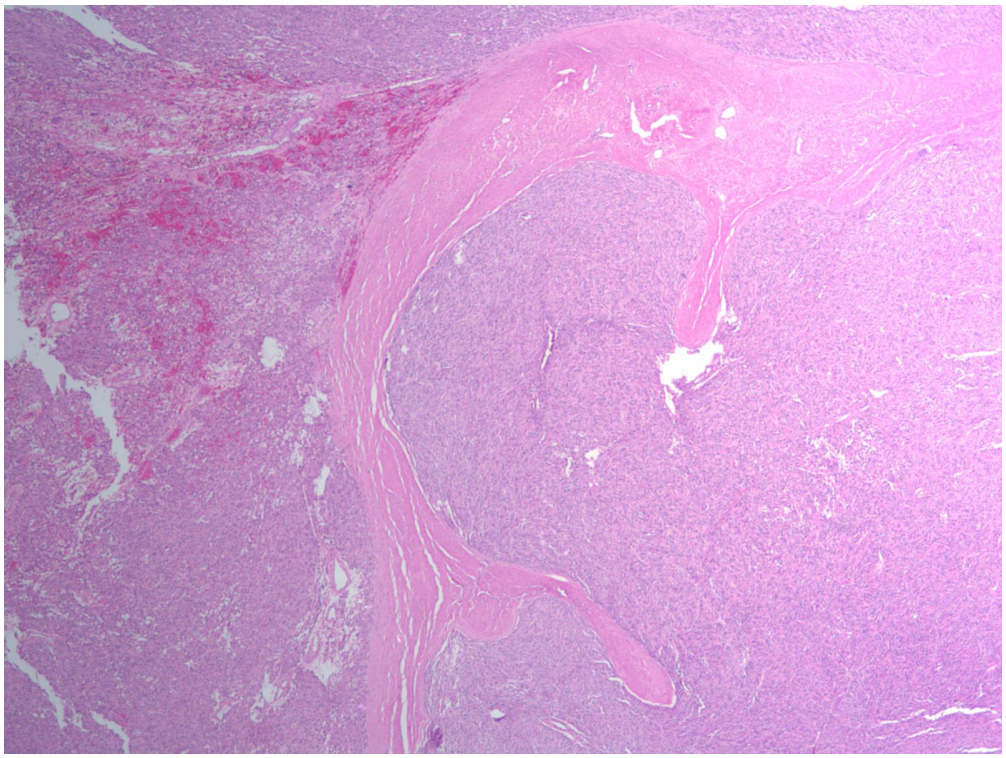
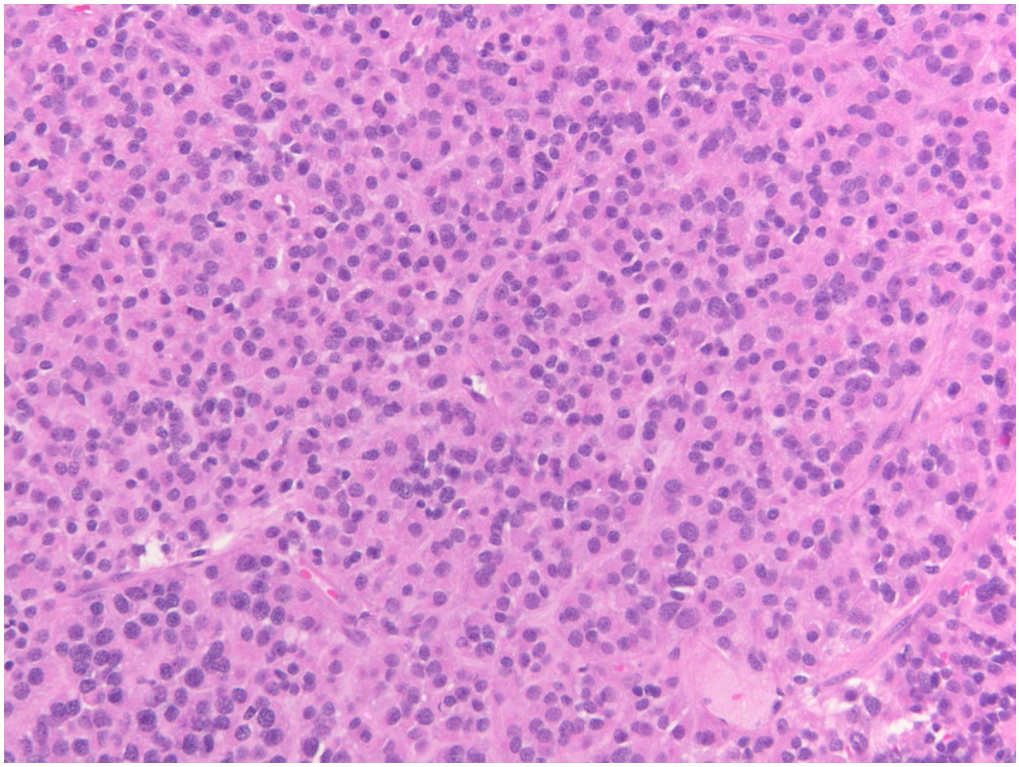
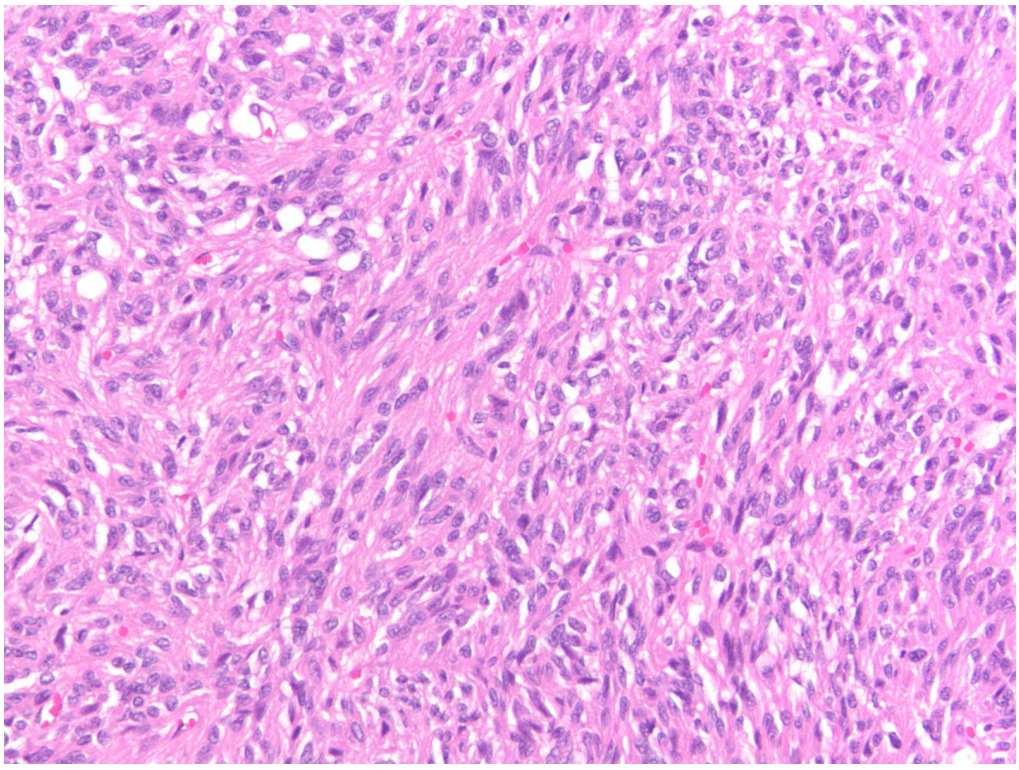
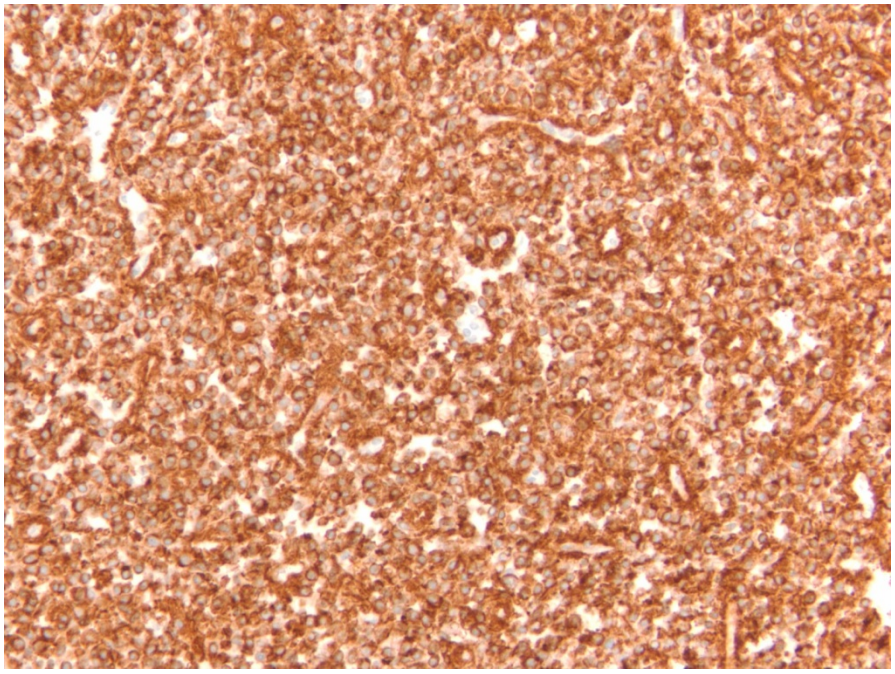
Case: The patient is a 24 year-old female who was found to have multiple mural nodules within the antrum. Solid and cystic components were noted on imaging. There is no significant past medical history. A subtotal gastrectomy was performed.

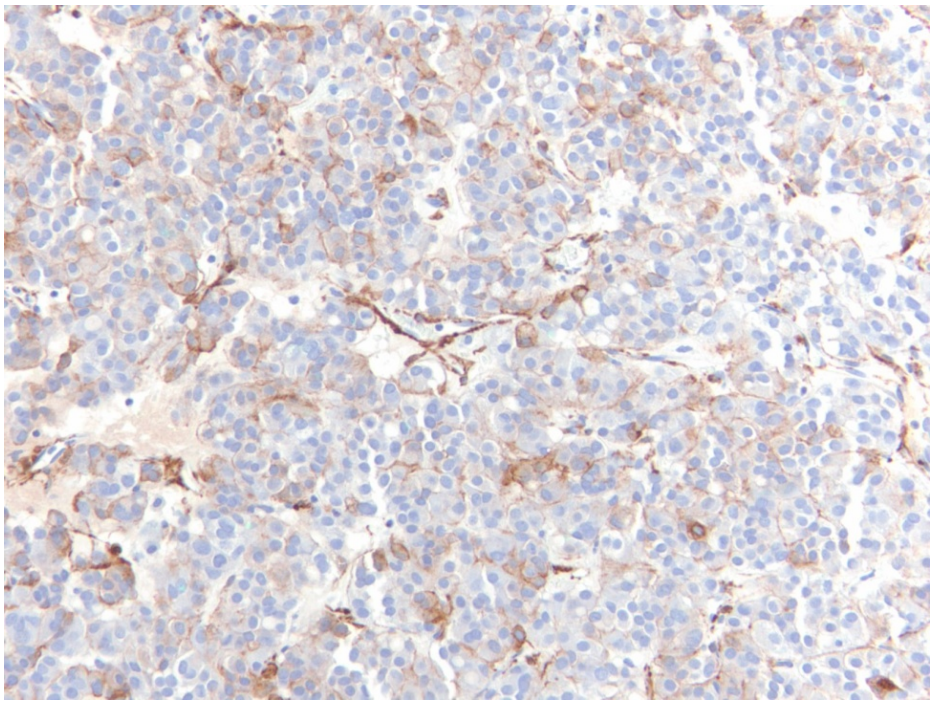




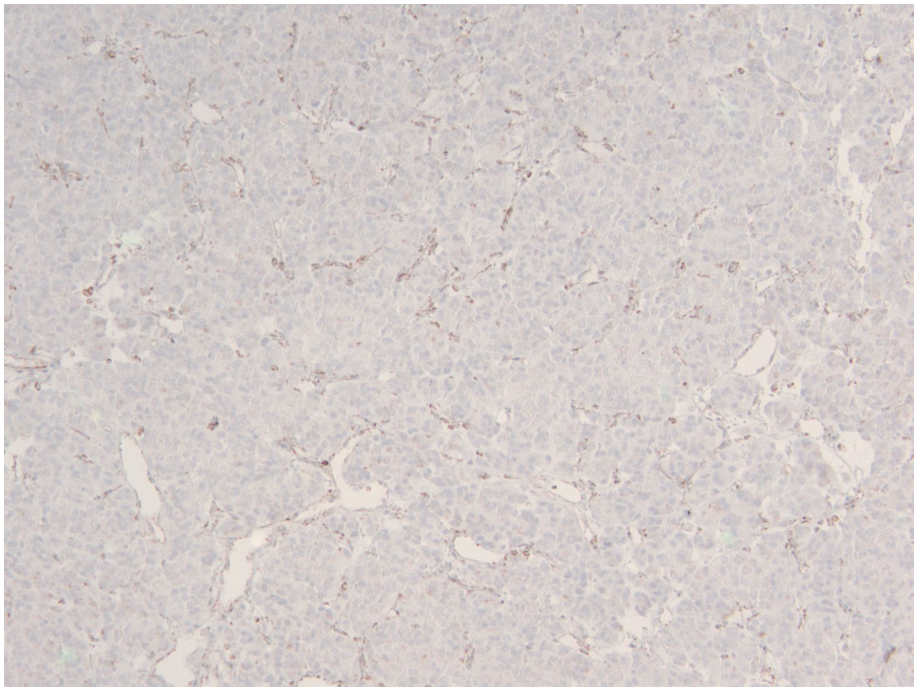




KIT



Smooth muscle actin



SDH-B protein immunostain

What is your diagnosis?

A. Leiomyoma
B. Glomus tumor
C. GIST
D. Schwannoma
E. Poorly differentiated carcinoma

Comment: The hematoxylin and eosin stained sections show a multinodular tumor located within the gastric wall that exhibits a plexiform growth pattern. The tumor is composed of sheets of predominantly epithelioid cells with minimal atypia and rare mitoses. Some nodules contain areas of hemorrhage and cystic degeneration. Foci suspicious for lymphovascular invasion were present. By immunohistochemistry, the tumor cells were strongly and diffusely positive for KIT and DOG-1, focally positive for cytokeratin AE1/AE3/CAM5.2, and smooth muscle actin; negative stains included S-100 and HMB45.

Choice A is incorrect. Although leiomyoma should be considered in the differential diagnosis of a gastrointestinal mesenchymal neoplasm, the multinodular configuration and prominent epithelioid cytomorphology, as well as the KIT/DOG-1 positivity, are not consistent with leiomyoma.

Choice B is incorrect. Glomus tumor is in the differential diagnosis of this lesion because of the multinodular architecture, epithelioid cytomorphology, and presence of focal SMA staining. However, these tumors are typically not multi-focal in distribution and do not stain with KIT/DOG-1.

Choice D is incorrect. Gastric schwannomas display uniform spindle cell morphology, prominent hyalinized vessels, and a characteristic peri-tumoral lymphoid "cuff"; they stain strongly for S-100 protein and are negative for KIT/DOG-1.

Choice E is incorrect. Carcinoma must be excluded in a tumor with epithelioid morphology and cytokeratin positivity. However, the bland cytologic features, areas of spindle cell morphology, and lack of mucosal involvement argue against carcinoma in this case.

The correct answer is C. SDH-deficient GISTs are a recently characterized subset of GISTs that occur predominantly in young women and exclusively involve the stomach, particularly the antrum. They are estimated to represent 8% of all gastric GISTs, lack KIT and PDGFR mutations and include those tumors associated with Carney-Stratakis syndrome and the Carney triad, as well as most "pediatric-type" GISTs. The SDH enzyme complex consists of four protein subunits: SDH-A, SDH-B, SDH-C, and SDH-D. Mutations in one or more of the corresponding genes are found in approximately 50-60% of all SDH-deficient GISTs, with SDH-A mutations being the most common. Patients with the Carney-Stratakis syndrome carry a germ line loss-of-function mutation in the SDH-B, SDH-C, or SDH-D genes. In contrast, SDH-deficient GISTs arising in patients with the Carney triad do not have SDH gene mutations, but do show loss of SDH-B expression by immunohistochemistry; the mechanism by which these tumors become SDH-deficient remains unknown. The SDH-B subunit protein is normally ubiquitously expressed in tissue with retained SDH function, and the loss of SDH-B expression by immunohistochemistry can be used as a marker of SDH deficiency.

Histologically, SDH-deficient GISTs are distinguished by their multinodular architecture, plexiform growth pattern, and epithelioid cytomorphology; they commonly present in a multifocal distribution. As mentioned above, these tumors lack KIT and PDGFRA mutations; however, by immunoshistochemistry the tumor cells usually demonstrate strong positivity for KIT and DOG-1. In contrast to conventional GISTs, lymph node metastasis is common in SDH-deficient GISTs, and treatment with imatinib typically results in a poor response. These are not necessarily negative prognostic features, however, as patients with these tumors generally follow an indolent clinical course.

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