Original Article
Plexiform fibromyxoma of the stomach: a clinicopathological study of 10 cases

Guiming Hu1*, Huiping Chen2*, Qiuyu Liu3, Jianguo Wei4, Yikun Feng1, Wengjing Fu1, Ming Zhang1, Huifang Wu1, Bin Gu1, Jingli Ren1

1Department of Pathology, The Second Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province, China; 2Department of Pathology, The Maternal and Child Health Hospital of Zhengzhou, Zhengzhou, Henan Province, China; 3Department of Pathology, Henan Provincial People’s Hospital, Henan Province, China; 4Shaoxing People’s Hospital, Zhejiang Province, China. *Equal contributors.

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Abstract: Plexiform fibromyxoma (PF) is a unique mesenchymal tumor of the stomach. The molecular characteristics of these tumors remain unclear. Here, we report 10 cases of PF with clinicopathological features and molecular features in detail. The patients ranged in age from 26 to 72 years (mean, 49 y) and most commonly presented with abdominal pain and distension, black stool, and anemia. Eight tumors were located at the antrum while two in the fundus of stomach. Histologically, tumor cells exhibited a plexiform growth pattern with multiple nodules in the muscularis propria of stomach wall and infiltrative borders. Immunohistochemically, all tumors were strongly positive for vimentin and smooth muscle actin (SMA), some were staining for CD10 (5/10), desmin (5/10), H-caldesmon (6/10) and progesterone receptor (PR, 6/10), however, CD34, S-100, Estrogen Receptor (ER), ALK, CD117 and DOG-1 were all negative in our cases. The glioma-associated oncogene homologue 1 (GLI1) gene translocation was detected in eight cases by FISH with three positive and five negative. Mutation analyses of C-KIT and platelet-derived growth factor receptor alpha (PDGFRA) genes were performed on five cases and all of which were wild-type for mutation. Our follow-up indicated that all of the patients made an uneventful recovery at 24 to 95 months after diagnosis. In summary, the distinctly histological features and immunohistochemical positivity of SMA, CD10 and PR can help differentiate PF from other gastrointestinal mesenchymal tumors. GLI1 gene translocation offers an additional molecular instrument for the diagnosis. The expression of PR and the existence of GLI1 gene translocation in PF highlights of our article.

Keywords: Plexiform fibromyxoma, gastrointestinal mesenchymal tumors, plexiform angiomyxoid myofibroblastic tumor, immunohistochemistry, GLI1 gene translocation

Introduction
Plexiform fibromyxoma (PF) is a recently identified tumor of the stomach which was firstly described by Takahashi and Shimizu [1] in 2007 and named plexiform angiomyxoid myofibroblastic tumor (PAMT). Two years later, Miettinen and Makhloof [2] reported two similar tumors, which they called PF. The term ‘plexiform fibromyxoma’ was added as the diagnostic term instead of PAMT in the 2010 WHO Classification of Tumors of the Digestive System. To date, there have been approximately 45 reported cases in the literature by searching from the ‘PubMed’. The study of this entity has been limited by its rarity, as a result, most of the tumors in the clinic were misdiagnosed as GISTs.

Although immunohistochemistry (IHC) related to myogenic marker expression is available for most published cases of PF, expression of other IHC markers and molecular feature has been limited in a comprehensive manner. In this study, we present ten cases of PF with a purpose to describe the clinical characteristics, histopathologic and immunophenotypical features, molecular features, and behavior of these rare tumors.

Materials and methods
Institutional Review Board approval was obtained before the initiation of this study. Eight cases of PF arising in the stomach were retrieved from the files of the Department of
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Pathology, the second affiliated hospital of Zhengzhou University, and two cases from Henan Provincial People’ Hospital covering a 11-year period (2006 to 2017). All patients had their primary surgery performed at our institution. The diagnosis of PF was confirmed by two senior doctors, respectively. Clinical information was obtained from the patients’ charts or their treating physicians. The following parameters were recorded: patients’ ages, sex, clinical presentation, tumor site and size, treatment, and follow-up data. In all cases, pathology reports and all available original hematoxylin and eosin (HE) stained slides were reviewed, additional IHC stains were performed using the EnVision method. These additional IHC stains included smooth muscle actin (SMA, Gene Tech, 1A4), CD10 (MXB, 56C6), CD117 (Gene Tech, poly), DOG-1 (Gene Tech, SP31), CD34 (Gene Tech, QBEnd-10), ER (MXB, SP2), PR (MXB, SP2), ALK (Gene Tech, 5A4) and S100 (Gene Tech, Poly). IHC stain results were assessed semiquantitatively as follows: negative (no cells stained), focally positive (less than 10% cells stained), patchy positive (11% to 49% cells stained), and diffusely positive (more than 50% of cells stained). Fluorescence in situ hybridization (FISH) was used to detect the GLI1 gene translocation in eight cases, and mutation of C-KIT (exons 9, 11, 13 and 17) and PDGFRA (exons 12, 14 and 18) were identified by Sanger sequencing of PCR products in five cases.

Results

The clinic features of the ten cases in this study are summarized in Table 1. The patients’ ages ranged from 26 to 72 years (median, 47 y; mean, 49 y). Seven of them presented with abdominal pain or distension (7/10), two presented with tarry-like black stool and associated with anemia (2/10). The remaining one patient had no clinic symptom and the mass was incidentally found during a routine check-up. Other presenting manifestations include upper gastrointestinal bleeding, anemia, nausea and vomiting and so on.

Grossly, eight tumors were mainly occupied at the submucosal layer at antrum (Figure 1) with mucosal ulceration and were relatively well demarcated, while the remaining two cases were located in the fundus of stomach and the endoscopic submucosal dissection (ESD) specimen were presented as isolated, flat masses. The maximum tumor dimension was ranged from 1.2 to 7.0 cm (median, 3.2 cm). Microscopically, the tumors were characterized predominantly by a plexiform growth pattern, spindle cells and

<table>
<thead>
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<th>Case</th>
<th>Gender</th>
<th>Age (y)</th>
<th>Presenting Symptom</th>
<th>Location</th>
<th>Ulcer</th>
<th>Tumor Size (cm)</th>
<th>Treatment</th>
<th>Follow-up (mo)</th>
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<td>DSG</td>
<td>NED, 70</td>
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ESD: Endoscopic submucosal dissection; DSG: Distal subtotal gastrectomy; NA, not available; NED, no evidence of disease.

Figure 1. Gross appearance of the tumor showed a submucosal mass at antrum and was relatively well demarcated.

Table 1. Clinic features of 10 cases of PF
myxoid stroma rich in arborizing blood vessels in the low power (Figure 2A). When high power, the tumor cells showed a bland looking, oval to slightly elongated nuclei and a mild eosinophilic cytoplasm (Figure 2B). There was no necrosis or significant cytological atypia in the tumor cells. The myxoid matrix was extending from mucosa to muscularis mucosa or muscularis. Collagen matrix was visible in four cases; therefore, it may be misdiagnosed as fibromatosis (Figure 2C). Furthermore, the stroma was abundant in variable shaped small dilated and arborizing vessels (Figure 2D). Mitotic index was very rare (0-3/50 high powered fields). Some inflammatory cells including mast cells, neutrophils, plasma cells and eosinophils were noted in the stroma, especially in the region adjacent to ulcers.

Immunohistochemical staining showed that tumor cells were diffusely and strongly positive for vimentin and SMA in all cases examined (Figure 3A). PR was patchy or diffusely positive in six cases (6/10 cases; Figure 3B), including three man and three female, the reaction position was in the nucleus, while CD10 (5/10 cases; Figure 3C), H-caldesmon (6/10 cases; Figure 3D) and desmin (5/10 cases) were patchy positive. In addition, CD34 was either negative or focal distribution in all cases. Other markers such as S-100, ER, ALK, CD117 and DOG-1 were all negative in every case. The myxoid matrix was positive for Alcian blue stain (Figure 4).

The GLI1 gene translocation was detected in eight cases by FISH with 3 positive cases (Figure 5) and 5 negative cases. Mutation analyses for exon 9, 11, 13, and 17 of C-KIT genes and 12, 14, and 18 of the PDGFRA genes were performed on five cases, all of which showed a wild-type for mutation.
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Female ratio was 1:1. Endoscopically, PF always appeared as submucosal mass [6], with the size ranging from 0.8 cm to 15 cm (mean, 6.3 cm). Although PF has a strong predilection for the gastric antrum (85.5%, 47/55), it may also present in the gastric fundus, body and esophagus [4, 14, 15], and also occasionally described in the small and large bowel [16], even in the gallbladder [17]. The overlying mucosa may be intact, dimpled or ulcerated. Representative clinical symptoms are ulceration, abdominal distension, upper gastrointestinal bleeding (including hematemesis or black stool) associated anemia [18]. Other symptoms included epigastric pain, nausea, emesis, weight loss, and pyloric obstruction [5]. Some patients have no symptoms and the tumor was found during a physical examination [3]. As to our cases, nine have some specific digestive tract symptom and one was incidentally found during a routine check-up. Imaging examination showed that the tumors were submucosal solid.

Seven patients underwent a distal subtotal gastrectomy and three patients underwent endoscopic submucosal dissection (ESD), none of the ten patients received a radiation therapy or chemotherapy after operation. Survival data were available for nine patients, of who were alive with no evidence of disease at follow-up periods of 24 to 95 months (median, 54 months).

Discussion

Rarity of PF is reflected by the fact that only 45 cases have been reported to date to further characterize this unusual group of stomach neoplasm in the literature [2, 13] since the initial description of PF in 2007, and most of these are single case reports. Together with our cases in this article, there are only 55 cases in total. The patients’ ages ranged from 26 to 72 years with mean age of 51, including 24 men and 27 women, and approximate male to female ratio was 1:1. Endoscopically, PF always appeared as submucosal mass [6], with the size ranging from 0.8 cm to 15 cm (mean, 6.3 cm). Although PF has a strong predilection for the gastric antrum (85.5%, 47/55), it may also present in the gastric fundus, body and esophagus [4, 14, 15], and also occasionally described in the small and large bowel [16], even in the gallbladder [17]. The overlying mucosa may be intact, dimpled or ulcerated. Representative clinical symptoms are ulceration, abdominal distension, upper gastrointestinal bleeding (including hematemesis or black stool) associated anemia [18]. Other symptoms included epigastric pain, nausea, emesis, weight loss, and pyloric obstruction [5]. Some patients have no symptoms and the tumor was found during a physical examination [3]. As to our cases, nine have some specific digestive tract symptom and one was incidentally found during a routine check-up. Imaging examination showed that the tumors were submucosal solid.
masses, however, cystic degeneration, fistulat-
ing abscess formation and perforation were
also reported [5, 19].

CT and MRI are the most commonly used non-
invasive modalities for detection, staging, and
surgical planning. However, due to the rarity of
PF, limited data were available in the literature
regarding the radiological features of this neo-
plasm. Particularly, some case included CT and
MRI imaging showing the cystic-solid tumor
with inhomogeneous attenuation but without
ulceration or calcification. These findings were
consistent with previous studies but demonstrat-
ed that our cases were different from other

PFs because of the cystic portion. In the litera-
ture, we found no reports of gastric fistula or
liquefactive necrosis in the tumor, except in a
mass with central necrosis and gas-fluid level
reported by Lee et al [5]. In our case, the most
important characteristic CT feature was that
the solid portion showed mild enhancement
during the arterial phase and strengthened
progressive enhancement during the venous
and delayed phases, which was consistent with
previous reports. The radiology findings ill-
ustrated the characteristic growth of PF, which
was a hypervascular tumor located in the myx-
oid stroma. However, Sing et al [3] reported a
case of PF with poor enhancement that we
thought might be due to technological prob-
lems with the contrast-enhanced CT scan. MRI
is superior to CT for visualizing tumor extent
and central necrosis, including hemorrhage.
Gastric PF showed low signal intensity on the
T1-weighted images and high signal intensity
on the T2-weighted images and exhibited no
associated hemorrhage. The solid portion also
exhibited heterogeneously gradual enhance-
ment on contrast-enhanced MR images. These
MRI findings were consistent with results re-
ported by Sakamotp et al [6]. Therefore, the
imaging features of gastric PF corresponded to
the pathological composition of the lesion. In
our study, pregastric lymph nodes were con-
firmed without evidence of neoplastic cells or
malignancy by pathology. However, radiograph-
ic examination is not specific in the diagnosis,
so that almost all patients preoperatively were
misdiagnosed as GIST.

Grossly, all tumors showed a multi-nodular sub-
mucosal or intermuscular mass, with a whitish
to brownish or reddish cut surface [2]. Mic-
roscopic examination was characterized by
plexiform or multiple nodular growth pattern in
the stomach wall, which rich in small thin-
walled blood vessels and myxoid matrix at low
power [7]. At high magnification, the tumor cells
possess bland spindle or oval nuclei and a
slightly eosinophilic cytoplasm, while the nucle-
oli were inconspicuous. The stroma was rich in
small and thin-walled blood vessels and posi-
tive for Alcian blue stain, occasional collage-
nization may be observed. In our cases, stro-
mal collagenization was seen in four cases, but
it was usually localized. Mitoses were usually
not detected (at most 3/50 high-power fields),
but no necrosis and pathological nuclear fis-
sion were observed in reported cases.
Immunohistochemically, tumor cells were strongly positive for vimentin and SMA, while positivity for desmin, CD10 and H-caldesmon was variable, but negative for CD34, S-100, ER, ALK, CD117 and DOG-1. The Ki-67 labeling index demonstrated a very low proliferation index, usually less than 2%. Interestingly, most of our cases showed a strong positive for PR. It’s identical with the reported in the literature [3]. Hence, although speculative, the novel finding of prominent PR immunopositivity in some of the cases may not only indicate origin from a hormonally sensitive precursor gastric mesenchymal cell but may also point to potential therapeutic hormonal manipulation of PFs.

In all reported cases, genetic studies showed no mutations in C-KIT gene and PDGFRα gene. To date, the diagnosis of PF is still depending on the morphological and immunohistochemical appearance, however, the molecular or genetic features of these tumors are unknown. Recently, Spans et al [20] described a recurrent translocation, t (11; 12) (q11; q13), involving the long non-coding gene metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) and the gene glioma-associated oncogene homologue 1 (GLI1) in a subgroup of PF. In our cases, the GLI1 gene translocation was detected in eight cases by FISH with three positive cases and five negative cases. Sequence analysis was also performed for mutational hotspots in the C-KIT (exons 9, 11, 13, and 17) and PDGFRα genes (exons 12, 14 and 18) in five cases, and no mutations were found in any case. The structure of the MALAT1-GLI1 fusion gene reported in the subset of PF is the same as that seen in gastroblastoma [21]. This, of course, raises the question of whether PF and gastroblastoma represent related entities, or even possibly different manifestations of the same entity. We strongly consider that the presence of MALAT1-GLI1 fusions in both PF and gastroblastoma represents simply another example of identical genetic events in unrelated neoplasms, just like PDGFRα genes mutations may be seen in GIST and inflammatory fibroid polyposes [22].

Although PF shows a characteristic pathological features, it should be differentiated other mesenchymal tumors of the stomach. The primary histological differential diagnoses include gastrointestinal stromal tumor (GIST), IFP, leiomyoma, leiomyosarcoma, solitary fibrous tumor (SFT), schwannoma, desmoids fibromatosis, and inflammatory myofibroblastic tumor (IMT) and so on. GIST is the most common primary mesenchymal tumor in the gastrointestinal tract and spans a clinical spectrum from benign to malignant. Myxoid GIST and SDH-deficient GIST may show plexiform or multinodular growth pattern, proliferation of spindle cells, presence of epithelioid cells, and abundant myxoid stroma with thin-walled blood vessels [23]. These histologic features are similar to PF, however, the typical characteristics of immunohistochemistry (positive for CD34, DOG-1 and CD117, and SDH-deficient GIST immunohistochemical loss of SDHB) confirmed the final diagnosis of GIST [24]. Accordingly, wild-type sequences of the C-KIT and PDGFRα genes can differentiate PF from GISTs. Leiomyoma often appears as a clearly defined mass and characterizes by the fascicular arrangement of tumor cells that possess spindle-shaped nuclei and markedly eosinophilic cytoplasm. Leiomyosarcoma shows high cellularity, cellular atypia, and remarkable mitoses and necrosis [25]. IFP is usually a small submucosal lesion characterized by bland spindle-cell proliferation in an onion skin-like pattern around vessels with eosinophilic infiltrates and positive-staining for CD34 [26]. Prominent lymphocyte and plasma cell infiltration, and positive immunoreactivity for ALK are the distinguishing features of IMT. Although schwannoma and SFT are extremely rare in this location, it should be considered in the differential diagnosis. Schwannoma are positive for S-100 and SFT express CD34, bcl2, CD99 and STAT-6 [27]. In desmoids fibromatosis, spindle cells are arranged in long fascicles and positive expression for β-catenin.

In all reported 45 cases to date, together with our ten cases, follow-up data were obtained for 39 cases of 55 (70.9%; 39/55), with the period ranged from 24 month to 25.5 years (median, 52 mo), there have no malignant change, recurrence or metastasis of disease been reported. However, in some cases, the follow-up duration was too short to precisely predict prognosis. Based on favorable prognoses, absence of nuclear atypia and vascular invasion, and low mitotic index, we suggest that PF can be categorized as a benign lesion.

According to the current literature, distal gastrectomy or partial gastrectomy is a major te-
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technique for dealing with PF when it occurs in the stomach [11], including endoscopic submucosal dissection [28]. Compared with gastrectomy, local excision can bring less harm to the patients. Together with our cases, only six patients underwent local excision of tumor [3, 15, 19, 28]. The common characteristic for the six cases is that the tumors are small enough to be removed under gastroscopy. Hence, it is important to diagnose PF as early as possible.

PF of the stomach is a very rare mesenchymal tumor with a unique histological appearance, and it needs to be distinguished from GIST and other gastrointestinal mesenchymal tumors. In the present study, we applied a panel of antibodies, inclusive of the myogenic markers (SMA, desmin, and H-caldesmon), PR, CD10, as well as the molecular features. Our results support that PF have a GLI1 gene translocation between chromosome 11 and chromosome 12. This finding highlights our study. Prominent plexiform or multiple nodular growth patterns, positive immunoreactivity for SMA, PR, CD10, and GLI1 gene translocation are the distinguishing features of PF. The limited follow-up evidence suggests the benign nature of this tumor, but the long-term clinical behavior of PF remains to be established.

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Disclosure of conflict of interest

None.

Address correspondence to: Guiming Hu, Department of Pathology, The Second Affiliated Hospital of Zhengzhou University, 2 Jingba Road, Zhengzhou 450014, Henan Province, China. Tel: +86-371-63974711; E-mail: huguiming2003@126.com

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