

Pheochromocytoma of the pancreas: A report of three cases and a literature review

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Abstract. Pheochromocytoma is primarily derived from the adrenal medulla. The majority of extra-adrenal pheochromocytoma cases occur in the superior para-aortic region and para-adrenal area. However, pheochromocytoma originating from the pancreas is rare. The present study reports the cases of three patients who had no history of hypertension but were post-operatively diagnosed with pheochromocytoma located in the pancreas. Of the three patients, two were admitted to hospital due to abdominal pain, and imaging examinations revealed a soft-tissue lesion in the head of pancreas. Local resection of the pancreatic tumor was successfully performed and a diagnosis of pheochromocytoma derived from the pancreas was subsequently made by pathologists. The third patient was admitted to hospital for surgical treatment due to the identification of a continuously growing lesion in the tail of pancreas during physical examinations. Distal resection of the pancreas was stopped during surgery when the patient's blood pressure and heart rate suddenly increased to 180/110 mmHg and 140 beats/min, respectively. Due to a marked rise in noradrenaline and adrenaline levels in the blood subsequent to surgery, the patient was diagnosed with pancreatic pheochromocytoma. The present study additionally reviewed the associated literature concerning pheochromocytoma in order to improve the understanding of this rare clinical phenomenon. The aim of the present study is to highlight to surgeons that although patients may not present with typical clinical manifestations due to the non-functional status of the tumor, undiagnosed pheochromocytoma of the pancreas should be considered when surgeons observe an unexpected hypertensive crisis during pancreatic tumor surgery.

Introduction

Pheochromocytoma is a catecholamine-secreting tumor that originates from chromaffin cells. The majority of these tumors arise in the adrenal medulla (1), and when they occur outside the adrenal gland they are known as an extra-adrenal pheochromocytoma or a paraganglioma (2). Pheochromocytoma is primarily sporadic, but may additionally be associated with multiple endocrine neoplasia syndrome (3) and mutations of mitochondrial complex 2 succinate dehydrogenase enzymes (4).

Extra-adrenal pheochromocytoma has been previously reported to account for ~10% of all pheochromocytoma cases during adulthood and for 30-40% of cases in children (5). These tumors may occur in the superior para-aortic region, the para-adrenal area and the inferior para-aortic region, as well as the organ of Zuckerkandl and the urinary bladder (6-8). Pancreatic localization of extra-adrenal pheochromocytoma is rare, and to the best of our knowledge, only one case has been previously reported in the Chinese literature (9). In the present study, the cases of three patients (Table I) with pheochromocytoma involving the pancreas are presented. To the best of our knowledge, the present report is the first to present three definite and comprehensive cases of this rare clinical phenomenon. In addition, the relevant literature is reviewed, with the aim of improving the understanding of pheochromocytoma, with an emphasis on sharing patient experiences of diagnosis and surgical treatment.

Case report

Case 1. A 55-year-old female was admitted to the People's Hospital of Jiangyou (Mianyang, China) in February 2013 with the symptom of recurrent abdominal pain over a period of >3 years. On admittance, the patient did not exhibit any weight loss, changes in appetite or bowel habits, jaundice or non-specific symptoms associated with hypertension, including palpitations, sweating, headache, dizziness or fainting. The patient's physical examination and pre-operative routine examinations did not identify any significant abnormalities. Serum tumor markers for cancer antigen 19-9, cancer antigen 125 and carcinoembryonic antigen (CEA) were additionally observed to be within the normal ranges. The patient underwent ultrasound (US) and computed tomography (CT; LightSpeed VCT CT

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Table I. Clinical features of three patients with pancreatic pheochromocytoma.

Variable	Case 1	Case 2	Case 3
Gender	Female	Male	Female
Age, years	55	44	30
Hypertension	No	No	No
Family history	No	No	No
Chief complaint	Abdominal pain	Abdominal pain	Neoplasm detected on routine physical examination
Tumor location	Uncinate process	Uncinate process	Pancreatic tail
Tumor size, cm	2.5	3.2	6
Surgery	Local resection	Local resection	Laparotomy
Complications	No	Pancreatic fistula	Mortality
Patient outcome	Alive	Alive	Succumbed

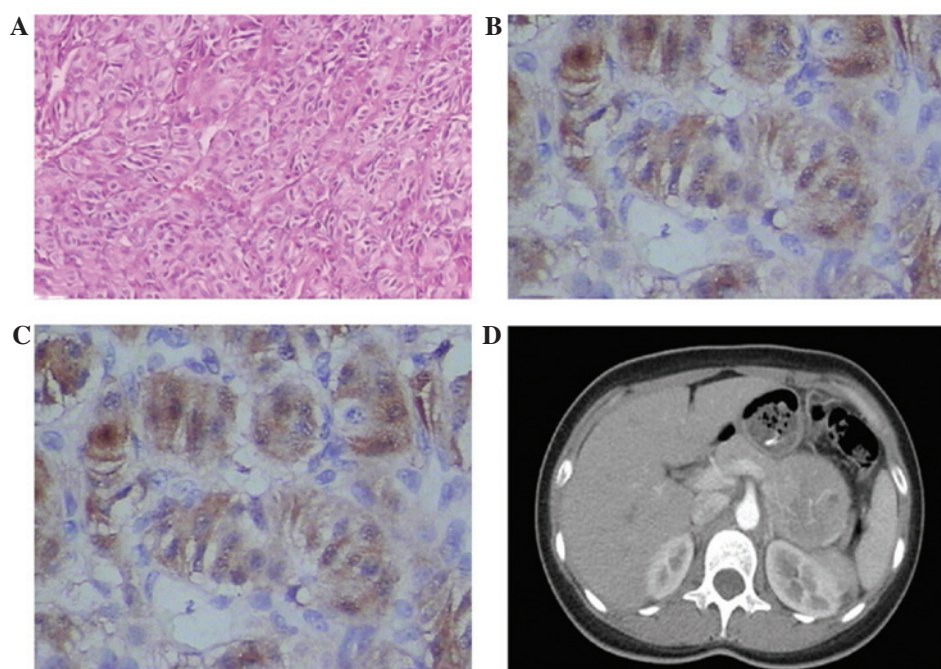


Figure 1. (A) Case 1: Hematoxylin and eosin staining of the resected tumor tissue showed a neuroendocrine tumor formed by round nests of densely packed cells, with palisading tumor cells (magnification, x400). (B) Case 1: Immunohistochemical staining revealed that the tumor tissue was positive for chromogranin A. (C) Case 2: Immunohistochemical staining revealed that the tumor tissue was positive for synaptophysin. (D) Case 3: Abdominal contrast-enhanced computed tomography scan of a circular neoplasm situated in the tail of the pancreas.

system; GE Healthcare Life Sciences, Chalfont, UK), which revealed a mass in the uncinate process of the pancreas, with a diameter of ~2.5 cm. Due to suspicions of a pancreatic malignant tumor, an exploratory laparotomy was performed, which confirmed the location of the mass in the uncinate process of the pancreas, with a relatively clear association with the surrounding tissues. A local resection of the pancreatic tumor was subsequently successfully performed. Resected tissue was formalin (Beijing Noble Ryder Technology Co., Ltd., Beijing, China)-fixed, paraffin (Beijing Noble Ryder Technology Co., Ltd.)-embedded and cut into 4- μ m sections. For histological examination, the tissue sections were stained with hematoxylin and eosin (Haibiao Technology, Co., Ltd., Xiamen, China) and observed under a microscope (CX31; Olympus Corporation,

Tokyo, Japan). Pathologists were able to histologically diagnose the tumor as pancreatic paraganglioma (extra-adrenal pheochromocytoma originating from the pancreas). The tumor cells were polygonal, had abundant cytoplasm and contained basophilic or amphotropic particles. The nuclei were round or irregular, and the tumor cells were arranged in cords or nests. According to the intraoperative and histological findings, the tumor was 2.5 and 3 cm in diameter, respectively. There was no evidence of distant metastasis, and no direct tissue or arterial or venous invasion. For immunohistochemical analysis, tissue sections were incubated with monoclonal mouse anti-human chromogranin A (CgA; cat. no. ZA0507; 1:50; Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd., Beijing, China), monoclonal mouse anti-human synaptophysin (Syn;

cat. no. M077629; 1:100; Dako, Glostrup, Denmark), S-100 (cat. no. ZA0507; 1:100; Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd.), monoclonal rabbit anti-human vimentin (cat. no. M072529; 1:50; Dako) and monoclonal mouse anti-human CEA (cat. no. ZA0507; 1:100; Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd.) antibodies at 4°C for 12 h and visualized under a microscope (CX31; Olympus Corporation). Immunohistochemical examination (Fig. 1A and B) revealed that the tumor was positive for S-100, CgA, Syn, vimentin and CEA expression. The patient recovered well following the procedure and was discharged 11 days post-surgery.

Case 2. A 44-year-old man, who had experienced continuous upper abdominal pain for 6 months was admitted to the People's Hospital of Jiangyou in March 2012. The patient demonstrated no notable abnormalities on physical examination and serum biochemical tests. In addition, the patient did not have a history of hypertension or a remarkable family history. CT scanning revealed a soft-tissue lesion located in the pancreatic uncinate process, measuring 3.2x3 cm, together with a normal pancreatic duct and common bile duct. The presence of the lesion was confirmed by magnetic resonance imaging (MRI; GE 1.5T Signa HDe; GE Healthcare Life Sciences). Due to concerns over the presence of an undetected malignancy, a diagnostic laparotomy was performed, which confirmed that the mass was located in the uncinate process of the pancreas without distorting the surrounding tissues. During surgery, fast-frozen pathological testing of the resected mass indicated a tumor-like lesion, which was suspected to be a high-grade pancreatic neuroendocrine tumor or cystic adenoma. A histological diagnosis of pancreatic pheochromocytoma was confirmed by pathologists following successful local resection of the pancreatic tumor. The tumor cells of the resected tissue were positive for S-100, Syn, CgA and inhibin expression (Fig. 1C). The patient experienced the post-operative complication of a pancreatic fistula, which was treated with drug therapy (0.1 mg sandostatin subcutaneously injected 3 times/day for 7 days) and percutaneous drainage, which prolonged the duration of the patient's hospital stay. The patient was subsequently discharged almost 2 months after surgery.

Case 3. A 30-year-old woman was admitted the West China Hospital of Sichuan University (Chengdu, China) in August 2011 due to the positive identification of a neoplasm in the pancreatic tail during routine abdominal US. The patient did not exhibit any typical symptoms associated with this disease, and had no history of hypertension. A physical examination and tumor-associated marker evaluation revealed no abnormalities. Following admission to hospital, abdominal enhanced CT detected a mass, ~6 cm in size, situated in the tail of the pancreas (Fig. 1D). Considering the rapid growth of the tumor and its potential malignancy, a laparotomy was suggested and subsequently performed. However, during surgery, the patient's heart rate and blood pressure suddenly increased to 140 beats/min and 180/110 mmHg, respectively, as surgeons attempted to dissect the neoplasm. The patient's vital signs were unstable and uncontrollable, which led the surgeons to hypothesize that the tumor may be a pheochromocytoma

of the pancreas. Following an emergency consultation, the planned surgery was halted and the patient was transferred immediately to the intensive care unit. The patient's post-surgical blood plasma test revealed noradrenaline and adrenaline levels of 318,306 and 346,940 ng/l, respectively (normal range, <174,357 and <60,104 ng/l, respectively), which confirmed the diagnosis of a pheochromocytoma of the pancreas. Due to an unstable post-operative heart rate and blood pressure, the patient succumbed to heart failure.

Discussion

Owing to excessive secretion of catecholamines, pheochromocytoma may cause life-threatening symptoms, including hypertension, cardiac arrhythmias, headaches and palpitations (1). However, clinical manifestations of this tumor are variable and non-specific, and in certain cases, the clinical symptoms are not clear. It has been reported that ~70% of extra-adrenal pheochromocytoma cases are non-functional and only ~30% of patients may manifest with different presentations; however, the number of patients who do not present with typical symptoms is increasing (10,11).

Due to variable and non-specific manifestations, a diagnosis of extra-adrenal pheochromocytoma is difficult and dependent on clinician experience (1,2,5). In general, a pre-operative diagnosis of extra-adrenal pheochromocytoma is established by taking into account the presence of clinical signs, the determination of catecholamines and their metabolites in blood or urine, and the presence of a mass in the extra-adrenal region. Imaging examinations (US, CT and MRI) are primarily used for locating the lesion, and additionally provide reference values for final histological diagnosis. As previously mentioned, pheochromocytoma derived from the pancreas is seldom observed. Guo *et al* (9) reported the first pancreatic pheochromocytoma in the Chinese literature: The patient was 40-year-old women that had a mass on the left-upper side of the abdomen for >1 month. The patient did not have abdominal pain, distension or discomfort, or a history of trauma, fever, headache, dizziness or high blood pressure. A gigantic pheochromocytoma was identified in the tail of pancreas, and the patient underwent surgery, from which the patient recovered well. The three patients in the present study did not have a history of hypertension nor the typical symptoms associated with this disease. The tumors of the first two patients were located in the uncinate process of the pancreas and were successfully resected. No significant changes in blood pressure or heart rate were detected during surgery, and the diagnosis of a pancreatic pheochromocytoma was primarily based on the pathological and immunohistochemical examination of the resected tissues following surgery. The third patient did not experience any discomfort, but presented with a positive indication of a neoplasm situated in the tail of the pancreas, for which a distal resection was planned as a treatment strategy. However, the surgery was halted intraoperatively due to a sudden increase in the patient's blood pressure and heart rate. Due to a marked post-operative increase in noradrenaline and adrenaline levels in the patient's blood plasma, a diagnosis of pheochromocytoma located in the pancreas was established.

Pheochromocytoma originates in chromaffin cells derived from primitive neural crest cells, which may react and stain

with chromic salts (8). Furthermore, pheochromocytoma or paraganglioma in the pancreas, to a certain extent, is a type of pancreatic neuroendocrine tumor (pNET), which means that the tumor cells of resected tumors may demonstrate positive reactions for CgA and Syn following immunohistochemical staining (12). With regard to the first two cases presented here, this pathological feature is of significant value for histological diagnosis of pancreatic pheochromocytoma.

Surgery is the only curative treatment for pNET and pancreatic pheochromocytoma (13). If pheochromocytoma of the pancreas is suspected, surgery should be suggested. Prior to this, pre-operative assessments should be managed for a certain period of time in case of sudden large increases in blood pressure and heart rate. Exploratory laparotomy is a method of diagnosis, but if there are not enough pre-operative preparations, surgery may lead to sudden hypertension resulting in patient mortality, as occurred in the third case reported in the present study. For surgeons who encounter an unexpected hypertensive crisis during pancreatic tumor surgery, an undiagnosed pheochromocytoma of the pancreas should be immediately considered. The surgery should be halted, and appropriate preparations should then be made for a safer second attempt at the surgery.

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