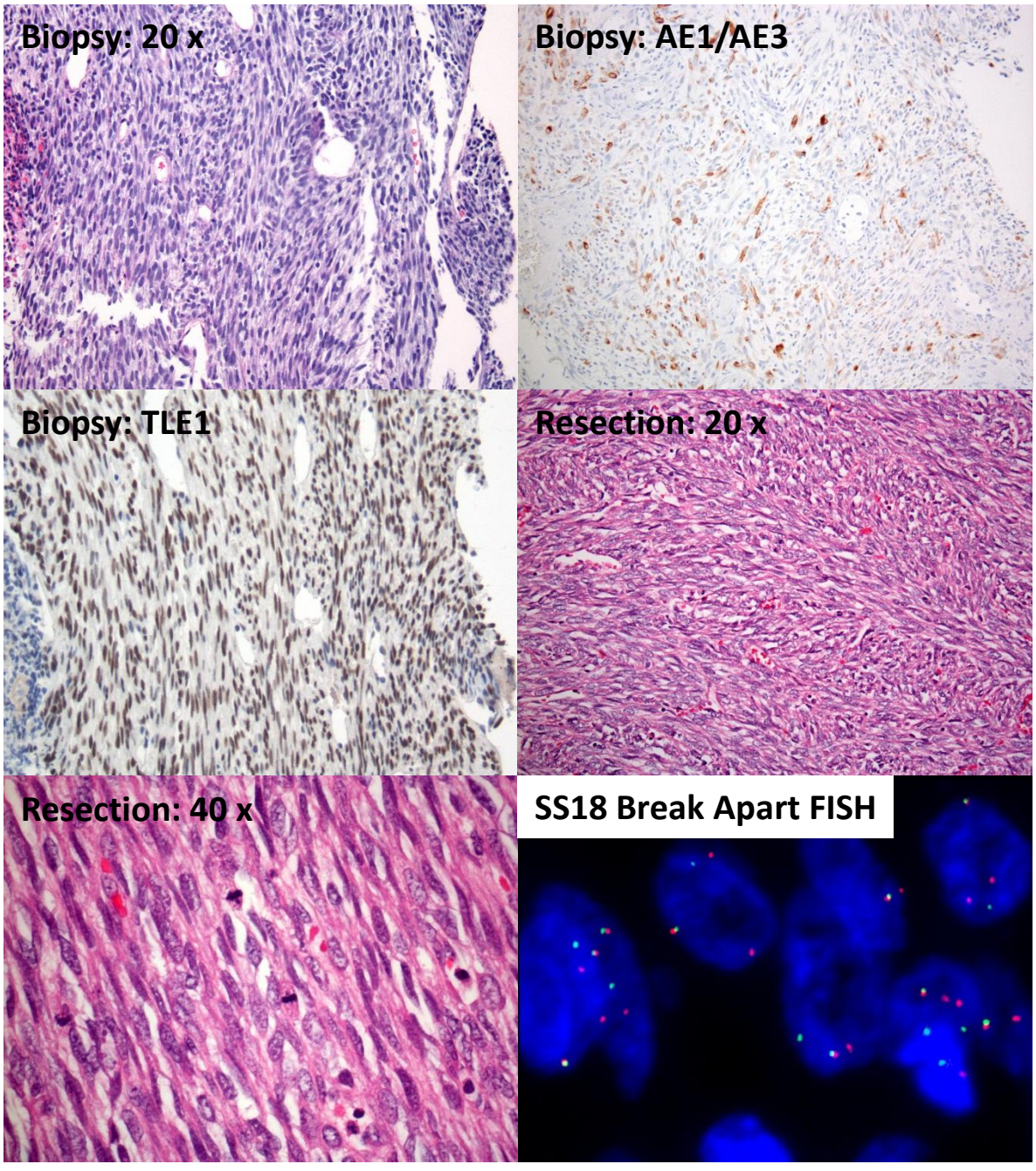
Case History

A 58 year-old male with past medical history of gastroesophageal reflux disease, long-standing (~30 years) alcohol abuse and smoking presented to emergency department after one day of coffee ground hematemesis and syncope. He also reported an episode of melena one day prior to the onset of hematemesis. He denied any abdominal pain, weight loss, or other recent illness. In the emergency department, he was found to be severely anemic (hemoglobin 3.8 g/dL). Upper endoscopy revealed a friable mass in the gastric body. A CT scan of the abdomen revealed a 6.1 x 5.9 cm heterogeneous, centrally necrotic circumscribed mass, arising from the proximal gastric body that was felt to be most consistent with a gastrointestinal stromal tumor (GIST). A partial gastrectomy was performed. The specimen contained a beige-gray ulcerated mass centered in the submucosa and measuring 6.3 x 5.9 x 5.6 cm. The tumor displayed hemorrhagic and necrotic cut surfaces. Representative H&E and immunohistochemical (IHC) stained images are shown below:



The following immuno-stains were negative: KIT, CD34, DOG1 and desmin. What is the diagnosis?

A. GIST

B. Leiomyosarcoma

C. Malignant peripheral nerve sheath tumor

D. Gastric synovial sarcoma

E. Carcinosarcoma

F. Clear cell sarcoma

(Answer and discussion on next page.)

Answer and discussion:

Gastric synovial sarcoma (choice D) is the correct answer. H&E sections showed intersecting fascicles of monotonous spindle cells with scant cytoplasm, round to oval nuclei, vesicular chromatin and abundant mitotic figures. The tumor cells were positive for TLE1 and vimentin, focally positive for AE1/AE3 and EMA, and negative for KIT, CD34, DOG1, SMA and desmin. Break-apart FISH showed positive rearrangement of SS18. The case was diagnosed as gastric synovial sarcoma.

Synovial sarcoma is a malignant mesenchymal neoplasm which accounts for about 5% to 10% of all soft tissue sarcomas. It occurs predominantly in young adults (15-40 years, mean age of 26 years at diagnosis) with a slight male preponderance (male:female 1.2:1). Synovial sarcoma was historically thought to originate from synovial lining, but later studies demonstrated that it does not show synovial differentiation. The cell lineage is presently unknown. Approximately 90% of synovial sarcomas occur in the extremities, and fewer than 5% occur in a joint or bursa. Synovial sarcoma has rarely been reported at many other sites, including head and neck, thoracic wall and cavity, abdomen and pelvis, male and female genitourinary tracts, gastrointestinal tract, bone and nervous system. To date, approximately 30 gastric synovial sarcomas have been reported in the English literature. The gastric body and fundus are the most common locations of gastric synovial sarcoma. Tumors located in the gastroesophageal junction, cardia, antrum and gastroduodenal junction have also been reported. The demographic features are similar to synovial sarcoma at other sites (median age of 45.5 years and a male:female ratio of 1.14). Patients usually present with epigastric pain, GI bleeding or anemia.

Grossly, synovial sarcomas are typically 3-10 cm in diameter, multinodular, non-capsulated, with relatively well-defined but infiltrative borders. The cut surface is usually pale brown to gray, varies from firm to soft and friable, with occasional cystic degenerative change, hemorrhage and necrosis. Synovial sarcomas display either a monophasic or biphasic pattern. The monophasic type is the most common, composed of hypercellular sheets or fascicles of uniform small spindle cells with scant cytoplasm, uniform ovoid overlapping nuclei, vesicular chromatin, and a high nuclear-to-cytoplasm ratio. The presence of hyalinized or wiry collagen bundles and focal calcification are also characteristic. Biphasic synovial sarcoma is comprised of intimately admixed spindle cells and epithelioid cells with round or ovoid vesicular nuclei, moderate amounts of amphophilic cytoplasm and distinct cell borders. Rare examples are poorly differentiated with polygonal cells that contain hyperchromatic nuclei and show more frequent mitoses and necrosis. Immunohistochemically, most of the gastric synovial sarcoma cases express CD56, Bcl-2, TLE1, vimentin and CD99. Most are also at least partially positive for EMA, AE1/AE3 and CK7. Fewer than half show expression of DOG1 and SMA, and <10% are positive for KIT and CD34. All reported cases that were molecularly analyzed showed rearrangement of SS18 (SYT) and were negative for KIT and PDGFRA mutations.

KIT-negative GIST, leiomyosarcoma, clear cell sarcoma, malignant peripheral nerve sheath tumor (MPNST) and sarcomatoid carcinoma are among the top differential diagnoses of gastric synovial sarcoma.

GISTs are the most common gastrointestinal mesenchymal tumor and usually occur in middle aged and elderly adults (median age around 60 years). The stomach is the most common site of GISTs, followed by the small intestine and colorectum. Morphologically, GISTs are classified as spindle cell type, epithelioid cell type and mixed type. Spindle cell GISTs are composed of variable cellular ill-defined fascicles of uniform elongated cells with eosinophilic cytoplasm, whereas epithelioid GISTs contain round cells with well-defined cell membranes and round nuclei. Gastric GISTs may show perinuclear vacuoles. Mitoses vary from very occasional to abundant, but are typically lower than that seen in gastric synovial sarcoma. Histologically, GISTs may be difficult to distinguish from gastric synovial sarcoma, but immunohistochemistry and molecular mutation analysis can be very helpful. The vast majority of GISTs are strongly positive for KIT and DOG1; they rarely show cytokeratin expression. Gastric synovial sarcomas are mostly KIT negative and TLE1 positive. DOG1 is negative in more than 70% of gastric synovial sarcoma cases. Most GISTs harbor KIT mutations, and a minority show platelet derived growth factor alpha (PDGFRA) mutation, BRAF mutation or succinate dehydrogenase deficiency; they are uniformly negative for SS18 rearrangement. Up to 5% of GISTs show low or negative expression of KIT (KIT-negative GISTs). Most of the KIT-negative GISTs are DOG-1 positive, about 72% of them harbor PDGFRA mutation and 12% have KIT mutation.

Primary leiomyosarcoma is a rare tumor in gastrointestinal tract that preferentially occurs in the colon and small intestine. Gastric leiomyosarcomas are extremely rare. Microscopically the tumors are composed mainly of spindle cells with eosinophilic cytoplasm and ovoid or elongated cigar-shaped nuclei with moderate to severe atypia. Necrosis is frequently present. Mitosis ranges from 20 to >100 per 50 HPFs. Immunohistochemically, majority of GI-leiomyosarcomas are positive for SMA and desmin, which are usually negative in gastric synovial sarcomas.

Gastric malignant peripheral nerve sheath tumor (MPNST) is very rare. Microscopically, most MPNSTs are composed of fascicles of spindle cells with buckled or wavy nuclei. Alternating cellularity with areas of myxoid stroma and perivascular accentuation are typical features of MPNST. Some cases may show fascicles of uniformly high cellularity with a fibrosarcoma-like growth pattern that mimics synovial sarcoma. Imunohistochemically, MPNSTs express focal or patchy S100 (about 50% of cases) and GFAP (30%-40% of cases), both of which are usually negative for gastric synovial sarcomas. EMA, CD99 and TLE1 are negative in MPNSTs.

Carcinosarcoma is a malignant tumor composed of both carcinomatous and sarcomatous components, which may morphologically mimic biphasic gastric synovial sarcoma. It is rare in the stomach. The gastric carcinosarcoma has been reported to occur in patients ranging from 29 to 80 years old (median age of 62 years). Grossly, most of the tumors are polypoid and frequently ulcerated, with a median size of 9 cm. Microscopically, the identification of the coexistence of carcinomatous and mesenchymal sarcomatous components is necessary for the diagnosis. The carcinoma component is commonly tubular or papillary adenocarcinoma, and the mesenchymal sarcomatous components are variable which may composed of leiomyosarcoma, rhabdomyosarcoma or osteosarcoma.

Clear cell sarcoma of gastrointestinal tract is a very rare malignant tumor that occurs predominantly in young adults (median age 35 years). The tumors usually arise in the wall of

small intestine, followed by stomach and large intestine, centered within the muscularis propria. Microscopically, clear cell sarcomas are usually composed of medium-sized primitive ovoid or epithelioid cells with pale or clear cytoplasm that are arranged in diffuse sheets, ill-defined nests or pseudopapillary arrangements. The nuclei of the tumors are centrally located with vesicular chromatin and small and inconspicuous nucleoli. Immunohistochemically, the tumors are positive for S-100 and negative for AE1/AE3, CD99, KIT, CD34, and melanocyte-specific markers (HMB-45, Melan-A and tyrosinase). Clear cell sarcoma usually harbors either EWSR1-CREB1or EWSR1-ATF1fusions.

References:

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