CASE REPORT

Multiple neuroendocrine tumors of the pancreas associated with pancreas divisum

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Abstract

Pancreas divisum is the most common congenital anomaly of the pancreas, characterized by missing fusion of the ventral and dorsal pancreatic duct. It may cause pancreatitis, but is rarely associated with malignancy.

We report herein for the first time the rare association, in a symptomless patient, of multiple neuroendocrine tumors of the pancreas with pancreas divisum and a failure of the exocrine system. Diagnosis was made incidentally by routine abdominal ultrasound. Laboratory examinations and a fine-needle aspiration revealed the neuroendocrine nature of the tumor. Spleen-preserving left pancreas resection was performed, with evidence of multiple neuroendocrine tumors of the pancreas with the typical histological characteristics. Eighteen months later the patient is still free of tumor burden.

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Introduction

Pancreas divisum, i.e. the lack of fusion of the dorsal and ventral pancreatic ducts during the seventh week of human gestation, is the most common developmental anomaly of the pancreas, more often seen in Western countries. The diagnosis is increasing, according to the wider use of endoscopic retrograde cholangiopancreatography (ERCP), and magnetic resonance cholangiopancreatography (MRCP). The frequency of this anomaly ranges between 1.3% and 10% in the general population worldwide (1–4), as determined from autopsic and endoscopic studies. The most common complications are acute and chronic pancreatitis (5–8), related to the huge amount of pancreatic secretion and the small orifice of the papilla duodeni minor (9).

Few reports supported a common occurrence of a pancreatic anomaly and gallbladder carcinoma, cholangiocarcinoma, adenocarcinoma or solid and papillary tumor of the pancreas (9–13). The present study represents the first report of a patient with pancreas divisum associated with multiple neuroendocrine tumors (NET).

Case report

A 55-year-old asymptomatic man with pancreas divisum was admitted for the incidental ultrasound (US)

evidence of a pancreatic tumor. He consumed neither tobacco nor alcohol and the past medical and family histories were negative. Mild, non-insulin-dependent diabetes mellitus type 2 and an exocrine pancreatic insufficiency were diagnosed. The laboratory findings including bilirubin, amylase, lipase, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) were within normal limits.

US, computed tomography (CT) (Fig. 1) and magnetic resonance imaging detected an atrophic tail of the pancreas containing three homogeneously hypoechoic tumors of the pancreas corpus. ERCP showed an incomplete major pancreatic duct without occlusion and a prominent papilla duodeni minor was seen, consistent with a pancreas divisum. CT-guided fine-needle aspiration cytology revealed a pancreatic NET. Further testing failed to find evidence of multiple endocrine neoplasia type I or a carcinoid-syndrome and showed an elevated serum chromogranin A level of 177 µg/l (reference level < 110 µg/l), with normal urinary levels of neuron-specific enolase, serotonin and 5-hydroxyindoleacetic acid and 5-hydroxytryptamine.

At laparotomy the pancreatic head was normal, whereas the body was aplastic and the tail dislocated, corresponding to pancreas divisum. A pancreatic tail tumor mass of 3 cm in diameter was identified and spleen-preserving left pancreas resection with the dissection margin at the superior mesenteric vein was performed, with an uneventful postoperative course.

Figure 1 Atrophic tail of the pancreas with a large tumor 1.5 cm in diameter (arrow).

Histopathological findings

The pancreatic NET was unusually structured with evidence of three different tumor nodules of 0.4, 0.9 and 2.4 cm in diameter respectively. Each nodule was surrounded by a fibrous capsule (Fig. 2a) and exhibited partly trabecular (Fig. 2b) and partly solid growth patterns (Fig. 2c). Moreover, tumor nodules were partly separated by fairly abundant fibrous stroma (Fig. 2d). Tumor cells were monomorphic, small to medium sized and mildly atypical (Fig. 2e). The mitotic index was 2 per 10 high-power fields and, as assessed by immunohistochemistry, the Ki-67 nuclear labeling index, indicating proliferation activity, proved to be approximately 10 percent (Fig. 2f). In addition, tumor cells were immunohistochemically strongly positive for chromogranin A (Fig. 2g), but negative for insulin, glucagon, somatostatin, gastrin and pancreatic polypeptide (data not shown). Primary antibodies used in this study are listed in Table 1. Finally, no tumor invasion of blood vessels, lymphatics or perineural spaces was seen. The NET nodules were embedded in

fatty tissue with fibrous bands and scattered islets of Langerhans, varying moderately in size and sometimes clustered in small groups (Fig. 2h). Except for only a very few ductal remnants no other structures of the exocrine pancreas were seen. Eventually, a well-differentiated, nonfunctioning, multinodular endocrine pancreatic tumor was diagnosed, the possible malignant potential of which was suggested both by its size of more than 2 cm and by the increased mitotic activity and increased Ki-67 labeling index.

Discussion

Neuroendocrine tumors of the gastrointestinal (GI) tract are rare and their course is generally less malignant than that of other malignancies of the GI tract. The pancreas represents one of the typical locations of NET. Of the 235 patients with a GI NET seen at our Institution since 1986, 178 (75.7%) had pancreatic NET, in the absence of pancreatic abnormalities. Normally, the endocrine pancreas consists of the islets of Langerhans, whereas in the case reported here, the balance of tissue remodeling and building of functional compartments was clearly altered. In fact, the neuroendocrine tumors and islets of Langerhans were surrounded by fat and fibrous tissue, and exocrine pancreatic tissue was limited to a few ductal remnants. These findings sharply contrast from those in nesidioblastosis, where the exocrine pancreas is present and hypertrophic B-cells are found within enlarged or normal-appearing islets, small scattered endocrine cell clusters, and ductolinsular complexes (14–16). Three different non-functional endocrine tumor nodules were found in our patient as well as scattered islets of Langerhans, varying in size and sometimes clustered in small groups. Both the tumor size and the increased mitotic activity, with an increased Ki-67 labeling index, suggested a possible malignant potential, even if an 18-months follow-up was uneventful.

As seen from ERCP findings, the lack of the exocrine tissue in our case is not likely to be a secondary effect induced by obstruction of the pancreatic duct and subsequent chronic inflammation. Alternatively, it could reflect a developmental defect, caused by a regulatory disorder of endodermal pluripotent progenitor cells, which differentiate into exocrine and endocrine cells under the influence and control of several factors (17, 18) such as transcription factor p48 and transforming growth factor-beta 1 (TGF beta-1). Their absence leads to a failure in the development of exocrine pancreatic tissue or to a dysregulation of pancreatic organogenesis respectively (19, 20). Moreover, different signaling pathways such as the Notch, TGF beta-1 and Hedgehog pathway are thought to be crucial in regulating the balance between endocrine and exocrine pancreatic development (21, 22). Specific signaling proteins play distinct roles at different developmental

Figure 2 Histopathological characteristics. (a) Representative tumor nodule with fibrous capsule (arrow). (b) Partly trabecular growth pattern with palisading of tumor cells. (c) Partly solid growth pattern of tumor cells. (d) The tumor was partly separated by abundant fibrous stroma. (e) Tumor cells were monomorphic, small to medium sized and mildly atypical, and some mitoses were seen (arrow). (f) Immunohistochemical determination of Ki-67 nuclear labeling. (g) Immunohistochemical staining for chromogranin A showing strong positivity of tumor cells. (h) Representative picture of tissue adjacent to the tumor, showing fatty tissue with fibrous bands and scattered islets of Langerhans, varying moderately in size and sometimes clustered in small groups. Magnification factors: (a, d) $\times 10$, (b, c, e) $\times 160$, (f) $\times 105$, (g) $\times 165$, (h) $\times 40$. Scale bars: (a, d) $1000\ \mu\text{m}$; (b, c, e, f) $100\ \mu\text{m}$; (g) $90\ \mu\text{m}$; (h) $250\ \mu\text{m}$.

Table 1 Primary antibodies used in this study.

Antibody	Clonality	Clone	Dilution	Supplier
Chromogranin A	m	LK2H10(2)	1:15 000	Chemicon, Hofheim
Mib-1	m	mono Ki-67	1:1000	Dako, Hamburg
Insulin	p	—	1:200	Dako, Hamburg
Glucagon	p	—	1:16 000	Dako, Hamburg
Somatostatin	p	—	1:20 000	Dako, Hamburg
Gastrin	p	—	1:3500	Dako, Hamburg
Pancreatic polypeptide	p	—	1:2000	Dako, Hamburg

m, monoclonal; p, polyclonal.

stages, which may explain a variety of anatomical defects of the pancreas. Mouse models have shown that inactivation of Sonic hedgehog causes overgrowth of ventral pancreatic tissue, leading to annular pancreas (20). Other defects identified in animal models include pancreatic hypoplasia (defects of Notch pathway genes Hes-1 and Jag-1), and pancreas divisum as seen in our patient, which can result from either Hedgehog or TGF beta-1 defects (23).

In conclusion, we have observed an asymptomatic 55-year-old man with a NET of the pancreas in a pancreas divisum, incidentally found at US scanning. Elevated chromogranin A and fine-needle aspiration cytology supported the preoperative diagnosis, and radical surgery was carried out with evidence of three endocrine tumor nodules and an almost complete lack of the exocrine pancreatic system. The subsequent course was uneventful. This is the first report of a pancreas divisum in association with a neuroendocrine tumor and failure of the exocrine system of the pancreas.

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