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CASE REPORT

Diffuse, Aggressive Metastatic Progression after Minimally Invasive Local Resection of Primary Gastric Synovial Sarcoma: a Case Report and Systematic Review of the Literature

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Introduction

Synovial sarcoma is a malignant mesenchymal neoplasm accounting for about 5 to 10% of all soft tissue sarcomas. It occurs predominantly in young adults (15–40 years) with a slight male preponderance (male/female 1.2:1) [1, 2]. Synovial sarcoma was historically thought to originate from synovial lining, but later studies have found that synovial differentiation is lacking [2], and cell lineage remains unknown. Approximately 90% of synovial sarcomas occur in the extremities, and fewer than 5% occur in a joint or bursa. Rarely, they have been reported in other sites, including head and neck, thoracic wall and cavity, abdomen and pelvis, male and female genitourinary tracts, gastrointestinal tract, bone, and nervous system [1, 2].

Synovial sarcoma of the stomach is extremely rare with only less than 30 cases reported in the literature. The diagnosis of this spindle cell tumor hinges on identification of the t(X;18)(p11.2;q11.2) translocation, which results in *SS18-SSX1*, *SS18-SSX2*, or *SS18-SSX4* gene fusion [1]. Here, we discuss an unusual case of primary synovial sarcoma arising from the gastric wall of a 58-year-old man, the consequences of starting treatment prior to proper diagnosis, and systematic review of all previously reported cases.

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Case Report

A 58-year-old male with a past medical history of gastroesophageal reflux disease, cigarette smoking, long-standing daily alcohol use, diabetes mellitus, and hypertension presented to emergency department with altered mental status. He reported several episodes of coffee ground emesis, a 2-week history of dark stools, and an episode of syncope. His initial lab work revealed a very low hemoglobin level. He was acutely treated with transfusion of packed red blood cells and IV pantoprazole to which he responded. Endoscopy was performed the next morning and revealed a 4 cm endophytic friable mass in the gastric body, which was identified as the likely source of bleeding and was biopsied (Fig. 1). A CT scan of the chest, abdomen, and pelvis with per oral and IV contrast shortly after showed a 6 cm necrotic mass arising from the stomach along with a 1.4 cm enlarged lymph node in the gastrohepatic ligament (Fig. 2) and no other sites of disease.

The endoscopic biopsy revealed a malignant spindle cell neoplasm, diffusely positive for TLE1 and focally positive for AE1/AE3 and EMA immunostains, with negative stains for KIT, DOG1, S-100, CD34, and desmin (Fig. 3). A preliminary diagnosis of malignant spindle cell lesion was clinically rendered as gastrointestinal stromal tumor (GIST) to be the most likely diagnosis, and the patient was taken for a robotic-assisted, laparoscopic, wedge resection prior to the final biopsy diagnosis due to continued bleeding. Of note, during the case, the mass was not placed into a bag for retrieval and was taken out through a widened umbilical incision.

The resected surgical specimen showed a beige-gray ulcerated mass centered in the submucosa, which measured 6.3 × 5.9 × 5.6 cm and displayed a hemorrhagic and necrotic cut surface. The tumor was composed of intersecting fascicles of monotonous spindle cells with scant cytoplasm, round to oval nuclei, vesicular chromatin, and abundant mitotic figures

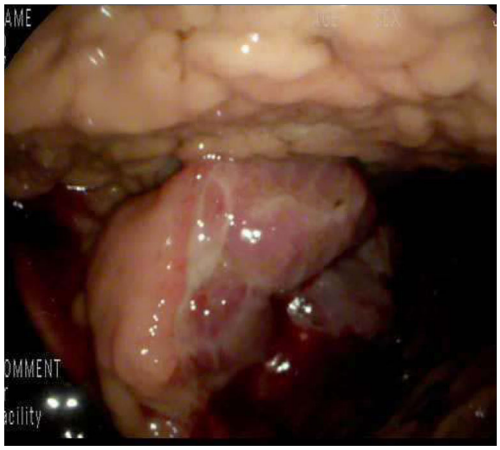

Fig. 1 Endoscopic photograph of gastric synovial sarcoma

(33/10 high-power field) (Fig. 4), with 10% tumor necrosis present. Florescence in situ hybridization (FISH) analysis was positive for *SS18* (a.k.a. *SYT*) rearrangement present on chromosome 18q11.2 in 90% of the cells tested (Fig. 5). A diagnosis of grade 3 gastric monophasic synovial sarcoma was made. All margins were negative, and there was no evidence of lymphovascular invasion.

This case was reviewed at our multidisciplinary tumor board (MDTB), where it was suggested that a lymph node dissection to clear the enlarged gastrohepatic lymph node seen on imaging (Fig. 2) should be performed prior to the initiation of chemotherapy. The patient was scheduled for a lymph node dissection approximately 2.5 months after his initial surgery, but presented the day prior to his elective date of surgery with complaints of abdominal pain. A repeat CT scan of the abdomen and pelvis revealed marked progression of abdominal disease, including peritoneal metastasis localized mainly in the upper abdomen and anterior abdominal wall and new masses in the stomach, lesser sac, right colon, segment 8 of the liver, and liver capsular surface segment 7/8 (Fig. 6). A CT-guided biopsy was performed on the abdominal wall tumor which was consistent with synovial sarcoma. In light of the disease progression, surgery was canceled and he is scheduled to receive an ifosfamide-based chemotherapy regimen.

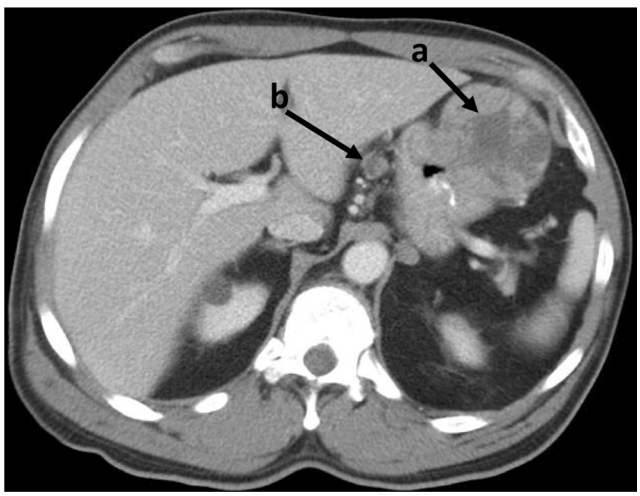

Fig. 2 Pre-surgery CT (*a* primary tumor in body of stomach; *b* enlarged, necrotic perigastric lymph node)

Literature Review and Discussion

To date, less than 30 primary gastric synovial sarcoma cases have been reported [3–13]. The first two gastric synovial sarcoma cases were reported by Billings et al. in 2000 [3]. Gastric synovial sarcoma occurs mostly in middle-aged patients with a median age of 45 years (range 21 to 68 years) (Table 1). Similar to synovial sarcoma at other sites, it has a slight male predominance, with a male/female ratio of 1.14:1. The median age of male and female patients is 42 (range 21 to 62 years) and 52 (range from 35 to 68 years) years, respectively. Patients usually present with epigastric pain, gastrointestinal bleeding, or anemia.

The gastric body and fundus are the most common locations for gastric synovial sarcoma [3–13]. Tumors located in the gastroesophageal junction, cardia, antrum, and gastroduodenal junction have also been reported. Grossly, gastric synovial sarcomas are usually white-grayish/tan-grayish polypoid masses ranging from 0.8 to 16 cm (median 5.2 cm) in size (Table 1). Ulceration, necrosis, and hemorrhage are frequently identified. Most tumors are centered in the submucosa and/or muscularis propria. About 20% of the tumors involved serosa or extended to the peritoneum, omentum, or pancreas.

Morphologically, gastric synovial sarcomas display either a monophasic or biphasic pattern, similar to that of synovial sarcoma at other sites [1–13]. The monophasic type is most common and accounts for 24 (80%) of the 30 reported cases (Table 1). Five (17%) of the cases were reported as biphasic type, and only one (3%) case was reported as poorly differentiated. The monophasic type is composed of hypercellular sheets or fascicles of uniform small spindle cells with scant cytoplasm, ovoid overlapping nuclei, vesicular chromatin, and a high nuclear-to-cytoplasm ratio [1–13]. The presence of hyalinized or wiry collagen bundles and focal calcification are also characteristic. The biphasic type of 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, forming nests or cords and glands [1–13]. Rare examples are poorly differentiated with polygonal cells that contain hyperchromatic nuclei and show more frequent mitoses and necrosis. At least 63% of all the 30 cases had a mitotic rate of 10 per 10 high-power-field or higher.

Immunohistochemically, most of the gastric synovial sarcoma cases express TLE1, CD56, Bcl-2, vimentin, and CD99 (Table 2). Most cases are also at least partially positive for

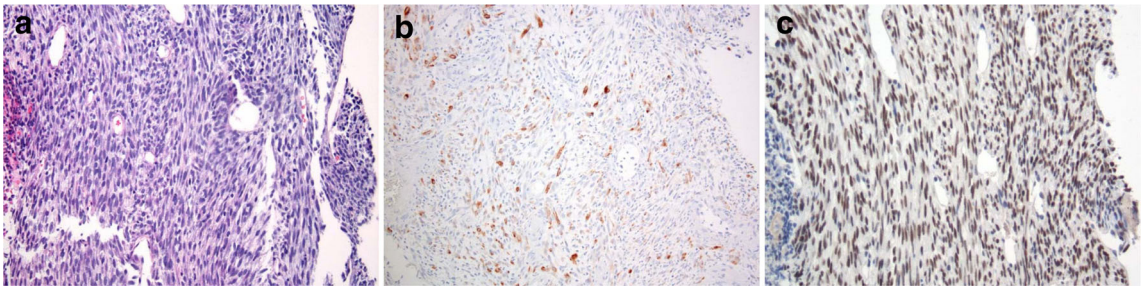

Fig. 3 Biopsy of gastric synovial sarcoma. **a** Tumor is composed of intersecting fascicles of monotonous spindle cells (H&E, ×20). **b**, **c** Tumor cells are partially positive for AE1/AE3 (**b**) and positive for TLE1 (**c**) stains

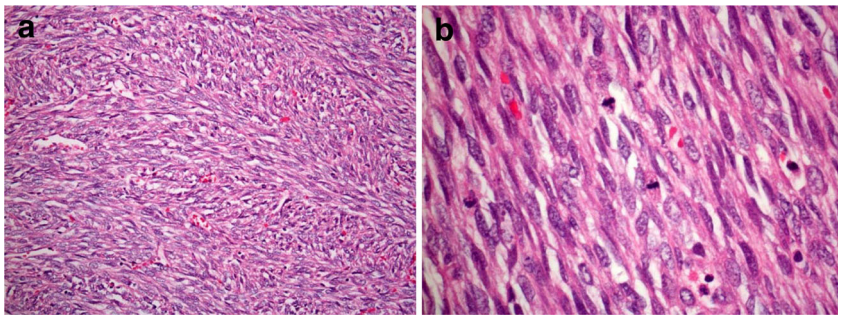

Fig. 4 H&E-stained sections from the resected tumor demonstrate monotonous spindle tumor cells with round to oval nuclei and abundant mitotic figures (**a** ×20, **b** ×40)

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.

GIST is the most important entity in the differential diagnosis of synovial sarcoma. GIST is the most common gastrointestinal mesenchymal tumor, display extensive morphologic overlap with synovial sarcoma, and are managed differently; thus, the distinction is critical. GISTs usually occur in middle aged and elderly adults (median age around 60 years) [14]. The stomach is the most common site for GISTs, followed by the small intestine and colorectum. GISTs also display both spindle cell and epithelioid morphology. Immunohistochemistry and molecular mutation analysis are usually definitive. The vast majority of GISTs are strongly positive for KIT and DOG1; they rarely show cytokeratin expression [14, 15]. Gastric synovial sarcomas are mostly KIT negative and TLE1 positive, and DOG1 is negative in more than 70% of gastric synovial sarcoma cases (Table 2). Most GISTs harbor *KIT* mutation, and a minority show *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 16% have *KIT* mutation [15].

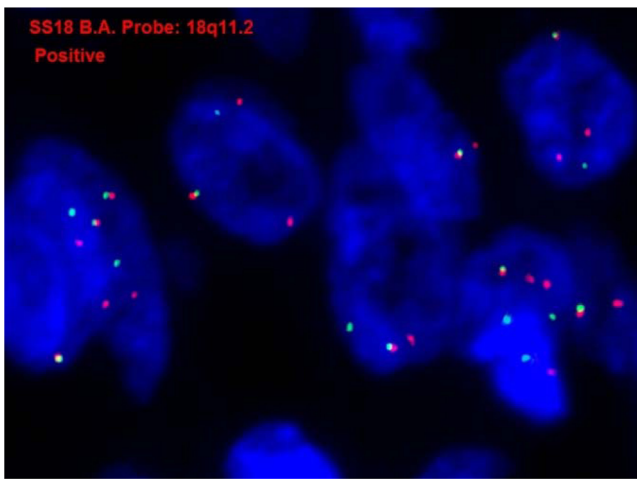

Fig. 5 FISH analysis with breakapart *SS18* DNA probe shows separated red and green signals indicating tumor cells with SS18 rearrangement

Other considerations in the differential diagnosis of gastric synovial sarcoma include primary leiomyosarcoma and carcinosarcoma. Primary leiomyosarcoma is a rare tumor in gastrointestinal tract that preferentially occurs in the colon and small intestine and rarely in the stomach. These tumors display severe atypia, necrosis, and up to >100 mitoses per 50 high-power field [16]. They are immunohistochemically positive for SMA and desmin, which are usually negative in gastric synovial sarcomas. Carcinosarcoma is a malignant tumor composed of both carcinomatous and sarcomatous components, and while rarely found in the stomach, morphologically may mimic biphasic gastric synovial sarcoma. Gastric carcinosarcoma has been reported to occur in patients ranging from 29 to 80 years old (median age of 62 years) [17]. The

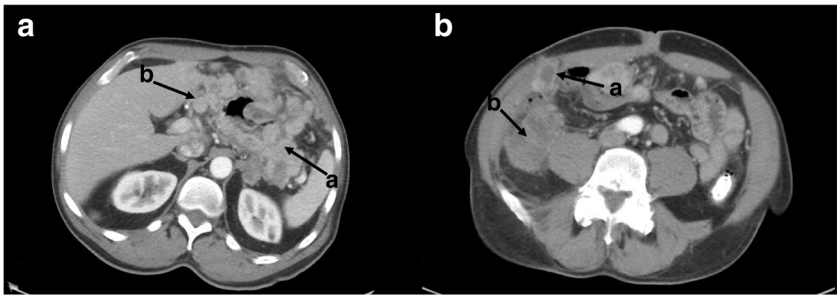

Fig. 6 Follow-up CT. **a** Diffuse metastasis around area of tumor excision in upper abdomen (*a* recurrent tumor in body of stomach; *b* enlarged, necrotic perigastric lymph node). **b** Port site metastasis (*a*) and ascending colon metastasis (*b*)

carcinoma component is commonly tubular or papillary adenocarcinoma, and the mesenchymal sarcomatous components are variable which may composed of leiomyosarcoma, rhabdomyosarcoma, or osteosarcoma.

The clinical outcomes of reported gastric synovial sarcoma cases are poor. Eight (27%) of the 30 reported cases had metastasis on diagnosis or after surgery (Table 1). The most common sites of metastasis were liver (six cases), peritoneum/omentum (four cases), and lung (one case). Twenty-four of the cases had been reported with clinical follow-up (median 23 months), with only 12 (50%) alive without disease. Six (25%) of the patients died of the disease, and six (25%) were alive with recurrence or metastasis. Our case demonstrates the highly malignant potential of this cancer, as we saw the patient go from a stage T2 N1 M0 upon presentation to a stage IV cancer with peritoneal carcinomatosis in only 11 weeks after tumor disruption. The pattern of spread was consistent with both tumor seeding along the area of resection of the tumor and removal through an abdominal port site as well as distant hematogenous spread to the liver, indicative of the highly aggressive nature of this tumor.

The literature for abdominal synovial sarcoma is lacking in evidence for dealing with regional lymph nodes. Current standard of care for treatment of regional lymph node metastasis (RLNM) in soft tissue sarcomas (STSs) of the extremities is lymphadenectomy, as it has been shown to be associated with an increase in median overall survival and 5-year survival rate [18]. Most of this evidence comes from retrospective studies on STS of different subtypes of the extremities, namely rhabdomyosarcoma, clear-cell sarcoma, epithelioid sarcoma, all which tend to have a slightly higher rate of lymph node spread than synovial sarcoma [19]. Wide local excision of lymph nodes with or without radiation and chemotherapy is recommended, as lymph node metastasis is also proven to be an independent, poor prognostic factor [20]. While there is no published literature on the specific treatment of primary gastric synovial sarcoma with RLNM, in practice, recommendations for STSs of the extremities, including synovial sarcoma are generally extrapolated from the aforementioned studies on extremity STSs. This particular patient had a suspicious perigastric node identified on pre-operative imaging, and a lymphadenectomy with the initial R0 resection should have been performed in the initial operation.

This case highlights the importance of diagnosis and surgical approach to resection with abdominal synovial sarcoma. While awaiting for the final pathologic result may not always be feasible, in this case, the pre-operative CT scan showing an enlarged lymph node as well as the need for further immunohistochemical staining for definitive diagnosis should alert physicians that this tumor may harbor a more uncommon diagnosis. While there are rare reports of lymph node metastasis from GIST [21], in general, this is not a common finding and other diagnoses should have been considered. Awaiting the final pathologic report and review at MDTB will likely have resulted in a different surgical management strategy, including lymph node dissection as well as extreme caution in handling of the tumor to minimize tumor seeding. Two considerations when considering laparoscopic/robotic procedures for cancer operations are safety and oncologic integrity. While there have been multiple studies on minimally invasive techniques for gastric cancer mostly performed in Asia where the gastric cancer incidence is significantly higher, at this time, only solid conclusions can be drawn for early stage I–II (T1 N0, T1 N1 or T2(MP)~T3(SS)N0) distal gastric cancers as having no reduction in curability after minimally invasive surgery [22]. It can be assumed that these studies do not include rare cancers of the stomach and therefore are not applicable. Given that sarcomas generally only require negative margins without need for prophylactic lymph node dissection, it is tempting to use a less invasive approach for synovial sarcoma. However, as demonstrated in this case, these tumors can be biologically aggressive, and extra care should be taken to avoid spillage both macroscopically and microscopically. It should be stressed that once the diagnosis of synovial sarcoma is made, then an open surgical approach should be considered.

Conclusions

Primary gastric synovial sarcoma is a rare disease with little known about its pattern of progression. We describe a case where synovial sarcoma demonstrated aggressive local and distant metastatic behavior. It is not unreasonable to fall prey

Table 1 Clinicopathological features of 30 reported gastric synovial sarcomas

Case no.	Reference	Site	Size (cm)	Morphology	Mitosis (per 10 HPF)	Gender	Age (years)	Clinical presentation	Surgery	Chemotherapy	Follow-up (months)	Metastasis
1	Billings et al., 2000 [3]	Gastroesophageal junction	5.2	Biphasic	1	M	47	Peptic ulcer disease and pyloric tenosis	Completion gastrectomy, partial esophagectomy	No	ADF (21)	No
2	Billings et al., 2000 [3]	Distal stomach	16	Biphasic	9	F	55	Abdominal swelling, abdominal pain, nousea/vomiting, rectal bleeding	Hemigastrectomy, retrocolic Billroth II procedure	N/A	DOD (6)	Liver (at diagnosis)
3	Akhunji et al., 2007 [4]	Posterior gastric wall	11.5	Biphasic	~100	M	42	Epigastric abdominal pain	Resection of the mass	Yes	DOD (24)	Mesenteric, peritoneal (after 3 months)
4	Makhlouf et al., 2008 [5]	Body-antrum junction	0.8	Monophasic	0 to >50 including 4 cases with >15	F	67	Upper gastrointestinal bleeding (4 patients), dysphagia and abdominal mass (1 patient), dysphagia and gastric ulcer symptoms (1 patient), nausea and vomiting (1 patient)	Partial gastrectomy	No	ADF (12)	N/A
5	Makhlouf et al., 2008 [5]	Body	2	Monophasic, with poor differentiated component		M	49		Segmental/wedge resection	No	DOD (29)	Omental (after 13 months)
6	Makhlouf et al., 2008 [5]	Body	2	Monophasic		F	68		Wedge resection	No	ADF (22)	N/A
7	Makhlouf et al., 2008 [5]	Body	2.8	Monophasic		M	29		Partial gastrectomy	No	ADF (224)	N/A
8	Makhlouf et al., 2008 [5]	Antrum, gastroduodenal junction	3	Monophasic		F	54		Antrectomy/gastroduodenal resection	No	N/A	N/A
9	Makhlouf et al., 2008 [5]	Lesser curvature/body	3	Monophasic		F	58		Wedge resection	No	ADF (21)	N/A
10	Makhlouf et al., 2008 [5]	Fundus	4	Monophasic		F	37		Partial gastrectomy	No	DOD (48)	N/A
11	Makhlouf et al., 2008 [5]	Distal fundus	6	Monophasic		M	50		Resection	Yes	AWD (6)	N/A
12	Makhlouf et al., 2008 [5]	Greater curvature/body	8	Biphasic		M	42		Partial gastrectomy	Yes	DOD (25)	N/A
13	Makhlouf et al., 2008 [5]	Fundus	15	Monophasic		F	66		Gastrectomy/partial esophagectomy	No	N/A	N/A
14	Sinniah et al., 2012 [6]	Lesser curvature/body	4.7	Monophasic	N/A	F	44	Melena and epigastric pain	Laparotomy-wide excision	N/A	ADF (60)	No
15	Wang et al., 2012 [7]	Middle body	7.2	Monophasic	>20	F	38	Hunger pain	Wedge resection	Yes	AWD (6)	Omentum (at diagnosis), liver (after 3 month)
16	Kamata et al., 2013 [8]	Body	3.5	Monophasic	2	F	42	Anemia	Partial gastrectomy	No	ADF (72)	No
17	Sahara et al., 2013 [9]	Posterior mid-gastric body	2.5	Monophasic	14	M	22	Epigastric pain	Wedge resection	No	N/A	No
18	Michot et al., 2014 [10]	Cardia and fundus	3.8	Monophasic	22	M	62	Anemia	Total gastrectomy	Yes	ADF (9)	No
19	Torres Rivas et al., 2014 [11]	Lesser curvature	15	Monophasic	11	M	44	Abdominal discomfort, weight loss	Total gastrectomy	No	ADF (18)	No
20	Romeo et al., 2015 [13]	Body	8	Monophasic	7	F	50	N/A	N/A	N/A	N/A	N/A
21	Romeo et al., 2015 [13]	Stomach	6	Poorly differentiated	11	M	36	N/A	N/A	N/A	AWD (36)	Liver
22		Stomach	2	Monophasic	6	M	37	N/A	N/A	N/A	N/A	N/A

Table 1 (continued)

Case no.	Reference	Site	Size (cm)	Morphology	Mitosis (per 10 HPF)	Gender	Age (years)	Clinical presentation	Surgery	Chemotherapy	Follow-up (months)	Metastasis
	Romeo et al., 2015 [13]											
23	Romeo et al., 2015 [13]	Stomach	N/A	Monophasic	Pretreated	M	26	N/A	N/A	N/A	AWD (185)	Liver, lungs
24	Romeo et al., 2015 [13]	Stomach	10	Monophasic	12	M	58	N/A	N/A	N/A	DOD (6)	N/A
25	Romeo et al., 2015 [13]	Stomach	10	Monophasic	Pretreated	M	21	N/A	N/A	N/A	ADF (48)	N/A
26	Romeo et al., 2015 [13]	Stomach	6	Biphasis	27	M	36	N/A	N/A	N/A	ADF (12)	N/A
27	Romeo et al., 2015 [13]	Stomach	3.8	Monophasic	14	F	54	N/A	N/A	N/A	N/A	N/A
28	Wong et al., 2015 [12]	Stomach	3.5	Monophasic	>10	F	49	Iron deficiency anemia	Local surgical excision	No	ADF (10)	No
29	Wong et al., 2015 [12]	Stomach	12	Monophasic	>10	F	35	Iron deficiency anemia	Local surgical excision	Yes	AWD (48)	Liver (after 2 years)
30	Current case	Greater curvature/body	6.3	Monophasic	33	M	58	Hematemesis	Wedge resection	N/A	AWD (7)	Liver, peritoneal (after 2.5 months)

ADF alive disease-free, *AWD* alive with disease, *DOD* died of disease, *N/A* not available

Table 2 Summary of the immunohistochemical (IHC) stain patterns of the 30 gastric synovial sarcoma cases

IHC markers	No. of positive cases	No. of negative cases	% Positive cases
CK7	8	1	89
AE1/AE3	23	6	79
EMA	25	1	96
KIT	2	24	8
CD34	2	19	10
DOG1	3	8	27
CD56	9	0	100
Bcl-2	6	0	100
CD99	12	2	86
TLE1	5	0	100
S-100	0	17	0
Vimentin	8	0	100
SMA	2	12	14
Desmin	0	15	0
Melan A	0	3	0
HMB-45	0	3	0
Chromogranin	0	4	0
Synaptophysin	0	4	0

to assuming that a spindle cell tumor is a GIST, given that it is by far the most common spindle cell tumor in the stomach. However, lack of diagnosis prior to surgery in this case resulted in suboptimal surgical management and omission of meticulous surgical handling typically used for aggressive sarcomas which likely resulted in metastatic implants which then showed significant and rapid growth over a short period of time. It is unknown whether it also contributed to the development of the metastatic disease to the liver. The lymphatic metastasis as well as progression due to tumor manipulation demonstrates the critical importance of determining pathologic diagnosis of intra-abdominal synovial sarcoma prior to resection, as it will influence surgical approach. It is strongly recommended that an open approach be taken to minimize manipulation of the tumor, as well as performing a therapeutic lymph node dissection in cases of macroscopically enlarged or suspicious lymph nodes.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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