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PRIMARY PANCREATIC PERIVASCULAR EPITHELIOID CELL TUMOR – CASE REPORT AND PROGNOSTIC ANALYSIS

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ABSTRACT

Perivascular epithelioid cell tumors (PEComas) are rare mesenchymal neoplasms and uncommonly arise from the pancreas. Our group encountered one such patient. Being that little is written about their behavior and prognosis, we sought to analyze the available literature and obtain a follow-up for previously reported patients to better ascertain the prognosis and biological behavior of these unusual neoplasms.

Pancreatic PEComas predominantly occur in women with an average age of 50. Patients present with abdominal pain (8/17), GI bleeding (1/17), upper right quadrant bulge or pain (3/17), nonspecific symptoms (3/17) or asymptomatically (2/17). 11 cases met the inclusion criteria for the prognostic study. Two cases were excluded due to unavailable data and inability for follow-up. The prognosis of pancreatic PEComas is excellent, with a 5-year survival rate of 100% and recurrence rate of 22%.

Pancreatic PEComas exhibit favorable survival rates but they do have the potential to recur. As such, we recommend radiological follow-up for all of these patients.

KEYWORDS : PEComa, pancreas, perivascular epithiliod cell tumor, pancreatic neoplasm

Introduction

Perivascular epithelioid cell tumors (PEComas) are a family of mesenchymal neoplasms that can originate from various organ systems. Most commonly, they are found in the genitourinary tract, the gastrointestinal tract as well as the pulmonary system with the pancreas constituting a rare primary site (Hornick & Fletcher, 2006; Liu et al., 2015). PEComas may also be referred to as angiomyolipoma (AML) or renal capsuloma when arising from the kidneys, lymphangioleiomyomatosis (LAM) or clear cell "sugar" tumor (CCST) when originating from the lungs, clear cell myomelanocytic tumor (CCMMT) in Falciform ligament/ Ligamentum teres, and lucency cell tumors when found in the rectum. PEComas are more commonly observed in females (Liu et al., 2015) and patients with tuberous sclerosis (Folpe et al., 2005; Martignoni, Pea, Reghellin, Zamboni, & Bonetti, 2008).

The World Health Organization (2002) characterizes PEComas as "a mesenchymal tumor composed of histologically and immunohistochemically distinctive perivascular epithelioid cells" (Fletcher, Unni, & Mertens, 2002). PEComas are well-circumscribed and separated from the surrounding parenchyma by a thin capsule. Histopathologically, they exhibit nests and sheets of epithelioid cells found in close proximity to blood vessel walls (Hornick & Fletcher, 2006). Occasionally spindle cells with clear to granular eosinophilic cytoplasm are identified instead of the characteristic epithelioid cells.

PEComas may be identified with MRI, CT, or endoscopic ultrasound. However, imaging alone is insufficient for diagnosis. Pathologic examination of the surgically resected tumor remains the gold-standard for diagnosis. Typical positive immunohistochemistry markers that prevail in PEComas are melan-A, HMB-45 (melanocyte reactivity markers), and SMA (smooth muscle actin markers) though a negative result of one of these markers does not rule out the diagnosis of a PEComa (Folpe et al., 2005).

The prognosis associated with PEComas is greatly affected by the prompt discovery and treatment initiation. Though most PEComas are characterized as benign, some exhibit signs of malignancy such as local invasion, distant metastases, and, in some cases, death (Gross, Vernea, Weintraub, & Koplewitz, 2010; Lai et al., 2012; Mourra, Lazure, Colas, Arrive, & de Gramont, 2013; Nagata et al., 2011). In 2003, the World Health Organization set criteria that two or more of the following determine malignancy in PEComas: infiltrating growth, tumor size of >5cm, a high cell density, nuclear enlargement, an increased number of mitotic figures, atypical nuclear division, coagulative necrosis, and vascular invasion. Liu et al. (2015) proposed that a Ki-67 index of less than 1% classifies PEComas as benign with lower recurrence rates. However, the inconsistency in predicting PEComa malignancy potential makes it an unreliable marker, and the behavior of PEComas remain difficult to predict. Flope et al. (2005) suggested a series of standards to sub divide tumors into three distinct categories: benign, of uncertain malignant potential, or with malignant potential. Because of their rarity, it is recommended to classify all pancreatic PEComas as having an uncertain malignant potential.

The mainstay and only potentially curative treatment for PEComas is complete surgical resection. To our knowledge, PEComas do not respond to standard chemo or radiation therapy (Fletcher et al., 2002; Wagner et al., 2010). m-TOR inhibitors have been shown to have some effectiveness in treating metastatic PEComas, although there has not been any clinical successes with m-TOR as an adjunct treatment in pancreatic PEComas (Martignoni et al., 2008; Wagner et al., 2010).

Pancreatic PEComas are extremely rare and insufficient long-term data exists on these tumors (Jiang et al., 2016; Mizuuchi et al., 2016). Therefore, we sought to profile the behavior and prognosis of these rare tumors based on the available literature.

Methods

Our institution's pancreatic PEComa case was reported and compared to previously published primary pancreatic PEComa case studies.

A review of all published primary pancreatic PEComa case studies was performed. Data was extracted for demographics, presenting

symptoms, tumor characteristics and treatment information. All authors included were contacted to complete the missing data and to ask for their patient's survival and recurrence status. If a date of surgery was not clear, it was approximated by subtracting the follow up time mentioned in the report by the year of submission of the case study. All cases that occurred prior to 2012 were included in our 5-year survival and recurrence analysis.

Case Report

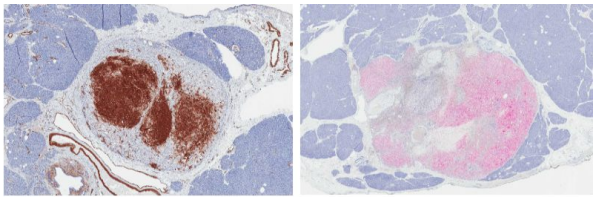
A 58-year-old Caucasian woman presented to the emergency department with a 3-month history of persistent left flank pain. No history of vomiting, weight loss or loss of energy was reported and she did not complain of any urinary symptoms. Her past medical history was mostly unremarkable, but she was known to suffer from anxiety which was treated with Fluoxetine (Prozac). The patient is an ex-smoker (7.5 pack-years) but does not consume alcohol or any illicit drugs.

An ultrasound was performed and showed a hypo-echoic mass in the body of the pancreas. MRI confirmed a 16 mm mass. An EUS described a 15 mm mass, during which biopsies were taken. They were reported as negative but deemed inconclusive by the gastroenterology team due to sampling errors. The chest CT performed for staging was negative for malignant lesions. The serum CA 19-9 was normal (3U/L).

This case was presented at our institutional tumor boards and with the high malignant potential of solid pancreatic lesions, the decision was to proceed with surgery. A laparoscopic distal pancreatectomy and splenectomy was performed without intra-operative complication. Her post-operative recovery was uneventful and the patient only reported minor post-prandial abdominal pain.

Gross pathologic report of resected organs at the time of the surgery revealed a 1 cm pancreatic PEComa with clear margins and Ki-67 index of <1%. The PEComa was well circumscribed with no mitotic activity or infiltrative growth pattern. It was positive for focal cytological atypia related to prior biopsy. The pathologic report of the PEComa revealed: a low nuclear-cytoplasmic ratio, solid proliferation of epithelial cells, pale eosinophilic cytoplasm with focal vacuolation, focal hyaline globules, no mitotic activity, poorly defined cell borders, and an overall well vascularized tumor. An area of hemorrhage with adjacent proliferation of fibroblast and foamy macrophages was reported. The PEComa tested positively for SMA, HMB-45, Melan-A, BCL-1 and estrogen receptor markers (Image 1).

Image 1:



(a) SMA low mag (smooth muscle actin) (b) MART1 low mag (Melan-A)

After the surgery, based on the oncologic uncertainty, the follow-up plan was for follow-up axial imaging every 3 months for the first year, every 6 months for the next two years and yearly thereafter for 5 years. It is now 2 years since the surgery and this patient has no sign of recurrence.

Results:

Given the rarity of primary pancreatic PEComas, there is no established typical clinical presentation and behavior for these tumors. According to the clinical data we gathered (Table 1), pancreatic PEComas predominately occur in women (15:2), with a median age of 51 (17-74). The presence of these tumors can be symptomatic (15/17), presenting as non-specific abdominal pain (8/17), GI bleeding (1/17), bulge or pain specific to the upper right quadrant (3/17) or other non-specific symptoms (3/17). At 10 mm this is the smallest pancreatic PEComa reported (avg. 34.6 mm). This was one of the only two cases that were performed laparoscopically.

We contacted the corresponding authors for follow-up performed on the 11 cases identified meeting the inclusion criteria. We were unable to obtain long-term data on 2 patients: 1 author did not respond and 1 patient had relocated and was lost to follow up. The remaining 9 patients were alive a minimum of 5-years post-operatively and only 2 of these patients developed hepatic metastatic lesions. These were discovered at 4 and 27 months post-operatively and both were resected in a subsequent surgery.

Table 1: Case Review of Primary Pancreatic PEComas

	Case	Sex	Age	Location in pancreas	Size (mm)	Symptoms	Treatment	Year of Sx	F/U (yrs)	Inclusion in prognostic analysis	Recurrence (months)
1	Zamboni et al. (1996)	F	60	Body	20	Abdominal pain	DP	1996	N/A	No- author did not respond	
2	Heywood et al. (2004)	F	74	Head	45	Abdominal pain	PPPD	1997	5.75	Yes	
3	Ramuz et al. (2005)	F	31	Body	15	Abdominal pain	LAP-SPDP	2004	11.17	Yes	
4	Périgny et al. (2008)	F	46	Body	17	Diarrhea	enucleation	2008	N/A	No- lost to follow up	
5	Hirabayashi et al. (2009)	F	47	Head	17	Abdominal pain	PPPD	2007	9.17	Yes	
6	Baez et al. (2009)	F	60	Body	32	Bulge in right upper quadrant	DP SPL	2008	8	Yes	
7	Zemet et al. (2011)	M	49	Head	32	Fever, cough, and malaise	PPPD	2010	6.67	Yes	
8	Nagata et al. (2011)	M	52	Head	40	Abdominal pain	PD	2011	5.5	Yes	27 months hepatic metastases
9	Finzi et al. (2012)	F	62	Head	25	Asymptomatic	total excision	2012	5	Yes	
10	Al-Haddad et al. (2013)	F	38	Uncinate process	18	Abdominal pain	PD	2013	N/A	No	
11	Okuwaki et al. (2013)	F	43	Body	100	Abdominal pain	DP	2012	4.5	No	
12	Mourra et al. (2013)	F	51	Head	60	Right hypochondric pain and prurit	PD	2010	5	Yes	4 and 22 months hepatic metastases
13	Petrides et al. (2015)	F	17	Head	42	Melena	PPPD	2013	1.5	No	
14	Jiang et al. (2016)	F	50	Head	20	Asymptomatic	excision	2014	1.17	No	
15	Mizuuchi et al. (2016)	F	61	Body	70	Abdominal pain	PD	2004	12	Yes	

16	Collins et al. (2017)	F	54	Body	26	Right upper quadrant abdominal pain	MPP	2015	1.92	No	
17	Our patient	F	58	Body	10	left flank pain	LAP-DP SPL	2015	1.58	No	
	17 patients	**15F :2M**	**Median age 51 (17-74)**	**Body: 8 Head: 8 Uncinate process: 1**	**Mean 34.6 mm (range 10-100)**	**Abdominal pain: 8 GI bleed: 1 RUQ mass/pain: 3 Nonspecific symptoms: 3 No symptoms: 2**				**11 prior to 2012 9 included in 5-year study**	

DP- distal pancreatectomy, PPPD- pylorus preserving pancreaticoduodenectomy, PD- pancreaticoduodenectomy, SPL- splenectomy, MPP- middle-preserving pancreatectomy, LAP- preformed laparoscopically

Discussion

Our institution was faced with a primary pancreatic PEComa case. The inability to define the expected clinical presentation or survival for the patient led us to conduct an analysis on primary pancreatic PEComas focusing on the 5-year survival and recurrence rates. Given their rarity, there was very little data on their behavior or prognosis.

From the 17 primary pancreatic PEComa cases reported, only two were reported to have metastatic hepatic lesions at 4 and 27 months post-operatively. Survival information for the resected metastatic hepatic lesions was obtained and included in the 5-year study. The follow up information was used to determine the prognosis of pancreatic PEComa which revealed a 5-year survival rate of 100% and a recurrence rate of 22%. These values reveal an overall favorable prognosis. Primary pancreatic PEComas are classified as having uncertain malignant potential as displayed by our data with only 2 cases with reported metastatic lesions on follow-up. Given the malignancy potential, complete surgical resection of the tumor and close follow-up with imaging for disease recurrence is still recommended.

PEComas found in the pancreas are extremely rare and long term behavioral and survival data is very limited. Our case is consistent with the typical presentation of pancreatic PEComas given the limited knowledge of this disease in today's literature. Our behavioral and prognostic profiling revealed a favorable 5-year survival rate with minimal evidence of recurrent metastatic disease for primary pancreatic PEComas that underwent surgical resection.

References:

1. Fletcher, C. D. M., Unni, K. K., & Mertens, F. (2002). Pathology and Genetics of Tumours of Soft Tissue and Bone. IARC.
2. Folpe, A. L., Mentzel, T., Lehr, H.-A., Fisher, C., Balzer, B. L., & Weiss, S. W. (2005). Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. The American Journal of Surgical Pathology, 29(12), 1558–1575.
3. Gross, E., Vernea, F., Weintraub, M., & Koplewitz, B. Z. (2010). Perivascular epithelioid cell tumor of the ascending colon mesentery in a child: case report and review of the literature. Journal of Pediatric Surgery, 45(4), 830–833. http://doi.org/10.1016/j.jpedsurg.2010.01.015
4. Hornick, J. L., & Fletcher, C. D. M. (2006). PEComa: what do we know so far? Histopathology, 48(1), 75–82. http://doi.org/10.1111/j.1365-2559.2005.02316.x
5. Jiang, H., Ta, N., Huang, X.-Y., Zhang, M.-H., Xu, J.-J., Zheng, K.-L., et al. (2016). Pancreatic perivascular epithelioid cell tumor: A case report with clinicopathological features and a literature review. World Journal of Gastroenterology, 22(13), 3693–3700. http://doi.org/10.3748/wjg.v22.i13.3693
6. Lai, C.-L., Hsu, K.-F., Yu, J.-C., Chen, C.-J., Hsieh, C.-B., Chan, D.-C., et al. (2012). Malignant perivascular epithelioid cell tumor of the mesentery: a case report and literature review. Onkologie, 35(3), 114–117. http://doi.org/10.1159/000336826
7. Liu, R., Jia, W., Zou, H., Wang, X., Ren, Y., Zhao, J., et al. (2015). Expression of CD44 and CD29 by PEComa cells suggests their possible origin of mesenchymal stem cells. International Journal of Clinical and Experimental Pathology, 8(10), 13023–13033.
8. Martignoni, G., Pea, M., Reghellin, D., Zamboni, G., & Bonetti, F. (2008). PEComas: the past, the present and the future. Virchows Archiv : an International Journal of Pathology, 452(2), 119–132. http://doi.org/10.1007/s00428-007-0509-1
9. Mizuuchi, Y., Nishihara, K., Hayashi, A., Tamiya, S., Toyoshima, S., Oda, Y., & Nakano, T. (2016). Perivascular epithelial cell tumor (PEComa) of the pancreas: a case report and review of previous literatures. Surgical Case Reports, 2(1), 59. http://doi.org/10.1186/s40792-016-0186-x
10. Mourra, N., Lazure, T., Colas, C., Arrive, L., & de Gramont, A. (2013). Perivascular epithelioid cell tumor: the first malignant case report in the pancreas. Applied Immunohistochemistry & Molecular Morphology : AIMM, 21(3), e1–4. http://doi.org/10.1097/PAI.0b013e3182392bb6
11. Nagata, S., Yuki, M., Tomoeda, M., Kubo, C., Yoshizawa, H., Kitamura, M., et al. (2011). Perivascular epithelioid cell neoplasm (PEComa) originating from the pancreas and metastasizing to the liver. Pancreas, 40(7), 1155–1157. http://doi.org/10.1097/MPA.0b013e318221fc0e
12. Wagner, A. J., Malinowska-Kolodziej, I., Morgan, J. A., Qin, W., Fletcher, C. D. M., Vena, N., et al. (2010). Clinical activity of mTOR inhibition with sirolimus in malignant perivascular epithelioid cell tumors: targeting the pathogenic activation of mTORC1 in tumors. Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 28(5), 835–840. http://doi.org/10.1200/JCO.2009.25.2981