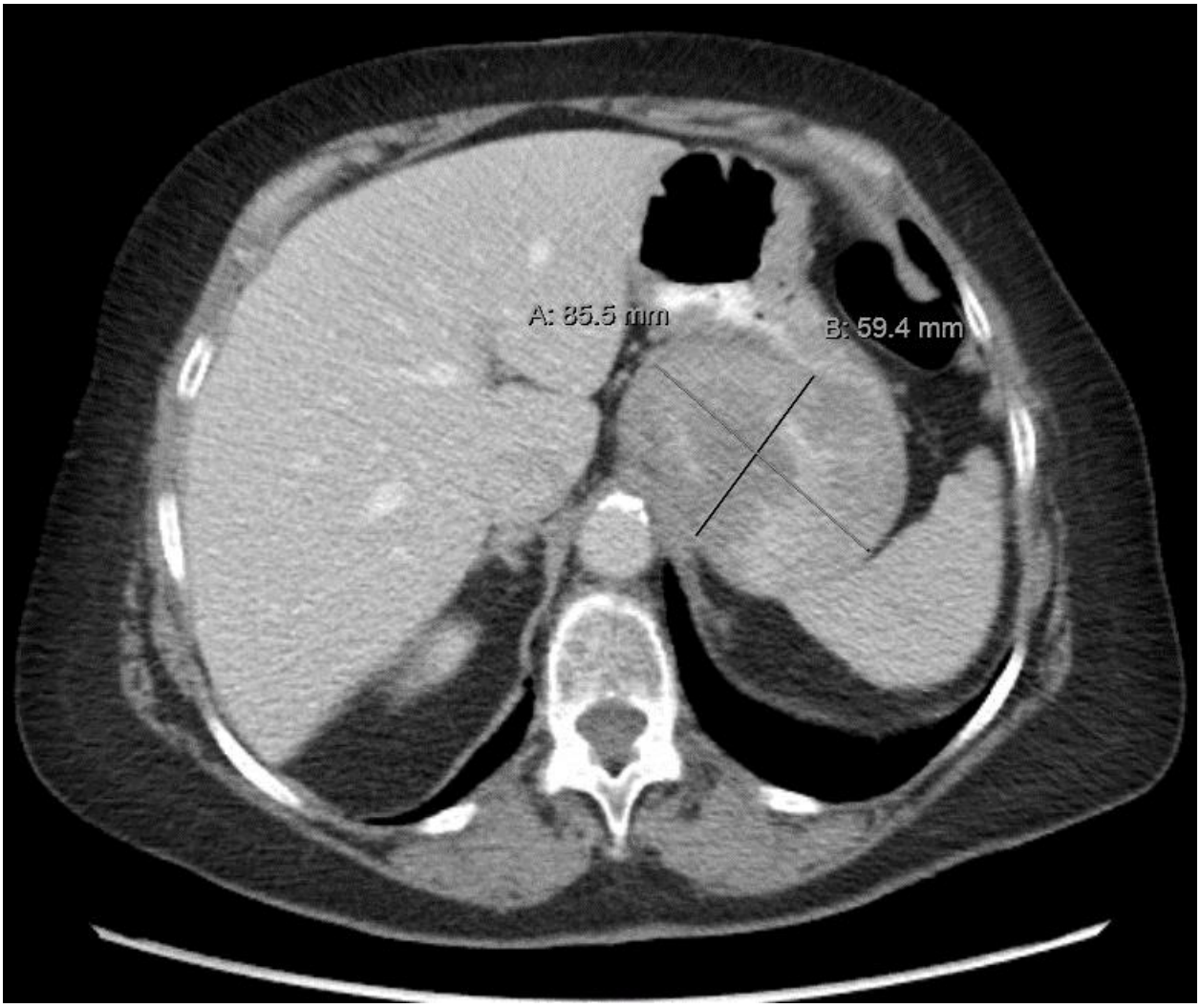
Case Presentation:

A 71-year-old female presented with dysphagia, intermittent left upper abdominal pain, and unintentional weight loss of approximately 7 lbs. over 4 months.

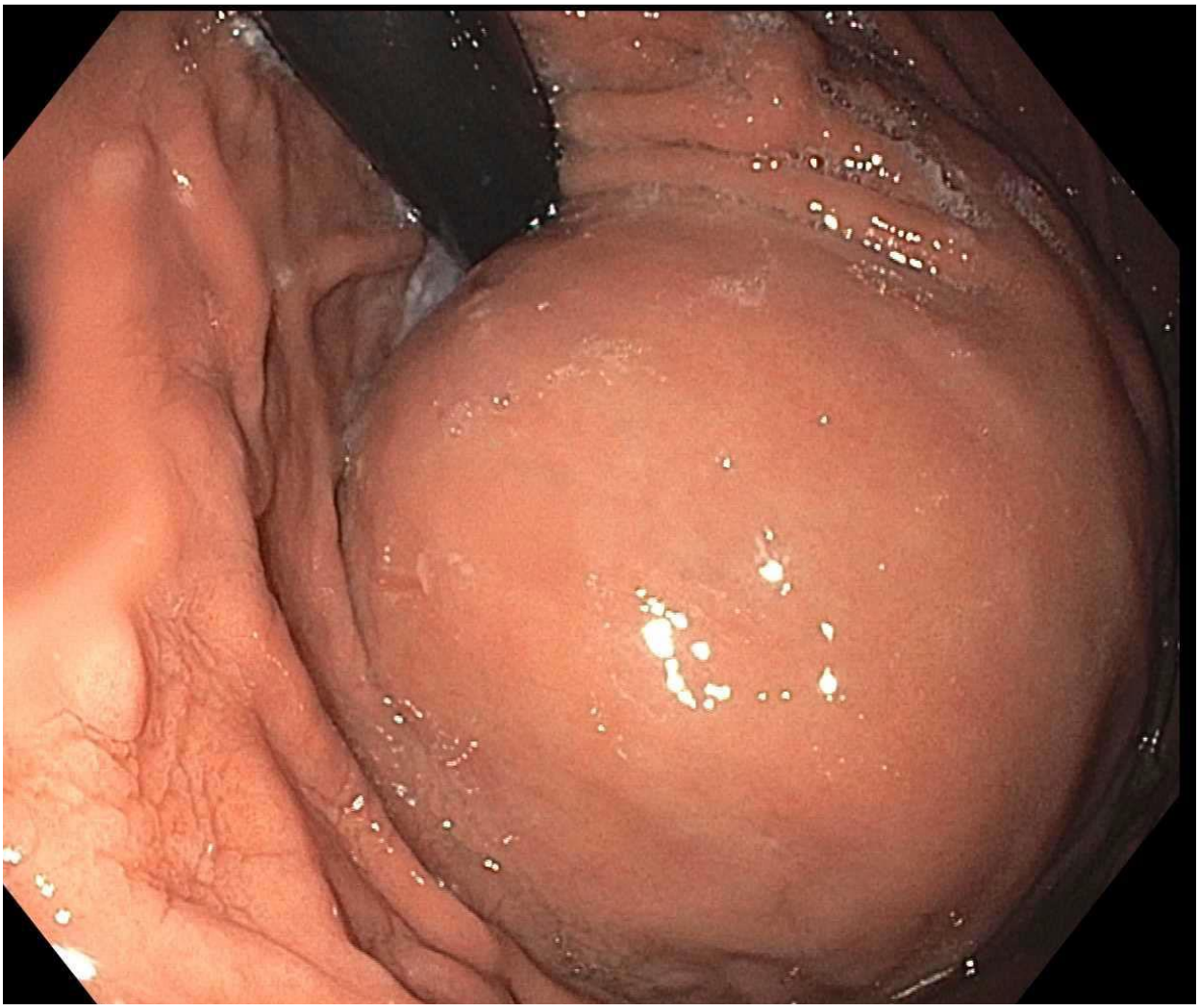
An abdominal CT scan with contrast demonstrated an 8.5 x 6.0 x 5.5 cm solid, well-marginated mass along the fundus of the stomach, extending to the gastroesophageal junction (Figure 1). Upper gastrointestinal endoscopy showed a large subepithelial gastric mass with no bleeding or ulceration of the mucosa located in the cardia/fundus of the stomach (Figure 2). EUS revealed a hypoechoic subepithelial gastric mass in the cardio-fundic region which appeared to originate from the muscle layer of the stomach wall. Fine needle aspiration and biopsy were performed (Figure 3) followed by a proximal gastrectomy. The gross photo and microscopic findings are shown below (Figure 4-5).

FIGURE 1.



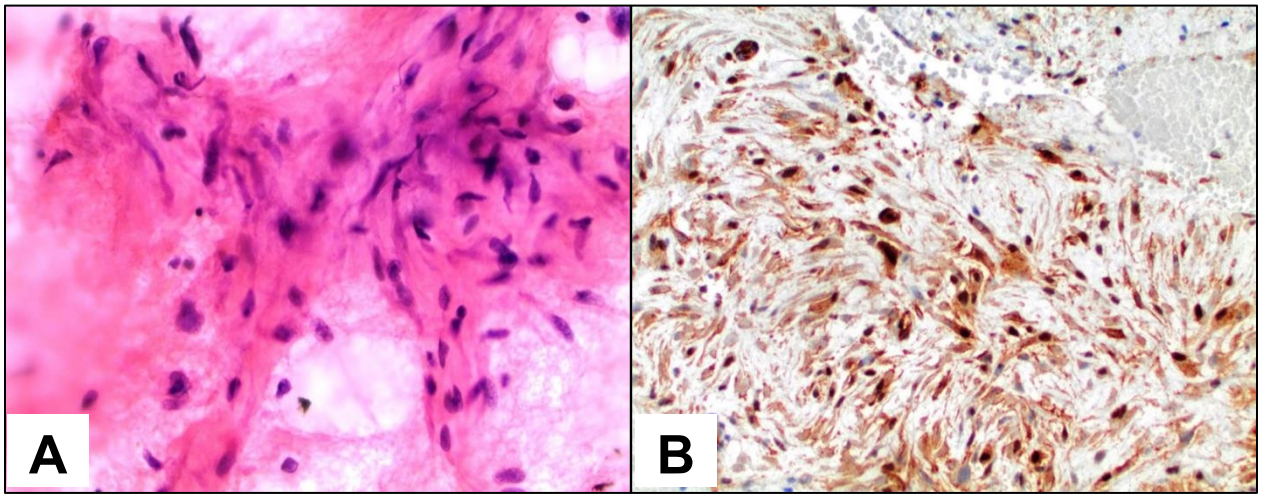
Abdominal CT scan demonstrating an 8.5 cm solid, well-marginated mass with non-homogeneous contrast enhancement along the fundus of the stomach extending to the gastroesophageal junction.

FIGURE 2.



Endoscopic picture of intact gastric mucosa with bulging subepithelial mass in the cardia/fundus of the stomach visible on retroflexion view.

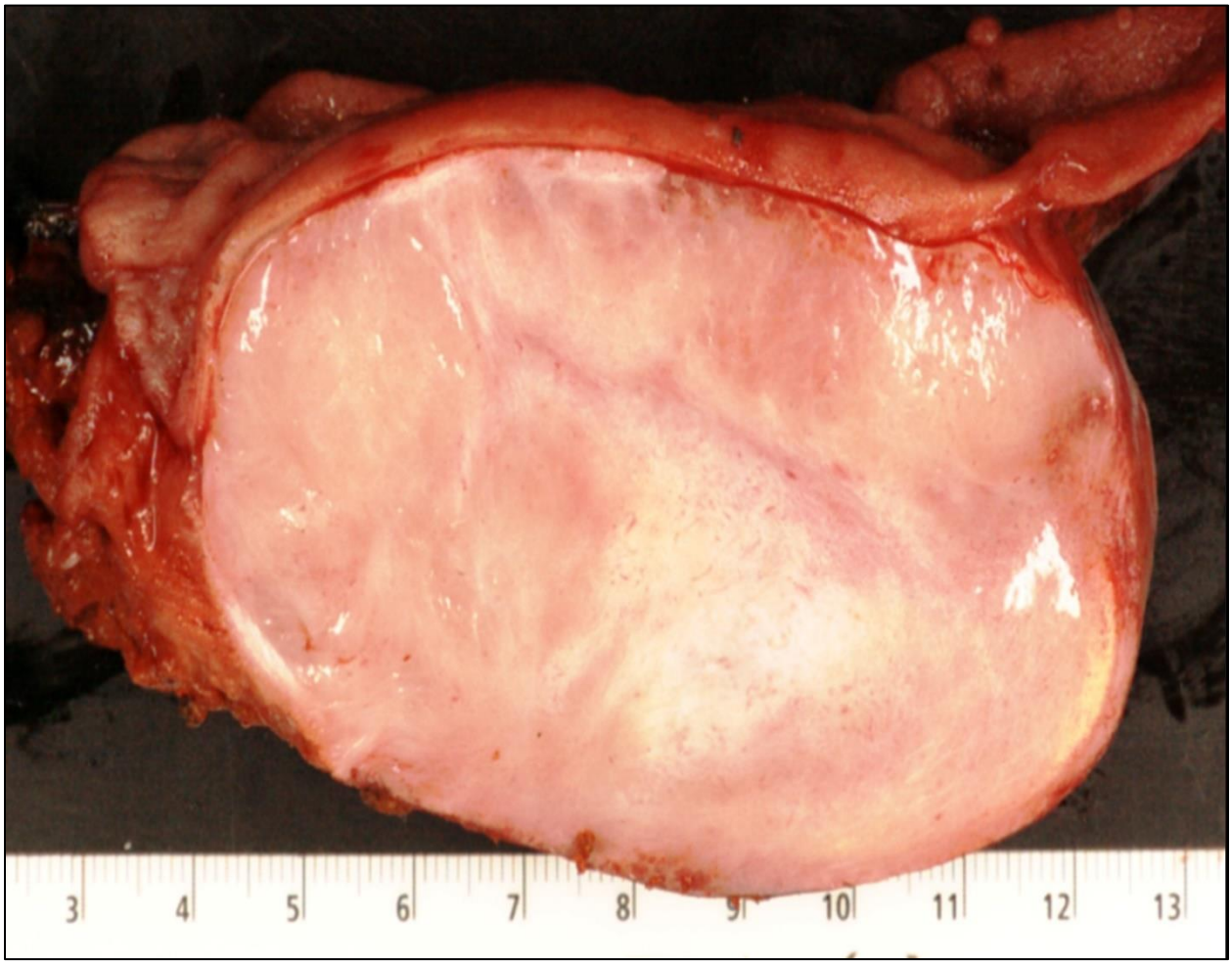
FIGURE 3



3A: FNA of submucosal lesion showing a few aggregates of cytologically bland spindle cells with myxoid background.

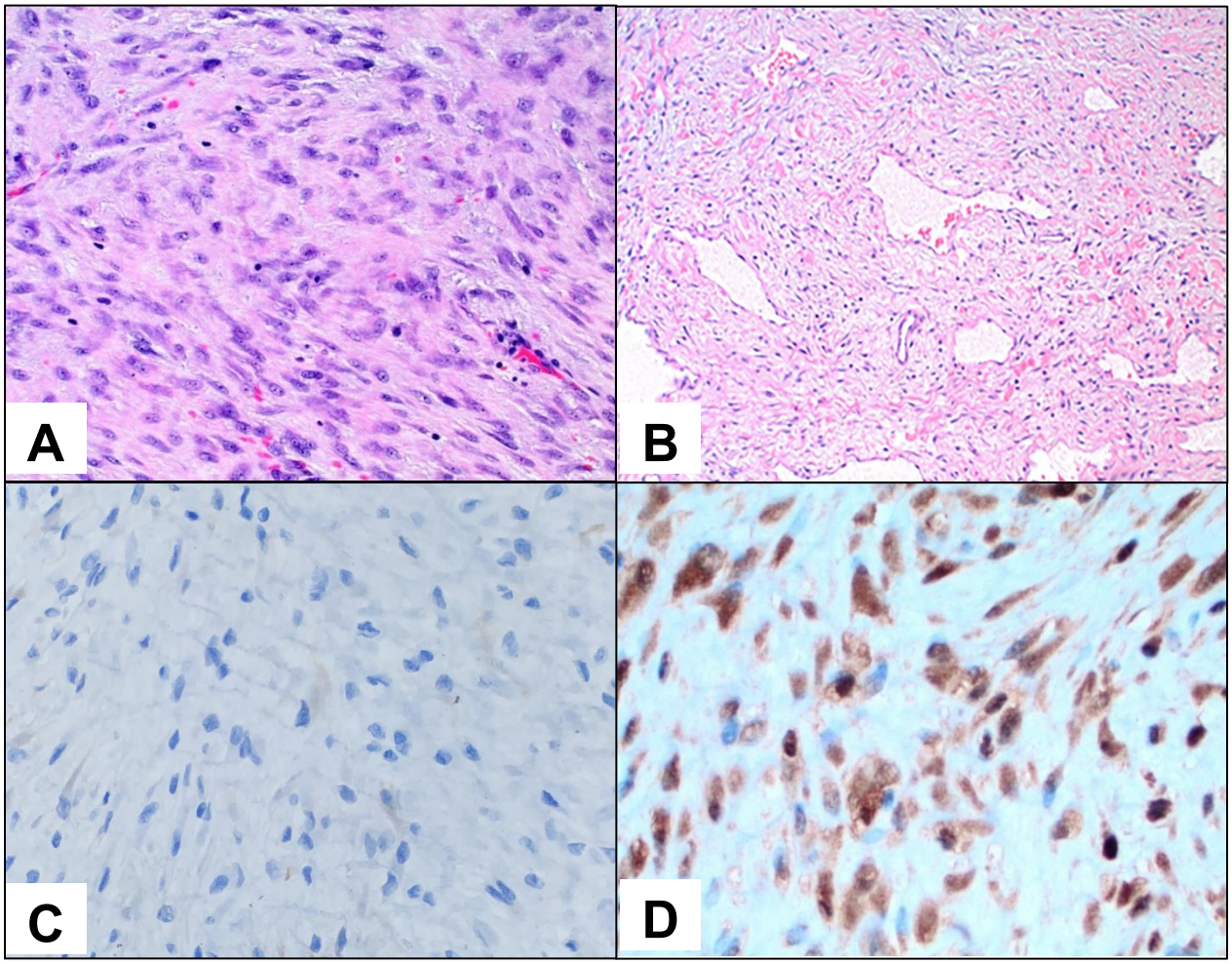
3B: Immunohistochemical stain for β-catenin shows strong and diffuse nuclear and cytoplasmic labeling in the tumor cells.

FIGURE 4.



Cross section of the resected gastric mass reveals a well-demarcated intramural heterogenous mass with discrete contours. The overlying mucosa (upper portion of the picture) and the serosal surface (lower portion of the picture) are both intact. Esophageal-gastric junction is on the left side of the picture.

FIGURE 5.



5A: High-power view of the central area of the lesion demonstrating a hypercellular storiform pattern of spindle cells with moderate nuclear pleomorphism and inconspicuous nucleoli.

5B: Intermediate-power of hypocellular area from the periphery of the mass demonstrating spindle cells in a myxoid background containing dilated blood vessels with a staghorn pattern.

5C: Immunohistochemical stain for CD117 is negative.

5D: Immunohistochemical stain for β-catenin shows cytoplasmic and strong nuclear labeling in the tumor cells.

What is the diagnosis?

A. Gastrointestinal stromal tumor (GIST)
B. Leiomyoma
C. Solitary fibrous tumor
D. Gastric desmoid fibromatosis
E. Inflammatory myofibroblastic tumor
F. Plexiform fibromyxoma

Answer: D. Gastric desmoid fibromatosis (DF)

Macroscopically, gastric DFs appear as large masses preferentially located either at the gastroesophageal junction or near the antrum. The cut surface shows a whorled, firm, tan-gray fibrous parenchyma without hemorrhage, necrosis, or cyst formation. They originate from the muscle layer, and usually infiltrate all layers of the stomach with occasional ulceration of the mucosa or extension into the adjacent organs.[1] However, occasionally, as in our case, DF may present as a well-circumscribed mass resembling a GIST.

Microscopically, DF usually demonstrates uniform, cytologically bland, spindle cells with long sweeping fascicles in a fibrotic background infiltrating into the adjacent tissues. Mitoses are rare and no necrosis is usually identified.

DF presenting as a discrete mass involving the GI tract is extremely rare, and due to its intramural location and occasionally expansile growth pattern within the bowel wall, may mimic a GIST.

The immunohistochemical profile of DF is characterized by diffuse nuclear labeling for β-catenin, and variable positivity for desmin and SMA. Dysregulation of the *WNT/beta-catenin* signaling pathway is identified in all tumors, and is due either to somatic activating mutations in the *CTNNB1* gene, or germline inactivating mutations in the adenomatous polyposis coli (APC) gene.[2] Approximately 85-95% of sporadic DFs are characterized by *CTNNB1* activating mutations in exon 3.[3] Abnormalities affecting the genes governing tissue repair have been suggested to be the underlying cause of DF development. It is assumed that DF develops when stimulating factors are added to these genetic abnormalities. Stimulating factors include: *APC* gene abnormalities such as familial adenomatous polyposis (FAP) and Gardner syndrome; mechanical stimulation such as laparotomy and abdominal injury, and changes in estrogen receptors during pregnancy and after delivery.[4]

The clinical behavior of DF is unpredictable; with the sporadic type DF reportedly having a relatively better prognosis than those associated with FAP. The mortality rate for all cases with intra-abdominal fibromatosis is approximately 30%, and spontaneous regression has been reported in abdominal wall lesions but rarely in intra-abdominal sites. Recurrence is usually associated with young age and larger tumor size**.**[2,4,5] The standard of care for DF is surgical resection with clear margins.

Choice A is incorrect.

Most mesenchymal tumors of the stomach belong to the category of GISTs. Smear preparations of spindle shaped GISTs (70% of GISTs) usually show large, hypercellular, irregularly-shaped cohesive aggregates of monomorphic cells with round to elongated tapering nuclei, fine chromatin distribution, inconspicuous nucleoli, and abundant pale cytoplasm with indistinct cell borders. However, a small percentage (2-5%) of GISTs may display marked nuclear pleomorphism making this diagnosis more challenging. Over 90% of GISTs are immunoreactive for CD117 and/or DOG-1. They are also commonly positive for CD34, show variable positivity for SMA, and less than 5% express S100. The great majority (90%) of GISTs have activating *KIT* mutations. Half of GISTs without *KIT* mutations are found to have gain of function mutations in the platelet-derived growth factor receptor alfa (*PDGFA*), and a smaller subset may be wild-type for both *KIT* and *PDGFA*, and may harbor *BRAF V600E* or more rare mutations such as SDHA/B/C/D, HRAS, NRAS, PI3KCA, or NF1 mutations.[6-8]

Choice B is incorrect.

Leiomyomas of the gastrointestinal tract are benign smooth muscle neoplasms arising from the muscularis mucosae or propria, commonly identified in the esophagus and large bowel, but rarely in the stomach. On smear preparations they consist of large, irregularly shaped fragments, usually less cellular than those of GISTs. These aggregates have ovoid nuclei with "cigar-shaped" blunted ends and fine chromatin distribution. Occasionally, nuclear atypia as seen in symplastic leiomyoma may be identified. Theneoplastic cells in leiomyomas are positive for SMA, and desmin and negative for S100, CD117, DOG-1, bcl2, β-catenin, and ALK.[8-10]

Choice C is incorrect.

Solitary Fibrous Tumors (SFTs) are very rare in the stomach.[11] On smear preparations, they present as fragments of dense fibrous stroma admixed with cellular aggregates of bland spindle cells with ovoid nuclei, smooth nuclear contours, fine chromatin distribution, and variable amount of cytoplasm. They are positive for CD34 and CD99, and show nuclear staining for bcl-2 and STAT6. This last immunostain is the most specific and sensitive marker for its diagnosis.[12] Molecular analysis of SFTs has identified a recurrent inversion of the long arm of chromosome 12 (12q13). The *NAB2-STAT6* fusion gene is a distinct molecular feature of SFT, present in up to 100 percent of cases, and may be used to confirm its diagnosis.[13-15]

Choice E is incorrect.

Inflammatory Myofibroblastic Tumors (IMTs) are mesenchymal neoplasms rarely reported in the stomach. They may recur locally but rarely metastasize. The cytology consists of a mixture of bland spindle cells and inflammation similar to those of inflammatory fibroid polyps. Immunostaining is positive for SMA and desmin in 90% and 60% of cases, respectively and

negative for CD117, DOG-1, CD34, S100, bcl-2, and β-catenin.[9] Approximately 60% of cases are also positive for anaplastic lymphoma kinase (*ALK*) by immunostaining which reflects an overexpression of *ALK* at the protein level due to a clonal rearrangement of *ALK* gene to a variety of fusion partners such as tropomyosin 3 or 4 (*TPM3/4,/ALK*), *CLTC*, and *RANBP2*.[16]

Choice F is incorrect.

Plexiform fibromyxomas (PFs) are rare mesenchymal tumors of the stomach composed of multiple nodules of spindle cells in myxoid stroma with a prominent capillary network, originating from the muscularis propria.[17] They almost always occur in the gastric antrum and histologically are composed of spindle cells in a myxoid background closely resembling myxoid GIST or a DF with a myxoid stroma. FNA and cell block show scattered particles of paucicellular mesenchymal tissue containing cytologically bland spindled cells in a myxoid background.[46] Immunohostochemically PF is characterized by expression of SMA and variable expression of CD10, while lacking expression for CD117 (KIT), DOG-1 , CD34, S-100, β-catenin, desmin and cytokeratins.[17,18] Recent studies have demonstrated that a subset (one-third) of PFs have activation of the *glioma-associated oncogene homologue 1 (GLI)* oncogene. This activation may occur via *MALAT1-GLI1* oncogenic fusion (24%), or *GLI1* amplification (8%). Both types of *GLI1* genomic alterations result in overexpression of GLI protein and activation of the hedgehog (Hh) signaling pathway.[19]

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