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Frequency of Plexiform Fibromyxoma relative to gastrointestinal stromal tumor: A single center study

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ABSTRACT

Plexiform Fibromyxoma (PF) is an exceedingly rare mesenchymal tumor of the gastric antrum that was first described in 2007. PF is a close mimic of gastrointestinal stromal tumor (GIST) clinically and histopathologically, but the frequency of PF relative to GIST is unknown. Moreover, although likely benign, long-term follow-up of PF is limited due to its recent description and rarity. PF has not been reported in distal jejunum. 118 primary GISTs that were surgically resected at our center (2000–2019) were retrieved. The patients' age, gender, clinical presentation, tumor location, size and number, and the presence or absence of metastasis, were documented. Risk of progressive disease was assessed according to the published GIST risk stratification model. Two unique cases of PF were compared. One gastric PF has been followed-up for 8 years, and the other occurred in the distal jejunum. In the latter, the PF diagnosis was rendered after the case was re-reviewed for the study. Clinical presentation resembled GIST in both PF cases. 14% of GISTs showed high risk features or were clinically malignant, whereas the PF patient with 8-year follow-up was free of disease. Based on this study, PF may be under-recognized, with 1 to 2% (1.7%) of GIST-like tumors possibly representing PF. PF may involve variable segments of intestine similar to GIST. Given the remarkable clinical and histopathologic overlap with GIST but differing outcomes, awareness and cognizance of this rare entity, plexiform fibromyxoma, is required for proper patient care.

1. Introduction

Plexiform Fibromyxoma (PF) is an exceedingly rare mesenchymal tumor of the gastric antrum that was first described as 'Plexiform angiomyxoid myofibroblastic tumor' in 2007 by Takahashi et al. [1]. The authors reported two cases, and as the nomenclature implies, considered PF to originate from myofibroblasts with a distinct plexiform and myxoid appearance, and abundant vasculature. The immunohistochemical staining and ultrastructural findings of the tumor supported its myofibroblastic origin. No exon mutations were found in *C-KIT* and platelet-derived growth factor receptor α (*PDGFRA*) genes, further supporting that the tumor is a new entity that is different than gastrointestinal stromal tumor (GIST) [1]. Since the first description, additional cases of PF have been reported as case reports or small case series in the literature [2]. So far 121 cases of PF have been documented in the literature [2]. Clinical presentation of PF may resemble other mesenchymal tumors of gastrointestinal tract, especially GIST, the most common mesenchymal tumors of the gastrointestinal tract [3]. GIST is driven by *KIT* or *PDGFRA* signaling activating mutation. A minor subset of GIST shows germline mutations of the succinate dehydrogenase (SDH) subunit genes, resulting in loss of function of SDH. SDH- deficient GIST usually shows a plexiform growth pattern, and is negative for *C-KIT* and *PDGFRA* mutations [4]. There are no diagnostic biochemical markers or imaging features that are characteristic of GIST [5,6]. Therefore, a GIST diagnosis is usually rendered on biopsy samples or surgical resection specimens.

Histopathologic overlap between PF and GIST has been recognized [3]. Both show a proliferation of spindle cells. Typically, PF is characterized by a multinodular, plexiform involvement of gastric muscularis propria. An extra-gastric non-plexiform component may be present. The tumor nodules are relatively paucicellular with a prominent capillary pattern, and contain abundant acid mucopolysaccharide-rich myxoid matrix. Mitotic activity is usually less than 5 per 50 high power fields [7]. GIST is characterized by short fascicles of spindle cells that

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are arranged in variable architectural patterns including storiform, herringbone palisades, and broad sheets and/or epithelioid cells that are arranged in organoid clusters or sheets. The lesional cells are usually immunoreactive for C-KIT (CD117) and DOG-1 [8].

PF appears to behave benignly, but long-term follow-up data is limited due to its recent description and rarity. In addition, while its clinical and histopathological mimicry with GIST has been recognized, the incidence of PF relative to GIST is unknown. The goals of this study were to estimate the incidence of PF relative to GIST in a single center, and secondly, to report two unique cases of PF in our center: one with a relatively long-term follow up and the other arising in the distal jejunum. Four cases of PF have been reported in the small bowel, thus our case would represent the 5th small bowel primary PF, to the best of our knowledge.

2. Materials and methods

The study was approved by the institutional review board with a waiver of informed consent. The pathology department validated C-KIT immunohistochemistry for clinical use in 2000. Therefore, the pathology reports of resected GIST cases from 2000 to 2019 were retrieved using the laboratory information system (LIS). The search terms included “stromal”, “tumor”, “mesenchymal” and “spindle”. Only primary GISTs that were resected in our center were included. Recurrent or metastatic GISTs, biopsies, and fine needle aspiration (FNA) specimens were excluded. When a pathology report was deemed inconclusive, such as focal or weak C-KIT positivity, original diagnostic slides of the case were retrieved and reviewed, and equivocal cases were excluded.

The patients' age, gender, clinical presentation, tumor location, size and number, and the presence or absence of metastasis, were documented by reviewing pathology reports and electronic medical records. Risk of progressive disease was assessed according to the published GIST risk stratification model that incorporates size, location and mitosis of the tumor [9].

Resected cases of PF during the same period (2000–2019) were retrieved and compared. For PF cases, representative tissue blocks containing the tumor were subjected to additional immunohistochemistry (desmin, actin, cytokeratin, CD34, C-KIT, DOG-1 and S-100) if had not been performed at the time of initial diagnosis. In addition, Alcian Blue special stain was performed on the representative tissue blocks.

3. Results

3.1. Gastrointestinal stromal tumor (2000–2019) [Table 1, Table 2]

3.1.1. Demography and clinical presentation

A total of 129 resected primary GIST cases were identified by LIS search. 11 cases were excluded for lack of confirmatory stain (7 cases) and misdiagnosis upon original slide review (2 cases). The follow-up was incompatible with GIST in 2 cases: one case in the jejunum was found to represent a metastasis from pulmonary sarcomatoid carcinoma upon follow-up. The other esophageal tumor did not show either *PDGFR* exon 12 or *C-KIT* mutation, and a biopsy from a metastatic lesion was negative for both C-KIT and DOG-1 immunostain. Finally, 118 primary GIST cases were included in the study.

The mean age was 63.6 years with a range from 19 to 88 years. There was a slight male predominance (66 male vs 52 female). The most common clinical presentation was gastrointestinal bleeding and/or anemia in 34 (29%), followed by abdominal pain/discomfort/burning in 21 (18%), and nonspecific mass effect in 8 (7%). The tumor was incidentally found in 43 (36%). The clinical presentation was unknown in 12 (10%) cases.

3.1.2. Number and location

GIST was multifocal in three cases. The most common location was stomach (90; 76%), followed by duodenum (8; 7%), jejunum (7; 6%), small bowel, unspecified (4; 3%) and rectum (3; 2%). Additional locations included duodenal-jejunal junction (1), ileum (1) and esophagus (1). The three multifocal GISTs were located in the duodenum and duodenal-jejunal junction (1), jejunum and ileum (1), proximal jejunum and mid-jejunum (1).

3.1.3. Diagnosis and follow-up

The diagnosis was confirmed by C-KIT (CD117) and DOG-1 immunostain on 118 and 37 cases, respectively. Eight cases were tested for KIT and/or PDGFRA mutations. Sixteen of 118 (13.6%) were classified as high risk of progressive disease and/or malignant GIST. Over 4 months of follow-up was available in 78 cases, with the mean follow-up duration of 4.8 months (ranging from 4 months to 16 years). At the end of the follow-up, there was no evidence of disease in 69, 5 had recurrence or metastasis and were alive. One patient died of disease and 3 died of other causes. The patients that had recurrence or metastasis, and the one who died of disease had high risk features.

3.2. Plexiform Fibromyxoma (2000–2019)

Two cases of PF were identified during the search period. The first case (Case A) was diagnosed in 2007 after recent literature review [1], and the diagnosis was confirmed when the case was unofficially reviewed by an expert. The second case (Case B) was sent out to an outside consultant after selective immunostains were performed to rule out GIST. The outside consultant also excluded GIST based on molecular study, and rendered a descriptive noncommittal diagnosis. The case was re-reviewed for this study and the diagnosis of PF was rendered following additional work-up.

Table 2
Characteristics of multifocal GIST.

Location	Size (cm)*	Age (years)	Gender	Risk of progressive disease [9]
Duodenum and DJJ	4.3	57	Male	Low
Jejunum and ileum	1.5	54	Female	Low
Proximal and mid jejunum	12.5	67	Male	High

DJJ: Duodenal-Jejunal Junction, *size of the largest nodule.

Table 1
Characteristics of unifocal GIST.

	Esophagus	Stomach	Duodenum	DJJ	Jejunum	Ileum	SB (NOS)	Rectum	Total
Case number	1	90	8	1	7	1	4	3	115
Mean size (cm)	3.5	4.5	3.3	2.1	4.6	2.5	8.0	1.9	4.4
Mean age (years)	48	65	55	52	68	70	53	57	64
Gender (male/female)	1/0	48/42	4/4	1/0	5/2	0/1	3/1	2/1	64/52
*None, low or intermediate risk	1	81	7	1	5	1	1	3	100
*High risk or malignant	0 (0%)	9 (10%)	1 (12.5%)	0 (0%)	2 (28.6%)	0 (0%)	3 (75%)	0 (0%)	15 (13%)

DJJ: Duodenal-Jejunal Junction, SB (NOS): small bowel, not otherwise specified, * risk stratification [9].

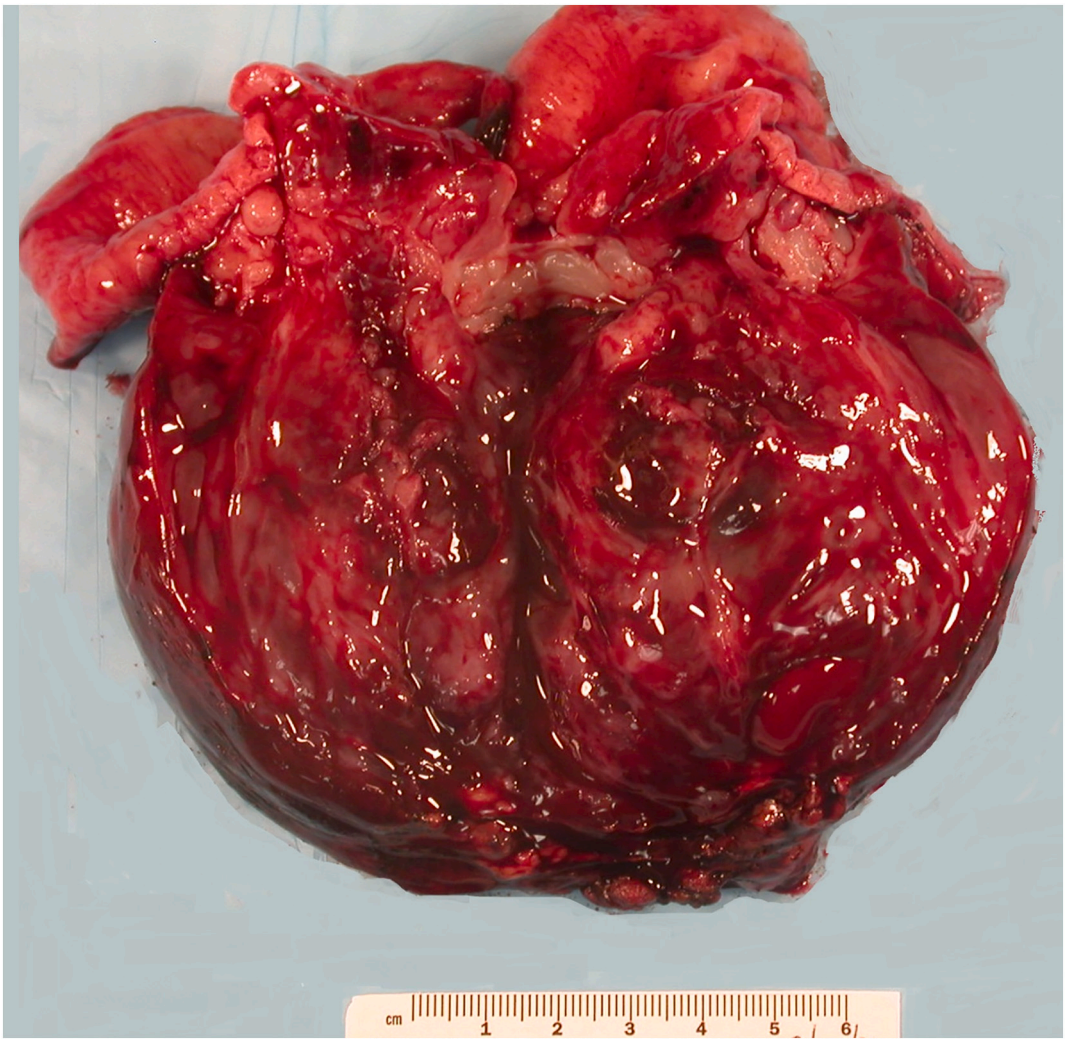

Fig. 1. Gross picture of the tumor (Case A). The tumor exhibits dark, hemorrhagic, and multi-cystic cut surface.

3.2.1. Case A

A 16-year-old female presented with gastrointestinal bleeding and gastric outlet obstruction. Imaging studies suggested a GIST arising in duodenum. A biopsy of the mass revealed a bland spindle cell neoplasm, thus a surgical resection of the tumor was performed. Intraoperatively, the epicenter of the tumor was in the gastric antrum, but not duodenum. The mass measured 15.0 cm in greatest dimension [Fig. 1].

3.2.2. Case B

A 68-year-old male presented with an incidental mesenteric mass on imaging during a work-up for hematuria. Imaging study suggested a GIST of the small bowel. An 8.0 cm mass arising in anti-mesenteric side of distal jejunum was surgically resected.

3.2.3. Histopathologic examination

Both tumors were based in the subserosa with focal extension to the muscularis propria in Case A. Sections of the tumors showed a proliferation of bland spindle cells in a prominent myxoid matrix in a multinodular plexiform growth pattern, with foci of cystic changes. Numerous vascular structures were noted within the tumor, without tumor necrosis, nuclear atypia, or mitotic activity. The lesional cells were positive for actin and negative for desmin. The lesional cells were negative for other markers including C-KIT, DOG-1, CD34, cytokeratin and S-100. Also, no *PDGFRA* mutation was detected in Case B. The myxoid matrix was positive for Alcian Blue mucin stain in both cases. [Fig. 2, Fig. 3].

3.2.4. Follow-up and incidence

The Case A was followed up for 8 years with no evidence of disease. The Case B was lost to follow-up. The frequency of PF was 1.7% (2 of 118) relative to GIST in our single center cohort.

4. Discussion

Plexiform fibromyxoma (PF) is a recently described, exceedingly rare mesenchymal tumor of gastrointestinal tract. Takahashi et al. coined the term “plexiform angiomyxoid myofibroblastic tumor” for this novel entity in 2007 [1]. Subsequently, Yoshida et al. reported 2 additional cases and referred to them as “plexiform angiomyxoid tumor”, as their cases showed focal smooth muscle differentiation [10]. Miettinen et al. retrospectively reviewed 4200 gastrointestinal mesenchymal neoplasms from 1970 to 1999 in their Armed Forces Institute of Pathology (AFIP) archives, and identified 10 tumors showing similar cytologic and morphologic features, along with 2 additional new cases. In this study, the authors used the name ‘plexiform fibromyxoma’, and emphasized its resemblance to myxoid GIST. The authors estimated that the frequency of PF is 1 PF per > 150 GIST [8]. Also, the authors reviewed the literature from 1959 and 1986, and identified tumors named as fibromyxomas and myxomas that shared similar morphology with PF [2]. Later, WHO 2010 classification of tumours of the digestive system officially recognized the tumor as a

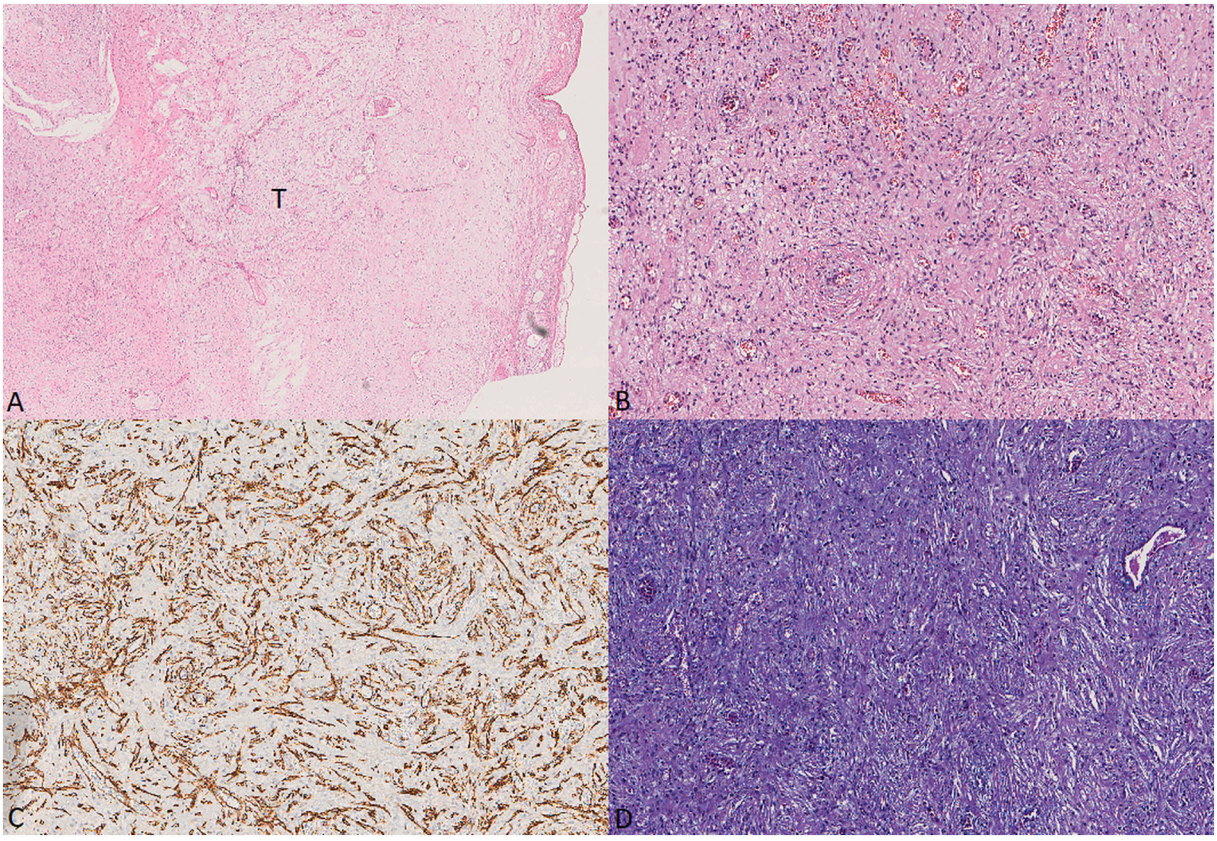

Fig. 2. Case A. A. Plexiform fibromyxoma (PF) in the subserosa of gastric antrum at scanning magnification (T: tumor) (x20, Hematoxylin and eosin (H&E)); B. The tumor exhibits plexiform growth pattern at higher magnification. The tumor is characterized by a prominent myxoid matrix within which hypocellular bland proliferation of round to oval cells and numerous vascular structures without tumor necrosis, significant nuclear atypia, or significant mitotic activity are noted (x100, H&E); C. Tumor cells are positive for smooth muscle actin (SMA) immunostain (x100, SMA); D. The stroma of the tumor is positive for Alcian Blue mucin stain (x100, Alcian Blue). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

benign gastrointestinal mesenchymal neoplasm and endorsed the term "plexiform fibromyxoma" [11].

We identified 2 cases of PF and 118 GISTs in a single center from 2000 to 2019, with a frequency of 1.7%. Our frequency appears to be similar to the estimated frequency of PF per GIST in Miettinen et al.'s study. The slightly higher incidence may be due to our strict inclusion criteria for GIST in our study. We included surgically resected primary GIST only, and excluded biopsies, FNAs, metastasis, and recurrences. Also, only immunohistochemically and/or molecularly confirmed GIST cases were included. Therefore, it is possible that some of the mesenchymal tumors that were excluded for variable reasons, i.e., unavailability of confirmatory work-up, could have been GISTs. Alternatively, this may be due to increased awareness of this entity, as demonstrated in the handling of Case B. Initially, this case was left descriptive without a firm diagnosis but with differential diagnoses to include angiomyxoma, inflammatory fibroid polyp and PF. This case was re-reviewed and additional work-up was performed when we were designing the study. The diagnosis of PF was finally rendered at the time of the study and the clinician was notified.

As this entity was first recognized in 2007(13 years ago), long-term follow up is not readily available. Our first patient (Case A) was followed up for 8 years after resection of the 15 cm tumor, with no evidence of disease. Miettinen et al. retrospectively reviewed their archived materials and reported that 4 patients with a median 19 years of follow-up did not show evidence of recurrence or metastasis, even in the cases with mucosal invasion, vascular invasion, and ulcerations. The mean size of the tumors with the long-term follow-up was 6.6 cm (range 5.5 to 10 cm) [8]. Similarly, Lai et al. and Hu et al. reported no recurrence or metastasis of PF with 11 years (tumor size unknown) and 95 months (tumor size 3 cm) of follow-up, respectively [3,12]. Other than these reports and our first case, follow-up is either much shorter or unavailable in the remaining reported PF cases [2]. Overall, PF appears to be an indolent disease with benign behavior independent of its histologic features or size.

We report the first case of PF (Case B) arising in the distal jejunum. This would be the fifth case of small bowel primary PF. The great majority of PF arise in the stomach, predominantly in the antrum [2,7]. Only four cases of PF in the small bowel have been reported, two in the duodenum and the other two in the proximal jejunum [13-16]. While small bowel PF appears to be much less common than gastric PF, the tumor seems to involve variable segments of the small bowel. Including our 2 cases herein, the frequency of small bowel PF in gastrointestinal tract PF would be 4.1% (5 of 121). Two extra-gastrointestinal PF cases have been reported in the gallbladder and posterior mediastinum, respectively [17,18].

Although we did not have any pediatric patients in the GIST cohort, it is well known that GISTs can be seen in young patients [4]. Likewise, PF is typically seen in adult population but pediatric cases, such as our Case A, have been also reported. The pediatric PF showed similar pathologic findings and clinical behavior but the size of the tumor tended to be larger than in adults [19].

As seen in our study and published studies, clinical presentation and imaging findings of PF resemble those of GIST. The most common symptom associated with PF is abdominal pain (20.6%) and 10% are found incidentally [2]. In our GIST cohort, abdominal pain was the second most common symptom and 37% of the cases were incidentally found. Similar to GIST, there are no characteristic imaging findings for PF. Cystic changes and hypervascular solid component may be seen

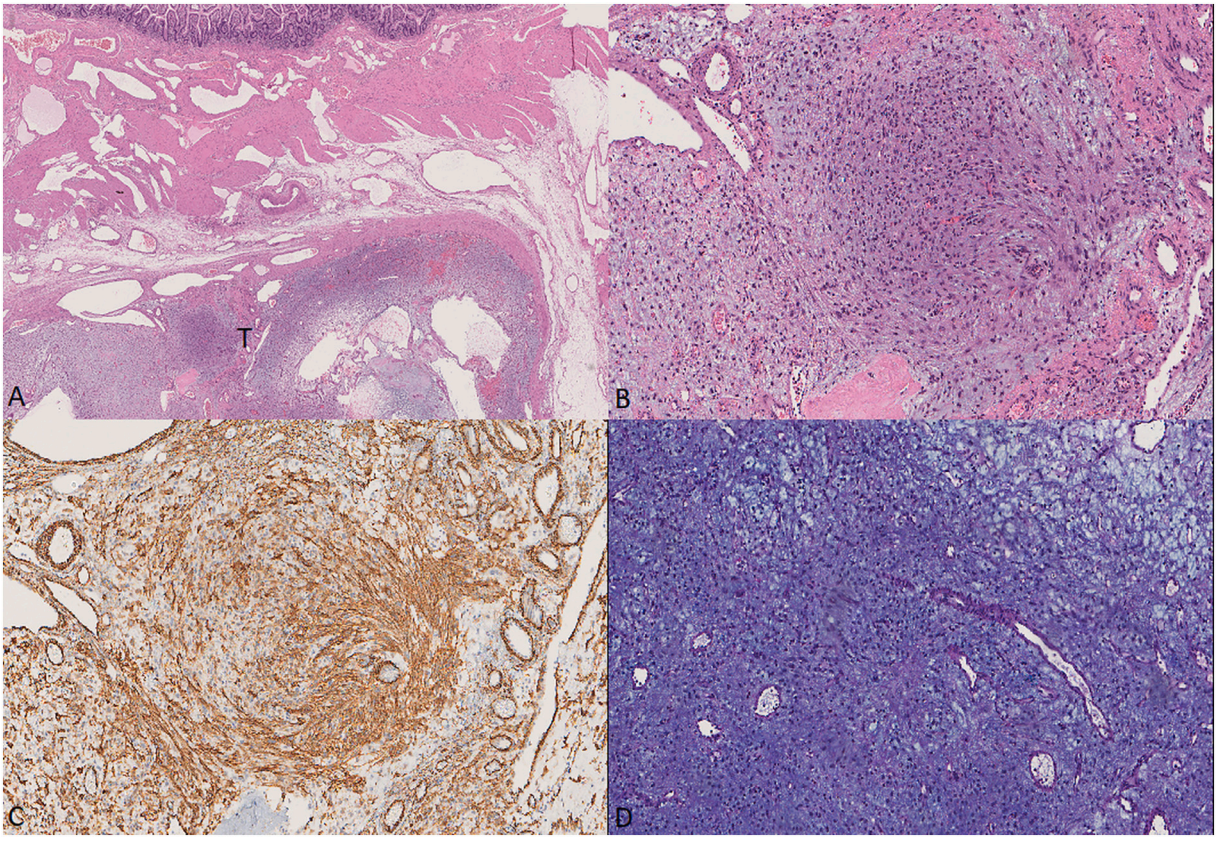

Fig. 3. Case B. A. Plexiform fibromyxoma (PF) of the distal jejunum at scanning magnification with multiple cystic spaces (T: tumor) (x20, hematoxylin and eosin (H &E)); B. The tumor exhibits plexiform growth pattern at medium magnification. The tumor exhibits a myxoid stroma with nodular growth pattern involving submucosa and muscularis propria of the small bowel. The tumor is composed of a relatively hypocellular proliferation of bland, round to oval cells associated with an eosinophilic inflammatory infiltrate and arborizing small vessels without increased mitotic activity or tumor necrosis (x100, H&E); C. The tumor cells are positive for smooth muscle actin (SMA) immunostain (x100, SMA); D. The stroma of the tumor is positive for Alcian Blue mucin stain (x100, Alcian Blue). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

[20]. Endoscopic ultrasound (EUS) may show heterogeneous hypoechoic submucosal mass [21].

Moreover, histologic overlap between PF and GIST, especially myxoid GIST, is recognized [2,3,7,8]. For example, Lai et al. carried out a multi-institutional collaborative study and collected 7 cases of gastric PF. Six of 7 cases were interpreted as GIST or probable GIST by preoperative EUS-FNA and/or intraoperative frozen sections based on histomorphology alone, and one patient received Gleevac therapy based on initial diagnosis. However, these tumors were correctly diagnosed as PF postoperatively after immunohistochemistry including C-KIT and DOG-1 was performed during additional work-up [3].

Given the remarkable clinical and histopathologic overlap and outcome differences between GIST and PF, raising awareness of PF amongst oncologists, surgeons and pathologists would be most helpful for correct diagnosis and patient care. For pathologists, when a bland spindle cell neoplasm is encountered in the gastrointestinal tract including small bowel, it is prudent to apply a broad panel of immunohistochemistry to definitely rule out GIST, even though the clinical presentation, location and histomorphology of the tumor may appear typical for GIST. The uncommon subset of SDH-deficient GIST can also be diagnosed by molecular testing or immunohistochemical staining for SDHB, that shows loss of SDHB immunoreactivity [4].

Other differential diagnoses of PF include leiomyoma, leiomyosarcoma, schwannoma, desmoid fibromatosis, solitary fibrous tumor (SFT), and inflammatory myofibroblastic tumor. These tumors can be differentiated from PF by histomorphology and immunohistochemistry such as desmin, S-100, beta-catenin, CD34 and ALK-1 [11,22]. Although there is no molecular alteration that defines PF, a subset of PF shows a mutation in *glioma-associated oncogene homologue 1 (GLI1)* and *metastasis-associated lung adenocarcinoma transcript 1 (MALAT1),* and *GLI1* polysomy [2,15]. Therefore, neoplasms harboring *MALAT1–GLI1* gene mutation such as gastroblastoma and malignant epithelioid neoplasm with *GLI1* fusions would be considered differential diagnoses of PF as well [23,24].

Currently, surgical excision is the treatment of choice for PF. Given the recent discovery of molecular alterations in a subset of PF, different management options may be offered to PF patients in the future.

5. Conclusions

In summary, PF is a rare mesenchymal tumor of the gastrointestinal tract that is probably under-recognized. Our study supports the previous estimation that about 1–2% of GIST-like tumors are PF. PF may involve variable segments of intestine including distal jejunum. It has significant clinical and pathologic similarity to GIST, requiring careful histologic assessment.

Declaration of interest

None.

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