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A 42YO Caucasian female with a history of obesity, type 2 diabetes mellitus, gastroesophageal reflux, and chronic back pain presented with lightheadedness and shortness of breath of two-day duration.

Contributed by:

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Clinical History

A 42YO Caucasian female with a history of obesity, type 2 diabetes mellitus, gastroesophageal reflux, and chronic back pain presented with lightheadedness and shortness of breath of two-day duration. She had noted dark stools for several months. The patient took NSAIDs for her back pain but denied iron supplements or bright red blood per rectum. Her surgical history was remarkable for a hysterectomy eight years ago for cervical adenocarcinoma (endometrioid type). In the emergency room, a complete blood count revealed a hemoglobin of 4.9 g/dL. Computed tomography was negative for gastric abnormalities or evidence of lymphadenopathy or metastasis. Esophagogastroduodenoscopy revealed a large (at least 2.5 cm in size) polypoid gastric mass with a stalk in the fundus along the greater curvature. A biopsy was performed. Representative hematoxylin and eosin-stained sections and selected immunohistochemistry are provided in Figures 1-5.

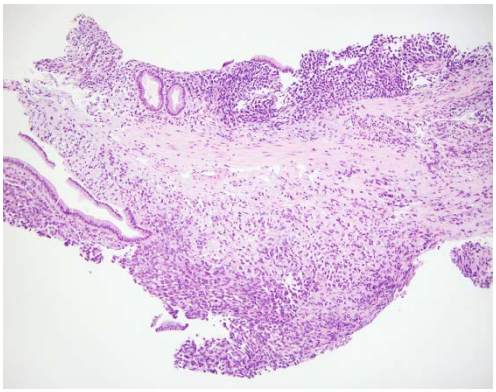


Figure 1: Representative field of the gastric mass biopsy
Hematoxylin and eosin; original magnification 100x.

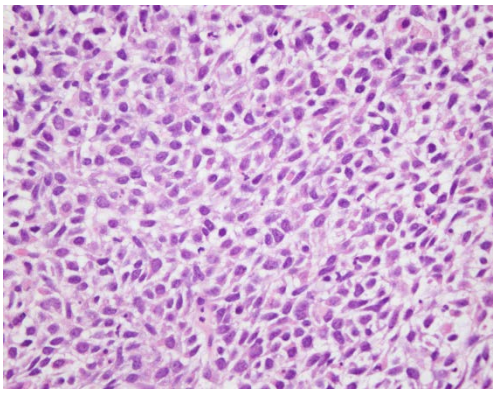


Figure 2: High power view of tumor cells from the gastric mass biopsy. Hematoxylin and eosin; original magnification 400x.

Figures 3-5: Immunohistochemistry of gastric mass biopsy. Original magnifications 200x.

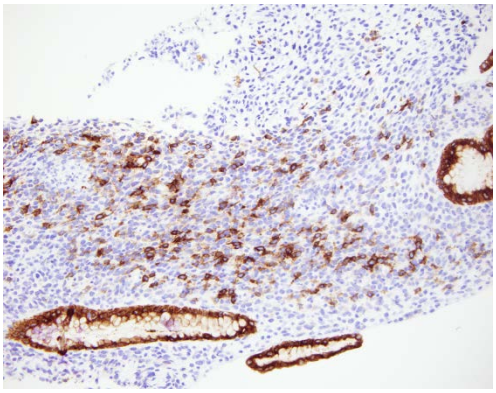


Figure 3 EMA.

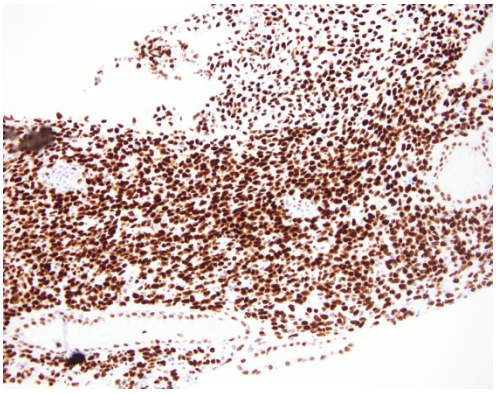


Figure 4 TLE1.

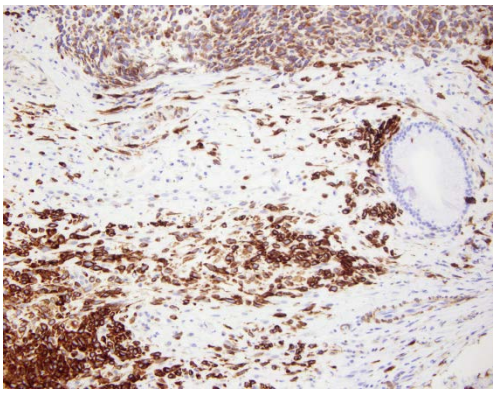


Figure 5 BCL2.

Cytokeratin cocktail was focally positive in the tumor cells and vimentin was diffusely and strongly positive.CD117, DOG1, S100, CD34, and CD45RB were all negative in the tumor cells with working controls.

After the final results of the biopsy were reported, the patient successfully completed three cycles of neoadjuvant doxorubicin and ifosfamide. A gastric wedge resection was performed. The gross appearance of the gastric tumor after neoadjuvant therapy is shown in Figures 6-7. The resection specimen showed good therapeutic response with negative margins. See Figure 8 for an hematoxylin and eosin-stained section of the residual tumor. The patient tolerated the procedure well and was discharged four days later. At one month of follow-up, the patient was recovering well.

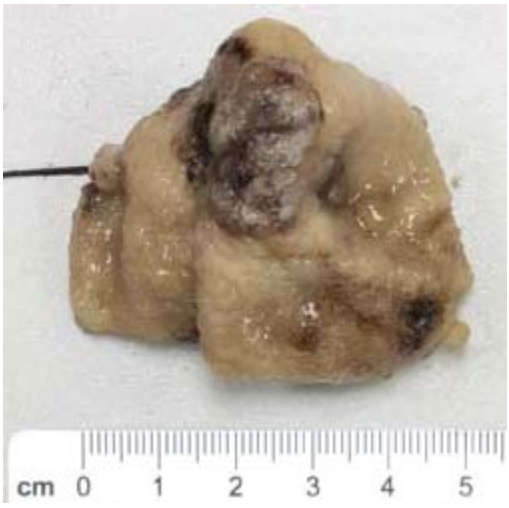
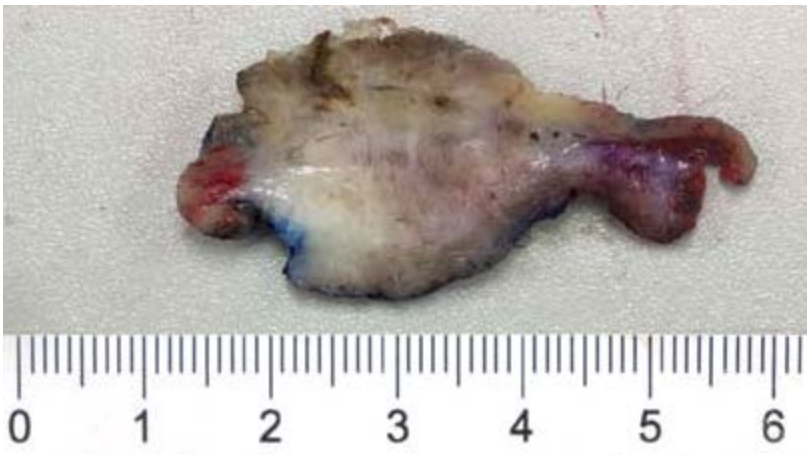


Figure 6: Gross appearance of mucosal surface of the gastric wedge resection

Figure 7: Transmural section (mucosal surface superior) of gastric tumor, which was grossly confined to the mucosal layer.



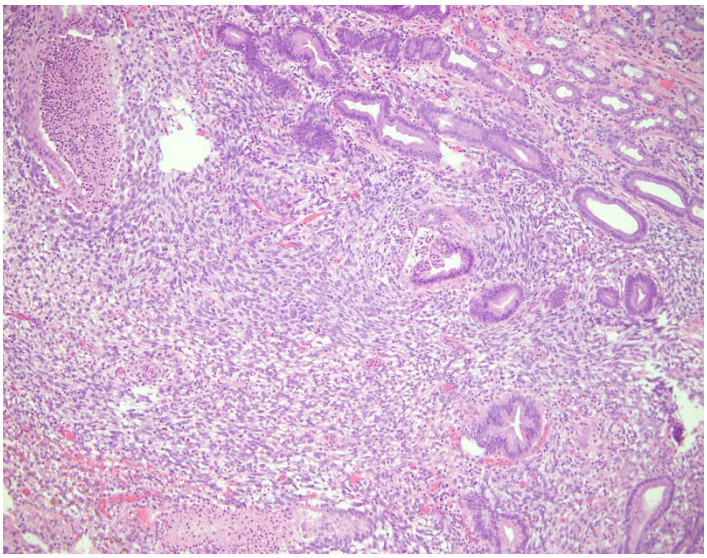


Figure 8: Hematoxylin and eosin-stained section of the residual tumor

Final diagnosis and Discussion

Monophasic Synovial Sarcoma

Discussion:

Synovial sarcoma was named as such due to early microscopic descriptions of this tumor and its common presentation in para-articular regions of the extremities. However, synovial sarcomas are significantly different from normal synovium, both immunophenotypically and ultrastructurally. Though 85-95% of synovial sarcomas are found in the extremities, they have also been reported in parts of the body far from the joints, including deep spaces in the head and neck, chest and abdominal wall, and

almost any visceral organ. The most common location is the lower extremity, the knee structures in particular. Less than 5% of cases directly involve joint structures including the synovium.

Synovial sarcoma accounts for 5% to 10% of all soft tissue sarcomas. Synovial sarcoma may arise in a patient of any age, but they are typically found in younger populations within the range of 15 to 40 years of age. Cases are roughly evenly distributed among males and females. No clear risk factors for the development of synovial sarcoma have been identified. These tumors have a generally slow growth and symptoms are dependent upon the location.

The typical appearance of synovial sarcoma on imaging is that of a round or oval lobular mass with or without septations. They are extraskeletal and usually do not widely involve the surrounding structures. Larger tumors of long duration are more likely to be poorly differentiated and locally destructive. The presence of tumoral calcification is an important clue for synovial sarcoma on imaging. Other sarcomas do not usually show calcifications, with the exception of extraskeletal osteosarcoma, which is seen in older patient populations.

The gross appearance of a synovial sarcoma is a well-circumscribed tumor with a smooth and glistening pseudocapsule. The tumor is adherent to the surrounding structures and cyst formation may be present. On cut section, synovial sarcomas are yellow to gray-white and calcification is not usually appreciable. More aggressive synovial sarcomas may appear variegated and friable with areas of necrosis and hemorrhage.

Microscopically, synovial sarcoma is classified into three subtypes based on the relative proportions of the epithelial and spindle cell components: biphasic, monophasic and poorly differentiated. The typical biphasic synovial sarcoma is composed of two cell types in close apposition: epithelial cells resembling carcinoma, and fibrosarcoma-like spindled cells. The epithelial cells are cuboidal or columnar with large, vesicular nuclei, abundant pale-staining cytoplasm, and well-defined cell borders. Architecturally, this component forms cords, nests, or glands. Glandular structures contain granular, eosinophilic secretions. Squamous metaplasia mimicking squamous cell carcinoma may be present. The spindled cells are uniform with dark-staining oval nuclei and scant, indistinct cytoplasm, forming compact sheets of cells. Features reminiscent of fibrosarcoma such as long, sweeping fascicles of spindled cells or a herringbone pattern are absent. Focal nuclear palisading as seen in nerve sheath tumors may be present. The mitotic count is typically low except in the poorly differentiated synovial sarcoma subtype. Areas of hyalinization, myxoid change, and calcification may be identified. The vasculature of these tumors is variable with some tumors resembling hemangiopericytoma. Tumoral inflammatory infiltrates are rare but the presence of mast cells is characteristic.

The monophasic subtypes have the same morphologic appearance as described for their respective component in the classical biphasic synovial sarcoma. Monophasic fibrous synovial sarcoma, consisting of sheets of spindled cells, is the most common subtype. Monophasic epithelial synovial sarcoma is rare and difficult to diagnose without cytogenetic or molecular testing. It is otherwise likely to be misdiagnosed as a carcinoma. Poorly differentiated synovial sarcoma is thought to be a progression of the other subtypes and is predictive of more aggressive tumors with a higher metastatic rate. Foci of

poorly differentiated morphology may be found in any of the other subtypes, necessitating thorough tumor sampling. This histologic appearance varies from high-grade epithelial areas with prominent nucleoli, high-grade spindle cells with a high mitotic rate, or a small round cell tumor appearance. There may be prominent vasculature with dilated, thin-walled blood vessels, again simulating hemangiopericytoma.

Most synovial sarcomas are at least focally positive for cytokeratins and EMA. These stains are expressed more highly in epithelial components and are more focal in monophasic fibrous synovial sarcoma. EMA is more sensitive than cytokeratins; the latter is more often negative in spindled components and poorly differentiated synovial sarcoma. Contrary to other spindled sarcomas, synovial sarcoma is often positive for CK7, CK19, and CK8/18 (CAM5.2) and negative for CD34. Two thirds of cases are positive for CD99 and all synovial sarcomas diffusely express BCL2, though these are nonspecific markers. TLE1 is diffusely and strongly positive in synovial sarcoma and has been reported to be highly specific for this diagnosis, however other authors have challenged the specificity of TLE1 for synovial sarcoma. About one third of cases are focally positive for S100, making malignant peripheral nerve sheath tumor a consideration in monophasic fibrous cases.

For difficult monophasic or poorly differentiated cases of synovial sarcoma, molecular testing can provide a definitive diagnosis. All synovial sarcomas possess a fusion between the SS18 (SYT) gene on chromosome 18 and a SSX gene found on the X chromosome. This translocation, t(X;18), can be reliably detected on formalin-fixed paraffin-embedded tissue by polymerase chain reaction or fluorescence in situ hybridization.

Synovial sarcoma responds to conventional chemotherapy in about half of cases. Radical local excision, often including removal of an entire muscle or extremity amputation, is recommended for synovial sarcoma. However, simple local excision and adjunctive radiation to avoid amputation is also acceptable. In either situation, synovial sarcoma recurs in less than 40% of cases. Recurrences usually develop within two years of treatment. About half of synovial sarcoma cases develop metastases, most commonly in the lung. Lymph node involvement is more common for synovial sarcoma than other sarcomas. The overall 5-year survival rate for synovial sarcoma is about 70%; however, the prognosis is worse for cases with metastases. Positive prognostic factors include young patient age (15 years or less), distal extremity location, tumor size smaller than 5 cm, and low tumor stage. Cases with extensive calcification seem to have a better prognosis. Tumors with poorly differentiated areas are more likely to metastasize. Emerging treatment options for synovial sarcoma include BCL2 blockers and EGFR inhibitors.[1, 2]

Rarely, synovial sarcomas have been reported in the luminal gastrointestinal tract. The esophagus and stomach are more common sites, but these tumors have also been reported in the duodenum, ileum, large intestine, rectum, and also in the liver. Sarcomas of the esophagus are exceedingly rare, but leiomyosarcoma warrants exclusion in this location. For the stomach, both leiomyosarcoma and gastrointestinal stromal tumor are in the differential diagnosis of synovial sarcoma cases. Cytokeratin expression and negativity for CD117 and DOG1 are helpful in this regard. The most common endoscopic

and gross description of gastrointestinal synovial sarcoma is a submucosal polypoid mass with a luminal component.

In 2000, Billings et al[3] reported two cases which were the first described primary synovial sarcoma in the gastroesophageal junction and stomach, respectively. This was also the first demonstration of t(X;18) by FISH in synovial sarcoma arising in the gastrointestinal tract. Later Makhlouf et al[4] reported a series of 10 synovial sarcomas of the stomach. The mean and median age for the group was 52 years. In this study, all recurrences or disease-related deaths involved tumors that either were larger than 3 cm or contained a poorly differentiated component. More recently, Romeo et al[5] reported clinicopathological features for 15 cases of primary synovial sarcoma of the digestive system. The age range was 17 to 61 years and the median age was 44 years. All cases were confirmed with the presence of the X;18 translocation. Interestingly, one case was positive for DOG1, highlighting the need for molecular testing to discriminate some synovial sarcomas of the stomach from KIT-negative gastrointestinal stromal tumors.

An important entity in the differential diagnosis of biphasic synovial sarcoma of the stomach is gastroblastoma. This gastric tumor also consists of a combination of an epithelial and a mesenchymal component. However, in gastroblastomas, neither component shows enough atypia to warrant a diagnosis of carcinoma or sarcoma, respectively. While the morphologic and immunohistochemical findings may be similar between synovial sarcoma and gastroblastoma, the X;18 translocation has not been reported in the latter.[6]

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