Abnormal Pancreas with Chronic Calcific Pancreatitis. Case Report, Review of the Literature and Genetic Basis

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ABSTRACT

Context Agenesis of the dorsal pancreas is a rare developmental anomaly. This anomaly may be complicated by recurrent acute and chronic pancreatitis.

Case report We report the case of a 28-year-old female with agenesis of the dorsal pancreas and chronic calcific pancreatitis. The diagnosis of agenesis of the dorsal pancreas is discussed and the genetic changes leading to it are reviewed. The possibility of the patient having tropical pancreatitis is mentioned.

Conclusions This is probably the first report of chronic calcific pancreatitis complicating agenesis of the dorsal pancreas.

INTRODUCTION

Developmental anomalies of the pancreas are rarely seen. Pancreas divisum is the most common anomaly (seen in 5-10% of Caucasians) the others being an annular pancreas, a heterotrophic pancreas, ansa pancreatica, anomalous pancreaticobiliary union and partial pancreatic agenesis [1, 2]. Agenesis of the dorsal pancreas is a very rare anomaly: it may be asymptomatic and incidentally detected on imaging or may be associated with attacks of pancreatitis.
kidneys were normal. With the suspicion of agenesis of the dorsal pancreas, endoscopic retrograde pancreatography (ERCP) was carried out. During ERCP, the minor papilla was not seen even after careful examination. The major papilla was normal. Selective cannulation of the pancreatic duct was carried out. The cannula could not be advanced beyond the head region. This was confirmed using a 0.018 inch hydrophilic guidewire (Glidewire, Terumo Co., Tokyo, Japan) which could not be passed across the spine (Figure 2). A pancreatogram showed a short branching duct in the head region with tapering and terminal arborization to the right of the spine (Figure 3). The diagnosis of agenesis of the dorsal pancreas with associated chronic pancreatitis and diabetes mellitus was made. There was no family history of pancreatitis. The SPINK1 mutation was negative on gene sequencing (done at the Bangalore Genei Division, Sanmar Speciality Chemicals, Bangalore, India). Contrast studies did not reveal any intestinal malrotation. The patient had no other associated congenital abnormalities.

The patient was started on analgesics, pancreatic enzyme supplements, a diabetic diet and human Mixtard® insulin (30/70) at a dose of 20 units in the morning and 12 units in the evening. Her symptoms have improved; she feels well and is currently being followed up in the clinic.

**DISCUSSION**

The present case is the first report of chronic calcific pancreatitis affecting the head of the pancreas in association with agenesis of the dorsal pancreas. Pancreatic anomalies may be due to malfusion (e.g., pancreas divisum) or malrotation (e.g., annular pancreas, partial agenesis) [3]. The exact prevalence of agenesis of the dorsal pancreas is not known;
however, only about 20 cases have been reported in the literature. There are no reports of autopsy series. Agenesis of the dorsal pancreas may be asymptomatic, detected only incidentally on abdominal imaging or may be associated with recurrent acute pancreatitis or diabetes mellitus.

Prior to 1979, agenesis of the dorsal pancreas was diagnosed only after laparotomy. The first pre-operative diagnosis of this anomaly was made by Sano et al. using ERCP and a CT scan. A diagnosis of agenesis of the dorsal pancreas can pose problems. Abdominal ultrasound has limitations in diagnosing pancreatic disorders because of non-visualization of the body and the tail of the pancreas due to interference from bowel gas or even technical failure [1, 4].

Computerized tomography [5] or MRI [6] helps in diagnosing agenesis of the dorsal pancreas by demonstrating the absence of the pancreatic body and tail and the presence of a normal head region. However, atrophy of the body and the tail of the pancreas secondary to acute pancreatitis, with sparing of the uncinate process may mimic dorsal pancreatic agenesis and has been labeled pseudo-agenesis [7]. Such atrophy may be associated with hypertrophy of the ventral pancreas. Suda et al. point out the fallacies of diagnosing dorsal pancreas agenesis by imaging modalities alone [8]. They reported two elderly patients, both of whom had an initial diagnosis of agenesis of the dorsal pancreas based on imaging; however, it was subsequently proven by surgery and biopsies to be atrophy of the body and the tail of the pancreas secondary to tumor obstruction of the proximal main pancreatic duct.

Magnetic resonance cholangiopancreatography (MRCP) [8] or ERCP can confirm the diagnosis of dorsal pancreas agenesis suspected on CT or MRI. ERCP can show the absence of the minor papilla and the complete absence of the dorsal duct system, and demonstrate a short ventral duct [9]. ERCP can also help in ruling out pancreas divisum, by demonstrating obstruction, tapering, or stenosis of the pancreatic duct and by differentiating it from a pancreatic tumor. Recently, endoscopic ultrasononography has been shown to be useful in the diagnosis of agenesis of the dorsal pancreas [10].

The association of agenesis of the dorsal pancreas with pancreatitis is controversial and the mechanism for associated pancreatitis is speculative. Sphincter of Oddi dysfunction or dyskinesia and compensatory hypertrophy and hypersecretion of the remaining ventral pancreas with raised intraductal pressure have been proposed to explain the pancreatitis [11]. Genetic mutations such as that of SPINK1 may be predisposing factors [12]. Mutations in the SPINK1 gene have been reported to be associated with idiopathic and tropical pancreatitis. However, these genes, because of their high frequency in the population and low penetrance, are more likely to be disease modifiers rather than the cause of the disease.

Abdominal pain and diabetes mellitus are the most common symptoms of dorsal pancreatic agenesis [1]. Most of the adult patients who are reported to have pancreatitis in association with agenesis of the dorsal pancreas have presented with these clinical features. A case of neonatal diabetes mellitus due to congenital pancreatic agenesis has been reported [13]. In addition to agenesis of dorsal pancreas, this baby had other congenital defects such as cardiac septal defects, gallbladder agenesis and duodenal malrotation. Fukuoka et al. have described a 47-year-old female with obstructive jaundice associated with dorsal pancreatic agenesis, confirmed by ERCP [14]. At laparotomy, an enlarged head of the pancreas with absence of the body and the tail was noticed. A biopsy of the pancreas showed scattered islets of Langerhans in diffuse fibrosis, with destruction of the glandular parenchyma. In a case report by Wang et al. [1], laparotomy showed a normal head of the pancreas with complete agenesis of the body and tail. A biopsy from the head revealed normal pancreatic tissue whereas a biopsy from the presumed body and tail presented only fatty tissue. Klein et al. [15] has reported a patient with agenesis of the dorsal pancreas with weight loss, diabetes mellitus and exocrine pancreatic deficiency. In another report, a
female who developed insulin-dependent diabetes mellitus at 39 years of age was found to have dorsal pancreas agenesis [16]. Both sons of the patient also had this anomaly, verified by CT, but they had no evidence of diabetes mellitus. Solid and papillary tumors of the pancreas complicating agenesis of the dorsal pancreas have been reported in two patients [17, 18]. In both patients, a successful resection of the tumor have been performed. The pancreas develops from the foregut endoderm as ventral and dorsal buds at the fourth week of gestation. These buds fuse and develop into a complex organ composed of endocrine, exocrine and ductal components. This developmental process depends upon an integrated network of transcription factors. Much of the recent knowledge on genes and transcription factors exerting influence on pancreas development has been gained from studies in knock-out mice [19]. The initial event in the development of the pancreas is the outcropping of two buds (ventral and dorsal) of cells from a specialized endodermal epithelium located in the region of the foregut which will become the duodenum (at embryonic day (e) e8.5 to e9.5 in the mouse). By e10.5, the partially differentiated epithelium of the two buds undergoes branching into a ductal tree. By e13 and e14, the dorsal and ventral pancreata rotate and fuse into a single organ. Between e14.5 and e15.5, the endocrine pancreas differentiates from the ductal epithelium; on e15.5, acini are clearly discernible from the ducts. Endocrine cells differentiate at about e9.5. They undergo proliferation and organize into islet-like clusters by e16. The islets are fully formed shortly after birth (e18-e19). Contrary to earlier views, the endocrine cells are now established to be of endodermal and not neural crest origin.

Expression of sonic hedgehog (Shh) or Indian hedgehog (Ihh) can suppress pancreas development. It has been shown that exclusion of Shh or Ihh in the developing pancreas anlage is essential for pancreas development [20]. At the level of the pancreas, Shh and Ihh are expressed in the endoderm anterior and posterior to the pancreas in the intestinal part but not in the anterior and posterior pancreatic epithelium. It has been suggested that the notochord which is in contact with the dorsal gut epithelium may exert a negative repressive signal on Shh expression at the prospective site of the dorsal pancreas. However, the notochord is not in contact with the ventral gut epithelium; hence, signals other than those from the notochord are likely to be in the region of the ventral epithelium.

The homeodomain protein HB9 (Hlxb9) is required for dorsal, but not ventral, bud initiation [21]. The pancreas-duodenum-homeodomain protein (Pdx1) is required for bud expression but the initiation of bud formation appears normal in homozygous mice which are mutant for this gene. The molecular determinants which define the position of the buds and the localized expression of Hlxb9 and Pdx1 in the endoderm are currently unknown. Several homeodomain and basic helix-loop-helix (bHLH) transcription factors, notably Isl1, Nkx2-2, Pax4, Pax6, and NeuroD/Beta2, have been shown to exert important functions in the control of pancreatic endocrine cell differentiation [22]. Even though these factors are expressed at the early stages of pancreas development, even in their absence, the initial steps of pancreas development proceed normally. In contrast to the bHLH class, the pancreas transcription factor1 p48 subunit (Ptf1a), which is required for the generation of exocrine, but not endocrine, cells and the homeodomain protein insulin promoter factor-1 (IPF1) (human locus) / Pdx1 (mouse locus) are expressed at an early stage in pancreas development.

The homeodomain protein Pdx1 is expressed in the developing pancreatic anlage and leads to the derivation of all the pancreatic cell types; mutations in gene IPF1 (human locus) / Pdx1 (mouse locus ) prevent the development of the pancreas [23, 24, 25]. Hlxb9, which encodes HB9, is a homeobox gene which is expressed in the early stages of pancreatic development and later in differentiated B cells [26, 27]. Isl1 is a LIM homeodomain protein required for the formation of the dorsal
mesenchyma for proper exocrine differentiation and also required in the pancreatic epithelium for islet survival [28]. The ngn3 gene, which codes for the neurogenin 3 protein, is the key regulator of endocrine development [29, 30]. Shh and Ihh are the signaling molecules for the inhibitory action on pancreas development [31, 32]. Recently, the transcription factor Ptf1a has been shown to play an essential role in the development of the pancreas from undifferentiated ventral foregut endoderm, necessary for the specification of the ventral pancreas and robust outgrowth of the dorsal bud [33]. In its absence, ventral pancreas progenitors differentiate into dorsal cells by default.

In their experiments on dorsal agenesis of the pancreas in mice, Li et al. [34] found that Hlx9 is expressed in two distinct developmental phases, first during the evagination of the pancreatic buds and later in differentiating B cells. At approximately e8 (8 somatic stage embryonic day), Hlx9 expression is first evident in the notochord, in the entire dorsal gut endoderm and in the ventral endoderm whereas the Pdx1 is expressed only in the ventral pancreatic endoderm so that both genes are concurrently expressed in the ventral anlage while, in the dorsal anlage, there will be the initiation of Hb9 expression. At e10.5, only a low level of Hlx9 expression remains in the dorsal pancreatic bud with no expression in the ventral bud and the notochord whereas, at this stage, Pdx1 will be expressed in both pancreatic buds. At e17.5, Hlx9 expression reappears in differentiating B cells (only in insulin-producing B cells, not in the glucagon or somatostatin cells). At e10.5, Hlx9 completes the evagination and therefore subsequent development of the dorsal pancreatic bud. But the ventral pancreatic epithelium generates both exocrine and endocrine cells in the absence of Hlx9. As a result, the dorsal pancreatic bud does not develop in Hlx9 mutant mice. In contrast, the ventral pancreatic epithelium develops and generates both exocrine and endocrine cell types, thus revealing an early molecular distinction between the programs for dorsal and ventral pancreatic development. They also suggest that the ventral pancreas of Hlx9 mutant embryos exhibits a more subtle perturbation in B cell differentiation and islet cell organization, indicating a later role for Hlx9 in the development of pancreatic B cells.

Harrison et al., in another set of experiments in mice, showed that during mouse development, the dorsal and ventral pancreatic buds and mature beta cells in the islets of Langerhans expressed Hlx9 [27]. In mice homologous for a null mutation of Hlx9, the dorsal lobe of the pancreas failed to develop. The remnant Hlx9-/- pancreas had small islets of Langerhans with reduced numbers of insulin-producing beta-cells. Hlx9-/- beta cells expressed low levels of the glucose transporter Glut-2 and homeodomain factor Nkx6-1. Thus, Hlx9 was shown to be a key to normal pancreas development and function.

In humans, mutations in the TCF2 (HNF1B, VHNF1) gene are associated with maturity-onset diabetes of the young Type-5, a form of dominantly inherited type II diabetes mellitus characterized by pancreatic beta cell dysfunction at the age of 25 years or younger, non-diabetic early-onset renal disease, liver dysfunction, and abnormal urogenital tract development. In addition to these phenotypes, variable levels of pancreatic atrophies have recently been associated with different TCF2 mutations [35]. Moreover, the authors quote having identified two fetuses with severe pancreatic hypoplasia, both carrying previously undescribed severe mutations in the TCF2 pancreatic genes. They further studied this gene in mice from the embryonic stem cells and found that, in the Tcf2 mutant embryo, the dorsal pancreatic bud was reduced and the ventral bud was undetectable. The important branching phase for pancreatic bud formation by the Tcf2 gene takes place between e10.5 and e12.5.

Martin et al. [36] studied the role of retinoic acid signaling in the development of the pancreas in mice. The principle behind the study was the induction of different stimuli
from neighboring mesodermal tissues for the development of the pancreas. Retinaldehyde dehydrogenase 2 (raldh2 gene), which encodes the enzyme required to synthesize retinoic acid, is expressed in the dorsal pancreatic mesenchyma at the early stage of pancreatic specification. Raldh2-deficient mice do not develop a dorsal pancreatic bud. These mutant embryos lack Pdx1 expression and early glucagon expressing cells, altered Isl1 and reduced Hlxb9 expressing cells. Therefore they realized the importance of this gene for the normal development of the dorsal pancreatic endoderm at a stage preceding Pdx1 function.

During pancreatic ontogeny, N-cadherin is initially expressed in the pancreatic mesenchyma and later in the pancreatic endoderm. The analysis of N-cadherin-deficient mice revealed that these mice suffer from selective agenesis of the dorsal pancreas [37]. Several other transcription factors are involved in pancreatic development. For example, members of the Pax gene family, Pax6 and Pax4 are expressed in the endocrine cells [20]. The NK2 family member, Nkx2-2, is supposed to be required for the terminal differentiation of B cells or alternatively, Nkx2-2 is critically required for the expression of the insulin gene but not for the expression of other B cell-specific genes. NeuroD/Beta2 is a bHLH transcription factor which is expressed in all pancreatic endocrine cells. Mist1 also belongs to the bHLH family of transcription factors and is expressed in the exocrine cells from e14.5 on. Still another transcription factor, HNF6, can be detected in both pancreatic buds as early as e10.5 but, later, the expression becomes limited to the exocrine pancreas.

The pancreas has rapidly become one of the most studied organs with respect to the functioning of the transcription factors, and many pancreatic phenotypes have been described [20]. However, the present data only allow more general comments to be made about the epigenetic control of pancreatic development. One major reason for this is that most genetic studies have so far failed to address whether a given transcription factor exerts its function in pancreatic progenitor cells and/or in postmitotic cells. Even though agenesis of the dorsal pancreas is a rare congenital anomaly, the genetic studies of this anomaly can provide further insights into early molecular events controlling pancreatic development.

The pathogenetic mechanism for chronic pancreatitis in our patient is not clear. This patient did not have any of the known risk factors for chronic pancreatitis. In most of the reported cases of agenesis of the dorsal pancreas, the association was with recurrent acute pancreatitis. In the case described by Fukuoka et al. [14], laparotomy and biopsy showed histological evidence of chronic pancreatitis. Our patient had mild atrophy of the head of the pancreas with speckled calcification on CT indicating chronic calcific pancreatitis. There was failure to demonstrate the body and the tail of the pancreas by CT and this was confirmed by ERCP during which the guide wire could not be advanced beyond the head of the pancreas and the contrast medium could not be pushed beyond the head where there was arborization. The patient was malnourished, had severe diabetes mellitus necessitating insulin injections and had exocrine pancreatic deficiency. She showed absence of the body and the tail of the pancreas. To our knowledge, this is the first report of chronic calcific pancreatitis associated with dorsal pancreatic agenesis. This patient comes from Southern India, which is geographically associated with a high prevalence of tropical pancreatitis. Tropical pancreatitis is a type of chronic pancreatitis, generally calcific, which is commonly seen in young non-alcoholic subjects in tropical countries [38]. The patients are often malnourished, with severe diabetes mellitus and a rapidly progressive course. The disease is sometimes seen in close relatives such as siblings or parents. It is especially common in Southern India where this patient comes from. These patients have a high incidence of malignancy complicating the pancreatitis. Whether the present patient had tropical pancreatitis is a matter of
speculation as there are no definite diagnostic markers for tropical pancreatitis. However, we could not elicit a history of malnutrition before the onset of her illness, nor of substantial cassava intake, both of which are common associations with tropical pancreatitis. None of the patient’s immediate relatives had chronic pancreatitis or diabetes mellitus. Genetic mutations have been reported to be associated with chronic pancreatitis [39, 40]. Mutations involving the SPINK1 gene have been reported in association with idiopathic pancreatitis in the West, in up to 45% of tropical pancreatitis patients [12] and in 4% of normal controls in India; however, the SPINK1 mutation was absent in our patient. The explanation for the association between pancreatitis and agenesis of the dorsal pancreas is far from clear.

In recent animal experiments, hedgehog signaling has recently been shown not to be restricted to developmental events in the pancreas, but to retain some of its activity during adult life [41]. Recent work has suggested the role of deregulated hedgehog signaling in pancreatic development and pancreatic diseases, including diabetes mellitus, chronic pancreatitis and pancreatic cancer [42]. Whether deregulations in hedgehog signaling have had any role in initiating pancreatitis in our patient is a moot question. While the exact risk factors for chronic pancreatitis in our patient are not apparent, it is possible that as yet unknown genetic factors or environmental toxins might have had a contributory role in the initiation or perpetuation of pancreatitis in this patient.

CONCLUSION

We report a case of chronic calcific pancreatitis in association with agenesis of the dorsal pancreas, which is a very rare anomaly of pancreatic development. To the best of our knowledge, this is the first time such an association is being reported. The cause of the pancreatitis in the present case is not known even though the possibility of associated tropical pancreatitis cannot be discounted. We have reviewed the literature on agenesis of the dorsal pancreas and its genetic basis.

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Keywords Islets of Langerhans; Mutation; Pancreatic Ducts; Pancreas; Pancreas, Exocrine; Pancreatitis; Pancreatitis, Acute Necrotizing; Pancreatitis, Chronic; Transcription Factors

Abbreviations bHLH: basic helix-loop-helix; e: embryonic day; HLXB9: homeobox HB9 [Homo sapiens]; Hlxb9: homeobox gene HB9 [Mus musculus]; HNF6: hepatocyte nuclear factor 6; Ihh: Indian hedgehog [Mus musculus]; IPF1: insulin promoter factor 1, homeodomain transcription factor [Homo sapiens]; Ipfl: insulin promoter factor 1, homeodomain transcription factor [Mus musculus]; Isl1: ISL1 transcription factor, LIM/homeodomain [Mus musculus]; Nkx2-2: NK2 transcription factor related, locus 2 (Drosophila) [Mus musculus]; Nkx6-1: NK6 transcription factor related, locus 1 (Drosophila) [Mus musculus]; Pax2: paired box gene 2 [Mus musculus]; Pax4: paired box gene 4 [Mus musculus]; Pdx1: pancreatic and duodenal homeobox gene 1 [Rattus norvegicus]; PTF1A: pancreas specific transcription factor, 1a [Homo sapiens]; Ptf1a: pancreas specific transcription factor, 1a [Mus musculus]; raldh2: retinaldehyde dehydrogenase 2 [Takifugu rubripes]; SHH: sonic hedgehog homolog (Drosophila) [Homo sapiens] Shh: sonic hedgehog [Mus musculus]; TCF2: transcription factor 2, hepatic; LF-B3; variant hepatic nuclear factor [Homo sapiens]; Tcf2: transcription factor 2 [Mus musculus]

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References


11. Rakesh K, Choung OW, Reddy DN. Agenesis of the dorsal pancreas (ADP) and pancreatitis - is there an association? Indian J Gastroenterol 2006; 25:35-6. [PMID 16567893]


24. Offield MF, Jetton TL, Labosky PA, Ray M, Stein RW, Magnuson MA, et al. PDX-1 is required for pancreatic outgrowth and differentiation of the rostral


Gu G, Dubauskaite J, Melton DA. Direct evidence for the pancreatic lineage: NGN3+ cells are islet progenitors and are distinct from duct progenitors. Development 2002; 129:2447-57. [PMID 11973276]


Balakrishnan V, Nair P, Radhakrishnan L, Narayanan VA. Tropical pancreatitis - a distinct entity, or merely a type of chronic pancreatitis? Indian J Gastroenterol 2006; 25:74-81. [PMID 16763335]


