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Plexiform fibromyxoma: Review of rare mesenchymal gastric neoplasm and its differential diagnosis

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Abstract

Plexiform fibromyxoma (PF) is a very rare mesenchymal neoplasm of the stomach that was first described in 2007 and was officially recognized as a subtype of gastric mesenchymal neoplasm by World Health Organization (WHO) in 2010. Histologically, PF is characterized by a plexiform growth of bland spindle to ovoid cells embedded in a myxoid stroma that is rich in small vessels. The lesion is usually paucicellular. While mucosal and vascular invasion have been documented, no metastasis or malignant transformation has been reported. Its pathogenesis is largely unknown and defining molecular alterations are not currently available. There are other mesenchymal tumors arising in the gastrointestinal tract that need to be differentiated from PF given their differing biologic behaviors and malignant potential. Histologic mimics with spindle cells include gastrointestinal stromal tumor, smooth muscle tumor, and nerve sheath tumor. Histologic mimics with myxoid stroma include myxoma and aggressive angiomyxoma. Molecular alterations that have been described in a subset of PF may be seen in gastroblastoma and malignant epithelioid tumor with glioma-associated oncogene homologue 1 (*GLI1*) rearrangement. The recent increase in publications on PF reflects growing recognition of this entity with expansion of clinical and pathologic findings in these cases. Herein we provide a review of PF in comparison to other mesenchymal tumors with histologic and molecular resemblance to raise the awareness of this enigmatic neoplasm. Also, we highlight the challenges pathologists face when the sample is small, or such rare entity is encountered intraoperatively.

Key Words: Plexiform; Fibromyxoma; Gastrointestinal; Mesenchymal; Neoplasm; Stomach

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Core Tip: Plexiform fibromyxoma (PF) is a rare mesenchymal tumor of the stomach. Due to its rarity, the pathogenesis and molecular alterations of PF are largely unknown. The incidence of the tumor seems to be increasing probably due to a growing awareness of this entity. Histologic mimics of PF include gastrointestinal stromal tumor, smooth muscle tumor, nerve sheath tumor, myxoma and aggressive angiomyxoma. Molecular mimics of PF include gastroblastoma and malignant epithelioid tumor with glioma-associated oncogene homologue 1 (*GLI1*) rearrangement. Surgical removal is the current mainstay of treatment.

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INTRODUCTION

Plexiform fibromyxoma (PF) is a recently described mesenchymal tumor of the gastrointestinal (GI) tract. Recently our group reported that the incidence of PF relative to GI stromal tumor (GIST), a close mimic of PF, is 1.7 % over a span of 20 years[1]. The tumor is mostly found in the gastric antrum, however PF involving other segments of the GI tract have been reported[1-5]. Due to its rarity, the pathogenesis and molecular alterations of PF are largely unknown[6]. However, its incidence appears to be rapidly increasing in the literature probably due to a growing awareness of this entity[1,7]. While PF behaves in a benign manner, its histologic mimics such as GISTs, smooth muscle tumors and nerve sheath tumors show malignant potential[8,9]. Moreover, its molecular mimics, such as gastroblastoma and malignant epithelioid tumor with glioma-associated oncogene homologue 1 (*GLI1*) rearrangement, need to be excluded especially when evaluating small samples and when the molecular profiling is included in the work-up[10]. Herein we provide a concise review of PF focusing on its histologic and molecular differential diagnoses. Also, we highlight the challenges pathologists face when the sample is small, or such rare entity is encountered intraoperatively.

HISTORY AND NOMENCLATURE

PF was first reported by Takahashi *et al*[11] in 2007. The authors identified two tumors in the gastric antrum showing similar histomorphology. The morphology of the tumors was not consistent with any known gastric neoplasm. The authors used the term "Plexiform Angiomyxoid Myofibroblastic Tumor" in their report implying its plexiform growth pattern, increased vascularity within the myxoid stroma, and the proliferation of bland spindle cells that were proven to be myofibroblasts by immunohistochemistry and ultrastructural examination. Both tumors lacked mutations in the exons 9, 11, 13 and 17 of *C-KIT* gene and the exons 12 and 18 of the platelet-derived growth factor receptor alpha (*PDGFRA*) gene, further supporting that these tumors represent new entity distinct from GIST[11].

In 2008, four additional cases were reported with similar morphology and were referred as "Plexiform Angiomyxoid Tumor"[12-14]. In 2009, Miettinen reported twelve additional PF cases. Also, he re-reviewed previous case studies that had reported tumors with similar morphology but using different terms including "stomach myxoma", "giant myxoma of the stomach", "gastric fibromyxoma", "fibromyxoma of the stomach", "gastric myxoma", and "fibromyxangioma of the stomach" between 1955-2004. However, despite the morphologic similarities between these tumors and PF, these cases were not proven to be PF due to the lack of immunohistochemistry[8]. In 2010, Takahashi *et al*[7] reported an additional case of PF and provided a review of eighteen PF cases that had been reported in the literature. The tumor was officially recognized as a subtype of gastric mesenchymal tumors and the term PF was endorsed by the 4th edition of World Health Organization (WHO)

classification of tumors of the digestive system in 2010[15].

PFs have been reported as either case reports or small case series. To date, a total of 130 PF cases have been reported in the English literature[1,6,16-22]. Given the fact that only nineteen cases had been described by 2010 (approximately three years after the first description of the entity), this remarkable increase in its incidence in a short period of time may be attributable to the increased awareness of PF by clinicians and pathologists[1,7].

CLINICAL PRESENTATION

PF has been reported roughly equally in males and females in most studies[7,15,23,24] whereas a slight female predominance was found in one study[6]. The median age at presentation is 40 years to 50 years (ranging from 5 years to 81 years), but it can also be seen in pediatric patients[6,15]. The most common site for PF is gastric antrum[6,9]. In addition, it has been reported in the duodenum, jejunum, gallbladder and mediastinum[1,3-6,25,26].

The clinical presentation is usually nonspecific. Most common symptoms are “abdominal symptoms” such as abdominal pain/discomfort, fullness, nausea and vomiting followed by symptoms of blood loss such as bleeding, syncope and anemia. These symptoms may be attributable to the tumor location as well as the hypervascular nature of the tumor[6]. Some PFs are found incidentally on imaging[6].

PF shows a benign behavior[1,6,9]. Even though vascular invasion, lymphatic invasion, mucosal invasion and ulcerations have been reported, neither recurrence nor metastasis has been reported[1,6,8,9,27].

IMAGING

Data regarding the radiologic features of PF are limited in the literature due to its rarity[28]. Imaging findings may be suggestive of another mesenchymal tumor such as GIST[22]. A small tumor can be missed on computed tomography (CT) and may require invasive imaging modality such as capsule endoscopic examination[4]. On CT and magnetic resonance imaging (MRI), PF presents as a solid, cystic or solid/cystic mass with well-defined borders[28] (Figure 1). Due to the increased vascularity of the tumor, CT may show mild enhancement of the solid portion during the arterial phase and strengthened progressive enhancement during the venous and delayed phases[28].

In a recent review, MRI was considered superior to CT for visualizing the extent and components of PF. On MRI, gastric PF consistently showed low signal intensity on the T1-weighted images and high signal intensity on the T2-weighted images. On contrast-enhanced MR images, the solid portion also exhibited heterogeneously gradual enhancement[28]. The gradual enhancement pattern with prominent enhancement in the delayed phase is compatible with the myxoid nature of PF[29].

ENDOSCOPY

The reported size of PF ranges from 0.8 cm to 17.0 cm[6]. On endoscopy, hemorrhage and ulceration can be observed due to hypervascularity of the tumor[4,6]. Indeed, tumor surface ulceration is common, and this finding is associated with hemorrhage-related signs or symptoms[6]. PF appears as a tan/pink, rubbery mass, and it usually arises from the submucosa or muscularis propria of the gastric antrum with a lobulated/nodular growth pattern and well-defined borders[6].

MACROSCOPIC EXAMINATION AND HISTOPATHOLOGY

PF demonstrates a multinodular, myxoid or gelatinous appearance with or without hemorrhage[8,15].

Histologically, PF shows a multinodular, plexiform growth pattern with a proliferation of ovoid to spindle cells within myxoid stroma, and an increased vascularity. The spindle cells are bland, without significant atypia or mitotic activity[6,8,15]

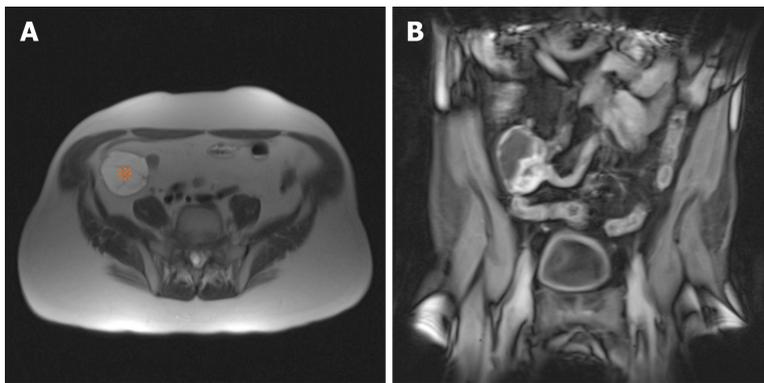


Figure 1 Magnetic resonance imaging of jejunal plexiform fibromyxoma. A: Plexiform fibromyxoma appears as a well-circumscribed mass (asterisk) in the right lower quadrant; B: Plexiform fibromyxoma shows enhancement with contrast.

(Figure 2). Usually features indicative of aggressive behavior such as vascular and lymphatic invasion are absent; however, these findings have been documented in some cases[4,6,8,27]. There is no tumor necrosis, however ulceration with necrosis has been reported in two cases[4,6,30].

Immunohistochemically, the tumor cells are positive for smooth muscle actin (SMA) and vimentin, and can show focal or partial staining for CD10, desmin and caldesmon. The spindle cells are negative for DOG-1, C-KIT, epithelial membrane antigen (EMA), ALK, S-100 and CD34 with a low Ki-67 proliferation index[6,15]. CD31 and/or CD34 can highlight prominent vascularity. The myxoid stroma is positive for Alcian Blue special stain[6,8,15]. Focal keratin positivity of the spindle cells has been reported in the literature only in two cases[31]. Thus, focal keratin staining does not exclude PF diagnosis.

FINE-NEEDLE ASPIRATION AND CYTOLOGY

The diagnosis of PF on pre- or intraoperative biopsy and/or fine-needle aspiration (FNA) specimens can be extremely challenging. Especially, PF can be misdiagnosed as GIST on FNAs without the aid of immunohistochemistry[32]. On FNA, PF shows bland spindle cells without nuclear hyperchromasia or prominent nucleoli[19,32,33].

MOLECULAR GENETICS

To date, no specific molecular or genetic alterations have been identified in PF. PF lacks *C-KIT* and *PDGFRA* gene mutations that are definitional alterations of GIST[6,8]. In Spans *et al*[2]'s study, 3 (18%) of 16 cases of PF have been found to harbor *MALAT1* (metastasis associated lung adenocarcinoma transcript 1; in 11q12) and *GLI1* (in 12q13) translocation, similar to alterations demonstrated in other tumors including gastroblastoma and malignant epithelioid tumor with *GLI1* rearrangement. Banerjee *et al*[34] reported 8 cases of PFs with *PTCH1* inactivation. One case also showed partial *PTCH1* deletion of exons 15–24 on chromosome 9q, and the other showed bi-allelic chromosome 9q deletions of *PTCH1* and *FANCC*.

DIFFERENTIAL DIAGNOSIS: HISTOLOGIC MIMICS

GIST

GIST is the most common mesenchymal neoplasm of the stomach and GI tract, and is the most important differential diagnosis of PF. Similar to PF, GISTs are frequently found incidentally on CT scan[35]. As opposed to PF, however, GIST can behave as malignant with a metastatic potential[15,36,37]. In symptomatic cases, small tumors usually present with nonspecific GI symptoms whereas large tumors can cause obstruction or bleeding. Imaging studies may show features suggestive of GIST but cannot render a definitive diagnosis of GIST. However, these studies can help to

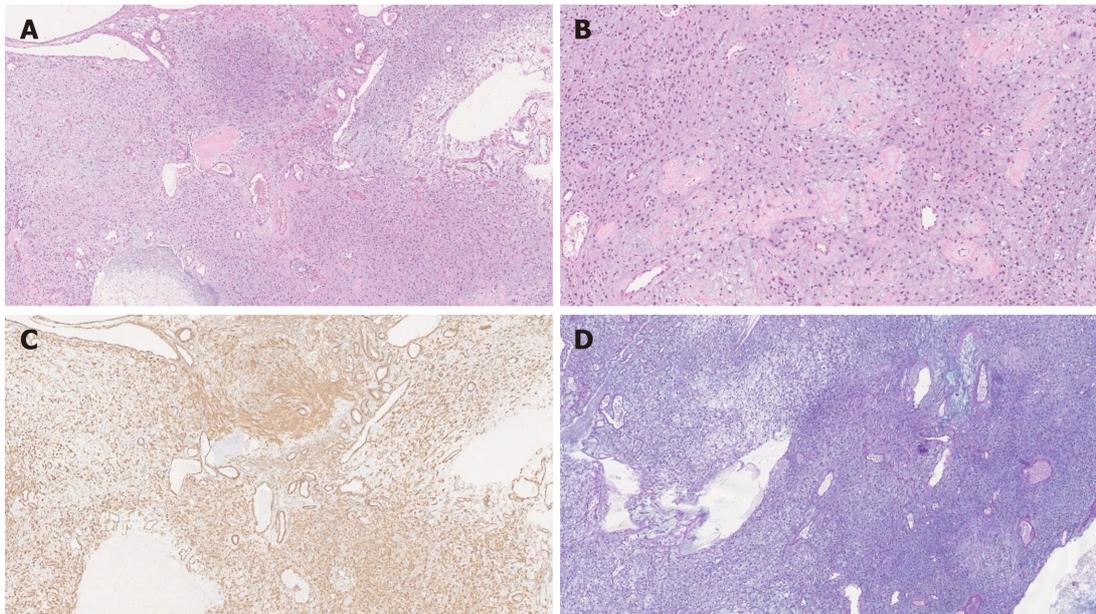


Figure 2 Plexiform fibromyxoma histology. A: Plexiform fibromyxoma shows characteristic plexiform growth as well as cystic degeneration [hematoxylin and eosin (HE), 50 ×]; B: The tumor is composed of bland spindle to ovoid cells embedded in myxoid stroma, and prominent vasculature (HE, 200 ×); C: The tumor cells are positive for SMA (SMA, 200 ×); D: The myxoid stroma is positive for Alcian Blue (Alcian Blue, 200 ×).

determine the behavior of the tumor based on its size, location, infiltration of nearby structures and the presence or absence of metastasis[38]. In cases without definitive features of malignancy, the risk for malignant transformation can be assessed based on tumor size, location and mitotic activity upon histologic examination of the resected specimen[39].

Histologically, GIST is composed of a proliferation of spindle cells and/or epithelioid cells[36,38] (Figure 3). Various cytologic and growth patterns have been described, to include sclerosing spindle cell, palisading and vacuolated spindle cell, hypercellular spindle cell, sarcomatous spindle cell, sclerosing epithelioid GIST with a syncytial pattern, epithelioid GIST with a dyscohesive pattern, hypercellular epithelioid, and sarcomatous epithelioid pattern. Paranuclear vacuoles are frequent findings and can be seen in over 90% of the cases[36]. Immunohistochemically, the tumor cells are diffusely positive for C-KIT and DOG-1. CD34 is positive in most spindle cell GIST and is less commonly expressed in epithelioid variants. Focal desmin, S-100 and keratin positivity can be seen in GIST[15,39].

The morphology and clinical behavior of GIST vary depending on underlying genetic alterations. For example, *NF1* and *C-KIT* mutated GISTs show spindle cell morphology whereas succinate dehydrogenase (SDH)-deficient GISTs show epithelioid cell morphology[40-43]. Most GISTs harbor gain of function *KIT* or *PDGFRA* mutations, exon 11 of *KIT* mutation being the most frequent. Small and large bowel GISTs usually show mutations in *KIT* while *PDGFRA*-mutated GISTs usually arise in the stomach[40].

Approximately 10%-15% of GISTs lack *KIT* or *PDGFRA* mutations[41]. Among these, SDH-deficient GIST shows multinodular growth pattern, thus closely mimic PF[9]. SDH-deficient GIST is usually encountered in young adults and predominantly found in the stomach. On microscopic examination, it shows a proliferation of epithelioid to spindle cells that shows plexiform involvement of the muscularis propria[41] (Figure 4). Immunohistochemically, SDHB (SDH) stain can be used to confirm SDH deficiency; SDHB expression is lost if any subunit of the enzyme is inactivated. Similar to common spindle cell and epithelioid GISTs, SDH-deficient GIST is strongly and diffusely positive for C-KIT and DOG-1 immunostain even though it lacks *KIT* mutations and shows a loss of SDHB[40]. Lymphovascular invasion is common in this subtype of GIST and is seen in > 50% of cases, while lymph node metastasis is uncommon[41]. The tumor may recur or present with peritoneal, hepatic and lymph node metastases. However, SDH-deficient GIST usually shows slow progression[37,41].

Myxoid GIST also can show multinodular growth pattern with spindle cells that are in myxoid stroma with thin blood vessels, and can closely mimic PF. However, the tumor cells are diffusely and strongly positive for C-KIT, DOG-1 and CD34 (and are

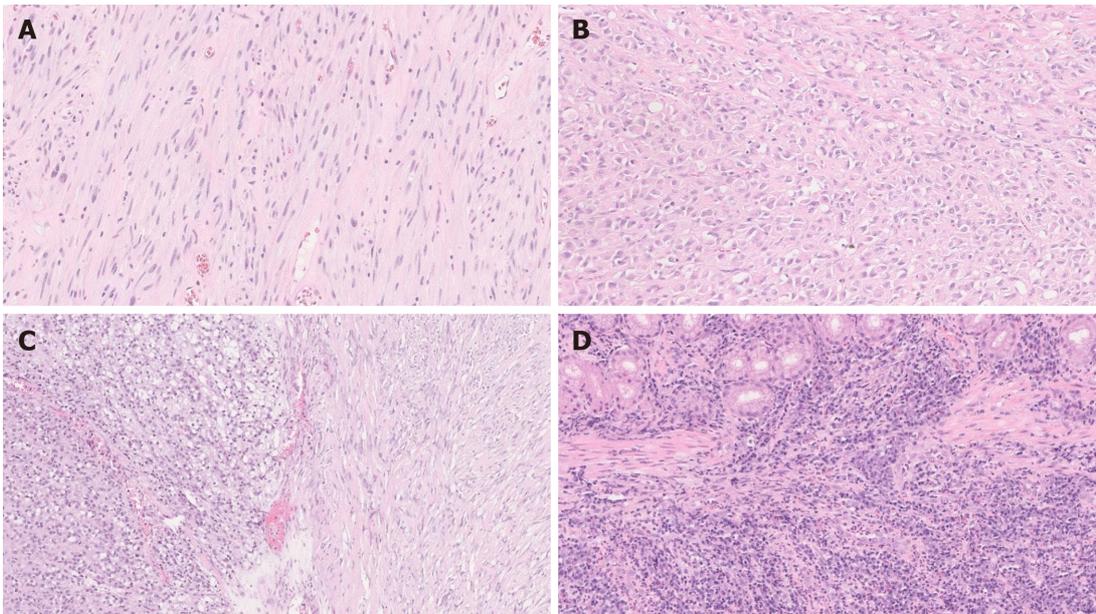


Figure 3 Gastrointestinal stromal tumor. A: Spindle gastrointestinal stromal tumor (GIST) [hematoxylin and eosin (HE), 200 ×]; B: Epithelioid GIST (HE, 200 ×); C: Spindle and epithelioid GIST (HE, 200 ×); D: Malignant GIST infiltrating muscularis propria of small bowel (HE, 200 ×).

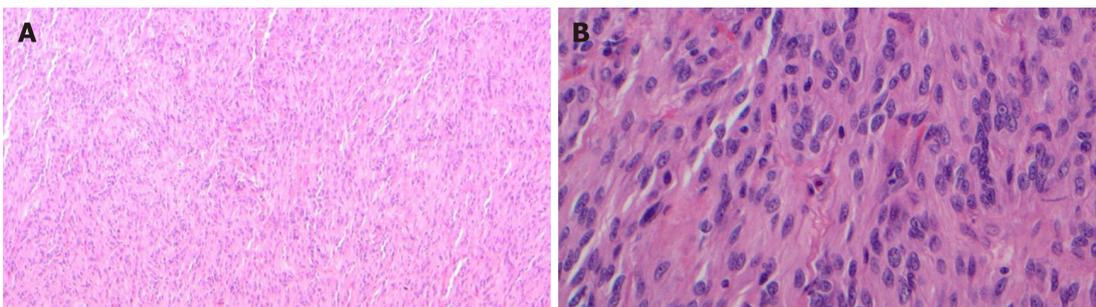


Figure 4 Succinate dehydrogenase-deficient gastrointestinal stromal tumor. A: Succinate dehydrogenase-deficient gastrointestinal stromal tumor shows vaguely nodular growth pattern at low power [hematoxylin and eosin (HE), 100 ×]; B: The cells are epithelioid and spindled without significant atypia (HE, 400 ×). Image courtesy of Abdullah Osme, MD, Resident Physician in Pathology and Laboratory Medicine, University Hospitals, Ohio, United States; used with permission.

negative for SMA, desmin, cytokeratin and CD10), which separate it from PF[44].

Patients with neurofibromatosis 1 (NF1) can develop GISTs due to biallelic inactivation of *NF1* gene. These patients most often present at middle age or later with multiple GISTs in the small intestine. NF1-associated GISTs are usually not aggressive with favorable prognosis, but malignant transformation has been documented[42].

Familial GIST syndrome is associated with rare germline *KIT* mutations. The patients are predisposed to an early development of GISTs. These patients often have multiple GISTs and show skin findings including maculopapular cutaneous mastocytosis and cutaneous hyperpigmentation. Also, interstitial cells of Cajal hyperplasia is common in these patients[40].

Smooth muscle tumors

Mesenchymal tumors originating from smooth muscle tissue show a proliferation of spindle cells, similar to PF. Smooth muscle tumors are rare in the GI tract compared to GISTs except in the esophagus and colon, wherein leiomyoma of the muscularis mucosa is the most common primary mesenchymal tumor[45].

Leiomyoma is the most common benign smooth muscle tumor of the GI tract and shows two histologic subtypes: polypoid and intramural. Polypoid leiomyoma is more common and is predominantly found in the esophagus and rectosigmoid colon. The tumors originate from the muscularis mucosa and usually present as small (< 1 cm) mucosal polypoid lesions. Intramural leiomyoma is less common than polypoid counterpart and is found in the muscularis propria of the distal esophagus and

proximal stomach[45,46]. Leiomyoma is extremely rare in the duodenum and small bowel[46].

Histologically, leiomyoma exhibits a proliferation of bland spindle cells with cigar shaped nuclei and abundant eosinophilic cytoplasm without atypia, mitosis, or necrosis. Leiomyomas may recur when incompletely excised[45] (Figure 5A).

Leiomyosarcoma is malignant mesenchymal smooth muscle tumor. Although rarer than leiomyoma, leiomyosarcoma can be encountered throughout the GI tract[45]. Similar to leiomyoma, leiomyosarcoma can present as polypoid mucosal lesion, or intra/transmural mass[45,46]. Colorectum is the most common site and the stomach is the least common site for leiomyosarcomas in the GI tract[15,45]. Histologically, leiomyosarcoma is composed of a proliferation of spindle cells with marked atypia, brisk mitotic activity with or without tumor necrosis[45,46] (Figure 5B).

Immunohistochemically, both leiomyoma and leiomyosarcoma are positive for desmin and SMA, and are negative for DOG-1, C-KIT, S-100 and CD34[15,45,46].

Nerve sheath tumors

Mesenchymal tumors with nerve sheath differentiation may show a proliferation of spindle and/or epithelioid cells and closely resemble PF histologically[40,47,48]. Nerve sheath tumor is the third most common mesenchymal neoplasm of the GI tract. It comprised < 5 % of the GI tract mesenchymal tumors in a single center study. The two most common nerve sheath tumors of the GI tract are granular cell tumor (GCT) and schwannoma[47].

The most common location for GCT in the GI tract is the distal esophagus/gastroesophageal junction. Histologically, GCT consists of a proliferation of sheets of large polygonal to spindled cells with abundant eosinophilic granular cytoplasm and bland nuclei[40,47,48]. The cells are positive for S-100 and the cytoplasmic granules are positive for PAS. In addition, GCTs in the esophagus are often associated with squamous pseudoepitheliomatous hyperplasia[40,47] and may mimic squamous cell carcinoma especially in a limited, superficial sample (Figure 6).

Schwannomas are most commonly seen in the stomach in the GI tract[49]. While schwannomas are characterized by a proliferation of spindle cells, the histomorphology of gastric schwannomas is different from that of peripheral schwannomas. For example, gastric schwannomas are unencapsulated, relatively well-circumscribed and have lymphoid cuffs sometimes with germinal centers at the periphery, whereas peripheral schwannomas are usually encapsulated, and without lymphoid cuffs[15,49]. Gastric schwannomas frequently show a microtrabecular growth pattern in a collagenous background[15,49], and can show an infiltrative spread between the muscularis propria. Nuclear palisading and hyalinized vessels are less common in gastric schwannomas compared to the peripheral counterparts[49] (Figure 7). Immunohistochemically, the lesional spindle cells are strongly and diffusely positive for S-100 and are negative for DOG-1 and C-KIT[47,49]. Gastric schwannoma can also be associated with NF1. Therefore, in a patient with NF1, mesenchymal tumor of the stomach is not necessarily neurofibroma[47]. A rare variant of gastric schwannoma with signet-ring-cell appearance of the tumor cells has been reported[50].

Moreover, NF1 patients can present with variable mesenchymal neoplasms of the GI tract including benign solitary neurofibroma, diffuse or plexiform neurofibroma, malignant peripheral nerve sheath tumor (MPNST), GIST, and neuroendocrine tumors. Neurofibroma exhibits a proliferation of bland spindle Schwann cells admixed with fibroblasts and mast cells in a myxoid or mucinous matrix. Therefore, neurofibroma is also considered a differential diagnosis of PF. Neurofibroma can be solitary or can show a plexiform growth pattern. Most of the cases are asymptomatic[51].

Other less common and rare nerve sheath tumors with spindled morphology include NF1-associated peripheral nerve sheath tumor (PNST) and gastric perineuriomas. Even though some PNSTs are associated with NF1 or NF2, a great majority of PNSTs are sporadic[47].

Histologically, PNST is composed of wavy spindle cells, fibroblasts, and strands of collagen[52]. The stroma can be myxoid and the tumor may show a plexiform multinodular growth[51,52] (Figure 8). The tumor cells are diffusely positive for S-100 and CD34 and are negative for C-KIT, DOG-1, and SMA[52]. Perineurioma shows slender cells with wavy nuclei that are diffusely positive for EMA and variably positive for CD34. The lesional cells are negative for S-100, C-KIT, desmin and SMA[47].

MPNST is extremely rare in the GI tract. Only a few cases have been reported in the literature. Histologically, MPNST is composed of alternating hypercellular and hypocellular zones of spindle cells with hyperchromatic and pleomorphic nuclei and

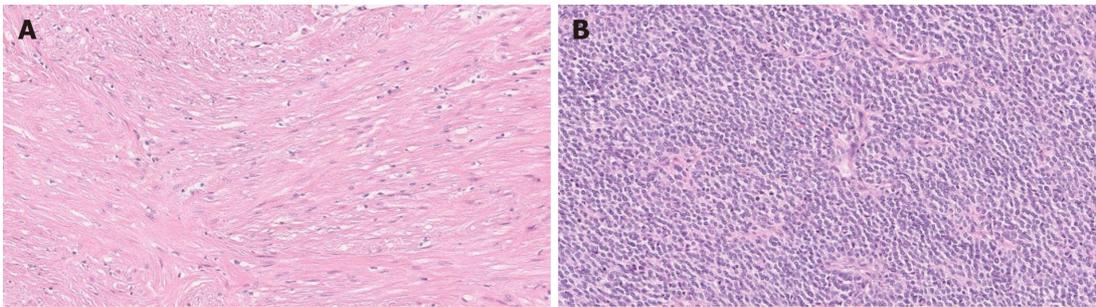


Figure 5 Leiomyoma vs Leiomyosarcoma. A: Leiomyoma shows a spindle cell proliferation. The lesion is hypocellular [hematoxylin and eosin (HE), 200 ×]; B: Epithelioid leiomyosarcoma is composed of epithelioid cells with high nuclear-cytoplasmic ratio. Compared to leiomyoma, it is highly cellular with frequent mitosis (HE, 200 ×).

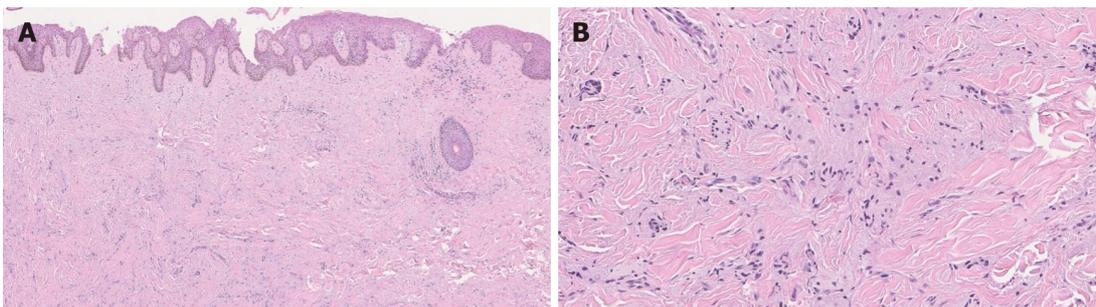


Figure 6 Granular cell tumor. A: Epithelioid cells with abundant granular cytoplasm are infiltrating the dermis [hematoxylin and eosin (HE), 50 ×]; B: Some tumor cells are spindled with granular cytoplasm (HE, 200 ×).

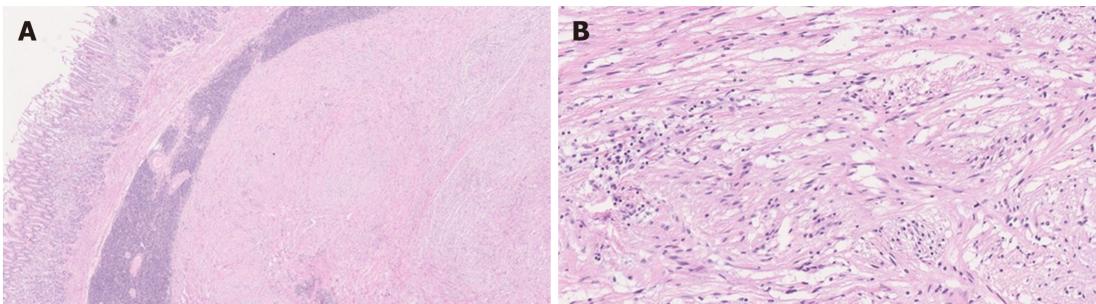


Figure 7 Gastric schwannoma. A: Gastric schwannoma exhibits a prominent lymphoid cuff at the periphery [hematoxylin and eosin (HE), 25 ×]; B: Schwannoma is composed of a bland spindle cell proliferation (HE, 200 ×).

frequent mitoses, with fascicular growth pattern (Figure 9). The tumor cells are weakly positive for S-100 and are negative for C-KIT, DOG-1, CD34, desmin, EMA and cytokeratin[53].

Myxoma and aggressive angiomyxoma

These two entities are considered as differential diagnoses of PF given their myxoid stroma.

Myxoma is extremely rare in the stomach. Only one case of gastric myxoma has been reported in the literature to the best of our knowledge[54]. In this report, the tumor was well circumscribed and situated mainly in the submucosa with an extension to the overlying mucosa. The stroma of the tumor was composed of hypocellular myxoid tissue that was poor in collagen and elastic fibers. Scattered small capillaries were noted within the tumor, however the capillaries did not show a plexiform architecture. Although the authors did not document cytomorphology of the lesional cells, the immunostains for AE1/AE3, CAM5.2, CK7, CK20, p53, α -SMA, desmin, S-100, C-KIT and CD34 were negative. Ki-67 proliferation index was 1%[54]. A few cases with similar morphology and immunohistochemistry have been reported in

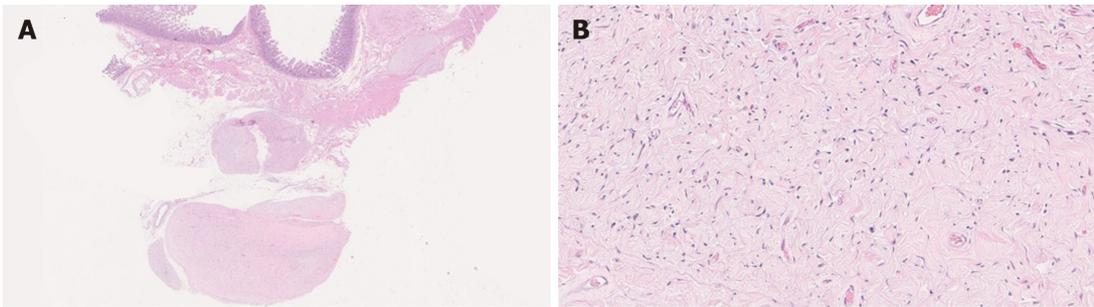


Figure 8 Small bowel neurofibroma. A: Plexiform neurofibroma shows characteristic multinodular plexiform growth pattern [hematoxylin and eosin (HE), 10 ×]; B: Neurofibroma is composed of wavy spindle cells, fibroblasts, and strands of collagen (HE, 200 ×).

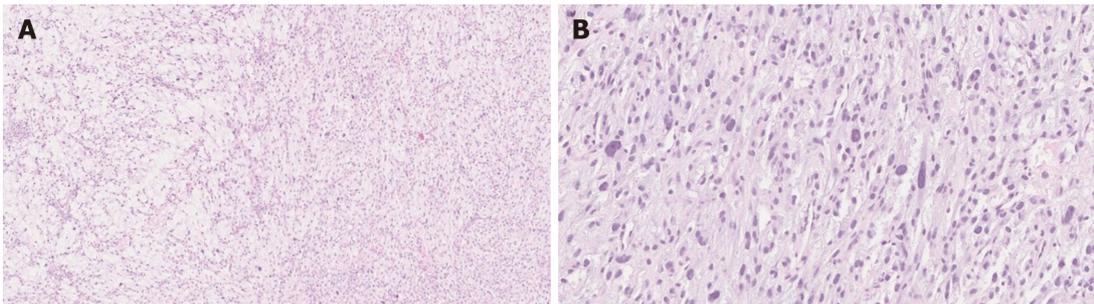


Figure 9 Malignant peripheral nerve sheath tumor. A: Malignant peripheral nerve sheath tumor (MPNST) shows alternating hypo (left) and hypercellular (right) areas [hematoxylin and eosin (HE), 50 ×]; B: Compared to benign nerve sheath tumors (shown above in Figures 6-8), MPNST exhibits hypercellularity, nuclear hyperchromasia and pleomorphism as well as frequent mitosis (HE, 200 ×).

the small and large bowel[55-57] (Figure 10A).

Aggressive angiomyxoma is a rare mesenchymal tumor of the pelvis and perineum of adults. The tumor is infiltrative, and there is a risk of recurrence following resection. The frequent sites of aggressive angiomyxoma include the vulvovaginal, perineal, and groin regions in women and less commonly in inguinoscrotal region and perineum in men[58].

Histologically, aggressive angiomyxoma is hypocellular and shows a proliferation of spindle and stellate-shaped cells in a myxoid background. Blood vessels varying in caliber may show hyalinization[59] (Figure 10B). The tumor cells are positive for estrogen (ER) and/or progesterone receptor (PR)s as well as SMA, desmin, vimentin and CD34. The tumor cells are negative for S-100, C-KIT, and cytokeratin[58,59]. Rearrangements involving *HMGA2* gene on chromosome 12 have been implicated in the pathogenesis of this tumor[60,61]. To the best of our knowledge, no primary angiomyxoma of GI tract has been reported in the literature.

Both tumors lack the plexiform architecture of PF. The spindle cells in myxoma are negative for SMA, which is different from PF. Likewise, the spindle cells in angiomyxoma are positive for ER and PR, which is different from PF.

DIFFERENTIAL DIAGNOSIS: MOLECULAR MIMICS

Gastroblastoma

Gastroblastoma is a rare gastric tumor that has been first described in 2009. The tumor has been reported both in pediatric and adult populations[40,62-64]. Histologically, gastroblastoma exhibits a biphasic growth pattern wherein areas of uniform spindled cells forming diffuse sheets are admixed with areas of epithelial cells with glandular/tubular differentiation forming nests, sheets or cords[40].

By immunohistochemistry, the epithelial cells are positive for AE1:AE3, CK18, and partially for CK7, while they are negative for CK5/6, CK20 and EMA. The spindle cells are positive for vimentin and CD10. Both elements are negative for C-KIT, SMA, desmin, S-100, CD34, CD99, ER, p63, calretinin, chromogranin, synaptophysin, and thyroid transcription factor 1[62].

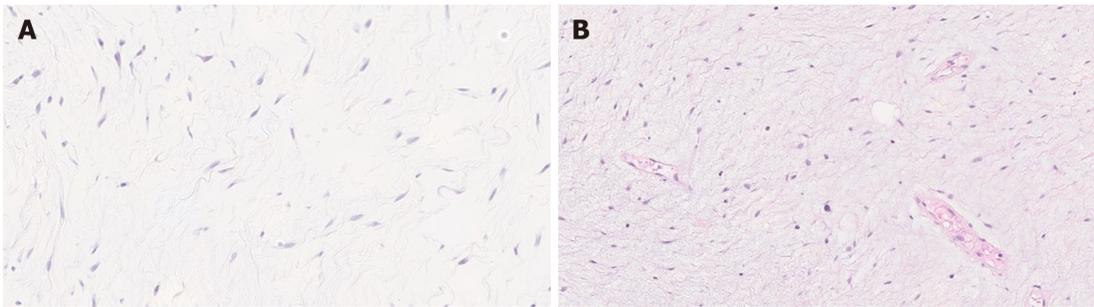


Figure 10 Myxoma vs aggressive angiomyxoma. A: Myxoma exhibits a proliferation of bland spindle cells within a myxoid stroma. The lesion is paucicellular [hematoxylin and eosin (HE), 200 ×]; B: Aggressive angiomyxoma is also hypocellular and shows a proliferation of spindle and stellate-shaped cells in a myxoid background. Blood vessels varying in caliber may show hyalinization (HE, 200 ×).

The tumor is negative for *SS18* rearrangement by in-situ hybridization that is usually present in synovial sarcoma, another tumor with a biphasic growth pattern[62].

Gastroblastoma has been recognized as a malignant epithelial tumor by WHO 2019. However, due to its biphasic and nodular growth pattern with spindle and epithelioid cells, as well as recurrent *MALAT1-GLI1* fusion, we consider this tumor as part of the differential diagnosis of PF[40,62,64].

Malignant epithelioid tumor with *GLI1* rearrangement

Malignant epithelioid tumor with *GLI1* rearrangement is a recently described epithelioid neoplasm of the soft tissue that harbors *MALAT1-GLI1* fusion with a metastatic potential[65]. In the GI tract, only one case in the jejunum has been reported[10]. Later, Agaram *et al*[66] reported *GLI1* gene amplifications in a subset of soft tissue tumors with similar morphology, even though these tumors showed broader morphologic spectrum and inconsistent immunohistochemistry. Recently, a soft tissue mass with similar morphology without *GLI1* rearrangement by FISH testing has been also described. This tumor lacked rearrangement of the *GLI1* locus. However, co-amplification *GLI1* and *DDIT3* that is near *GLI1* on chromosome 12, was identified[66]. Subsequently, the term “*GLI* activated epithelioid cell tumour” has been proposed to redefine the genetic background of this entity[67].

Although the cytomorphology of the lesional cells vary (epithelioid, ovoid, round to spindle), given that a subset of PF harbors *MALAT1* (in 11q12) and *GLI1* (in 12q13) translocation[66], we include these tumors in the differential diagnosis of PF. The tumor cells show variable positivity for S-100, SMA and cytokeratin[67].

POTENTIAL PITFALLS IN INTERPRETATION OF MESENCHYMAL NEOPLASMS OF GI TRACT

We herein summarize aforementioned findings that may pose diagnostic challenges (Table 1).

SDH-deficient and myxoid GIST can show multinodular growth pattern similar to PF, however the tumor cells are reactive with C-KIT and DOG-1 in both[9,40,44]. GIST can show focal desmin positivity similar to PF and leiomyoma[36]. Similarly, C-KIT immunostain can highlight the interstitial cells of Cajal that are entrapped in leiomyoma giving a false impression of GIST in a small sample. However unlike GIST, leiomyoma does not show diffuse C-KIT and DOG-1 staining[9,43]. Pseudoepitheliomatous hyperplasia of the squamous mucosa overlying GCT can mimic squamous cell carcinoma[40]. Differential diagnosis of neurofibromatosis-associated GI mesenchymal neoplasm is broad and include GIST, neurofibroma and schwannoma. Therefore, not all NF1-associated mesenchymal neoplasms are neurofibroma[51,68]. A distinct signet ring cell variant of gastric schwannoma has been reported and should not be mistaken for signet ring cell carcinoma[50].

Table 1 Differential diagnoses of plexiform fibromyxoma

Neoplasm	Morphology	Immunohistochemistry	Molecular alteration	Location	Behavior
Plexiform fibromyxoma	Ovoid to spindle	SMA (+), CD10 (+/-), desmin (+/-), caldesmon (+/-), C-KIT (-), DOG-1 (-), S-100 (-), CD34 (-), ALK (-), cytokeratin (usually -)	<i>MALAT1-GLI1</i> , <i>PTHC1</i> inactivation	Stomach	Benign
GIST	Spindle, epithelioid or mixed	C-KIT (+), DOG-1 (+), S-100 (usually -), CD34 (+), desmin (usually -), cytokeratin (-), SDHB (no loss)	<i>KIT</i> , <i>PDGFRA</i>	Stomach, small intestine, entire GI tract	Benign or malignant
SDH deficient-GIST	Usually epithelioid	C-KIT (+), DOG-1 (+), S-100 (-), CD34 (+), SDHB (loss), desmin (-), cytokeratin (-)	No <i>KIT</i> or <i>PDGFRA</i> mutation	Stomach	Benign or malignant
Smooth muscle tumor	Mostly spindle, rarely epithelioid	Desmin (+), SMA (+), DOG-1 (-), C-KIT (-), S-100 (-), CD34 (-)		Esophagus, colon	Benign or malignant
Nerve sheath tumor	Wavy spindle	GCT: S-100 (+), Schwannoma: S-100 (+); Neurofibroma: CD34 (+), S-100 (+); Perineurioma: EMA (+); MPNST: S-100 (weak +)	<i>NF1</i> , <i>NF2</i>	Esophagus (GCT), stomach (schwannoma)	Benign or malignant
Myxoma	Bland spindle or stellate	Vimentin (+), CD34 (+/-), S-100 (+/-), cytokeratin (-), SMA (-)		Rare in GI tract	Benign
Angiomyxoma	Spindle to stellate	ER (+), PR (+), SMA (+), desmin (+), vimentin (+), CD34 (+/-), C-KIT (-), DOG-1 (-), S-100 (-), cytokeratin (-)	<i>HMGA2</i> rearrangement	Extremely rare in GI Tract	Benign, locally aggressive
Gastroblastoma	Biphasic with epithelial and spindle	Epithelial cells: AE1:AE3 (+), CK18 (+); Spindle cells: vimentin (+), CD10(+); Both: C-KIT (-), SMA (-), desmin (-), S-100 (-), CD34 (-), CD99 (-), ER (-), p63 (-), calretinin (-), chromogranin (-), synaptophysin (-), TTF-1 (-)	<i>MALAT1-GLI1</i>	Stomach	Malignant
Malignant epithelioid tumor with <i>GLI1</i> rearrangement	Epithelioid, ovoid, round to spindle	S-100 (+/-), SMA (+/-), cytokeratin (+/-)	<i>MALAT1-GLI1</i> , <i>GLI</i> amplification, <i>GLI1</i> fusions	Soft tissue, jejunum	Malignant

GIST: Gastrointestinal stromal tumor; SDH: Succinate dehydrogenase; SDHB: Succinate dehydrogenase immunostain; GCT: Granular cell tumor; MPNST: Malignant peripheral nerve sheath tumor; GI: Gastrointestinal.

TREATMENT

The current treatment of choice for PF is surgical excision. No molecular alteration-based targeted therapy is available[6].

CONCLUSION

PF is an extremely rare entity that is likely under-recognized. Even though histologic features indicative of aggressive behavior such as vascular and lymphatic invasion have been reported, no malignant transformation or metastasis have been reported. Differential diagnosis includes variable mesenchymal tumors of the GI tract with spindled morphology and/or myxoid stroma, among which GIST is the closest mimic. A subset of PF has been shown to harbor certain molecular alterations, however no

universal molecular alterations have been identified. Recently described mesenchymal tumors share some molecular alterations described in PF and broaden the differential diagnoses. Notable increase in publications regarding PF appear to reflect growing awareness of this entity, which may aid in the correct diagnosis of PF and help to better understand the biology of this tumor.

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