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The Histopathology of *PRSS1* Hereditary Pancreatitis

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Abstract

Hereditary pancreatitis is an autosomal dominant disorder with 80% penetrance and variable expressivity. The vast majority of cases have been linked to mutations within the cationic trypsinogen gene, also referred to as serine protease 1 (*PRSS1*). Other than inheritance, *PRSS1* pancreatitis has been considered clinically and pathologically indistinguishable from other etiologies of chronic pancreatitis. However, to date, the histologic findings of *PRSS1* pancreatitis have not been well described. We, therefore, collected pancreatic specimens from 10 *PRSS1* patients of various ages and examined their clinicopathologic features. Patients at the time of resection ranged in age from 9 to 66 years (median, 29 y), with a slight female predominance (60%). All patients reported a history of intermittent abdominal pain, with an age of onset ranging from infancy to 21 years of age. Examination of the gross and microscopic findings suggested a sequential pattern of changes with increasing patient age. In pediatric patients (n=4), although in most cases the pancreas was grossly normal, there was microscopic variation in lobular size and shape. Although the central portions of the pancreas displayed parenchymal loss accompanied by loose perilobular and interlobular fibrosis, the periphery was remarkable for replacement by mature adipose tissue. These changes were more developed in younger adults (n=2), in whom fatty replacement seemed to extend from the periphery to the central portions of the pancreas. With older patients (n=4), the pancreas showed marked atrophy and extensive replacement by mature adipose tissue with scattered islets of Langerhans and rare acinar epithelium concentrated near the main pancreatic duct. In summary, *PRSS1* hereditary pancreatitis is characterized by progressive lipomatous atrophy of the pancreas.

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Keywords

PRSS1; hereditary pancreatitis; chronic pancreatitis; cationic trypsinogen; serine protease 1

Chronic pancreatitis is a progressive condition characterized by irreversible damage to both the exocrine and endocrine components of the pancreas. It is multifactorial in etiology, highly variable in clinical presentation, and challenging to treat. In industrialized countries, chronic pancreatitis represents a serious health issue, with a prevalence and incidence ranging from 25 to 30 cases and 3 to 9 cases per 100,000, respectively.[1–3] In the United States, it accounts for >120,000 outpatient visits and >50,000 hospitalizations per year.[4] Although the exact cause of chronic pancreatitis remains elusive, risk factors include alcohol consumption and abuse, obstruction of pancreatic ducts (eg, injury, gallstones, or tumors), smoking, hypercalcemia, hyperlipidemia, nutrition, autoimmunity, and genetics.

Hereditary pancreatitis is a rare, inheritable form of chronic pancreatitis. It is an autosomal dominant disorder with an 80% penetrance and variable expressivity. Patients with hereditary pancreatitis suffer from recurrent episodes of acute pancreatitis, which progress in the majority to chronic pancreatitis. The disease usually begins in early childhood, but onset can vary from infancy to the sixth decade of life.[5] By microsatellite linkage analysis, Whitcomb et al[6] identified the gene responsible for 80% of hereditary pancreatitis families on the long arm of chromosome 7 (7q35). Subsequently, mutations within the cationic trypsinogen gene, also referred to as serine protease 1 (*PRSS1*), were identified as the underlying defect by candidate gene approach.[7] Several mutations within both the coding sequence and introns of *PRSS1* have been described, but the *R122H* and *N29I* mutations are the most prevalent.[8,9] Although the clinical phenotype associated with these mutations is quite similar, there are some noticeable differences. For instance, data suggest that the *R122H* mutation results in early onset of symptoms and increased severity of pancreatic disease.[5]

To date, other than a report of 2 young adult patients by Felderbauer et al,[10] the histopathologic findings of *PRSS1* hereditary pancreatitis have not been well described. Practical difficulties in obtaining biopsies from the pancreas have prevented research during the early stages of the disease. In addition, studies obtaining specimens at later stages from patients undergoing surgery or from autopsies are lacking. Therefore, we have collected pancreatic specimens from 10 *PRSS1* patients of various ages, who underwent total pancreatectomy. We describe the patient demographics, radiographic findings, gross features, and histomorphology.

MATERIALS AND METHODS

Cases

Study approval was obtained from the University of Pittsburgh Institutional Review Board. Patients were accrued through 2 multidisciplinary conferences at the University of Pittsburgh Medical Center: Auto-Islet Committee and Pancreatic Cancer Conference. In total, 10 patients with confirmed *PRSS1* germline mutations were identified who underwent

total pancreatectomy (Table 1) between 2006 and 2013. For 6 patients (cases 1 through 6), upon resection of the pancreas, the specimen was grossly evaluated, and a representative section was submitted for histologic evaluation (2 formalin-fixed paraffin-embedded tissue blocks submitted for evaluation). The pancreas was then subsequently subjected to islet cell harvest and autotransplantation. In the remaining 4 patients (cases 7 through 10), owing to the risk of harboring a minute pancreatic cancer, islet cell harvest was not performed. The specimens were submitted for pathologic assessment and the entire pancreas submitted for histologic examination. The total number of formalin-fixed paraffin-embedded tissue blocks examined for each case was as follows: 35 (case 7), 38 (case 8), 51 (case 9), and 46 (case 10).

Electronic medical records for each patient were reviewed to include patient age, sex, clinical presentation, onset of symptoms, family history, radiographic findings including endoscopic ultrasound (EUS), and germline genetic testing results. For cases 1, 4, 6, and 8, germline testing for *PRSS1*, *SPINK1*, and *CFTR* was performed by Ambry Genetics (Aliso Viejo, CA). Of the remaining 6 patients, germline testing for *PRSS1* and *SPINK1* was done within the University of Pittsburgh Medical Center Department of Pathology, Division of Molecular Genetics. *CFTR* testing was performed through Quest Diagnostics (Madison, NJ).

For each surgical specimen, the gross findings were well documented to include the color, texture, lobularity, calcifications, cysts, and mass lesions. Paraffin-embedded, hematoxylin and eosin–stained sections for each case were reviewed by 2 surgical pathologists (A.D.S. and R.K.P.), independently. Particular attention was paid to document the number, distribution, and changes of pancreatic acini, ducts, and islets of Langerhans. Furthermore, the amount and location of both acute and chronic inflammation, presence of calcifications, and extent and distribution of parenchymal fibrosis and fat were noted.

Germline Genetic Testing

The methodology of germline testing for *PRSS1* and *SPINK1* was performed by polymerase chain reaction (PCR)/restriction fragment length polymorphism. Total genomic DNA was isolated from patient peripheral blood collected in EDTA. After DNA isolation, PCR-specific primers for exons 2 (encompasses amino acids 16, 23, and 29) and 3 (amino acid 122) for *PRSS1* and exon 3 for *SPINK1* were amplified. For *PRSS1* exon 2, 2 individual restriction digestions using *Taa*I and *Fnu*4HI were performed. *PRSS1* exon 3 was digested with *Afl*III. Exon 3 of *SPINK1* was digested with *Taa*I. The restriction digests were then run on an agarose cast gel and stained with ethidium bromide. A DNA ladder was also run for size comparison. The size of *PRSS1* exon 2 is 387 bp. When digested with *Taa*I, the *N29I PRSS1* mutant demonstrates the following DNA fragments: 230, 86, and 71 bp. For the *A16V* mutation, no digestion was seen using *Fnu*4HI. The size of *PRSS1* exon 3 is 911 bp, and the *R122H* mutant allele, when digested with *Afl*III, results in 565 and 346 bp products. *SPINK1* PCR reactions were 308 bp in size. For *N34S SPINK1* heterozygotes, 3 DNA fragments were identified: 308, 189, and 119 bp. Homozygotes for *N34S* resulted in only 2 fragments: 189 and 119 bp.

RESULTS

The clinical, genetic, and radiographic findings are summarized in Table 1. Patients at the time of total pancreatectomy ranged in age from 9 to 66 years (mean, 32 y; median, 29 y), with a slight female predominance (6 of 10, 60%). All of the patients reported a history of intermittent abdominal pain, with an age of onset ranging from infancy to 21 years of age. Two of the youngest patients required either chronic nasojejunal tube feeds (case 1) or total parenteral nutrition (case 2). Three patients also reported a history of diabetes mellitus, all of whom were older adults (cases 7, 8, and 10). In addition, 2 patients were status post a Puestow (pancreaticojejunostomy) procedure, with only initial symptomatic improvement in 1 patient. A sphincteroplasty was performed on 1 patient, but without symptomatic relief. Nine of 10 (90%) patients reported a family history of chronic pancreatitis, most of which involved several family members. In 2 cases, the patient's family history was also remarkable for pancreatic cancer. Other risk factors for pancreatitis, including alcohol consumption (>5 drinks/d), were absent; however, tobacco smoking or second-hand smoke was identified in 2 patients.

Germline testing for *PRSS1*, *CFTR*, and *SPINK1* was performed in all cases. Heterozygous *PRSS1* mutations were identified in all patients, with 9 of 10 (90%) patients harboring either the *R122H* (n=6) or *N29I* (n=3) missense mutation. The remaining patient was found to have a heterozygous cytosine to thymine substitution 24 bp into intron 4 (IVS4-24 C>T). In addition, 1 patient harbored a heterozygous adenine to guanine substitution −329 bp within the *CFTR* promoter (5′-UTR 329 A>G). No *CFTR* mutations were identified in the remaining 9 patients. *SPINK1* mutations were absent within all 10 patients.

Computed tomography studies before surgical resection were available for all patients and demonstrated diffuse atrophy of the pancreas in 8 of 10 (80%) cases. A dilated main pancreatic duct (>2 to 3 mm) was identified in 6 (60%) patients, ranging in diameter from 6 to 22 mm. Four (40%) cases showed numerous intraductal calcifications. Multiple pseudocysts were seen in only 1 of 10 (10%) patients. It is noteworthy that case 10 was remarkable for a 2.5 cm heterogenous, ill-defined area within the head of the pancreas that was suspicious for a pancreatic neoplasm. Follow-up EUS confirmed an irregular, hypoechoic, and heterogenous mass measuring 2.5 by 1.6 cm in cross-sectional diameter. At the time of EUS, fine-needle aspiration was performed and considered less than optimal with the presence of rare clusters of atypical cells; however, a reactive process was favored. Upon resection, no neoplasm was identified within the entirely submitted pancreas. As discussed in the Pathologic findings section, the mass lesion was consistent with fatty replacement of the pancreatic head.

Pathologic Findings

Upon gross and microscopic examination of all cases, a sequential pattern of changes became apparent based on patient age. Grossly, all pancreata obtained from pediatric patients (n=4) except for case 1 retained their normal lobular architecture. Case 1 had multiple pseudocysts present within the distal body and tail of the pancreas, whereas the head of the pancreas was grossly unremarkable. However, microscopically, in all cases, there was variation in lobular size and shape because of patchy loss of acinar and ductal

tissue. Proximal to the main pancreatic duct, parenchymal loss was accompanied by loosely packed, perilobular and interlobular fibrosis encircling islands of residual acinar epithelium (Fig. 1A). In addition to ductal atrophy, other ductal alterations included dilatation, squamous metaplasia (n=2), intraductal calcifications (n=2), and pancreatic intraepithelial neoplasia (PanIN) of highest-grade PanIN-1A (n=1). The islets of Langerhans were preserved and in many areas were found to aggregate, imparting a “hyperplastic” appearance. The periphery of the pancreas was characterized by further loss of acinar and ductal tissue with residual islet cell aggregates and surrounded by mature adipocytes and thin wisps of collagen (Fig. 1B). A mild lymphocytic inflammatory infiltrate was also present and often centered around the ducts.

Pancreatic specimens from young adults (n=2) aged 28 and 30 years showed increased loss of acinar cell mass and ductal epithelium with replacement by perilobular and interlobular fibrosis. Similar to the pediatric patients, the fibrosis was composed of loosely packed collagen and fibroblasts, but with intermingled adipocytes (Fig. 1C). Ductal alterations included further ectasia, squamous metaplasia, and intraductal calcifications (Fig. 1D). In addition, the islets of Langerhans remained preserved and often seen in aggregates.

In older adults (n=4) with ages ranging from 45 to 66 years, the gross specimens were soft and shrunken with marked atrophy and fat replacement, ductal dilatation, and multiple intraductal calcifications (Fig. 2A). Histologically, the pancreatic parenchyma was almost entirely replaced by mature adipose tissue with scattered islets of Langerhans and nerves (Figs. 2B–D) consistent with lipomatous atrophy. Amyloid deposition within the islets was present in 2 cases (Fig. 2C). Fibrosis was primarily periductal and cuffed the main pancreatic and larger interlobular ducts (Fig. 2B). Whereas intralobular and smaller interlobular ducts were markedly reduced and/or scarred, the larger interlobular ducts and main pancreatic duct were dilated with intraductal calcifications (n=4) and squamous metaplasia (n=3). Rare islands of acinar epithelium were present in 2 cases (2 of 4) but concentrated proximal to the main pancreatic duct rather than the periphery. Fat necrosis and saponification were absent. PanINs of highest-grade PanIN-2 were identified in 2 of 4 cases, both of which were the oldest patients within this series. As discussed previously, for case 10, no neoplasm was identified within the specimen. The mass lesion seen on radiographic imaging was attributed to extensive fatty replacement within the head of pancreas. However, an extensive number of PanINs (both PanIN-1 and PanIN-2) was identified throughout the pancreas (Fig. 3). With regard to specific *PRSS1* and *CFTR* mutations, no significant pathologic differences were identified.

DISCUSSION

In 1952, Comfort and Steinberg[11] reported a family of 3 generations with “hereditary chronic relapsing pancreatitis.” Thereafter, >200 kindreds have been described worldwide.[5] Patients with hereditary pancreatitis are defined by their pedigree: 2 or more first-degree relatives or 3 or more second-degree relatives with unexplained recurrent acute or chronic pancreatitis in 2 or more generations. [12] The prevalence of hereditary pancreatitis is variable and dependent on the geographic region, with the highest among the mid and southeastern regions of the United States and parts of France, England, and Germany.[12,13] The greater

ease of mobility in the past decades has resulted in migration of patients throughout the world. In addition, the incomplete penetrance, difficulty in getting accurate family history, and small family sizes have proved challenging in establishing a definitive diagnosis of hereditary pancreatitis on the basis of clinical criteria alone. The discovery of *PRSS1* mutations in the majority of well-defined hereditary pancreatitis families has allowed for the development of genetic testing. Consequently, this has resulted in better classification of the etiology of chronic pancreatitis within a subset of patients and their families. Furthermore, a major motivation for identifying patients with hereditary pancreatitis is the increased risk for developing pancreatic cancer. Recent studies have found a lifetime risk for pancreatic cancer of approximately 40% at 70 years of age.[14,15]

To date, >30 mutations within the coding sequence and introns of *PRSS1* have been identified; however, the 2 missense mutations, *R122H* and *N29I*, are the most frequently encountered. Although the precise disease mechanisms have not been unraveled, it is generally accepted that increased intrapancreatic trypsin activity is responsible for pancreatitis within these patients. Site-directed mutagenesis of recombinant *R122H* and *N29I* mutations results in increased propensity for trypsin-mediated trypsinogen activation in vitro, referred to as autoactivation.[16,17] In addition, the *R122H* mutation is located within the hydrolysis site of trypsin and can prevent the autodegradation of active trypsin.[9] Thus, the *R122H* mutation represents a dual gain-of-function mutation, which facilitates intracellular trypsin activity and stability of *R122H* trypsin. The direct pathogenic role of the *R122H* in the development of pancreatitis was confirmed by Archer et al.[18] The authors generated a transgenic mouse model in which the expression of the murine *R122H* mutation (R122H_mPRSS1) was targeted to pancreatic acinar cells by fusion to the elastase promoter. Pancreata from transgenic mice displayed early-onset acinar cell injury and chronic inflammation. As the mice aged, they developed increasing chronic inflammation and fibrosis. Considering these animals manifest many of the key histologic hallmarks of chronic pancreatitis, this model was thought to recapitulate human disease. Indeed, the histopathologic findings of 2 patients, 25 and 32 years old, as reported by Felderbauer et al,[10] showed acinar atrophy, ductal distortion, and fibrosis.

In contrast, the pathologic findings described herein suggest that patients with *PRSS1* mutations undergo a sequential pattern of gross and microscopic findings leading to lipomatous atrophy of the pancreas. In the majority of pediatric cases, their pancreas was characterized by gross preservation of the normal lobular architecture but microscopic variation in lobular size and shape. These changes were characterized by central parenchymal loss with accompaniment by mild chronic inflammation and loosely packed perilobular and interlobular fibrosis. More significantly, the periphery of the pancreas was remarkable for patchy parenchymal replacement with mature adipose tissue. These changes were more developed with increasing patient age, when fatty replacement of the pancreatic parenchyma seemed to extend from the periphery to the central portions of the pancreas. In agreement with Felderbauer and colleagues, fibrosis was present; however, it was thin and loosely packed as compared with chronic pancreatis due to alcohol or obstruction. With advanced age, pancreata from *PRSS1* patients showed, both grossly and microscopically, marked atrophy and extensive replacement by mature adipose tissue with scattered islets of

Langerhans and rare islands of acinar epithelium concentrated near the main pancreatic duct. Rather than fibrosis, the unifying theme within these patients was progressive lipomatous atrophy of the pancreatic parenchyma. In addition, for case 10, the extensive fatty replacement mimicked a mass lesion within the head of the pancreas.

Lipomatous atrophy of the pancreas is a frequent occurrence and seen with increasing age. In fact, it is the most common degenerative lesion of the pancreas and regarded as a normal finding in the obese and elderly.[19,20] However, it typically presents focally and is not as extensive as seen in *PRSS1* patients. Other conditions associated with fatty replacement and pancreatic atrophy include Cushing syndrome, steroid therapy, malnutrition, viral infections, and main pancreatic duct obstruction.[21–23] Genetic syndromes, such as Shwachman-Diamond, Bannayan, Johanson-Blizzard, and cystic fibrosis, are also associated with lipomatous atrophy.[20,24–28] It is noteworthy that the most common etiology of pancreatitis in children is cystic fibrosis, an autosomal recessive disorder caused by *CFTR*. In the vast majority of patients, exocrine pancreatic insufficiency occurs in utero or soon after birth, whereas 1% to 2% of patients harboring minor *CFTR* mutations present with idiopathic chronic pancreatitis in which the pulmonary, intestinal, and cutaneous manifestations of the disease are silent.[29] As *CFTR* mutations result in thick inspissated secretions and mucus plugs within the pancreatic ducts, ductal obstruction has been postulated to be responsible for lipomatous atrophy.[30,31] A similar phenomenon could be envisioned in *PRSS1* patients as they often present with ductal obstruction by intraductal calculi. Further studies focused on the pathophysiology of *PRSS1* chronic pancreatitis are required.

Besides lipomatous atrophy, the identification of only 3 patients with pancreatic neoplastic precursor lesions, PanINs, was surprising. As mentioned previously, *PRSS1* hereditary pancreatitis is associated with a high relative and absolute risk for pancreatic ductal adenocarcinoma. This risk is increased in patients who smoke daily, have diabetes mellitus, and are older.[32] In a comparative study of familial and sporadic pancreatic cancer patients, Shi et al showed that there was an increased prevalence of precursor lesions (PanINs and intraductal papillary mucinous neoplasms) in familial pancreatic cancer patients.[33] Although the authors did not stratify patients on the basis of germline mutations, an increase number of precursor lesions would be expected in *PRSS1* patients. Of the 3 *PRSS1* patients with PanINs, only case 10 showed an extensive number of PanIN-1 and PanIN-2 throughout the pancreas. Moreover, no intraductal papillary mucinous neoplasms were identified in any of the patients.

In addition to *PRSS1* and *CFTR*, mutations in *SPINK1* have also been shown to be associated with hereditary and idiopathic chronic pancreatitis.[34] *SPINK1* is a potent protease inhibitor and a specific inactivation factor of intrapancreatic trypsin activity. Mutated *SPINK1* genes seem to behave as disease modifiers that either lower the threshold of initiating pancreatitis or worsen the severity of pancreatitis caused by other genetic or environmental factors. Similar to *PRSS1*, the role of *SPINK1* in pancreatitis has been evaluated in 2 genetically engineered mouse models. Transgenic expression of rat *SPINK1* in mice, which leads to increased trypsin inhibition, significantly reduced the severity of cholecystokinin analog cerulean-induced pancreatitis.[35] In addition, a knockout of the mouse homolog of human *SPINK1*, murine Spink3, resulted in autophagic degeneration of

acinar cells, impaired regeneration, and death within 2 weeks after birth. But enhanced tryptic activity was detected in pancreatic acini prepared 1 day after birth.[36,37] Although these models support the inhibitory role of *SPINK1* on trypsin activation, the histopathologic findings associated with *SPINK1* in humans remain unknown. Certainly, similar studies as those performed herein with *PRSS1* would greatly facilitate our understanding of *SPINK1* chronic pancreatitis.

In summary, *PRSS1* patients develop a progressive form of pancreatitis characterized by lipomatous atrophy leading to pancreatic insufficiency. Similar observations have been made with *CFTR* patients, and, although both *PRSS1* and *CFTR* affect different pancreatic cell types, they may follow a common pathophysiological mechanism. Interestingly, in 1 patient within this study, both *PRSS1* and *CFTR* mutations were identified. As genetic testing for hereditary pancreatitis becomes more widespread, especially considering the increased lifetime risk for pancreatic cancer in these patients, future studies should provide greater insight into this debilitating disease.

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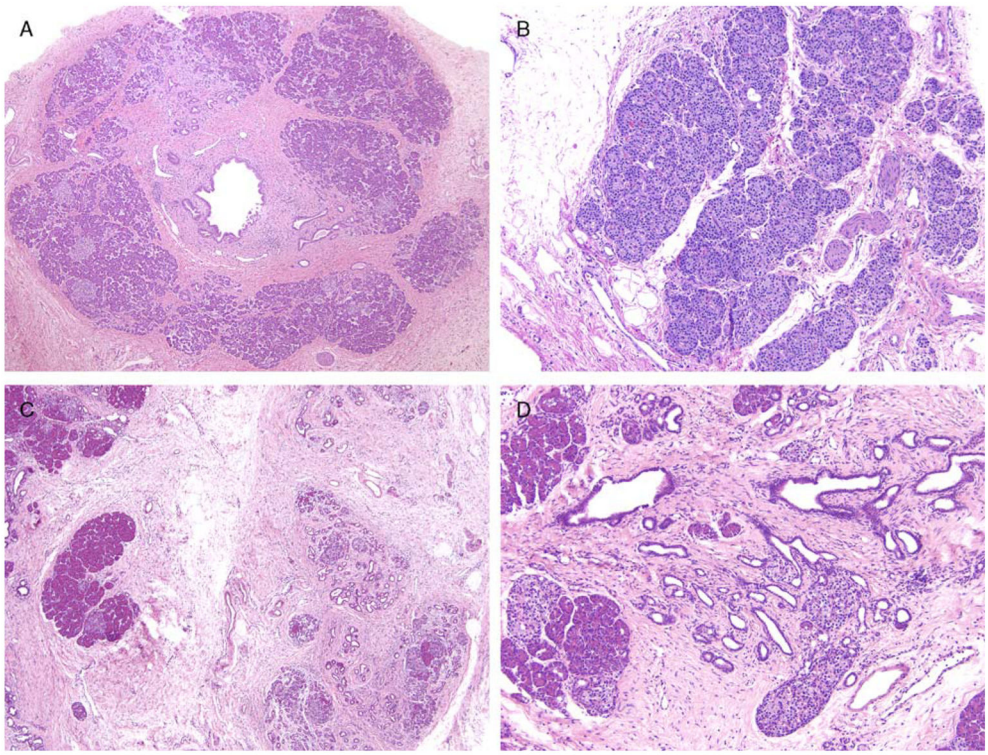

FIGURE 1.

A sequential pattern of histologic changes were identified in patients with germline mutations in *PRSS1*. A, Pancreata from pediatric patients were characterized by patchy parenchymal loss with replacement by loosely packed, perilobular and interlobular fibrosis. In addition, a mild increase in chronic inflammation was identified and primarily localized around dilated pancreatic ducts. B, At the periphery of the pancreas, a greater loss of acinar and ductal tissue was seen with residual islet of Langerhans organized in aggregates and surrounded by mature adipocytes and thin wisps of collagen. C, In young adults, progressive parenchymal collapse was observed with replacement by perilobular and interlobular fibrosis and scattered adipocytes. D, Ductal alterations including ectasia and metaplasia were common findings.

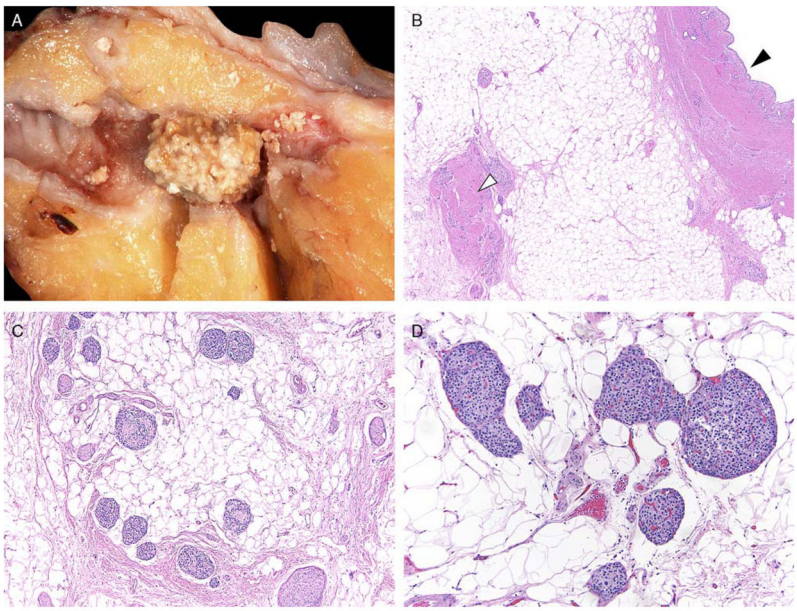

FIGURE 2.

A, In older adults with germline *PRSS1* mutations, the pancreas was grossly soft and shrunken. Marked atrophy with fatty replacement, ductal dilatation, and multiple intraductal calculi were seen in all cases. B, Microscopically, there was extensive parenchymal replacement by adipose tissue. Residual fibrosis was found cuffing the main pancreatic duct (filled arrowhead) and larger interlobular ducts, whereas intralobular and smaller interlobular ducts were reduced and/or scarred (open arrowhead). C and D, Among mature adipose tissue were scattered nerves and islets of Langerhans. C, In 2 cases, amyloid deposition was seen within the islets of Langerhans.

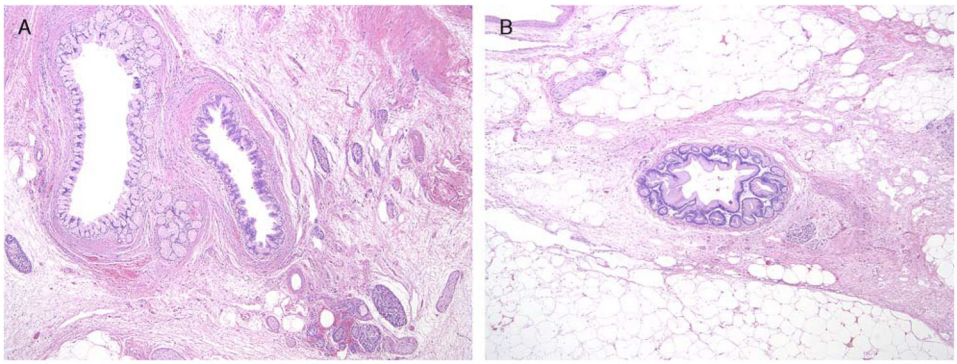

FIGURE 3.

A, PanIN was identified in 3 patients with germline *PRSS1* mutations. B, In these patients, PanINs were often situated in the background of mature adipose tissue.

TABLE 1

Clinical, Genetic, and Radiographic Findings of 10 Patients With PRSS1 Germline Mutations

Case No.	Age (y)	Sex	Clinical Symptoms	Family History	Tobacco Smoking and Alcohol History	Genotype	Radiographic Findings
1	9	M	2 y history of constipation, gas, and worsening, intermittent abdominal pain; chronic nasojejunal tube feeds	Father, paternal aunt, and paternal grandfather with chronic pancreatitis	Mother smokes 1 to 1.5 packs/d	*PRSS1* N29I	Diffuse atrophy of the pancreas with a dilated main pancreatic duct (6 mm) and multiple pseudocysts
2	10	F	6 y history of worsening, intermittent abdominal pain; s/p Puestow procedure with only initial improvement; unable to tolerate oral intake and TPN-dependent	Mother, maternal uncle, maternal grandmother, and maternal great-grandfather with chronic pancreatitis	None	*PRSS1* R122H	Dilatation of pancreatic duct within the pancreatic head
3	10	M	3 y history of intermittent abdominal pain	No family history of chronic pancreatitis or pancreatic cancer	None	*PRSS1* N29I	Diffuse atrophy of the pancreas
4	14	F	5 y history of intermittent abdominal pain	Maternal cousin with chronic pancreatitis	None	*PRSS1* N29I/*CFTR* 5′-UTR 329 A > G	Dilatation of main pancreatic duct (9 mm) within the pancreatic head
5	28	F	22 y history of intermittent epigastric pain; s/p sphincteroplasty without improvement	Mother, brother, and son with chronic pancreatitis	None	*PRSS1* R122H	Diffuse atrophy of the pancreas with calcifications within the pancreatic head
6	30	M	15 y history of worsening epigastric pain with diarrhea; last 3 mo with 40–50 lb weight loss	Sister and brother with chronic pancreatitis (both confirmed *PRSS1* mutations); family history of pancreatic cancer	Smokes 1 pack/d for 10 y	*PRSS1* IVS4-24 C > T	Diffuse atrophy of the pancreas
7	45	F	Intermittent abdominal pain since infancy; 10 y history of diabetes requiring an insulin pump	Mother and daughter with chronic pancreatitis	None	*PRSS1* N29I	Diffuse atrophy of the pancreas with a dilated main pancreatic duct and (7 mm) calcifications within the pancreatic neck
8	53	F	Worsening, intermittent abdominal pain starting at a young age; 14 y history of diabetes requiring insulin injections	Mother, maternal aunt, maternal uncle, sister, and granddaughter with chronic pancreatitis	None	*PRSS1* R122H	Atrophy of the pancreatic body and tail with dilatation of the main pancreatic duct (22 mm) and intraductal calcifications
9	55	F	Intermittent epigastric pain starting at a young age; s/p Puestow procedure with no improvement	Father, brother, and sister with chronic pancreatitis; family history of pancreatic cancer	None	*PRSS1* R122H	Diffuse atrophy with intraductal calcifications
10	66	M	45 y history of intermittent abdominal pain; 12 y history of diabetes requiring insulin injections	2 brothers and maternal cousin with chronic pancreatitis	None	*PRSS1* R122H	2.5 cm heterogenous area in the pancreatic head with diffuse atrophy and dilated main pancreatic duct (6 mm)

F indicates female; M, male, s/p, status post, TPN, total parenteral nutrition.