

Extra-Gastrointestinal Stromal Tumor Arising in the Pancreas: A Case Report and Literature Review

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ABSTRACT

Context Extra-gastrointestinal stromal tumors (EGISTs) of pancreatic origin are extremely rare entities, of which the prognoses as well as biological behavioral patterns are yet to be completely unraveled. To our knowledge, only fourteen cases being reported in English literature till date. We intend to present such a case of EGISTs, primarily located in the pancreas, which will most probably be the fifteenth of all the cases to be reported in English medical literature. Apart from presenting this one case we further wish to review and highlight the salient features, i.e. clinical manifestations, diagnostic parameters, prognoses etc. Case report A fifty-five year old female presented with the complaints of pain in the upper abdominal region, with gradual increment in the intensity. The reason for which were found to be a mass, located in the head of the pancreas, accompanied by chronic cholecystitis with multiple stones in gall bladder. Contemplating of a pancreatic malignancy, the patient underwent an abdominal laprotomy, during which a rapid intra-operative frozen biopsy sample was extracted. Further biopsy revealed a malignant gastrointestinal stromal tumour of the pancreatic head. Thus having arrived at a confirmatory diagnosis, malignant cystic neoplasm of the pancreas, local tumour resection followed by pancreaticojejunostomy with Roux-en-Y anastomosis and cholecystectomy were executed. Conclusion Despite a being rarity, differential diagnosis of solid and cystic pancreatic masses that could involve the pancreas as the primary site, without GISTs in view would be a highly imprudent one, particularly owing to the unusually eminent risk of malignancy. The current case consolidates the extra-gastrointestinal stromal tumour of primary pancreatic localization can involve, and should be considered in the differential diagnosis of solid and cystic pancreatic masses.

INTRODUCTION

Although gastrointestinal stromal tumors [GISTs], representing a majority of primary non-epithelial neoplasm of the digestive tract, predominantly involving the stomach (60-70%), small intestine (20-25%), colorectum (5%), and oesophagus (<5%), are not clinical rarities^[1]; However, primary extra-gastrointestinal stromal tumors [EGISTs] arising from the pancreas are extraordinarily inconceivable clinical findings. The fact that they display no connection with the gastric and/or intestinal wall, makes them classifiable as a larger family of neoplasms capable of involving other portions out of the digestive tract, such as the omentum, the mesentery, and the retroperitoneum as well. Thus, a well formulated definition of GISTs, depicting as close a picture as possible, would be, "intra-abdominal mesenchymal tumours most frequently expressing the KIT protein having a gain of function mutation in the regulatory juxtramembrane domain of the c-kit gene"^[2]. While we have already been able to retrieve a lot of information regarding the histogenesis, prognostic parameters, and the possible foreseeable outcomes; a number of important aspects are still, at best evasive to us, such as incidence, pathogenesis, and the prognoses of EGISTs. Thus a prospective comparison between the two, i.e. GISTs and EGISTs, is yet, for the reasons of not having known about all the common parameters of comparison; a matter of dilemma and speculation. Here, we intend to report a new case of primary pancreatic GISTs, supplemented by radiological and pathological documentation and review the previously reported cases of primary EGISTs of the pancreas.

CASE REPORT

A fifty-five year old woman presented with a vague upper abdominal pain, gradually increasing in intensity from last four days and plausible

deniability of any previous history of jaundice, gastro-intestinal bleeding, acute and/or chronic pancreatitis as well as no symptoms pointing towards such things. A through physical, radiological and biochemical-pathological examination concurred with her history and also revealed some new findings; there was deep abdominal tenderness, without any rebound tenderness in the epigastrium and without any palpable mass as well. Ultrasonographic examination of the abdomen showed a solid mass in the head of the pancreas along with chronic cholecystitis with multiple stones in gall bladder. CT scan of the abdomen revealed a heterogeneously enhancing solid mass located in the head of the pancreas of the following dimensions: 5×4×3 cm (figure 1). The CT and the USG findings neither indicated that the mass had invaded or compressed any of the adjacent vascular structures nor were there any signs of the dilatation of the biliary and the main pancreatic ducts or any evidence of ascites or peripheral lymphadenopathy. All the laboratory tests involving the liver function, serum amylases, and tumor markers were within normal limits. As the findings did not tally with the commonly encountered pancreatic malignancy, we decided to perform an abdominal laparotomy, during which a rapid intra-operative frozen biopsy was sent for examination, and examined biopsy revealed a pancreatic spindle cell tumor, thus suggestive of extra-gastrointestinal stromal tumors of the pancreas; the immediate unanimous decision was to go for a pancreatic head including local tumor resection followed by a pancreaticojejunostomy with Roux-en-Y anastomosis and cholecystectomy. Although due to economic constraints, patient didn't receive any adjuvant therapy: the recovery was uneventful with no recurrence and/ or metastasis during the eleven months period of follow up.

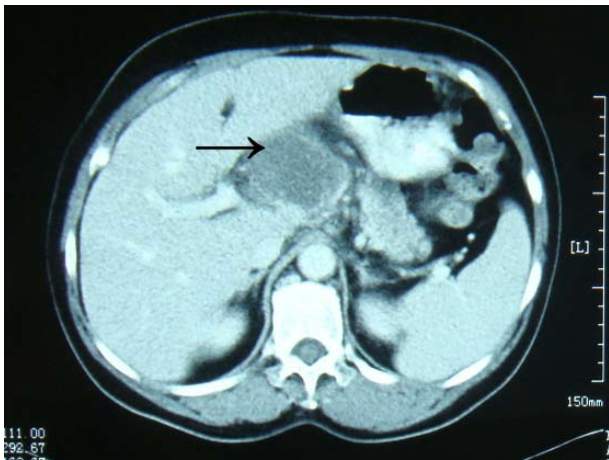


Figure 1 Abdominal computed tomography scan: axial image showing a heterogeneously enhancing lobulated lesion in the region of the pancreatic head.

Histopathological Examination

Sections of the specimen were encapsulated and well demarcated, invading the pancreatic head. Twelve peripancreatic lymph nodes, proximal and distal duodenal margins, as well as pancreatic resection margin, were all negative for tumour. Whole bulk of the tumour was derived from pancreatic parenchyma without infiltrating the adjacent organs, shows no any connection with gastric and intestinal wall. The histological section of the tumour showed a sheets of spindle cells tumour arranged in fascicles with brisk mitotic rate 6-8/50 HPF (high power field). On immunohistochemistry, the tumour cells were strongly positive for c-Kit (CD117), CD34 (figure-2) and DOG1 within the tumour. While negative for SMA, desmin, S-100, and cytokeratin. The Ki-67 labeling index was reported to be a value of <5%.

DISCUSSION

In a clinical practice setting, gastrointestinal stromal tumors are not uncommon; a vast majority of them occurring in the stomach, the small intestine, colorectum, and other parts of the digestive system, often manifesting clinically with one or more of the following features-abdominal pain, gastrointestinal bleeding and/or palpable abdominal mass. Further analyses revealed that, apart from occurrence within the gastrointestinal tract, extragastrointestinal incidences were less than 10%. The analysis of Agaimy A *et al*^[1] showed that, out of 200 cases of gastrointestinal stromal tumors, 65% occurred in the stomach (130 cases), 24% in the small intestine (48 cases), 4.5% in the duodenum (9 cases), 0.5% in appendix (1 case), 1.5% in indeterminate locations (3 cases), and another 7% diagnosed as EGISTs (14 cases), including one case involving the tail of the pancreas. Foreign EGISTs occurring in the omentum^[2], transverse mesocolon^[3], diaphragm^[4], uterus^[5], and even in the scrotum^[6], the pleura^[7], and other rare parts have also been reported in literatures.

So far, beginning from 2004, a total of fourteen reported cases of EGISTs in pancreatic localization have been published in various literatures around the world^[8-21] (Table 1). Pancreatic part of EGISTs is a rarity without any clinical manifestation, thus making a preoperative diagnosis very difficult. As can be recalled from our own case history, most of the patients do not present with any specific symptoms; many a times this disease has been an incidental finding, often during routine procedures done with any other pathology in mind. Similarly, a majority of these cases were reported in a similar fashion, with a suspicion of pancreatic tumors, however not taking into account the EGISTs. Among the existing papers pertaining to this matter, although four authors have reported of conducting a preoperative percutaneous fine needle aspiration cytology^[13,15,16,18], we did not resort to it, because of apprehensions of rupturing the tumor as well as causing tumor spreading. Based on previous studies as well as our own experience; we were of an opinion that, we should suspect this disease if the patient will be presenting with very vague clinical symptoms, or a larger mass located in the head of the pancreas without jaundice, or any other associated symptoms which co-relates with a malignancy of pancreas. Moreover, tumour markers such as CA19-9 and other biochemical as well as pathological parameters non suggestive of a carcinoma would suggest a very definite possibility of E-GISTs occurring in the pancreas.

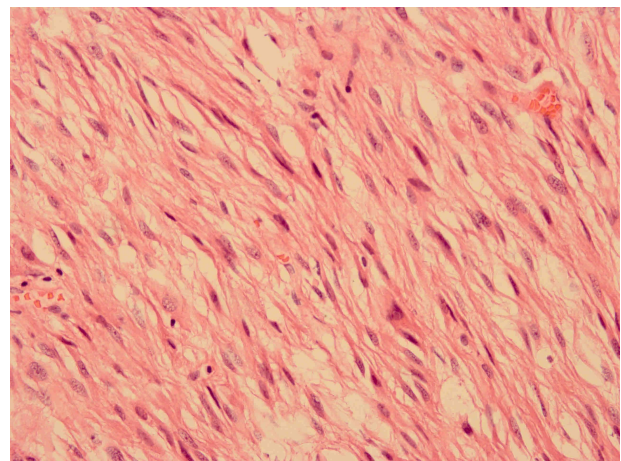


Figure 2 Immunohistochemistry showing an elongated spindle cells in the reactivity with C-Kit for the tumour cells of (CD117).

GISTs are usually considered to be derived from intestinal cells of cajal; nevertheless the exact origin of E-GISTs are yet unclear. It can be diagnosed incidentally during a radiologic imaging; however diagnosis of GISTs is based on histological, immunohistochemical and molecular features (oncogenic C-kit mutation). Most GISTs express c-kit (CD117) (95%), CD34 (70%), and heavy caldesmon (80%), in which 25% are

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Table 1 Histopathological findings, treatment and recurrence data of reported cases of Pancreatic GISTs.

Case/Authors/Year,	Age/Sex,	Features	Pathology	Treatment	Recurrence
1. Neto <i>et al</i> , 2004 ^[8]	67 years Female	Epigastric pain bloating, weight loss	Size: 20 cm Solid cystic mass with necrotic foci located in body and tail Mitotic count: 120/50 HPF IHC: CD117(+), CD34(+)	Distal pancreatectomy and splenectomy Imatinib mesylate	Recurrence with peritoneal dessemination 1 month after surgery
2. Yamura <i>et al</i> , 2004 ^[9]	54 years Female	Incidental finding	Size: 14cm Solid mass with cystic degeneration located in tail Few mitosis IHC: vimentin(+), CD34(+), CD117(-), S-100(-)	Distal pancreatectomy splenectomy, and partial gastrectomy	NER at 30 months
3. Krska <i>et al</i> , 2005 ^[10]	38 years Female	Abdominal pain	Size: 17cm located in body and head Mitotic count: 1/50 HPF IHC: vimentin(+), CD34(+) Actin(-), CD117(-), S-100(-)	Partial pancreatectomy	NER at 30 months
4. Daum <i>et al</i> , 2005 ^[11]	70 years Female	Incidental finding	Size: 10cm located in head Mitotic count: 2/50 HPF IHC: vimentin(-), CD34(-), actin(-) CD117(-), desmin(-), S-100(-)	Whipple procedure matinib therapy	NER at 6 months
5. Showalter <i>et al</i> , 2008 ^[12]	72 years Female	Incidental finding	Size: 7cm Solid mass with necrotic foci located in tail Mitotic count: 3/50 HPF IHC: CD117(+), SMA(-), S-100(-)	Laparoscopic distal pancreatectomy, and splenectomy	NER at 27 months
6. Yan <i>et al</i> , 2008 ^[13]	47 years Male	Nausea and vomiting	Size: 2.4×2.1cm Solid mass with necrotic foci located in uncinat process Mitotic count: 3/50 HPF IHC: CD117(+), SMA(-), S-100(-)	N/A	N/A
7. Trabelsi <i>et al</i> , 2009 ^[14]	52 years Female	Epigastric pain	Size:10.5×8×3cm located in head Mitotic count: 6/50 HPF IHC: CD117(+),CD349+)	Hemipancreaticoduodenectomy with antrectomy and partial colectomy	NER at 10 months
8. Haridhanavudi <i>et al</i> , 2008 ^[15]	63 years Female	Fatigue and weakness	Size: 16×11cm Haemorrhagic cyst located in body Mitotic count: <5/50 HPF IHC: CD117(+), CD34(+), SMA(+), MSA(+) SMA(-), S-100, CK(-), synaptophysin(-)	Cyst drainage and cystojejunostomy patient refused surgery and imatinib therapy	N/A
9. Saif <i>et al</i> , 2010 ^[16]	31 years Male	Abdominal pain, anemia weight loss	Size: 5.1×4.2×5.6cm located in head with liver space - occupying lesion of 9*7cm Mitotic count: 24/25 HPF IHC: CD117(+)	Whipple procedure imatinib therapy	Recurrence with liver dessemination 9 month after surgery
10. Padhi <i>et al</i> , 2010 ^[17]	42 years Female	Abdominal pain, loss of weight and appetite	Size: 35×30×25cm located in body and tail Mitotic count: 6-8/50 HPF IHC: CD117(+), CD34(+), SMA(-) S-100(-), CK(-)	Distal pancreatectomy splenectomy and left hemicolectomy	NER at 10 months
11. Rao <i>et al</i> , 2011 ^[18]	40 years Male	Abdominal pain, weight loss	Size: 6.5×5.0cm located in body and head with liver space occupying lesion - of 9×7 cm Mitotic count: 8-10/50 HPF IHC: CD117(+), CD34(-), SMA(-), S-100(-), CK(-)	Whipple procedure imatinib therapy	Recurrence with liver dessemination 24 month after surgery
12. Vij <i>et al</i> , 2011 ^[19]	35 years Male	weakness, postprandial fullness and pain	Size: 6.5×6.0cm located in head Mitotic count: 12-15/50 HPF IHC: CD117(+), CD34(-),SMA(-) S-100(-), CK(-)	Whipple procedure imatinib therapy	Recurrence with liver dessemination 24 month after Surgery
13. Cecka <i>et al</i> , 2011 ^[20]	74 years Female	Abdominal mass	Size: 11×8×4cm located in tail Mitotic count: <5/50 HPF IHC:CD117(+), CD34(+), SMA(-), S-100(-),CK(-)	Distal pancreatectomy and splenectomy	NER at 5 years
14. Feng <i>et al</i> , 2011 ^[21]	55 years Male	Abdominal discomfort	Size: 2.5×3cm located in body and tail IHC: CD117(+), CD34(+)	Distal pancreatectomy and splenectomy	NER at 17 months
15. Present case	55 years Female	Abdominal pain	Size: 5×4×3cm located in head Mitotic count: 6-8/50 HPF IHC: CD117(+), CD34(+), S-100(-), CK(-)	Local tumour resection and cholecystectomy	NER at 11 months

positive for smooth muscle actin and less than 5% for desmin. Moreover the discovery of pancreatic interstitial cells of cajal supports the diagnosis of an extragastrointestinal stromal tumour arising solely from the pancreas^[17]. In a detailed re-evaluation of fourteen post surgical specimens of EGISTs conducted by Agaimy A *et al* and colleagues^[11] (four mesentric, four omental, one pararectal, one pelvic, one perivesical, one of the mesentric root, one involving the omentum and the abdominal wall and one located between liver and stomach) it was found that, it was possible to reclassify most of these cases (11/14) either as GISTs with extramural growth or as metastases from a GISTs. By means of critical revaluation of the surgical reports and clinical histories shows a diversity of presentation and a concept behind of so-called extra-gastrointestinal stromal tumours. Likewise Popescu *et al*^[22] found out that in human endocrine pancreas are similar to the gastrointestinal tract, the ministry of cajal cells, suggesting that the pancreas has the possibility of occurrence of EGISTs.

The most effective means of treatment was surgical resection, and the treatment of choice for pancreatic part of the EGISTs, due to the high degree of malignancy. Among which the local excision should be the preferred procedure, and mostly do not need line of regional lymph node dissection. In fact surgical resections depends upon the site of the lesion in which variety of surgical procedures were reported in the literature, pancreaticoduodenectomy (including pylorus-preserving pancreaticoduodenectomy), pancreatic body and tail resection with splenectomy (including laparoscopy), partial resection of the pancreas, e.t.c, some patients got good results, no recurrence after 5 and half years reported^[20]. Although patient with lesion of the pancreatic head, we have diverted it from pancreaticoduodenectomy to pancreatic head resection (local tumour resection) which would be probably a first case reported in the worldwide literature. Patient respond well after surgery without any postoperative complications and was on strictly follow up for eleven months without a complication, metastases or recurrence. Patients with conventional chemotherapy and radiotherapy have been reported to be effective in the treatment of GISTs as well EGISTs with metastasis or recurrence. An inhibitor of the tyrosine kinase activity of c-Kit Imatinib (Gleevec®) has revolutionized the treatment of this disease and long-term treatment is an important measure to reduce the relapse.

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