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CASE REPORT

Pancreatic paraganglioma diagnosed by endoscopic ultrasound-guided fine needle aspiration: A case report and review of literature

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Abstract

BACKGROUND

Pancreatic paragangliomas (PPGL) are rare benign neuroendocrine neoplasms but malignancy can occur. PPGL are often misdiagnosed as pancreatic neuroendocrine tumor or pancreatic adenocarcinoma.

CASE SUMMARY

We reviewed 47 case reports of PPGL published in PubMed to date. Fifteen patients (15/47) with PPGL underwent endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). Only six (6/15) were correctly diagnosed as PPGL. All patients with PPGL underwent surgical resection except three (one patient surgery was aborted because of hypertensive crisis, two patients had metastasis or involvement of major vessels). Our patient remained on close surveillance as she was asymptomatic.

CONCLUSION

Accurate preoperative diagnosis of PPGL can be safely achieved by EUS-FNA with immunohistochemistry. Multidisciplinary team approach should be considered to bring the optimal results in the management of PPGL.

Key Words: Pancreatic paraganglioma; Endoscopic ultrasound-guided fine needle aspiration; Meta-iodobenzylguanidine scan; Metanephrines; GATA-3; Immunohistochemistry; Case report

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Core Tip: The morphologic overlap between pancreatic paraganglioma and neuroendocrine tumor is significant. An accurate diagnosis by endoscopic ultrasound-guided fine needle aspiration requires firstly that the possibility of paraganglioma is considered and secondly that a cell block is available for immunohistochemical stains. A patient-centered approach supported by a multidisciplinary team of radiologists, advanced endoscopists, endocrinologists, pathologists, oncologists, and surgeons is paramount in the management of pancreatic paraganglioma.

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INTRODUCTION

Paragangliomas are rare neuroendocrine neoplasms arising from the sympathetic and parasympathetic paraganglia. This tumor is called pheochromocytoma in the adrenal medulla and elsewhere is known as extra-adrenal paraganglioma or simply as paraganglioma. The malignant potential of these tumors is difficult to predict. Most behave in a benign manner, but metastasis, which best defines malignant paraganglioma, may occur in 15%-20%[1]. When found in or around the pancreas this tumor is often misdiagnosed as pancreatic neuroendocrine tumor (PNET) or even pancreatic adenocarcinoma. In this study, we report a case of pancreatic paraganglioma diagnosed by endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) and review of the literature on pancreatic paraganglioma.

CASE PRESENTATION

Chief complaints

A 73-year-old female presented with a chief complaint for evaluation of an incidental finding of peripancreatic lymph node.

History of present illness

She underwent computed tomography (CT) of the abdomen and pelvis as part of her routine surveillance for extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma) of the lung and was found to have peripancreatic lymph node. She denied any abdominal pain, change in bowel habit, weight loss, nausea, or vomiting.

History of past illness

Her medical history was significant for MALT-lymphoma, invasive lobular breast carcinoma, hypertension, atrial fibrillation, mitral valve prolapse, mitral valve stenosis, and actinic keratosis. Her surgical history included a mastectomy with sentinel lymph node dissection, laparoscopic cholecystectomy, tonsillectomy, left knee replacement, and bilateral carpal tunnel repair.

Personal and family history

Her family history was significant for colon cancer in maternal grandmother at the age of 65 years, prostate cancer in brother at the age of 63 years, and melanoma in mother. She had no history of alcohol or tobacco abuse. She has 2 children and attained menopause at the age of 52 years. Her medications included aspirin, furosemide, carvedilol, rosuvastatin, amiodarone, digoxin, anastrozole, and Eliquis.

Physical examination

Her physical examination was unremarkable, and her abdomen was soft nontender, nondistended with no palpable mass.

Laboratory examinations

Laboratory exam including fractionated metanephrines, chromogranin, and gastrin were negative.

Imaging examinations

CT of the abdomen and pelvis showed 2 cm × 1.1 cm lymph node adjacent to the pancreatic head (Figure 1A).

Endoscopy

EUS showed a 19 mm × 11.5 mm hypoechoic lesion near the pancreatic head (Figure 1B). Two FNA passes using a 25-gauge needle were performed *via* trans-duodenal approach (Figure 1C).

Pathology

Direct FNA smears showed tumor with neuroendocrine features. Initial immunoperoxidase stains performed on cell block sections were positive for synaptophysin and chromogranin, which seemed to confirm the morphologic impression of PNET. The pathologist was subsequently informed about the peripancreatic location and lack of a definite pancreatic lesion.

FINAL DIAGNOSIS

After additional testing showed the tumor to be positive for GATA-3 and negative for keratin with low expression of Ki-67 (less than 1%), the FNA diagnosis was revised to paraganglioma.

TREATMENT

Our patient was referred to endocrine surgery team after the FNA diagnosis of paraganglioma. After a thorough discussion with the patient on the benefits and risks of surgical resection, the patient elected to remain on close surveillance since she was asymptomatic with a 2-cm, nonfunctioning paraganglioma.

OUTCOME AND FOLLOW-UP

After a 1-year follow up, patient was found to have stable asymptomatic peripancreatic paraganglioma with no increase in size.

DISCUSSION

Paragangliomas are non-epithelial neuroendocrine neoplasms arising in close association with components of the parasympathetic and sympathetic nervous systems [2]. Most parasympathetic paragangliomas are nonfunctional and located along the glossopharyngeal and vagal nerves in the neck and base of the skull[3]. Sympathetic paraganglia secrete catecholamines (functional) and they are commonly located in the paravertebral ganglia of thorax, abdomen, and pelvis[3]. The incidence of extra-adrenal paraganglioma is unclear as these are often described with pheochromocytoma. In the United States, approximately 500-1600 cases are diagnosed every year and the combined annual incidence of pheochromocytoma/paraganglioma is approximately 0.8 per 100000 person-years[4,5]. Pancreatic paragangliomas are more common in women than men (2:1) and the mean age of incidence is 52 years (19-85 years)[6].

Patients with functional paragangliomas can experience hypertension, headache, sweating, and palpitations due to the excessive secretion of catecholamines[7]. Nonsecretory paragangliomas may present with abdominal mass with or without abdominal pain, but most are found incidentally on imaging studies[8,9]. CT has a sensitivity of approximately 90% in the identification of extra-adrenal paragangliomas, which frequently appear as highly vascular structures with areas of intralesional hemorrhage and necrosis[8,10]. The CT findings of pancreatic paragangliomas differ from those of pancreatic ductal adenocarcinoma by their location at the pancreatic

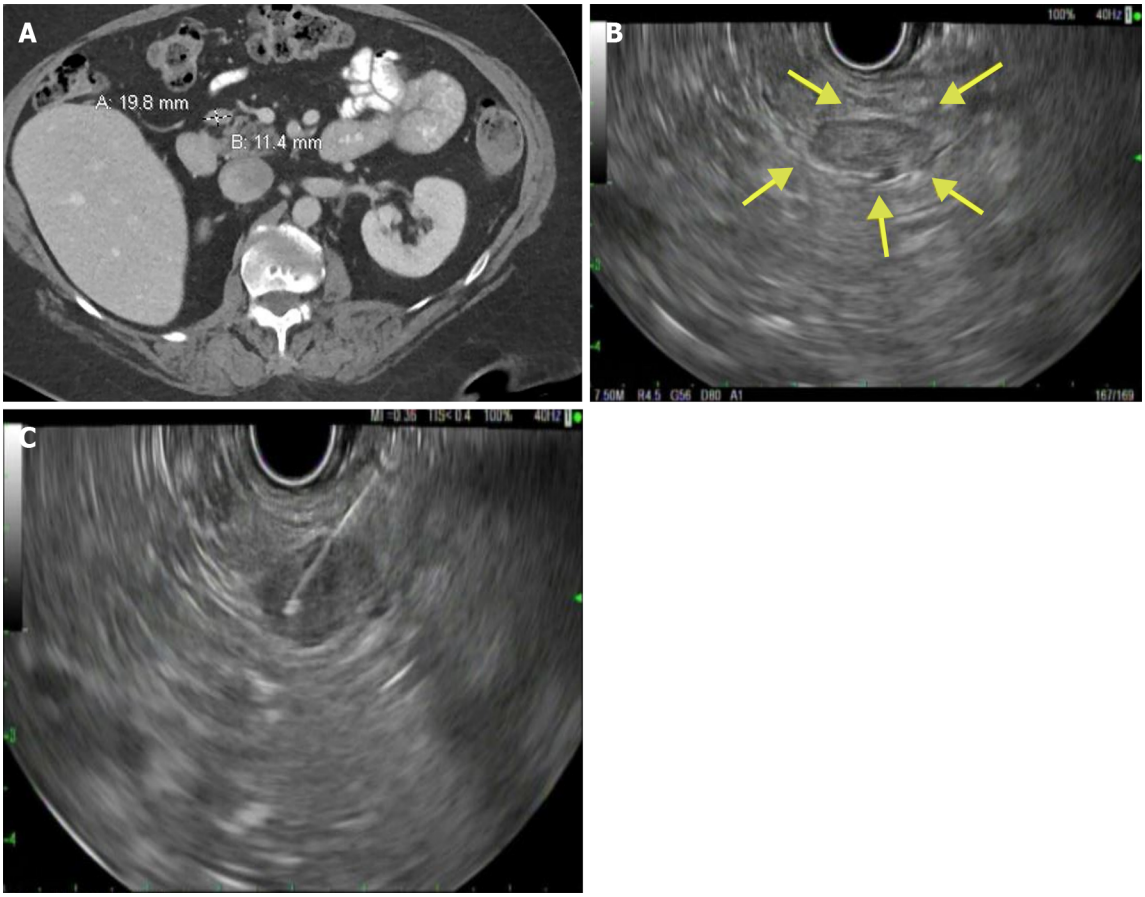

Figure 1 Computed tomography and endoscopy examinations. A: Computed tomography of abdomen pelvis showing a peripancreatic lymph node adjacent to the pancreatic head; B: Endoscopic ultrasonography showing a hypoechoic lesion near the pancreatic head; C: Endoscopic ultrasound-guided fine needle aspiration of the peripancreatic lesion.

head and absence of biliary dilation, although mild pancreatic duct dilatation is sometimes seen[11]. Paragangliomas are also differentiated from nonfunctioning islet cell tumor of the pancreas by observation of early contrast filling of the prominent draining veins of the tumor and the portal vein[12]. Magnetic resonance imaging (MRI) provides tissue characterization superior to CT without radiation[13]. Working synergistically, meta-iodobenzylguanidine (MIBG, I^{123} or I^{131}) scan is useful in differentiating functional from nonfunctional paragangliomas as well as in the detection of tumors in unusual locations, multiple primary tumors, and metastasis[13]. MIBG scan has a sensitivity of 85% and specificity of 95%-100% in the detection of extra-adrenal paragangliomas. Plasma or urinary metanephrines can be used to further establish the diagnosis of functional paragangliomas[13,14].

While most paragangliomas are solitary and sporadic, they can be multicentric and hereditary. Genetic testing should be considered in all patients diagnosed with paraganglioma as nearly 40% (pheochromocytoma and paraganglioma) carry germline mutations. Genetic testing allows for the identification of simultaneous cancers in hereditary syndromes and assists with screening family members at high risk[15]. The most common genetic mutations associated with paragangliomas are *RET* gene in multiple endocrine neoplasia type 2A and 2B, *VHL* in von Hippel-Lindau disease, *NF1* in neurofibromatosis type 1, and succinate dehydrogenase (*SDH*) B, D, C genes[15].

One of the most valuable tools that can assist in establishing the diagnosis of paraganglioma is EUS, which both enables localization of the mass and acquisition of tissue samples for cytology *via* FNA. When not considered in the differential diagnosis, pancreatic paragangliomas can be easily misdiagnosed on EUS-FNA cytology as pancreatic neuroendocrine tumor (NET)[16,17]. Some authors suggest that EUS-FNA should not be done in functional paragangliomas as it can trigger the secretion of catecholamines[18]. In our case, the diagnosis was not established before EUS-FNA and there were no complications during and after the procedure.

On cytology, the cells of paragangliomas are relatively uniform in size, epithelioid in appearance with round to oval nuclei, and arranged in loosely cohesive clusters

Table 1 Reported cases of pancreatic paraganglioma in the literature

No.	Ref.	Age	Gender	Size	Location	EUS-FNA	Preop-diagnosis	Surgery	Postop diagnosis
1	Fujino *et al* [21]	61	Male	2.5 cm	Uncinate process	No	PNET	Pancreaticoduodenectomy	PPGL
2	Ohkawara *et al*[33]	72	Female	4 cm	Head	No	NET	Surgical resection of head	PPGL
3	Perrot *et al* [34]	41	Female	4.3 cm	Tail	No	PPGL	Tumor resection	PPGL
4	Tsukada *et al* [35]	51	Male	2.5 cm	Uncinate	No	PNET	Surgical resection	PPGL
5	Kim *et al*[12]	57	Female	7 cm	Head	No	Non-functioning islet cell tumor	Pancreaticoduodenectomy	PPGL
6	Paik[36]	70	Female	4.2 cm	Tail	No	None	Distal pancreatectomy	PPGL
7	He *et al*[37]	40	Female	4.5 cm	Uncinate	No	None	Surgical resection	PPGL
8	Higa and Kapur[38]	65	Female	2.1 cm	Uncinate	No	None	Pancreaticoduodenectomy	PPGL
9	Al-jiffry *et al* [39]	19	Female	9.5 cm	Head and neck	No	Sarcoma	Pancreaticoduodenectomy	PPGL
10	Zhang *et al* [27]	50	Female	6 cm	Head	Yes	Functional PPGL	Chemotherapy	PPGL
11	Zhang *et al* [27]	63	Female	4 cm	Head	No	Functional PPGL	Surgical resection	PPGL
12	Borgohain *et al*[40]	55	Female	19 cm	Tail	No	Pancreatic cancer	Surgical resection	PPGL
13	Straka *et al* [41]	53	Female	Not mentioned	Head	No	None	Surgical resection	PPGL
14	Meng *et al* [11]	54	Female	3 cm	Head	No	None	Surgical resection	PPGL
15	Meng *et al* [11]	41	Female	6.2 cm	Head	No	None	Surgical resection	PPGL
16	Misumi *et al* [42]	47	Female	1.5 cm	Head	EUS only	PNET	Pancreaticoduodenectomy	PPGL
17	Bartley *et al* [43]	75	Female	15 cm	Tail	No	Pancreatic cyst	Not available	PPGL
18	Bartley *et al* [43]	70	Female	3 cm	Head	No	Pancreatic cyst	Not available	PPGL
19	Cope *et al* [44]	72	Female	14 cm	Head	No	Cystadenoma	Not available	PPGL
20	Zamir *et al* [45]	47	Male	10 cm	Body	No	Pancreatic cyst	Not available	PPGL
21	Parithivel *et al*[46]	85	Male	6 cm	Head	No	NET	Surgical resection	PPGL
22	Wang *et al* [32]	30	Female	6.4 cm	Tail	No	None	No surgery	PPGL
23	Ganc *et al*[18]	37	Female	4.8 cm	Head	Yes	NET	Pancreatico duodenectomy	PPGL
24	Tumuluru *et al*[47]	62	Female	2.9 cm	Body	Yes	NET	Distal pancreatectomy/splenectomy	PPGL
25	Ginesu *et al* [48]	55	Male	2.5 cm	Uncinate	No	NET	pancreaticoduodenectomy	PPGL
26	Liang and Xu[6]	41	Male	6.4 cm	Uncinate	No	NET	pancreaticoduodenectomy	PPGL
27	Lin *et al*[3]	42	Female	6.3 cm	Body	No	NET	Middlesegment pancreatectomy	PPGL

28	Nguyen *et al* [23]	70	Female	5.8 cm	Tail	Yes	PPGL	Surgical resection	PPGL
29	Zeng *et al*[19]	58	Female	6.5 cm	Head	Yes	NET	Surgical resection	PPGL
30	Zeng *et al*[19]	53	Female	2.5 cm	Head	Yes	NET	Surgical resecion	PPGL
31	Singhi *et al* [16]	61	Female	14 cm	Tail	Yes	Pseudocyst	Surgical resection	PPGL
32	Singhi *et al* [16]	52	Female	14 cm	Body	Yes	PPGL	Not performed	PPGL
33	Singhi *et al* [16]	54	Female	6.5 cm	Head	Yes	PPGL	Surgical resection	PPGL
34	Singhi *et al* [16]	40	Male	5.1 cm	Body	Yes	NET	Surgical resection	PPGL
35	Singhi *et al* [16]	78	Female	17 cm	Body	Yes	Spindle cell neoplasm	Surgical resection	PPGL
36	Singhi *et al* [16]	44	Male	5.5 cm	Head	Yes	PPGL	Surgical resection	PPGL
37	Singhi *et al* [16]	38	Male	15 cm	Body	No	None	Surgical resection	PPGL
38	Singhi *et al* [16]	47	Male	7.5 cm	Body	No	NET	Surgical resection	PPGL
39	Singhi *et al* [16]	37	Female	5.7 cm	Tail	No	NET	Surgical resection	PPGL
40	Fite and Maleki[49]	40	Male	5.1 cm	Peripancreatic	No	NET	Surgical resection	PPGL
41	Fite and Maleki[49]	23	Female	7.0 cm	Peripancreatic	No	NET	Surgical resection	PPGL
42	Malthouse *et al*[50]	58	Male	8 cm	Head	No	NET	Not available	PPGL
43	Malthouse *et al*[50]	45	Female	8 cm	Head	No	Retro peritoneal tumor	Not available	PPGL
44	Sangster *et al* [10]	50	Male	Not available	Head	Yes	Poorly differentiatedcarcinoma	Radiation treatment	PPGL
45	Lightfoot *et al*[51]	66	Male	6 cm	Head/uncinate	No	None	Pancreaticoduodenectomy	PPGL
46	Abbasi *et al* [52]	61	Female	7.2 cm	Head/uncinate	Yes	NET	Pancreaticoduodenenctomy	PPGL
47	Present case	73	Female	2 cm	Head	Yes	PPGL	No surgery	PPGL

PPGL: Pancreatic paraganglioma; PNET: Pancreatic Neuroendocrine tumor; EUS-FNA: Endoscopic ultrasound-guided fine needle aspiration.

[19]. Morphological patterns like acinar/glandular architecture and rosette-like arrangements can be observed in paragangliomas[20]. In histologic sections, the tumor is typically composed of nests of cells separated by a highly vascularized network[21].

Although the morphologic overlap between paraganglioma and NET is significant, the distinction can be confidently made with immunoperoxidase stains, which require a cell block preparation. Both pancreatic paragangliomas and NETs readily express neuroendocrine markers like synaptophysin and chromogranin[19]. While most NETs are immunoreactive to pancytokeratins (AE1/AE3 and CAM 5.2) but not vimentin, paragangliomas show the opposite profile[19]. GATA-3 and PAX-8 can also be used to distinguish paragangliomas from NETs. Paragangliomas from any anatomic site are immunoreactive to GATA-3 in approximately 55% of the cases, but NETs are always nonreactive[22]. Of note, GATA-3 can be positive in cells of breast, urothelial, and pancreatic origin[23]. PAX-8 has a sensitivity of 88% and specificity of 74% for primary pancreatic NETs, but paragangliomas have weak or negative immunoreactivity to PAX -8[24-26]. In our case, FNA smears with Papanicolaou stain showed abundant, tangled cellular processes and relatively uniform nuclei with finely granular chromatin and indistinct nucleoli (Figure 2). FNA cell block with hematoxylin and eosin stain (Figure 3A), diffuse cytoplasmic staining with chromogranin (Figure 3B),

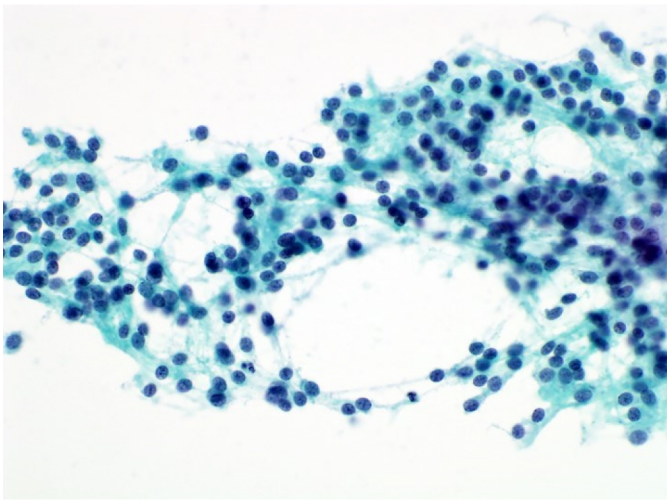

Figure 2 Fine needle aspiration direct smear. Papanicolaou stain, × 400.

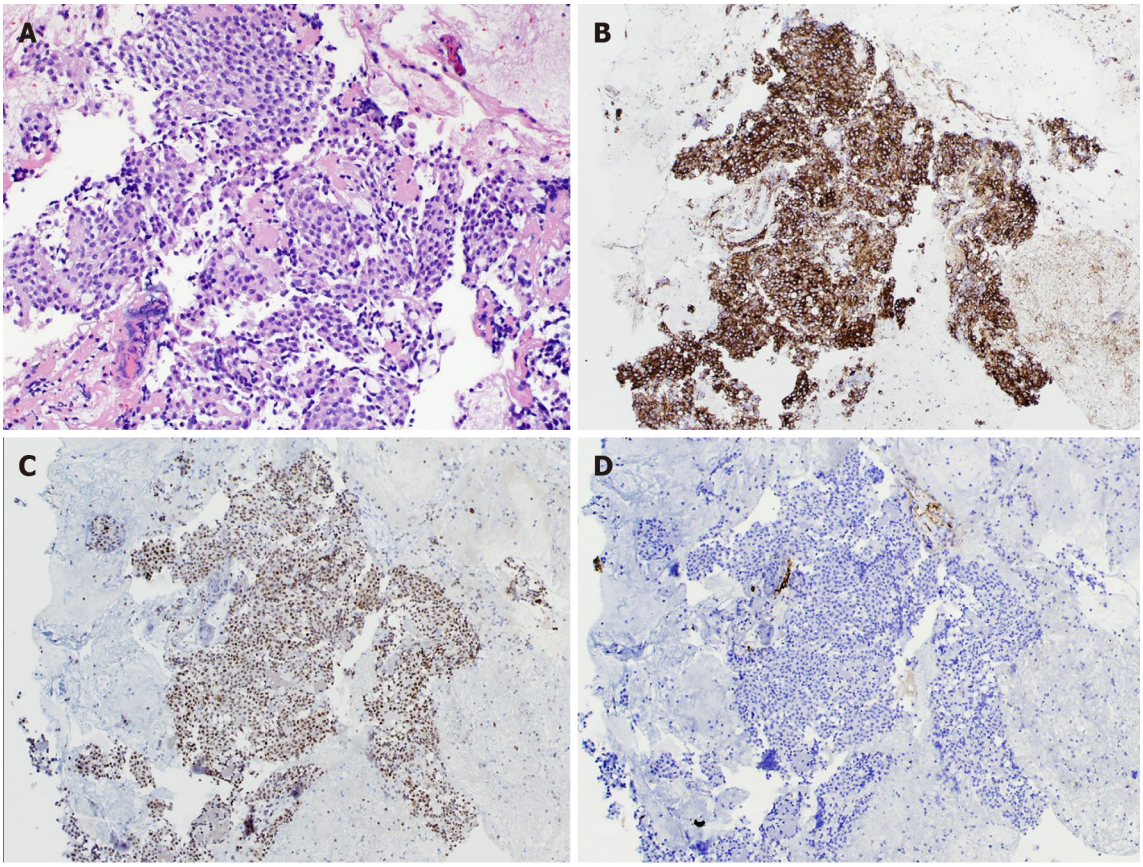

Figure 3 Fine needle aspiration cell block. A: Hematoxylin and eosin stain, × 200; B: Diffuse cytoplasmic staining, chromogranin (× 100); C: Diffuse nuclear staining, GATA-3, (× 100); D: No staining, keratin cocktail (× 100).

diffuse nuclear staining with GATA-3 (Figure 3C), and no staining with keratin cocktail (Figure 3D).

Since there are no definitive criteria for the diagnosis of malignancy in paraganglioma apart from metastasis, the treatment of choice for paraganglioma is surgical resection. For functional paragangliomas, preoperative administration of α-adrenergic receptor blocker can help prevent a hypertensive crisis during the surgery[27]. The most common sites of metastasis include the regional lymph nodes, bone, lung, and liver, and the dissemination usually occurs through blood or lymph nodes[28]. When surgery is not feasible, radiation therapy can be considered[29]. For malignant paragangliomas, treatment with I^{131} MIBG or combination chemotherapy (cyclophos-

phamide, vincristine, and dacarbazine) is effective[30]. Octreotide is also useful in inoperable paragangliomas[31].

Our review of the literature in the English language found 47 case reports of pancreatic paragangliomas published in PubMed to date (Table 1). Fifteen patients with pancreatic paragangliomas underwent EUS-FNA; six were correctly diagnosed as paraganglioma; six were misdiagnosed as NET; one had no diagnosis; one was diagnosed as spindle cell neoplasm; and one was diagnosed as pseudocyst. All patients with a pancreatic paraganglioma underwent surgery except three: one patient who developed a hypertensive crisis during the surgery (thus surgery was aborted) [32]; and two patients with metastasis or involvement of the major vessels[10,16].

Our case illustrates that accurate preoperative diagnosis of paraganglioma can be safely made by EUS-FNA. When paragangliomas are small and asymptomatic, it would be reasonable to follow them with periodic imaging studies.

CONCLUSION

Pancreatic paragangliomas are rare and EUS-FNA is a valuable tool in establishing the diagnosis. When assessing a lesion in the pancreas, paraganglioma should be included in the differential diagnoses along with PNET and pancreatic ductal adenocarcinoma. As EUS-FNA can trigger a hypertensive crisis in functional pancreatic paragangliomas, pre-procedure use of alpha-adrenergic blocker should be considered. To bring the optimal result in the management of paraganglioma, it is imperative to have a multidisciplinary team approach involving radiologists, advanced endoscopists, endocrinologists, pathologists, oncologists, and surgeons.

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