

Dorsal pancreas agenesis and ductal adenocarcinoma: surgical implications of an extremely rare association

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Rezumat

Agenezia pancreasului corporeo-caudal asociată cu adenocarcinom ductal cefalic: implicații chirurgicale

Este prezentat cazul unei paciente în vârstă de 44 de ani, diagnosticată cu adenocarcinom cefalic pancreatic, cu agenezie parțială a pancreasului corporeo-caudal. În cazul asocierii celor două patologii, chirurgia cu viză curativă necesită practicarea pancreatectomiei totale, având drept consecințe insulino-terapia și insuficiența pancreatică exocrină. O trecere în revistă a literaturii de specialitate a fost deasemenea realizată.

Cuvinte cheie: adenocarcinom ductal, agenezie pancreas distal, pancreatectomie

Abstract

It is presented the case of a 44-year-old woman with ductal adenocarcinoma of the pancreatic head with associated dorsal pancreas agenesis. In this case, curative intent surgery implies removal of the whole pancreas with its consequences – parental insulin requirement and exocrine pancreatic insufficiency. A review of the literature on the previously reported cases was performed.

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Key words: ductal adenocarcinoma, dorsal pancreas agenesis, pancreatectomy

Introduction

Dorsal pancreas agenesis is an extremely rare congenital anomaly and only 53 cases have been reported in the literature until 2009 (1). Association with different pancreatic tumors was previously reported in the literature (2) and ductal adenocarcinoma was described in no more than 5 patients (3-5). We recently experienced a pancreatic head ductal adenocarcinoma with associated dorsal pancreas agenesis in a young woman.

Case Report

A 44-year-old woman, with a history of two years of non-insulin-dependent diabetes, presented with progressive jaundice and epigastric pain. Laboratory tests revealed cholestasis (total bilirubin 13.7 mg/dl, reference range 0.2 – 1.2; conjugated bilirubin 10.3 mg/ dl, 0 – 0.5; gamma glutamyltransferase 1113 U/l, 50 – 150; alkaline phosphatase 502 U/ l, 40 – 150) and cytotoxicity (alanine aminotransferase 372 U/ l, 0 – 55; aspartate aminotransferase 270, 5 – 34). Serum glucose level was 108 mg/ dl (70 – 105). The CA 19-9 level was elevated at 400 U/ml (0 – 37), while CEA level was slightly elevated at 9.4 ng/ ml (0 – 5). Contrast enhanced computed tomography features are shown in Figures 1 and 2. No distant metastases to the liver, peritoneum or lung were observed on preoperative work-up. Based on jaundice, elevated CA 19-9 serum level and imaging appearances, the

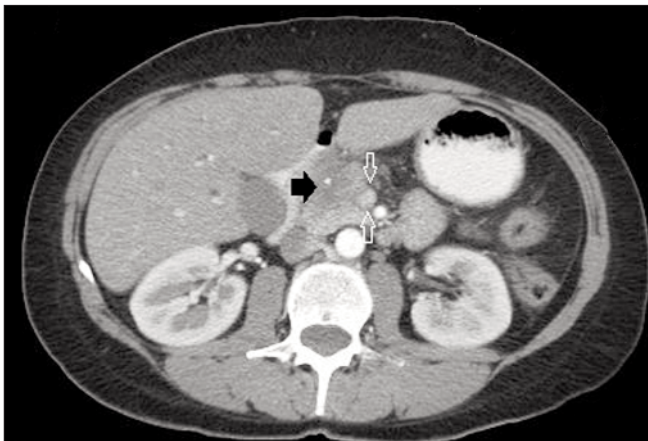


Figure 1. Contrast enhanced computed tomography showing an enlarged pancreatic head, presenting a 2.3/ 2.8 cm hypodense, irregular mass (black arrow), with circumferential invasion of the superior mesenteric vein between 90° and 180° (white arrows) and secondary mild dilatation of intrahepatic and common bile ducts

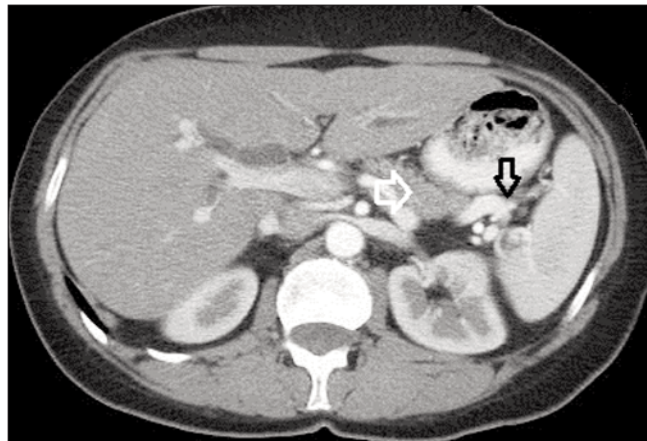


Figure 2. Contrast enhanced computed tomography showing a short pancreatic body (white arrow), along with the absence of the pancreatic tissue ventral to the splenic vein; on noticed the dependent stomach sign – the space between the pancreas and splenic hilum is occupied by contrast-walled stomach (black arrow)

clinical diagnosis of pancreatic head cancer with invasion in the superior mesenteric vein was established, and the patient was referred to surgery. At laparotomy, the tail and most of the pancreatic body were absent (no fat tissue between the short pancreatic body and splenic hilum), while there was a 2/ 2.5 cm, firm mass in the head, invading the first part of the duodenum and superior mesenteric vein. No enlarged lymph nodes or distant metastases to the liver or peritoneum were observed intraoperatively. Due to the short pancreatic body and taking into consideration the invasion into the first part of the duodenum, a Whipple pancreatic resection of the head, uncinete process and short pancreatic body (total pancreatectomy) (Fig. 3) with and en-block segmental resection of the superior mesenteric vein was performed. Venous reconstruction was done by an end-to-end mesenterico-portal anastomosis without graft interposition, while biliary and digestive reconstructions were done by an end-to-side hepatico-jejunostomy and gastro-jejunostomy on the same jejunal loop. The postoperative outcome was uneventful and the patient was discharged on the 10th postoperative day on parental insulin therapy (around 21 UI/ day) and with pancreatic enzyme substitutes for pancreatic exocrine insufficiency prevention. Macroscopic aspects of the operative specimen are shown in Fig. 4. Pathology revealed a well-differentiated tubular ductal adenocarcinoma involving the head and uncinete process, with microscopic invasion into the first duodenum and superior mesenteric vein, with negative surgical resection margins and no metastases into the loco-regional lymph nodes (T3 N0 M0, G1, V1, R0 – stage IIA TNM).

The patient underwent 6 cycles of gemcitabine-based chemotherapy and is alive with no clinical, laboratory (CA 19-9 within normal range) or imaging signs of recurrence at 13 months after surgery.

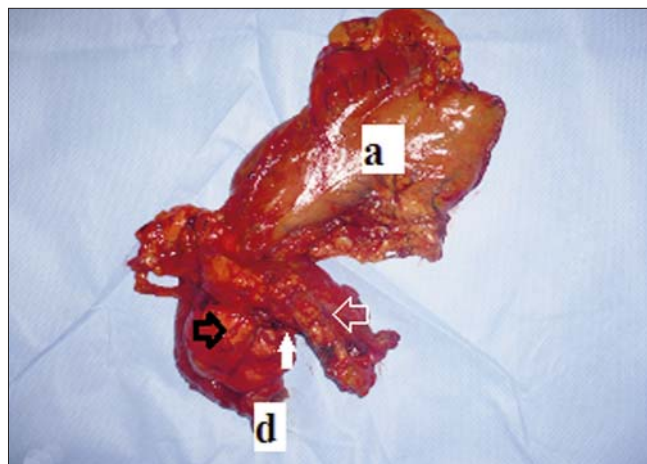


Figure 3. Pancreatic head tumor (black arrow) invading the superior mesenteric vein and first part of the duodenum; on noticed the short (3 cm) pancreatic body (open white arrow) – operative specimen (a, antrum; d, duodenum; white arrow, superior mesenteric vein groove)

Discussion

Developmental disorders of the pancreas are an unusual appearance (6). The pancreas develops embryologically from two pancreatic buds: ventral and dorsal; the two buds fuse in the seventh week (1). Because the dorsal bud contributes mainly to the tail and body of the pancreas (1), any dysgenesis of the dorsal pancreatic bud may lead to dorsal pancreas agenesis. Thus, a total absence in the development of the dorsal pancreatic bud implies complete dorsal pancreas agenesis, while an impaired development lead to a partial dorsal pancreas agenesis, the latter being more frequent (2).

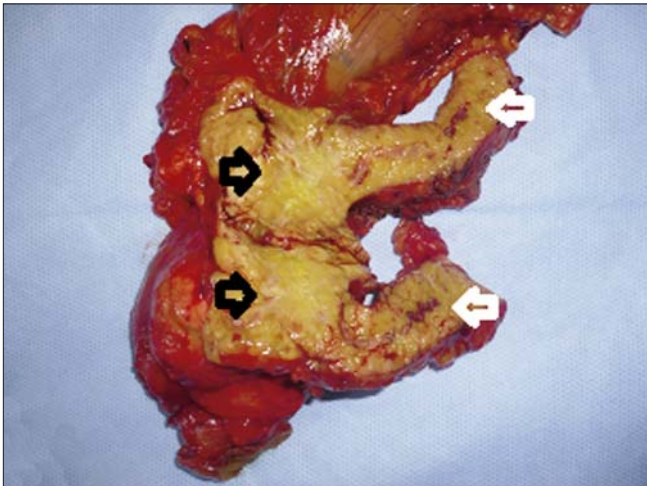


Figure 4. Infiltrative tumor of the pancreatic head (black arrows) and a short, ventrally reclined pancreatic body (white arrows) – operative specimen transected

The pathogenesis of the dorsal pancreas agenesis remains unclear.

The first description of a living patient with dorsal pancreas agenesis in English literature was made by Lechner and Read in 1966, at a time of surgery for superior mesenteric artery syndrome (7).

Several diseases, such as diabetes, acute/ chronic pancreatitis or polysplenia syndrome were described in association with dorsal pancreas agenesis (1,2). Hyperglycemia was found in more than half of the patients, probably due to the fact that most of the islet-cells are distributed in the distal pancreas (1).

The diagnosis is challenging and imaging studies shows absence of the tail and total or partial absence of the

pancreatic body (absence of the pancreatic tissue ventral to the splenic vein) (1). Absence of the dorsal duct at endoscopic retrograde (8,9) or magnetic resonance cholangiopancreatography (8), along with the absence of minor papilla at endoscopy (8,10) are characteristics of the complete dorsal pancreas agenesis. Partial agenesis is characterized by the finding of a minor papilla and remnant of the accessory duct and pancreatic body parenchyma (11).

Dorsal pancreas agenesis was associated with malignancies and potentially malignant tumors of the pancreas, such as malignant intraductal papillary mucinous neoplasms (2) or solid pseudopapillary tumors (12). To date, only 4 patients with resections for ductal adenocarcinoma of the head with dorsal pancreas agenesis were described in the literature (Table 1) (3,4); in 2 patients a nonalcoholic chronic calcific pancreatitis was present (4).

In a patient with ductal adenocarcinoma of the head and dorsal pancreas agenesis, the differential diagnosis should include atrophy of normal pancreatic tissue and distal fat replacement (2). Distal fat replacement was observed in ductal adenocarcinoma of the pancreatic head, ductal obstruction or arterial ischemia being presumed as pathogenesis (13). In clinical practice it is difficult to differentiate the acquired distal fat replacement from a congenital dorsal pancreas agenesis. Absence of the fat tissue between pancreatic neck/ short pancreatic body and splenic hilum, along with the stomach adjacent to splenic vein (dependent stomach sign) are imaging characteristics for congenital distal pancreas agenesis (14), while the presence on microscopy of the islet-cells in the replaced distal fat confirms the acquired disease (13). Nevertheless, in both cases removal of the whole pancreas is mandatory.

Recently, it was suggested an apparent increased risk of

Table 1. Clinico-pathological characteristics and postoperative outcome in 5 patients with curative-intent resection for ductal adenocarcinoma of the pancreatic head with associated dorsal pancreas agenesis

	Case 1 [‡]	Case 2 [§]	Case 3 [§]	Case 4 [§]	Case 5 [†]
Reference	Matsusue 1984 (3)	Rittenhouse 2011 (4)	Rittenhouse 2011 (4)	Rittenhouse 2011 (4)	Present case 2012
Sex/Age	F/53 y	F/37 y	M/59 y	M/68 y	F/44 y
Symptoms	Abdominal pain Weight loss	Abdominal pain	Abdominal pain Weight loss	No	Jaundice Abdominal pain
Diabetes mellitus	NIDDM	IDDM	IDDM	No	NIDDM
CA 19-9 (U/ml)	NA	3	62	439	400
Tumor diameter	NA	3 cm	8.5 cm	2.1 cm	2.5 cm
Pathology	NA	T3N1M0 G2R0	T3N1M0 G2R0	T2N0M0 G2R0	T3N0M0 G1V1R0
Postoperative parental insulin	NA	Yes	Yes	Yes	Yes
Adjuvant therapy	NA	GEM RxT	GEM RxT	GEM	GEM
Survival	15 months alive no recurrence	17 months dead recurrence	38 months alive no recurrence	52 months alive no recurrence	12 months alive no recurrence

[‡] total pancreatectomy; [§] pylorus preserving resection of the pancreas; [†] Whipple resection of the pancreas with en-block segmental resection of the superior mesenteric vein; F, female; M, male; NIDDM, non-insulin dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; NA, not available; GEM, gemcitabine-based chemotherapy; RxT, external radiotherapy

developing pancreatic cancer in patients with dorsal pancreas agenesis (4). In Fundeni Clinical Institute experience (1086 pancreatic resections for pancreatic diseases or other diseases involving the pancreas performed between 2002 and 2011, data not shown), dorsal pancreas agenesis was observed in a single patient (the above reported one). Moreover, out of 250 resections for pancreatic ductal adenocarcinoma performed during the same period of time at our unit, dorsal pancreas agenesis was observed in only one patient (0.4% of the cases) (data not shown).

Pancreaticoduodenectomy is considered nowadays the standard surgical approach for curative intent surgery of pancreatic head ductal adenocarcinoma (15,16). A recent study showed that, on long-term follow-up, new-onset or worsening diabetes after pancreaticoduodenectomy is around 20% (12% of the patients require insulin therapy), while around 7% of the patients have clinical signs of exocrine pancreatic insufficiency (17). Curative intent surgery of a pancreatic head adenocarcinoma with partial dorsal agenesis implies total pancreatectomy. All patients with total pancreatectomy require insulin therapy and exocrine pancreatic enzymes replacements, but the post-operative morbidity and the quality of life are comparable to standard pancreaticoduodenectomy (18).

Preexisting diabetes mellitus was recently found to have a negative impact on long term survival in patients resected for pancreatic ductal adenocarcinoma (19). Long-standing diabetes is an etiological factor for ductal adenocarcinoma of the pancreas, while new-onset diabetes represents a clinical sign for pancreatic cancer. However, pancreatic cancer associated diabetes is predominantly new-onset (20). In our reported case, the relatively recent onset of the diabetes suggests that pancreatic cancer is rather the cause, not the dorsal pancreas agenesis. Diabetes mellitus or hyperglycemia in dorsal pancreas agenesis appears to be clinically relevant at a younger age (1).

Although some signaling pathways (i.e. retinoic acid and hedgehog) are implicated in the pathogenesis of both dorsal agenesis and ductal adenocarcinoma of the pancreas (4), it is not known how to use it in clinical decision-making.

In conclusion, ductal adenocarcinoma of the pancreatic head is rarely associated with dorsal pancreas agenesis. Curative intent surgery in these cases implies total pancreatectomy (with spleen preservation) with its consequences – diabetes mellitus with parental insulin therapy and exocrine pancreatic insufficiency.

References

- Schnedl WJ, Piswanger-Soelkner C, Wallner SJ, Reittner P, Krause R, Lipp RW, et al. Agenesis of the dorsal pancreas and associated diseases. *Dig Dis Sci*. 2009;54(3):481-7.
- Sakpal SV, Sexcius L, Babel N, Chamberlain RS. Agenesis of the dorsal pancreas and its association with pancreatic tumors. *Pancreas*. 2009;38(4):367-73.
- Matsusue S, Kashihara S, Koizumi S. Pancreatectomy for carcinoma of the head of the pancreas associated with multiple anomalies including the preduodenal portal vein. *Jpn J Surg*. 1984;14(5):394-8.
- Rittenhouse DW, Kennedy EP, Mascaro AA, Brumbaugh JL, Stein LH, Rosenberger LH, et al. The novel triad of dorsal agenesis of the pancreas with concurrent pancreatic ductal adenocarcinoma and nonalcoholic chronic calcific pancreatitis: a case series and review of the literature. *J Gastrointest Surg*. 2011;15(9):1643-9.
- Ulusan S, Yakar T, Koc Z, Kayaselcuk F, Torer N. Adenocarcinoma of the pancreas associated with dorsal agenesis. *Pancreas*. 2006;33(4):437-9.
- Lerch MM, Zenker M, Turi S, Mayerle J. Developmental and metabolic disorders of the pancreas. *Endocrinol Metab Clin North Am*. 2006;35(2):219-41, vii.
- Lechner GW, Read RC. Agenesis of the dorsal pancreas in an adult diabetic presenting with duodenal ileus. *Ann Surg*. 1966;163(2):311-4.
- Lang K, Lasson A, Muller MF, Thorlacius H, Toth E, Olsson R. Dorsal agenesis of the pancreas - a rare cause of abdominal pain and insulin-dependent diabetes. *Acta Radiol* 2011 Dec 2.
- Lingareddy S, Duvvuru NR, Guduru VR, Lakhtakia S, Kalapala R. Dorsal agenesis of pancreas: CT and ERCP. *Gastrointest Endosc*. 2007;65(1):157-8.
- Guclu M, Serin E, Ulucan S, Kul K, Ozer B, Gumurdulu Y, et al. Agenesis of the dorsal pancreas in a patient with recurrent acute pancreatitis: case report and review. *Gastrointest Endosc*. 2004;60(3):472-5.
- Doxey BW, Jackson WD, Adler DG. A unique presentation: dorsal agenesis of the pancreas manifesting as pancreatic exocrine insufficiency in the absence of diabetes mellitus in an 8-year-old boy. *Dig Dis Sci*. 2008;53(7):2005-6.
- Ulusan S, Bal N, Kizilkilic O, Bolat F, Yildirim S, Yildirim T, et al. Case report: solid-pseudopapillary tumour of the pancreas associated with dorsal agenesis. *Br J Radiol*. 2005;78(929):441-3.
- Toyama N, Kamiyama H, Suminaga Y, Namai K, Ota M, Konishi F. Pancreas head carcinoma with total fat replacement of the dorsal exocrine pancreas. *J Gastroenterol*. 2004;39(1):76-80.
- Karcaaltincaba M. CT differentiation of distal pancreas fat replacement and distal pancreas agenesis. *Surg Radiol Anat*. 2006;28(6):637-41.
- Popescu I, Dumitrascu T. Total meso-pancreas excision: key point of resection in pancreatic head adenocarcinoma. *Hepatogastroenterology*. 2011;58(105):202-7.
- Popescu I, Dumitrascu T. Pancreatoduodenectomy - past, present and future. *Chirurgia (Bucur)*. 2011;106(3):287-96.
- Orfanidis NT, Loren DE, Santos C, Kennedy EP, Siddiqui AA, Lavu H, et al. Extended follow-up and outcomes of patients undergoing pancreaticoduodenectomy for nonmalignant disease. *J Gastrointest Surg*. 2012;16(1):80-8.
- Muller MW, Friess H, Kleeff J, Dahmen R, Wagner M, Hinz U, et al. Is there still a role for total pancreatectomy? *Ann Surg*. 2007;246(6):966-74.
- Chu CK, Mazo AE, Sarmiento JM, Staley CA, Adsay NV, Umpierrez GE, et al. Impact of diabetes mellitus on perioperative outcomes after resection for pancreatic adenocarcinoma. *J Am Coll Surg*. 2010;210(4):463-73.
- Pannala R, Basu A, Petersen GM, Chari ST. New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. *Lancet Oncol*. 2009;10(1):88-95.