Primary Leiomyosarcoma of the Pancreas

A Case Report and Review of the Literature

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• **Primary leiomyosarcoma of the pancreas is a rare tumor for which only 21 reports appear in the world literature. We describe an additional case of pancreatic leiomyosarcoma in a 76-year-old man, who complained of persistent high fever. Histologic examination revealed a pleomorphic spindle cell tumor. Reactivity for muscle-specific actin, α-smooth muscle actin, and basement membrane components, along with negative staining for epithelial and neural markers, were consistent with a smooth muscle sarcoma. The patient died of disease 1 year after complete surgical excision. This report highlights the need to use a complete antibody panel in order to accurately immunophenotype pleomorphic malignant tumors of the pancreas. A review of the cases compiled in the literature indicates that pancreatic leiomyosarcoma, like its counterpart arising in deep soft tissues, is an aggressive neoplasm characterized by short survival and a high rate of metastases.**

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Primary sarcomas of the pancreas are extremely rare, accounting for 0.1% of malignant pancreatic (non-islet) neoplasms.[1] In most instances, malignancies of sarcomatous appearance involving this organ are undifferentiated (sarcomatoid) carcinomas or pancreatic extensions of retroperitoneal and gastroduodenal sarcomas. Malignant mesenchymal tumors arising within the pancreas include leiomyosarcomas, malignant peripheral nerve sheath tumors, malignant fibrous histiocytomas, liposarcomas, rhabdomyosarcomas, and hemangiopericytomas.[2] However, most have been reported in small series or as single cases without definitive evidence of cell differentiation by electron microscopy or immunohistochemistry.[1,3–18] These investigations may be relevant in definitively confirming the cell lineage of the tumor because sarcomas of different histogenesis, especially pleomorphic tumors, may display similar histologic features.[19] We describe an additional case of primary pancreatic leiomyosarcoma, with discussion of the clinical, histologic, and immunohistochemical characteristics of this neoplasm.

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REPORT OF A CASE

A 76-year-old man presented with a 5-month history of persistent high fever. He was otherwise asymptomatic, with no anorexia, weight loss, or jaundice. Physical examination and a complete laboratory profile were unremarkable. Preoperative investigations included a computed tomography (CT) scan, which demonstrated a large, solid mass replacing the tail of the pancreas, without invasion of surrounding tissues (Figure 1). There was no evidence of liver involvement. Chest radiographs and a scintigraphic bone scan were negative. Laparotomy revealed a large, well-circumscribed tumor located in the tail of the pancreas. It protruded mainly anteriorly and was intimately associated with the pancreatic parenchyma posteriorly. No direct invasion of adjacent structures, including the retroperitoneal fat, was found. Distal pancreatectomy with splenectomy was performed. The patient remained well for 9 months. He was then readmitted with dull epigastric pain and a spiking fever. Sonography of the upper abdomen, followed by laparotomy, demonstrated recurrence in the form of a multiloculated, cystic mass with a thick, irregular wall. The patient died 1 year following initial surgery. Neither a confirmatory biopsy nor an autopsy study was performed.

MATERIALS AND METHODS

The operative specimen was fixed in 10% neutral buffered formalin. One section for each centimeter of tumor diameter was embedded in paraffin and stained with hematoxylin-eosin for routine histology. Five additional sections were submitted after a preliminary evaluation, bringing the total up to 13. Immunohistochemical studies were performed on serial sections with the streptavidin-biotin complex method (Dako labeled streptavidin-biotin [LSAB] kit, Dako Corporation, Carpinteria, Calif), using a panel of antibodies against the following antigens: cytokeratin (monoclonal antibody [MoAb] clone AE1/AE3; BioGenex, San Ramon, Calif); epithelial membrane antigen (EMA) (MoAb clone E29/EP1; Dako); vimentin (MoAb clone V9; BioGenex); muscle-specific actin (MSA) (MoAb clone HHF35; Dako); α-smooth muscle actin (MoAb clone 1A4; Sigma Chemical Co, St Louis, Mo); S100 protein (polyclonal; Dako); neuron-specific enolase (NSE) (MoAb clone MIG-N3; BioGenex); laminin (MoAb clone 4C7; Dako); and type IV collagen (MoAb clone CIV 22; Dako).

PATHOLOGIC FINDINGS

On macroscopic examination, an 8.0 × 7.0 × 6.5–cm firm, solid mass replacing the tail of the pancreas was noted. The cut surface was fleshy, with yellow areas of necrosis. The spleen was unremarkable.

Histologic examination revealed a nonencapsulated spindle cell proliferation with expanding margins and entrapment of the residual ductal, acinar, and endocrine structures (Figure 2). The tumor cells were arranged in bundles and fascicles, intersecting at right angles and occasionally displaying a cartwheel pattern. The nuclei were

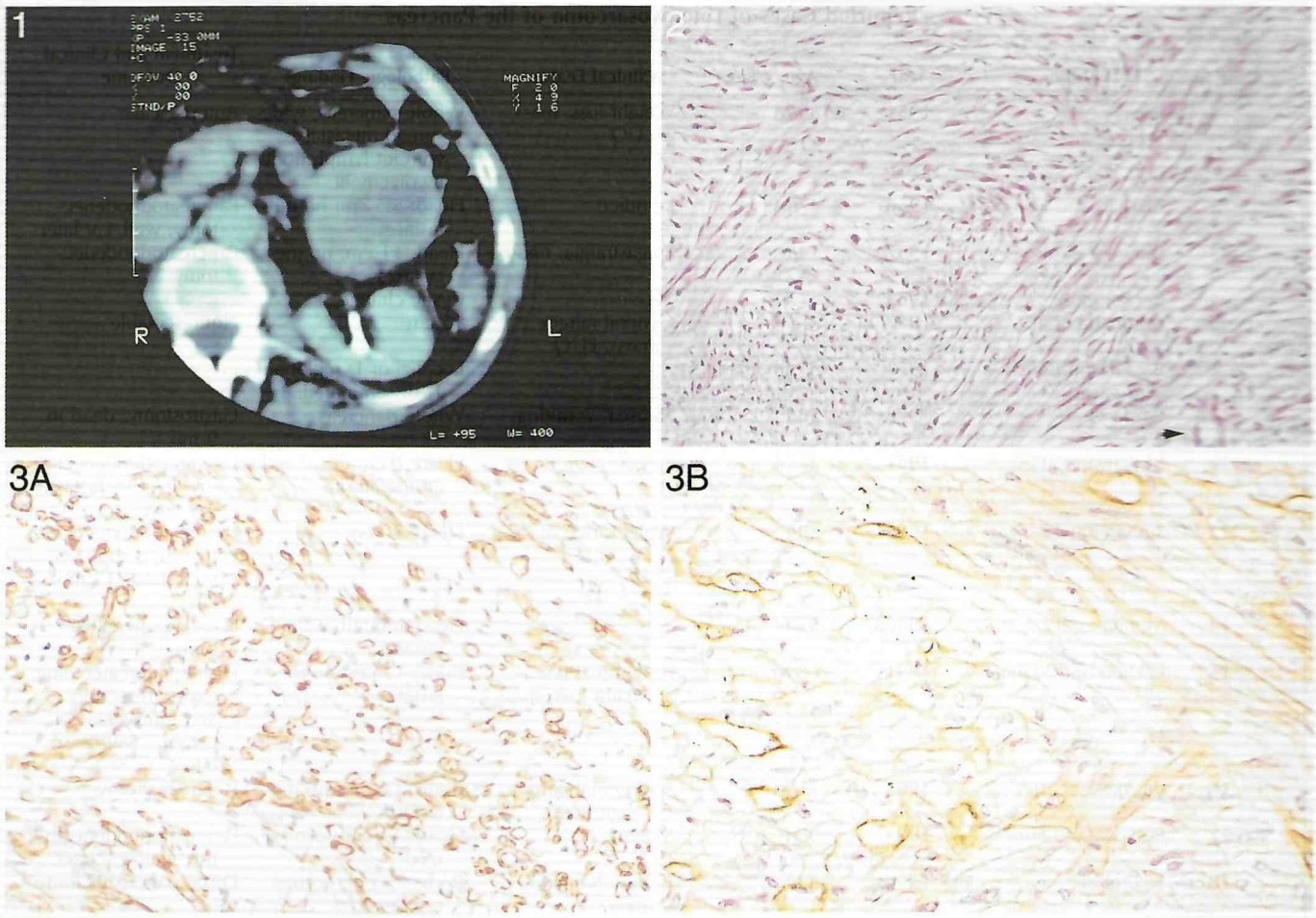

Figure 1. *Computed tomographic (CT) scan showing a solid mass in the tail of the pancreas.*

Figure 2. *Spindle cells arranged in fascicles intersecting at right angles. An entrapped pancreatic ductule can be seen in the lower right corner (arrow) (hematoxylin-eosin, original magnification ×250).*

Figure 3. *A, Strong immunoreactivity of tumor cells to α-smooth muscle actin (labeled streptavidin-biotin [LSAB], original magnification ×400). B, Laminin-staining basal lamina around individual tumor cells (LSAB, original magnification ×400).*

generally elongated and occasionally cigar shaped with blunt ends. The cytoplasm was weakly to distinctly eosinophilic. Foci of round rather than spindle-shaped cells, with a diffuse pattern of growth, comprised less than 10% of the tumor mass. Despite extensive tumor sampling, conventional adenocarcinomatous or squamous elements were not found. Nuclear atypia and pleomorphism were marked in the more densely cellular areas, where frequent mitotic figures, up to 12 mitoses per 10 high-power fields (HPFs), could be identified.

The resected peripancreatic lymph nodes and surgical margins were free of tumor. Immunohistochemical analyses demonstrated strong positive cytoplasmic labeling for vimentin, MSA, and α-smooth muscle actin. Laminin and type IV collagen decorated the cell surface, whereas desmin, CD34, S100 protein, cytokeratin, and NSE were not detectable (Figure 3, A and B).

The morphologic and immunohistochemical features of the tumor were consistent with a leiomyosarcoma with pleomorphic areas (high-grade leiomyosarcoma).

COMMENT

We report a case of primary pancreatic leiomyosarcoma. The tumor was solitary and located within the anatomic boundaries of the pancreas. No direct invasion of neighboring structures was demonstrated, and a complete clinical evaluation of the patient excluded secondary pancreatic involvement by a sarcoma of the retroperitoneal tissue or gastrointestinal tract. Immunoreactivity for MSA and α-smooth muscle actin, coupled with positive labeling with basement membrane components (ie, laminin and type IV collagen) and negative staining for cytokeratin and EMA, qualified this tumor as a smooth muscle sarcoma.

Leiomyosarcomas arising in the pancreas must be differentiated histologically from sarcomatoid carcinomas and other nonmyogenic spindle cell sarcomas, namely fibrosarcomas, malignant fibrous histiocytomas, and malignant peripheral nerve sheath tumors. The differential diagnosis should also include myofibroblastic proliferations (so-called inflammatory myofibroblastic tumors), which have been occasionally reported in the pancreaticobiliary region.[20] In order to arrive at a correct diagnosis, extensive sampling should be performed to identify any areas of well-formed fascicles of spindle cells with blunt-ended nuclei intersecting at right angles, displayed by typical myogenic tumors. Immunohistochemical analyses are of great value in evaluating spindle cell tumors with prominent

Reported Cases of Leiomyosarcoma of the Pancreas

Case No.	Author	Year	Age, y/Sex	Clinical Features	Pathologic Findings	Treatment and Clinical Outcome
1	Ross[3]	1951	80/M	Weight loss, mass, LUQ	Whole pancreas; widespread metastases without lymph node involvement	Autopsy case
2	Berman and Levene[4]	1956	47/M	Jaundice	Head; 5.5 cm; no metastases	Pancreatoduodenectomy; well 1 y later
3	Feinberg et al[5]	1957	14/M	Epigastralgia, nausea	Head; 11 cm; no metastases	Pancreatoduodenectomy
4	Becker et al[6]	1965	. . .	. . .	Cystic change	. . .
5	Oyamada et al[7]	1970	47/M	General fatigue, mass, LUQ	15 cm	Nonresectable
6–10	Baylor and Berg[1] (5 cases)	1973	51 (median); M:3, F:2	. . .	Localized: 1; regional: 1; disseminated: 3	. . .
11	Carda et al[8]	1976	56/F	Nausea, vomiting	Whole pancreas	Gastrostomy; dead in 9 mo
12	Ishikawa et al[9]	1981	44/M	Epigastralgia, mass	Head; 8 cm; localized at operation	Pancreatoduodenectomy; liver metastasis 4 y later
13	Tulha et al[10]	1982	28/F	Weight loss, mass	Head; 20 cm	Pancreatoduodenectomy; lung and liver metastases 15 mo later
14	Murata et al[11]	1990	55/F	. . .	Head and tail; no metastases	Caudal pancreatectomy
15	Lakhoo and Mannell[12]	1991	68/M	Abdominal pain, weight loss, mass	Body; 17 cm; no metastases	Distal pancreatectomy, gastric resection, and transverse colectomy; well 2 y later
16	de Alava et al[13]	1993	71/M	Abdominal pain, weight loss	Body; 3.6 cm; no metastases	Pancreatectomy
17	Peskova and Fried[14]	1994	68/F	Melena	Head; 15 cm; localized	Pancreatoduodenectomy; well 3 y later
18	Sato et al[15]	1994	53/F	Abdominal pain, mass	Body; 25 cm; no metastases	Distal pancreatectomy
19	Ishii et al[16]	1994	66/M	Incidental finding	Tail; 14 cm; widespread metastases without lymph node involvement	Nonresectable
20	Aranha et al[17]	1995	46/F	Epigastralgia, nausea, vomiting	Body; 3 cm; localized	Distal pancreatectomy; dead in 9 mo
21	Owen et al[18]	1997	40/M	Abdominal pain	Head; 6 cm; no metastases	Pancreatoduodenectomy; well 10 y later
22	Present case	2000	76/M	Fever	Tail; 8 cm; localized	Distal pancreatectomy; dead in 12 mo

cellular pleomorphism and/or a focally storiform pattern, supposed to be of smooth muscle origin. They reveal positivity for muscle markers (ie, MSA, α-smooth muscle actin, and desmin) with negative reactions for epithelial (ie, cytokeratin, EMA, and CEA) and neural (ie, S100 protein) antigens. Immunoreactivity for MSA is consistent with a myogenic line of differentiation, and staining with α-smooth muscle actin seems to be a valuable marker for smooth muscle, whereas reactivity for desmin is more variable, depending on fixation, and is less consistently found in leiomyosarcomas.[21] However, the expression of either smooth muscle actin or desmin should not be equated with myogenic differentiation because myofibroblasts may also exhibit this immunophenotype in a variety of neoplastic and nonneoplastic conditions. Electron microscopy or immunohistochemical demonstration of basement membrane components (ie, laminin and type IV collagen) outlining individual tumor cells provides additional evidence of smooth muscle lineage.[22] Smooth muscle tumors may display epithelioid features, consisting of round to polygonal cells with variable nuclear pleomorphism and atypia. The immunophenotype allows them to be distinguished from carcinomas on the basis of their reactivity for muscle markers, notwithstanding their occasional keratin positivity.[2,21]

As leiomyosarcomas most commonly arise in the female genital tract, gastrointestinal tract, and soft tissues of the extremities and retroperitoneum, careful clinical evaluation is mandatory to rule out a primary extrapancreatic neoplasm.

To the best of our knowledge, only 21 cases of pancreatic leiomyosarcoma have been reported in the literature, in addition to the case described here (Table).

This tumor primarily affects adults in the fifth decade of life or older (mean age, 53.6 years; range 14 to 80 years) with a nearly equal male-to-female ratio. The presenting signs and symptoms, including an abdominal mass or swelling, pain, and weight loss, are nonspecific. The tumors have ranged in size from 3 to 25 cm in greatest dimension (median, 11 cm). The largest tumors frequently

underwent cystic degeneration, at times mimicking a pancreatic pseudocyst at sonography or CT examination. Although in some cases the huge size of the pancreatic mass was suggestive of a nonepithelial malignancy, the diagnosis was usually made postoperatively.

The rare incidence and incomplete clinicopathological documentation of the reported cases make it difficult to characterize the clinical behavior and identify reliable prognostic factors in primary leiomyosarcomas of the pancreas (Table).

Nine of the 22 cases were stated to have locoregional or metastatic disease at presentation. In one patient, the lesion was discovered at autopsy.[3] Another patient underwent bypass surgery and died 9 months after onset of symptoms.[8] Chemotherapy was employed in a third patient who died within 33 months of diagnosis.[16] Survival data are not available in the remaining 6 cases that were nonresectable.

Thirteen cases appeared to be localized at the time of diagnosis and susceptible to surgical resection. Of the 8 patients for whom follow-up information is available, 4 patients, including the present one, died of their tumors 9 to 48 months after diagnosis,[9,10,17] whereas 4 patients were alive and free of disease at 12, 36, 48, and 120 months after initial surgical treatment.[4,12,14,18]

Although size is a decisive factor with regard to tumor resectability, it does not seem to affect the clinical course after surgical resection. However, available published data indicate that mitotic counts of more than 10 mitoses/10 HPFs appear to be associated with a shortened interval to an adverse outcome.

In conclusion, although the number of the cases reviewed here is small, leiomyosarcoma of the pancreas is a highly malignant neoplasm and usually pursues an aggressive clinical course, like its counterpart arising in deep soft tissues. An attempt at complete tumor resection can offer patients the best hope for prolonged survival.

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