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Pancreatic extragastrointestinal stromal tumor: A case report and comprehensive literature review

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Abstract

AIM: To provide an overview of the literature on pancreatic extragastrointestinal stromal tumors (EGISTs).

METHODS: We report a case of pancreatic EGIST and review published studies on pancreatic EGIST accessed *via* the PubMed, MEDLINE, Google Scholar, and Google databases. The keywords used were "pancreas and GIST", "pancreas and extra GIST", "pancreas and gastrointestinal stromal tumor", and "pancreas and extragastrointestinal stromal tumor". Literature reviews and/or duplicate studies were excluded. The search included articles published in the English language between January 1, 2000 and May 15, 2014.

RESULTS: From our literature survey, 30 manuscripts on pancreatic EGISTs were considered, of which 27 met the search criteria and three were excluded. The studies involved 30 patients (15 men, 15 women) with a mean age of 55.3 ± 14.3 years (range 30-84 years). The mean age of the male patients was 50.8 ± 13.7 years (range 30-84 years); that of the female patients was 59.9 ± 13.3 years (range 38-81 years). Tumor dimensions were obtained for 28 cases (mean 114.4 ± 78.6 mm; range 20-350 mm). Tumors were diagnosed incidentally in 23.3% of patients; abdominal discomfort and weight loss were the major complaints in symptomatic patients. Risk of aggressive behavior according to Fletcher criteria was determined in 25 of 30 patients (68%: high risk, 28%: intermediate risk, 4%: low risk). Histopathological examination revealed the presence of spindle cells in 96.1% of cases; CD117 and CD34 were present immunohistochemically in 96.6% and 84% of patients, respectively. The most common surgical procedures were distal pancreatectomy with splenectomy (n = 9) and pancreaticoduodenectomy (n = 7). The total follow-up period for the 28 patients ranged from 3-66 mo, during which locoregional or distant metastases were diagnosed in six patients and two patients died.

CONCLUSION: Studies on EGISTs have only been published in the last decade. The lack of studies with large patient cohorts and long-term follow-up limits evidence-based commentary. In theory, each case should be assessed individually and further genetic and immunohistochemical studies are needed.

Key words: Gastrointestinal stromal tumor; Extra-gastrointestinal stromal tumor; Pancreas; Imatinib mesylate; CD117

Core tip: Gastrointestinal stromal tumors are the most common gastrointestinal (GI) tract tumors of mesenchymal origin. Stromal tumors of extragastrointestinal origin are termed extragastrointestinal stromal tumors (EGISTs) and are not associated with the walls of GI

tubular organs or the serosal walls. The pancreas is among the organs that are rarely the site of origin, and according our knowledge, about 30 cases of pancreatic EGISTs have been reported to date. In this study, we reviewed studies on pancreatic EGISTs and report a case of pancreatic head EGIST.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common tumors of mesenchymal origin in the gastrointestinal (GI) tract[1-3]. The disease originates from neoplastic transformation of the interstitial cells of Cajal or their precursors in the GI tract. Although GISTs can be diagnosed in all sites of the GI tract, *i.e.*, from the esophagus to the anus, they are most commonly diagnosed in the stomach and intestines[1-6]. Stromal tumors of extragastrointestinal origin are termed extragastrointestinal stromal tumors (EGISTs) and are not associated with the walls of GI tubular organs or serosal surfaces[3,7,8]. The morphological, histopathological, immunohistochemical, and molecular profiles of EGISTs are similar to those of GISTs[2,9,10]. Although EGISTS potentially originate from a variety of sites in the abdominal cavity, the majority of initial tumor progression sites include the omentum, retroperitoneum, mesentery, and the liver[1,2,11,12]. The pancreas is rarely the site of origin, and according our knowledge, 30 cases of pancreatic EGISTs have been reported to date[1-5,7-31]. We report a case of pancreatic EGIST and review the literature on pancreatic EGISTs.

MATERIALS AND METHODS

Our primary aim was to report the rare case of a 61-year-old patient who underwent surgical treatment for pancreatic head EGIST. The secondary aim was to analyze previously published articles related to pancreatic GIST. We searched for published studies on pancreatic GIST using different keyword combinations, including "pancreas and GIST", "pancreas and extra-GIST", "pancreas and gastrointestinal stromal tumor", and "pancreas and extragastrointestinal stromal tumor" in the PubMed, MEDLINE, Google Scholar, and Google databases. Studies for which full-text versions were available and that contained adequate patient details for comparison were included; literature reviews and duplicate reports were excluded. The publication language was not an exclusion criterion, and studies published before May 15, 2014 were included. Tables 1 and 2 lists the year of publication, country, patient age and sex, clinical presentation, physical examination, radiological tests, tumor size (mm), cell type (spindle, epithelioid, mixed), mitotic count [per high-power field (HPF)], immunohistochemical staining (CD117, CD34), surgical procedure, recurrence, outcome, and follow-up obtained from the studies.

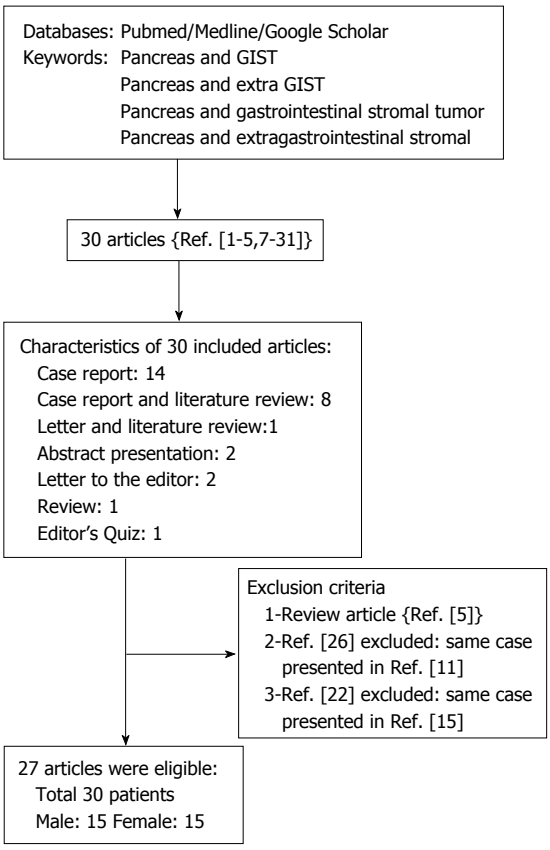

Figure 1 Flow chart of the study selection process. GIST: Gastrointestinal stromal tumor.

RESULTS

Literature review

Based on the above-mentioned search criteria, 30 manuscripts were identified[1-5,7-31]: 27 met the criteria and three were excluded[5,22,26]. The criteria are detailed in the flow chart in Figure 1. The studies involved 30 patients with pancreatic GIST: 15 were male and 15 were female; mean age was 55 ± 14.3 years (range 30-84 years). The mean ages of male and female patients were 50.8 ± 13.7 years (range 38-81 years) and 59.9 ± 13.3 years (range 38-81 years), respectively. Information regarding tumor size was obtained from 28 cases (mean 114.4 ± 78.6 mm; range 20-350 mm). The demographic and clinical data of the 30 patients are presented in Table 1. Table 2 summarizes the morphological characteristics, treatments, and outcomes of the 30 patients.

Case report

A 61-year-old woman was admitted to our clinic for a routine check-up. One year previously, she had visited another clinic complaining of loss of appetite, weight loss,

Table 1 Demographic and clinical characteristics of 30 patients with pancreatic extragastrointestinal stromal tumors identified from literature published between January 2004 and May 2014

Ref.	Year	Country	Age (yr)	Sex	Clinical presentation	Examination	Radiologic tools	Tumor location	Tumor size (cm)
Tian *et al*[4]	2014	China	61	M	Incidental finding	Abdominal mass	CT	Tail	60 × 80
			60	M	Incidental finding	NS	CT	Head	60 × 50
Paklina *et al*[11]	2013	Russia	38	F	Abdominal discomfort	NS	CT	Head	90
Serin *et al*[1]	2013	Turkey	30	M	Abdominal distension	NS	US + CT	Tail	130
Soufi *et al*[16]	2013	Morocco	39	M	Weight loss + abd pain + constipation	Distension	CT + endoscopy	Head	90 × 70 × 50
Wegge *et al*[2]	2012	USA	55	M	Haematemesis + haematochezia	Non-specific	CT + MRCP + endoscopy	Head	46 × 45 × 44
Babu *et al*[13]	2012	China	55	F	Upper abdominal pain	Non-specific	CT + US	Head	50 × 40 × 30
Kim *et al*[3]	2012	Korea	55	M	Abdominal discomfort	Non-specific	CT + MR	Tail	130 × 90 × 85
Čečka *et al*[9]	2011	Czech	74	F	Abdominal mass	Palpable mass	US + CT	Tail	110 × 80 × 40
Vij *et al*[14]	2011	India	35	M	Weight loss + abdominal discomfort	Non-specific	US + CT	Head	80 × 60
Rao *et al*[7]	2011	India	40	M	Weight loss + abdominal pain + anemia	Non-specific	US + CT	Head + Body	65 × 60
Yang *et al*[15]	2011	China	55	M	Abdominal discomfort	Abdominal mass	CT + MR	Body + Tail	178 × 196
Barros *et al*[12]	2011	Brasil	63	F	Abdominal pain + ponderal loss	NS	NS	NS	NS
			81	F	Difficult gastric emptying + ponderal loss	NS	NS	NS	100
Joshi *et al*[17]	2010	USA	84	M	Weight loss + abdominal distension	Distension	CT	Entire pancreatic tissue	340 × 240 × 270
Crisan *et al*[18]	2010	Romania	61	M	Weight loss + fever + intense sweating	Diffuse tenderness	CT X	Tail + Body	140
Saif *et al*[19]	2010	USA	31	M	Weight loss + abdominal pain + anemia	NS	CT + MR + endoscopy	Head	56 × 51 × 42
Padhi *et al*[8]	2010	India	42	F	Weight loss + abdominal pain	Palpable mass	CT + MR	Body + Tail	350 × 300 × 250
Harindhanavudhi *et al*[20]	2009	USA	63	F	Fatigue + weakness+anemia	Non-specific	CT + EUS	Body	160 × 110
Trabelsi *et al*[21]	2009	Tunisia	52	F	Epigastric pain	Palpable mass	US + CT	Head	105 × 80 × 30
Goh *et al*[10]	2009	Singapore	58	M	Incidental finding	NS	NS	Head	90
Showalter *et al*[23]	2008	USA	72	F	Incidental finding	NA	MR	Tail	70
Yan *et al*[24]	2008	USA	47	M	Nausea + vomiting + (hepatitis B)	Splenomegaly	CT + EUS	Uncinate process	24 × 21
Ganesh *et al*[25]	2008	UK	76	F	Weight loss + abdominal pain	Diffuse tenderness	CT + endoscopy	Tail + body	NS
Daum *et al*[27]	2005	Czech	70	F	Incidental finding	Palpable mass	CT	Head	100 × 80 × 60
Krska *et al*[28]	2005	Czech	38	F	Abdominal pain + fatigue	Tenderness	CT + US + EUS + CT + endoscopy	Head + Body	170 × 120
Pauser *et al*[29]	2005	USA	51	M	Incidental finding	NS	US + CT + endoscopy	Tail	30
			54	F	Abdominal discomfort	NS	US	Body	20
Neto *et al*[30]	2004	Brasil	67	F	Weight loss + abd pain + gastric bloating	NS	NS	Body + Tail	200 × 190 × 120
Yamaura *et al*[31]	2004	Japan	54	F	Incidental finding	Palpable mass	US + CT + MR + angiography	Tail	140 × 120 × 80

US: Ultasonography; CT: Computed tomography; MR: Magnetic resonance; EUS: Endoscopic ultrasound; MRCP: Magnetic resonance cholangiopancreatography; X: Partial thrombosis detected in both portal vein and inferior vena cava at the level of left renal vein; NA: Not-available; NS: Not-stated; M: Male; F: Female; UK: United Kingdom; USA: United States of America.

and jaundice. Blood tests showed elevated liver enzymes and leucocyte count. Abdominal ultrasonography (USG) revealed bile duct dilatation, multiple metastatic liver lesions, and a pancreatic head mass. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a 97 mm × 63 mm heterogeneous mass with well-defined margins in the pancreatic head, which had resulted in the bile duct dilatation. Perihilar gross lymphadenopathy was also detected. Following bile duct decompression by percutaneous transhepatic cholangiography, percutaneous biopsy samples were collected from the liver lesions and portal lymph nodes under USG guidance. The specimens were evaluated histopathologically and immunohistochemically [CD117(+); CD34(−); smooth muscle actin (SMA)(−)], and GIST was diagnosed. As the primary tumor was metastatic prior to surgery, 400 mg/d imatinib mesylate (Gleveec®, Novartis) was started and administered for four months. MRI subsequently showed a reduction in tumor size to 15 × 15 mm. CT performed during the same period showed that the tumor had shrunk to 15 × 20 mm and that the liver lesions had disappeared. Based on these findings, surgical treatment was advised, but the patient refused surgery; therefore, she was discharged and prescribed imatinib. When admitted to our clinic, she had no significant physical findings except

Table 2 Morphological characteristics, treatments, and outcomes of 30 patients with pancreatic extragastrointestinal stromal tumor identified from literature published between January 2004 and May 2014

Ref.	Cell type	Mitotic count (/50 HPF)	CD117	CD34	Surgical procedures	Recurrence (after surgery)	Outcome (follow-up)	Medical treatment
Tian *et al*[4]	Spindle	< 5 (intermediate risk)	(+)	(+)	Distal pancreatectomy + splenectomy	No	Alive (36 mo)	No
	Spindle	> 5 (high risk)	(+)	NS	Tumor resection	Yes (liver, 12 mo)	Alive (36 mo)	Gleevec + TACE
Paklina *et al*[11]	Spindle	1-2 (intermediate risk)	(+)	NS	NS	NS	NS	NS
Serin *et al*[1]	NS	NS (high risk)	(+)	NS	Distal pancreatectomy + splenectomy	No	Alive (21 mo)	No
Soufi *et al*[16]	Spindle	< 5 (intermediate risk)	(+)	(+)	Whipple + segmental colectomy	No	Alive (24 mo)	Gleevec
Wegge *et al*[2]	Spindle	6 (intermediate risk)	(+)	(+)	Whipple	No	Alive (5 mo)	Gleevec
Babu *et al*[13]	Spindle	6-8 (high risk)	(+)	(+)	Pancreatic head resection	No	Alive (11 mo)	No
Kim *et al*[3]	Spindle	7 (high risk)	(+)	(+)	Distal pancreatectomy + splenectomy	No	Alive (4 mo)	Gleevec
Čečka *et al*[9]	Spindle	5 (high risk)	(+)	(+)	Distal pancreatectomy + splenectomy	No	Alive (66 mo)	No
Vij *et al*[14]	Spindle	12-15 (high risk)	(+)	(-)	Whipple	Yes (liver, 24 mo)[a]	Alive (48 mo)	Gleevec
Rao *et al*[7]	Spindle[b]	8-10 (high risk)	(+)	(+)	Whipple	Yes (liver, 24 mo)	Alive (30 mo)	Gleevec
Yang *et al*[15]	Spindle	> 30/10 HPF (high risk)	(+)	(+)	Distal pancreatectomy + splenectomy	Yes (intraperitoneal, 24 mo)[c]	Alive (41 mo)	Gleevec
Barros *et al*[12]	NS	< 5	(+)	(+)	No	NS	Death (8 mo)	No
	NS	< 5 (intermediate risk)	(+)	(+)	Laparotomy + biopsy	Surgery not performed	Alive (12 mo)	Gleevec
Joshi *et al*[17]	Spindle	NS	(+)	(+)	None performed[d]	Surgery not performed	Death (5 d)	No
Crisan *et al*[18]	Spindle	(high risk)	(+)	(+)	Distal pancreatectomy + splenectomy + partial colectomy + duodenojejunal resection	NS	Alive (3 mo)	NS
Saif *et al*[19]	Spindle[e]	48 (high risk)	(+)	(-)	Whipple, pylorus preserving	Yes (liver, 9 mo)	Alive (NS)	Gleevec
Padhi *et al*[8]	Spindle	6-8 (high risk)	(+)	(+)	Distal pancreatectomy + splenectomy + left hemicolectomy	No	Alive (10 mo)	No
Harindhanavudhi *et al*[20]	Spindle	< 5 (high risk)	(+)	(+)	Cystojejunostomy[f]	NS	Alive (NS)	Gleevec
Trabelsi *et al*[21]	Spindle	6 (high risk)	(+)	(+)	Whipple + partial colectomy	No	Alive (10 mo)	No
Goh *et al*[10]	Spindle	> 10 (high risk)	(+)	NS	Whipple	No	Alive (58 mo)	NS
Showalter *et al*[23]	NA	3 (intermediate risk)	(+)	(-)	Distal pancreatectomy + splenectomy - laparoscopic	No	Alive (27 mo)	NS
Yan *et al*[24]	Spindle[g]	3 (low risk)	(+)	NS	NS	NS	NS	NS
Ganesh *et al*[25]	Spindle[h]	NS	(+)	(+)	No (inoperable)	Surgery no performed	Alive (30 mo)	Gleevec
Daum *et al*[27]	Spindle	2 (intermediate risk)	(+)	(-)	Whipple	No	Alive (6 mo)	Gleevec
Krska *et al*[28]	Spindle[i]	1 (high risk)	(-)	(+)	Partial pancreatectomy	No	Alive (30 mo)	NS
Pauser *et al*[29]	Spindle	NS	(+)	(+)	Resection	No	Alive (24 mo)	NS
	Spindle	NS	(+)	(+)	Resection	No	Alive (48 mo)	NS
Neto *et al*[30]	Mixed	120 (high risk)	(+)	(+)	Distal pancreatectomy	Yes (peritoneum)	Alive (NS)	Gleevec
Yamaura *et al*[31]	Spindle	Few (high risk)	(+)	(+)	Distal pancreatectomy + splenectomy + partial gastric resection	NS	Alive (30 mo)	NS

[a]Liver metastasis at postoperative month 24. Metastasectomy performed. Two years followed without recurrence; [b]Diagnosed using USG-guided fine needle aspiration (FNA); [c]Intraperitoneal recurrence at postoperative month 24. Resection performed. Imatinib treatment both before and after resection. Following second resection, followed-up without recurrence; [d]CT-guided liver biopsy diagnosed metastatic EGIST. Clinical status deteriorated prior to surgery and died five days following diagnosis; [e]Diagnosed with Endo-USG (EUS)-guided FNA. Liver lesion diagnosed with CT and PET at postoperative month 9. Biopsy diagnosis was EGIST. Gleevec treatment dose increased to 800 mg. Due to resistance to treatment, was switched to sunitinib; [f]Pancreatic mass diagnosed four years ago, patient refused surgical treatment. CT revealed 10-cm enlargement in four years. Diagnosis was made with EUS-guided FNA. Explorative laparotomy revealed pancreatic hemorrhagic cyst; cystojejunostomy performed to obtain an incisional biopsy sample diagnosed high-risk GIST. Patient refused definitive surgical treatment; [g]Diagnosis made with EUS-guided FNA; [h]Diagnosed using USG-guided FNA. Further surgical treatment aborted as the patient was inoperable, and Gleevec treatment was initiated. Clinical follow-up period of 30 mo revealed significant tumor reduction; [i]USG-guided biopsy could not provide diagnosis. CT: Computed tomography; USG: Ultrasonography; EGIST: Extragastrointestinal stromal tumor; PET: Positron emission tomography; TACE: Transcatheter arterial chemoembolization; NA: Not-available; NS: Not-stated.

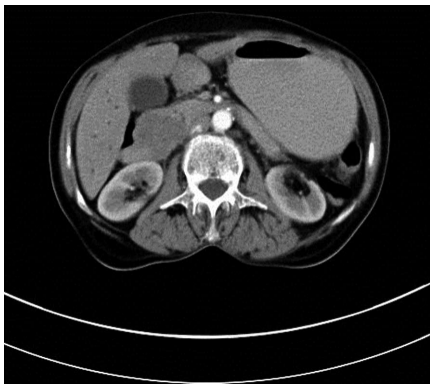

Figure 2 Contrast-enhanced abdominal computed tomography shows a well-defined solid mass of the pancreatic head.

cachexia. Laboratory test parameters, including tumor markers, were within the normal limits. Control abdominal CT scan showed that the tumor measured 45 mm × 40 mm (Figure 2). The common bile duct and major pancreatic duct diameter was 17 mm and 7 mm, respectively. No metastatic liver lesions were detected. F-18 fluorodeoxyglucose positron emission tomography-CT (PET-CT) detected a mass with increased glucose consumption at the duodenal site, consistent with a malignant lesion. Given the increased tumor size and the current complaints of the patient, surgical treatment was recommended. We detected a well-demarcated, 50 × 40 mm, semi-solid, visually heterogeneous pancreatic head mass without invasion to the surrounding tissues. Metastatic liver lesions were not observed, and lymphadenopathy was detected in the peripancreatic site and hepatoduodenal ligament. Standard pancreaticoduodenectomy with lymph node dissection was performed. The postoperative course was uneventful; she was discharged on day 13. Pathologically, the specimen contained tumor cells with low mitotic activity, severe pleomorphism, and cellularity (spindle cells); we diagnosed GIST. Postoperative imatinib mesylate was started, and there was neither locoregional nor distant metastases at the last follow-up 48 mo later.

DISCUSSION

In 1892, Cajal first observed interstitial cells of Cajal in the intestinal wall under a light microscope, which were termed "interstitial neural cells". Approximately 80 years later, Faussone-Pellegrini *et al*[32] viewed the same cells under an electron microscope and renamed them interstitial cells of Cajal[5,32]. Studies conducted during the 1970s showed that pathological changes to interstitial cells of Cajal may result in GI motility disorders and GISTs[5]. Since they were first described histologically, physiological testing has proven that interstitial cells of Cajal function as GI pacemakers[5,20,32,33].

Defined by Mazur and Clark in 1983, GISTs are the most common non-epithelial mesenchymal tumors of the GI tract[5]. Genetic studies have revealed that 90% and 5%-7% of GISTs have tyrosine kinase gene mutations in c-KIT and platelet-derived growth factor receptor alpha (PDGFRA), respectively[1,5]. The incidence of GIST varies between 10 and 20 cases per million people annually[5,9]. GISTs represent 0.1%-3% of all GI tumors and 80% of GI mesenchymal tumors, and may present at any site in the GI tract where there are interstitial cells of Cajal. The most frequently affected GI organs are the stomach (40%-70%), intestines (20%-40%), rectum and colon (< 10%), and the esophagus (rare)[5].

"EGIST" was initially used by Reith *et al*[33] in 2000 to define stromal tumors originating from outside the GI tract. EGISTs represent 5%-10% of all GISTs[1,4,5,9,12]. Although the locations from which EGISTs originate do not contain interstitial cells of Cajal, cells with the same clinical, pathological, immunohistochemical, transmission electron microscopy morphology, and biological behavior patterns as interstitial cells of Cajal have been detected[2,5,6]. Experimental and clinical studies have detected cells with biological and histopathological features similar to interstitial cells of Cajal in pancreatic tissue (interstitial Cajal-like cells = telocytes)[5,34]. The pancreas and GI tubular organs have a common embryological origin, suggesting that EGIST and GIST cells originate from multipotent mesenchymal stem cells (intestinal mesenchymal precursors)[1,5,21]. Several EGIST studies have suggested that most EGISTs are likely mural GISTs with diffuse extramural invasion resulting in loss of communication with the intestinal muscularis propria. This may occur during operative or postoperative manipulation. Furthermore, true EGISTs may be extramurally growing GISTs that lose communication with the muscularis propria after reaching this layer[2,10,16]. This is known as extensive extramural growth and requires further study.

More than 80% of EGISTs originate from EGI abdominal wall structures, including the intestinal mesentery, mesocolon, omentum, retroperitoneum, abdominal wall, liver, and pancreas[10,13]. Pancreatic EGISTs represent less than 1% of malignant pancreatic tumors, and less than 5% of EGISTs originate from the pancreas[16].

The majority of EGISTs are well demarcated and unencapsulated. Due to their slow growth rate, they may exist without any clinical signs until the majority of the abdominal cavity is invaded. Among the reported cases, tumors are 100-120 mm in diameter (range 10-400 mm)[4]. EGISTs are usually diagnosed in adults, predominantly in females[14]. Our literature review determined near equal rates of occurrence between females and males.

Pancreatic EGISTs are usually asymptomatic or minimally symptomatic and diagnosed incidentally by radiological examination[7,9]. When present, the severity of symptoms is related to tumor dimensions and location in the pancreatic tissue[2,4,7,9,16]. The most common symptoms and findings are nonspecific abdominal pain, weight loss, fatigue, abdominal mass and distention, fever of unknown origin, obstruction, GI bleeding, anemia, portal vein thrombosis, jaundice, and hepatic encephalopathy (rare)[4,16,18]. Of the cases we reviewed, 23.3% were diagnosed incidentally. The most common symptoms were

weight loss and abdominal discomfort.

The most common diagnostic studies for pancreatic masses involve biochemical [carbohydrate antigen 19-9, carcinoembryonic antigen (CEA)], radiological, histopathological, immunohistochemical, and genetic testing[3-5,21]. However, the diagnostic value of tumor markers such as CA 19-9 and CEA for pancreatic EGIST is limited, and are rarely used[4]. Abdominal CT, MRI, USG, endoscopic USG (Endo-USG), and PET-CT are the most frequently used radiological techniques, and aid in determining tumor localization, dimensions, margin irregularity, invasion of surrounding tissues, distant metastases, and resectability; however, most of them are non-diagnostic. USG and CT are often used in fine needle biopsies[5,7,17,20,24,25,28]. Endo-USG is a valuable diagnostic tool, allowing simultaneous diagnosis and biopsy of solid or cystic pancreatic masses[4,5,16,19,20,24]. PET-CT is used more frequently for both diagnosing and monitoring GIST and is very efficient in cases where CT and MRI are inconclusive[35].

Histopathologically, GISTs are classified into spindle (70%), epithelioid (20%), or mixed (< 10%) type. Most pancreatic EGISTs consist of spindle cells[4]. Therefore, leiomyoma, leiomyosarcoma, liposarcoma, rhabdomyosarcoma, schwannoma, fibromatosis, inflammatory fibroid polyps, solitary fibrous tumor, and malignant fibrous histiocytoma should be considered in the differential diagnoses[3,8,11,24,27]. Of the cases presented here, 26 had detailed histopathological data and 25 (96.1%) had spindle cells.

EGISTs have typical immunohistological staining features, among which CD117 is the most well known. KIT is a transmembrane receptor for binding tyrosine kinase enzymes, and c-KIT is a newly discovered member of this receptor family, on whose receptor CD117 is an epitope that can be stained immunohistochemically. The introduction of CD117 staining in the 1990s changed the terminology for connective tissue tumors; since then, 95% of tumors defined as GIST or EGIST stain CD117-positive. For the 5% of tumors with negative staining, another tyrosine kinase receptor family member, PDGFRA, was investigated in immunohistochemical studies, with 33.3% positive staining[5]. Additionally, GISTs stain positive for CD34 (60%-70%), heavy caldesmon (80%), SMA (30%-40%), S100 (5%), and desmin (< 5%)[2-4,8,9]. Of the 30 cases presented, 29 (96.6%) stained CD117-positive and 21 (84%) of 25 cases stained CD34-positive.

Predicting GIST clinical and biological behavior is difficult. Fletcher defined the criteria of the National Institutes of Health (Fletcher criteria) to estimate the risks of GIST aggressive behavior and metastasis (locoregional and/or distant) using tumor dimensions (cm) and mitotic counts (per 50 HPF)[2,9]. According to the criteria, GISTs are classified based on their risk of aggressive behavior: very low (< 2 cm, < 5/50 HPF), low (2-5 cm, < 5/50 HPF), intermediate (< 5 cm, 6-10/50 HPF or 5-10 cm, < 5/50 HPF), and high (> 5 cm, > 5/50 HPF or > 10 cm, any mitotic count)[3,4,9,21]. This classification aids in surgical treatment selection or neoadjuvant and/or adjuvant treatment planning. The risk of aggressive behavior according to the Fletcher criteria was determined in 25 of the 30 patients in our literature review: risk of pancreatic EGIST aggressive behavior was high in 17 cases. The remaining 8 cases were intermediate risk (n = 7; 28%) and low risk (n = 1; 4%).

The goal of surgical treatment, which is the most desirable treatment option for primary pancreatic EGISTs, is complete resection with microscopically clean (R0) margins[4,5,36]. Generally, primary surgery, surgical treatment following neoadjuvant chemotherapy, and debulking surgery for metastatic and/or advanced disease are considered in the surgical treatment of GISTs[2,5]. Surgical treatment selection depends on pancreatic EGIST localization. Standard or pylorus-preserving pancreaticoduodenectomy is the optimal treatment for pancreatic head tumors[4]. Duodenum-preserving pancreatic head resection may be performed for small tumors, low-grade tumors, or patients who cannot tolerate the Whipple procedure[4,36]. Conversely, radical surgical treatment may be the best option for preventing locoregional and/or distant metastases[13,15]. Regional lymph node metastases are rare in pancreatic EGIST cases, and routine systematic regional lymph node dissection is not indicated[4,13,16,18]. In our patient, EGIST was diagnosed after lymph node biopsy. Therefore, we suggest lymphadenectomy for cases of pathological lymphadenopathy observed during surgical exploration and for lymph node metastasis-positive cases based on intraoperative frozen section analysis. Depending on intraoperative findings and the surgeon's experience, pancreaticoduodenectomy, distal pancreatectomy with splenectomy, or partial pancreatic resection may be used for treating tumors in the pancreatic tail and corpus[13]. Nine and seven of the 30 patients underwent distal pancreatectomy with splenectomy, and the Whipple procedure, respectively.

The responses of GISTs to conventional chemotherapy and radiotherapy were very limited, being 10% and 5%, respectively[9,21]. These response rates changed when imatinib mesylate, an agent used for treating chronic myelogenous leukemia, was administered to a GIST case in the early 2000 s. Philadelphia chromosome-positive leukemia patients carry a mutation in the *BCR-ABL* gene, which is a KIT receptor family member. Additionally, the mutated *c-KIT* and *PDGFRA* genes seen in GISTs are members of the same family. Consequently, tyrosine kinase transmembrane receptors have been targeted in GIST treatment using two agents: imatinib mesylate and sunitinib malate. Imatinib was the first c-KIT tyrosine kinase inhibitor used for treating GISTs, specifically metastatic and unresectable GISTs, and was approved by the US Food and Drug Administration. Sunitinib was subsequently introduced for patients who could not tolerate imatinib or who were imatinib-resistant[2,23]. Recently, new tyrosine kinase inhibitors, such as nilotinib, sorafenib, dovitinib, and dasatinib, were introduced[5]. Despite the controversial approach of "which tyrosine kinase inhibitor, which patient and when", there is consensus for

initiating imatinib treatment in patients with high mitotic activity, gross dimensions, necrosis, and locoregional and/or distant metastasis[2,15]. Imatinib may be used as a neoadjuvant agent to downstage gross tumor volume for R0 resection and contributes to good prognosis[4]. Imatinib may be used as adjuvant treatment in cases with R1 (positive microscopic margin) or R2 (residual gross visible tumor) resection, risk of aggressive behavior, or poor prognostic features[4,5]. Similarly, imatinib treatment may be used as a primary modality in metastatic or unresectable cases to reduce tumor size, resulting in better prognosis[4]. Metastatic pancreatic EGIST cases benefit from debulking surgery, which increases the efficacy of imatinib[2]. The positive response to imatinib in patients with GISTs is 60%-70%, which can extend overall survival up to 5 years[4].

In conclusion, the term EGIST was introduced into the literature in the last decade. Debates on the similarities and differences between EGISTs and GISTs are ongoing. Despite their behavioral similarities, the initial asymptomatic period accounts for the gross tumor size of EGISTs. The lack of comprehensive case reports on EGISTs, including pancreatic EGISTs, limited our evidence-based review. Long-term follow-up studies of EGISTs are currently unavailable, limiting the amount of available information on tumor behavior. We are limited to the case reports that have been published to date and further immunohistochemical and genetic studies regarding EGIST behavior and response to treatment are needed.

COMMENTS

Background

Gastrointestinal stromal tumors (GISTs) are the most common tumors of mesenchymal origin in the gastrointestinal (GI) tract. The disease originates from neoplastic transformation of interstitial cells of Cajal or their precursors in the GI tract. Stromal tumors of extragastrointestinal origin are termed extragastrointestinal stromal tumors (EGISTs) and are not associated with the walls of GI tubular organs or serosal surfaces. The morphological, histopathological, immunohistochemical and molecular profiles of EGISTs are similar to those of GISTs.

Research frontiers

The primary aim was to report the rare case of a 61-year-old patient who underwent surgical treatment for pancreatic head EGIST. The secondary aim was to analyze previously published articles related to pancreatic GIST. To this end, the authors searched for studies on pancreatic GIST using different keyword combinations in the PubMed, MEDLINE, Google Scholar, and Google databases.

Terminology

GISTs are the most common mesenchymal tumors of the GI tract. EGISTs are defined as tumors originating from outside the GI tract. Imatinib mesylate was the first c-KIT tyrosine kinase inhibitor used to treat GISTs. The Fletcher criteria are used to estimate the risk of GIST aggressive behavior and metastasis using tumor size and mitotic counts.

Peer review

This paper comprises a case history, and a comprehensive review of the literature on pancreas GIST. The strength of the paper is that the authors have tried to collect available literature of the limited articles published on this topic.

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