Review

Endoscopic Ultrasound

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Comments and illustrations of the European Federation of Societies for Ultrasound in Medicine contrast-enhanced ultrasound guidelines: Multiparametric imaging and EUS-guided sampling in rare pancreatic tumors. Benign mesenchymal pancreatic tumors

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ABSTRACT

The focus of the review is on primary benign mesenchymal pancreatic tumors and their imaging appearance. These tumors are extremely rare. Usually, they are not diagnosed until postoperative histology is available, and so even benign tumors have undergone extensive pancreatic resection. The very limited data on abdominal and EUS findings including contrast-enhanced techniques of these pancreatic lesions are summarized here. Case reports will be presented for some of these rare tumors with application of modern ultrasound and endosonographic techniques.

Key words: Benign mesenchymal pancreatic tumors; Misdiagnoses; Contrast-enhanced ultrasound (CEUS); EUS; Imaging

INTRODUCTION

The World Federation for Ultrasound in Medicine and Biology has published guidelines on the use of contrast-enhanced ultrasound (CEUS) for the evaluation of focal liver lesions[1–5] and the European Federation of Societies for Ultrasound in Medicine for the evaluation of nonhepatic indications.[6,7] More recently, the guidelines have been commented and illustrated.[8–19] Improved detection and characterization of common focal pancreatic lesions such as ductal adenocarcinoma, neuroendocrine tumors, and pancreatic metastases are the main topics of these guidelines. The Asian Federation of Societies of Ultrasound in Medicine and Biology has established guidelines for contrast-enhanced EUS.[20] However, there are few data and no generalizations for pancreatic mesenchymal tumors. Mesenchymal tumors of the pancreas are very rare. Mesenchymal tumors occurring in the digestive tract and their biological potential are reported in the 2019 World Health Organization classification.[21] A possible manifestation on the pancreas is mentioned. Primary mesenchymal tumors account for approximately 0.3%–0.5% of all histologically confirmed pancreatic tumors.[22,23] One-third of these are benign, intermediate, or malignant mesenchymal tumors, respectively.[22,23]

Primary pancreatic mesenchymal tumors reported in the literature are listed in Table 1. Preoperative diagnosis is a major challenge. Most mesenchymal tumors were surgically resected under a different presumptive diagnosis, and the diagnosis was made postoperatively. The diagnostic pitfalls are shown in Figure 1: a neuroendocrine tumor is suspected.[120–122] EUS-guided sampling cannot confirm this diagnosis. Instead, features of a mesenchymal tumor are found without being able to differentiate and classify it more precisely [Figure 1]. This case reflects the dilemma of nonsurgical diagnosis of benign mesenchymal pancreatic tumors.

Preoperative diagnoses of all mesenchymal tumors in the retrospective study of Kim et al.[22] and Zhang et al.[23] were as follows: pancreatic ductal adenocarcinoma (PDAC), pancreatic neuroendocrine tumor (PanNEN), mucinous cystadenoma, serous microcystic adenoma, Castleman disease, chronic pancreatitis, solid pseudopapillary neoplasm (SPN), and invasive intraductal papillary mucinous neoplasm. The diagnoses of mesenchymal tumor in these series were

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Table 1

Mesenchymal tumors with primary pancreatic manifestation.

Benign mesenchymal pancreatic tumors	Intermediate mesenchymal pancreatic tumors	Malignant mesenchymal pancreatic tumors
Lipoma[24–32]	Solitary fibrous tumor[22,23,33–46]	Leiomyosarcoma[22,23,47–53]
Schwannoma[22,23,54–59]	Fibromatosis (desmoid tumor)[22,23,60–63]	Ewing sarcomas/primitive neuroectodermal Ewing sarcomas/PNETs[22,64–70]
Hamartoma[22,71–78]	PEComa[79–85]	Undifferentiated/unclassified sarcomas (malignant fibrous histiocytoma)[22,23,86]
Hemangioma[22,87–95]	Inflammatory myofibroblastic tumor (inflammatory pseudotumor)[96–100]	Liposarcoma[22,101]
Angiomyolipoma[22,102]		Angiosarcoma[103–107]
Ganglioneuroma[23]		Fibrosarcoma[108–111]
Myofibroblastoma[23]		Kaposi sarcoma[112,113]
		Rhabdomyosarcoma[114,115]
		eGIST[23,116–119]

eGIST: extragastrointestinal stromal tumor; PNETs: primitive neuroectodermal tumors.

possible only postoperatively.[23] The following work gives an overview of primary benign mesenchymal tumors of the pancreas, with data on imaging and the difficulties in preoperative diagnosis. Intermediate and malignant mesenchymal pancreatic tumors are not presented in this review but in separate reviews.

LIPOMA

Lipomas are usually incidental findings on imaging. They are masses of mature fat cells that are arranged in lobules and may contain fine connective tissue septa. Vascular soft tissue is absent. Lipomas, unlike focal fatty infiltration, have a thin capsule. Butler et al. diagnosed lipomas in 74 patients who underwent cross-sectional imaging (0.012% of more than 500,000 computed tomography [CT] and 100,000 magnetic resonance imaging [MRI] scans).[26] The most common location was the pancreatic head (51%).[26]

Sonographically, lipomas correspond to focal hyperechoic homogeneous lesions, which, in contrast to focal fatty infiltration, are well and smoothly circumscribed.[24] Xiao et al. described a large, histologically confirmed lipoma on ultrasound as a hypoechoic flaky lesion.[32] In the retrospective analysis by Butler et al., none of the 74 pancreatic lipomas had been initially diagnosed by ultrasound but were predominantly diagnosed by CT.[26] The pancreatic duct is not dilated.[123,124] Lipomas are mostly smaller than 5 cm and asymptomatic. Larger findings may lead to local complications, for example, duodenal stenosis or bile duct dilatation when localized to the pancreatic head.[30,31] Symptomatic, locally advanced and size progressive as well as initially large findings must be differentiated from (well-differentiated) liposarcoma.[24] Heterogeneity, contrast enhancement, or internal calcifications may correspond to liposarcoma. Lesions that exhibit those features should be further evaluated.[25,32] On CT, lipomas are homogeneous, well demarcated, fatty (HU –80 to –120), and without enhancement. Within the lesion, thin fibrolobular septa may be displayed.[24,26] On MRI, lipomas were hyperintense on T1- (T1WI) and T2-weighted images (T2WI), whereas T1 hyperintensity was suppressed on fat-suppressed sequences.[24,26] Endosonographically, the pancreatic lipoma is described as a heterogeneous lobular lesion, with hyperechoic strands and an irregular hyperechoic rim suggestive of the presence of a fibrous capsule.[27,30] Elastographically, a lipoma was not stiffer than the surrounding area.[30] An isoechoic appearance compared with the surrounding normal parenchyma has also been described in EUS.[29] In the cytology of EUS-guided sampling, mature fat cells are expected without any atypia.[27,28] Characteristics of pancreatic lipoma on imaging are listed in Table 2 [Figures 2 and 3].

Differential diagnoses of pancreatic lipomas include focal fatty infiltration, which is usually irregularly circumscribed, lipomatous pseudohypertrophy of the pancreas, focal fatty replacement,[125,126] liposarcoma, and fatty teratomas. Differentiation to PDAC and PanNEN is usually not necessary because they are not fatty.

SCHWANNOMA

Schwannomas are peripheral nerve sheath tumors. They originate from Schwann cells, which surround each axon and form the myelin sheath for the myelinated nerve fibers. Schwann cells were first described by the histologist and physiologist Theodor Schwann.[127] Pancreatic schwannomas mostly correspond to conventional schwannomas (85%), more rarely ancient (12%) or melanocytic (3%) schwannomas. Most cases are sporadic (96%). Rarely, schwannomas may occur in the setting of neurofibromatosis/Recklinghausen disease (3%) or schwannomatosis (1%).[54] Schwannomas are usually benign tumors. However, in the review of 75 published cases by Zhang et al., 5% were malignant[54] with a higher malignancy risk associated with neurofibromatosis type 1. The mean age was 55 years, and women were slightly more likely to be affected (57%). One-third of patients were asymptomatic, and abdominal pain was present in 44%. All others had nonspecific symptoms. Jaundice occurred in 7%. The mean tumor size was 5.5 +/– 5.0 cm with a range of 1.0–30.0 cm. The most common location was the pancreatic head (44%). More than half had cystic portions, 12% were purely solid, and no detailed information was available for the remainder.[54] Thus, cystic tumors represent the most important differential diagnosis.

Schwannomas are usually encapsulated. Sonographically and endosonographically, schwannomas present as smooth-bordered, hypoechoic mass, possibly with cystic parts and without macrovessels.[56,58,59,128] Calcifications and thin septations may be present, as well as a fine fibrous pseudocapsule, which is better seen on EUS, CT, or MRI compared with ultrasound. Schwannomas have 2 main microscopic growth patterns, namely, Antoni A (hypercellular component) and Antoni B (hypocellular component),

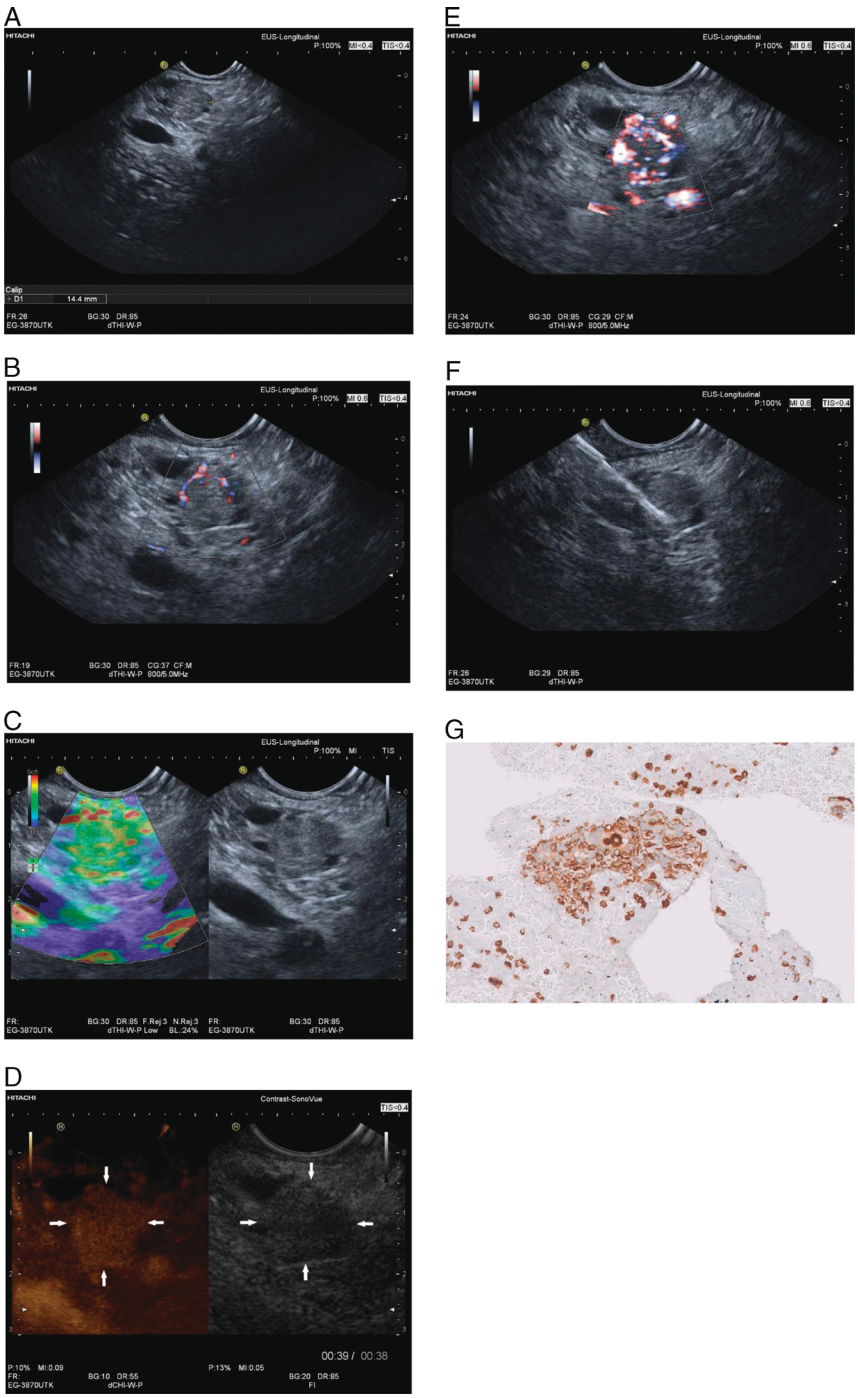

Figure 1. Suspected mesenchymal tumor of unclear classification. Female, 82 years old. In the pancreatic head, a 14-mm isoechogenic, slightly heterogeneous lesion was found between the pancreatic duct and the distal common bile duct (between the markers). Fine echogenic strands were visible in the lesion (A). Native power Doppler showed small vessels (B). On elastography, the lesion appeared softer than the surrounding pancreatic parenchyma (C). On contrast-enhanced harmonic EUS with 4.8 mL SonoVue, the lesion showed homogeneous hyperenhancement (D). A contrast-enhanced power Doppler showed many macrovessels as an expression of hypervascularization (E). A neuroendocrine tumor was suspected. EUS-guided sampling was performed with a 22-gauge needle (F). The cell groups are negative for the neuroendocrine marker's chromogranin and synaptophysin. No proliferative activity in Ki-67 imaging. Negativity of cell nests for neuron-specific enolase and progesterone receptor, but positivity for vimentin (G). With negativity for neuron-specific enolase and progesterone receptor also, there is no evidence for a solid-pseudopapillary neoplasia. The cells are not typical of lymph node tissue or metastatic renal cell carcinoma, which could explain the expression of vimentin. Vimentin expression was the reason for the suspected diagnosis of a mesenchymal tumor. All other markers were not indicative of another tumor. Cytologic, histologic, and immunohistological examination could not assign the tumor with certainty. The 82-year-old patient did not agree to surgery. Follow-up is available over 4 years. The tumor showed no size progression. Image source of histological image: Drs Bettina Fiedler, Daniel Bethmann, and Uwe Schlichting (Institute of Pathology, Sana Hospital Berlin-Lichtenberg), expression of vimentin, 200-fold magnification.

Table 2

Pancreatic lipoma on imaging.

Method	Appearance
US	Well-defined, hyperechoic (hypoechoic), pancreatic duct is not dilated[24]
CT	Well-defined, homogeneous, thin intralobular septae within the lesion, HU 80–120; nonenhanced in CE CT[24,26]
MRI	T1 and T2 hyperintense, T1 hyperintensity was suppressed on fat suppressed sequences[24,26]
EUS	Heterogeneous, lobular, hyperechoic strands, irregular hyperechoic rim (fibrous capsule)[27,30]

CE: contrast-enhanced; CT: computed tomography; HU: Hounsfield unit; MRI: magnetic resonance imaging.

named after the Swedish neurologist Nils Ragnar Eugène Antoni.[127] Antoni A and B have significance for the appearance on CT. Typical on CT is an encapsulated hypodense lesion with or without cystic degeneration. Antoni A areas are dense, with compact cellular organization and high lipid content. Therefore, schwannomas in Antoni A areas appear heterogeneous, solid, and hypodense. On contrast-enhanced CT (CE CT) scan, Antoni A areas show heterogeneous enhancement. In contrast, Antoni B areas are hypocellular and show a homogeneous pseudocystic appearance on CT without significant contrast enhancement. In addition, true cystic degeneration may occur in Antoni B areas because of vascular thrombosis and necrosis. Due to different extent of Antoni A and B areas, the appearance of schwannomas on imaging can vary considerably.[54,127] On CEUS of a cystic solid schwannoma, the capsule and septal structures showed early enhancement.[129] In another example of solid cystic schwannoma, CEUS showed an early contrast-enhanced peripheral zone and a hypoenhanced central area compared with the surrounding pancreatic parenchyma.[55] In contrast-enhanced harmonic EUS of a single case, a smooth-bordered hypoechoic schwannoma showed hypoenhancement of the solid components.[130] This is in contrast to the heterogeneously hyperenhanced Antoni A areas on CE CT. MRI has described hypointensity on T1WIs and common inhomogeneous hyperintensity on T2WIs.[54,57,59] Few schwannomas studied with fluorodeoxyglucose positron emission tomography showed uptake, but this is not evidence of malignancy in schwannomas.[54] Pancreatic schwannomas are positive for S100, vimentin, and CD56. However, spindle cells in pancreatic schwannomas are negative for cytokeratin, CD117, desmin, CD34, AE1/AE3, alpha smooth muscle actin, and smooth muscle myosin.[58,59]

Preoperative diagnostic confirmation is difficult. Twenty-five of 75 cases reviewed by Zhang et al. underwent EUS-guided sampling. Correct diagnosis of schwannoma was made in 48%, by EUS fine-needle aspiration (FNA) in only 37% and by EUS fine-needle biopsy (FNB) in 71% of cases. In 15 cases, frozen section was performed intraoperatively, leading to a correct diagnosis in 47%. Thus, in a large number of patients, the diagnosis could not be made correctly preoperatively and intraoperatively, which led in 57% of cases to Whipple surgery and distal pancreatectomy instead of limited surgery.[54] Hanaoka et al. researched 18 cases of schwannoma up to 20 mm. Twelve were investigated by EUS-guided sampling, and the diagnosis was confirmed in 9 patients (75%). EUS-FNA was performed using a 25-gauge needle in 4 patients and a 22-gauge needle in 3 patients. A biopsy needle was used in 3 patients.[58] Hanaoka et al. used a 22-gauge Acquire FNB needle to get successful material for histological and immunohistological investigation.[58] In 7 of 9 cases of successfully assigned schwannomas <20 mm, follow-up was performed instead of surgery.[58] Bruno et al.[131] reported EUS-FNA of a pancreatic schwannoma using a 25-gauge needle. However, histology specimens are shown in the figures. Diagnosis was confirmed by detection of spindle cells and positive immunostaining for S100 protein.[131] In retrospective analysis of EUS-FNA of nonpancreatic schwannomas with 19- to 25-gauge needles, the diagnostic accuracy was 66.7%.[132] However, the results were independent of needle diameter.[132] If the diagnosis is made preoperatively by EUS- or image-guided sampling, surgery can either be avoided[58,128] or limited to a local resection procedure such as enucleation or central pancreatectomy. For this purpose, obtaining histologic material is recommended.[54,59] Descriptions of pancreatic schwannoma on imaging are summarized in Table 3 [Figure 4].

Differential diagnosis

Preoperative diagnoses in 68 cases of surgically resected pancreatic schwannomas were SPN (20%), PanNEN (23%), pseudocyst (5.7%), acinar cell carcinoma (ACC) (8.6%), and mucinous cystadenocarcinoma (17%).

HAMARTOMA

Pancreatic hamartomas are not tumors but benign lesions consisting of mature cells with malformed structures. The lesion usually contains disarranged mature ducts and acini, disorganized, well-differentiated exocrine and endocrine pancreatic tissue, and abundant fibrous stroma. The excretory ducts and acini have distorted architectures but without atypia.[73,77,78] The first description was by Albrecht as "tumor-like malformation."[133] Hamartomas develop either sporadically or as part of genetic syndromes such as in tuberous sclerosis or PTEN (phosphatase and tensin homolog) hamartoma tumor syndrome.[134] In an analysis of 40 reported pancreatic hamartomas, 64% had solid pattern, and 35% had mixed cystic and solid pattern. Again, half were multicystic. Most lesions (65%) were located at the pancreatic head. The mean size was 4.4 cm (1.0–11.0 cm). Every age group was affected.[73] The pancreatic duct was not dilated.[73,75]

Sonographically, the pancreatic hamartoma was smooth-bordered, hypoechoic, and heterogeneous, without any vessels on Doppler ultrasound.[74,75] On CT and MRI, the lesions were mostly well demarcated and internally heterogeneous.[73] On CE CT, pancreatic hamartomas showed a late enhancement pattern compared with the pancreatic parenchyma. Typically, there was hypodensity with well demarcation in the arterial phase and then mild enhancement from the marginal area in the portal phase and isodensity to hyperdensity with heterogeneous contrast in the late phase.[73] Magnetic resonance imaging showed a T2WI with high signal intensity and a T1WI with low intensity.[73]

In a single CEUS report of a lipomatous hamartoma, the lesion was initially hypoenhanced at 13 seconds in the early arterial phase and then showed uneven enhancement at 19 and 25 seconds. The authors described the contrast behavior as centripetal enhancement with time progression. In the images, the lesion was less enhanced than the surrounding area despite heterogeneous enhancement. In the parenchymal phase, the lesion was hypoenhanced again after 50 seconds.[74] Endosonographically, a mosaic pattern was conspicuous; elastographically, the lesion was stiffer than the surrounding area.[73] In another report, the hamartoma on the pancreas was

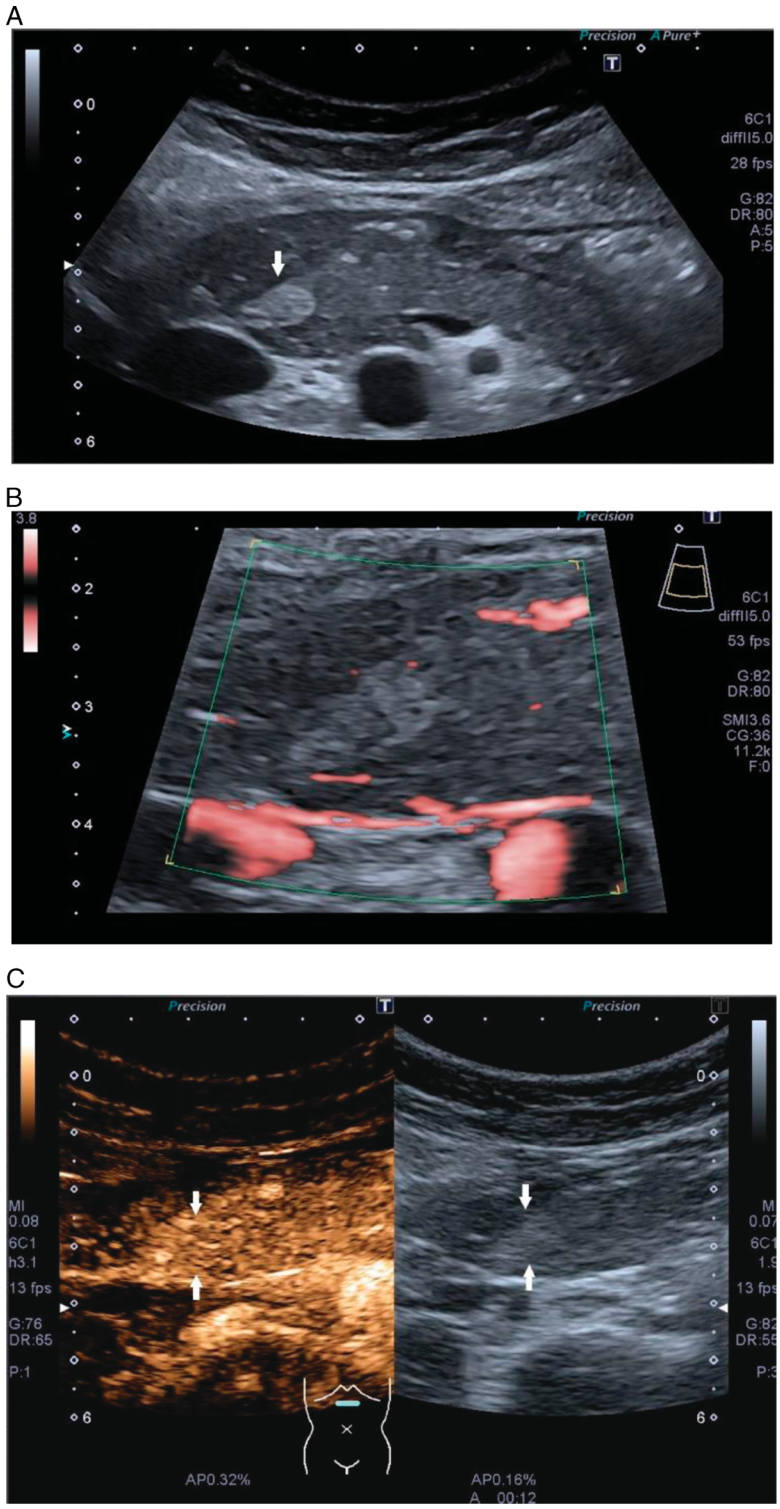

Figure 2. Lipoma. Female, 31 years old. Sonographic incidental finding of an oval, sharply circumscribed, homogeneous, hyperechoic lesion on the pancreatic head. No evidence of macrovessels on power Doppler. On CEUS, the lesion is isoenhanced. EUS-guided sampling was performed without evidence of a solid tumor. Differential diagnosis with the very distinct smooth boundary, a lipoma is possible. CEUS: contrast-enhanced ultrasound.

hypoechoic and well demarcated, and on Contrast Harmonic EUS (CH-EUS) with Sonazoid, the lesion showed hypoenhancement in both arterial and delayed phases. Thus, differentiation from ductal adenocarcinoma would be difficult.[76]

There are no cases in the literature in which a pancreatic hamartoma was diagnosed preoperatively.[76] In the 40 cases reviewed by Katayama et al.,[73] imaging findings (CT and/or MRI) were reported in 28 cases. Preoperative biopsy had been performed in

only 14 cases.[73] As far as verification of the cited sources was possible, sampling was performed using EUS-FNA. Katayama et al. described that in their case specimens obtained by EUS-FNA were

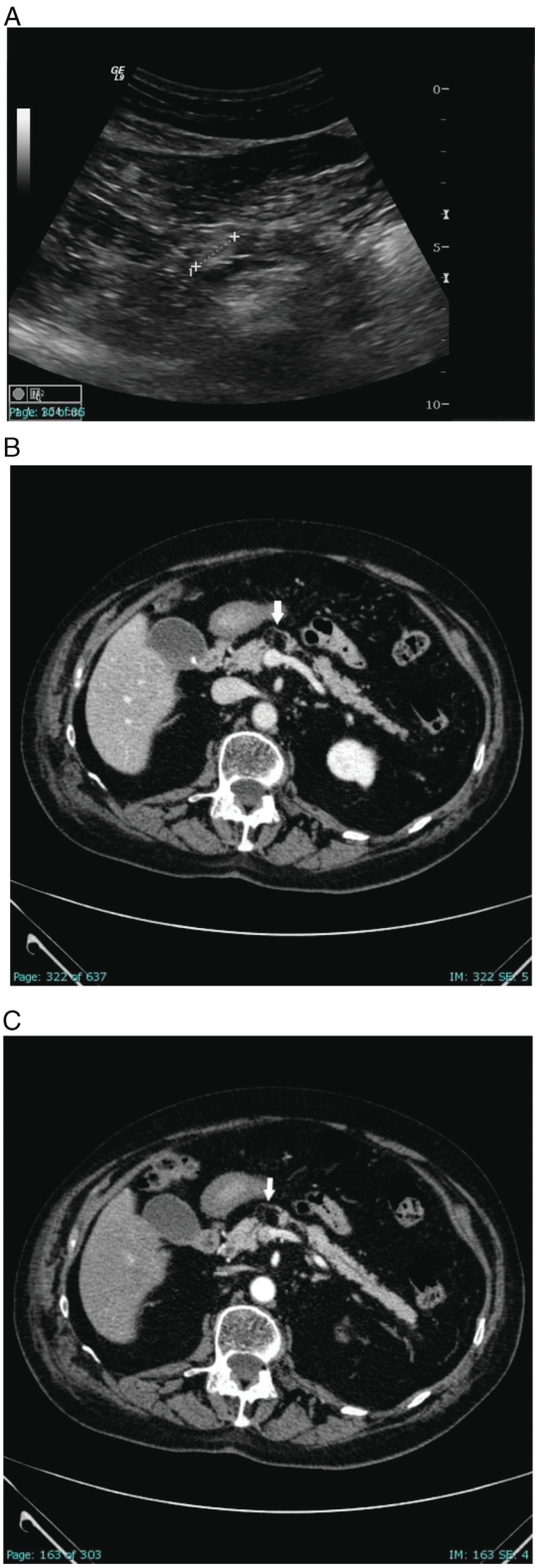

Figure 3. Lipoma. Hyperechoic lesion in the pancreatic neck on ultrasound (A), hypodense (B), and nonenhanced on computed tomography (CT) (C).

Table 3

Pancreatic schwannoma on imaging.

Method	Appearance
Morphology	Solid, cystic-solid, encapsulated, well-defined, pancreatic duct is not dilated[54–56]
US	Well-defined, hypoechoic, without macrovessels on CDI[55,56,58] Possible: calcifications, narrow septations, fibrous capsule
CEUS	Enhancement of capsule and septations[55,129]
CT	Antoni A—heterogeneous, solid, hypodense with heterogeneous enhancement; Antoni B—nonenhancement.[54,127]
MRI	T1 hypodensity, T2 hyperdensity[54,57,59]
EUS, CH-EUS	Well-defined, hypoechoic solid parts, cystic parts. Hypoenhancement of solid parts (single case)[58,128,130]

CDI: color Doppler imaging; CEUS: contrast-enhanced ultrasound; CH-EUS: contrast harmonic endosonography CT: computed tomography; MRI: magnetic resonance imaging.

almost normal tissue.[73] Because hamartoma is a malformation and not a real tumor, it is also understandable that the diagnosis cannot be made using FNA or FNB. Hamartoma has an abnormal admixture of normal components specific to the affected organ. A hamartoma is not a neoplasm and does not require surgical resection in asymptomatic patients. In a review of 46 reported cases, surgical resection was performed because malignancy could not be ruled out. Preoperative suspected diagnoses were as follows: PanNEN, SPN, PDAC, ACC, and liposarcoma, but also benign lesions such as lipoma, epidermoid cyst, mass-forming pancreatitis, and serous cystic neoplasm.[76] The appearance of pancreatic hamartoma in some case reports is presented in Table 4 [Figure 5].

The most important differential diagnosis is PanNEN. In contrast to hamartomas, these are homogeneous and show increased enhancement on contrast-enhanced imaging at the onset of the arterial phase.

HEMANGIOMA

Hemangiomas are vascular tumors composed of blood vessels lined with endothelial cells. Pancreatic hemangiomas are rare. In a 2020 review, 19 cases were researched.[91] Predominantly women were affected with a mean age of 49 years (range, 18–78 years). Patients were either asymptomatic or had unspecific epigastric symptoms. The pancreatic hemangiomas were mostly large, about half located in the pancreatic head. Obstructive jaundice occurred only occasionally.[91] Diagnosis of pancreatic hemangioma is difficult. In the review of Jin et al.,[91] only 11% (2/18) of hemangiomas were confirmed preoperatively. Other cystic tumors such as cystadenoma, cystic neuroendocrine neoplasms, or intraductal papillary mucinous neoplasms were suspected preoperative diagnoses.[91] The diagnosis was made by surgical pathology, whereby the detection of CD31 and CD34 by immunohistochemistry was regarded important.[95] In one case report, multiple hypervascularized lesions presented intrapancreatically all over the organ; the largest measured 14 mm in the uncinate process. PanNENs were suspected. A distal pancreatectomy was performed for diagnostic reasons. Histology revealed a hemangioma.[135]

Pancreatic hemangiomas have cavernous (cystic) parts with fluids. Other cystic tumors are the most important differential diagnosis. Pancreatic hemangioma does not show the typical contrast behavior of hepatic hemangiomas. Usually, pancreatic hemangiomas do not show significant enhancement in the arterial phase, possibly

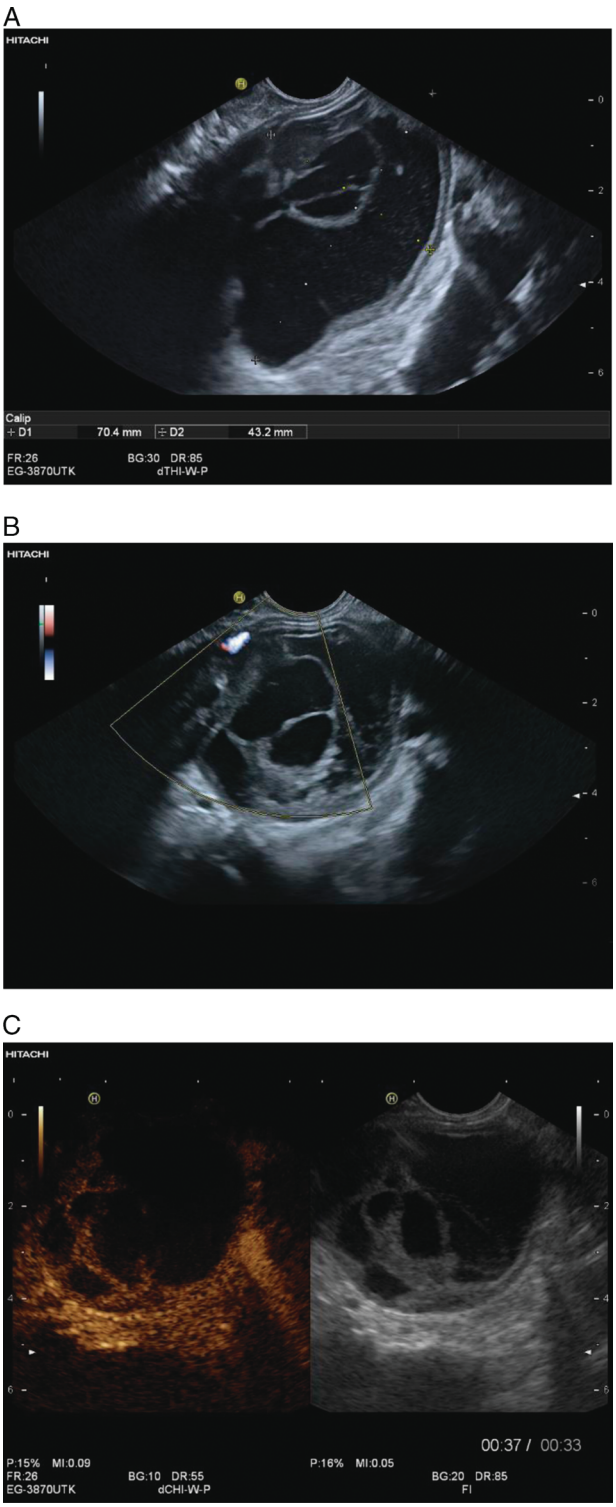

Figure 4. Pancreatic schwannoma. Female, 70 years old. As an incidental finding in nonspecific abdominal complaints, a 70 × 40-mm predominantly cystic mass was seen adjacent to the pancreatic head and paraduodenal. This appeared encapsulated. Solid parts were seen at the periphery and thick septa in the lumen. On native power Doppler, the internal structures showed no macrovessels. On contrast-enhanced harmonic EUS with 4.8 mL SonoVue, the thick septa were contrast enhanced. EUS-guided sampling failed to identify the mass with certainty, and resection was performed. Postoperative histology revealed a retroperitoneal schwannoma.

due to cavernous changes that contain areas of neovascularization and arteriovenous shunt [Table 5]. Calcifications are reported.[91]

On nonenhanced MRI, pancreatic hemangiomas often showed low signal attenuation on T1WIs and high signal attenuation on T2WIs. Pancreatic hemangiomas showed moderate gadolinium enhancement with washout on delayed phase images.[91] Complex cystic processes are described endosonographically without evidence of macrovessels in Doppler ultrasound. The diagnosis of the hemangioma could not be made in individual reports. EUS-guided sampling did not lead to a diagnosis. Carcinoembryonic antigen and amylase in the aspirate were normal.[88]

ANGIOMYOLIPOMA, EPITHELIAL ANGIOMYOLIPOMA

Angiomyolipomas are well known lesions in the kidney and because of their characteristic features in ultrasound are often diagnosed.[136] Extrarenal angiomyolipomas are rare, and most of those tumors are described in the liver.[137] However, those lesions can occur in other organs such as the lung, spleen, colon, heart, skin, parotid gland, mediastinum, spermatic cord, nasal cavity, and retroperitoneal soft tissue as well.[138] Pancreatic angiomyolipomas are very rare. In the current literature, there are only 3 mentions of pancreatic angiomyolipoma and 1 mention of an epithelial angiomyolipoma.[102,138] The difference between those 2 entities is the natural behavior of the lesions. Whereas angiomyolipomas are strongly benign lesions, it is known that one-third of the epithelial angiomyolipoma can turn malignant.[139]

Diagnosing angiomyolipoma is a challenge. The tumors are described in all pancreatic locations, including the pancreatic head, body, and tail. Whereas the typical angiomyolipoma in the kidney is normally hyperechoic due to the high fatty content, extrarenal angiomyolipoma can be hypoechoic and highly vascularized.[138] The typical tumor shows a clear delineation and does not affect the pancreatic duct. The main differential diagnosis is a neuroendocrine tumor. If highly vascularized, contrast-enhanced EUS can mislead the diagnosis even further. If the fat content is higher than the vascularization of the tumor, even pancreatic carcinoma can be a differential diagnosis.

EUS-FNA cytology is rarely helpful because of the absence of dysplastic cells. Mostly, the result will be unsatisfactory, but the diagnosis can be made if the cytologist has the clinical suspicion.[140] In all published cases, the diagnosis was made after surgery was arranged

Table 4

Pancreatic hamartoma on imaging.

Method	Appearance
US	Smooth bordered, hypoechoic, heterogeneous, no macrovessels on CDI, pancreatic duct is not dilated[74,75]
CEUS	Uneven enhancement at 19 and 25 s[74]
CT	Mostly well-demarcated and internally heterogeneous, hypodensity with well demarcation in the arterial phase, then mild enhancement from the marginal area in the portal phase, and isodensity to hyperdensity with heterogeneous contrast in the late phase[73]
MRI	T1WI with low signal intensity, T2WI with high signal intensity[73,76]
EUS	Well demarcated, hypoechoic[73,76]
CH-EUS	Hypoenhancement in both arterial and delayed phases[76]

CDI: color Doppler imaging; CEUS: contrast-enhanced ultrasound; CT: computed tomography; MRI: magnetic resonance imaging; T1WI, T1-weighted image; T2WI, T2-weighted image.

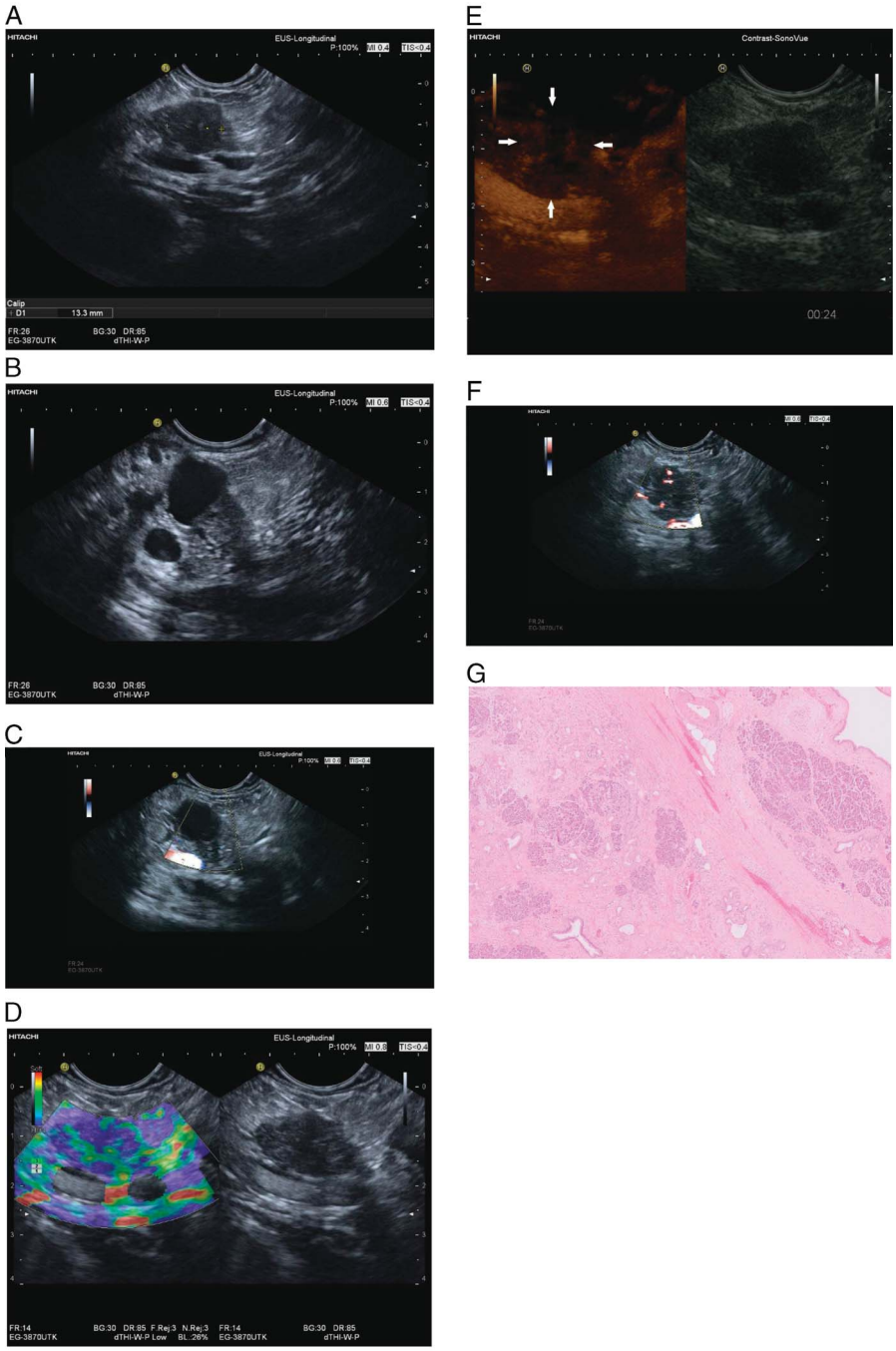

Figure 5. Hamartoma of the pancreatic tail. Male, 46 years old. The pancreatic tail showed a 13-mm, well-defined, hypoechoic lesion with dilatation of the proximal pancreatic duct (A). A 10-mm cystic lesion was located at the periphery of the lesion (B). Hardly any vessels were visible on native power Doppler (C). On strain elastography, the lesion was stiffer than the surrounding parenchyma (D). On contrast-enhanced harmonic EUS, the lesion was hypoenhanced in comparison to the surrounding parenchyma (narrows) (E). In contrast-enhanced power Doppler, small macrovessels are visible (F). EUS fine-needle aspiration was performed with a 22-gauge aspiration needle. Pathological evaluation of the aspiration material could not assign the diagnosis. The histological workup of the resected specimen revealed a hamartoma of the pancreatic tail; hematoxylin-eosin stain, magnification ×50 (G). Image source of the histologic figure: Dr Ukrow (Institute of Pathology, Unfallkrankenhaus Berlin-Marzahn) and Drs Daniel Bethmann and Uwe Schlichting (Institute of Pathology, Sana-Hospital Berlin-Lichtenberg).

due to the suspicion of a neuroendocrine tumor of the pancreas. Surgery is indicated in case of epithelial angiomyolipoma but would not be required in case of a benign angiomyolipoma. However, the discrimination is basically impossible before surgery, and therefore, the surgical approach has to be considered necessary.

An angiomyolipoma of the pancreas should be suspected in cases of a well-delineated tumor of the pancreas with absence of tumor cells in EUS-FNA cytology. In such a case, histological diagnosis should be attempted using EUS-FNB or percutaneous ultrasound-guided core biopsy to avoid surgery [Figure 6].

Table 5

Pancreatic hemangioma on imaging.

Method	Appearance
Morphology	Mostly large, cavernous (cystic) parts, compression on the bile duct possible, calcifications are possible[91]
CT	Usually nonsignificant enhancement in the arterial phase, possibly due to the cavernous changes, not comparable with liver hemangiomas[91]
MRI	Low signal attenuation on T1-weighted images and high signal attenuation on T2-weighted images[91]
EUS	Without macrovessels[88]

CT: computed tomography; MRI: magnetic resonance imaging.

GANGLIONEUROMA

Ganglioneuroma is the most mature variant in the group of sympathetic neuroectodermal tumors (ganglioneuroblastoma and neuroblastoma). Ganglioneuroma is composed of gangliocytes of sympathetic nerve fibers and is a benign tumor. The most frequent localization is the mediastinum and retroperitoneum and less frequently the pelvis. Localization in the pancreas is extremely rare. Mazzola et al.[141] summarized a series of 6 cases in the literature. Additional cases of primary pancreatic ganglioneuromas have been described anecdotal thereafter.[142,143] Mainly children or younger adults were affected. Reported cases had nonspecific complaints. Paragangliomas can rarely produce vasoactive intestinal polypeptide, androgenic hormones, and catecholamines with corresponding

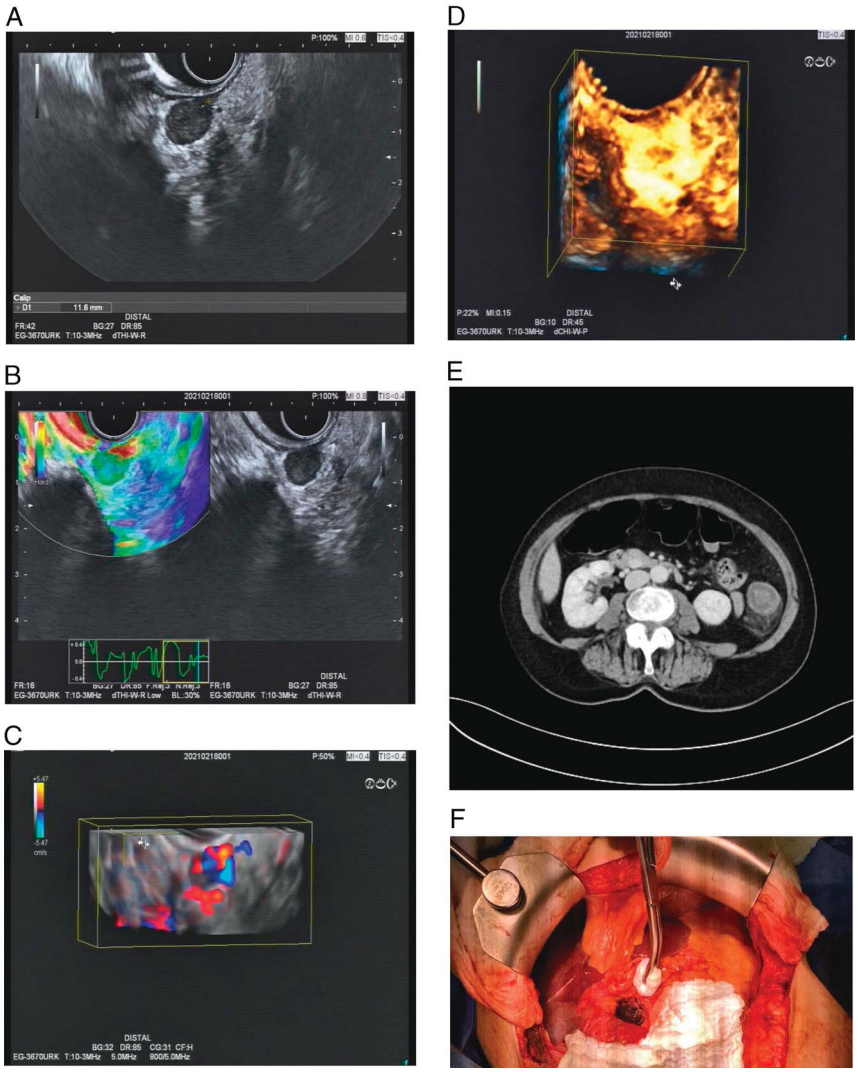

Figure 6. A 79-year-old woman with a suspected neuroendocrine tumor of the pancreatic head. The tumor could be enucleated during surgery and turned out to be a benign angiomyolipoma of the pancreatic head. EUS shows a hypoechoic tumor in the uncinate region of the pancreas with a very good delineation (A). The tumor appears green, indicating soft tissue in elastography (B). In 3-dimensional EUS with color Doppler imaging, the tumor shows lots of vessels in keeping with a neuroendocrine lesion of the pancreas (C). After administration of 4.8 mL SonoVue in contrast mode, the tumor clearly shows high vascularization in this 3-dimensional imaging (D). The tumor can be reproduced on top of the vena cava in the uncinate region of the pancreas; no metastasis are detected in a full body scan (E). The tumor appears highly vascularized during surgery but could be successfully enucleated from the pancreas (F). Image source of CT: Dr H.-J. Hald, Helios Hospital Meiningen, Radiology.

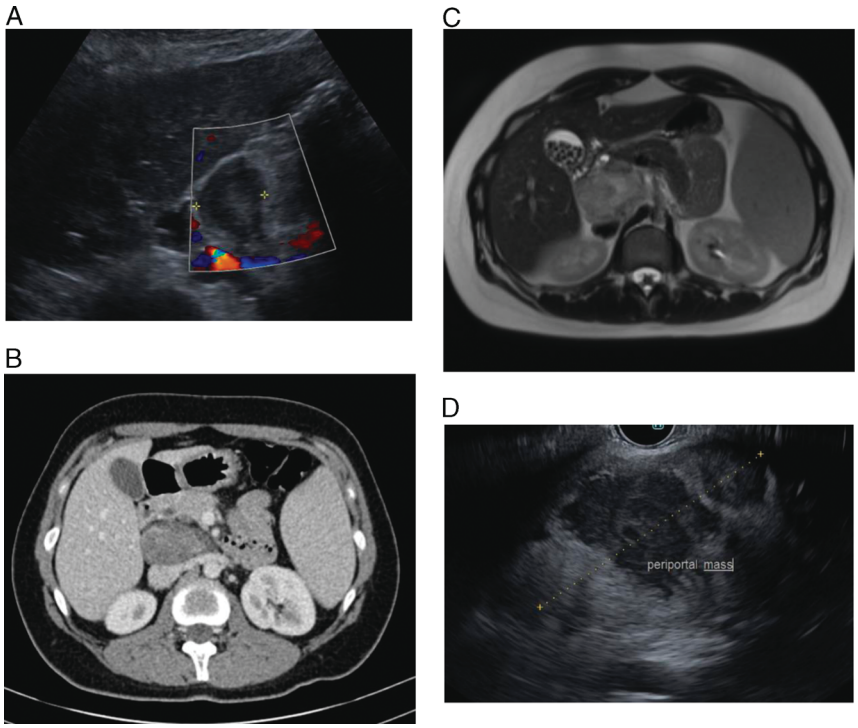

Figure 7. A 29-year-old woman presented with epigastric discomfort and underwent an ultrasound (A), which demonstrated a lobulated, heterogeneous lesion in the region of the porta hepatis. A subsequent computed tomography (CT) (B) demonstrated the abnormality in the retroperitoneal space, abutting the portal vein but distinct from the pancreatic gland. On T2-weighted magnetic resonance imaging scans (C), the lesion exhibited mixed signal characteristics with areas of enhancement. EUS (D) showed a periportal mass of mixed echogenicity and scattered anechoic foci. FNB confirmed the diagnosis of ganglioneuroma. FNB: fine-needle biopsy.

symptoms such as flushing, diarrhea, and hypertension.[141] In a case report, a pancreatic ganglioneuroma is described as a homogeneous, weakly enhancing, well-defined solid mass on CT.[143] On MRI scan, the lesion is described as T1 hypointense, T2 heterogeneously hyperintense.[143,144] Only 1 of 5 ganglioneuromas could be diagnosed preoperatively in the review of Mazzola et al.[141,145] Diagnostic features are the detection of both spindle cells and ganglion cells and the absence of immature cells, necrosis, and inflammation (in distinction from ganglioneuroblastomas and neuroblastomas).[145] EUS-FNA with cytology alone revealed spindle cells but did not allow a diagnosis of ganglioneuroma.[143] On EUS, the lesion was oval, well-defined hypoechoic,[142] or heterogeneous.[144] EUS-guided core-needle biopsy was able to confirm the diagnosis. Immunohistochemistry showed positivity for S100, synaptophysin, and SOX-10.[142] In the surgical specimens, positivity for vimentin, S100 protein, neurofilament, and neuron-specific enolase is described.[143] Preoperative diagnosis of a ganglioneuroma had the consequence of local enucleation instead of extensive pancreatic resection[145] [Figure 7].

SCLEROSING EPITHELIOID MESENCHYMAL TUMOR

Sclerosing epithelioid mesenchymal tumor is a new entity in the World Health Organization classification 2019.[21,146,147] These are tumors of distinct histology, but they do not correspond to any of the known types of epithelial neoplasms of the pancreas or mesenchymal neoplasms. They are characterized by well-demarcated nests of epithelioid and spindle-shaped cells in a dense sclerotic stroma. This histologic pattern has been termed "sclerosing epithelioid mesenchymal neoplasm" of the pancreas.[147] In a single-center retrospective analysis including 8 cases,[147] they were found predominantly in the head and neck region of the pancreas of middle-aged female patients and showed an indolent clinical course. The median size of the tumors was 1.8 cm (range, 1.3–5.8). Macroscopically, the tumors had no capsule but were well circumscribed and solid. All patients underwent surgery. With a median follow-up of 53 months (range, 8–94 month), all patients were tumor-free.[147] Only one case is described with imaging. This presented as solid mass with a cystic component. Computed tomography showed a well-demarcated hypovascular tumor. The tumor showed mild enhancement in the late phase. On MRI, the tumor showed hypointensity on T1WIs and hyperintensity on T2WIs.[148] On EUS, the tumor was well defined and hypoechoic. EUS-guided sampling with immunohistochemistry was performed. However, the diagnosis could only be made on the surgical specimen.[148]

CONCLUSION

Benign mesenchymal pancreatic tumors are very rare. Although contrast-enhanced abdominal and EUS are powerful methods to characterize tumors, there are only isolated case reports available that do not allow generalizations. Benign mesenchymal tumors are usually well defined and hypoechoic (except for lipoma). Mainly schwannomas, hemangiomas, and hamartomas may have cystic parts. Angiomyolipomas and solid portions of schwannomas are vascularized in contrast enhancement. Based on the limited data and isolated case reports only, no general imaging features can be derived. Predominantly, patients underwent CT and MRI. All

of the above mesenchymal tumors had a common theme of being diagnosed by surgical pathology. The most common preoperative differential diagnoses are other rare pancreatic tumors rather than ductal adenocarcinoma. In cases where EUS-guided sampling was performed, most of the results did not lead to the final diagnosis. However, the performance of immunohistochemistry appeared to be advantageous in some. Thus, the suspected diagnosis leading to surgery was PanNEN, SPN, less commonly ACC, PDAC, or generally suspected mesenchymal tumor. For cystic tumors, it was cystic PanNEN, ACC, or mucinous neoplasms that were suspected diagnoses. This is unfortunate, as also benign pancreatic tumors underwent extensive resection instead of localized resection or simple observation. According to the authors' experience, EUS-guided sampling should be performed with the intention of histologic and immunohistochemical evaluation of the specimen. Ideally, EUS-guided sampling should be carried out with a core needle and the pathologist should be made aware of the particular problem. Even if the diagnosis cannot be confirmed preoperatively, limited surgery instead of radical pancreatic resection could be considered in the therapeutic concept, if an adequate core specimen shows no criteria of malignancy.

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Conflicts of Interest

Siyu Sun is the Editor-in-Chief of the journal, and Christoph F. Dietrich is a Co-Editor-in-Chief. Christian Jenssen and Michael Hocke are Editorial Board Members of the journal. The article was subjected to the standard procedures of the journal, with a review process independent of the editors and their research group.

Author Contributions

All authors contributed to the study conception and design. The concept was developed by Christoph F Dietrich and Kathleen Möller. Material preparation, data collection and analysis were performed by Kathleen Möller. Image collection was performed by Kathleen Möller, Christoph F Dietrich, Christian Jenssen, Riccardo De Robertis Lombardi, Mirko D´Onofrio Michael Hocke, Wei On, Simon M. Everett. The first draft of the manuscript was written by Kathleen Möller and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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