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Case Report

Perivascular epithelioid cell tumor of the pancreas: case report and literature review

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Abstract: Neoplasms with perivascular epithelioid cell differentiation (PEComas) of the pancreas are rare, and only 22 cases have been reported globally. Therefore, clinician and pathologist knowledge of this tumor's biologic behavior and molecular genetics has been limited. A 40-year-old female patient presented with a space-occupying mass in the pancreas found by abdominal B-mode ultrasonography upon physical examination. Laparoscopic resection of the pancreatic body and tail was performed, and a cystic-solid tumor of about 2 × 2 cm was identified. PEComa is a type of mesenchymal tumor with uncertain biologic behavior, more frequently found in females. PEComa features a unique histomorphology and immunophenotype. We summarize the characteristics and research progress of the pancreatic PEComa, which will be convenient for physicians and pathologists to fully understand the disease to avoid misdiagnosis and to provide a reference for treatment and prognosis.

Keywords: Pancreas, perivascular epithelioid cell tumor, pathologic diagnosis

Introduction

A neoplasm with perivascular epithelioid cell differentiation (PEComa) arising in pancreas is extremely rare. Zamboni et al. [1] reported the first case of clear cell sugar tumor of the pancreas and proposed the concept of perivascular epithelioid cell tumor (PEComa). 2016 WHO (World Health Organization) Classification of Soft Tissue Tumors defined PEComa as a mesenchymal tumor composed of distinctive cells that show a focal association with blood vessel walls and usually express melanocytic and smooth-muscle markers. However, only 22 cases have been reported in the English and Chinese literature to date [1-22]. Herein, we report one case of PEComa in the pancreas and review the literature to discuss the clinicopathologic features of PEComa in the pancreas.

Case presentation

A 40-year-old female patient was found to have a mass in the pancreas by abdominal B-mode ultrasonography during physical examination. She reported no abdominal pain or distension, nausea, or vomiting symptoms. Abdominal CT scan revealed a circular isodense shadow in the pancreatic body with rich blood supply and mild protrusion. Contrast-enhanced CT scan revealed moderately progressive enhancement, and solid pseudopapillary tumor was suspected (**Figure 1**). Laboratory data were as follows: prealbumin: 93.69 mg/L (reference range: 280-360 mg/L), total protein: 56.1 g/L (reference range: 60~80 g/L), albumin: 34.4 g/L (reference range: 35-51 g/L), and with normal liver and kidney function tests. After admission, a pancreaticoduodenectomy (PPPD) procedure was ultimately performed on the patient. In the pancreatic body, a cystic-solid tumor of about 2 × 2 cm was found during surgery. The tumor had penetrated the connective tissue membrane of the pancreatic surface. It was expansile and had a relatively clear boundary with the normal pancreatic tissues.

The submitted tissue sample was fixed in 4% neutral formaldehyde, paraffin-embedded, sectioned, and subjected to Hematoxylin-eosin

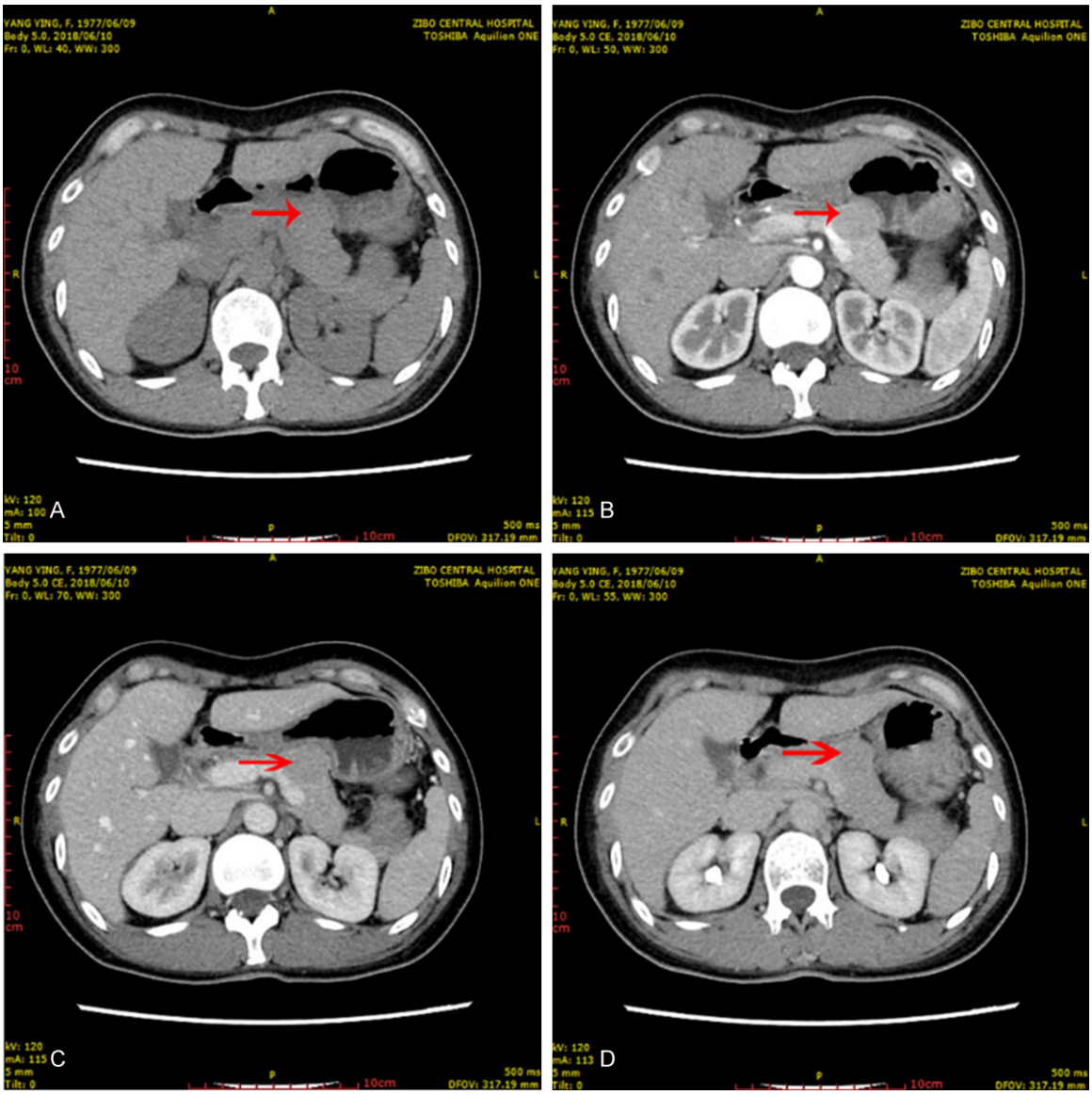

Figure 1. CT revealed a circular isodense shadow in the pancreatic body with rich blood supply and mild protrusion. Contrast-enhanced CT scan revealed moderately progressive enhancement and solid pseudopapillary tumor was suspected. A. CT scan showed an isodense shadow. B. Arterial phase showed the tumor density was lower than that of the pancreatic parenchyma. C. Venous phase. D. The delayed phase showed that the tumor density was almost equivalent to the pancreas density. (Red arrow)

(H&E) staining. The EnVision system was used for immunohistochemical staining. The antibodies against cytokeratin, vimentin, HMB-45, MelanA, SMA, desmin, CD117, S-100, synaptophysin, Ki-67, and TFE-3 were purchased from Fuzhou Maixin Biotechnology Development Co., Ltd. The vimentin antibody was a rat anti-pig monoclonal antibody, and the remaining antibodies were rat anti-human monoclonal antibody. To detect glycogen, the tissues were digested and stained with PAS.

There was a well-demarcated tumor in the pancreatic body of the tissue sample of 13 cm × 4 cm × 3.5 cm in size. The cross-sectional area was 2.3 cm × 2.0 cm, with a cystic-solid nature. The solid components were grayish-white and of a brittle texture; the cystic components contained a small amount of bloody fluid. The inner wall was mildly rough (**Figure 2**). The tumor had a clear boundary with the surrounding pancreatic tissues (**Figure 3A**). The tumor cells were in a patchy distribution and uniformly were epithe-

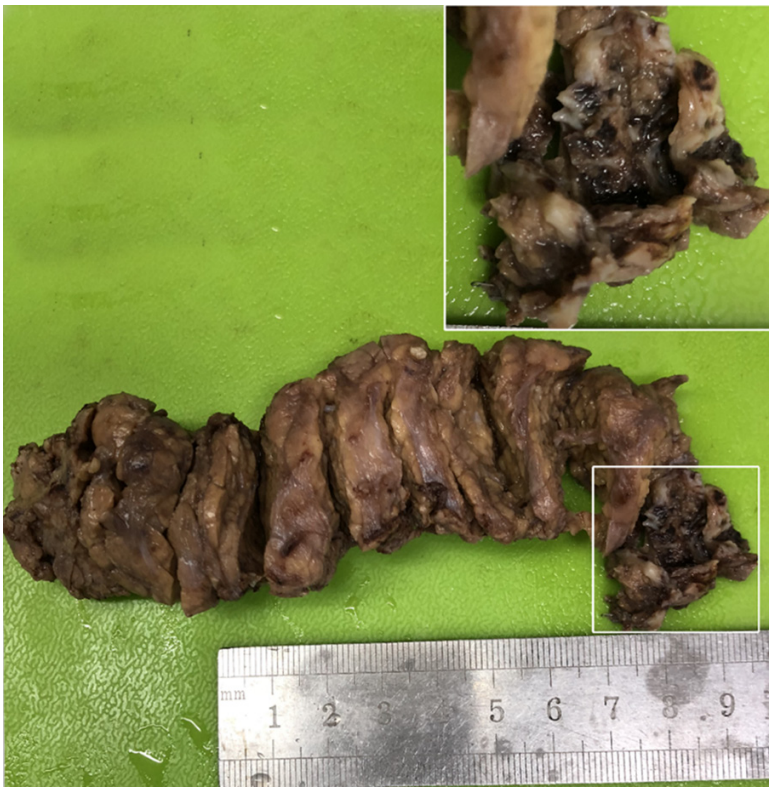

Figure 2. Gross observation of the tumor. There was a cystic-solid tumor in the pancreatic body with clear boundary, which had a cross-sectional area of 2.3 cm × 2.0 cm. The solid components were grayish white and of a brittle texture, the cystic components contained a small amount of bloody fluid, and the inner wall was mildly rough. The upper right is magnification of the tumor.

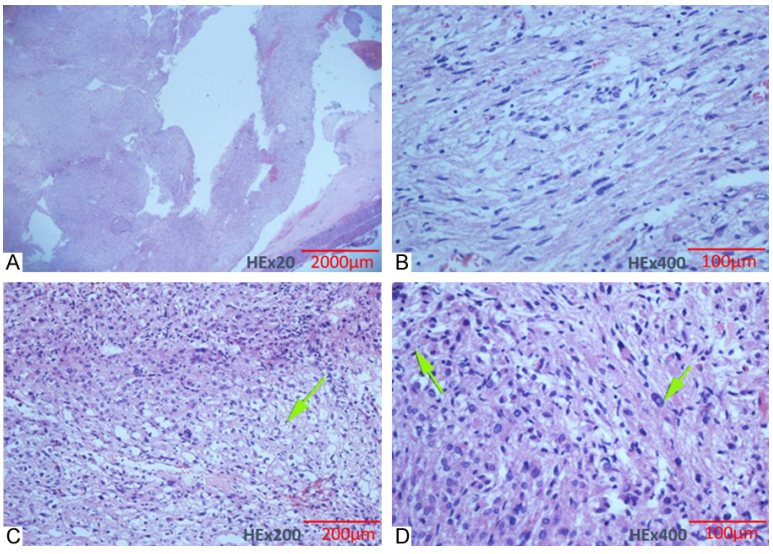

Figure 3. Microscopy of PEComa with H&E. The tumor had a clear boundary with the surrounding pancreatic tissues (A, H&E × 20). The tumor cells were in a patchy distribution and uniformly epithelioid or fusiform in morphology (B, H&E × 400). The cells were large in size, which were of a circular or polygonal shape and contained rich cytoplasm and a large amount of transparent or eosinophilic cytoplasm (C, green arrow, H&E × 200). The tumor cells had round or oval nuclei with nucleoli and intranuclear pseudo-inclusions (D, green arrow, H&E × 400). Mitosis was rare.

lioid or fusiform in morphology (**Figure 3B**). The cells were large, circular, or polygonal, and contained a rich cytoplasm and a large amount of transparent or eosinophilic cytoplasm (**Figure 3C**). The tumor cells had round or oval nuclei with nucleoli and intranuclear pseudo-inclusions (**Figure 3D**). HMB-45 (**Figure 4A**), MelanA (**Figure 4B**), and SMA (**Figure 4C**) were all positive. The positive rate of Ki-67 was 5% (**Figure 4D**). CK, desmin, CD117, S-100, Syn, vimentin (**Figure 4E**), and TFE-3 (**Figure 4F**) were all negative. The tissues were positive for PAS staining (**Figure 4G**) and could be digested by amylase (**Figure 4H**).

Pathologic diagnosis: PEComa in the pancreatic body

Postoperatively, the patient had no surgical incision infection, no pancreatic leakage, delayed gastric emptying, and fat malabsorption. The patient was discharged on the 9th day after surgery. 30 months after the operation, the patient had no discomfort and no tumor recurrence.

Discussion

PEComa is characterized by differentiation of the perivascular epithelioid cells arranged in a radial pattern around the blood vessels and specifically expresses melanophore markers and smooth-muscle cell markers. The PEComa family includes angiomyolipoma (AML), clear cell sugar tumor (CCST), lymphangioleiomyoma (LAM), and a group of tumors originating from the soft tissues and organs with similar histology and immunophenotype. Except for AML, CCST, and LAM, other

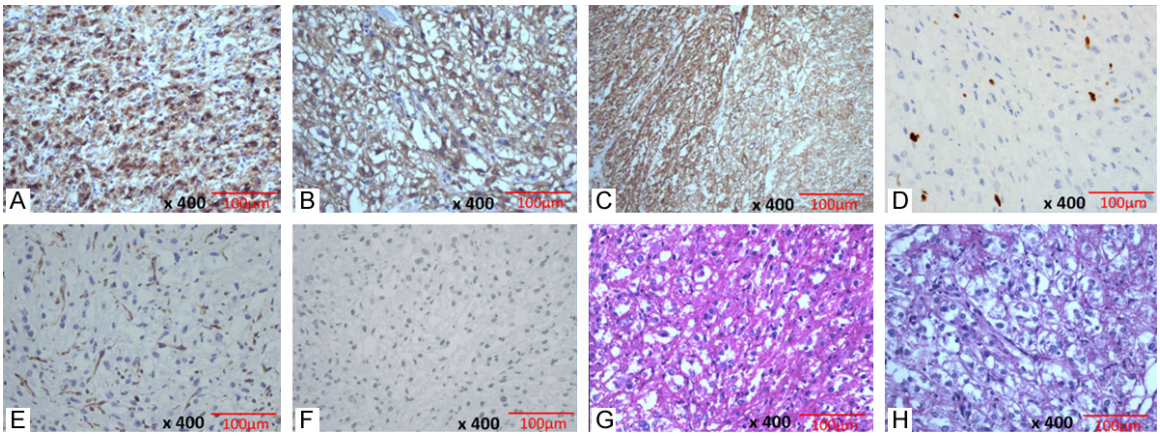

Figure 4. Immunohistochemistry and special staining of the tumor tissues. HMB-45 (A), MelanA (B), SMA (C) were all positive. The Ki-67 index was 5% (D). CK, desmin, Both vimentin and TFE3 were negative (E and F). The tumor cells were positive for PAS staining (G) and could be digested by amylase (H). × 400 magnifications.

PECcomas are named non-specific PEComa (PEComa-not otherwise specified, PEComa-NOS). PEComa may affect a variety of organs with varying morphology, which makes diagnosis difficult. PEComa-NOS of the pancreas is very rare. Our research may inform clinicians and pathologists about the features of PEComa at the pancreas.

PEComa of the pancreas affects females more frequently, and the pancreatic head and body are usually affected. Among all reported cases, there are 18 females and 4 males, with a male-to-female ratio of 1:4.5, indicating that females' incidence is significantly higher than that among males. Consistent with the prevalence of the disease, this case is also a female patient. The youngest patient is aged 17 years old, and the oldest is aged 76. 81.82% (18/22) of the cases are aged 30 to 60, indicating that young and middle-aged people are mostly affected. 59.09% (13/22) of the cases present with abdominal pain or discomfort, while some (31.82%, 7/22) are found without specific symptoms upon physical examination. Most PEComas in the pancreas are benign. There are only 2 reports of metastatic cases [8, 17] and a cyst was enlarged from 8 mm to 5.8 cm in one case during a 3-year follow-up [22] (**Table 1**).

Abdominal B-mode ultrasonography usually indicates a hypoechoic cystic-solid lesion rich in blood supply. The lesion may be hyperechoic in the presence of calcifications. Those with typical CT manifestations usually have homogeneous solid lesions presenting as a coin-like shape and a quasi-circular hypodense shadow with a clear boundary in the pancreas. A slightly higher density is usually found when the lesion was accompanied by bleeding. Typical MRI findings include a cystic-solid lesion with a relatively clear boundary and mildly hyperdense signals on T2W1, fat-suppressed and DWI images, and low signals on T1W1 images (**Table 1**).

PEComa of the pancreas is usually composed of even epithelioid cells, some of which are fusiform. Tumor cells are lobulated or in a patchy distribution. Between the lobules and patchy tumor cells are fibrous vascular septa rich in thick- and thin-walled vessels. The cells are large, and are of a circular or polygonal shape. The rich cytoplasm is transparent and contains eosinophilic granules, which are stained positive by PAS and could be digested by amylase, indicating that the cytoplasm is rich in glycogen other than mucus. The tumor cells have small nuclei, which are mildly heteromorphic and located in the middle or deviated. The nuclei are round, oval, or found with an irregular notch. The chromatin is refined in texture, and the nucleolus is inconspicuous. Mitosis is rare. Histologic malignant features include nuclear pleomorphism, pronounced heteromorphic nuclei, multinucleated giant cells, high mitotic index, accompanying bleeding and necrosis, tumor infiltrating the adjacent normal pancreatic tissues, and distant metastasis. Our case showed typical histologic features of PEComa of the pancreas without signs of malignancy. Depending on biologic behavior, PEcoma is divided into benign, uncertain malignant poten-

Table 1. Clinical features of perivascular epithelioid cell tumor of the pancreas in the literature

	Author	Year	Age	Sex	Symptoms	Location	Imaging findings	Operative procedures	Recurrence	Size (cm)	Diagnosis	Follow up (months)
1	Zamboni	1996	60	F	Abdominal pain	Body	CT revealed a well-demarcated solid lesion with even texture	DP	-	2	Clear cell sugar tumor	3
2	Heywood	2004	74	F	Abdominal pain	Head	CT revealed cystic lesion with irregular thick capsules	PPPD	-	4.7	Angiomyolipoma	69
3	Ramuz	2005	31	F	Abdominal pain	Body	CT indicated a round-like solid lesion with bleeding	SPDP	-	1.5	Sugar tumor	9
4	Perigny	2008	46	F	Diarrhea	Body	CT indicated a nodule of 1.7 cm	Enucleation	-	1.7	PEComa	3
5	Ferga	2008	33	F		Head, body and tail	Ultrasonography indicated a hypoechoic cystic lesion		-	1		12
6	Hirabayashi	2009	47	F	Abdominal pain	Head	MRI indicated a solid round lesion, with low T1W1 signals	PPPD	--	1.7	PEComa	12
7	Baez	2009	60	F	Abdominal bulge	Body	CT indicated a solid round lesion with bleeding	DP	-	3.5	PEComa (sugar tumor)	7
8	Zemet	2011	49	M	Fever, cough and malaise	Head	CT revealed a mass with calcifications, which was 30 × 40 mm in size and located at the head of the pancreas. EUS identified a well demarcated hyperechoic calcified mass	PPPD	-	4	PEComa	10
9	Nagatas	2011	52	M	Abdominal pain	Head	Imaging examinations revealed a 4.0 cm mass located in the pancreatic head	PD	Liver metastasis	4	PEComa	27
10	Feilai Xie		58	M	Recurrent abdominal pain	Head	MRI indicated a round-like nodule, with slightly high T2W1, adipose inhibition and DWI signals and low T1W1 signals					5
11	Finzi	2012	62	F	None	Head	EUS showed a 2.0 × 2.0 cm solid and well-demarcated mass in the posterior pancreatic head. MDCT indicated a 2.5 cm round, solid, well-defined, and homogeneous nodule, which was slightly hyperdense without a significant contrast enhancement	Total excision	-	2.5	PEComa	5
12	Al-Haddad	2013	38	F	Abdominal pain	Uncinate process	CT demonstrated a hypervascular pancreatic uncinate lesion. EUS confirmed an 18 mm, well-circumscribed, hypoechoic, homogenous mass without vascular invasion	PD	N.A	1.8	PEComa	NA
13	Okuwaki	2013	43	F	Abdominal pain	Body and tail	CT showed a relatively well-demarcated mass (10 cm, maximum diameter) in the body and tail of the pancreas, with an intermingling of high signal intensity inside the tumor	DP	-	10	PEComa	7
14	Moura N	2013	51 -	F	Abdominal pain, jaundice	Head	e. Imaging studies showed dilatation of common and intrahepatic bile ducts related to an intrapancreatic mass, consistent with endocrine or secondary tumor	PD	Liver metastasis	6	malignant PEComa	6
15	Yunyuan Li	2016	47	F	None	Body	Ultrasonography indicated a hypoechoic lesion, which was presented as a low-density shadow on CT	Surgical removal (unknown details)	-	1.7	PEComa	8
16	Petrides C	2015	17	F	Melena, anemia	Head	CT demonstrated a mass at the head of the pancreas, which was 4.2 cm in diameter. EUS showed an ulcerating malignant looking mass infiltrating 50% of the wall of the second part of the duodenum in the region of the ampulla	PPPD	-	4.2	PEComa	18

17	Yusuke	2015	61	F	Abdominal pain	Body	CT revealed that a solid low-density mass of approximately 7 cm in diameter, which was circumferentially well-demarcated and located in the pancreatic body	PD	-	7	PEComa	12
18	TAN Y	2016	58	F	None	Body	Ultrasonography indicated a hyperechoic mass at the pancreatic body, which was well-demarcated and 1.8 cm in size; MRI showed a solid round nodule with low T1-weighted signals, and there was no dilation and stenosis of the main pancreatic duct and interlobar ducts	middle pancreatectomy	-	2	PEComa	5
19	Maurizio	2017	68	M	Abdominal pain	Head	Ultrasonography and CT showed a hypervascular, well-demarcated lesion of the pancreatic head which had a maximum diameter of 28 mm and no relation with neighboring organs	EUS-FNA, not selected for surgery but follow-up alone	A couple episodes of abdominal pain and the lesion remained stable in size	2.8	PEComa	13
20	J.Wei	2016	58	F	None	Body	CT: an asymptomatic pancreatic body mass. Abdominal ultrasonography: a slightly hyperechoic pancreatic body mass	Middle pancreatectomy	-	1.8	PEComa	18
21	Hui	2016	50	F	None	Head	CT: a relatively low-density nodule in the uncus of the pancreas; MRI: low T1W1 signal nodule, which had clear contrast with adjacent normal pancreatic of a relatively high signal	Operation	-	1.4	PEComa	14
22	Christopher	2016	31	F	History of de novo TSC	Body	Enhanced CT scan identified an 8 mm cyst in the body of the pancreas, which enlarged to 5.8 cm by 2013. Endoscopic ultrasonography demonstrated a cystic lesion with no connection to pancreatic ducts, with a solid oligolocular cyst	Distal pancreatectomy	-	5.8	PEComa	-
23	Our case	2018	40	F	None	Body	Moderately progressive enhancement and solid pseudopapillary tumor, cystic & solid lesion	Laparoscopic distal pancreatectomy	-	2.3	PEComa	30

DP, distal pancreatectomy; PPPD, pylorus preserving pancreaticoduodenectomy; PD, pancreaticoduodenectomy; EUS, endoscopic ultrasonography; PEComa, perivascular epithelioid cell tumor.

tial, and malignant. Benign PEcoma is usually smaller than 5 cm in diameter, presenting with non-infiltrative growth, bland cell morphology, number of mitotic figures ≤ 1/50 HPF, no necrosis, and no vascular invasion. Uncertain malignant potential is considered if any of the below situations are found: (1) Polygonal or multinucleated giant cells; or (2) Tumor diameter > 5 cm. There are no clear criteria for the diagnosis of malignant PEComa. The latest version of the 2016 WHO classification about soft tissue and bone tumor only briefly mentions that malignant PEComas are characterized by mitotic activity, necrosis, marked nuclear atypia, and pleomorphism. There are reports in the literature that suggest malignant PEComa is considered if any two or more of the below situations are found: (1) Tumor diameter > 5 cm; (2) Infiltrative growth; (3) Pronounced heteromorphic nuclei; (4) Number of mitotic figures > 1/50 HPF; (5) Necrosis; (6) Vascular invasion [23, 24]. So far, only 2 cases of malignant PEcoma have been reported, and all the remaining cases (including ours) have been benign. Our case of PEcoma was 2.3 cm in diameter (< 5 cm), presenting with non-infiltrative growth, mild cell morphology, number of mitotic figures ≤ 1/50 HPF, no necrosis, and no vascular invasion. Based on these above characteristics, this case was diagnosed as benign PEComa.

Specific expressions of melanin markers feature the immunophenotype of PEComa at the pancreas. The HMB-45 expression is usually the highest, followed by MelanA. Markers for smooth muscle cell differentiation are also expressed, such as SMA and desmin. Epithelial cell markers (CK, EMA) and endocrine markers (S-100, Syn, and CgA) are negative, and so are ER and PR. The immunophenotype of PEComa at the pancreas is consistent with PEComa in other sites.

It has been shown [25, 26] that liver and kidney AML and lung LAM are usually accompanied by tuberous sclerosis complex (TSC), which is an autosomal dominant inherited disease, probably associated with the mutations in the TSC1 gene (9q3.4, 27%) and TSC2 gene (16p13.3, 73%). TSC genes primarily work by regulating the Rheb/mTOR/p70S6K signaling pathway, and their mutations may lead to activation disorder of mTORC1, thus resulting in a tumor. Kenerson et al. [27] found that the upregulation of phosphorylated p70S6K (a marker of mTOR activity) in AML agreed with the functional damage of TSC1 or TSC2. Gondran et al. [28] reported the first case of pancreatic PEComa treated by mTOR inhibitor Sirolimus without surgery, which showed a significant reduction in size of the tumor after 3.5 years suggesting a good efficiency of mTOR inhibitor therapy. There are still limited cellular and molecular genetics studies about PEComa at the pancreas, and most of the reported cases of PEComa at the pancreas, including our case, are not correlated with TSC. The correlation between PEComa at the pancreas and TSC remains unclear. Additional knowledge can be gained in this field with more reported cases and advances in molecular genetic technology.

Several types of tumors are associated with the upregulation of genes in the microphthalmia-associated transcription factor (MiTF) family, which share some similar histomorphologic features as PEComa. TFE3 is a member of the MiTF family. Several recent studies have reported the positive expression of TFE3 in PEComa of the liver and kidney [29, 30]. About 23% of cases with PECcoma are associated with TFE3 rearrangement plus SFPQ/PSF-TFE3 and DVL2-TFE3 gene fusions, or only TFE3 rearrangement without gene fusions. In our case, TFE3 protein was negatively expressed, so gene detection was not carried out. Some cases with PEComa in other sites are positive for TFE3, but so far, positive TFE protein expression and gene fusion have not been reported in PEComa of the pancreas, which may be attributed to the limited number of cases. Also, the pathogenesis of PEComa at the pancreas may not be related to TFE3 translocation. Alternatively, it may just be an independent subtype of PEComa.

The reported cases of PEComa of the pancreas are generally treated by en-bloc or complete resection of the pancreas and tumor. Given the fact that PEComa is benign in most cases, surgery may not be recommended unless the lesions grow, and the cytology is atypical in the preoperative puncture pathologic diagnosis. The patients can receive regular follow-up in the absence of symptoms. Maurizio et al. [19] believes that surgery may not be the best choice for PEComa of the pancreas, since it is generally benign. Follow-up is recommended

for the patients and is confirmed pathologically by fine-needle aspiration. The pancreas is an important digestive organ, and pancreatic resection has an adverse impact on patients' digestive function and impairs patients' life quality. Endoscopic ultrasound-guided fine-needle aspiration biopsy of the pancreas has been widely used clinically, If pancreatic tumors undergo fine needle aspiration and mTOR pathway activity detection can be used for the diagnosis of PECOMA before surgery, mTOR inhibitor would be a good treatment option for the clinician and patient to avoid surgical damage. Although this type of treatment is not yet supported by clinical data it still has good application prospects. Our case was followed up for 30 months, and relapse was not found.

Conclusions

This article reports one rare case of classic PEComa at the pancreas, and the literature review was performed to analyze the clinical history, imaging findings, histopathology, immunohistochemistry, genetic molecular research progress, treatment, and prognosis of pancreatic PEComa. It is not easy for clinicians to consider this disease due to the rare characteristics of this kind of tumor, and this paper summarizes the characteristics and research progress of the pancreatic PEComa, which is convenient for physicians and pathologists to fully understand the disease to avoid misdiagnosis and to provide a new treatment and prognosis reference.

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Disclosure of conflict of interest

None.

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