Primary synovial sarcoma of the duodenal bulb: a case report and review of the literature

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Abstract: Primary synovial sarcoma of the duodenal bulb is a rare mesenchymal tumor with special morphological features. It usually originates from the major joints or tendon sheaths of the extremities and mostly seen in young population, but rarely found in gastrointestinal tract. In this manuscript, we reported the first case of synovial sarcoma arising between the intestinal wall of the duodenal bulb with a concomitant SYT/SSX type of the t(X;18) translocation. A 49-year-old male presented to our hospital with a 2-month history of upper abdominal pain along with a 4-day amply jaundice. Tumor marker testing showed only a slight increase of carbohydrate antigen 19-9 (CA19-9). A computed tomography scan of his abdomen showed that indeterminate tissue occupied the duodenal bulb wall, compressed the surrounding tissues, and measured roughly 5.0 cm × 7.7 cm × 8.7 cm. Since the sarcoma grows between the intestinal wall, which cannot be detected by endoscopy, an initial diagnosis of duodenal wall stromal tumor was made at that time. Postoperative Immunohistochemistry results showed that the tumor was positive for the expression of transducin-like enhancer of split 1, B-cell lymphoma 2, and Vimentin. These pathological findings were indicative of the diagnosis of synovial sarcoma, but still did not provide sufficient diagnostic evidence. Finally we confirmed the diagnosis by using fluorescence in situ hybridization (FISH) with detection of the t(X;18) (SYT-SSX) translocation. No such lesions were found on preoperative examination, so a diagnosis of primary duodenal synovial sarcoma was made. After literature review, we found four reports of duodenal synovial sarcomas, all of which could be detected endoscopically, but there were no results of long-term follow-up. This case is the first reported case of synovial sarcoma arising between the intestinal walls of the duodenal bulb treated twice with ifosfamide and followed up for 13 months without recurrence.

Keywords: Synovial sarcoma; duodenal bulb; immunohistochemistry; fluorescence in situ hybridization

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Introduction

Synovial sarcoma is a type of mesenchymal tumor that originates from soft tissue rather than from synovial tissue. This sarcoma originates from soft tissue, has a special predilection for local recurrence and distant metastasis, and it accounts for 5–10% of all soft tissue tumors (1,2). synovial sarcoma usually occurs in young adults around major joints or tendon sheaths (1) and occasionally in the head and neck (3), lungs (4), heart (5), retroperitoneum (6), prostate (7), within nerves (8), and the kidney (9). Here, we report a 49-year-old Chinese male with primary synovial sarcoma of the duodenal bulb. We also retrieved relevant data on SS in other parts of the digestive system and reviewed the literature. We present the following article in accordance with the CARE reporting checklist (available at http://
Case presentation

A 49-year-old male presented to our hospital with a 2-month history of upper abdominal pain along with a 4-day amply jaundice. The patient was previously healthy, normotensive, did not have diabetes, and did not have a history of alcohol intake or smoking. According to the blood test results, he had a total bilirubin level of 43.3 µmol/L and a direct bilirubin level of 40.4 µmol/L, a γ-GGT level of 1,798 U/L, an ALP level of 1,454 U/L, and a carbohydrate antigen 19-9 level of 29.16 U/L. A computed tomography (CT) scan of his abdomen revealed that the lump occupied the duodenal bulb wall, compressed the surrounding tissues, and measured roughly 5.0 cm × 7.7 cm × 8.7 cm. The arterial phase of an enhanced CT scan showed that the mass was obviously strengthened and that the branch of the pancreaticoduodenal artery was supplied with sufficient blood (Figure 1A,B). A Magnetic Resonance Imaging (MRI) scan of his abdomen showed that the duodenum bulb contained a large lump with an approximate size of 9.1 cm × 5.5 cm × 7.1 cm; the T1 signal was slightly longer, and the T2 signal was dominant. The arterial phase of an enhanced MRI showed that the mass was obviously strengthened and had an irregular shape (Figure 1C,D). On gastroduodenoscopy, the duodenal bulb and descending portion exhibited no abnormalities. Since the tumor was located between the duodenal walls, it could not be examined by endoscopic ultrasound and needle biopsy. We thus considered a diagnosis of duodenal wall stromal tumor.

After a multidisciplinary discussion, the patient was originally diagnosed with a malignant duodenal tumor with obstructive jaundice, and consequently, underwent radical pancreatoduodenectomy. Surgical specimens showed that the duodenal papilla had some edema, and a nodular mass observed below the nipple measured 12 cm × 8 cm × 5 cm. The tumor surface was grayish red and gray, and some areas appeared as translucent nodules. The postoperative pathological examination showed that the tumor tissue was fusiform, arranged in a bundle with oval nuclei that were long and fusiform, and contained pink cytoplasm (Figure 2A–C). Immunohistochemistry showed that the tumor was positive for the expression of transducin-like enhancer of transduction-like enhancer of activation transcription 1 (TENpson-1).
split 1 (TLE-1), B-cell lymphoma 2 (Bcl-2), Vimentin, and smooth muscle actin (Figure 3A-D), but was negative for CD34 (Figure 3E), Desmin and S-100 protein; 67% of cells were Ki-67-positive (Figure 3F,G). These pathological findings were indicative of the diagnosis of synovial sarcoma, but still did not provide sufficient diagnostic evidence.

Cytogenetic and fluorescence in situ hybridization (FISH) examination were performed on formalin-fixed paraffin-embedded tumor specimens. FISH was used to detect the fusion of the SSX gene, which is located on the X chromosome, and the SS18 gene (SYT) located on chromosome 18; this fusion produces the SS18 (SYT)-SSX fusion gene (Figure 4A,B,C) and thus, we detected SS18 gene translocations (Figure 4A,B,C). Therefore, FISH demonstrated the t(X;18) (SYT-SSX) gene rearrangement and confirmed the above diagnosis. No such lesions were found on preoperative examination, so a diagnosis of primary duodenal synovial sarcoma was made. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

At the time of the reported case, the patient had been treated with ifosfamide twice in the 3 months after surgery. The dose of ifosfamide was 2 g/time for 5 days, and the interval between two chemotherapy was 1 month. After 13 months of follow-up, his condition was stable and remained no signs of clinical or imaging recurrence, and timely follow-up has been conducted. The patient’s treatment and follow-up timeline was shown in Figure 5.

**Discussion**

Synovial sarcoma is a type of mesenchymal tumor that originates in soft tissue rather than from synovial tissue. Synovial sarcoma is divided into three tissue types (2). One is the monophasic type, which consists only of spindle-shaped blastomas arranged in bundles, vortices, and herringbone. Another is the biphasic type, which is composed of different proportions of epithelial cells and spindle cells. The other is the poorly differentiated type, which is characterized by darkly stained oval or round cells, as seen in other small round-cell tumors. Synovial sarcoma is difficult to diagnose and is easily misdiagnosed, which is closely related to the diagnostic methods used. CT, MRI, and digestive endoscopy are used to diagnose SS of the digestive system, but considering the current state of the technology, it is difficult to make a definitive diagnosis before surgery. Since the diagnosis of synovial sarcoma relies on histology, immunohistochemistry [TLE-1 and Bcl-2 positivity can indicate a diagnosis of synovial sarcoma (10,11)], and cytogenetics, in most cases, the disease is confirmed using the above three methods to examine surgical specimens. Moreover, 90% of SS is associated with the t(X;18)(p11.2;q11.2) chromosomal translocation, which results in the fusion of the SYT gene on chromosome 18 with the SSX1 or SSX2 gene on the X chromosome. This results in the SYT-SSX fusion protein under certain
conditions (cytogenetics, fluorescence in situ hybridization, and RT-PCR can detect this fusion). If the translocation can be identified in tumor tissue, then histology can be used to make a diagnosis (12). The molecular test results of SYT-SSX were positive in our case (Figure 4A,B,C), and combined histological and immunohistochemical analyses showed multiple characteristics of monophasic synovial sarcoma. Therefore, the diagnosis of synovial sarcoma of the duodenal bulb was established (2,10,11). The differential diagnoses of synovial sarcoma include digestive lymphoma, gastrointestinal stromal tumor (GIST), giant juvenile polyp, sarcoma, and ectopic pancreas. It is worth mentioning that GIST is the most common mesenchymal cell tumor. Sometimes, it is difficult to identify GIST and gastrointestinal synovial sarcoma under the microscope. The diagnosis thus needs to be confirmed by TLE-1 and Bcl-2 positivity by immunohistochemistry or the presence of the t(X;18) chromosomal translocation by cytogenetics testing.

In this case, confirmation of the diagnosis was not easy. The tumor originated between the intestinal walls of the duodenal bulb, so gastroduodenoscopy failed to detect it, and the location of the tumor was ultimately confirmed by enhanced CT and MRI. Therefore, imaging physician made the diagnosis of duodenal stromal tumor before surgery. After pathological and immunohistochemical examination of the postoperative specimen, the pathologist considered synovial sarcoma, but still could not make a definite diagnosis. FISH examination was not routinely conducted in our institution due to its high cost, however, in order to obtain a definitive diagnosis, we had the patient’s consent and performed FISH on the specimen, which helped us make the final diagnosis of duodenal synovial sarcoma. This case may serve as experience for gastrointestinal surgeons. First, the tumor is located between the intestinal walls of the duodenal bulb, which is rare and made biopsy difficult.
Figure 4 Detection of the t(X,18) (SYT-SSX) translocation by fluorescence in situ hybridization by a break apart probe demonstrated one fused (yellow arrow) and one separate red and green (red and green arrow) signal indicating the rearrangement of the SYT gene.

2019-01 The patient developed intermittent epigastric pain without nausea, vomiting, icteric skin or sclera.

2019-02-03 The patient was admitted to our hospital due to ‘aggravated upper abdominal pain with jaundice’. After admission, CT, MRI and digestive endoscopy were performed, and a mass between the intestinal walls of the duodenal bulb was found. Thus, an initial diagnosis of malignant duodenal tumor and obstructive jaundice was considered.

2019-02-08 The patient underwent radical pancreaticoduodenectomy. Intraoperatively, the tumor was found to be located between the intestinal walls of the duodenal bulb, approximately 12 cm × 8 cm × 5 cm in size. Then, symptomatic and supportive treatment such as antibiotics, somatostatin, and parenteral nutrition was given postoperatively, and the patient was discharged uneventfully on the 12th postoperative day.

2019-05-10 For the first cycle of chemotherapy, ifosfamide was used at a dose of 2 g/time for 5 days.

2019-06-15 For the second cycle of chemotherapy, ifosfamide was used at a dose of 2 g/time for 5 days. The patient received chemotherapy for 2 cycles with stable conditions. Then, patient gave up subsequent chemotherapy.

2019-02-15 Postoperative pathological examination showed that the tumor tissue was shuttle shaped, arranged in bundles, with oval and long shuttle nuclei and pink cytoplasm. Immunohistochemical staining revealed TLE-1 and Bcl-2 positivity. SYT/SSX type of the t(X;18) translocation by fluorescence in situ hybridization. Since no distant metastatic lesion was found during the operation, a diagnosis of primary duodenal bulb synovial sarcoma was made.

2020-03 Up to now, the patient has been followed up for 13 months. His condition was stable and remained no signs of clinical or imaging recurrence.

Figure 5 The timeline figure of patient treatment and follow-up.
and we cannot make a correct diagnosis in a timely manner. Second, in the previous reports, the location of duodenal synovial sarcoma was all in the duodenal lumen, but in this case, the lesion occurred between the intestinal walls of the duodenal bulb and could not be found endoscopically, and the same report has not been seen in the past. Therefore, the report of this case helps gastroenterologists to increase vigilance when encountering such diseases to avoid misdiagnosis.

Until now, 33 cases of synovial sarcoma of the digestive system have been reported, including 10 cases in the esophagus, 1 case in the esophagogastric junction, 13 cases in the stomach, 1 case in the gastroduodenal junction, 5 cases in the duodenum, 1 case in the jejunum, 1 case in the ileum, and 1 case in the colon. The four cases previously reported can be found under endoscopy. One case relapsed 8 months after surgery, and three cases lost follow-up results. We first reported the case of synovial sarcoma originating between the intestinal wall of the duodenal bulb, and had a follow-up time of 13 months. The clinical situation of previous cases and our case are summarized in Table 1 (12-33). Symptoms include dysphagia, upper abdominal pain, and bleeding. We can conclude that the median age of patients with synovial sarcoma of the digestive system is 42 years old (range, 14–76 years), and although there is no obvious gender difference, the ratio of males to females is approximately 1:1. The tumor size ranges from 2 to 16 cm. The macroscopic morphology is primarily polypoid. There have been 17 cases of the monophasic type, 12 cases of the biphasic type, and 2 cases of the poorly differentiated subtype. The histological type of 2 cases was not reported in the literature. The monophasic type is common in synovial sarcoma. In the literature, 32 cases were treated with chemotherapy twice without significant adverse reactions. Up to now, there was no recurrence or metastasis.

The 5- and 10-year survival rates of patients with synovial sarcoma of bone tissue are 76.4% and 60.4%, respectively, which are related to tumor size, tumor grade, chemotherapy, and radiation therapy (37). Since synovial sarcoma of the digestive system is difficult to diagnose, easily misdiagnosed, has a high degree of malignancy, and few cases are seen, there is no relevant literature that reports the long-term survival rate of patients with this disease. After following up for 13 months, our case was no recurrence or metastasis. Bergh et al. (38) divided synovial sarcoma patients into a low-risk group (patients age <25 years, tumor size <5 cm, histological classification as monophasic or biphasic) and a high-risk group (patient age <25 years, tumor size ≥5 cm, histological classification as poorly differentiated). It has also been suggested that
Table 1: Reported cases of synovial sarcoma of the digestive tract

<table>
<thead>
<tr>
<th>Author, year, reference</th>
<th>Location</th>
<th>Presenting symptoms</th>
<th>Age, years</th>
<th>Gender</th>
<th>Gross features</th>
<th>Size, cm</th>
<th>Histologic type</th>
<th>Translocation</th>
<th>Treatment</th>
<th>Follow-up status and (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmer et al. 1983, (13)</td>
<td>Esophagus</td>
<td>Dysphagia</td>
<td>75</td>
<td>Female</td>
<td>Polypoid</td>
<td>2.5</td>
<td>Biphasic</td>
<td>–</td>
<td>Surgery + radiotherapy</td>
<td>Died of other cause, 24</td>
</tr>
<tr>
<td>Bonavina et al. 1998, (21)</td>
<td>Esophagus</td>
<td>Achalasia</td>
<td>63</td>
<td>Female</td>
<td>Polypoid</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Billings et al. 2000, (22)</td>
<td>Gastroesophageal junction</td>
<td>Incidental finding for pyloric Stenosis</td>
<td>47</td>
<td>Female</td>
<td>Polypoid</td>
<td>5.2</td>
<td>Biphasic</td>
<td>t(X;18)</td>
<td>Surgery</td>
<td>Alive without evidence of disease, 21</td>
</tr>
<tr>
<td>Billings et al. 2000, (22)</td>
<td>Stomach</td>
<td>Abdominal pain, nausea, vomiting</td>
<td>55</td>
<td>Female</td>
<td>Spherical intramural</td>
<td>16</td>
<td>Biphasic and poorly differentiated synovial sarcoma</td>
<td>t(X;18)</td>
<td>Surgery</td>
<td>Died of other cause, 6</td>
</tr>
<tr>
<td>Chan et al. 2004, (23)</td>
<td>Jejunum</td>
<td>Epigastric pain, vomit, fever</td>
<td>28</td>
<td>Male</td>
<td>Polypoid intramural</td>
<td>15</td>
<td>Monophasic</td>
<td>t(X;18)</td>
<td>Surgery</td>
<td>Died of other cause, 1</td>
</tr>
<tr>
<td>Butori et al. 2006, (24)</td>
<td>Esophagus</td>
<td>Dysphagia</td>
<td>72</td>
<td>Female</td>
<td>Polypoid</td>
<td>11</td>
<td>Biphasic</td>
<td>t(X;18)</td>
<td>Surgery + chemotherapy</td>
<td>6</td>
</tr>
<tr>
<td>Akhunji et al. 2007, (25)</td>
<td>Stomach</td>
<td>Epigastric pain</td>
<td>42</td>
<td>Male</td>
<td>–</td>
<td>11</td>
<td>Biphasic</td>
<td>t(X;18)</td>
<td>Surgery + chemotherapy</td>
<td>Died of other cause, 24</td>
</tr>
<tr>
<td>Parfitt et al. 2007, (26)</td>
<td>Colon</td>
<td>Rectal bleeding</td>
<td>32</td>
<td>Male</td>
<td>Polypoid</td>
<td>2</td>
<td>Monophasic</td>
<td>t(X;18)</td>
<td>Surgery</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 1 (continued)
<table>
<thead>
<tr>
<th>Author, year, reference</th>
<th>Location</th>
<th>Presenting symptoms</th>
<th>Age, years</th>
<th>Gender</th>
<th>Gross features</th>
<th>Size, cm</th>
<th>Histologic type</th>
<th>Translocation</th>
<th>Treatment</th>
<th>Follow-up status and (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schreiber-Facklam et al. 2007, (27)</td>
<td>Duodenum</td>
<td>Abdominal pain</td>
<td>39</td>
<td>Female</td>
<td>Polypoid</td>
<td>5</td>
<td>Monophasic</td>
<td>t(X;18)</td>
<td>Surgery + chemotherapy</td>
<td>Recurrence 8 months after surgery</td>
</tr>
<tr>
<td>Makhlouf et al. 2008, (28)</td>
<td>Stomach</td>
<td>–</td>
<td>67</td>
<td>Female</td>
<td>–</td>
<td>0.8</td>
<td>Monophasic</td>
<td>t(X;18)</td>
<td>Surgery</td>
<td>Alive without evidence of disease, 12</td>
</tr>
<tr>
<td>Makhlouf et al. 2008, (28)</td>
<td>Stomach</td>
<td>–</td>
<td>49</td>
<td>Male</td>
<td>–</td>
<td>2</td>
<td>Monophasic with a poorly differentiated component</td>
<td>t(X;18)</td>
<td>Surgery</td>
<td>Died of other cause, omental metastasis, 29</td>
</tr>
<tr>
<td>Makhlouf et al. 2008, (28)</td>
<td>Stomach, gastroduodenal junction</td>
<td>–</td>
<td>54</td>
<td>Female</td>
<td>–</td>
<td>3</td>
<td>Monophasic</td>
<td>t(X;18)</td>
<td>Surgery</td>
<td>Recent case</td>
</tr>
<tr>
<td>Makhlouf et al. 2008, (28)</td>
<td>Stomach</td>
<td>–</td>
<td>58</td>
<td>Female</td>
<td>–</td>
<td>3</td>
<td>Monophasic</td>
<td>t(X;18)</td>
<td>Surgery</td>
<td>Alive without evidence of disease, 21</td>
</tr>
<tr>
<td>Makhlouf et al. 2008, (28)</td>
<td>Stomach</td>
<td>–</td>
<td>37</td>
<td>Female</td>
<td>–</td>
<td>4</td>
<td>Monophasic</td>
<td>t(X;18)</td>
<td>Surgery</td>
<td>Local recurrence, re-excised, died of other cause, 48</td>
</tr>
<tr>
<td>Makhlouf et al. 2008 (28)</td>
<td>Stomach</td>
<td>–</td>
<td>50</td>
<td>Male</td>
<td>–</td>
<td>6</td>
<td>Monophasic</td>
<td>t(X;18)</td>
<td>Surgery + chemotherapy</td>
<td>Alive with recurrence, 6</td>
</tr>
<tr>
<td>Makhlouf et al. 2008, (28)</td>
<td>Stomach</td>
<td>–</td>
<td>42</td>
<td>Male</td>
<td>Polypoid</td>
<td>8</td>
<td>Biphasic</td>
<td>t(X;18)</td>
<td>Surgery + chemotherapy</td>
<td>Died of other cause, 25</td>
</tr>
<tr>
<td>Makhlouf et al. 2008, (28)</td>
<td>Stomach</td>
<td>–</td>
<td>66</td>
<td>Female</td>
<td>Polypoid</td>
<td>15</td>
<td>Monophasic</td>
<td>t(X;18)</td>
<td>Surgery</td>
<td>Lost to follow up</td>
</tr>
<tr>
<td>Borens-Fefer et Duodenum al. 2009, (29)</td>
<td>Duodenum</td>
<td>Pain</td>
<td>14</td>
<td>Male</td>
<td>–</td>
<td>5</td>
<td>Monophasic</td>
<td>t(X;18)</td>
<td>Surgery + chemotherapy</td>
<td>Lost to follow up</td>
</tr>
<tr>
<td>Company Campins et al. 2009, (12)</td>
<td>Proximal duodenum</td>
<td>Weight loss</td>
<td>69</td>
<td>Female</td>
<td>Spherical intramural</td>
<td>8</td>
<td>Monophasic</td>
<td>t(X;18)</td>
<td>Surgery</td>
<td>Died due to complications, 1</td>
</tr>
<tr>
<td>Garcia Ruiz et al. 2010 (30)</td>
<td>Duodenal</td>
<td>Pain</td>
<td>70</td>
<td>Male</td>
<td>Polypoid</td>
<td>9</td>
<td>Biphasic</td>
<td>t(X;18)</td>
<td>Surgery</td>
<td>Lost to follow up</td>
</tr>
</tbody>
</table>
the genotyping and prognostic correlation of SS remains uncertain (39). Synovial sarcoma appears in the head and neck, trunk, lung pleura, and peritoneal organs, and areas other than the limbs usually have a worse prognosis. Moreover, tumor size (>5 cm), nerve infiltration, vascular invasion, P53 overexpression, and high expression of Ki-67 increase the risk of SS metastasis and recurrence (40-42).

We would like to know if the prognosis of synovial sarcoma of the digestive system is related to the above-mentioned factors. Unfortunately, no clinical data have demonstrated the prognostic factors of digestive system synovial sarcoma. Therefore, in order to solve this problem, we should collect more cases and join more medical institutions to make a breakthrough in the prognosis of synovial sarcoma in digestive system.

In conclusion, primary synovial sarcoma of the digestive system is rare and easily misdiagnosed. We reported the first case of synovial sarcoma arising between the intestinal walls of the duodenal bulb with a concomitant SYT/SSX type of the t(X;18) translocation. At present, there are few reports on the diagnosis and treatment of duodenal synovial sarcoma. We hope to deepen our general perception and understanding of synovial sarcoma through report of this rare sarcoma.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-1107). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are
appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

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References


