The management of pancreatic metastasis from synovial sarcoma of the soft tissue: A case report

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Abstract
Pancreatic metastases are rare, accounting for 2%–3% of pancreatic tumors. The pancreas represents an unusual metastatic site of synovial sarcoma (SS) outside the usual localizations (regional nodes, lung, bone, and liver). The diagnosis is evoked by the personnel medical history of SS and imaging then confirmed by histological examination of the guided pancreatic biopsy. Its therapeutic management is mainly surgical with extensive removal of the lesion. So far only four cases have been reported in the English literature. We reported the case of a male aged 30-year-old who was admitted to our Institute for a local recurrence of SS of the left thigh which was initially treated by surgical excision. The patient underwent a wide surgical excision followed by chemotherapy and radiotherapy. About 15 months later, he experienced a pancreatic metastasis of his SS. He had a caudal splenopancreatectomy with partial resection of the transverse colon followed by chemotherapy. This report highlights the diagnostic difficulties of this rare localization and therapeutic challenge.

Keywords
Pancreatic, metastasis, synovial sarcoma, therapeutics

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Introduction
Soft tissue sarcoma is a rare mesenchymal neoplasm, accounting for approximately 1% of all adult cancers.¹ Synovial sarcoma (SS), a malignant soft tissue tumor, forms up to 10% of sarcomas in soft tissue.²⁻⁴ Indeed, metastasis occurs in approximately 50% of patients due to its aggressive potential. Lung, lymph nodes, and bone are respectively the most common sites of metastasis.⁵ Pancreatic SS metastasis is very rare, and they are mostly detected in the autopsy. In the majority of cases, the disease can affect several organs at the same time, and even though they were detected before death, there is no surgical treatment.⁶ Isolated pancreatic SS metastasis can be treated by surgery, in rare cases. In this article, we present a case of surgically treated solitary pancreatic metastasis from SS, and we discuss the clinical, radiological, and treatment characteristics of SS pancreatic metastasis.

Case report
We report the case of a 30-year-old male patient who was treated initially in another facility for SS of the left thigh. He underwent wide excision with free margins. The tumor measured 3 cm in its greatest diameter. Anatomopathological examination showed: a monophasic spindle cell synovial sarcoma in a fascicular arrangement. Immunohistochemistry showed positivity for bcl2, cytokeratin, epithelial membrane antigen

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Rare Tumors (EMA), CK, and negativity for chromogranin A, synaptophysin, and vimentin. About 6 months later, he was admitted to our institute for a local recurrence confirmed by biopsy. A thoracic-abdominopelvic computed tomography (CT) scan was performed and didn’t reveal any secondary locations. The patient underwent a wide excision, with a vascular replacement of the femoral artery and coverage with a flap of the left rectus abdominis muscle. The following operations were straightforward. The surgical limits were free. The search for the SYT-SXX fusion transcript was not completed. The patient underwent six cycles of ifosfamide-based chemotherapy followed by adjuvant external radiotherapy at a dose of 54 Gy. After 15 months of regular clinical and radiological follow-up, the patient presented a pancreatic mass diagnosed on a CT scan. The mass was located on the tail of the pancreas. It was heterogeneous, solid, enhanced after the injection of the contrast agent. Tumor markers: ACE, CA19-9, and NSE were negative. A biopsy under CT scan was performed and the histologic exam confirmed the metastatic nature of the pancreatic mass. The patient was reluctant to surgical treatment, and he was lost of view for 4 months. Due to the onset of transfixed abdominal pain and the increase in abdominal volume, the patient consulted after 4 months. An abdominal ultrasound showed an increase in the size of the lesion to 15 cm. The thoracic-abdominopelvic CT scan was performed and it showed a pancreatic mass invading the transverse colon without any other metastatic localizations (Figure 1). The patient underwent a laparotomy. Upon exploration, a mass of the tail and body of the pancreas was discovered invading the transverse colon. There was no ascites or carcinosis. The rest of the abdominal cavity was free of sarcomatosis (Figure 2). The procedure consisted of a caudal splenopancreatectomy with partial resection of the transverse colon.

Pathological examination showed a pancreatic localization of the previously diagnosed monophasic synovial sarcoma with free surgical margins (Figures 3 and 4). He underwent four cycles of first-line metastatic chemotherapy with high-dose ifosfamide and doxorubicin. The patient developed an endocrine pancreatic insufficiency requiring insulin therapy. The patient died 6 months later due to a diabetic coma.

Discussion

Sarcoma is a malignant tumor arising from mesenchymal tissue. It is less common than carcinoma and occurs mainly in young people.1 SS, a malignant soft tissue tumor, forms up to 10% of sarcomas in soft tissue.2-4 Owing to its
aggressive potential, metastasis occurs in around 50% of patients. The most common sites of metastasis are respectively: lungs, lymph nodes, and bone.5

The pancreas is an uncommon metastatic site, accounting for around 2% of pancreatic cancers.7–9 The most usual primary malignancy of pancreatic metastasis is renal cell cancer, colorectal cancer, melanoma, and lung cancer, while pancreatic metastasis from the synovial soft tissue sarcoma is extremely rare, with only four cases recorded worldwide to date.10–13

We present the fifth case of pancreatic metastasis from soft tissue SS.

The metastases of sarcomas are preferentially propagated by the hematogenous pathway.5

The isolated pancreatic metastasis is still unclear. Reviewing the reported cases of pancreatic metastasis of SS resumed in Table 1, we notified that in all the cases, the primary tumor was located in the lower limbs. This observation may lead to think about the presence of a shunt between the lower limbs and the pancreas. This theory has to be confirmed by autopsy to look for abnormal vascularization that may explain the isolated pancreatic metastasis.

With the presented patient, the pancreatic metastasis was asymptomatic initially, and then the patient developed symptoms such as pain and an increase in abdomen volume. Clinically, we can observe non-specific symptoms in the pancreatic metastasis from SS like pain, jaundice, nausea, anorexia, weight loss, and palpable abdominal mass as a primary pancreatic tumor.10–13 In the reported cases the pancreatic metastasis was discovered incidentally in three cases and symptomatic in two cases.

Tumors markers in pancreatic metastasis are often negative when they were reported.

The diagnosis of pancreatic metastasis remains difficult. Imaging findings can not differentiate between the pancreatic metastasis and the primary pancreatic carcinoma.10–13

The imaging characteristics of synovial sarcoma pancreatic metastasis have a wide variety of differential diagnoses, as primary pancreatic cancer, pancreatic neuroendocrine tumors, pancreatic metastases from renal cell carcinoma (RCC), and other rare pancreatic tumors.14,15

In endoscopic ultrasonography, Krishna et al.12 reported a cystic appearance of the mass.

In computed tomography scan (CT), the mass was heterogeneous, hypervascular, enhanced after injection of contrast product. The microcalcifications were inconstant. The dilatation of the intra and extrahepatic ducts depends on the pancreatic localization.10,11,13

Makino et al reported a heterogeneous enhancement on contrast-enhanced ultrasonography. The MRI features of the pancreatic metastasis showed a heterogeneous mass and were described as a hypo-, hyper-, and hyper-intense lesion on T1-, T2-, and diffusion-weighted images, respectively.13

18 F fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) in high-grade bone and soft tissue sarcoma may bring significant benefit to routine CT/MRI staging. The benefit consists of upstaging tumors and to detect any microfocus metastasis that not have been detected in the routine imaging.16

To date, only Makino et al performed a PET scan to stage the tumor, and there was no abnormal uptake in the whole body.13 In our case, we didn’t perform a PET scan due to a lack of availability at the moment of diagnostic.
We summarized the radiologic characteristics in the table below of the reported cases (Table 2).

As we have reported there is no pathognomonic clinical, radiological or biological sign of pancreatic metastasis from SS. However, the diagnosis of pancreatic SS metastasis still relies on medical SS history and histological findings.

We performed a CT guided biopsy to confirm the diagnosis of pancreatic metastasis from SS. Diagnostic confirmation can be obtained by biopsy either under CT scan control or under echoendoscopy,\textsuperscript{11–13} in one case the diagnosis of pancreatic metastasis from SS was obtained after pancreatectomy (Table 3).\textsuperscript{10}

Histological findings of pancreatic metastasis from SS are similar to the primary tumor.

Histologically, SS is subdivided into three subtypes: Monophasic type consisting only of spindle cells (50%–60%), biphasic type consisting of both epithelial and spindle cell components (20%–30%), and poorly differentiated type (15%–20%).\textsuperscript{3,4} The prognostic of monophasic and biphasic SS is similar.\textsuperscript{2} However, the poorly differentiated type clinical path seems to be aggressive with early recurrence and metastasis.

In four of the reported cases, the histological subtype of SS was monophasic.

On immunohistochemistry, synovial sarcoma is positive for keratins and EMA, bcl-2, and transducin-like enhancer of split-1, and negative for desmin and a-SMA, and CD34.\textsuperscript{3,17,21,22} However, the sensitivity and specificity of these markers are insufficient.\textsuperscript{17–19}

SS is characterized by the presence of a pathognomonic translocation between chromosomes X and 18, t(X;18)(p11.2;q11.2), which results in several SS18:SSX fusion proteins expression. The most common of which are SS18-SSX1, SS18:SSX2, and much more rarely, SS18:SSX4. In 95% of patients, fusion is detectable and constitutes an effective diagnostic tool.\textsuperscript{23}

In our case we identified the same histologic features of the primary SS (monophasic), however, the genetic identification of the SS18-SSX1 or SS18-SSX2 fusion gene wasn’t performed.

The standardized treatment of primary localized SS consists of wide surgical resection of the tumor followed by radiotherapy in high-risk patients (i.e. tumor > 5 cm, grade 3, and deeply located).\textsuperscript{24,25}

Doxorubicin and ifosfamide regimen are also considered for patients with localized SS in both the neoadjuvant and adjuvant settings.\textsuperscript{24–26}

SS is generally considered a high-grade sarcoma, characterized by a poor prognosis, with expected 5-year survival.

### Table 1. The characteristics of the primary tumor of reported cases and our case of pancreatic metastasis from synovial sarcoma.

| Author             | Sex | Age (Y) | Location                  | treatment                  | Recurrence | Interval of recurrence | Recurrence location     | Treatment of recurrence |
|--------------------|-----|---------|---------------------------|----------------------------|------------|------------------------|-------------------------|-------------------------|
| Yamamoto et al. 10 | F   | 26      | Right thigh              | Surgical resection         | Yes        | 24 months              | Local + lungs           | Surgical resection      |
| Patel et al. 11    | F   | 34      | Left thigh               | Wide resection + RT        | No         | –                      | –                       | –                       |
| Krishna et al. 12  | M   | 37      | Right ilium + left glenoid | NT                        | –          | –                      | –                       | –                       |
| Makino et al. 13   | M   | 32      | Left pelvis + femur      | Wide resection + CT + RT   | No         | –                      | –                       | –                       |
| Our case           | M   | 30      | Left thigh               | Surgical resection         | Yes        | 6 months               | Local                   | Wide resection + CT + RT |

F: female; M: male; Y: years; RT: radiotherapy; CT: chemotherapy.

### Table 2. Radiologic characteristics of reported cases and our case of pancreatic metastasis from synovial sarcoma.

| Authors            | Imaging methods | Size (mm) | location | Description                                      |
|--------------------|----------------|-----------|----------|--------------------------------------------------|
| Yamamoto et al. 10 | CT             | UF        | Head     | Heterogenous                                    |
| Patel et al. 11    | CT             | 80        | Head     | Heterogenous, dilatation of the intrahepatic and extrahepatic ducts to the level of the pancreas. |
| Krishna et al. 12  | CT/EUS         | 19, and 12 | Tail     | Cystic appearance, septated, and had a thick wall. |
| Makino et al. 13   | CT/CEUS/MRI/ PET CT | 35       | Body     | CT: Heterogeneous, enhanced hypervascular mass. CEUS: Heterogeneous enhancement MRI: hypo-, hyper-, and hyper-intense lesion on T1, T2-, and diffusion-weighted images, respectively PET CT: low uptake |
| Our case           | CT             | 150       | Tail     | CT: Heterogeneous, enhanced mass.              |

CT: computed tomography scan; EUS: Endoscopic ultrasound; CEUS: Contrast-enhanced ultrasonography; MRI: Magnetic resonance imagery; PET CT: positron emission tomography-computed scan; UF: unspecified.
ranging from 50% to 60% in adult patients and 5-year metastatic disease-free survival (DFS) ranging from 40% to 60%.27,28

The treatment of SS metastasis remains non-codified. To date, there are only 4 cases of pancreatic metastasis from SS, and only 2 cases had a surgical treatment.10–13

We had an isolated pancreatic metastasis, therefore we have opted for a wide surgical resection: a caudal splenopancreatectomy with partial resection of the transverse colon followed by 4 cycles of high-dose ifosfamide and doxorubicin.

Due to the rarity of the pancreatic metastasis from SS, there is no evidence of treatment guidelines, and the therapeutic strategy has been extrapolated from the treatment of pulmonary metastases from SS and treatment of isolated pancreatic metastases from other cancer types.7–9,29,30

In the case of pulmonary metastasis from SS, long-term survival was observed in the case of complete resection of the metastasis.29,30 Moreover, the efficacy of pancreatic metastasectomy in different cancer forms such as RCC has been demonstrated.7–9

Strobel et al. defined four factors associated with a good prognosis after resection for pancreatic metastases from different malignant tumors: primary RCC, a >3-year interval between resection of the primary tumor and development of pancreatic metastases, isolated pancreatic metastases, and no prior recurrence.9

There were only two cases that have been treated surgically (Table 3). The first case met one criterion, she had a pancreaticoduodenectomy without adjuvant chemotherapy and the patient achieved a disease-free survival period of >6 years after resection.10 the fourth case met 3 criteria, he underwent laparoscopic distal pancreatectomy followed by chemotherapy and the patient achieved 30 months disease-free.13 Our case met one criterion of the Strobel factors.

| Author          | Biopsy          | Histological subtype | Interval between primary/last recurrence and PM, Y | Number of PM | Treatment            | Adjuvant therapy | Prognosis       |
|-----------------|-----------------|----------------------|---------------------------------------------------|--------------|----------------------|------------------|-----------------|
| Yamamoto et al.17 | ND              | NA                   | 2                                                 | 1            | PPPD                 | No               | DFS 6 years    |
| Patel et al.18   | CT-GB           | Monophasic           | 10                                                | 1            | Biliary drainage     | NA               | NA              |
| Krishna et al.19 | EUS-FNA         | Monophasic           | 0                                                 | 2            | NA                   | NA               | NA              |
| Makino et al.13  | EUS-FNA         | Monophasic           | 4                                                 | 1            | Laparoscopic DP      | CT: AI + ICE     | DFS 30 months  |
| Our case         | CT-GB           | Monophasic           | 1.25                                               | 1            | DP + splenectomy + partial resection of the transverse colon. | CT: ID           | DFS 6 months  |

ND: not done; NA: not available; Y: years; CT-GB: computed tomography-guided biopsy; EUS-FNA: endoscopic ultrasound-guided fine-needle aspiration; PM: pancreatic metastasis; DP: distal pancreatectomy; PPPD: pylorus-preserving pancreaticoduodenectomy; CT: chemotherapy; AI: adriamycin/ifosfamide; ICE: ifosfamide, carboplatin, and etoposide; ID: ifosfamide and doxorubicin; DFS: disease-free survival.

The standard frontline chemotherapy in SS is anthracycline in advanced SS, whereas the combination of an anthracycline with ifosfamide is a heated topic that is mostly a histology-driven decision.31

Thus, in first-line chemotherapy for patients with advanced disease, the options are anthracycline as a single agent or combined with ifosfamide, provided that the regimen associated with the best expected antitumor effect is the combination, with an expected response rate (RR) ranging between 25% and 60%.31–33

Trabectedin has demonstrated an antitumor effect in patients resistant to anthracycline.34–36

Tyrosine kinase inhibitors have some activity in SS, but pazopanib is the only one approved for the treatment of SS. Metabolic therapy, molecular targets, and immunotherapy for advanced SS are under investigation.26

In conclusion, we have presented a rare entity of pancreatic metastasis from SS that was treated by splenopancreatectomy with partial resection of the transverse colon followed by chemotherapy. Within our presented case we have highlighted the importance of monitoring late postoperative complications. However pancreatic metastasectomy can be a therapeutic approach if the metastasis is unique.

Further cases are needed to establish the treatment guidelines of this rare entity.

Authors’ contributions
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