Review Article

The malignancy among gastric submucosal tumor

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Abstract: The origin and characteristics of most submucosal tumors (SMTs) cannot easily be confirmed by gastrointestinal endoscopy or other radiological examinations. Excluding GISTs, for those other gastric SMTs, most of which are deemed benign, the necessity and timing of intervention has been ignored. Thus, the malignancy of gastric SMTs still remains unknown. In order to summarize the malignancy of these gastric SMTs, we reviewed literatures and analyzed cases of gastric SMTs including heterotopic pancreas, leiomyoma, schwannoma, glomus tumor, hemangioendothelioma, granular cell tumor (GCT), lipoma, hemangiopericytoma, lymphangioma and neurofibroma. In these literatures, there are cases of malignancy among heterotopic pancreas, leiomyoma, schwannoma, glomus tumor, hemangioendothelioma and GCT. As a result, it suggests that although most of gastric SMTs are considered benign, there are still possibilities of malignancy, which requires our attention, even active intervention and long-term follow-up.

Keywords: Gastric submucosal tumor (gastric SMT); malignancy

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Introduction

The submucosal tumor (SMT), or subepithelial tumor (SET), is clinically common protuberant lesions or lumps covered with intact mucosa (1). The origin and characteristics of most SMTs cannot easily be confirmed by gastrointestinal endoscopy or other radiological examinations. These SMTs can be divided into mesenchymal tumors and non-tumorous submucosal lesions (2). And the mesenchymal tumors include benign, borderline malignant and malignant tumors (3). The majority of SMTs seldom cause symptoms, but are detected incidentally by endoscopic or radiologic examinations (4).

As is known to all, gastrointestinal stromal tumor (GIST) has been already widely studied. There are relatively reliable guidelines for the diagnosis and treatment of gastric GISTs in Western and Asian countries, such as the clinical guidelines of GISTs published by the National Comprehensive Cancer Network (NCCN) in 2004 (5), and by the European Society of Medical Oncology (ESMO) in 2014 (6). However, excluding GISTs, for those other gastric SMTs, most of which are deemed benign, the necessity and timing of intervention has been ignored.

For reference, this paper will focus on the malignancy of gastric SMTs which are generally considered benign.

Heterotopic pancreas

Heterotopic pancreas is defined as pancreatic tissue abnormally situated, which is anatomically characterized by the separation of pancreatic tissue from glands, without neurological or vascular continuity (7). The most common site of gastrointestinal heterotopic pancreas is the stomach (25–62%), followed by the duodenum (25–35%), and jejunum (16%) (8). The clinical manifestations of heterotopic pancreas is asymptomatic or non-specific, such as epigastric pain, nausea, vomiting and so on. Therefore, it is usually detected by endoscopy examination or autopsy

Table 1 Information of reviewed gastric submucosal tumors

Histological diagnosis	Reference No.	Total case No.	Gender (M/F)	Age (Y)	Size (cm)	Malignant case No.
Heterotopic pancreas	291	1724	405/457	Newborn–89	0.4–12.5	29
Leiomyoma	133	946	80/85	16–86	0.5–21	16
Schwannoma	83	530	121/275	5–90	0.3–15	11
Glomus tumor	97	195	73/109	19–90	0.8–17	11
Hemangioendothelioma	5	5	3/2	21–71	4–7	2
Granular cell tumor	27	35	14/15	20–76	0.5–10.5	1
Lipoma	80	141	55/37	22–84	0.4–16	0
Hemangiopericytoma	1	1	0/1	56	0.8	0
Lymphangioma	11	11	4/6	16–68	1.5–22	0
Neurofibroma	13	13	9/4	14–62	1.1–9	0

incidentally (9).

The malignant tumors of gastric heterotopic pancreas are comparatively rare but need to be alarmed. There were 1,724 cases reported in the literature, which were composed of newborn to 89 years old patients. The sex ratio (M/F) was about 0.9. The tumor size ranged from 0.4 to 12.5 cm. Of all the 1,724 cases reported from 1980 to 2018, we found 29 cases with malignant features (*Table 1*). For a carcinoma to be described as arising from heterotopic pancreatic tissue, three criteria have been proposed: (I) the tumor must be found within, or close to, the ectopic pancreatic tissue; (II) transition between pancreatic structures and carcinoma must be observed (i.e., duct-cell dysplasia and/or carcinoma in situ); (III) the non-neoplastic pancreatic tissue must include at least fully developed acini and duct structures. The lesion in this case met all three criteria (10). The 29 cases were confirmed pathologically originated from gastric heterotopic pancreas. Among the 29 malignant cases, most of them were adenocarcinoma (21/29), and other pathological types included papillary cystadenocarcinoma, mucinous cystadenocarcinoma, neuroendocrine carcinoma, acinar cell carcinoma and so on. Mean age of the cases was 58.4±15.6 [27–86] years old and the male to female ratio was 14/15. The tumor size ranged from 1.7 to 12.5 cm (*Table 2*).

In addition to malignant cases of heterotopic pancreas, pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasms (IPMN) have also been found in heterotopic pancreas. In 1,724 cases, 47 PanINs/IPMNs were found. Based on the mathematical analysis by Yachida *et al.* (75), it takes about 12 years for PanIN-1 to transform into PanIN-3, which can cause pancreatic ductal adenocarcinomas. According to the study by Jun *et al.* (76), PanINs/IPMNs were more frequently found in heterotopic pancreas of large size, deep location and infiltrative growth pattern. And most PanINs/IPMNs associated with heterotopic pancreas were low-grade, so progression to ductal adenocarcinoma during a short follow-up period is unlikely.

Therefore, although the malignant cases are rare in gastric heterotopic pancreas, we also need to be cautious when we find gastric heterotopic pancreas.

Leiomyoma

Leiomyoma is the most common SMT of upper gastrointestinal tract (77). Until the 1980s, GIST was not significantly different from a leiomyoma. It was not until 1983 when Mazur and Clark (78) proposed the concept of stromal tumors that their differences were gradually noticed. And in 1998, Hirota *et al.* (79) confirmed the pathogenic effect of Kit (CD117) proto-oncogene activating mutation on GISTs. Subsequently, GISTs were confirmed to have the characteristics of Cajal interstitial cells, which more specifically differ leiomyoma from GIST. So in order to get more reliable data, we only searched literatures between 2008–2018.

From 2008 to 2018, we reviewed 133 literatures and found 946 cases of gastric leiomyoma reported. Of the 946 cases, 16 were leiomyosarcomas. The clinical manifestations of these malignant tumors were not specific, such as epigastric pain, melena, gastric outlet obstruction and so on. The average age of these 16 cases was 52.7±20.7

Table 2 Details of malignant gastric submucosal tumors

Histological diagnosis	Reference	Age/gender	Appearance	Size (cm)	Treatment	Follow up
Heterotopic pancreas						
Adenocarcinoma	Nakao *et al.* (11) [1980]	54/M	Abdominal pain, weight loss	Nd	Surgery	Deceased, 9 months after surgery
Adenocarcinoma	Nakao *et al.* (11) [1980]	28/F	Epigastric pain	Nd	Nd	Uneventful at 2 years
Adenocarcinoma	Hickman *et al.* (12) [1981]	58/M	weight loss, periodic epigastric pain, vomiting	2.3	Subtotal gastrectomy	Metastatic pancreatic adenocarcinoma, 7 years after surgery
Papillary cystadenocarcinoma	Mibayashi *et al.* (13) [1983]	44/F	Epigastralgia	Nd	Subtotal gastrectomy	Nd
Adenocarcinoma	Bedossa *et al.* (14) [1991]	42/M	Gastric stasis	Nd	Gastrectomy	Uneventful at 4-month follow-up
Heterotopic pancreas with malignant transformation	Jeng *et al.* (15) [1991]	27/F	Epigastric fullness, heart-burn, nausea, acid regurgitation	2.5×2.0	Subtotal gastrectomy with radical lymph node resection	Uneventful at 2-year follow-up
Adenocarcinoma	Ura *et al.* (16) [1998]	60/F	Asymptomatic	3×3.3	Proximal gastrectomy with regional lymph node dissection	Nd
Mucinous cystadenocarcinoma	Cho *et al.* (17) [2000]	73/F	Nd	Nd	Nd	Nd
Adenocarcinoma	Osanai *et al.* (10) [2001]	57/F	Epigastric discomfort and periodic nausea	12.5×9	Total gastrectomy	Deceased, 13-mo follow-up
Adenocarcinoma	Halkic *et al.* (18) [2001]	60/M	Epigastric pain, dysphagia, weight loss	6×4.5×4	Surgery	Died 4 months following surgery
Adenocarcinoma	Jeong *et al.* (19) [2002]	64/M	Dyspepsia, vomiting	3×3	Roux-en-Y esophagojejunostomy and a Braun anastomosis	Uneventful at 1 year
Adenocarcinoma	Emerson *et al.* (20) [2004]	52/M	Epigastric, left upper quadrant pain, emesis, and bloating	4×2.5	50% gastrectomy with vagotomy	Uneventful 9 months after surgery
Neuroendocrine carcinoma (grade I)	Chetty *et al.* (21) [2004]	85/M	Dyspepsia, increase in stool frequency	1.7	Distal gastrectomy	Uneventful at 1 month
Adenocarcinoma	Eun *et al.* (22) [2004]	35/M	Asymptomatic	2×1.7×1.2	Wedge resection	Uneventful at 5 months

Table 2 (*continued*)

Table 2 (*continued*)

Histological diagnosis	Reference	Age/gender	Appearance	Size (cm)	Treatment	Follow up
Acinar cell carcinoma	Sun *et al.* (23) [2004]	86/F	Anemia	5×3×2	Partial gastrectomy with a Billroth-II reconstruction	Nd
Adenocarcinoma	Matsuki *et al.* (24) [2005]	58/F	Vomiting	2.5×1.7	Partial gastrectomy	Uneventful, 1.5 years later
Adenocarcinoma	Yoshida *et al.* (25) [2007]	64/M	Abdominal fullness	Nd	Gastrectomy	Nd
Acinar cell carcinoma	Mizuno *et al.* (26) [2007]	73/M	Epigastralgia	7.6×4.9	Pancreaticoduodenectomy	Uneventful at 11 months
Adenocarcinoma	Kimura *et al.* (27) [2008]	31/F	Epigastralgia	5×2	Distal gastrectomy	Nd
Adenocarcinoma	Papaziogas *et al.* (28) [2008]	56/F	Epigastric pain	2×1.2	Distal gastrectomy	Uneventful at 6 months
Adenocarcinoma	Suk *et al.* (29) [2011]	69/F	Vomiting	7×2	Gastrectomy	Nd
Adenocarcinoma	Fukumori *et al.* (30) [2011]	76/F	Nd	Nd	Gastrectomy on the pylorus side, lymph node dissection (D2), and cholecystectomy	Nd
Adenocarcinoma	Okamoto *et al.* (31) [2012]	75/F	Epigastralgia	4	Laparotomy	Uneventful, 11-year follow-up
Adenocarcinoma	Endo *et al.* (32) [2014]	73/M	Epigastric pain	4.5×3×2.5	Distal gastrectomy with regional lymph node dissection and cholecystectomy	Lymph node metastasis at 2-year follow-up
Adenocarcinoma	Lemaire *et al.* (33) [2014]	60/M	Dyspepsia and epigastric heaviness	7.5×4.4	Total gastrectomy with D2 lymphadenectomy	Uneventful, 4-year follow-up
Adenocarcinoma	Priyathersini *et al.* (34) [2017]	45/M	Early satiety, vomiting, constipation	5×4.3×3.5	A subtotal gastrectomy with anterior jejunostomy	Uneventful at 12-month follow-up
Acinar cell carcinoma	Kim *et al.* (35) [2017]	54/M	Incidental finding	2.7	Laparoscopic wedge resection	Uneventful at 33-month follow-up
Adenocarcinoma	Wang *et al.* (36) [2017]	63/F	Asymptomatic	2.4	Gastric wedge resection	Uneventful at 8-month follow-up
Neuroendocrine tumor (grade I)	Tanaka *et al.* (37) [2018]	72/F	Incidental finding	1.6×1.2×0.6	Laparoscopic and endoscopic cooperative surgery	Nd

Table 2 (*continued*)

Table 2 (*continued*)

Histological diagnosis	Reference	Age/gender	Appearance	Size (cm)	Treatment	Follow up
Leiomyoma						
Leiomyosarcoma	Pauser *et al.* (38) [2008]	37/M	Reflux	1	Resected endoscopically	Uneventful, 3-year follow-up
Leiomyosarcoma	Masuzawa *et al.* (39) [2009]	29/F	Upper abdominal pain and occasional black stool	11×9.7×3.2	Distal gastrectomy and regional lymphadenectomy	Uneventful at 8-month follow-up
Leiomyosarcoma	Soufi *et al.* (40) [2009]	16/F	Massive hematemesis and shock without epigastralgia	Nd	Subtotal gastrectomy	Uneventful at 18-month follow-up
Leiomyosarcoma	Park *et al.* (41) [2011]	79/M	Epigastric pain and gastric subepithelial tumor	4.6×4.2	Laparoscopic wedge resection	Recurrent leiomyosarcoma with multiple liver metastases, 1-year follow-up
Leiomyosarcoma	Aggarwal *et al.* (42) [2012]	26/M	Abdominal pain, black stools, and lightheadedness	7.2	Gastrectomy	Lost to follow-up 1 month after surgery
Leiomyosarcoma	Damiano *et al.* (43) [2012]	71/M	Anemia and melena	9	Atypical gastric resection	Uneventful at 28-month follow-up
Leiomyosarcoma	Insabato *et al.* (44) [2012]	51/M	Asthenia, weight loss, and slight sideropenic anemia	4×1.6	Total gastrectomy with Roux-en-Y esophagojejunal anastomosis	Uneventful at 10-month follow-up
Leiomyosarcoma	Yamamoto *et al.* (45) [2013]	51/M	Nd	2.5	Resected surgically	Uneventful at 18-month follow-up
Leiomyosarcoma	Weledji *et al.* (46) [2014]	69/M	Vomiting associated with upper abdominal bloatedness, epigastric pain	10×8×7	Billroth-II gastrectomy	Nd
Leiomyosarcoma	Rou *et al.* (47) [2015]	48/F	Abdominal discomfort and generalized weakness	2	Chemotherapy	Died after 1 year due to tumor progression
Leiomyosarcoma	Tarchouli *et al.* (48) [2015]	32/F	Painful mass of the left hypochondrium	21×14×12	Ne-piece resection with mass, spleen, large omentum and a flange of the gastric wall	Died 2 years later in an array of pulmonary metastases
Leiomyosarcoma	Hasnaoui *et al.* (49) [2018]	63/F	Hematemesis, melena and hemodynamic instability	9	Total gastrectomy	Nd
Leiomyosarcoma	Kitagawa *et al.* (50) [2018]	64/M	Abdominal mass and mild anemia	3	Partial gastrectomy	Uneventful, 2-year follow-up

Table 2 (*continued*)

Table 2 (*continued*)

Histological diagnosis	Reference	Age/gender	Appearance	Size (cm)	Treatment	Follow up
Leiomyosarcoma	Mehta *et al.* (51) [2018]	47/M	Pain in the left hypogastric region	13×13×10	Laparotomy with total excision of the greater curvature of the stomach	2 years later, liver metastases, died 11 months after metastases
Leiomyosarcoma	Roh (52) [2018]	86/F	Nd	Nd	Partial gastrectomy and chemotherapy, Y-90 therapy treated liver metastasis	Liver metastasis
Leiomyosarcoma	Sato *et al.* (53) [2018]	74/F	Asymptomatic	1.5	Endoscopic submucosal dissection (ESD)	Uneventful at 36-month follow-up
Schwannoma						
Malignant schwannoma	Petersen *et al.* (54) [1984]	42/M	Upper gastrointestinal bleeding	2	Electrocautery under endoscopy	Died 7 days later of gram-negative sepsis
Malignant schwannoma	Radulescu *et al.* (55) [1995]	27/F	Epigastric pains accompanied by melena	Nd*	Nd	Nd
Malignant schwannoma	Bees *et al.* (56) [1997]	10/F	Poor appetite, fatigue, pallor, fainting and tarry stools	3	Billroth-I	Nd
Malignant schwannoma	Loffeld *et al.* (57) [1998]	41/F	Melaena	4	Gastrectomy	Uneventful at 5 years
Malignant schwannoma	Watanabe *et al.* (58) [2011]	34/M	Asymptomatic	1.9×1.8	Laparoscopy-assisted partial gastrectomy	Uneventful at 2 years
Malignant schwannoma	Takemura *et al.* (59) [2012]	70/M	Melena	6×5	Distal gastrectomy with regional lymph node dissection	3 months after surgery with liver metastases, died 5 months after surgery
Malignant schwannoma	Zheng *et al.* (60) [2014]	67/M	Gastric pain	6.7	Surgery	Died of unrelated causes, 80 months
Malignant schwannoma	Zheng *et al.* (60) [2014]	73/F	Hematemesis, melena	5.2	Surgery	Died of metastasis or recurrent of the primary disease, 15 months
Malignant schwannoma	Zheng *et al.* (60) [2014]	61/M	Gastric pain	5.7	Surgery	Uneventful at 28 months
Malignant schwannoma	Zheng *et al.* (60) [2014]	65/F	Detected during CT for unknown symptoms	6.2	Surgery	died of metastasis or recurrent of the primary disease, 15 months
Malignant schwannoma	Kim *et al.* (61) [2015]	48/M	Melena	9	Subtotal gastrectomy with D1+ lymph node dissection and Billroth-II reconstruction	Nd

Table 2 (*continued*)

Table 2 (*continued*)

Histological diagnosis	Reference	Age/gender	Appearance	Size (cm)	Treatment	Follow up
Glomus tumor						
Malignant glomus tumor	Folpe *et al.* (62) [2001]	69/M	Nd	8.5	Surgery	Liver metastasis, 3 years later
Malignant glomus tumor	Miettinen *et al.* (63) [2002]	69/M	Nd	6.5×6×3	Surgery	Died, 50 months, liver metastases
Malignant glomus tumor	Bray *et al.* (64) [2009]	58/M	Nd	11×9×17	Surgery	Cutaneous metastasis 6 years later
Malignant glomus tumor	Lee *et al.* (65) [2009]	65/F	Epigastric pain and a loss of appetite	3	A wedge resection of the gastric mass	Metastases in the kidney and brain, died of respiratory insufficiency 8 months later
Malignant glomus tumor	Lee *et al.* (65) [2009]	63/M	Epigastric pain	9	Chemotherapy	Died, extensive bleeding from the main tumor mass
Malignant glomus tumor	Hong *et al.* (66) [2010]	61/M	Dizziness and tarry stool	4	Palliative wedge resection of the stomach	Nd
Malignant glomus tumor	Teng *et al.* (67) [2012]	66/F	Abdominal fullness	5.3×5×4.9	Subtotal gastrectomy	Uneventful at 9-month follow-up
Malignant glomus tumor	Teng *et al.* (68) [2012]	43/F	Melena	2.5	Endoscopic therapy	Nd
Malignant glomus tumor	Akahoshi *et al.* (69) [2014]	Nd	Nd	1.2	Surgical local resection	No recurrence
Malignant glomus tumor	Zaidi *et al.* (70) [2016]	53/F	Fullness and pain in the left hypochondrium	10	Laparotomy and resection of the gastric mass	Uneventful at 15-month follow-up
Malignant glomus tumor	Davis *et al.* (71) [2018]	46/F	Incidental finding	1	Wedge excision of the stomach tumor	Liver metastasis
Hemangioendothelioma						
Hemangioendothelioma	Seki *et al.* (72) [1985]	21/F	Melena	6	Laparoscopy	Nd
Epithelioid angiosarcoma	Xia *et al.* (73) [2018]	56/M	Melena and epigastric dull pain	7	Total gastrectomy with D2 lymph node dissection	Liver and retroperitoneal lymph node metastasis 1 month later
Granular cell tumor	Matsumoto *et al.* (74) [1996]	64/F	Epigastric discomfort after meals	5.5/7	Billroth-I	Recurrence, 21 months after surgery. Uneventful, 6-month follow-up after last operation

*, Nd: no data.

[16–86] years old. The male to female ratio was 9/7. The average size of tumors was 7.06±5.60 [1–21] cm. The literature indicates that gastric leiomyosarcomas often occurs in the elderly and are typically of high grade malignancy (38). However, our review showed that some middle-aged and even young patients also suffer from this disease. And the tumor size was also extensively ranged. So neither age nor tumor size can be used as criteria for judging malignant potential. Some leiomyosarcomas had distant metastases at initial diagnosed. And liver and lungs were the most common sites.

Schwannoma

Schwannomas of the GI tract, firstly presented by Daimaru *et al.* in 1988 (80), which are mostly benign tumors arising from the schwann cells of the nerve sheath. The most common site (60–70% of all GI cases) is the stomach, followed by the colon and rectum (3%). Small intestinal and esophageal schwannomas are rarely reported (81).

Malignant gastric schwannomas are extremely rare, with only a few cases reported (*Table 1*). Of all the 530 cases reviewed, 11 showed malignancy (*Table 2*). Based on these conditions, we may conclude that malignant gastric schwannoma has atypical appearance with common gastrointestinal symptoms. Among these cases, there were 6 males and 5 females. The mean age of these cases was 48.9±20.2 [10–73] years old and the mean size of tumors was 4.97±2.25 [1.9–9] cm. Although the data of all the 530 cases showed a female predominance, the sex ratio of malignant schwannoma was close to 1:1, even male patients accounted for the majority. So we speculate that the possibility of malignancy is more likely to occur in males. With the increase of malignant cases, gender preference may decrease, and we can more intuitively analyze the characteristics of malignant schwannoma.

Vascular tumor

Vascular tumors, including angiogenic tumors and lymphangiomas, are relatively rare. Angiogenic tumors include glomus tumor, hemangioendothelioma, hemangiopericytoma and so on.

Glomus tumor, which is composed of modified smooth muscle cells (82), is an arteriovenous anastomosis functioning without an intermediary capillary bed (83). Most glomus tumors are benign neoplasms that occur in the dermis or subcutis of the extremities (84). Glomus tumors of stomach are relatively rare and often lead to gastrointestinal bleeding due to ulceration of the mucosa over which it is covered (85). We reviewed 97 articles and 195 cases from 1980 to 2018. According to the literature, the ages ranged from 19 to 90. Pathologically confirmed malignancy was found in 11 cases, and potential malignancy was uncertain in 3 cases. The others were benign. Folpe *et al.* (62) suggested malignant criteria of glomus tumors: tumors with a deep location and a size of more than 2 cm, or atypical mitotic figures, or moderate to high nuclear grade and ≥5 mitotic figures/50 HPF. All these 11 tumor cases met the above criteria. Of the 10 cases, 5 were male and 5 were female. The gender of the remaining 1 patient was not mentioned. The average age was 59.3±9.2 [43–69] years and the average tumor size was 6.18±4.75 [1–17] cm. As mentioned above, we can conclude that malignant cases usually occur in elderly patients and the risk of distant metastases cannot be ignored. And there seems to be no correlation between tumor size and malignant potential. The clinical manifestations of malignant tumors are mostly gastrointestinal symptoms without specificity. Although malignancy is rare in glomus tumors, we still need to pay close attention to it. What's more, due to the risk of distant metastasis, long-term follow-up is necessary.

Hemangioendotheliomas which affects various parts of the digestive system (86) is classified into four types: Epithelioid hemangioendothelioma, spindle cell hemangioendothelioma, kaposiform hemangioendothelioma and endovascular papillary hemangioendothelioma (malignant tumor known as Dabska) (87). Gastric hemangioendotheliomas were rarely reported, only 5 cases, 2 of which were malignant tumors (*Table 2*). The tumor size of these 2 cases was relatively large. However, due to the limited number of cases, we cannot summarize the reliable common features of their malignancies.

Hemangiopericytoma of the stomach is even rarer and we found only one benign case of gastric lipomatous hemangiopericytoma. Lipomatous hemangiopericytoma is a variant of hemangiopericytoma, which is histologically composed of benign hemangiopericytomatous and mature lipomatous components (88). This was the first case of lipomatous hemangiopericytoma that occurred in the stomach, and more data is needed to deduce the possibility of malignancy.

Lymphangiomas are relatively rare compared with hemangiomas. And the digestive tract is rarely involved (89). We found 11 cases of gastric lymphangiomas, none of which were malignant.

Granular cell tumor (GCT)

GCT, first described by Abrikosoff in 1926 (90), is a benign mesenchymal tumor originating from schwann cell (91). GCTs most commonly affect the tongue, skin and subcutaneous tissue. And, 5% to 11% of GCTs are found in the gastrointestinal tract, and they mostly affect the esophagus, colon, or stomach (92). According to Fanburg-smith, there are six histologic criteria: necrosis, spindling, vesicular nuclei with large nucleoli, increased mitotic activity (>2 mitoses/10 high-power fields at 200× magnification), high nuclear to cytoplasmic (N:C) ratio, and pleomorphism. Neoplasms that met three or more of these criteria were classified as histologically malignant; those that met one or two criteria were classified as atypical; and those that displayed only focal pleomorphism but fulfilled none of the other criteria were classified as benign (93).

From January 1st, 1980 to December 31st, 2018, we found 36 cases of gastric GCTs (*Table 1*). Some of these gastric GCTs may coexist with gastric carcinoma and early gastric cancer. However, the pathology of these GCTs was confirmed benign. There was only one case of malignant gastric GCT, which was reported in 1996 by Matsumoto *et al.* A 64-year-old female was referred to the hospital for treatment due to upper abdominal discomfort after eating and gastroscopic evidence of enlargement of a SMT which had been managed conservatively by the hospital since 5 years ago. This neoplasm consisted of two tumor masses, 5.5 and 7.0 cm in diameter, respectively, which were connected to form a dumbbell-shaped lesion. After distal partial gastrectomy, reconstruction was performed by Billroth-I Method. The pathology of this case met the following criteria mentioned above: increased mitotic activity and pleomorphism. Although it only met two of the criteria, 21 months after the operation, the tumor recurred along the inferior border of the liver, 10.5 cm × 7.5 cm × 7.5 cm. Pathological characteristics of the tumor were similar to those of the primary tumor. Thus, considering the clinical and pathological evidence of local recurrence, the neoplasm was considered malignant (74).

Lipoma

Gastric lipomas account for less than 1% of gastric tumors and 5% of gastrointestinal lipomas (94). Lipomas are completely benign, although there is a risk of local recurrence, less than 5% (95). Of the 141 cases reviewed, no malignancy was reported (*Table 1*).

Neurofibroma

Neurofibroma often occurs in neurofibromatosis and solitary neurofibromas are rare (96). Neurofibromatosis type 1 is more common, frequently involving gastrointestinal tract (97). We reviewed 13 cases of gastric neurofibroma and none of them had malignant features. However, the clinical manifestations of neurofibromatosis are various, ranging from localized microscopic proliferative lesions of autonomic nerves and interstitial cells of Cajal and diffuse microscopic ganglio/neuro/fibromatosis to grossly recognizable mass-forming neurofibromas and GIST (98). Therefore, when gastric neurofibroma is diagnosed, neurofibromatosis needs to be considered and be alert.

Conclusions

We reviewed literatures and analyzed cases of gastric SMTs including GCT, lipoma, schwannoma, heterotopic pancreas, leiomyoma, vascular tumor (glomus tumor, hemangioendothelioma, hemangiopericytoma, lymphangioma) and neurofibroma. In this literature, there are cases of malignancy among GCT, schwannoma, heterotopic pancreas, leiomyoma, glomus tumor and hemangioendothelioma. It suggests that although most of these gastric SMTs are considered benign, there are still possibilities of malignancy, which requires our attention, even active intervention and long-term follow-up.

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Footnote

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