Case Report

Pancreatic GIST in a Patient with Limited Stage Small Cell Lung Cancer: A Case Report and Review of Published Cases

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1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract and usually occur in the stomach and the small intestine. The pancreas is an extremely rare primary site for GISTs. The annual incidence of GIST in the United States is 5000–6000/year and the males, blacks, and the elderly [1, 2]. Workup of these lesions includes morphologic study and immunohistochemical and molecular diagnostic analysis. Historically, these neoplasms had been included under a number of diagnostic categories including leiomyoma, leiomyosarcoma, schwannoma, and leiomyoblastoma. Surgery was the only available treatment and this changed in 2001 after discovery of mutational activation of the KIT or PDGFRA genes [3] and the use of targeted therapies.

2. Methods

Abstracts, case reports, and case series of pancreatic GIST in the English literature were identified with no date limits until November 2015, by searching the keywords “pancreatic gastrointestinal tumors”, “pancreatic GIST”, and “extra gastrointestinal stromal tumors” in the National Library of Medicine, PubMed, OVID, and EMBASE search engines. Bibliographies of publications were also reviewed for additional relevant studies.

3. Case Presentation

A 52-year-old African-American female was diagnosed with limited stage small cell carcinoma in November 2009 and treated with concurrent cisplatin/etoposide chemotherapy and radiation. She achieved complete remission and underwent prophylactic whole brain radiation in March 2010. Two years later she started to complain of vague abdominal pain and this was investigated with computed tomography (CT) scans which revealed a 3.5 cm enhancing lesion in the pancreas in addition to multiple uterine fibroids (Figure 1).

She underwent endoscopic ultrasonography guided fine needle aspiration (EUS-FNA) of the pancreatic lesion...
Figure 1: CT scan of the abdomen demonstrate a mass, arising from the uncinate process of the pancreas.

Figure 2: EUS showing hypoechoic mass in the pancreatic uncinate process during FNA procedure.

Table 1: Immunohistochemical stains performed on our pancreatic GIST case.

<table>
<thead>
<tr>
<th>Stain</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD117 (c-KIT)</td>
<td>Strongly and diffusely positive in spindle cells</td>
</tr>
<tr>
<td>DOG-1</td>
<td>Strongly and diffusely positive in spindle cells</td>
</tr>
<tr>
<td>Smooth muscle actin (SMA)</td>
<td>Negative in spindle cells</td>
</tr>
<tr>
<td>S-100 protein</td>
<td>Negative in spindle cells</td>
</tr>
<tr>
<td>ALK-1</td>
<td>Negative in spindle cells</td>
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</tbody>
</table>

(Figure 2). Cytopathology revealed atypical cells with spindle cell features. Another EUS-FNA along with core biopsy sampling was performed, yielding the pathological diagnosis of gastrointestinal stromal tumor. Immunohistochemical staining of stromal cells was positive for CD117 (c-kit) and DOG-1 and negative for smooth muscle actin, S-100 protein, and ALK-1 (Figure 3 and Table 1).

We proceeded with medical therapy as patient declined surgical approach, and she was started on treatment with imatinib 400 mg PO daily. During treatment, she experienced imatinib side effects including nausea, vomiting, and leg cramps; we controlled these with promethazine and carisoprodol. Her disease is stable based on CT scans 40 months after diagnosis without any evidence of metastatic disease.

4. Discussion

GISTs are group of tumors showing differentiation or derived from the interstitial cells of Cajal which works as the GI pacemaker cells and like GISTs, these cells express both KIT and CD34 [4, 5]. Eighty percent of GIST cases have a mutation in the KIT gene exon 8, 9, 11, 13, or 17 [6]. In around 7% of cases there are mutations in PDGFR exon 12, 14, 18 D842V, or 18 [7].

Rarely, wild-type adult GIST tumors are associated with activation of the succinate dehydrogenase (SDH) complex like cases of GIST associated with Carney triad or Neurofibromatosis 1 [8]. On the other hand, wild type is very common in pediatric GIST [9] in around 85% cases while only 10–15% of adult cases do not harbor any mutation in the KIT and PDGFR genes [10].

GISTs commonly involve the stomach (60%), jejunum and ileum (30%), duodenum (4-5%), rectum (4%), colon and appendix (1-2%), and esophagus (<1%) and rarely present as primary tumors outside the gastrointestinal lumen such as the omentum, mesentery, and urinary bladder [11–13] or as in our case the pancreas. Both extragastrointestinal GIST and GIST are thought to originate from the gut smooth muscle cells and interstitial cells of Cajal; the former is thought to contribute to the growth outside of the gastrointestinal tract [14]. Another theory is that extragastrointestinal GISTs are mural GISTs which result in extramural growth [14].

The incidence of GIST is around eleven per million population in an Icelandic study [15]. It is difficult to determine the incidence due to the rarity of extragastrointestinal GIST.
The mean age at diagnosis was 63 [1] for GIST compared to 53 for pancreatic GIST from the reviewed case reports. Gender involvement was not different between the pancreatic and extragastrointestinal GIST. A formal statistical analysis was not performed with the available case report data.

GISTs display two morphologic variants represented by the spindle cell and epithelioid subtypes. The spindle cell type is the most frequent, while the histological patterns relate to site of primary origin [16]. The majority of GISTs are strongly positive when stained with antibodies directed against the KIT protein (CD117), and the combination of CD34 and CD117 positivity aids in confirmation of the diagnosis of GIST. There are two targets that have been found to be useful in the diagnosis of GISTs: both C (PKC)-O and DOG1 are expressed in KIT positive and KIT negative GIST [17, 18].

Mutational analysis can aid in determining prognosis or if GIST will be responsive to imatinib therapy, it can also predict which dose level is most appropriate [19, 20]. For example, exon 9 mutant tumors carry the worst prognosis but have superior objective response to tumors with mutations in exon 11, and those patients with documented exon 9 mutations benefit from an 800 mg dose of imatinib rather than the standard 400 mg PO daily dose [21]. Routine mutation analysis is not recommended by the National Comprehensive Cancer Network (NCCN) GIST Task Force due to insufficient data for risk stratification and relapse prognostication [22]. Because of this report, we did not perform the mutation analysis on our patient. This is in contrast to the European Society for Medical Oncology guidelines which support administering an imatinib dose of 800 mg daily for exon 9 mutation [23]. The imatinib 400 mg regimen was chosen due to the Gastrointestinal Stromal Tumor Meta-Analysis Group data [24].

While imatinib can be used in the neoadjuvant or adjuvant setting, sunitinib—which is another tyrosine kinase inhibitor (TKI)—is frequently used as second-line therapy in refractory disease or in case of imatinib intolerance [25]. Sunitinib is administered at 50 mg starting dose in 6-week cycles with 4 weeks on and 2 weeks off treatment and can be also given as 37.5 mg PO daily which appears safe and effective [26]. Regorafenib is a TKI that targets multiple kinases including PDGFR, KIT, and vascular endothelial growth factor receptors; it can be used in advanced GIST after failure of both imatinib and sunitinib [27]. In the third-line setting, other TKIs such as sorafenib and nilotinib have significant clinical activity in imatinib and sunitinib resistant GIST and may represent an alternative for rechallenge treatment with imatinib, which is of limited benefit; nevertheless, it is superior to best supportive care in terms of overall survival [28]. Ganjoo et al. reported the use of pazopanib, another TKI, in a phase 2 clinical trial as a single agent with marginal activity in unselected heavily pretreated patients with advanced GIST [29].

To the best of our knowledge, our case is unique in terms of long survival with single nonsurgical modality and it is the second case of localized pancreatic GIST treated only with TKI. In the English literature there are 25 reported cases of pancreatic GIST (Table 2). Padhi et al. reported nineteen cases of pancreatic GIST gathered from 2000 to 2012 [30]. In 2015, Joseph et al. reported a case of a patient with pancreatic GIST that was started on imatinib but later developed metastatic disease and died 9 months later [31]. If the tumor can be resected, then treatment of choice would be surgery. The stabilization of the lesion in our patient with TKI therapy suggests that this is a reasonable therapeutic course in patients who are not surgical candidates. The lesion should
be reevaluated for resection within three to four months [56]. Given the limited long term follow-up of patients with the pancreas as the site of origin, it is unclear whether pancreatic GISTs have a different natural history relative to luminal GISTs.

**Consent**

Written informed consent was obtained from the patient for the publication of this case report.

**Competing Interests**

All authors have no competing interests.

**References**


Case Reports in Oncological Medicine


