



## Pancreatic Extra Gastrointestinal Stromal Tumor: A Case Report and Review of the Literature

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### Abstract

We report a case of 60 years old male who presented with complains of abdominal pain and multiple episodes of vomiting. Endoscopic examination revealed a 2.5 cm ulcer in second part of duodenum with elevated margins. CECT abdomen revealed a 10 x 10 cm lesion in the head of pancreas with perilesional lymphadenopathy. Pylorus preserving pancreaticoduodenectomy was performed. Histopathology and immunohistochemistry examination confirmed the diagnosis of extra intestinal GIST of pancreas with positivity for CD117 and vimentin. This case further proves that this rare tumor can involve pancreas as the primary site. Therefore emphasis should be to include this rare tumor in the differential diagnosis of pancreatic neoplasm.

**Keywords:** extra gastrointestinal stromal tumor, pancreas, CD117, vimentin, histopathology.

### Introduction

The most common malignant condition of pancreas is ductal adenocarcinoma of the exocrine pancreas (about 85% of all the cases) <sup>46,47</sup>. Whereas primary EGIST of pancreas are extremely rare and constitute only 5% of GIST<sup>37</sup>, GIST may occur in the entire length of gastrointestinal tract from esophagus to anus, however the most common sites are stomach (60%), small intestine (30%), rectum(5%) and esophagus (<5%)<sup>37</sup>. Duodenal GIST constitute

30% of all primary duodenal tumors and less than 5% of GIST<sup>38,39,40</sup>. Sometimes GIST tumor arises from omentum, mesentery, gall bladder, retro peritoneum, but separate from stomach and intestine<sup>3,7,8,33,42,43</sup>, in such cases the neoplasm is defined as extra gastrointestinal stromal tumor. EGIST do not display connection to the wall or serosal surface of the viscera. The pancreas is a rare site of origin of EGIST and according to our knowledge only 30cases of EGIST have been reported till date<sup>7-31</sup>.GIST occurs due to the

neoplastic transformation of interstitial cells of Cajal (ICCS), which normally are the pacemakers of intestinal motility<sup>14,52,53</sup>. EGIST are essentially identical to gastrointestinal counterparts in terms of morphology, molecular profile and IHC. We hereby report a case of pancreatic EGIST and review the literature on pancreatic EGIST.

### Case Report

We report a case of 60 years old male an ex-smoker, hypertensive, hypothyroid, from the last sixteen years on medical treatment who presented with complaints of abdominal pain and multiple episodes of vomiting associated with restlessness and giddiness. Physical examination of patient revealed stable general condition. The patient was conscious and oriented. No icterus or cyanosis were present, however, mild pallor was seen. Pulse rate was 78 per minute, B.P 120/60 mm Hg, respiratory rate 16/minute, SpO<sub>2</sub> 94% off oxygen, temperature 97 degree Fahrenheit. Respiratory system and cardiovascular system examination did not reveal any abnormality. Abdominal examination revealed mild tenderness in epigastrium however abdomen was soft and not distended. Routine investigations revealed: Hb- 8.8 gm/dl, TLC – 5900/mm<sup>3</sup>, DLC- neutrophils 65%, lymphocytes 32%, eosinophils 2%, monocytes 1%, Platelets 375,000/mm<sup>3</sup>. Urea 42, creatinine 1.2, bilirubin 0.6, ALT 14, ALP 47, albumin 3.99, Na 138, K 3.6, calcium 8.72. Endoscopy revealed a 2.5 cm ulcer in D2 with elevated margins. CECT abdomen (figure 1) revealed a 10 x 10 cm lesion in the head of pancreas with perilesional lymphadenopathy. Patient subsequently underwent pylorus preserving pancreaticoduodenectomy (PPPD). Intra operatively a growth measuring 10 x 10 cm was seen occupying the periampullary region which appeared to arise from the pancreas (figure 2). Pancreatic duct / common bile duct size was normal. No ascitis was seen. Liver and peritoneum were free. Postoperative period was uneventful and patient was discharged after 15 days.

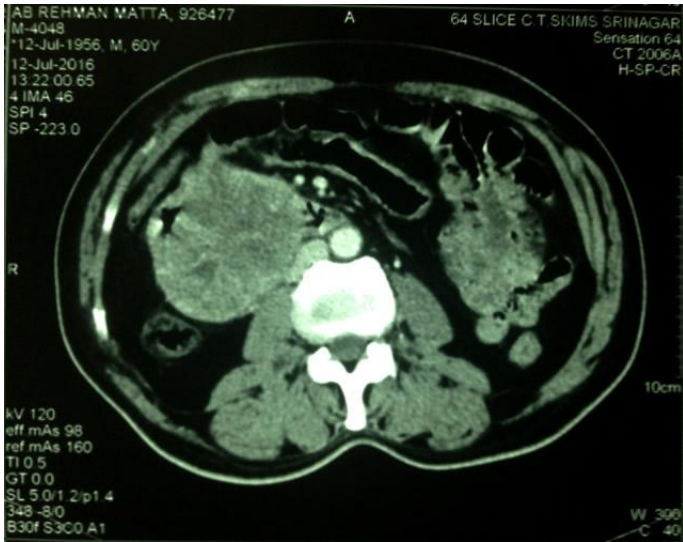
### Macroscopic Examination

Pancreaticoduodenectomy specimen with duodenum measuring 22x3x3 cm and pancreas measuring 10x8x8 cm. This lesion was 8 cm from proximal and 10 cm from distal duodenal resection margins. On cutting open through duodenum, mucosa was flattened and few ulcerated areas were also seen. While cut section through the pancreas revealed a firm mass in the head of pancreas measuring 8 x 8 cm, firm in consistency, abutting the ampullary areas of the duodenum. Serial sectioning through the mass revealed grayish white firm area, with focal cystic and hemorrhagic areas, however no areas of necrosis were seen grossly (figure 3).

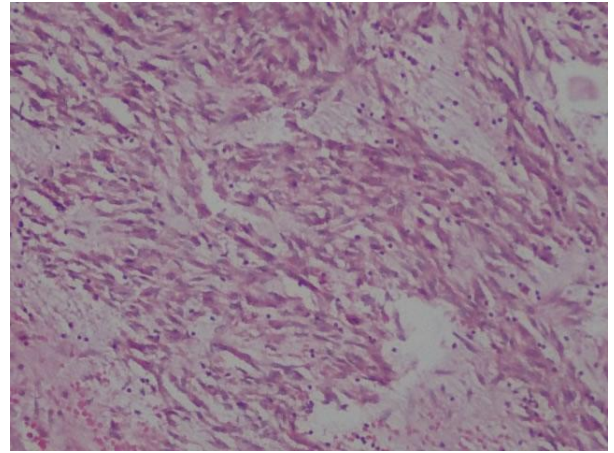
Microscopic examination: sections from the pancreas showed tumor consisting of sheets of spindle cells with intervening fine loose edematous connective tissue. The spindle cells exhibited regular nuclei with fine chromatin, scant to moderate amount of cytoplasm without significant atypia. Mitotic count was < 5/50 HPF (figure 4). At places these spindle cells were arranged in whorled pattern. Few hemorrhagic areas were identified. Sections from the duodenum adjacent to the pancreas and randomly were free of tumor. All the resection margins were free of tumor.

Immunohistochemistry showed strong positivity for CD117(c-kit) (figure 5) and vimentin (figure 6). IHC examination for CD10, PR, CK 8/18, CK 19, pan CK, S-100, synaptophysin and chromogranin were negative. Ki -67 showed <5/50 hpf mitotic count. Thus a final diagnosis of extra gastrointestinal stromal tumor of pancreas was confirmed.

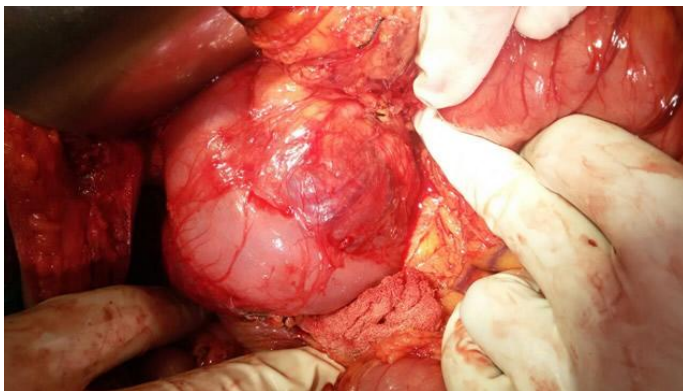




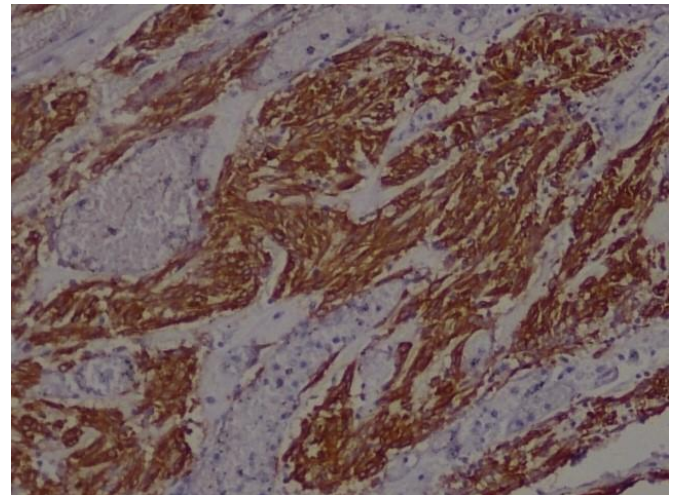
**Figure 1** (CECT abdomen)



**Figure 4** (HPE 40 x)



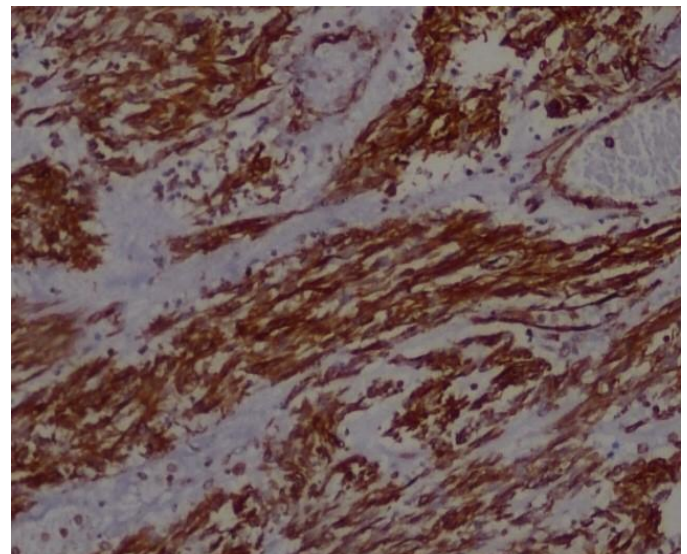
**Figure 2** (intra-operative)



**Figure 5** (vimentin)



**Figure 3** (Gross)



**Figure 6** (CD 117)

**Discussion**

We report a rare case of primary extra intestinal stromal tumor pancreas. Initial histomorphological examination suggested a differential diagnosis of

spindle cell neoplasm of pancreas with diagnostic possibilities of

- 1- spindle cell predominant solid pseudo-papillary tumor of pancreas
- 2- EGIST of pancreas.

However on IHC the final diagnosis of pancreatic EGIST was confirmed which showed strong positivity for CD117 and vimentin.

Cajal was the first to observe interstitial cells of Cajal in intestinal wall in 1882, which were termed "interstitial neural cells". Faussonne-Pellegrini et al<sup>5,32</sup> viewed the same cells under electron microscope about 80 years later and renamed them interstitial cells of Cajal<sup>5,32</sup>. Physiological testing has proved that the interstitial cells of Cajal function as the GI pacemakers<sup>5,20,32,33</sup>. Defined by Mazur and Clark in 1983, GIST is the most common non epithelial mesenchymal tumors of the GI tract<sup>5</sup>. Genetic studies have shown that 90% cases of GIST have tyrosine kinase gene mutation in c-kit and 5-7% have mutation in PDGFRA<sup>1,5</sup>. Additional immunomarkers for GIST include DOG 1, and CD117 (a cell adhesion molecule also known as L1)<sup>48,49,50,51</sup>. These markers are expressed independently of kit or PDGFRA status and can therefore be useful for identification of CD117 negative tumors<sup>44,45</sup>. Mesenchymal tumors other than GIST that may stain for CD117 (eg. fibromatosis) tend to show only cytoplasmic positivity with coarse granular pattern. Therefore convincing pattern of CD117 positivity in GIST is one featuring a cell membrane component in addition to the cytoplasmic one. GIST represent 0.1-3% of all GI tumors and 80% OF GI mesenchymal tumors. GIST may be present in any site in the GIT where there are interstitial cells of Cajal.

In 2000 Reith et al<sup>33</sup> first used "EGIST" to define stromal tumors originating from outside the GIT. EGIST represent 5-10% of all GISTs<sup>1,4,5,9,12</sup>.

In contrast to GISTs, the origin of EGIST is still controversial. It is proposed that these tumors may result from extramural growth of a primary GIST so extensively that they completely lose contact

with the muscularispropria of the adjacent structure<sup>14,55</sup>. Alternate suggestions are that both GISTs and EGISTs arise from a common precursor to both the interstitial cells of Cajal (ICCS) and smooth muscle cells. This seems to be more appropriate explanation as the recent studies have confirmed the existence of c-kit positive interstitial cells of Cajal (ICCS) within intestinal organs and vessels. In further support, these cells have also been documented within the exocrine pancreas, further explaining the origin of pancreatic EGISTs<sup>8,14,34</sup>, additionally these pancreatic cells have been shown to respond to imantinib<sup>54</sup>. Studies suggest that EGISTs have a histologically similar presentation to GISTs, but probably behave differently in terms of prognosis and malignant potential. Thus they may require different risk stratification. Furthermore, it has been observed that EGISTs behave similar to GIST in the distal GI tract, in that they are more aggressive with a greater propensity of metastasis<sup>14,23,28,31,41,52,53</sup>. Some studies have shown high recurrence rates despite adequate resection and adjuvant therapy<sup>12</sup>.

On the other hand pancreatic EGISTs seem to remain fairly asymptomatic with treatable and favorable survival with low malignant potential. But as there are very few cases available, it is difficult to determine statistically significant trends<sup>15,23</sup>. The severity of symptoms of pancreatic EGIST is related to tumor dimensions and location in pancreas<sup>2,4,7,9,16</sup>. The most common signs and symptoms are abdominal pain, weight loss, fatigue, abdominal mass, abdominal distension, fever, obstruction, GI bleed, anemia, portal vein thrombosis, jaundice, and hepatic encephalopathy<sup>4,16,18</sup>.

The most common diagnostic studies for pancreatic masses include biochemical (carbohydrate antigen 19-9, CEA), radiological, histopathological, immunohistochemical and genetic testing<sup>3,4,5,21</sup>. However the diagnostic value of tumor markers such as CA 19-9 and CEA for pancreatic EGIST is limited and is rarely used<sup>4</sup>. Abdominal CT, MRI,USG, endoscopic



USG and PET-CT are the most frequently used radiological techniques in determining tumor localization, dimension, margins, irregularity, invasion of surrounding tissues, distant metastasis and resectability. However, most of them are non diagnostic. USG and CT are often used in fine needle biopsies<sup>5,7,17,20,24,25,28</sup>. Endoscopic –USG is a valuable diagnostic tool, allowing simultaneous diagnosis and biopsy of solid or cystic pancreatic masses<sup>4,5,16,19,20,24</sup>.

Histopathologically, GISTs are classified into spindle (70%), epithelial (20%) or mixed (<10%) types. Most common variant being spindle cell type<sup>4</sup>. It is therefore, important to differentiate it from other lesions like leiomyoma, leiomyosarcoma, liposarcoma, rhabdomyosarcoma, schwannoma, fibromatosis, inflammatory fibroid polyps, solitary fibrous tumor and malignant fibrous histiocytoma<sup>3,8,11,24,27</sup>. Out of the 30 cases of pancreatic EGIST we reviewed, 26 had detailed histopathological data and 25 cases (96%) were spindle cell type.

GIST are classified according to their risk of aggressive behavior into

1. very low (< 2 cm size, <5/50 HPF )
2. low (2-5 cm size, <5/50 HPF)
3. intermediate (< 5 cm size, 6-10 HPF or 5-10 cm size, < 5/50 HPF)
4. High (> 5 cm size, > 5/50 HPF or >10 cm size with any mitotic count)<sup>3,4,9,21</sup>

The risk of aggressive behavior according to these criteria (Fletcher criteria) was determined in 25 cases out of 30 cases in our literature review. Risk of pancreatic EGIST aggressive behavior was high in 17 cases. Out of remaining 8 cases, 7 cases were intermediate risk and one case was low risk.

The most effective treatment option for pancreatic EGISTs is complete resection with microscopically clean margins (R 0)<sup>4,5,36</sup>, followed by neoadjuvant therapy and debulking surgery for advanced or metastatic disease<sup>2,5</sup>. Duodenum preserving pancreatic head resection may be performed for small tumors, low grade tumors or patients who cannot tolerate the Whipples procedure<sup>4,36</sup>. Standard pylorus preserving

pancreaticoduodenectomy is the optimal treatment for pancreatic head tumors<sup>4</sup>. Radical surgical treatment may be the best option for preventing loco-regional or distant metastases<sup>13,15</sup>. Routine and regional lymph node dissection is not indicated in pancreatic EGIST as nodal metastasis is rare<sup>4,13,16,18</sup>.

In our patient, pylorus preserving pancreaticoduodenectomy was performed. No adjuvant therapy was given as the tumor showed low mitotic activity and no necrosis or metastasis was seen either. Complete resection and clean margins were obtained.

The response of GIST to conventional chemotherapy and radiotherapy were very limited, being 10% and 5% respectively<sup>9,21</sup>. However with the induction of imatinibmesylate, a tyrosine kinase inhibitor, the response rates changed quite dramatically. The positive response to imatinib in patients with GISTs is 60-70%<sup>4</sup>. Recently new tyrosine kinase inhibitors such as sunitinib, nilotinib, sorafenib, divitinib and dasatinib were introduced<sup>2,5,23</sup>. Imatinib may be used as a neoadjuvant agent to downstage gross tumor volume for R0 resection and contributes to good prognosis<sup>4</sup>. Imatinib can also be used as adjuvant treatment in cases with R1 (microscopic positive margin) or R2 (residual gross visible tumor) resection, risk of aggressive behavior or poor prognostic features<sup>4,5</sup>. Similarly imatinib treatment may be used as a primary modality in metastatic or unresectable cases to reduce tumor size, resulting in better prognosis<sup>4</sup>.

Out of the thirty cases we reviewed from the literature the age of patients ranged from 30 years to 84 years, with mean age of 62 years. Male and female ratio was 1:1. Most common location of the tumor was head of pancreas followed by tail and the least common site was the uncinate process. The most common clinical presentation was abdominal pain which was presenting symptom in ten cases followed by abdominal discomfort (3 cases) and fatigue (3 cases); however it was an incidental finding in 7 cases. Most frequently used radiological investigation

was CT scan followed by USG and MR. The most frequent surgical procedure performed was distal pancreatectomy with splenectomy followed by whipple procedure. Most common cell type was spindle cell type EGIST (25 cases), with high risk cases being the most frequent (17 cases) followed by intermediate risk (7 cases) and low risk (1 case) whereas, in 5 cases no information about the mitotic count was provided. On IHC examination all the cases were positive for CD117 and CD34 was positive in 21 cases. Recurrence after surgery was noted in 6 cases (12 months -24 months), no recurrence was noted in 15 cases, whereas in 6 cases no information was available and in 3 cases surgery was not performed. Death was reported in 2 cases, in 2 cases no follow up information was available, remaining 26 cases were alive in the follow up period ranging from 1 month to 58 months. Medical treatment with gleevec was given in 13 cases, no information was available in 9 cases whereas, 8 cases did not receive any post surgical chemotherapy<sup>1-4,7-21,23-25,27-31</sup>.

In conclusion EGIST is a recently introduced concept and because of the limited cases and studies on EGIST including pancreatic EGIST, limited our evidence based study. Long term follow up studies are needed to further enhance our knowledge about the behavior, prognosis and treatment response of EGIST and to know the differences and similarities of GIST and EGIST.

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