Primary pancreatic synovial sarcoma: Report of a rare case and review of the literature

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Abstract. Synovial sarcoma is a mesenchymal spindle cell tumor. Primary pancreatic sarcomas are extremely rare. The present study describes a rare case of synovial sarcoma in the head of the pancreas. A 35-year-old male presented with left upper quadrant abdominal pain. An endoscopic ultrasound examination revealed a complex solid-cystic lesion in the pancreatic head. He had undergone pancreaticoduodenectomy (Whipple procedure). A histological examination yielded negative results for AE1/AE3, CD10, S100, CD34, desmin, smooth muscle actin, β-catenin, CD117, HMB45, chromogranin and synaptophysin. However, the results were positive for TLEI and vimentin, which is consistent with synovial sarcoma. Synovial sarcoma is a soft tissue malignant tumor. Primary pancreatic sarcomas frequently present as large, high-grade tumors in the pancreatic head. Histologically, there are several types of synovial sarcoma, such as monophasic, biphasic and poorly differentiated. A histological examination is necessary for the diagnosis as the imaging findings are not specifically suggestive of synovial sarcoma. The preferred course of treatment is complete resection with wide margins, followed by adjuvant chemotherapy and/or radiotherapy. Primary mesenchymal tumors of the pancreas are extremely uncommon. As a result, a diagnosis requires careful evaluation. Surgical resection is the main modality of treatment.

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Introduction

Approximately 1% of all adult cancers are soft tissue sarcomas, which are uncommon mesenchymal neoplasms. Synovial sarcoma is a mesenchymal spindle cell tumor that exhibits variable epithelial differentiation (1). Synovial sarcoma typically affects young and middle-aged individuals, and it has a predilection for the extremities (2).

Primary pancreatic sarcomas are extremely rare and typically represent <0.1% of all primary pancreatic malignancies (3). The patient's age, tumor size, the number of mitoses, type of translocation and tumor-free resection margins are among the predictors of prognosis. The preferred course of treatment is total resection with wide margins, followed by adjuvant chemotherapy and/or radiotherapy. The overall survival rate at 5 years is between 36 and 76%, and at 10 years it is between 20 and 63% (4).

The present study describes a rare case of a primary spindle cell tumor that developed in the pancreatic head. For the literature review, a Google Scholar and PubMed literature search was conducted using the combinations of the following key words 'synovial sarcoma; spindle cell tumor; pancreatic metastasis; primary pancreatic tumor'. For the literature review, nine articles that were associated with the present study were selected from 40 available articles. Table I summarizes the pathological characteristics and mode of treatment for the pancreatic primary mesenchymal tumors in the reviewed cases.

Case report

Patient information. A 35-year-old male with a known family history of pancreatic cancer was referred to Hiwa Oncology Hospital (Sulaimani, Iraq) and presented with left upper quadrant abdominal pain, aggravated by eating, associated with anorexia, vomiting, and a weight loss of 20 kg in 1 month (from 98 to 78 kg).

Clinical examination. A physical examination revealed tenderness in the left quadrant of the abdomen. There was no jaundice or fever, and the vital signs were normal.

Table I. Pathological characteristics and management of pancreatic primary mesenchymal tumors in the reviewed studies.

Author, year	Pancreatic tumor site	Diagnosis	Treatment	(Refs.)
Makino *et al*, 2016	Body	Pancreatic metastasis from synovial sarcoma	Distal pancreatectomy	(1)
Nagaraju *et al*, 2017	Head	High-grade spindle cell sarcoma	Laparotomy with allograft/ pancreatectomy	(3)
Luc *et al*, 2013	Body	Monophasic Grade II synovial sarcoma of the pancreas	Distal pancreatectomy with splenectomy	(4)
Malek *et al*, 2020	Body, tail	Pancreatic metastasis from synovial sarcoma	Laparotomy/ splenopancreatectomy	(5)
Owen *et al*, 1997	Head	Myofibroblastic differentiation	Pancreaticoduodenectomy/ without preservation of the pylorus	(8)
Srinivasan *et al*, 2008	Body	Solitary fibrous tumor	Distal pancreatectomy	(6)
Kim *et al*, 2014	Head	Undifferentiated/unclassified sarcoma	Pylorus-preserving pancreaticoduodenectomy	(10)
Kim *et al*, 2014	Head	Undifferentiated/unclassified sarcoma	Biopsy without surgical resection	(10)
Kim *et al*, 2014	Tail	Undifferentiated/unclassified sarcoma	Biopsy/chemotherapy/ radiotherapy	(10)
Kim *et al*, 2014	Tail	Solitary fibrous tumor	Distal pancreatectomy	(10)
Kim *et al*, 2014	Body	Solitary fibrous tumor	Resection	(10)
Kim *et al*, 2014	Tail	Leiomyosarcoma	Distal pancreatectomy/ radiotherapy	(10)
Kim *et al*, 2014	Body	Schwannoma	Excision	(10)
Kim *et al*, 2014	Body	Schwannoma	Resection	(10)
Kim *et al*, 2014	Body	Atypical lipomatous tumor/well-differentiated liposarcoma	Excision/chemotherapy	(10)
Kim *et al*, 2014	Tail	Angiomyolipoma	Distal pancreatectomy	(10)
Kim *et al*, 2014	Tail	Solid and cystic hamartoma	Distal pancreatectomy	(10)

Diagnostic assessment. Liver biochemical tests revealed an increased level of alanine transaminase (72 IU/l; normal range, 10-50 IU/l); however, aspartate aminotransferase (22 IU/l; normal range, 10-50 IU/l) and alkaline phosphatase (96 IU/l; normal range 40-130 IU/l) levels were in the normal , reference range. As regards pancreatic enzyme levels, amylase levels were normal (39 U/l; normal range, <100 U/l), whereas lipase levels (169 U/l, normal range: ≤ 60) were elevated. The leukocyte count was normal ($7.4x10^9$/l; normal range, $4\text{-}11x10^9$/l. Endoscopic ultrasound imaging revealed a bulky heterogeneous texture of the pancreatic body and tail, diffuse lobularity of the pancreatic parenchyma, and a honeycomb appearance of the pancreas with a normal main pancreatic duct. Scanning through the duodenum revealed an anechoic cystic lesion measuring 22.6x27.6 mm in the pancreatic head with some solid components in the wall of the cyst and no communication was observed with the main pancreatic duct (data not shown; ultrasound images are not available as these were performed in another center). The findings indicated the presence of a complex pancreatic solid-cystic lesion.

Therapeutic intervention. The patient underwent a pancreaticoduodenectomy (Whipple procedure). The pancreatic head, a portion of the small intestine, the gall bladder and the bile duct were all removed during the procedure. The resected tumor size was 1.5x1.5 cm. The histological examination (performed as described below) revealed a cellular tumor composed of neoplastic spindle cells with faint cytoplasm and elongated oval-nuclei, illustrating mild atypia arranged in a syncytial manner (Fig. 1). The tumor was infiltrative into the surrounding pancreatic tissue, with the pathological stage of pTI-pN0 Mx. There was no necrosis, and the tumor mitotic activity revealed sparse mitosis (<5/50 high-powered field). The immunohistochemistry work-up was negative for each of the epithelial markers (AE1/AE3), vascular markers CD34, smooth muscle markers (desmin, smooth muscle actin and β-catenin), gastrointestinal stromal tumor (CD117),

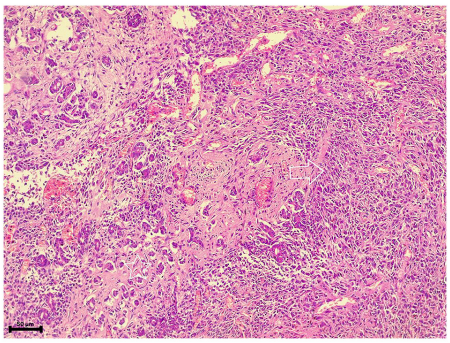

Figure 1. Image (x400 magnification) illustrating an infiltrative lesion composed of malignant spindle cells (arrow) with the presence of benign pancreatic acini (star).

melanoma marker (HMB45) and progesterone receptor as well. Chromogranin and synaptophysin staining were negative in Langerhans islet cells and scattered endocrine cells. Positive stains for TLEI and vimentin (moderate and diffuse nuclear staining patterns) and negative for other markers were consistent with synovial sarcoma. No neoadjuvant or adjuvant therapy was used for the patient, as the patient was young and the tumor was small, localized and had a low mitotic rate.

Histopathological staining procedure. The specimen (3 mm) was fixed in 10% neutral-buffered formalin for 2-3 days at 25˚C. The DiaPath Donatello automated processor (Diapath S.P.A.) was used for further processing the sample through the following steps: Using 10% neutral-buffered formalin with an average time of 20 min; deionized water for 10 min; dehydration and fixation by alcohol (70%), followed by 95 and 99% (each step lasted 1-1:30 min); washing by three stations of xylene (total 3 h); paraffin wax infiltration (three stations, each lasted for 1 h).

The Sakura Tissue-Tek embedding system (Sakura Finetek USA, Inc.) was used for embedding the blocks in paraffin wax. The tissue sections were then placed through the Sakura Accu-Cut SRM microtome (Sakura Finetek USA, Inc.). The sections were floated in a Sakura 1451 water bath at 40-50˚C and placed on regular glass slides. The DiaPath Giotto autostainer (Diapath S.P.A.) was used to color the slides with hematoxylin and eosin stains. The following steps were used: i) Washing the slides with xylene three times for 7, 7 and 5 min, respectively; ii) using pure alcohol for 3 min, followed by 90% alcohol for 4 min, 70% alcohol for 3 min and finally, tap water for 2 min; iii) using hematoxylin Gill II for 8 min at room temperature (Sigma-Aldrich Hematoxylin Natural Black 1; Sigma-Aldrich; Merck KGaA); iv) using tap water for 4 min, followed by ammonia water and tap water for 1 min for each, and then 70% alcohol for 2 min. Eosin, prepared from Sigma-Aldrich Eosin-Y disodium salt was used for 5 min at room temperature, and the slides were then washed with tap water for 1 min. Following that, 70% alcohol was used for 15 sec, 90% for two min, and 100% three times, each for 3 to 4 min. Finally, xylene was used in three stations lasting 3, 5 and 4 min, respectively. The slides were allowed to dry for 5 min before being screened under a light microscope (Leica microsystems, Germany).

Follow-up. The patient experienced mild surgical site pain following the procedure. He was discharged from the hospital after an abdominal ultrasound revealed no notable findings. At 3 months following the surgery, a computed tomography (CT-scan) and magnetic resonance imaging (MRI) revealed mild pancreatic duct dilatation with a 1.5 cm cyst at the site of anastomosis without any obvious signs of recurrence.

Discussion

A sarcoma is a malignant tumor that develops from mesenchymal tissue. It is less frequent than carcinoma and affects mostly adolescents. Synovial sarcomas are malignant soft tissue tumors of unknown etiology (4,5). These tumors can appear in a variety of sites and are currently considered to result from a mutation in mesenchymal cells. Primary pancreatic sarcomas commonly present as large, high-grade tumors in the pancreatic head, and they are more common in females than in males (4). Liposarcoma, leiomyosarcoma and malignant fibrous histiocytoma are identified as other types of malignant pancreatic mesenchymal tumors (6). According to the literature, the first surgical excision of a pancreatic spindle cell sarcoma was likely performed by Trendelenburg in 1882, and Segre provided the first pathological descriptions of two cases of pancreatic primary sarcoma (7,8). Primary pancreatic tumors are relatively large at presentation. The average size of a primary pancreatic tumor was reported to be 7.5 cm in the study by Youngwirth *et al* (9) and Kim *et al* reported a mean tumor size of 5.8 cm in primary pancreatic sarcomas (10).

The tumor size, high mitotic activity, the appearance of cellular atypia, or malignant indicative characteristics are all associated with a poor prognosis. Late recurrences or metastases are not infrequent (8,11). Histologically, there are three types of synovial sarcoma, including monophasic (consisting only of spindle cells) (50-60%), biphasic (consisting of both epithelial and spindle cell elements (20-30%) and poorly differentiated (15-20%) (1). The prognosis of both the monophasic and biphasic histological subtypes has been reported to be the same in the literature. Moreover, poorly differentiated types have an aggressive clinical history that often includes early recurrence and metastasis (12).

Due to the rarity of primary pancreatic mesenchymal tumors, further attention is required for diagnosis. First, it is crucial to exclude metastasis from primary tumors originating from locations outside the pancreas, such as the retroperitoneum, female genital tract, extremities, or gastrointestinal tract. Second, in the case that a microscopic examination reveals the malignant spindle cell components, the possibility of sarcomatoid carcinoma should be considered (10). Synovial sarcoma is often portrayed as a heterogeneously enhanced, well-defined tumor on a contrast-enhanced CT scan-or MRI. However, as these imaging features are not specifically indicative of synovial sarcoma, a histological examination is required for the diagnosis (1). The case described in the present study was a 35-year-old male, and an endoscopic ultrasonography revealed a complex solid cystic lesion in the pancreas.

Thus, histology and immunohistochemistry (IHC) examinations are used to demonstrate the presence of synovial sarcoma. Recently, gene expression profiling studies

have revealed overexpression of the transcriptional corepressor, TLE1, in synovial sarcoma (11,13,14), and further research discovered that >90% of synovial sarcomas had moderate-to-strong TLE1 nuclear staining by IHC (11). As in the present study, IHC staining for TLEI and vimentin was positive, the patient was diagnosed with synovial sarcoma. The specific genetic abnormality that characterizes synovial sarcoma is a non-random chromosomal translocation between the long arm of chromosome 18 and the short arm of chromosome X; these specific markers are helpful in making a definitive diagnosis using reverse transcription PCR (2). Therefore, to confirm the diagnosis, the existence of the SS18-SSX1 or SS18-SSX2 fusion gene needs to be examined (1). A definite protocol for treating these lesions is not discussed as there are a few case reports of primary mesenchymal tumors of the pancreas. Furthermore, the effectiveness of neoadjuvant or adjuvant chemotherapy or radiotherapy is also inconclusive due to the rarity of this lesion and the limited long-term follow-up (10). When deciding whether to remove a pancreatic tumor surgically, numerous factors are considered. In the study by Youngwirth *et al* (9), younger patients, smaller tumors and lower grades of tumors were associated with more successful decisions about resection. Therefore, complete resection with wide margins is the preferred course of treatment, followed by radiation and/or chemotherapy. Systemic chemotherapy is usually attempted for unresectable masses (1,4). In the study by Youngwirth *et al* (9), only 39.5% of patients had surgery. Other treatment modalities, such as chemotherapy and radiation therapy, were only utilized in a small number of cases and it has been discovered that patients who underwent surgical resection had a higher chance of survival. A study from the Mayo Clinic data (15) confirmed the same outcomes (9). Previous representative large case series studies have demonstrated that the 5-year overall survival rate of adults with synovial sarcoma ranges from 57 to 75%. The high application of adjuvant chemotherapy may be responsible for this relatively improved outcome (12,16,17). Although Takenaka *et al* (12) did not demonstrate a significant difference in survival between patients receiving adjuvant chemotherapy and those who did not, this was probably due to the diversity of chemotherapeutic regimens in each center. Makino *et al* (1) managed a case of left pelvic and femoral synovial sarcoma. The patient underwent extensive tumor resection followed by reconstruction and a constrained complete hip megaprosthesis, with neoadjuvant adriamycin/ifosfamide (AI) therapy for four cycles and adjuvant AI therapy for one cycle. Following regular monitoring, the diagnosis of pancreatic metastases from synovial sarcoma was confirmed (1). The patient then received two cycles of adjuvant AI chemotherapy, followed by two cycles of ifosfamide, carboplatin and etoposide, with no significant adverse events and no recurrence for 30 months (1). In the study by Luc *et al* (4), no adjuvant therapy was used after the pancreatic monophasic grade II synovial sarcoma was diagnosed. They performed a distal pancreatectomy with splenectomy and found a pathologically poorly differentiated intrapancreatic tumor that had central necrosis and inflammation (4). Patients in the study by Youngwirth *et al* (9) who underwent surgical resection had smaller tumors and tumors that were poorly or undifferentiated, similar to the case described herein. Owen *et al* (8) concluded that a pancreatoduodenectomy was an effective treatment for two cases of large, pathologically malignant stromal tumors that presented in the head of the pancreas. After 2 and 10 years of follow-up, both patients were still alive and exhibited no signs of either locally recurrent disease or distant metastasis (8). Guillou *et al* demonstrated that the histological grade (grade 2 vs. 3) of the French Federation of Cancer Centers (FNCLCC) is the most critical prognostic factor for survival in patients with synovial sarcoma (18). Youngwirth *et al* (9) revealed that a worse tumor grade and patient age were related to decreased adjusted survival in patients who underwent surgical resection. This is crucial as it differentiates pancreatic sarcomas from other types of pancreatic cancer. In addition, they demonstrated a relatively high margin positivity, which is known as a poor prognostic indicator due to the size and location of the tumors in the pancreatic head (9). Margin involvement and lymph node metastases have been found to be the most significant prognostic factors in previous studies on pancreatic cancer as a whole. However, a higher tumor grade has been linked to a lower overall survival rate in sarcomas (19). Pancreaticoduodenectomy was performed in the patient described herein. Neoadjuvant or adjuvant therapy was not used due to four favorable prognostic factors: A small, localized tumor, a low mitotic rate, and the patient's age.

The major limitations of the present study are the lack of biomarker evaluation and FDG-PET-CT scan evaluation reports, as these could not be retrieved. As no standard guideline was available for primary synovial carcinoma, the patient was followed-up as a case of pancreatic adenocarcinoma.

In conclusion, pancreatic primary mesenchymal tumors are extremely rare. Consequently, a diagnosis requires a careful evaluation. Further investigations, such as IHC examinations are helpful for a differential diagnosis. Due to the rarity of the reported cases, information on the clinicopathologic characteristics and the benefits of different treatment modalities are limited. Surgical resection is the main method of treatment.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KS and OH were the surgeons who performed the operation. SMA and RMA were the oncologists who managed the case. AMA was the pathologist who examined the specimen, and was also a major contributor to the conception of the study. BJM and FA were major contributors to the conception of the study, as well as in the literature search for related studies. FHK and DMH were involved in the literature review, the writing of the manuscript, as well as in the analysis and interpretation of the

patient's data. MK and BAA were involved in preparing and obtaining the staining image from histopathological analysis. MK and BAA confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Written informed consent was obtained from the patient whose case is presented herein.

Patient consent for publication

Written informed consent was obtained from the patient whose case is presented herein for the publication of his data and any related images.

Competing interests

The authors declare that they have no competing interests.

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