissue anywhere outside of the anatomical pancreas, is rare and typically an incidental finding. This manuscript reports two index cases of unusual presentations of pancreatic heterotopia masquerading as malignant lesions. **Case reports** Case #1: Fifty-five year-old female with right upper quadrant pain was found to have a retroperitoneal tumor between the right kidney and liver. Case #2: Thirty-eight-year-old female with a 20-year history of right upper quadrant pain and pancreatitis was found to have an incidental jejunal mass. An intraoperative frozen section was ordered on these two patients for suspected malignancy. Frozen section analysis in both cases showed the presence of benign glandular tissue admixed with ducts in a typical lobular fashion consistent with benign pancreatic tissue, confirming pancreatic heterotopia. The two index cases were investigated and analyzed in detail with relevant review of the literature as available in PubMed and Medline. A fifteen-year retrospective computer-based histopathological surgical review was conducted in our laboratory and the results were analyzed in the context of evidence-based literature of pancreatic heterotopias. 153 pancreatic pathologies were identified of which the commonest lesion was adenocarcinoma (58.8%) followed by pancreatic heterotopia (10.5%), pancreatic neuroendocrine tumors (7.2%) and pancreatitis (7.2%). **Conclusions** Pancreatic heterotopia is rare and most often an incidental finding; however, occasionally patients may present with a mass suggestive of malignancy, leading to clinical diagnostic dilemmas. Awareness of this uncommon lesion is of particular importance at intraoperative frozen section analysis for lesions in atypical locations.

INTRODUCTION

Pancreatic heterotopia (PH) is a rare lesion defined by the presence of pancreatic tissue with no anatomicor vascular continuity with the native pancreas, and is most often found within the gastrointestinal tract.

This anatomical anomaly is often asymptomatic and as such goes undetected or is found incidentally; however, they can present clinically with an 'acute abdomen' with pain or hemorrhage. Additionally, anypathology that arises in the native pancreas can also develop in this heterotopic tissue resulting inconfounding clinical presentations. PHs are classified depending on the pancreatic components present: type I (all pancreatic tissue types), type II (only ducts) and type III (only acini) [1].

In this manuscript, we discuss two index cases of PH that clinically masqueraded as malignant lesionsin the context of the published literature. A 15-year retrospective single institutionalsurgical pathology review is also discussed.

Received April 4th, 2015-**Accepted** May 20th, 2015
Keywords Jejunal Neoplasms
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CASE REPORT

The following index cases depict two unusual presentations of pancreatic heterotopia.

Case #1: Retroperitoneal tumor

A Fifty-five-year-old female presented with a six-month history of worsening right upper quadrant pain, abdominal bloating, diarrhea, fatigue, and back pain. She denied history of jaundice or melena. Imaging, including abdominal/endoscopic ultrasound, CT scan, and an MRI (**Figures 1a, 1b**) demonstrated the presence of a right retroperitoneal tumormeasuring 60 mm × 46.9 mm located beyond the duodenumsituated between the kidney and the liver, suggestive of a GIST. At intraoperative frozen section, therewas no evidence of GastroIntestinal Tumor [GIST] or malignancy. A laparoscopic right retroperitoneal excision was carried out fora 6cm well-circumscribed encapsulated mass.

The cut section of the mass showed the presence of benign pancreatic ductal cells in a typical lobular fashion of exocrine pancreatic tissue. The stroma was composed of bland spindle cells with few scatteredacini and multiple ducts lined by simple cuboidal epithelium (**Figure 1c**) with no atypia, mitoses, or pleomorphism. Endocrine elements were not recognized.

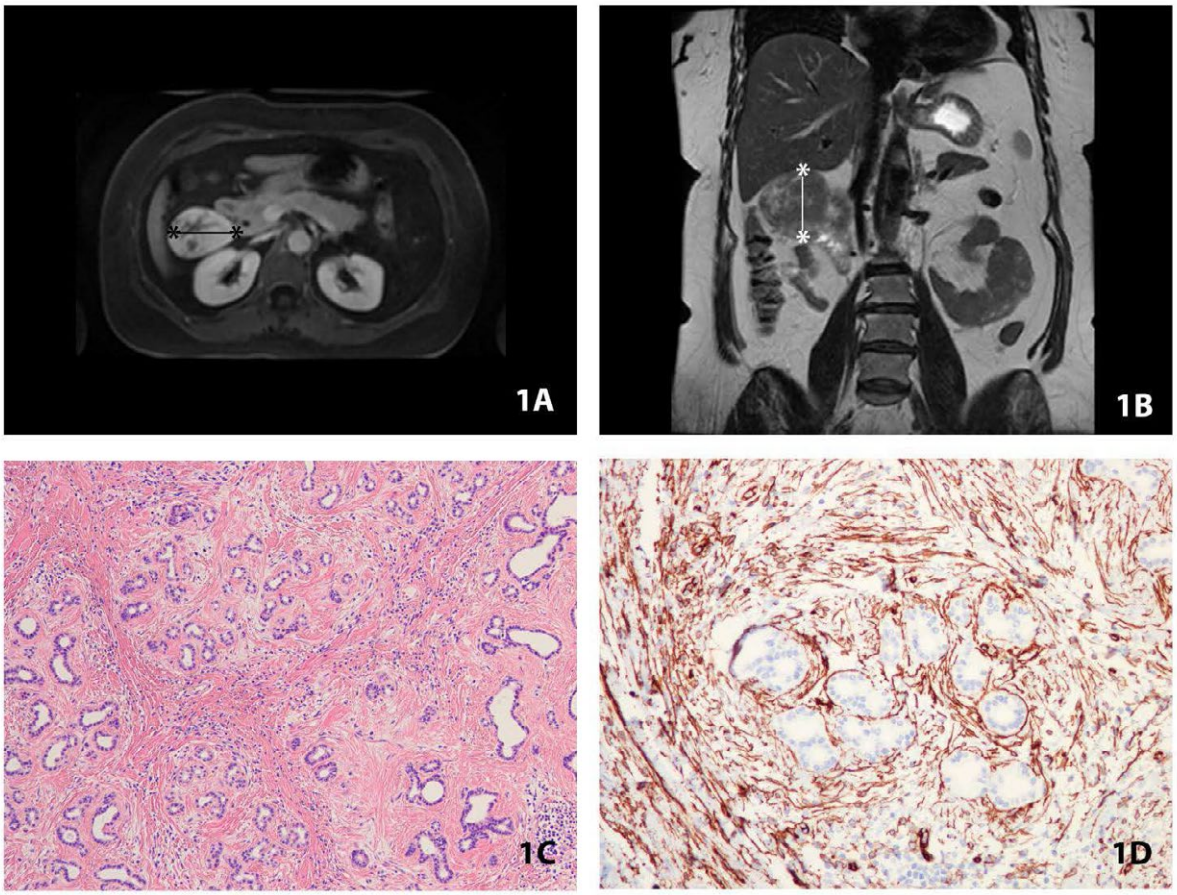

Figure 1. Case #1: A55-year-oldfemale with a retroperitoneal tumor? GIST. (a.). Transverse plane of an abdominal MRI delineates a smooth well-circumscribed retroperitoneal mass lesion located between the liver and the right kidney, measuring 57.7 mm in maximal dimension. (b.). Coronal plane of an abdominal MRI high lights a mass lesion located below the liver measuring 60.0 mm x 46.9 mm. (c). Photo micrograph of haematoxylin and eosin stained slide at low magnification shows ductal cells arranged in a lobular fashion in keeping with benign pancreatic tissue. (d). Photomicrograph of immunohistochemically stained slide with CD34 antibodies at medium magnification shows over expression in the periductal stroma.

On immunohistochemical analysis, lesional cells were negative for chromogranin A and synaptophysin.

Focal expression of neuroendocrine marker CD56 was identified within a few of the cells lining the duct. Differential endocrine cell markers for alpha, beta, or delta cells were not undertaken. CD34 was expressed inthe stroma surrounding the ducts (**Figure 1d**). Ki67 was not overexpressedin thislesion.Theoverallhistomorphological features and immunophenotype therefore confirmed the presence of pancreaticheterotopia, Type II.

Case #2: Jejunal tumor

A Thirty-eight-year-old female with a twenty-year history of right upper quadrant (RUQ) pain associated withpancreatitis presented with another typical episodeof dull constant nonradiating pain in the RUQ with no identifiable aggravating or alleviating factors, She had a past medical history of recurrent pancreatitis diagnosed based on clinical presentation and confirmatory laboratory findings as well as chronic cholecystitis, and choledocholithiasis. Imaging showed a choledochal cyst, and a jejunal mass in the mesentery suspicious for a carcinoid tumor. Laparotomy with cholecystectomy, choledocystectomy for the choledochal cyst and segmental bowel resection were performed. An intraoperative frozen section analysis of the jejeunal mass was negative for malignancy.

The cut sections of this mass were composed of a mixture of benign acinar, ductal, and islet cellsconfirming the presence of heterotopic pancreas, Type I (**Figures 2a, b**). Immunohistochemical stainswith chromogranin A and synaptophysin highlighted the islet cells of this lesion (**Figures 2c, 2d**).

Surgical Pathology Review

A fifteen-year (1998-2013) retrospective surgical pathology review identified a total of 153 pancreaticspecimens received in our laboratory using the Laboratory Information System (LIS)'s "Complex Query" function with the specimen search term 'pancreas'. Sixteen pancreatic heterotopias were detected (10.5%). The commonest pathology wasadenocarcinoma in 90 cases, followed by pancreatitis (20 cases), pancreatic neuroendocrine tumors (11 cases), mucinous neoplasm (6 cases), adenoma (4 cases), and pseudocyst (3 cases). Miscellaneouspathology included hemorrhage, pseudopapillary tumor, duct dilation, and carcinoid tumour (**Table 1**).

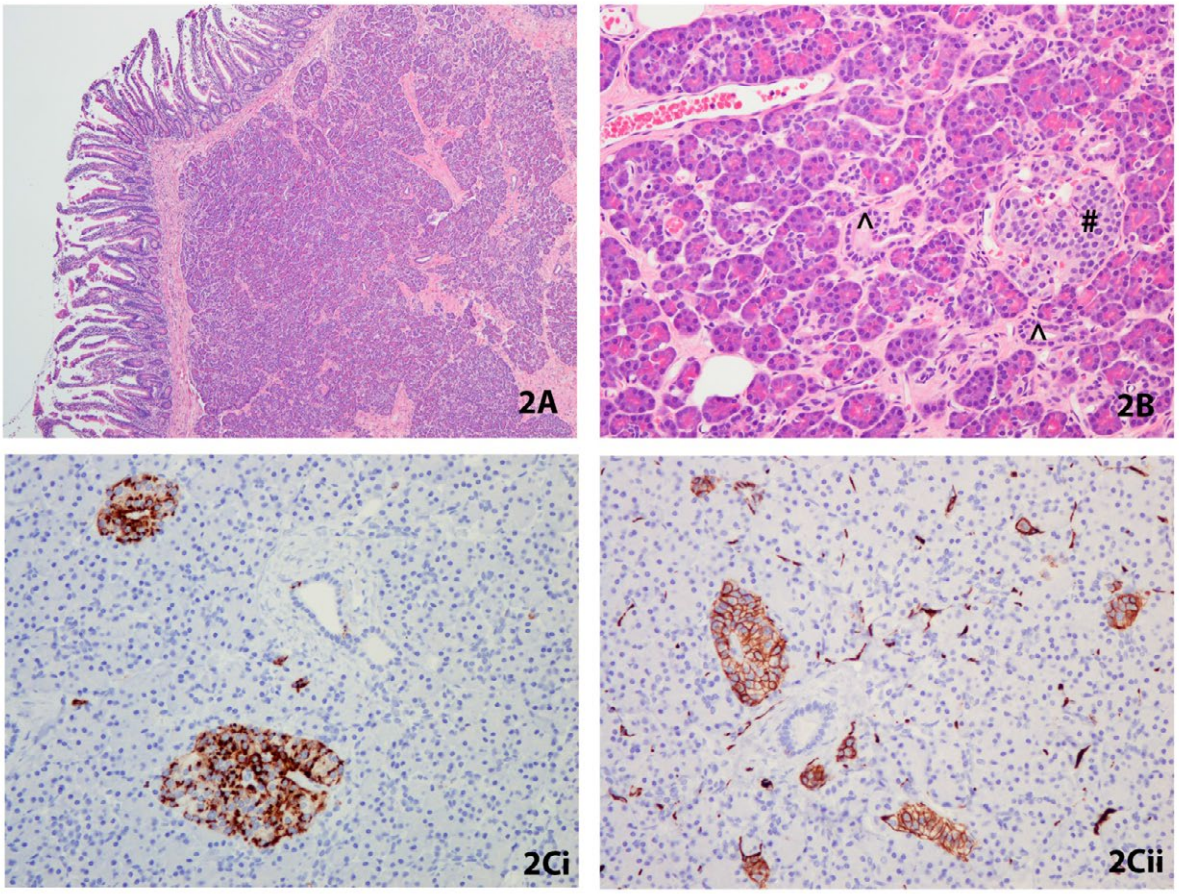

Figure 2. Case #2: A38-year-old female with a jejunalmass? Carcinoid. (a.). Photomicrograph of haematoxylin and eosin-stained slide at low magnification shows a submucosal neoplastic lesion in the jejunum. (b). Photomicrograph of haematoxylin and eosin-stained slide at medium magnification shows the neoplastic lesion to be compose do facinar, ductal (^), and islet cells (#) in keeping with ectopic pancreatic tissue. (c). Photomicrograph of immunohistochemically-stainedslide with chromogranin A [i] and Synaptophysin [ii] antibodies at medium magnification high lights the islet cells/ endocrine component.

The most common location of PH was the stomach (6) followed by the duodenum (4 cases), jejunum (2case), and a single case each in the colon, gastroesophageal junction, Meckel's diverticulum, and retroperitoneum. Incontrast to the literature, the majority (69%) of our patients were female, and patient's age ranged from 16-85 (mean 52 years). Based on the Heinrich classification scheme, 8 cases of pancreatic heterotopiawere type I (exocrine/endocrine), 5 Type II (duct/acini) and 3 Type III (ducts only) (**Table 2**).

DISCUSSION

The term 'heterotopia' is derived from Greek etymology "other" and "location" [2]. Pancreatic heterotopia (PH), defined as the presence of pancreatic tissue located outside of the anatomical pancreaswithout any physical or vascular connection to the pancreas itself [3], is also known as 'pancreatic choristoma' [4], 'pancreatic rest' [5], or 'pancreatic acinar metaplasia' [6]. PH's were first described in 1727 by Schultz, with the first histopathological confirmation by Klob in 1859 [4]. The overall incidence of PH ranges widely with publications reporting figures from 0.5-15% or one in every 500 laparotomies [3, 7, 8]. These lesions are three-times more common in men between thefourth and sixth decades of life [4, 9]. However, PH**'s** located above the gastroesophageal junction aremore common in females, particularly those infected with Helicobacter pylori [6].

Though PH lesions may be located anywhere within the gastrointestinal tract, 90% occur in the upper tract [10]. Common sites of occurrence include the stomach (25-36%), duodenum (17-36%), and jejunum (15-22%) [3, 10]. Within the stomach, 85-95% are located in the antrum, predominantly the greatercurvature [9]. Additional sites of occurrence include the esophagus, gallbladder, common bile duct, liver,omentum, Meckel's diverticulum, lungs, mediastinum, fallopian tubes, umbilicus and brain [3, 9]. Suchlesions have also been identified in mature teratomas [11] and in congenital anomalies includingduplication stomach, intralobar sequestrations of the lung, gastroenteric cyst, and esophagealdiverticulum [5]. It has also been identified alongside tubercular ileitis [12]. Lesions are typically unifocal; however, multifocal PH**'s** have been reported [13].

The cause of the occurrence of a PH is poorly understood. Though, it is generally accepted that this lesionoriginates during antenatal development, the exact mechanism remains ill-defined [14]. Several theorieshave been proposed to explain the origins of this ectopic pancreatic tissue. These theories include:

Misplacement theory: During embryologic rotation with the fusion of the ventral and dorsal budsof the developing pancreas, some tissue separates with aberrant migration and transplantation toadjacent structures. This remnant remains grafted in its new location and develops as individualpancreatic tissue separate from the native pancreas. Ectopic tissue found in thestomach/duodenum is thought to be derived from the dorsal segment, whereas jejunal and ilealPH originates from the ventral bud [3, 5, 11, 14].

Metaplastic theory: This theory proposes that pancreatic ectopic tissue arises frommetaplasia of the multipotent endodermal cell [9]. As the stomach, duodenum and pancreas all arise from the foregut, multipotent regionalendoderm may abnormally differentiate in these regions. Thus, many authors believe that theorigin of gastric and duodenal PH may be the result of abnormal differentiation of multipotentregional endoderm rather than abnormal engraftment [14].

The majority of PHs are asymptomatic, often detected incidentally at laparotomy or on radiographic orendoscopic examination of the upper GI tract [11]. The frequency of PH in autopsy series varies from0.55% to 13% [7]. Signs and symptoms associated with PH depend on the location and size of thelesion. Thirty to forty percent of patients may experience nonspecific gastrointestinal symptoms. The majority of symptomatic lesions are greater than 1.5 cm in diameter and usually directly involve the mucosa [15]. Symptomatic lesions commonly present with abdominal pain; hemorrhage secondary tomucosal erosion, ulcer formation, or perforation of the small bowel have additionally been described [3]. Other presentations include intestinal obstruction, intussusception, jaundice, pancreatitis, cholecystitis, or mass lesions [16]. Generalized symptoms including anorexia, nausea and vomiting, diarrhea, weightloss, and peri-umbilical pain have been described [14].

Table 1. Pancreatic Pathologies- 15-year Retrospective Computer-Based Histopathological Surgical Review

Pathology	#Cases	%Patients
Adenocarcinoma	90	58.1
Pancreatitis	20	12.9
Pancreatic heterotopia	16	10.3
Pancreatic neuroendocrine tumor	11	7.1
Mucinous neoplasm	6	3.9
Adenoma	4	2.6
Pseudo cyst	3	1.9
Hemorrhage	2	1.3
Pseudo papillary tumor	1	0.6
Duct dilation	1	0.6
Small carcinoid tumor	1	0.6

Table 2. Pancreatic Heterotopia – 15-year Retrospective Histopathological Surgical Review

No.	Age (y)	Sex	Site	Heinrich's Classification
1	16	M	Meckel's diverticulum	Type I
2	30	F	Gastric	Type III
3	32	F	Gastric	Type I
4	33	F	Duodenum	Type I
5	38	F	Jejunum	Type I
6	46	M	GE Junction	Type II
7	49	F	Colonic polyp	Type I
8	55	F	Duodenum	Type I
9	55	F	Retro peritoneum	Type II
10	57	M	Gastric	Type II
11	59	F	Duodenum	Type I
12	63	M	Duodenum	Type II
13	68	M	Gastric	Type III
14	70	F	Jejunum	Type III
15	79	F	Gastric	Type II
16	85	F	Gastric	Type I

A wide range of presentations occur because any disease that can occur in the native pancreas including acute/ chronic pancreatitis, pseudocystic changes, malignant transformation, intraductal papillarymucinous neoplasm (IPMN), or pancreatic neuroendocrine tumors can also arise in this ectopicpancreatic tissue [17]. PH has been reported to cause melena and to serve as a lead-point for ileo-ileal intussusception [18]. Similar to the pancreas, ectopic pancreatic tissue may secrete enzymes/hormones[9]. Thus, patients presenting with hormonal syndrome should undergo extensiveimaging/intraoperative exploration to detect unsuspecting pancreatic heterotopia [19]. The presence ofsymptoms, size of the lesion (>1.5 cm) and extent of mucosal involvement is strongly correlated with exocrine differentiation of the PH [15, 20].

Investigational imaging studies, specifically ultrasound and CT scans, often result in nonspecific and inconclusive results. Due to the rarity of these lesions, characteristic endoscopic or radiographic featureshave yet to be elucidated.PHs often have a characteristic central umbilication and are located in the submucosa; however, GISTs and carcinoids can also appear with similar features [21]. Video capsule enterography has been described to identify the lesion causing an upper GI bleed diagnosed on histopathology to be PH [22]. Nevertheless given the diverse clinical picture, patients typically undergo a) ultrasound, b) CT scan and/or c) endoscopic ultrasound in the diagnostic work-up of these lesions [23].

Ultrasound has a poor specificity for accurately identifying PH's, as it is impossible to distinguishsuch lesions from cholesterol polyps, adenomas, or carcinomas [2]. These lesions typically appearbetween the echodense submucosa and the hypoechoic muscularis propria [5].

Even though ectopic pancreatic tissue enhances similarly to normal pancreatic tissue, computedtomography (CT) scanning is often ineffective in delineating and accurately identifying PH, as thefindings are nonspecific and the diagnosis of submucosal lesions is difficult. It is therefore oftenimpossible to differentiate ectopic pancreatic

tissue from gastrointestinal stromal tumors,lymphomas, adenomatous polyps, peptic ulcers, or malignancies [3].

Lesions often appear as an intramural nodule or sessile polyp with central umbilication atendoscopy [9]. These lesions may mimic intestinal carcinoid tumors, fibromas, eosinophilicgranulomas, granular cell myoblastomas, or malignancies [5]. Endoscopic ultrasound combined with a fineneedle aspiration biopsy has a high sensitivity [3]. Such sampling technique is however limited in deep-seated lesions,as the biopsy material often samples the overlying mucosa and yields false negative results [5].

The majority (76%) of PHs are submucosal; 17% in the muscular layer and 10% in the subserosa [3, 24]. Ongross examination, PH are typically submucosal nodules, intramural masses, or nodular lesions thatappear yellow to yellow-white, ranging in size from 1mm to 5 cm, with a lobulated cut surface. Theselesions are often covered by an intact mucosa, and a central umbilication may be present containing arudimentary pancreatic duct [9, 25]. If this duct is not open to a cavity, a buildup of secreted materialsmay be present within the duct. The surrounding organ tissue may demonstrate inflammatory changes [26].

Histopathological examination of ectopic pancreatic tissue often reveals overlying mucosal inflammation with underlying intramural nodules composed of acini, ducts and/or islet cells [2]. Though "endocrine(islets) heterotopia" is rare, such heterotopia may be difficult to differentiate from a neuroendocrine tumor as histologically both contain monomorphic, medium-sized cells often arranged in microlobules[20]. The presence of small neuroendocrine nests in the absence of a discrete mass without a stromalreaction supports endocrine heterotopia [27].

PH's were initially classified by Heinrich into three types based on the tissue-types present:

Type I: all components of pancreatic tissue (acini, ducts, islet cells).

Type II: only the exocrine components (acini & ducts), no islet cells.

Type III: solely of ducts and rare acinar cells or only dilated ducts, the 'adenomyomas' [1].

PH has been suggested to be a manifestation of the same pathologic process resulting in adenomyomas Aschoff-Rokitansky sinuses, and adenomyomatosis. Adenomyomas may be a PH variant with a missingexocrine/endocrine component. Pilloni *et al*. suggests that these lesions are linked by a commonhistogenetic origin [28]. The morphologically indistinguishable ductal epithelia of PH and adenomyomassupport this theory. Additionally, the immunophenotype of these two lesions, including expression ofcytokeratins 7, 8, 18, 19, and CA19-9, are identical [13].

Heinrich's classification however did not address the endocrine component of the pancreas, and was modified by Gaspar Fuentes into four types:

Type I: "complete heterotopia" including all pancreatic tissue types (acini, ducts, islet cells)

Type II: "canalicular heterotopia" containing only ducts

Type III: "exocrine heterotopia" with only acini

Type IV: "endocrine heterotopia" containing islet cells [29].

Of these, Type IV is the most uncommon [9] and only 50% of all PH contain islet cells (Types I, IV) [30]. Classifying pancreatic heterotopias is, however, purely an academic exercise as the subtype has no clinical significance nor correlation with disease or laboratory findings [21].

The risk of malignancy arising in a PH is exceptionally rare [31]. It has been suggested that ectopicpancreatic tissue may be more prone to malignant change as the tissue is less differentiated and moresubject to irritation; however, the scant number of case reports of malignant PH in the context of theestimated prevalence of PH does not support this concept [11]. The likelihood of malignanttransformation, if any, has not been correlated with the size, site, or histologic type of PH [32]. Neoplastic proliferation may arise from either exocrine or ductal components [33]. Three criteria havebeen proposedby Guillou *et al.* in 1994 to define neoplastic transformation of pancreatic ectopic tissue:

a) The tumor must be within or close to the ectopic pancreatic tissue

b) A direct transition between the pancreatic structures and the neoplasm must be present

c) Non-neoplastic pancreatic tissue must comprise at least fully developed acini and ductalstructures [34, 35].

In conclusion, pancreatic heterotopia is rare and often an incidental asymptomatic finding; however,patients presenting with a mass suggestive of malignancy, continues to pose clinical challenges and remains a diagnostic dilemma despite advances in investigative techniques [36]. Accurate identification of PH mass-lesions is critical to guide patient management; as such lesions are oftenincorrectly identified as a metastatic tumor or an extension/recurrence of a neighboring malignancy. Awareness of this anomaly is of particular importance during frozen section analysis of these unusuallesions. The current recommendations for the treatment of these lesions depend on its clinicalpresentation. Asymptomatic patients with confirmed incidentally discovered PHs require periodicclinical and radiological reviews, with no invasive therapy indicated. Uncomplicated symptomatic PHsshould be excised either endoscopically or by local surgical resection [9]. Endoscopic techniques under investigation includes mucosal resection, band ligation, snare polypectomy, or endoscopic submucosal dissection [21]. If a local excision is not possible,a radical operation may be warranted [16]. The rationale for complete surgical removal is to avoidpotential future complications including pancreatitis, ulceration, cystic changes, and/or

the developmentof malignant or benign neoplasms from either exocrine or endocrine components [37].

Conflicting Interest

The authors had no conflicts of interest

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