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CASE REPORT

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Pancreatic leiomyosarcoma

Case report with immunohistochemical and flow cytometric studies

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Abstract A leiomyosarcoma originating from the pancreas of a 57-year-old man is presented. A 6×5×4 cm tumour was located in the head region, and the patient underwent surgical palliation. Immunohistochemical studies excluded an epithelial origin; a myogenic origin was suggested by strong vimentin and smooth muscle actin positivity. Flow cytometric analysis revealed an aneuploid pattern (DNA index: 1,561). The patient died with widespread metastases 7 month after the operation.

Key words Leiomyosarcoma · Pancreatic neoplasms · Human tumours · Immunohistochemistry · Flow cytometry

Introduction

Histologically, the vast majority of the pancreatic malignancies are adenocarcinomas of ductal origin, while mesenchymal tumours account for only a small fraction (approx. 0.6%) of the cases [15]. Fibrosarcomas [18], malignant fibrous histiocytomas [2], haemangio-pericytomas [4], malignant schwannomas [17], and liposarcomas [7] are all found, and an islet cell tumour exhibiting rhabdomyosarcomatous differentiation has also been described [8]. Primary leiomyosarcomas are exceptional findings in the pancreas, with 26 cases reported so far [1, 3, 6, 11–13, 15, 19–22, 25, 27]. We now add a new case to this series, supplemented with immunohistochemical and flow cytometric studies.

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Clinical history

The patient was a 57-year-old man. His past medical history was unremarkable except for a transient sick sinus syndrome 8 years before. He was admitted to the Surgical Clinic because of dull abdominal pain and repeated vomiting. Apart from a slightly increased sedimentation rate (13 mm/h) the laboratory findings were within normal limits and no jaundice was noted (serum bilirubin level: 19.6 μmol/l, SGOT: 21, SGPT: 33, alkaline phosphatase: 155, serum amylase: 27, urine amylase: 198 U/l). Abdominal ultrasound and CT revealed a nonhomogeneous mass measuring 6×5×4 cm located in the head of the pancreas; no metastatic foci were seen in the liver. At surgery, definitiv resection proved to be impossible, because the tumour was firmly attached to the duodenum, resulting in compression. The inferior vena cava was also compressed. An intraoperative biopsy specimen was taken, and a frozen section diagnosis of nonepithelial spindle-cell neoplasm of indeterminate histogenesis was established. For palliation a retrocolic gastroenteroanastomosis was constructed. In the postoperative period clinical signs of partial intestinal obstruction developed, necessitating resection of adhesions and a Braun anastomosis, but finally the patient was discharged in a good general condition.

One month later at the control check-up the serum bilirubin level was found to be elevated (42.6 μmol/l), but the transaminase,

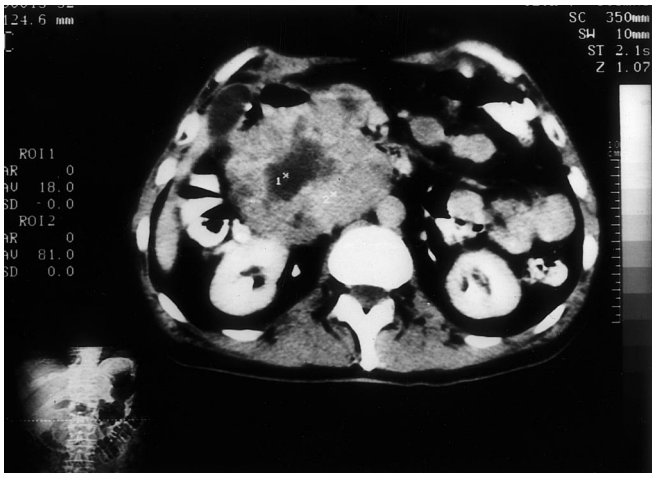

Fig. 1 Abdominal CT scan showing a large, nonhomogeneous tumour mass in the head of the pancreas. The central portion of the tumour shows irregular cystic degeneration

alkaline phosphatase and amylase activities were within the normal ranges. Abdominal CT revealed that the tumour mass had increased in size (10×9×9 cm) and that the surrounding tissues were infiltrated, but the liver was still free of metastases. In the central areas of the neoplasm a cystic degeneration (Fig. 1.) was observed (by Dr. Kutas).

Six months later the patient was readmitted with obstructive jaundice, melaena and tumour recurrence and he died shortly afterwards.

Materials and methods

The tumour tissue obtained during the operation measured 2×2×0.5 cm. Its consistency was firm, the cut surface was homogeneous and greyish-yellow, without any cystic changes. Microscopically, the tumour was almost entirely composed of elongated, closely packed cells arranged in storiform or herring-bone patterns (Fig. 2a). The ovoid nuclei had blunt edges. Blood vessels were not predominant elements, and glandular components were completely lacking. Necrotic areas were seen in the centre of the specimen, surrounded by bizarre, multinucleated giant tumour cells (Fig. 2b). There was a small amount of connective tissue. Occasionally, individual cells displayed pale, foamy or vacuolated cytoplasm. Mitotic figures were frequent (7/10 HPF).

Immunohistochemistry was carried out by an indirect method, with visualization by streptavidin and a biotinylated enzyme system. The following primary antibodies were used: cytokeratin (DAKO, Clone MNF116, which reacts with CKs 5, 6, 8, 17 and probably also 19; 1:40), neuron-specific enolase (NSE; DAKO, 1:20), neurofilament (DAKO, 1:1), chromogranin A (BioGenex, 1:1), S-100 protein (DAKO, 1:1), CD68 (DAKO, 1:50), vimentin (DAKO, 1:25) and smooth muscle actin (DAKO, 1:50). The tumour expressed no cytokeratin, NSE, neurofilament, chromogranin A or S-100 protein, but it exhibited a strong diffuse positivity for vimentin and smooth muscle actin (Fig. 2c). Moderate positive reaction for CD68 was also found in isolated cells with pale or foamy cytoplasm.

Grade III leiomyosarcoma was given as the final histological diagnosis.

At autopsy, the whole of the pancreatic head was replaced by a friable, greyish-red tumour measuring 17×10×6 cm, with obstructive icterus. The body and tail of the pancreas were spared. No ascites was noted. The tumour had infiltrated the omental bursa, the inferior vena cava and the retroperitoneal tissues and metastasized to the right lobe of the liver (a solitary tumour 3 cm in diameter was observed). In the cortical areas of the kidneys multiple metastatic foci measured around 0.5 cm. No peritoneal dissemination was observed, and the lungs were devoid of secondary deposits. The histological picture and the immunohistochemical pattern of the tumour were identical to those of the surgical specimen.

Flow cytometric DNA analysis (FACStar; Becton-Dickinson) was performed on formalin-fixed, paraplast-embedded sections 50 μm thick, according to our standard method [14]. DNA index and the synthetic S phase fraction (SPF) were determined by using Rabinovitch's Multicycle Software. The proliferation index was defined as the sum of SPF% and G_2% of the cell cycle. The tumour proved to be aneuploid, the DNA index being 1.561, with a high proliferation index (19.8%). More than 11% of the cells were in S-phase (Fig. 3).

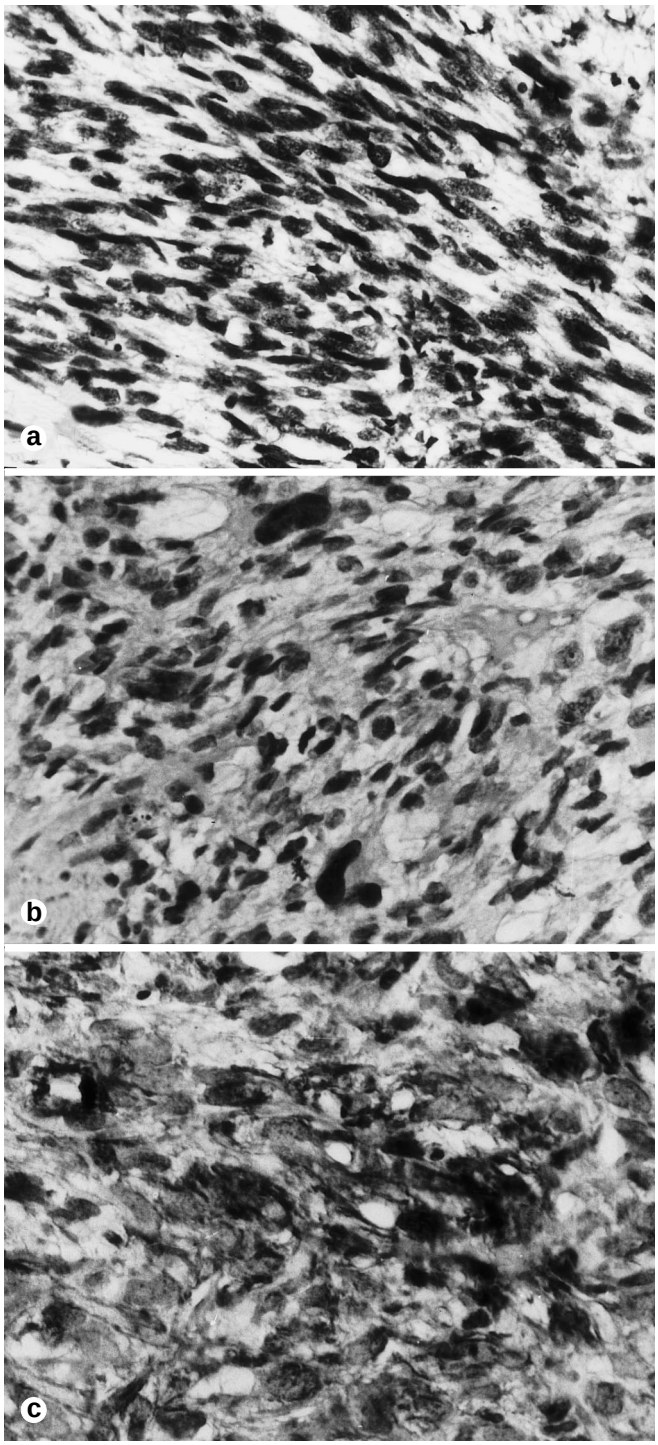

Fig. 2a–c Microscopic appearance of the leiomyosarcoma. **a** The tumour is composed of fusiform, interlacing elements arranged in a herring-bone pattern. In the centre some mitotic figures are observed. HE, ×400 **b** Among the spindle cells some tumour giant cells are seen with hyperchromatic, bizarre nuclei. HE, ×400 **c** The myogenic origin of the tumour is shown by immunohistochemical studies: the cells express strong smooth muscle actin positivity. ×400

Discussion

The overwhelming majority of pancreatic malignancies are of epithelial origin, and other histological types are exceptional findings. Lüttges et al. [15], analysing a large series of primary pancreatic neoplasms, found 5 nonepithelial tumours (1 malignant peripheral nerve

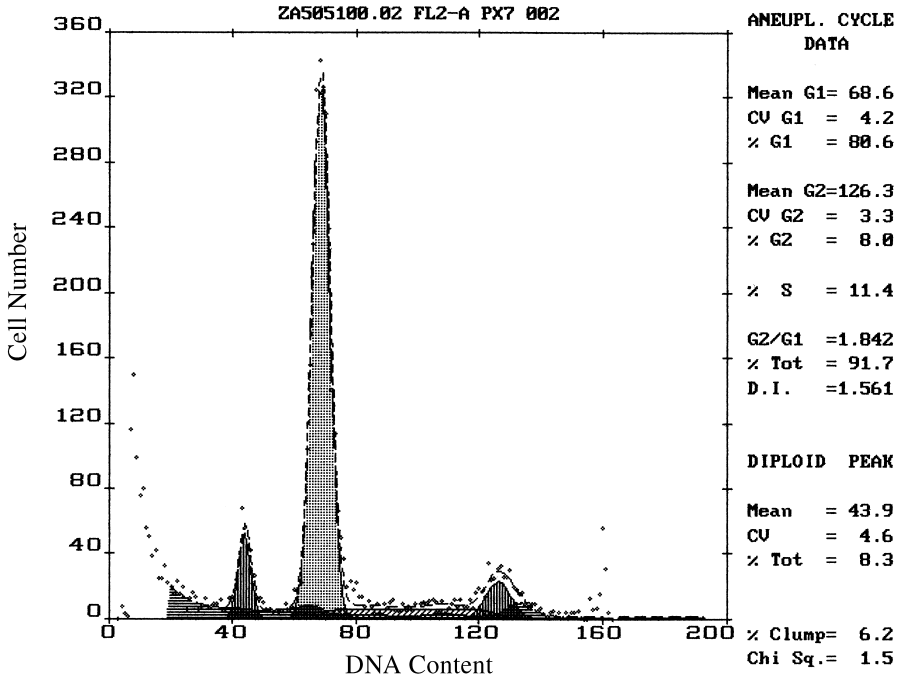

Fig. 3 On the DNA histogram an aneuploid pattern is seen (DNA index=1.561; S-phase fraction=11.4%; G_2 phase=8%)

sheet tumour, 1 leiomyosarcoma, 1 malignant mesothelioma and 2 PNETs). Pure sarcomas are very rare, and any leiomyosarcomatous tissue may be a component of a carcinosarcoma [16]. Since 1951 when Ross presented the first case [20], very few additional leiomyosarcomas have been reported [1, 3, 6, 11–13, 15, 19, 22, 25, 27].

The differential diagnosis of leiomyosarcoma includes highly anaplastic ductal adenocarcinomas, which have significant pleiomorphism or bizarre giant cells [26], and the carcinomas of fusiform cells (spindle cell or sarcomatoid carcinomas) must also be considered [5]. Negative cytokeratin and positive vimentin staining ruled out an epithelial origin for our tumour. Malignant fibrous histiocytoma may closely resemble leiomyosarcoma [2], but although some pale cells with foamy cytoplasm exhibited CD68 positivity, the vast majority of the tumour cells (over 90%) expressed an unequivocal, strong positive reaction for smooth muscle actin, indicating a myogenic origin [9]. The diagnosis of carcinosarcoma was not considered, because no part of the tumour proved to be cytokeratin positive [16].

It may be difficult to exclude secondary deposits on the basis of operative findings alone, and in some cases leiomyosarcomas have metastasized to the pancreas from a distant primary tumour [10]. In our case, however, the autopsy confirmed that the pancreas was the primary site of origin.

Roughly two-thirds of patients with this tumour are women, and the mean age at presentation is the middle of the 5th decade. In some cases the pancreatic head is the site of origin; however, because these tumours are typically huge, they frequently replace the whole organ. Cystic changes like those in our case are not uncommon. Widespread metastases occur frequently, and the liver is typically affected. DelGallo et al. have recently reported a very unusual intracanalicular spread via the bile ducts, but this peculiar form of metastasis is a curiosity [6].

The tumour is thought to originate from either the smooth muscle elements of the pancreatic ducts or the wall of small intrapancreatic vessels. In this context, Russ suggests that leiomyosarcoma might derive from the splenic vein and spread to the pancreas [21].

Although the prognosis of the gastrointestinal stromal tumours is unpredictable, and there are cases with exceptionally long survival after operation [28], pancreatic leiomyosarcomas seem to be highly aggressive malignancies. They are discovered at an advanced stage and have a propensity to invade the surrounding organs and vessels. In our case the tumour had attached to the duodenum and the inferior vena cava, preventing radical operation.

The value of flow cytometric analysis in the prognosis of gastrointestinal smooth muscle tumours is debatable. Some leiomyosarcomas display a diploid pattern [23, 24], but the high-grade tumours are generally very aggressive and aneuploidy is associated with a significantly worse prognosis [24]. In our case the brisk mitotic rate and the aneuploidy suggested a grave prognosis and survival was indeed short.

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