Pancreatic heterotopias: clinicopathological analysis of 18 patients

Heterotopia pancreática: análise clínico-patológica de 18 doentes

Sansom Henrique Bromberg, ACBC SP [1]; Carlos Camilo Neto [2]; Antonio Fernando Allemand Borges[3]; Maria Isete Fares Franco [4]; Luis Celso Mattosinho França [5]; Nagamassa Yamaguchi ECBC SP [6]

A B S T R A C T

Objective: To analyze the clinical and pathological features of heterotopic pancreatic tissue in abdominal digestive organs. Methods: We retrospectively studied 18 patients with histologically diagnosed heterotopic pancreas. Clinical and histopathologic data were reviewed. Heterotopic pancreatic tissues were classified in three histological models: Type I consists of three components of normal pancreas (acini, ducts and islets), type II with two components and type three with only one component. Results: The mean age was 52.7 years, ranging from 34 to 73 years, nine of them men and nine women. Symptoms were observed in only four patients, and their lesions were diagnosed by gastroscopy. The remaining 14 were asymptomatic and their anomalies were discovered accidentally. Most of the lesions were located in the upper gastrointestinal tract: seven (38.9%) in the stomach, six (33.3%) in the duodenum and three (16.6%) in the jejunum. Heterotopia was mostly located in the submucosa (83.3%) but was also observed in the muscularis propria and in the sub-serosa. In seven specimens (38.9%) all pancreatic components were found (type I), in eight (44.4%) exocrine glands and excretory ducts were present (type II) and in three (16.7%) only exocrine tissue was observed (type III). Conclusion: Pancreatic heterotopia is rare. Patients with pancreatic ectopia diagnosed by pathological study, whether asymptomatic or with mild symptoms, should be observed. Lesions incidentally detected during surgeries need to be removed by conservative procedures.

Key words: Choristoma. Pancreas. Digestive system. Surgery.

INTRODUCTION

Heterotopic, aberrant or ectopic pancreas is defined as the presence of pancreatic tissue in topographic anomaly, with no anatomical, neural or vascular connection to the normal pancreas[1].

The heterotopic pancreas (HP) is a relatively uncommon congenital anomaly, with an incidence between 0.55% and 13.7% in autopsy series and mean frequency between 1 and 2%[1,2]. One ectopic pancreas in found every 500 surgical procedures in the upper abdomen[1]. In adults it occurs preferentially in males between the fourth and sixth decades of life. It is found mainly in the stomach, duodenum and jejunum, in much smaller proportions in the ileum and Meckel's diverticulum, and it is rarely found in the esophagus, liver, gallbladder, omentum, lungs, mediastinum, fallopian tubes and umbilicus[3,4].

Most patients with ectopic pancreas are asymptomatic and diagnosis is usually performed during radiological examination or endoscopy of the digestive tract or during surgical explorations motivated by other diseases.

Its importance relates to the fact that it is an extra-mucous parietal lesion, therefore included in the differential diagnosis of important diseases[5].

This study aimed to review all patients in whom the histological diagnosis of ectopic pancreas was performed at our institution, analyzing clinical and pathological parameters of this anomaly.

METHODS

During the time between December 1968 and January 2003 (34 years), 18 patients with heterotopic

Work performed at the Gastroenterology Surgery Service and Department of Pathology, Hospital do Servidor Público Estadual de São Paulo - Francisco Morato de Oliveira, São Paulo – SP, Brazil.

1. Surgeon, Gastroenterology Surgery Service, Department of Pathology, Hospital do Servidor Público Estadual de São Paulo - Francisco Morato de Oliveira (HSPE-FMO) - São Paulo – SP, Brazil; 2. Pathology Resident, Department of Pathology, Hospital do Servidor Público Estadual de São Paulo - Francisco Morato de Oliveira, São Paulo – SP, Brazil; 3. Pathologist, Department of Pathology, Hospital do Servidor Público Estadual de São Paulo - Francisco Morato de Oliveira, São Paulo – SP, Brazil; 4. Head, Department of Pathology, Hospital do Servidor Público Estadual de São Paulo - Francisco Morato de Oliveira, São Paulo – SP, Brazil; 5. Director, Department of Pathology, Hospital do Servidor Público Estadual de São Paulo - Francisco Morato de Oliveira, São Paulo – SP, Brazil; 6. Director, Gastroenterology Surgery Service, Hospital do Servidor Público Estadual de São Paulo - Francisco Morato de Oliveira, São Paulo – SP, Brazil.

pancreas were treated at the HSPE-FMO Gastroenterology Surgery Service, receiving a definitive diagnosis after histological analysis of specimens in the Department of Pathology of the same institution. The data contained in their medical records were reviewed and clinical and pathological parameters were analyzed. The slides that were used for diagnosis, stained with hematoxylin and eosin, were all reviewed and, when necessary, new sections of the stored paraffin blocks were properly prepared for study.

The data referred to age, color, sex, clinical presentation, diagnosis, adopted therapy and outcome. During the pathological study we noted the organ in which the aberrant pancreas was found, its location on the organ wall layers and its histological composition. The heterotopic pancreatic tissue was classified in three types: type I, having three components of normal pancreatic tissue (acini, ducts and Langerhans islets), type II, displaying two pancreatic components and type III, when only one component was present. Special care was devoted to the research of cellular abnormalities suggestive of atypical or malignant degeneration.

RESULTS

The patients' ages ranged from 34 to 73 years, mean 52.7 years and median 54 years. The greatest number of individuals (six) was in the sixth decade, four were in the fifth, three in the fourth, three in the seventh and two in the eighth decade. Sixteen patients were Caucasian, one Asian and one African-american. Nine patients were female and nine male.

The aberrant pancreatic tissue was located in the stomach of seven (38.9%) patients, in the duodenum in six (33.3%), in the jejunum in three (16.6%), in the gallbladder in one (5 5%) and in a Meckel's diverticulum in one (5.5%) (Table 1).

In the stomach, heterotopic pancreas was located in six patients in the greater curvature of the antral region, less than 5 cm from the pylorus and in one patient it was located in the posterior wall of the gastric body. Macroscopically, it was nodular five times, being recognized during endoscopy in four of them, covered by intact mucosa, yellowish and with a central umbilication in three of them; they were biopsied and histological study recognized pancreatic tissue in all of them. The one subcutaneously located nodule was noted, palpated and removed (nodulectomy) during a Bariatric Surgery. In the remaining patients they were found during the microscopic examination of the stomach, one resected for cancer and the other for peptic ulcer (Table 2).

Those located in the duodenum were recognized by microscopic examination of the surgical specimens excised for peptic ulcer (five) and gastric cancer (one) (Table 2).

One of the specimens found in the jejunum was recognized during operation motivated by peptic ulcer; it was nodular, yellowish and sub-serosal, being removed by nodulectomy. The other two specimens, in the form of small

Table 1 - Location, parietal level and histologic composition of 18 heterotopic pancreas.

	Local	Parietal Level	Components
1	Duodenum	MM	acini – ducts – islets
2	Duodenum	SM	acini – ducts
3	Duodenum	SM MM	acini – ducts
4	Duodenum	SM MM	acini – ducts
5	Jejunum	SM MM SS	acini – ducts – islets
6	Duodenum	SM MM	acini – ducts
7	Stomach	SM MM SS	acini – ducts – islets
8	Stomach	SM	acini
9	Gallblader	MM	acini – ducts
10	Stomach	SS	acini – ducts – islets
11	Meckel's Diverticulum	SM MM	acini – ducts – islets
12	Stomach	SM	acini
13	Duodenum	SM	acini
14	Jejunum	SM MM SS	acini – ducts – islets
15	Stomach	SM	acini – ducts – islets
16	Jejunum	SM MM	acini – ducts
17	Stomach	SM	acini – ducts
18	Stomach	SM	acini – ducts

SM: sub-mucosa; MM : muscularis propria; SS : sub-serosa.

Table 2 – Basic diseases and procedures in 18 patients with pancreatic heterotopia.

	Sex	Age	Anderlying Condition	Procedure
1	M	63	Peptic Ulcer	Partial gastrectomy
2	M	43	Peptic Ulcer	Vagotomy + duodenectomy
3	M	50	Peptic Ulcer	Partial gastrectomy
4	F	48	Gastric Cancer	D2 gastrectomy
5	F	52	Peptic Ulcer	Jejunal nodulectomy
6	M	63	Peptic Ulcer	Partial gastrectomy
7	F	70	Peptic Ulcer	Partial gastrectomy
8	M	36	Dyspepsia	Endoscopy + biopsy
9	F	40	Gallstones	Cholecistectomy
10	M	67	Gastric Cancer	D2 gastrectomy
11	F	57	Intussusception	Enterectomy + Meckel's diverticulectomy
12	F	57	Dyspepsia	Endoscopy + biopsy
13	M	56	Peptic Ulcer	Partial gastrectomy
14	F	59	Intestinal Obstruction	Enterectomy
15	F	34	Obesity	Nodulectomy
16	M	73	Intestinal Obstruction	Enterectomy
17	F	46	Dyspepsia	Endoscopy + biopsy
18	M	36	Dyspepsia	Endoscopy + biopsy

nodules, were located in the intestinal segments excised for the treatment of intestinal obstruction and intussusception, being recognized macroscopically (Table 2).

The ectopic pancreas located in the Meckel's diverticulum, excised due to intussusception, was detected only in the histological study. The same happened to the nodule located in the gallbladder removed for symptomatic gallstones.

From 15 specimens, the HP was observed in the sub-mucosa in seven of them in that layer alone; in five others it was also present in the muscularis propria and in three specimens it was noted in the sub-mucosa, muscular and sub-serosa. In the remaining three, the aberrant pancreas was present in only one layer, two in the muscular and one in the sub-serosa (Table 1).

Of the 18 individuals, seven had the size of PH recorded, the smallest measuring 2 mm and the largest 20 mm in diameter, with a mean of 10.7 mm.

The histological study recognized the presence of all pancreatic components in seven (38.9%) patients (type I), the presence of acini and ducts (type II) in eight (44.4%) and only acini (type III) in three (16.7%) patients (Table 1). Acini were present in all cases (Figures 1 and 2).

There were no atypical or neoplastic cells in the examined samples.

DISCUSSION

The pancreas develops from two embryonic diverticula, dorsal and ventral, originating in the primitive duodenum. During the sixth week of gestation they merge, giving rise to the cephalic portion and the unciform process of the ventral bud while the dorsal invagination will form the remainder of the body[6].

Although the pathogenesis of ectopic pancreas remains unknown, different theories have been proposed to explain its appearance, the transplantation of embryonic pancreatic cells to adjacent structures during axial rotation of the intestine being one of them[2]. Moreover, embryonic buds that remain adhered to the primitive duodenum could be taken to proximal or distal sites during the growth and development of the gastro-intestinal tract. The incidence of pancreatic tissue in distant organs such as the thyroid gland, lungs, or fallopian tubes should deserve further explanation, remembering the possibility of having been originated by multipotent cell endodermic metaplasia or teratomas[7]. Multipotent cells of the primitive gut, capable of broad differentiation, could also foster the emergence of this entity[8,9].

In a study of 11,265 patients, 24 (0.21%) abdominal heterotopias were found, of which the pancreas was the most common (0.12%), followed in descending order by the stomach, adrenal and bone[10].

HP has been found in all age groups, predominantly in the sixth decade of life. In studies with larger numbers of patients, the median age ranged from 47.5 to 51 years[4,7,8], displaying lower values – 42.5 years – when the juvenile population was included[11]. The mean age found in our study was slightly above – 52.7 years – being higher in males.

In adults the incidence is higher in males, while in pediatric patients the female gender prevails[3].

The ectopic pancreatic tissue is detected more frequently in the submucosa and muscularis propria layers of the gastrointestinal tract and may be observed in the sub-serosa or even in the serosa of the affected segment. In 32 specimens observed by Pang[12], 15 were sub-mucosal, 11 were observed in all layers except the mucosa, three were located in the muscularis propria and other three in the sub-serosa. Similarly, this study found 15 specimens of HP in the sub-mucosa, seven of which exclusively sub-mucosal, five in conjunction with the muscularis propria and three were observed in the sub-mucosa, muscular and sub-serosa. In the other three, the aberrant pancreas stood on two occasions in the muscular wall and, in the last, exclusively in the sub-serosa.

Usually HP lesions present in the form of small yellowish nodules, ranging from 1 mm to 5 cm, typically covered by intact mucosa, and often exhibit a central hole. In this umbilication, there is exteriorization of the usually rudimentary pancreatic duct, which can be detected by endoscopic study or barium contrast[13]. However, lesions smaller than 1.5 cm do not usually show such an orifice. Gastroduodenal lesions are usually larger than those of other locations[8,12]. The average lesion size of this study was 10.7 mm, similar to reports of predominantly asymptomatic cases[2,9,11]. In children these formations measure 1-2 mm in diameter, but increase in size with the growth of their hosts, thus explaining cases of late onset of symptoms[14].

Histologically, pancreatic heterotopia was rated by Heinrich in three types: type I, composed of all pancreatic cell representatives, known as complete pancreatic heterotopias; type II, containing acini and ducts; and type III, composed only of ducts and rare acinar cells or only dilated ducts, the adenomyomas[10]. This classification is incomplete for not typifying the endocrine component alone or in combination with one of the other components.

Gaspar Fuentes et al. [15], in their turn, divided the ectopic pancreas in four types: type I, with all pancreatic representatives (complete heterotopia); type II, composed of ducts only (canalicular heterotopia); the type III, with only acini (exocrine heterotopia); and type IV, only with the islets of Langerhans (endocrine heterotopia). This classification does not contemplate findings showing the presence of two components, such as ducts and acini, observed in our histological analysis.

As in the present study, we believe it is simpler to characterize a type I as reported by both classifications, a type II with only two components, whatever they might be, and a type III containing a single component. The terms complete, exocrine, canalicular or endocrine heterotopias would remain to facilitate the understanding.

In general, the endocrine component is the less frequent pancreatic representative in the heterotopias, almost always prevailing the exocrine and canalicular ones; concomitant chronic pancreatitis and consequent fibrosis, almost always present, could cause atrophy to such structures, resulting in selective ablation[11,16].

In this work, the endocrine representative (islets) did not appear in isolation and the exocrine (acini) was present in all specimens. The three components together and acini accompanied by ducts were detected in 83.3% of cases. However, these findings are not homogeneous; Armstrong et al.[8] detected islets in 68% of cases and ducts in 85%. Tanaka et al.[4] found three components in 66.6% of their 15 patients and acini ducts in only 26.6%. Factors such as patient age and size of ectopy also help to explain such disagreements.

Evidence of chronic inflammation – peri-ductal or intra-lobular fibrosis and ductal dilatation – was frequently seen (Figures 1 and 2); these lesions can be interpreted as consequences of repeated episodes of acute pancreatitis, similar to what happens in normal pancreas. In this study there were no lesions compatible with acute inflammatory process.

The ectopic tissue was long thought to be unable to secrete enzymes or hormones. Currently, immunohistochemical studies are helping to recognize products secreted by ectopic cells in ways similar to those of normal pancreas. In reality these studies demonstrated the existence of complete endocrine and exocrine activity in these anomalous pancreas[12,17,18].

Eighty-nine percent (16) of cases of this study were located in the upper gastrointestinal region, 38.9% (seven) in the stomach, 33.3% (six) in the duodenum and 16.6% (three) in the jejunum, confirming data from studies with larger numbers of patients, which indicate that 70-90% of cases are located in this segment; two classic studies on ectopic pancreas detected a gastric incidence ranging from 25.5% to 38.2%, duodenal 27.7% to 36.3%, and jejunal 15.6% to 15.9%[1,2].

In the stomach lesions are antral in 85 to 95% of cases, usually in the greater curvature, less than 5 cm from the pylorus [2,9,11], as also observed in this study.

Meckel's diverticulum is a common site of heterotopic tissue, the most incident being the stomach, which occurs in 50 to 60% of the cases, and the pancreas, responsible for 5 to 16%[10,12]. The presence of aberrant pancreas in a Meckel's diverticulum, besides causing motor disorders, can serve as an invaginating fulcrum of intussusception, especially when located in its extremity[19].

Patients in this study were mostly asymptomatic, in accordance with other reports,[1,2,8,12]. Those who underwent endoscopy presented epigastric pain and dyspeptic symptoms of irregular appearance, being treated with symptomatic, anti-ulcer medications and handled as outpatients without developing new symptoms or digestive diseases. No other patient in this study developed symptoms that could be attributed to ectopia.

When symptomatic, about 30% of total mimic clinical symptoms similar to diseases that affect the organ in which the heterotopia is located[4]. Since it is primarily

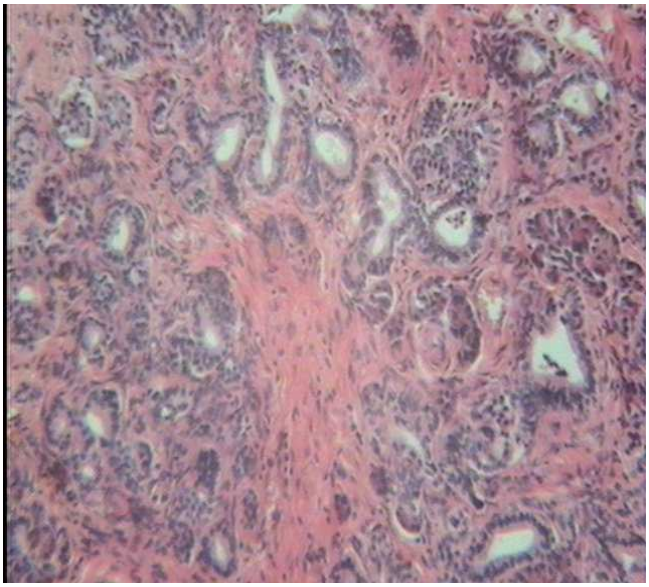

Figure 1 – *Numerous pancreatic ducts, with acini grouping and foci of fibrosis (HE x 40).*

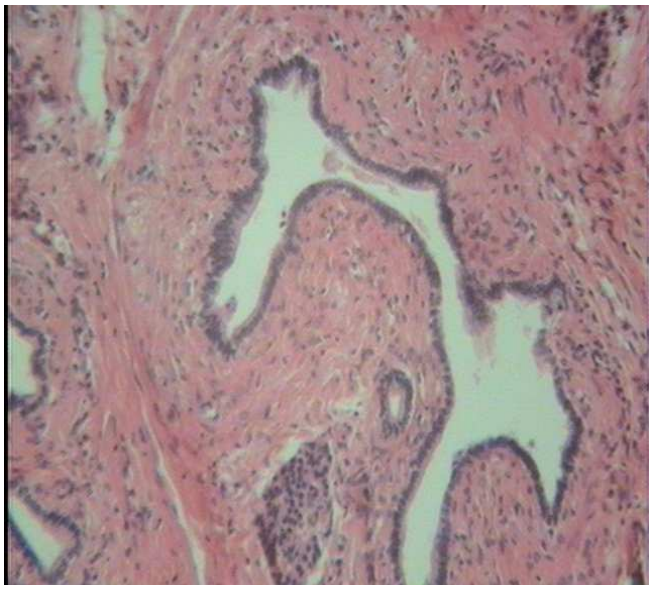

Figure 2 – *Dilated pancreatic ducts, interspersed with smooth muscle tissue, fibrotic trabeculae and pancreatic acini grouping (HE x 25).*

located in the upper gastrointestinal tract, dyspeptic complaints, epigastric pain, nausea, vomiting, jaundice and hematemesis are common[2,4,8,20]. Obstructive scenarios due to the mass effect caused by HP are represented by pyloric obstruction (polyps, mucosal prolapse, thickened pylorus), obstruction or intussusception of the small intestine (the most common presentation of this segment), obstruction of the biliary tree (cystic duct , distal common bile duct, major papilla)[8,11,16,21-23].

Because the ectopic tissue is capable of reproducing all the original pancreas diseases, symptoms related to pancreatitis, formation of cysts and pseudocysts, neuroendocrine syndromes and malignancies can ensue[3,4,24-26]. The careful research for pancreatic atypical cells in this study is hence justified.

Cyst formation results from the impossibility of the exocrine secretion to drain to the body cavity where they are located (retention cysts); when punctured, they show increased levels of amylase; the presence of pseudocysts is uncommon[24].

The symptoms seem to have a relationship with lesion size and extent to the vicinity of the mucosa, so lesions larger than 1.5 cm and of highest expression were associated with more severe symptoms[8].

Other scholars have cast doubt on whether the presence of many of these symptoms might be caused by heterotopic pancreas[2,7].

The emergence of non-specific symptoms is explained by local dysmotility caused by the ectopic pancreas and its secretion of enzymes, determining the onset of spasms, chemical irritation of surrounding tissue and inflammatory processes of varying natures[16]. When specific they are usually accompanied by slightly elevated serum amylase, explained by the smaller amount of forming tissue[3,27].

The diagnosis of ectopic pancreas is difficult, despite modern advances in the laboratory and image fields and other instrumental diagnostic procedures; there are no specific indicators or markers for HP, so that the diagnosis is always histopathological, obtained by the material removed by endoscopic biopsies or resections.

The more evident radiological signs in barium study reveal a parietal defect by a sub-mucosal, well delineated formation, sometimes with its characteristic central umbilication[8.11-13]. Solitary wall thickening in the distal antrum wall is other important finding[10,28]. In cases of intussusception the typical target lesions are present, suggesting this entity[21].

On endoscopic examination aberrant pancreas typically presents as an intra-mural nodule or in the form of a sessile polyp with central umbilication, covered by normal mucosa[29]. When the umbilication is enlarged it can be mistaken for an ulcer, but the umbilication is not present in formations smaller than 1.5 cm[12]. In most cases, endoscopic biopsies using tweezers are superficial, not including the pancreatic tissue in the samples and therefore missing diagnosis[7,29]. This did not happen in the present study, as the four biopsied cases were positive.

The contribution of diagnostic ultrasound may reside in the easily recognizable polypoid lesion within the gallbladder and the images of concentric rings with alternating ecogenecity typical of small bowel intussusceptions[17,19,21]. However, it is unable to differentiate these lesions from others that affect the same organs.

Computerized Tomography (CT), besides revealing the aforementioned lesions (wall thickening, polypoid lesions and nodules, luminal or compressive obstructions), easily identify the morphology of the normal

pancreas, important in the presence of elevated enzyme values[10,28].

The endoscopic ultrasound (EUS) easily recognizes submucosal lesions smaller than 2 cm but is not specific; yet, it provides precision in the determination of the layer of origin of submucosal lesions, allowing suspicion of some of them.

The images of ectopic pancreas are characterized by its heterogeneous, hypoechoic appearance, with slightly outlined margins, located on the third and fourth echoic layer (fusion type) or only in the third layer (separate type); there seems to be an association of the fusion type with total heterotopia and of the separate type with the presence of a single ectopic component[29]. Anechoic areas within the HP represent ductal structures.

Gastrointestinal stromal tumors (GIST) display a hypoechoic, well demarcated, homogeneous internal structure, originating from the second or fourth echoic layer (muscularis and muscularis propria). When malignant, they present with necrosis and scant echoes[5]. Lipomatous lesions, on their turn, are characteristically hyperechoic and originate from the third layer (sub mucosa)[30]. Another significant contribution of EUS is the recognition of extrinsic lesions capable of exerting compressiom[30].

Although the diagnosis of malignancy can only be defined by a pathological study, some data on endoscopic ultrasound are often associated with these lesions: diameter larger than 4 cm, poorly defined margins, cystic spaces and internal echogenic foci, adjacent lymphadenopathy and rapid growth[30].

Asymptomatic patients with positive diagnosis must remain under medical supervision and be reviewed periodically. Uncomplicated symptomatic patients should have their lesions excised, preferably by local resection. In sites accessible to the fiberscope, in seasoned hands and in adequate institutions, endoscopic removal can be performed satisfactorily in selected patients. The use of endoscopic ultrasonography in this kind of intervention is imperative[30].

Heterotopic pancreas found during surgical procedures motivated by other diseases should be excised and submitted to a frozen section study whenever necessary, thus avoiding possible complications and the need for reoperation.

In the cases of lesions associated with bleeding, obstruction or suspicion of malignancy, the appropriate surgical approach is imposed. In the presence of intussusception in adults surgical resection is recommended, as undertaken in this study, due to high rates of malignancies.

Although pancreatic heterotopia is rare, it should be remembered in the differential diagnosis of various gastrointestinal lesions. By being intra-parietal it needs to be differentiated from other non-mucosal lesions. The possibility of generating obstructive phenomena, inflammatory processes of varying intensity, as well as neoplastic degeneration should also be considered.

R E S U M O

Objetivo: *Analisar as características clínico-patológicas do tecido pancreático heterotópico em órgãos digestivos abdominais.* ***Métodos***: *Realizamos estudo retrospectivo analisando 18 portadores de pâncreas heterotópico diagnosticados histologicamente. Seus dados clínicos e histopatológicos foram revistos. O tecido pancreático heterotópico foi classificado em três modelos histológicos: tipo I constituído por três componentes do pâncreas normal (ácinos, ductos e ilhotas), tipo II com dois componentes e tipo três com somente um componente.* ***Resultados***: *A média de idade foi de 52,7 anos, variando de 34 a 73 anos, com nove homens e nove mulheres. Sintomas foram observados em somente quatro doentes, sendo suas lesões diagnosticadas por gastroscopia. Os 14 restantes eram assintomáticos e suas anomalias descobertas acidentalmente. A maioria das lesões situava-se no trato superior: sete (38,9%) no estômago, seis (33,3%) no duodeno e três (16,6%) no jejuno. A heterotopia localizou-se preferencialmente na submucosa (83,3%), mas também foi observada na muscular própria e na sub-serosa. Em sete (38,9%) espécimes todos os componentes pancreáticos foram constatados (tipo I), em oito (44,4%) estavam presentes glândulas exócrinas e ductos excretores (tipo II) e em três (16,7%) somente o tecido exócrino foi observado (tipo III).* ***Conclusão***: *A heterotopia pancreática é rara. Doentes com ectopia pancreática diagnosticadas pelo estudo patológico, assintomáticos ou com sintomas discretos devem permanecer em observação. As lesões detectadas acidentalmente durante procedimentos cirúrgicos necessitam ser removidas por procedimentos conservadores.*

Descritores: *Coristoma. Pâncreas. Sistema digestório. Cirurgia.*

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Address correspondence to:
Dr. Sansom Henrique Bromberg
E-mail: brombergsh@yahoo.com.br