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BEYOND GIST: UNDERSTANDING PLEXIFORM FIBROMYXOMA IN GASTRIC MESENCHYMAL TUMORS

Surgical Oncology

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ABSTRACT

Background: Plexiform fibromyxoma (PF) is an exceptionally rare, benign mesenchymal neoplasm of the gastrointestinal tract, first recognized by the World Health Organization in 2010. Due to its spindle cell morphology and submucosal origin, it is frequently misidentified as a gastrointestinal stromal tumor (GIST). Accurate diagnosis is essential to avoid overly aggressive treatment or unnecessary targeted therapies. **Case Presentation:** We present the case of a 39-year-old female who presented with a one-month history of abdominal pain, recurrent vomiting, significant weight loss, and severe anaemia (Haemoglobin - 7 g/dl). Clinical examination and CECT imaging revealed a massive 21.4 cm solid-cystic mass originating from the gastric antrum, causing gastric outlet obstruction (GOO). Repeated preoperative biopsies were inconclusive. The patient underwent a distal gastrectomy with loop gastrojejunostomy. Histopathological examination revealed a multinodular growth of bland spindle cells embedded in an abundant myxoid stroma with a characteristic arborizing capillary network. Immunohistochemistry showed the tumor was positive for SMA and negative for CD117, DOG1, and S100, conclusively establishing a diagnosis of PF.**Discussion:** PF typically presents in the fourth to fifth decades of life, with a strong predilection for the gastric antrum (~80% of cases). While non-specific GI symptoms and bleeding are common, presentation with GOO is rare. Pathogenesis is increasingly linked to the MALAT1-GLI1 fusion and activation of the Sonic Hedgehog signalling pathway. Unlike GISTs, PFs lack KIT or PDGFRA mutations and exhibit indolent biological behaviour.**Conclusion:** Plexiform fibromyxoma is a distinct diagnostic entity that must be differentiated from more aggressive gastric mesenchymal tumors through rigorous morphological and immunohistochemical assessment. Complete surgical resection (R0) remains the definitive, curative treatment with an excellent long-term prognosis.

KEYWORDS

Plexiform Fibromyxoma, Gastric Mesenchymal Tumor, Gist, Gastric Outlet Obstruction, Case Report.

INTRODUCTION

Plexiform fibromyxoma (PF) is a recently recognized, rare benign mesenchymal neoplasm that primarily affects the gastrointestinal (GI) tract. First described by Takahashi et al. in 2007 under the preliminary moniker “plexiform angiomyxoid myofibroblastic tumor” (PAMT), this distinct entity was officially incorporated into the World Health Organization (WHO) Classification of Tumours of the Digestive System in 2010 under the nomenclature "plexiform fibromyxoma" by Miettinen et al. [1, 2]. This revised terminology more accurately reflects the tumor's characteristic histological architecture: a plexiform, multinodular growth pattern composed of bland spindle cells that are deeply embedded in a prominent myxoid stroma rich in arborizing capillaries [3, 4]. Although initially considered an exceptionally rare and underrecognized occurrence [4], the reported incidence of PF has seen a notable increase in recent literature. This rise is primarily attributable to growing clinical and pathological awareness, which has allowed clinicians to accurately distinguish PF from other, more common gastrointestinal mesenchymal tumors, most notably gastrointestinal stromal tumors (GISTs) [3, 5].

Case Report

A 39-year-old female with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 and body mass index of 16.4 kg/m², with no comorbidities, presented with complaints of abdominal pain and generalized weakness for one month. The pain was diffuse and insidious in onset, aggravated after taking meals, and relieved with medications. Pain was associated with recurrent postprandial vomiting and significant unintentional weight loss over the past month. There was no history of hematemesis, melena, jaundice, fever, or backache. Notably, she had been admitted to a peripheral hospital 15 days prior, where she received a transfusion of three units of packed red blood cells (PRBCs) for severe anaemia. She had no significant past surgical or familial history.

Clinical examination revealed moderate to severe pallor. Abdominal examination revealed a large palpable mass of approximately 20 × 15 cm in size, spanning from the epigastric region down to the infraumbilical area. There were no palpable supraclavicular or axillary lymph nodes. Blood parameters reported severe anaemia (Haemoglobin - 7 g/dL) and hypoalbuminemia (Serum Albumin - 2.48 g/dL).

Contrast-enhanced computed tomography (CECT) of the abdomen and pelvis revealed a large, well-defined complex lesion originating from the gastric antrum, extending through the pyloric canal and into the first part of the duodenum. The mass measured 10.9 × 18.1 × 21.4 cm, with cystic and necrotic components which caused compression of the gastric lumen, leading to gastric outlet obstruction (GOO). (Fig. 1) No significant lymphadenopathy was noted. CECT of the thorax showed no abnormality. Upper gastrointestinal endoscopy (UGIE) revealed an ulceroproliferative lesion in the antrum. Endoscopic ultrasound (EUS) showed a cystic lesion with a possible cystogastric fistula, raising suspicion of GIST. However, repeated preoperative endoscopic and ultrasound guided biopsies failed to yield a conclusive histopathological diagnosis.

To bypass the GOO and improve the patient's nutritional status pending a final diagnosis and therapeutic strategy, enteral feeding was initiated via an endoscopically inserted nasojejunal (NJ) tube. Given the symptomatic GOO, the suspicious nature of the mass, and persistently inconclusive biopsy results, the patient was planned for a diagnostic laparotomy.

Intraoperatively, a large solid-cystic tumor (approximately 18 × 12 cm) arising from the antro pyloric region was identified, with dense adhesions to the anterior abdominal wall and transverse colon. The cystic component ruptured intraoperatively upon deepening the abdominal incision, releasing approximately 300–400 ml of purulent fluid with necrotic material. Samples from both the solid and cystic components of the lesion were sent for frozen section, which reported it as a spindle cell neoplasm. Based on the frozen section reports, the patient underwent a distal gastrectomy with loop gastrojejunostomy reconstruction. (Fig. 2)

The postoperative period was uneventful. She received 6 units of PRBCs (3 units preoperatively and 3 units postoperatively) and 4 units of albumin during her entire hospital stay to manage anemia and hypoalbuminemia. She was transitioned from enteral NJ tube feeding to an oral diet on postoperative day (POD) 8 and the patient was discharged in stable condition on POD 15.

The final histopathological examination of multiple sections showed tumor cells arranged in a multinodular pattern composed of bland spindle cells in a myxoid matrix with a prominent arborizing thin-walled capillary network dissecting the muscularis propria. (Fig. 3)

On immunohistochemistry, the tumor cells were positive for SMA, focally positive for Desmin, and negative for CD117, DOG1, S100, CD34, Pan-CK, ALK1, and EMA. The Ki-67 labeling index was 2 to 3% in the highest proliferating areas. This distinct morphological and immunophenotypic profile conclusively established the diagnosis of a gastric plexiform fibromyxoma (PF) localized to the antrum. (Fig. 4)

DISCUSSION

Epidemiology and Clinical Presentation

To date, slightly over 120 cases of PF have been thoroughly documented and reported in the literature [4, 6]. The tumor affects a broad demographic, presenting in patients across a wide age spectrum ranging from pediatric populations (as young as 5 years) to the elderly (up to 81 years). The median age of presentation typically falls within the fourth to fifth decades of life [6]. While earlier reports suggested a relatively equal gender distribution, comprehensive updates to the literature have noted a slight female predominance [3, 6].

The vast majority of PFs originate within the stomach. There is a striking topographical predilection for the gastric antrum and pylorus, which account for nearly 80% of all documented cases [6]. Less commonly, the tumor arises in the gastric body, fundus, or cardia [5]. Extra gastric locations are considered exceedingly rare, though isolated cases have been reported in the duodenum, jejunum, esophagus, gallbladder, and mediastinum [3, 6-8].

Clinical presentation is largely dictated by the tumor's size, its exact anatomical location, and the presence or absence of mucosal ulceration. Patients most frequently report non-specific gastrointestinal symptoms, including chronic abdominal pain, dyspepsia, nausea, vomiting, abdominal distension, and unintentional weight loss [6, 7, 9]. More acute presentations have also been noted; for instance, instances of paroxysmal abdominal pain and diarrhea have been documented [10]. Bleeding-related symptoms are a classic hallmark of PF, occurring in a significant proportion of patients due to the tumor's marked hypervascularity and its propensity to ulcerate the overlying mucosa. These symptoms manifest as iron-deficiency anemia, melena, hematemesis, or, in severe cases, syncope and hemodynamic instability [6, 7, 9]. Symptoms like GOO are uncommon but was present in our case. Interestingly, an elevation in specific tumor markers, such as carbohydrate antigen 72-4 (CA 72-4), was reported in a case report by Zhang et al., but no other literature reported an association with these lesions [10]. A subset of cases remains entirely asymptomatic and is discovered only incidentally during endoscopic or radiological examinations performed for unrelated indications [7, 9].

Endoscopic and Radiological Findings

Preoperative diagnosis of PF remains challenging due to its morphologic and symptomatic resemblance to other submucosal tumors. On endoscopic evaluation, PF typically presents as a firm, rubbery, lobulated, or polypoid submucosal mass that protrudes into the gastric lumen [3]. The overlying mucosa frequently appears erythematous or exhibits central ulceration [6]. Endoscopic ultrasound (EUS) often reveals a hypoechoic, heterogeneous lesion arising from the submucosa or the muscularis propria [6].

Radiological imaging, particularly computed tomography (CT) and magnetic resonance imaging (MRI), plays an indispensable role in assessing the tumor's extent and planning surgical intervention. On contrast-enhanced CT, PF presents as a well-circumscribed, solid, or mixed solid-cystic nodular mass [10]. A highly characteristic feature is its dynamic enhancement pattern: mild enhancement during the arterial phase, followed by progressive and delayed enhancement in the venous and delayed phases. This distinct pattern reflects the tumor's rich underlying capillary network and its abundant myxoid stromal matrix [3, 10]. MRI further delineates the myxoid composition of the tumor, classically demonstrating low signal intensity on T1-weighted images and characteristically high signal intensity on T2-weighted images [3].

Pathological Features

Macroscopically, PFs are well-demarcated, unencapsulated, multinodular masses that typically span the submucosa and muscularis propria, occasionally extending outward into the subserosa or serosa [7, 9]. The cut surface is distinctive, routinely exhibiting a gelatinous, myxoid, or mucoid appearance. The tissue is usually colored gray-white to tan-pink and is frequently interspersed with visible areas of hemorrhage or focal cystic degeneration [4, 7, 9]. The size of the tumor varies considerably at the time of diagnosis, ranging from as small as 0.8 cm to as large as 17 cm, with a mean diameter of approximately 4.8 cm [6].

Microscopically, PF is defined by a triad of hallmark morphological features:

- **Architecture:** It displays a highly characteristic plexiform or multinodular growth pattern. The tumor nodules characteristically dissect between the smooth muscle bundles of the muscularis propria, creating a plexiform appearance [5].
- **Cellularity:** The tumor is composed of a paucicellular proliferation of bland, uniform spindle to ovoid cells. These cells lack significant nuclear atypia, pleomorphism, or prominent nucleoli [7, 9]. Mitotic activity is characteristically low, typically observing fewer than 3-5 mitoses per 50 high-power fields, and tumor necrosis is exceptionally rare [6, 7, 9].
- **Stroma:** The neoplastic cells are suspended in an abundant, Alcian blue-positive myxoid or fibromyxoid stroma. This stroma is permeated by a prominent, arborizing network of delicate, thin-walled capillary vessels [4].

While secondary features such as mucosal ulceration, lymphatic, and vascular invasion have been documented in pathological specimens, long-term follow-up indicates that these findings do not correlate with aggressive biological behavior in PF [3].

Immunohistochemical Profile

Immunohistochemistry is an absolute requirement for establishing a definitive diagnosis of PF and definitively excluding its morphologic mimics. The neoplastic spindle cells consistently exhibit diffuse and strong cytoplasmic positivity for vimentin and alpha-smooth muscle actin (SMA), effectively underscoring their myofibroblastic lineage [4, 10].

There is also a variable, often focal or partial, expression of desmin, CD10, CD99, and h-caldesmon [7, 9, 10].

Crucially, PF is uniformly negative for the specific markers that define other common mesenchymal tumors of the GI tract. It strictly lacks expression of c-KIT (CD117) and DOG-1, which effectively rules out GIST [7, 9]. Furthermore, the tumor cells are typically negative for CD34 (although the rich background vascular network will stain strongly positive), S-100 protein, SOX10, beta-catenin, STAT-6, anaplastic lymphoma kinase (ALK), and epithelial membrane antigen

(EMA) [5, 10]. Furthermore, succinate dehydrogenase (SDHB) expression is retained [10]. The Ki-67 proliferation index is consistently low, almost universally remaining below 2-5%, which perfectly aligns with the tumor's indolent clinical nature [4, 5].

Molecular Genetics

The underlying molecular landscape of PF is an area of rapid and active investigation. Unlike GISTs, PFs are defined by the complete absence of activating mutations in the *KIT* and *PDGFRA* genes [3, 11]. Recent advanced molecular analyses have successfully identified recurrent genetic alterations in a distinct subset of cases. The most widely recognized alteration is the balanced translocation t(11;12)(q11;q13). This translocation results in the oncogenic fusion of the *MALAT1* gene with the *GLI1* gene [5, 6]. This specific fusion event, in conjunction with *GLI1* polysomy or amplification observed in other non-translocated cases, results in the dramatic upregulation and overexpression of the GLI1 protein. This overexpression subsequently drives the anomalous activation of the Sonic Hedgehog (Shh) signaling pathway, a mechanism central to the tumor's pathogenesis [11]. Another smaller subset of PFs has been found to harbor inactivating mutations or targeted deletions in the *PTCH1* tumor suppressor gene, further implicating the Shh pathway [3]. Moreover, a recent comprehensive next-generation sequencing study of a gastric PF revealed a novel, complex profile of pathogenic missense mutations in genes including *ABL1, KDR, CSF1R, FGFR4,* and *CCND3* which might explain the rapid tumor growth and angiogenesis in these tumors [11].

Differential Diagnosis

The differential diagnosis for PF is broad and encompasses a variety of spindle cell and myxoid neoplasms of the gastrointestinal tract:

- **Gastrointestinal Stromal Tumor (GIST):** GIST represents the foremost and most critical mimic, particularly the myxoid or succinate dehydrogenase (SDH)-deficient variants, which can occasionally exhibit a multinodular pattern [3]. However, GISTs are strongly and diffusely positive for c-KIT and DOG-1, and possess defining *KIT* or *PDGFRA* mutations, which stand in stark contrast to PF [3].
- **Smooth Muscle Tumors (Leiomyoma/Leiomyosarcoma):** While myxoid leiomyomas can share a plexiform architecture, they exhibit diffuse, strong positivity for desmin and lack the abundant, delicate capillary network characteristic of PF [4, 7, 9].
- **Nerve Sheath Tumors (Schwannoma/Neurofibroma):** Gastric schwannomas often present with a distinct peripheral lymphoid cuff and are strongly positive for neural markers S-100 and SOX10, both of which are reliably negative in PF [5].
- **Inflammatory Fibroid Polyp (IFP):** IFPs are typically submucosal polyps centered around blood vessels, featuring a characteristic "onion-skin" arrangement of spindle cells, an eosinophil-rich stroma, and strong CD34 positivity [4].
- **Gastroblastoma:** A rare, biphasic tumor that can similarly harbor the *MALAT1-GLI1* fusion [3]. It is definitely distinguished from PF by the presence of a distinct epithelial component that stains strongly positive for cytokeratins [3].
- **Inflammatory Myofibroblastic Tumor (IMT):** IMT features a prominent inflammatory stroma and frequently exhibits ALK positivity alongside *ALK* gene rearrangements, differentiating it fundamentally from PF [4].

Treatment and Prognosis

Extensive long-term follow-up data indicate that PF demonstrates unequivocally benign biological behavior. Despite occasional pathological findings of local tissue infiltration, mucosal ulceration, or microscopic vascular invasion, there have been zero documented cases of malignant transformation, local recurrence, or distant metastasis following complete surgical resection [3, 4]. Therefore, the definitive standard of care and curative treatment for PF is complete surgical excision with negative margins (R0 resection) [7, 9]. Depending on the precise tumor size and anatomical location, viable surgical approaches range from local wedge resection and advanced endoscopic submucosal dissection to partial or distal gastrectomy [6, 7]. Avoidance of overdiagnosis is of paramount clinical importance; misclassifying a benign PF as a potentially malignant GIST could subject patients to unwarranted aggressive surgical resections or the unnecessary administration of targeted therapies (such as imatinib), which carry significant morbidity and side effect profiles [4].

CONCLUSION

Plexiform fibromyxoma is a distinct, rare, and benign myofibroblastic neoplasm of the gastrointestinal tract, predominantly localized to the gastric antrum. It presents a unique clinicopathological challenge due to its significant morphological overlap with more aggressive neoplasms, particularly GISTs. A high index of clinical suspicion, coupled with a rigorous morphological assessment revealing a plexiform architecture, a myxoid stroma, and an arborizing vasculature—supported by a precise immunohistochemical panel (SMA-positive, c-KIT/DOG-1-negative)—is imperative for accurate diagnosis. Emerging molecular insights, particularly the identification of the *MALAT1-GLI1* fusion and other novel genomic mutations, continue to expand our understanding of its unique pathogenesis. Complete surgical resection remains the definitive treatment, yielding an excellent long-term prognosis without the risk of recurrence or metastasis. Continued global documentation and extensive molecular profiling of PF cases remain essential to fully elucidate the complete biological spectrum of this enigmatic tumor.

Figures

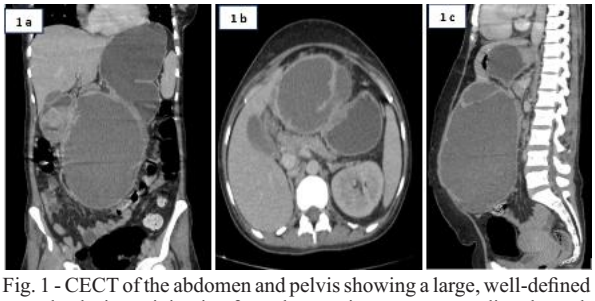

Fig. 1 - CECT of the abdomen and pelvis showing a large, well-defined complex lesion originating from the gastric antrum, extending through the pyloric canal and into the first part of the duodenum measuring 10.9 × 18.1 × 21.4 cm, with cystic and necrotic components which caused compression of the gastric lumen. a) Coronal section b) Axial section c) Sagittal section.

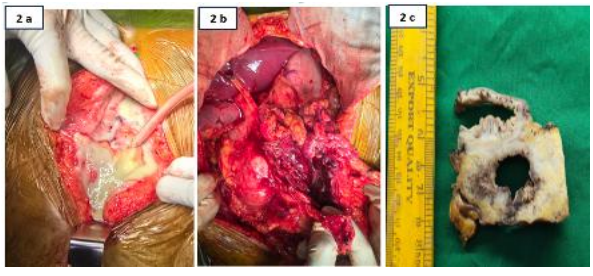

Fig. 2 a) Intra-op photo showing pus upon entering the abdominal cavity due to rupture of the cystic component of tumor. b) Intra-op photo showing the mass arising from the antro-pyloric region of stomach. c) Grossing - The tumor is centered in the muscularis propria with no surface ulceration and solid, firm in consistency, greyish white in appearance

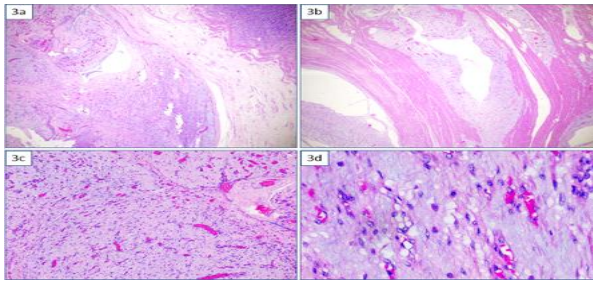

Fig 3 a,b) The tumor is arranged in a multinodular pattern underneath the epithelium and dissecting the muscularis propria. c) The nodules are composed of bland spindle cells in a myxoid stroma with a prominent arborising thin-walled capillary network without significant cytological atypia or mitotic activity. d) Few admixed mast cells also seen.

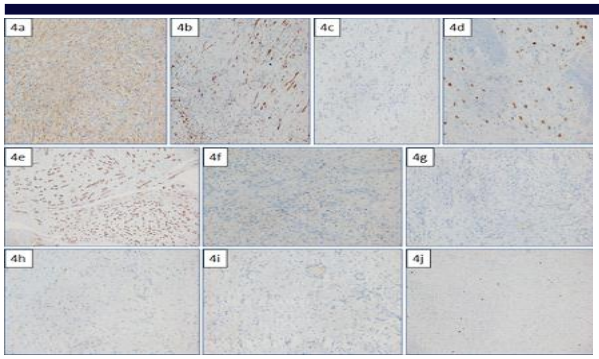

Fig 4 a) The spindle cells are positive for SMA (DABx200). b) The spindle cells are focally positive for desmin (DABx200). c) Spindle cells are negative for DOG1 (DABx200). d) CD117 is negative in lesional cells and highlighting few admixed mast cells (DABx200). e) The spindle cells are negative for CD34 (DABx200). f) Spindle cells are negative for panCK (DABx200). g) Spindle cells are negative for EMA(DABx200). h) Spindle cells are negative for S100 (DABx200). i) Spindle cells are negative for ALK1 (DABx200). j) Ki67 labelling index is 2/mm2 (DABx200)

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