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A Pancreatic Polypeptide-Producing Pancreatic Tumor Causing WDHA Syndrome

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Key Words
Endocrine pancreatic tumor · Pancreatic polypeptide · WDHA syndrome

Abstract
We report the case of a 46-year-old female patient with WDHA (watery diarrhea/hypokalemia/achlorhydria) syndrome caused by a pancreatic polypeptide-producing tumor in the head of the pancreas. Whereas VIP and other pancreatic endocrine hormones were in the normal range, only serum levels of pancreatic polypeptide were elevated. Imaging studies identified a pancreatic tumor in the head of the gland. After laparotomy, the tumor of 3 cm in size was enucleated. Final pathology documented a pancreatic endocrine tumor with immunohistochemical staining demonstrating the presence of pancreatic polypeptide. The patient remained cured after a follow-up of more than three years. The present case illustrates that, although rare, WDHA syndrome may be associated with a pancreatic polypeptide-secreting endocrine tumor of the pancreas.

Introduction

Endocrine tumors of the pancreas (ETPs) are rare but fascinating tumors. They occur in approximately 1 in 100,000 or represent 1–2% of all pancreatic neoplasms. Some of the tumors may be part of the multiple endocrine neoplasia type one syndrome (MEN-1). ETPs are categorized on the basis of their clinical manifestation into functioning and nonfunctioning tumors. Functioning tumors are associated with a clinical syndrome caused by inappropriate secretion of hormones. Within this group are insulinomas, glucagonomas, somatostatinomas, gastrinomas, vasoactive intestinal polypeptide producing tumors (VIPomas) and other less common tumors. VIPomas have been associated with watery diarrhea syndrome. It has also been called Verner-Morrison syndrome, pancreatic cholera or WDHA (watery diarrhea/hypokalemia/achlorhydria)

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syndrome. This syndrome is characterized by secretory diarrhea which ranges between 0.5 and 15 l/24 h and which is usually the most prominent symptom at presentation. It results in severe loss of potassium and bicarbonate, which in turn lead to metabolic acidosis and dehydration. Additional features include hypercalcemia with normal parathyroid hormone levels, hyperglycemia, and occasionally flushing of the face and the chest. The diagnosis of a VIPoma is confirmed by measurement of plasma VIP, and levels above 60 pmol/l are diagnostic.

Nonfunctioning ETPs are not associated with a distinct hormonal syndrome, but may still show elevated hormone levels in the blood or immunoreactivity in tissue sections. The majority of nonfunctioning ETPs express and/or secrete pancreatic polypeptide (PP), which can therefore serve as a general tumor marker in ETPs. PP was discovered in 1968, when Kimmel and colleagues [1], while purifying chicken insulin, found a new peptide hormone which they named 'pancreatic polypeptide'. The role of PP in ETPs may be involved in several ways. First, cases of pure PP-producing tumors, so-called PPomas; second, mixed ETPs containing PP cells; and third, cases of PP cell hyperplasia. Although PP frequently occurs in patients with ETPs, elevated serum levels of PP were not connected with specific clinical symptoms.

Herein, we report only the fifth case of the world literature with a pure PPoma of the pancreatic head causing WDHA syndrome.

Case Report

A 46-year-old woman was admitted to our hospital because of a 2-year history of diarrhea. This watery diarrhea occurred 3–10 times daily and was painless and without blood. She reported a weight loss of 5–6 kg in these two years. All tests for infectious disease as well as a colonoscopy were negative. One month prior to admission, she had undergone CT imaging of the abdomen, which showed a pancreatic head tumor, 4.2 × 3.3 cm in size (**fig. 1**a). Her medical history revealed an appendectomy as a child and a benign cyst of the right breast. On admission, physical examination revealed a thin woman in no acute distress. No lymphadenopathy was noted. Determination of peptide hormones in the serum showed greatly increased concentrations of PP with 4,370 pg/ml (normal up to 80 pg/ml). Surprisingly serum levels of VIP were normal with 8.5 pmol/l (norm up to 36 pmol/l), the same was found for gastrin with levels of 12 pg/ml (norm up to 60 pg/ml). Abdominal ultrasound showed a hypoechoic tumor in the pancreatic head 4.8 × 3.6 × 3.2 cm in size. None of the diagnostic procedures showed any signs of distant metastases.

After laparotomy the tumor was visualized by intraoperative ultrasound (fig. 1b), which showed the tumor next to the uncinate process. The tumor was enucleated (**fig. 2**a) and a pancreaticojejunostomy was done for closing the defect of the gland. Further exploration of the abdomen revealed no evidence of metastatic disease. Postoperatively the patient had to be reoperated after three days because of bleeding. The further postoperative course was uneventful. Her serum PP level after removal of the tumor was 55 pg/ml and was completely suppressed by 1 mg intravenous atropine. After a follow-up of three years she remained well without any watery diarrhea or any other signs of tumor recurrence.

Histopathological Examination

The tumor specimen showed a tumor with 3 cm (fig. 2b) in diameter, with a weight of 12 g. Microscopically the neoplasm was an endocrine tumor, proven by a strong expression of chromogranin A (fig. 2c). It had a well-defined capsule and was made up of small cuboidal to slightly elongated cells with round nuclei and clear to eosinophilic cytoplasm. The tumor cells were arranged in various patterns, a characteristic feature of islet cell tumors. These included solid, ribbon-like and glandular growth pattern. Results of immunohistochemical staining specific for insulin, glucagons, somatostatin, and gastrin were negative. However, staining for PP was positive in the main tumor mass (fig. 2d).

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Discussion

In mammals, virtually all of the PP-producing cells are located in the pancreas. They have been found within the islets, scattered in the exocrine compartment, and lining the ducts. Within the islets the PP cells are located mainly in the periphery, wedged between the A and B cells. PP islet cells are relatively abundant in both the murine ventral and dorsal pancreatic buds by day 15.5 of gestation. Subsequently, at day 18.5 of gestation, the total number of PP cells in the murine ventral bud has doubled, whereas the number in the murine dorsal bud has essentially remained unchanged [2]. This nonhomogenous distribution of PP cells can also be seen in the human neonate. Indeed, PP cells are more numerous in the uncinate process than in the body and tail and rest of the pancreatic head. This anatomic distribution of PP cells is also present in the adult human pancreas [3]. Infusions of PP in man demonstrate that, at physiological levels, it acts solely on the pancreas and gallbladder by inhibiting the secretion of bile and of pancreatic enzymes and juice [4]. Thus a tumor deriving from PP cells is predicted to be clinically silent. That is this not always the case as illustrated in this case and **table 1**. In 1979, there was still controversy about how often WDHA syndrome, with a causal pancreatic tumor, is mediated by excessive secretion of VIP [4]. Although elevated VIP serum levels were measured in the majority of patients, there have been reports about so-called Pseudo-Verner-Morrison syndromes with a clinical WDHA syndrome in the presence of normal VIP serum levels.

Larsson et al. were the first to report on a patient with diarrhea due to a pancreatic tumor in whom PP was markedly elevated in the plasma with normal levels of VIP in the plasma [5]. In 1980 Hayes presented a case of a PP-producing islet cell tumor causing WDHA [6]. Unfortunately there are no more data like VIP serum levels of this case available. Four years later, Strodel et al. published a series of eight patients with PP-producing islet cell tumors [7]. Two patients presented with diarrhea, but in only one of them a pancreatic tumor was found and resected. The last report came from Mortenson and Bold [8]. They described a 64-year-old woman who presented with watery diarrhea in the presence of MEN-1 syndrome. Of various potential pancreatic endocrine hormones, only serum levels of PP were elevated. Radiologic imaging failed to identify a pancreatic tumor; her diarrhea was therefore managed with subcutaneous administration of somatostatin. Three years later she developed gallstone pancreatitis with the subsequent development of a pancreatic pseudocyst. At exploration for drainage of the pseudocyst, intraoperative ultrasound identified a 6-mm tumor in the distal pancreas that was resected. Final pathology documented a pancreatic endocrine tumor with immunohistochemical staining demonstrating the presence of PP. Beside these four cases, there have been multiple case reports about PPomas, excluded from table 1 because either of lacking WDHA syndrome or because no real circumscribed pancreatic tumor could be identified [9, 10].

As shown in table 1, the normal serum level of VIP and the elevated serum level of PP suggest that the symptoms in our patient seem to be derived from the high levels of circulating PP. A correlation between the serum PP concentrations and the WDHA syndrome could be demonstrated by absence of the syndrome after removal of the tumor due to an immediate fall in serum PP. PPomas should be treated as nonfunctioning ETPs. Preoperatively US, CT scan or endoscopic ultrasound are the procedures of choice and are usually effective, because these tumors are relatively large [11, 12]. Also SRS can be performed to differentiate endocrine from nonendocrine pancreatic tumors. Recognition of ETPs is imperative because of their good resectability and excellent long-term survival compared to that of ductal pancreatic carcinoma [13, 14]. The major goal is a potentially

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curative resection with no tumor tissue left behind. This may require partial pancreatoduodenectomy in large tumors with local signs of malignancy or enucleation like in the present case.

Some years ago, Jensen described eight different neoplastic disorders that can cause chronic diarrhea [15]. This list included gastrinomas, VIPomas, glucagonomas, somatostatinomas, and calcitonin-producing tumors. The present case suggests that, although rare, PPomas have to be added to this list.

Table 1. Pure PPomas with WDHA syndrome

Author, reference	Year	Localization of tumor	PP serum levels preoperatively	VIP serum levels preoperatively	Operation	PP serum levels postoperatively	Follow-up
Larsson [5]	1976	pancreatic head	47 nmol/l	normal	yes	5 nmol/l	DOD
Hayes [6]	1980	NA	NA	NA	NA	NA	NA
Strodel [7]	1984	pancreatic body	3,5100 pg/ml	NA	yes	228 pg/ml	NED postoperatively
Mortenson [8]	2002	pancreatic tail	elevated	normal	yes	NA	NA
Present study	2007	pancreatic head	4,370 pg/ml	normal	yes	60 pg/ml	NED after 3 years

NED = No evidence of disease; DOD = death of disease; PP = pancreatic polypeptide; VIP = vasoactive intestinal polypeptide; NA = not available.

Fig. 1. **a** CT imaging of the abdomen showing a pancreatic head tumor 4.2 × 3.3 cm in size. **b** Intraoperative ultrasound showing a hypoechogenic tumor.

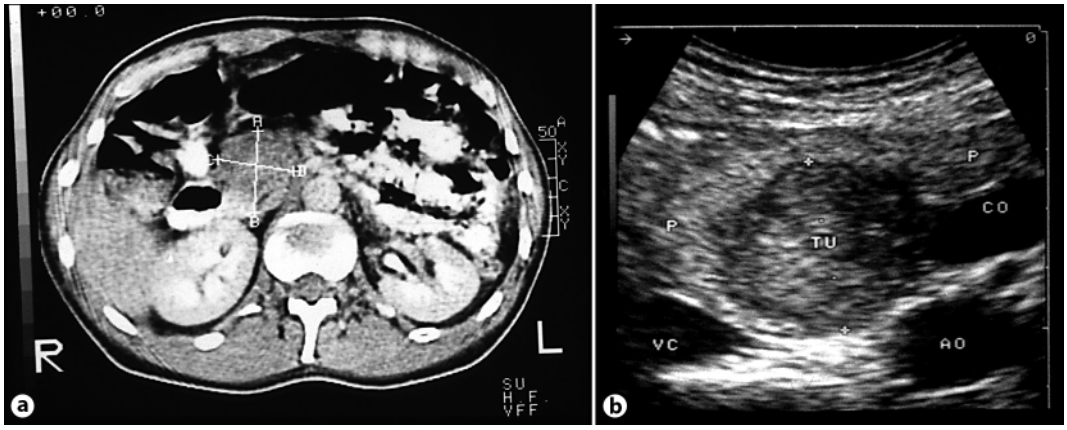

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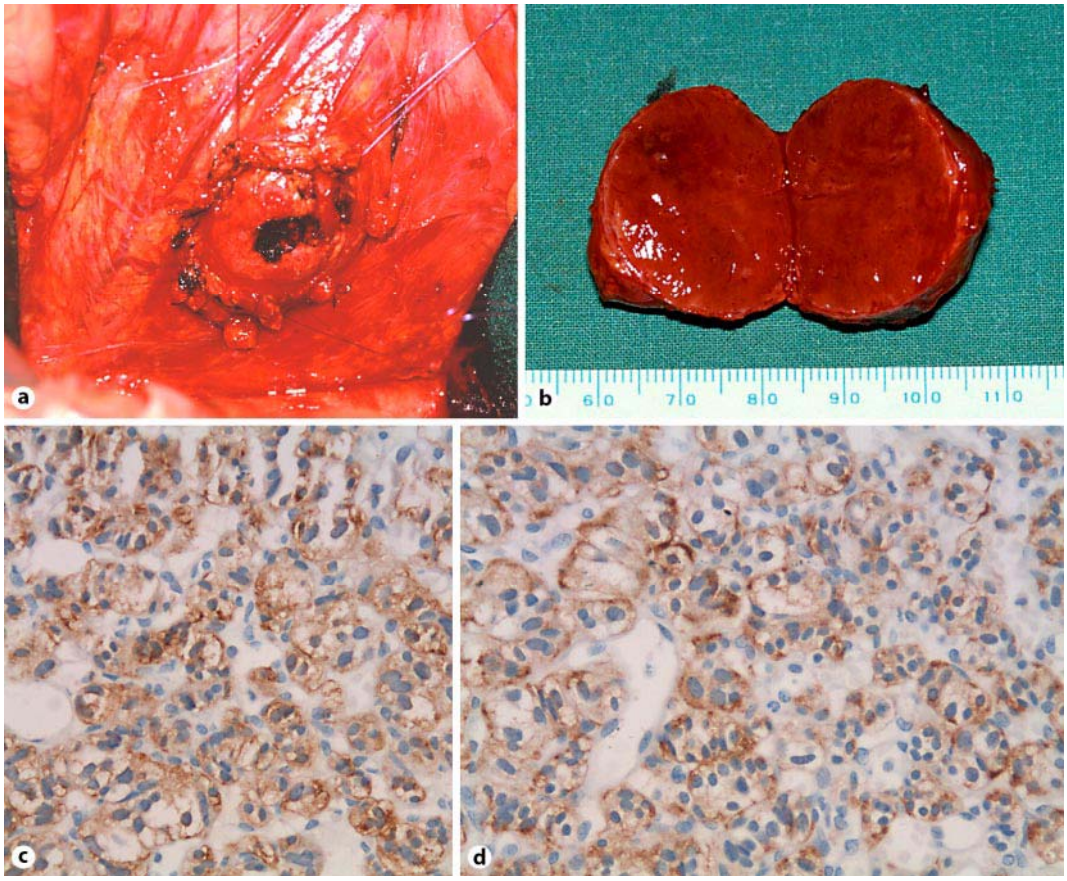
Fig. 2. a Intraoperative situs showing the tumor shortly before its enucleation. The tumor is flanked by four holding sutures and enucleated from the surrounding tissue. **b** Tumor specimen showing a tumor 3 cm in diameter. **c**, **d** Immunohistochemistry staining revealing strong positive staining for chromogranin A (**c**) and PP (**d**).



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References

1 Kimmel JR, Pollock HG, Hazelwood RL: Isolation and characterization of chicken insulin. Endocrinology 1968;83:1323–1330.

2 Herrera PL, Huarte J, Sanvito F, Meda P, Orci L, Vassalli JD: Embryogenesis of the murine endocrine pancreas; early expression of pancreatic polypeptide gene. Development 1991;113:1257–1265.

3 Orci L, Malaisse-Lagae F, Baetens D, Perrelet A: Pancreatic-polypeptide-rich regions in human pancreas. Lancet 1978;2:1200–1201.

4 Bloom SR, Polak JM, Welbourn RB: Pancreatic apudomas. World J Surg 1979;3:587–595.

5 Larsson LI, Schwartz T, Lundqvist G, Chance RE, Sundler F, Rehfeld JF, Grimelius L, Fahrenkrug J, Schaffalitzky de Muckadell O, Moon N: Occurrence of human pancreatic polypeptide in pancreatic endocrine tumors. Possible implication in the watery diarrhea syndrome. Am J Pathol 1976;85:675–684.

6 Hayes MM: Report of a pancreatic polypeptide-producing islet-cell tumour of the pancreas causing the watery diarrhoea, hypokalaemia, achlorhydria syndrome in a 55 year old Zimbabwean African male. Cent Afr J Med 1980;26:195–197.

7 Strodel WE, Vinik AI, Lloyd RV, Glaser B, Eckhauser FE, Fiddian-Green RG, Turcotte JG, Thompson NW: Pancreatic polypeptide-producing tumors. Silent lesions of the pancreas? Arch Surg 1984;119:508–514.

8 Mortenson M, Bold RJ: Symptomatic pancreatic polypeptide-secreting tumor of the distal pancreas (PPoma). Int J Gastrointest Cancer 2002;32:153–156.

9 Tomita T, Kimmel JR, Friesen SR, Mantz FA Jr: Pancreatic polypeptide cell hyperplasia with and without watery diarrhea syndrome. J Surg Oncol 1980;14:11–20.

10 Tomita T, Friesen SR, Kimmel JR, Doull V, Pollock HG: Pancreatic polypeptide-secreting islet-cell tumors. A study of three cases. Am J Pathol 1983;113:134–142.

11 Rodallec M, Vilgrain V, Couvelard A, Rufat P, O'Toole D, Barrau V, Sauvanet A, Ruszniewski P, Menu Y: Endocrine pancreatic tumours and helical CT: contrast enhancement is correlated with microvascular density, histoprognostic factors and survival. Pancreatology 2006;6:77–85.

12 Buscail L, Faure P, Bournet B, Selves J, Escourrou J: Interventional endoscopic ultrasound in pancreatic diseases. Pancreatology 2006;6:7–16.

13 Alexakis N, Connor S, Ghaneh P, Lombard M, Smart HL, Evans J, Hughes M, Garvey CJ, Vora J, Vinjamuri S, Sutton R, Neoptolemos JP: Hereditary pancreatic endocrine tumours. Pancreatology 2004;4:417–433; discussion 434–435.

14 Fendrich V, Langer P, Celik I, Bartsch DK, Zielke A, Ramaswamy A, Rothmund M: An aggressive surgical approach leads to long-term survival in patients with pancreatic endocrine tumors. Ann Surg 2006;244:845–853.

15 Jensen RT: Overview of chronic diarrhea caused by functional neuroendocrine neoplasms. Semin Gastrointest Dis 1999;10:156–172.