Published in final edited form as:

J Gastrointest Surg. 2011 September ; 15(9): 1643–1649. doi:10.1007/s11605-011-1542-6.

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

David W. Rittenhouse, Eugene P. Kennedy, Andres A. Mascaro, Jennifer L. Brumbaugh, Louis H. Stein, Laura H. Rosenberger, Patricia K. Sauter, Charles J. Yeo, and Harish Lavu
Department of Surgery, Thomas Jefferson University, Jefferson Pancreas, Biliary and Related Cancer Center, 1025 Walnut Street, College Bldg., Suite 605, Philadelphia, PA 19107, USA

Abstract

Introduction—Dorsal agenesis of the pancreas (DAP) is a rare congenital anomaly, with only 44 cases having been reported in the English literature since 1966.

Materials and Methods—A retrospective review of our IRB-approved pancreatic surgery database was performed from November 2005 to November 2010 searching for cases of DAP.

Discussion—Disorders in the retinoic acid (*Raldh*) and hedgehog (*Hh*) signaling pathways, which appear to play a role in the development of DAP, have been implicated in other diseases of the pancreas such as pancreatic ductal adenocarcinoma (PDA) and nonalcoholic chronic calcific pancreatitis (NCCP).

Conclusion—In this report, we describe three cases of DAP in the setting of PDA, two of which include the third component of NCCP. We provide a discussion of the clinical features of this novel triad and address the molecular pathways that relate to these respective diseases.

Keywords

Dorsal agenesis of the pancreas; Pancreatic ductal adenocarcinoma; Nonalcoholic chronic calcific pancreatitis

Introduction

Congenital abnormalities of the pancreas are quite rare. The most common congenital abnormality is pancreas divisum, which has a reported incidence of 1.3–5.8%.¹ Other pancreatic congenital abnormalities are significantly less common, such as annular pancreas, ectopic pancreas, and dorsal agenesis of the pancreas (DAP). Forty-four cases of DAP have been reported in the English literature since 1966. The most common presenting symptom of this condition is abdominal pain, with nearly 68% of patients presenting with vague abdominal discomfort. Additionally, one third of patients are found to have diabetes mellitus at the time of presentation.² The diagnosis of DAP is often made by computed tomography (CT) or magnetic resonance imaging (MRI) during the evaluation for abdominal pain, though a significant number of cases have also been identified incidentally during the workup for an unrelated problem. DAP is typically suspected when no pancreatic tissue is

seen to the left of the superior mesenteric vessels (Fig. 1). The exact etiology of DAP remains unclear; however, the retinoic acid (*Raldh*) and hedgehog (*Hh*) signaling pathways have been shown to play a role in its pathogenesis. These signaling pathways have also been implicated in the pathogenesis of pancreatic ductal adenocarcinoma (PDA) and nonalcoholic chronic calcific pancreatitis (NCCP).

While DAP remains a rare disease, NCCP and PDA occur more commonly. NCCP occurs primarily in tropical countries, with a prevalence of 10–15 per 100,000 people. NCCP is characterized by irreversible destruction of the pancreatic parenchyma leading to pancreatic endocrine and exocrine insufficiency.³ Patients may classically present with a constellation of symptoms including abdominal pain, steatorrhea, and diabetes mellitus. NCCP carries an increased risk for the development of PDA. Chari et al. followed 185 patients for 4.5 years to assess the risk for the development of PDA.⁴ During the follow-up period, 25% of patients died from PDA. Although PDA is only the 10th most common cancer in the USA, it remains the fourth leading cause of cancer death. Less than 20% of patients with PDA are candidates for curative surgical resection at the time of diagnosis, and the overall 5-year survival rate is a dismal 4%.

Developing a better understanding of the processes that link these seemingly disparate diseases may offer insight into their early detection and clinical management. In this report, we describe three patients with PDA in the setting of DAP, two of whom had the novel triad of DAP, PDA, and NCCP. Herein, we also place these three patients in the context of the world literature of patients with DAP and PDA.

Materials and Methods

In this study, we performed a retrospective review of the prospectively acquired, IRB-approved pancreatic surgery database in the Department of Surgery of Thomas Jefferson University from 28 November 2005 to 31 November 2010, searching for cases of DAP. We reviewed patient demographics, preoperative studies, operative variables, adjuvant therapy, and survival. We identified three cases of DAP out of 870 patients who underwent surgical resection for pancreatic diseases during the study period. A literature review was conducted searching the English language literature for all cases of DAP with associated pancreatic neoplasms from 1966 to the present. We used the search terms “dorsal agenesis of the pancreas,” “pancreatic ductal adenocarcinoma,” and “nonalcoholic chronic calcific pancreatitis.”

Clinical Material and Results

Case 1

A 37-year-old woman originally from the Indian subcontinent, with a history of insulin dependent diabetes, presented with a history of vague epigastric abdominal pain of 2 months duration. A CT scan (Fig. 1) was performed that showed a 1-cm cystic mass in the uncinate process of the pancreas, associated with peripancreatic fat stranding, consistent with acute pancreatitis. Dorsal agenesis of the pancreas was noted on CT scan as well. Endoscopic retrograde cholangiopancreatography (ERCP) demonstrated a dilated and truncated main pancreatic duct with intraductal calculi (Fig. 2). A pancreatic ductal sphincterotomy was performed with stone extraction and placement of a biliary endoprosthesis. An endoscopic ultrasound (EUS) procedure revealed a 2.2×2.1 cm hypoechoic mass in the uncinate process, with calcifications and an absent pancreatic body and tail. Fine-needle aspiration (FNA) of the mass at the time of EUS revealed atypical cells suspicious for adenocarcinoma. The patient's CA19-9 level was normal at 3 U/mL, but the carcinoembryonic antigen (CEA) level was elevated at 8.2 ng/mL. On operative exploration, a firm mass was identified in the

uncinate process of the pancreas, and there was no evidence of metastatic disease. The pancreatic body and tail appeared to be replaced with fat (Fig. 3). A pylorus-preserving resection of the pancreatic head and uncinate process was performed with an end-to-side hepaticojejunostomy and a downstream retrocolic duodenojejunostomy. Pathology revealed a 3-cm moderately differentiated ductal adenocarcinoma involving the uncinate process of the pancreas with negative surgical margins of resection. One of 21 specimen lymph nodes was positive for metastatic disease leading to an American Joint Commission on Cancer (AJCC) pathologic stage of IIb (T3N1M0). The pancreatic neck margin showed benign adipose tissue with no evidence of pancreatic glandular tissue, consistent with an aplastic body and tail. The patient's postoperative course was uneventful, and she was discharged to home on postoperative day 7, on parental insulin therapy and exogenous pancreatic enzyme supplementation. She received adjuvant treatment with gemcitabine-based chemotherapy but died of recurrent malignant disease 17 months postresection.

Case 2

A 59-year-old woman, also originally from the Indian subcontinent and with a history of insulin dependent diabetes mellitus, presented with a 4-month history of abdominal pain and weight loss. The patient had previously undergone a CT scan 2 years earlier which showed a small cystic lesion in the pancreatic head with surrounding calcifications. Repeat CT scan demonstrated a 4×4 cm mass in the head of the pancreas with multiple calcifications causing biliary dilatation and duodenal narrowing, as well as agenesis of the body and tail of the pancreas. Tumor marker analysis revealed a mildly elevated CA19-9 level of 62 U/mL and a normal CEA level of 1.8 ng/mL. The patient underwent operative exploration which revealed a firm mass occupying the entire head and uncinate process of the pancreas, with the pancreatic body and tail replaced by fat. A pylorus-preserving resection of the pancreatic head and uncinate process was performed with a hepaticojejunostomy and duodenojejunostomy. Pathology revealed an 8.5×6 cm moderately differentiated ductal adenocarcinoma of the pancreas. The surgical margins of resection were negative and 1/13 specimen lymph nodes harbored metastatic disease leading to an AJCC pathologic stage of IIb (T3N1M0). No pancreatic tissue was present at the pancreatic neck margin. The patient recovered from surgery uneventfully and was discharged to home on postoperative day 6, on parental insulin therapy and exogenous pancreatic enzyme supplementation. She received adjuvant gemcitabine-based chemotherapy and radiation and remained alive 38 months postresection.

Case 3

A 68-year-old Caucasian man was found to have abnormal liver function tests on routine laboratory analysis performed by his primary care physician. His total and direct bilirubin (2.8/1.8 mg/dL), alkaline phosphatase (461 IU/L), aspartate aminotransferase (227 IU/L), and alanine aminotransferase (418 IU/L) were all elevated. Tumor marker analysis revealed an elevated CA19-9 level of 439 U/mL and a mildly elevated CEA level of 3.1 ng/mL. CT scan revealed a dilated extrahepatic biliary tree with a calcified cystic lesion within the head of the pancreas extending into the uncinate process. The patient underwent an ERCP with sphincterotomy and placement of a biliary endoprosthesis. Upon surgical exploration, the mass in the head of the pancreas was identified, and there was noted to be an absence of pancreatic tissue to the patient's left of the superior mesenteric vessels. As in the two previous cases, a pylorus-preserving resection of the pancreatic head and uncinate process was performed with a hepaticojejunostomy and duodenojejunostomy. Pathology revealed a 2.1-cm moderately differentiated ductal adenocarcinoma of the pancreas with negative surgical margins of resection. None of the 17 specimen lymph nodes harvested harbored metastatic disease, leading to an AJCC pathologic stage of Ib (T2N0M0). The patient was

discharged to home on postoperative day 10 and underwent adjuvant treatment with gemcitabine-based chemotherapy and radiation. He remains alive 52 months postresection.

Table 1 depicts all of the previously published cases of DAP and associated PDA or NCCP, including our own three cases. Two cases of prior PDA in the setting of DAP have been documented in the English literature, the first having been reported by Matsusue in 1984.^{5,6} Since that time, various neoplastic lesions have also been reported including leiomyosarcoma, endocrine tumors, and intraductal papillary mucinous neoplasms in association with DAP. Most cases of concurrent pancreatic neoplasm and DAP in the literature, including our own, underwent a resection of all remaining pancreatic tissue. Balakrishnan reported a case of DAP in the setting of NCCP.⁷

Discussion

This study documents three patients with DAP and PDA (Fig. 4), two of whom had the novel triad of DAP, PDA, and NCCP. Although they never underwent genetic testing, our two patients with NCCP fit the criteria for this diagnosis, in that, they were from an area endemic for NCCP and had chronic abdominal pain, diabetes, and early-onset PDA. The patient who had an ERCP had the presence of large intraductal calculi. All three of our patients underwent successful operative treatment with pylorus-preserving resection of the pancreatic head and uncinate process with construction via a hepaticojejunostomy and duodenojejunostomy. A short description of pancreatic organogenesis and a discussion of the molecular and genetic mechanisms that play a role in the development of these three separate but related entities follow.

The pancreas begins its development in the fourth week of gestation, starting as two separate buds arising from the primordial foregut (Fig. 5). The ventral pancreatic bud develops from the hepatic diverticulum arising from the duodenum, and the dorsal pancreatic bud arises separately from the dorsal aspect of the duodenum.⁸ As the duodenum rotates to the right assuming the C shape, the ventral pancreatic bud continues its rotation before fusing with the dorsal pancreatic bud.⁹ The dorsal pancreatic bud forms the body and tail of the pancreas and also gives rise to the accessory pancreatic duct which empties into the minor duodenal papilla of Santorini.⁸ Any failure in the development of the dorsal bud therefore leads to an absence of a functional pancreatic body, tail, and accessory pancreatic duct. While complete agenesis of the pancreas is a rare congenital disorder that is associated with impaired intrauterine growth and is often fatal,¹⁰ DAP results in only partial impairment of pancreatic function and may often go undetected. The specific etiology of DAP remains unclear, but developmental and genetic causes have been implicated in its occurrence.

In mouse models, certain genetic alterations or knockouts are linked to the failure of dorsal pancreatic development. Reduced expression of homeobox gene *Hlxb9* in mice causes failure of dorsal pancreatic development,¹¹ whereas normal retinoic acid signaling through the *Raldh2* gene leads to the development of the dorsal pancreatic bud. Martin et al. showed that mice with the *Raldh2* knockout fail to develop a dorsal pancreatic bud.¹² Also, early expression of either sonic (*Shh*) or indian (*Ihh*) hedgehog, two members of the hedgehog (*Hh*) cell signaling family, can suppress pancreas development.¹³ In addition to DAP, alterations in the *Raldh2* and *Hh* signaling pathways are also implicated in the development of NCCP and PDA, respectively.

Singh et al. demonstrated that increased retinoic acid concentrations inhibited the growth of pancreatic cancer cells in vitro.¹⁴ Conversely, one could hypothesize that perhaps a defect in the retinoic acid signaling pathway may lead to an increased risk of developing pancreatic cancer in patients who have DAP. Despite belonging to different molecular pathways, the

Hh and *Raldh2* genes represent some of the complementary molecular “on” and “off” mechanisms that are involved in pancreatic development and function. Importantly, when these molecular mechanisms are abnormal, they can lead to aberrant pancreatic phenotypes.

The development of NCCP and other forms of chronic pancreatitis has been associated with a number of genetic alterations. Mutations in *SPINK1*, a serine protease inhibitor that suppresses intrapancreatic trypsin activity, have been associated with the development of NCCP.¹⁵ Bhatia et al. examined 66 unrelated patients in northern India with a history of NCCP and compared them to 92 healthy control patients from the same region.¹⁵ They found that 50% of the patients with NCCP had a heterozygous NS34S *SPINK1* mutation, and 14% had a homozygous mutation. Only 2.2% of the healthy control patients had the mutation. *Ihh* and its receptors patched (*Ptc*) and smoothened (*Smo*) are overexpressed in tissues from patients with chronic pancreatitis but weakly expressed in normal ductal cells.¹³ Increased *Hh* signaling marks the progression of normal to fibrotic tissue in chronic pancreatitis.⁷ These suggest that perhaps the development of these diseases, DAP, PDA, and NCCP, may be rooted in certain common pathways of pancreatic development and function

All three patients in the current study underwent pylorus-preserving resection of the pancreatic head and uncinate process. Parsaik et al. reported the metabolic consequences following total pancreatectomy.¹⁶ One hundred forty-one patients were retrospectively studied, and nearly 89% of patients were on a complex insulin regimen with a mean daily insulin requirement of 35 U. Seventy-nine percent of these patients reported episodic hypoglycemia, which demonstrates the difficulty in balancing postoperative glucose management. Twenty-eight percent of patients reported chronic diarrhea from lack of pancreatic exocrine function postoperatively. It is vital that the patient be educated regarding the metabolic consequences of undergoing a total pancreatectomy prior to surgical intervention.

Difficulty can arise in trying to distinguish congenital agenesis of the pancreas from acquired fatty replacement of the pancreas. Small to large amounts of fat replacement can normally occur in obese and elderly patients.¹⁶ Total fat replacement of the dorsal pancreas has been reported but is quite rare. A proposed mechanism for the replacement of normal pancreatic endocrine and exocrine tissue with adipose tissue is chronic obstruction of the pancreatic duct. Blockage can arise from calculi or tumors. Pancreatic duct obstruction by a stone can cause fibrosis in canine models.¹⁷ Ligation of the pancreatic duct in mice causes complete intralobular replacement.¹⁸ Proposed criteria for confirming true congenital DAP as opposed to fatty replacement include the complete absence of exocrine features, acinar cells, and islets of Langerhans on histologic examination.¹⁹ Suggested radiologic criteria to diagnose dorsal agenesis of the pancreas have included the lack of a dorsal and transverse pancreatic artery on angiography (rarely performed) and the absence of an accessory pancreatic duct on ERP.¹⁹ However, the most common means of diagnosis is by cross-sectional imaging (CT or MRI/MRCP).

Conclusion

In summary, this review documents three patients with DAP and PDA, two of whom had the novel triad of DAP, PDA, and NCCP. All three patients underwent successful operative treatment via pylorus-preserving resection of the pancreatic head and uncinate process. This series raises a number of interesting questions. Is there a potential common molecular pathway in the development of dorsal agenesis of the pancreas and the development of PDA involving the retinoic acid signaling pathway? Did the malignant transformation in two of our patients have a greater association with DAP or NCCP? Patients with known DAP may

benefit from early screening given the apparent increased risk of developing pancreatic cancer.

References

1. Wang JT, Lin JT, Chuang CN, Wang SM, Chuang LM, Chen JC, Huang SH, Chen DS, Wang TH. Complete agenesis of the dorsal pancreas—a case report and review of the literature. *Pancreas*. 1990; 5:493–7. [PubMed: 2199969]
2. Sakpal SV, Sexcius L, Babel N, Chamberlain RS. Agenesis of the dorsal pancreas and its association with pancreatic tumors. *Pancreas*. 2009; 38:367–73. [PubMed: 19390403]
3. Barman KK, Premalatha G, Mohan V. Tropical chronic pancreatitis. *Postgrad Med J*. 2003; 79:606–15. [PubMed: 14654569]
4. Chari ST, Mohan V, Pitchumoni CS, Viswanathan M, Madanagopalan N, Lowenfels AB. Risk of pancreatic carcinoma in tropical calcifying pancreatitis: an epidemiologic study. *Pancreas*. 1994; 9:62–6. [PubMed: 8108373]
5. Matsusue S, Kashiara 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; 14:394–8. [PubMed: 6513208]
6. Ulasan S, Yakar T, Koc Z, Kayaselcuk F, Torer N. Adenocarcinoma of the pancreas associated with dorsal agenesis. *Pancreas*. 2006; 33:437–9. [PubMed: 17079954]
7. Balakrishnan V, Narayanan VA, Siyad I, Radhakrishnan L, Nair P. Agenesis of the dorsal pancreas with chronic calcific pancreatitis. case report, review of the literature and genetic basis. *Jop*. 2006; 7:651–9. [PubMed: 17095847]
8. Skandalakis LJ, Rowe JS Jr, Gray SW, Skandalakis JE. Surgical embryology and anatomy of the pancreas. *Surg Clin North Am*. 1993; 73:661–97. [PubMed: 8378816]
9. Sadler TW. Susceptible periods during embryogenesis of the heart and endocrine glands. *Environ Health Perspect*. 2000; 108(Suppl 3):555–61. [PubMed: 10852854]
10. Schnedl WJ, Piswanger-Soelkner C, Wallner SJ, Reittner P, Krause R, Lipp RW, Hohmeier HE. Agenesis of the dorsal pancreas and associated diseases. *Dig Dis Sci*. 2009; 54:481–7. [PubMed: 18618254]
11. Li H, Arber S, Jessell TM, Edlund H. Selective agenesis of the dorsal pancreas in mice lacking homeobox gene Hlx9. *Nat Genet*. 1999; 23:67–70. [PubMed: 10471501]
12. Martin M, Gallego-Llamas J, Ribes V, Keding M, Niederreither K, Chambon P, Dolle P, Gradwohl G. Dorsal pancreas agenesis in retinoic acid-deficient Raldh2 mutant mice. *Dev Biol*. 2005; 284:399–411. [PubMed: 16026781]
13. Kaye H, Kleeff J, Osman T, Keleg S, Buchler MW, Friess H. Hedgehog signaling in the normal and diseased pancreas. *Pancreas*. 2006; 32:119–29. [PubMed: 16552330]
14. Singh B, Murphy RF, Ding XZ, Roginsky AB, Bell RH Jr, Adrian TE. On the role of transforming growth factor-beta in the growth inhibitory effects of retinoic acid in human pancreatic cancer cells. *Mol Cancer*. 2007; 6:82. [PubMed: 18157915]
15. Bhatia E, Choudhuri G, Sikora SS, Landt O, Kage A, Becker M, Witt H. Tropical calcific pancreatitis: strong association with SPINK1 trypsin inhibitor mutations. *Gastroenterology*. 2002; 123:1020–5. [PubMed: 12360463]
16. Parsaik AK, Murad MH, Sathananthan A, Moorthy V, Erwin PJ, Chari S, Carter RE, Farnell MB, Vege SS, Sarr MG, Kudva YC. Metabolic and target organ outcomes after total pancreatectomy: Mayo Clinic experience and meta-analysis of the literature. *Clin Endocrinol (Oxf)*. 2010; 73(6): 723–31. [PubMed: 20681992]
17. Maeda H. Ductal and vascular factors in the etiology of experimentally induced pancreatic fibrosis and fat replacement in dogs. *Nippon Shokakibyo Gakkai Zasshi*. 1986; 83:2580–7. [PubMed: 3560492]
18. Watanabe S, Abe K, Anbo Y, Katoh H. Changes in the mouse exocrine pancreas after pancreatic duct ligation: a qualitative and quantitative histological study. *Arch Histol Cytol*. 1995; 58:365–74. [PubMed: 8527243]

19. 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; 39:76–80. [PubMed: 14767740]

Fig. 1.

CT showing agenesis of the dorsal pancreas. Pancreatic tissue does not extend to the left of the superior mesenteric vein. No additional pancreatic tissue to the patient's left of this arrowhead was seen on additional axial CT images. *Arrow head* marks the most distal aspect of pancreatic tissue, *thin arrow* superior mesenteric vein

Fig. 2. ERCP demonstrating a dilated and truncated main pancreatic duct with intraductal calculi. Patient's status postcholecystectomy with a somewhat dilated extrahepatic biliary tree. *Thin arrow* dilated and truncated main pancreatic duct with intraductal calculi. *Thick arrow* dilated common bile duct

Fig. 3. Intraoperative image of DAP with underlying superior mesenteric vein. There is an absence of pancreatic tissue to the left of the superior mesenteric vein. *Arrow head* marks the most distal aspect of pancreatic tissue. *Thin arrow* superior mesenteric vein

Fig. 4. Illustration of DAP. There is an absence of pancreatic tissue to the left of the neck of the gland. In this case, a cancer of the head of the pancreas is also depicted

Reproduced with permission from Environment Health Perspectives. Sadler T.W. Environment Health Perspectives Supplements Volume 108, Number S3, June 2000.

Fig. 5.

Embryology of pancreatic development. **a** 30 days after fertilization. The ventral and dorsal buds develop on opposite sides of the primordial foregut. **b** The ventral pancreatic bud develops from the hepatic diverticulum arising from the duodenum, and the dorsal pancreatic bud arises separately from the dorsal aspect of the duodenum. **c** As the duodenum rotates to the right assuming the C shape, the ventral pancreatic bud continues its rotation before fusing with the dorsal pancreatic bud. **d** The dorsal pancreatic bud forms the body and tail of the pancreas and also gives rise to the accessory pancreatic duct which empties into the minor duodenal papilla of Santorini. Permission to use this figure was obtained from Hugh A. Tilson, Ph.D., Editor in Chief of Environmental Health Sciences on March 01, 2011

Table 1

Current series and literature review of DAP associated with PDA or NCCP

Author	Age/Sex	Presentation	Imaging	Operation	Diagnosis	Pathology	Adjuvant Therapy	Survival
Case 1	37/F	Abdominal pain, hyperglycemia	CT, ERCP	Pylorus preserving resection of the pancreatic head and uncinate process	DAP, PDA, NCCP	T3N1M0	Gemcitabine	Dead (17 months)
Case 2	59/F	Weight loss	CT	Pylorus preserving resection of the pancreatic head and uncinate process	DAP, PDA, NCCP	T3N1M0	Radiation, gemcitabine	Alive (38 months)
Case 3	68/M	Elevated LFTs	CT, ERCP	Pylorus preserving resection of the pancreatic head and uncinate process	DAP, PDA	T2N0M0	Radiation, gemcitabine	Alive (52 months)
Ulusan (2006)	72/M	Abdominal pain, jaundice, hyperglycemia	Unknown	Hepaticojejjunostomy, cholecystectomy	DAP, PDA	–	–	–
Balakrishnan (2006)	28 F	Abdominal pain, weight loss, hyperglycemia	CT, ERCP	–	DAP, NCCP	–	–	–
Matusue (1984)	53/F	Abdominal pain, weight loss, hyperglycemia	CT	Total pancreatectomy	DAP, PDA	–	–	–

LFTs: liver function tests, CT: computed tomography, ERCP: endoscopic retrograde cholangiopancreatography, DAP: dorsal agenesis of the pancreas, PDA: pancreatic ductal adenocarcinoma, NCCP: nonalcoholic chronic calcific pancreatitis