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Pancreatic Cysts and Intraductal Papillary Mucinous Neoplasm in Autosomal Dominant Polycystic Kidney Disease

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Abstract

Objectives: Pancreatic lesions in autosomal dominant polycystic kidney disease (ADPKD) are primarily cysts. They are increasingly recognized, with isolated reports of intraductal papillary mucinous neoplasia (IPMN).

Methods: Retrospective study to determine prevalence, number, size, and location of pancreatic abnormalities using abdominal magnetic resonance imaging (MRI) of genotyped ADPKD patients (seen February 1998-October 2013) and compared with age- and sex-matched non-ADPKD controls. We evaluated presentation, investigation, and management of all IPMNs among individuals with ADPKD (January 1997-December 2016).

Results: Abdominal MRIs were examined for 271 genotyped ADPKD patients. A pancreatic cyst lesion (PCL) was detected in 52 patients (19%; 95% confidence interval, 15%−23%). Thirty-seven (71%) had a solitary PCL; 15 (28%) had multiple. Pancreatic cyst lesion prevalence did not differ by genotype. Intraductal papillary mucinous neoplasia was detected in 1% of ADPKD cases.

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Potential Competing Interest

All authors have no financial disclosure to declare.

Among 12 IPMN patients (7 branch duct; 5 main duct or mixed type) monitored for about 140 months, 2 with main duct IPMN required Whipple resection, and 1 patient died of complications from small-bowel obstruction after declining surgical intervention.

Conclusions: With MRI, PCLs were detected in 19% and IPMNs in 1% of 271 ADPKD patients with proven mutations, without difference across genotypes. Pancreatic cyst lesions were asymptomatic and remained stable in size.

Keywords

autosomal dominant polycystic kidney disease; intraductal papillary mucinous neoplasm; magnetic resonance imaging; pancreatic cysts

Introduction

Autosomal dominant polycystic kidney disease (ADPKD), the most common inherited renal cystic disease, is characterized by multiple renal cysts and various extrarenal cystic manifestations.[1,2] Cysts have been described in the liver, pancreas, spleen, arachnoid membrane, and seminal vesicles.[3,4]

Pancreatic lesions, mainly pancreatic cyst lesions (PCLs), are common in the general population (prevalence, 2.5%−13.5%). The prevalence of PCLs increases with age,[5–7] but these lesions increasingly are detected in younger people because of the more frequent use of cross-sectional imaging and improvements in image resolution.[8]

Development of invasive adenocarcinoma in PCLs is rare. An incidental cyst seen on magnetic resonance imaging (MRI) has a 10 in 100,000 chance of being a mucinous invasive malignancy and a 17 in 100,000 chance of being ductal cancer.[9,10] Currently, the American Gastroenterological Association recommends MRI monitoring of PCLs <3 cm without solid components or of a dilated pancreatic duct at 1 year, then every 2 years for a total of 5 years if no change occurs in size or characteristics.[9]

Pancreatic cyst lesions are a recognized component of the ADPKD phenotype.[2] Animal models of *PKD1* and *PKD2* genes also have PCLs.[11,12] In a 1995 study, PCL prevalence was 5% to 9% in ADPKD cases with use of ultrasonography.[13] In the Halt Progression of Polycystic Kidney Disease (HALT) trial, in which MRI was limited to the coronal plane, PCLs were identified in 1.8% of 560 patients and solitary in 8 cases (62%).[14] The most comprehensive recent MRI study noted a PCL prevalence of 36.4% in ADPKD cases, compared with 22% in age- and sex-matched controls,[15] with greater prevalence in individuals with *PKD2* mutations. Six had PCLs of >1 cm; the PCLs of 3 patients had a connection to the main pancreatic duct (MPD) or uncinate duct, consistent with intraductal papillary mucinous neoplasm (IPMN).[15] Although the malignancy potential of PCLs is miniscule, lesions connecting to the MPD may represent IPMNs and potentially have an increased cancer risk.[16] Cancer risk in IPMN lesions increases when size exceeds 3 cm, with duct dilatation, or with presence of solid components.[16–19] Investigation and management in patients with asymptomatic ADPKD can be hampered by altered anatomy and complex medical comorbidities.[20–22]

We evaluated prevalence and characteristics of PCLs in patients with genetically confirmed ADPKD who had an abdominal MRI at Mayo Clinic in Rochester, Minnesota, between February 1998 and October 2013 and compared them with matched controls without ADPKD. We determined changes in PCLs over an 8-year follow-up for individuals with repeat imaging. In addition, we evaluated clinical outcomes for patients with ADPKD who had a diagnosis of IPMN irrespective of MRI between January 1997 and December 2016.

MATERIALS AND METHODS

The Mayo Clinic Institutional Review Board (IRB) approved this study in accordance with the Declaration of Helsinki and Health Insurance Portability and Accountability Act. Mayo Clinic provided funding support. All authors had access to study data and have reviewed and approved the final manuscript.

Study Population

All patients consented to the use of their health records for research, and informed consent was waived by Mayo Clinic internal review board. All persons consented for minimal risk health record review studies. Genotyped patients with ADPKD who underwent MRI between 1997 and 2008 were eligible for inclusion and separately consented for genotyping studies. Controls matched for sex and age were selected from an archive of MRIs; they had undergone abdominal MRI between 1998 and 2013 for non–pancreas-related indications and had no cystic kidney disease. Age, sex, race/ethnicity, and estimated glomerular filtration rate (GFR) attained within 6 months of their MRI were obtained for study participants and controls. Genotypes were obtained from the Mayo Clinic Polycystic Kidney Disease (PKD) database. Estimated GFR was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation.[23] For those who underwent multiple MRIs, the first scan was analyzed for this study. For patients with PCLs noted on initial MRI with follow-up imaging available, changes in PCL characteristics were compared with their most recent abdominal MRIs.

Individuals who had a diagnosis of IPMN and ADPKD reported in their health records or imaging report and had been seen at Mayo Clinic in Rochester, Minnesota, between 1997 and 2016 were identified through the clinical data repository databases using the search terms *autosomal dominant polycystic kidney disease [ADPKD]* and *intraductal papillary mucinous neoplasm [IPMN]*), the PKD database, and Mayo Clinic Medical Index (Fig. 1A). ADPKD inclusion criteria were based on having either 1) a proven pathogenic mutation associated with ADPKD, 2) modified Ravine criteria in addition to a positive family history, [1] or 3) presence of >10 bilateral renal cysts and hepatic cysts in the absence of evidence for other inherited renal cystic diseases on imaging.[24] Thirty-six persons were excluded from the study because they did not meet these criteria for ADPKD or had autosomal dominant liver disease or autosomal recessive polycystic kidney disease, simple PCLs not consistent with IPMN, mucinous cystic neoplasm, serous cystadenoma, or pancreatic adenocarcinoma without IPMN. Pancreatic cystic lesions deemed IPMNs were classified as 1) suspected branch duct (BD)-IPMN, PCL >5 mm in diameter that communicated with the MPD, cyst fluid analysis with carcinoembryonic antigen (CEA) >192 ng/mL, or multifocal cysts with at

least 1 that clearly communicated with the MPD,[25] or a combination of these; 2) suspected IPMN or segmental or diffuse dilation of the MPD >5 mm without an obvious cause of pancreatic duct obstruction[25]; and 3) mixed type (MT)-IPMN with cysts meeting criteria for both main duct (MD-IPMN) and BD-IPMN.[25]

Intraductal papillary mucinous neoplasm-related complications were assessed through evaluation of follow-up imaging (Y.K. and N.T.) and chart review (B.A.M., S.T.C., and M.C.H.). Among ADPKD patients with IPMN, follow-up imaging and health records were reviewed to assess for complications related to IPMN. Demographic and clinical variables (eg, age at PCL diagnosis, sex, race/ethnicity) were abstracted from the health records. Imaging studies were reviewed by MRI and abdominal imaging expert radiologists (Y.K. and N.T.). MRI characteristics that make IPMN more likely than PCL are its multifocal or grapelike appearance, its communication with the MPD, and absence of non-IPMN cysts (e.g., serous and mucinous cyst neoplasms, pseudocyst, other neoplasms).

Gadolinium can be used for determination of whether IPMN cysts have malignant characteristics (where GFR permits). Reports of endoscopic and pancreatic imaging were reviewed by 2 experts in the Mayo Pancreas Clinic group (A.S. and S.T.C.). The collected imaging data included, where available, the modality, cyst number, maximum cyst diameter, MPD diameter, cyst location, and observed changes in cyst characteristics. For patients who underwent endoscopic ultrasonography or endoscopic retrograde cholangiopancreatography (ERCP), the findings and CEA levels were noted, and clinical records, imaging, and pathology reports were reviewed by an expert gastroenterologist in pancreatic diseases and IPMN (S.T.C.).

PKD Gene Sequence Analysis

DNA was isolated from blood specimens with use of standard methods, and Sanger sequencing or multiplex ligation-dependent probe amplification of *PKD1* and *PKD2* was performed as previously described.[11,26,27]

Imaging Protocol

All patients underwent MRI on a 1.5- or 3.0-T magnetic resonance machine (Signa; GE Healthcare) with a body-phased-array coil for rapid image acquisition. Axial or coronal, or both, single-shot fast-spin echocardiography images were used to evaluate PCLs. These coronal and axial images were obtained over a single or multiple breath holds.

Image Analysis

Scans were reviewed by 2 radiologists with experience in genitourinary and pancreatic MRI evaluation (Y.K. and N.T.). Pancreatic cystic lesions were defined as round structures identified on MRI as sharply demarcated from the surrounding parenchyma and with homogeneous signal intensity. Location, size, and number of PCL characteristics were recorded as seen with imaging. Maximum PCL dimensions were measured from inner wall to inner wall. A minimum threshold of 2 mm was used.

Statistical Analyses

Quantitative variables are presented as mean (standard deviation [SD]) or median (interquartile range). Differences in demographic variables between patient group and control group were assessed with *t* test and χ^2 test for quantitative and categorical data, respectively. Age- and sex-matched controls for MRI study were selected from a pool of 1,986 sequential abdomen MRI scans. The χ^2 test was used to evaluate differences in cyst prevalence of persons with *PKD1* or *PKD2* mutations or the presence or absence of cysts of patients with ADPKD. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Of 271 genotyped ADPKD cases with abdominal MRIs between February 1998 and October 2013, 52 (19%) had PCLs. Clinical indications for imaging (Fig. 1B) included determination of prognosis, evaluation for hypertension or kidney pain, organomegaly, and surgical renal transplant planning (n = 250). Patients with ADPKD were compared with 271 age- and sex-matched controls (without ADPKD or an underlying pancreatic condition) as their indication for MRI (Table 1). Most control MRIs were conducted with gadolinium (n = 244, 90%) compared with 38% (n =104) of gadolinium-enhanced MRI for individuals with ADPKD, reflecting reduced contrast agent use for individuals with impaired renal function due to risk of nephrogenic systemic fibrosis. Patients with ADPKD were predominantly white (n = 248, 92%); with mean (SD) estimated GFR of 69 (30) mL/min/1.73 m^2. At least 1 PCL was noted in the ADPKD patients compared with 10.2% of controls (n = 28) ($P = 0.03$).

Patients with ADPKD and PCLs were younger (mean [SD] age, 43.0 [12.2] years vs 50.3 [9.1] years; $P < 0.001$) than controls, without differences in average number or frequency of PCLs (Table 1). Minimum PCL diameter was 2 mm (mean [SD], 6.4 [4.1] mm in ADPKD patients vs 6.2 [3.1] mm in controls; $P = 0.20$). In the ADPKD group, 33% (n = 17) of PCLs were in the pancreatic head; 23% (n = 12), the body; 23% (n = 12), the tail; 2% (n = 1), the uncinate; and 19% (n = 10), multiple pancreatic locations.

Among the ADPKD group, 82% (n = 221) had a *PKD1* mutation and 18% (n = 50) had a *PKD2* mutation (Fig. 1B and Table 2). Those with a *PKD1* mutation were younger than patients with a *PKD2* mutation (mean [SD] age, 41 [12] vs 49 [9] years), but the difference was not significant ($P = 0.05$). No difference was observed in the prevalence of PCLs between the *PKD1* and *PKD2* cases (18% [41/221] vs 22% [11/50], respectively; $P = 0.20$). A tendency toward larger PCLs was observed in the *PKD2* group, but no difference was seen in the prevalence of multiple PCLs in either group (Table 2).

Among 52 ADPKD patients with PCLs, 75% (n =39) underwent repeat MRI over 2 to 18 years (mean [SD] follow-up, 6.1 [3.1] years). Pancreatic cystic lesions remained stable in size for 50% (n = 26), decreased for 17% (n = 9), and increased for 7% (n = 4) (Fig. 2 and Supplemental Figure 1).

IPMN in ADPKD

Initially, PCLs that communicate with the MPD were noted in 2 of the 52 genotyped ADPKD cases, suggestive of BD-IPMN (Fig. 1B), with a prevalence of 3.8% for IPMN in

ADPKD patients with PCL and 0.7% within the entire cohort of ADPKD patients. Ten additional cases were identified (Table 3) independent of the patients with ADPKD studied in the MRI cohort. Of these additional cases, 2 were diagnosed elsewhere and referred to Mayo Clinic for additional evaluation of the IPMN (case 9 and 12). Compared with the ADPKD patients who had PCLs, the IPMN patients were older (mean [SD] age, 62 [2.8] vs 43 [12] years; $P < 0.001$). We found BD-IPMN was present in the majority (n = 7), MD-IPMN in 3 patients, and MT-IPMN in 2 patients. Of genotyping available (n = 4), all cases were *PKD1*; ADPKD was confirmed with family history and imaging for 5 and radiologic criteria alone for 3 patients. Seven patients were kidney transplant recipients. Eleven of the 12 IPMN cases were observed for a mean (range) period of 61 (12–124) months, in which time 5 patients were alive without IPMN-related complications, 2 underwent the Whipple pancreatectomy procedure, 3 died of complications unrelated to IPMN, and 1 who had MPD-IPMN died of IPMN-related complications after declining surgical intervention (Fig. 3). No patient with BD-IPMN required surgical intervention or succumbed to IPMN-related disease. Figure 3 and Supplemental Figures 2–9 show computed tomography, MRI, or endoscopic evidence in each case.

DISCUSSION

Nephrologists encounter pancreatic lesions in ADPKD patients, given widespread use of imaging, improved scan resolution, and patient survival.[28] Prevalence of PCLs using MRI was 19%, higher than for non-ADPKD cohort. This is higher than previously reported using ultrasonography but lower than a recent MRI study that also found that PCLs occurred more frequently in *PKD2* cases.[13] Most PCLs were solitary. We found a nonsignificant tendency to greater PCL prevalence and more numerous PCLs in *PKD2* patients, who comprised a smaller proportion of our cohort. Our findings reflect the population prevalence of individuals with ADPKD (~15%). Our cohort was younger and reflective of more *PKD1* cases—*PKD1* manifests earlier than *PKD2*—and with more women than men represented.

Kim et al[15] observed that 3 of 40 ADPKD patients with PCLs (all asymptomatic) had MRI findings suggestive of IPMN, of which 1 underwent endoscopic ultrasonography. Several other reports describe IPMNs in ADPKD.[20,21,29] Intraductal papillary mucinous neoplasias —grossly and radiographically visible epithelial tumors[30]—are classified into 3 types based on imaging or histology (with special sectioning), depending on the caliber of ducts involved: MD-IPMN, BD-IPMN, and a combined type involving both MPDs and BDs (MT-IPMN)[31] The BD-IPMN is more likely to involve the uncinate or pancreatic tail with less likelihood of malignant transformation.[16,17]

In ADPKD, IPMNs may be found during assessment of kidney and liver disease, infection, or transplant. Investigation and management are not easy. We identified 12 IPMN cases, mostly BD-IPMN (noted incidentally), who underwent serial imaging without development of worrisome characteristics. Two were referred for IPMN treatment at our institution. One death was related to MD-IPMN of a patient who declined surgery; only MD- or MT-IPMN cases required intervention.

The presence of IPMN provides a management dilemma for asymptomatic persons because further investigations and therapy can be hampered by the altered anatomy, comorbidities, and the need to avoid contrast imaging because of increased risk of acute renal failure or inability to receive gadolinium.[32,33] Some may be receiving immunosuppression for organ transplant (reflected in our series), adding to management complexity. In a series of 62 ADPKD patients who received donor grafts, 5 (8%) had malignancy, including 1 with pancreatic cancer, and malignancy was the main cause of death and graft failure.[34] In another study, about 30% of IPMN cases had metachronous tumors.[35]

Nevertheless, IPMN can have a favorable prognosis (postoperative 5-year survival, approximately 100% for benign tumors and noninvasive carcinoma and approximately 60% for invasive carcinoma).[35] Differences in cancer progression between MD-IPMN and BD-IPMN range from 57% to 92% and 6% to 46%, respectively. Therefore, correct sub-classification is important.[31] Depending on radiologic and clinical features, surgical or conservative management may be offered.[36,37] Predictive factors of malignancy include mural nodules and MPD dilatation (≥7 mm).[16–18,38] Pancreatoduodenectomy and distal or total pancreatectomy performed in high-volume medical centers carries a mortality rate <5%.[39] Surgical risk is greater for older patients with renal insufficiency and/or transplant recipients.

This study has limitations—single center, possible selection bias for more severe cases, and controls matched for age and sex but not GFR. The role of GFR is unclear regarding PCL development. Given that this group was younger, matching for age, sex, and GFR may have resulted in a nonrepresentative control group for assessment of prevalence of PCL, which typically involves a higher prevalence due to an older age group. Not all IPMN cases underwent genotyping. Intraductal papillary mucinous neoplasias may have been underestimated in small PCLs.

We observed higher PCL prevalence for ADPKD patients than controls and report characteristics of IPMN cases with ADPKD followed approximately 10 years. In the conservatively managed cases, none had IPMN-related complications, and most did not require operative intervention. We highlight the need for multidisciplinary management involving nephrologists, gastroenterologists, surgeons, and radiologists to ensure the best outcome when PCLs are identified in ADPKD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACE	Advanced Cohort Explorer
ADPKD	autosomal dominant polycystic kidney disease
BD	branch duct
BD-IPMN	branch duct intraductal papillary mucinous neoplasm
CEA	carcinoembryonic antigen
ERCP	endoscopic retrograde cholangiopancreatography
GFR	glomerular filtration rate
HALT	Halt Progression of Polycystic Kidney Disease
IPMN	intraductal papillary mucinous neoplasm
IRB	institutional review board
MD-IPMN	main duct intraductal papillary mucinous neoplasm
MPD	main pancreatic duct
MRI	magnetic resonance imaging
MT-IPMN	mixed type intraductal papillary mucinous neoplasm
PCL	pancreatic cyst lesion
PKD	polycystic kidney disease

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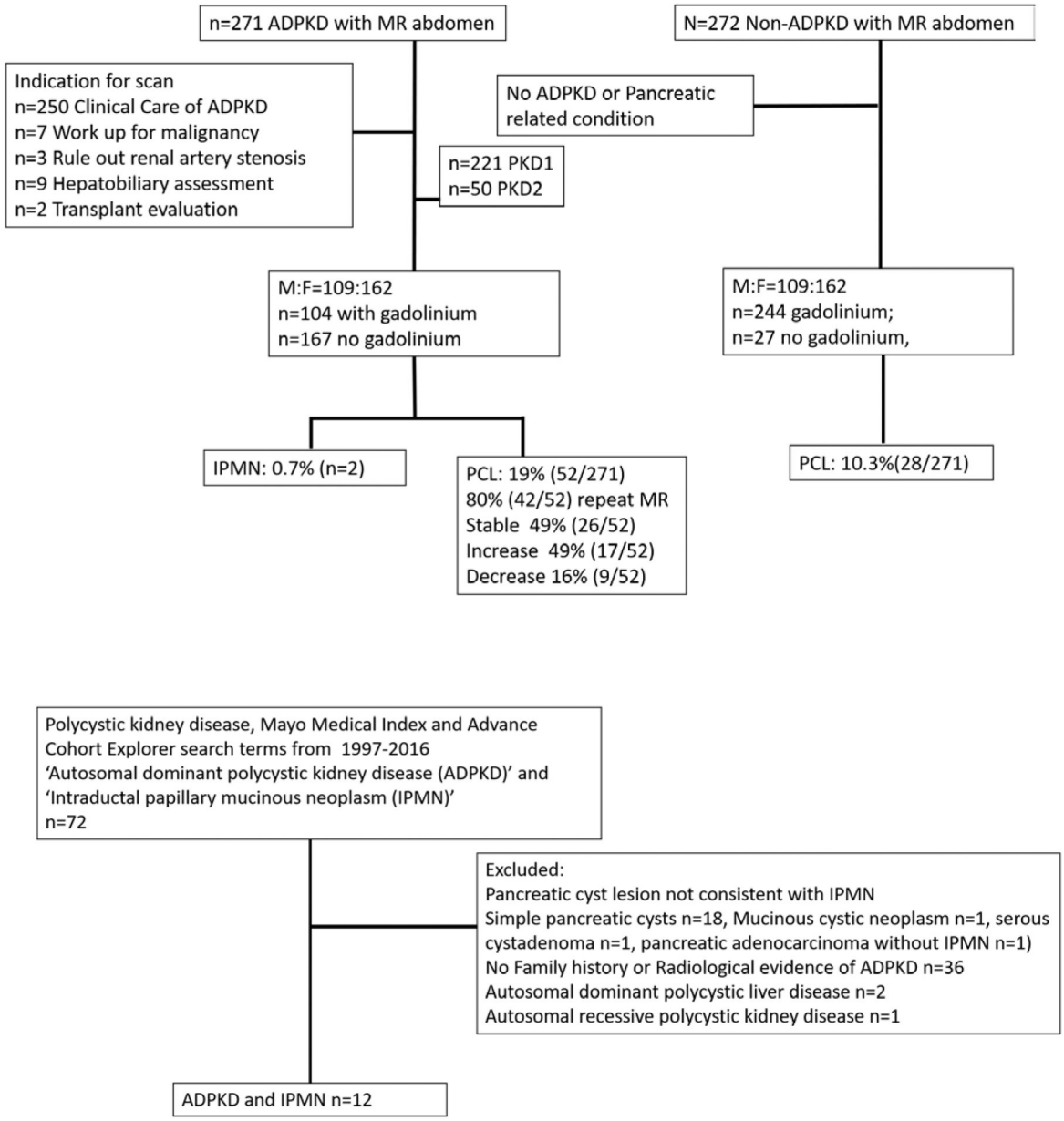

FIGURE 1.

Flowchart of PCLs in the ADPKD Study and the Search Criteria to Identify ADPKD Patients With IPMN. A, The Advanced Cohort Explorer database was used to search for individuals presenting to Mayo Clinic with a diagnosis of PKD and IPMN. Health record review by radiology, gastroenterology, and nephrology services was used to further evaluate and exclude 60 patients as not having PCLs consistent with IPMN or having cystic kidney disease consistent with ADPKD. B, MRI scans of ADPKD patients from Mayo Clinic (n = 271) between February 1998 and October 2013 were compared with age- and sex-matched non-ADPKD individuals (n = 271). ADPKD indicates autosomal dominant polycystic kidney disease; F, female; IPMN, intraductal papillary mucinous neoplasm; M, male; MRI, magnetic resonance imaging; PCL, pancreatic cyst lesion; PKD, polycystic kidney disease.

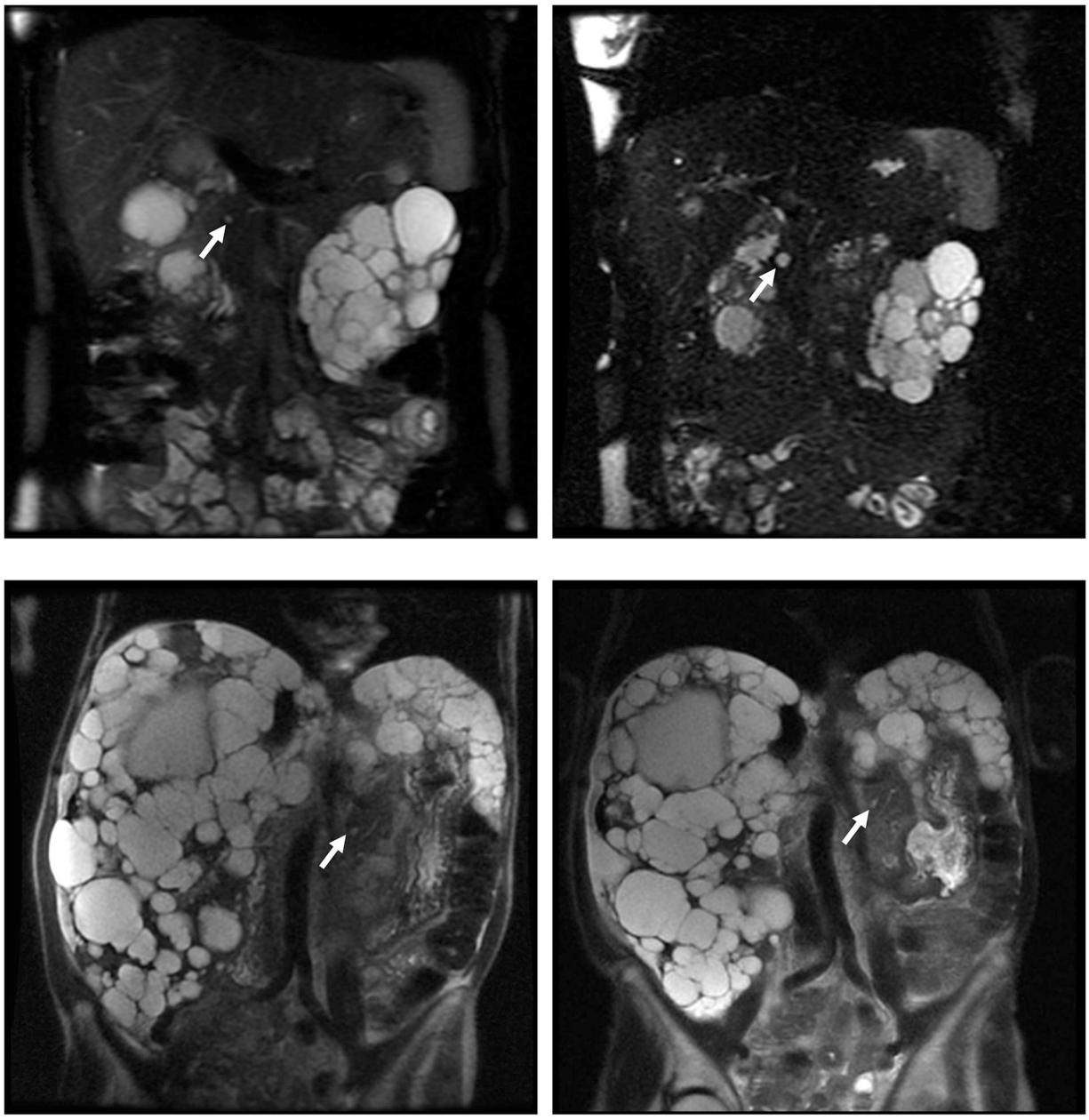

FIGURE 2.

Pancreatic Cyst Lesions (PCLs) From Magnetic Resonance Imaging (MRI) of Patient With *PKD1* and *PKD2* Genes. A, Coronal single-shot fast-spin echocardiography (SSFSE) MRI showing a PCL (arrow) in 28-year-old woman with *PKD1* from 2006. B, Coronal SSFSE MRI showing increased PCL size (arrow) in the same woman with *PKD1* in 2011. C, Coronal SSFSE and coronal half-Fourier acquired single-shot turbo-spin echocardiography (HASTE) MRI showing a PCL (arrow) in the tail of the pancreas of a 65-year-old woman with *PKD2* from 2006. D, Coronal SSFSE and coronal HASTE MRI showing increase in PCL size (arrow) from 2011.

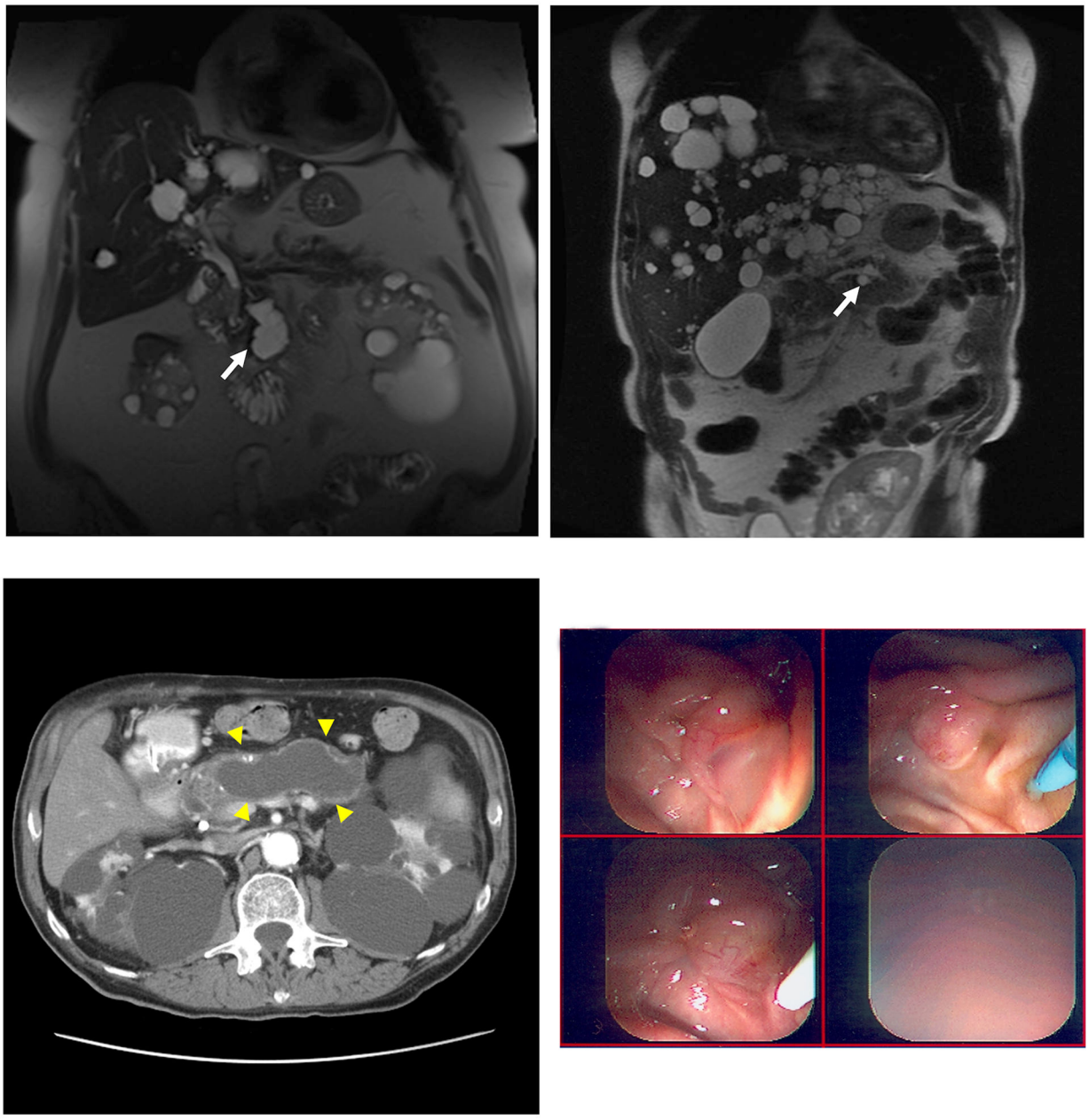

FIGURE 3.

Magnetic Resonance Imaging (MRI) Scans of Branch Duct (BD) Intraductal Papillary Mucinous Neoplasm (IPMN). A, Axial T2-weighted MRI showing a BD-IPMN (arrow) of a 69-year-old woman (case 1) with autosomal dominant polycystic kidney disease (ADPKD). Seven cysts were noted in the head of the pancreas (maximum diameter, 30 mm). The main pancreatic duct (MPD) measured 3 mm. The patient has not had follow-up imaging at this institution to evaluate any increase in size of BD-IPMN. B, Coronal single-shot fast-spin echocardiography (SSFSE) MRI of 58-year-old patient with *PKD1* (case 2) with polycystic liver and bilateral nephrectomies with BD-IPMN based on endoscopic ultrasonography showing clear communication (arrow), seen with 3-mm MPD. The patient had 2 pancreatic

cystic lesions (maximum diameter, 20 mm) that increased in size over 124 months but has had no indication for surgical intervention to date. C, A 72-year-old man (case 3) with ADPKD diagnosed with MPD-IPMN on presentation with abdominal pain. Abdominal computed tomography shows grossly dilated MPD (arrowheads on sagittal section) and polycystic kidneys. D, On endoscopic retrograde cholangiopancreatography, major and minor papillae were identified easily by the profuse thick mucus coming through widely patent orifices from an irregular and dilated pancreatic duct. The patient declined surgical management and succumbed to bowel obstruction secondary to the mucus at 56 months after diagnosis.

TABLE 1.

Comparison of Clinical and Radiologic Characteristics, Including PCL Prevalence, of Patients With ADPKD and Control Patients

Characteristic*	ADPKD Group (n = 271)	Control Group (n = 271)	*P*
Age at first MRI, mean (SD), y	42 (12)	42 (12)	>0.99
Age of PCL patients, mean (SD), y	43 (12)	50 (9)	<0.001
Sex, male, n (%)	109 (40)	109 (40)	>0.99
White race/ethnicity, n (%)	247 (91)	228 (84)	0.02
eGFR with CKD-EPI, mean (SD), mL/min/1.73 m^2	69 (30)	94 (28)	0.001
MRI with gadolinium, n (%)	104 (38)	244 (90)	0.03
Presence of ≥1 PCL, n (%)	52 (19)	28 (10)	0.03
No. PCL, mean (SD)	1.6 (1.1)	1.6 (1.2)	0.90
PCL size, mean (SD), mm	6.4 (4.1)	6.2 (3.1)	0.80
PCL location in pancreas (n = 52), n (%)			
Head	17 (33)	11 (42)	
Body	12 (23)	6 (21)	
Tail	12 (23)	5 (18)	
Uncinate/neck	1 (2)	1 (4)	
Multiple	10 (19)	5 (17)	
No. PCL, n (%)			
0	219 (81)	244 (90)	
1	37 (14)	16 (6)	
2	7 (3)	7 (3)	
3–10	8 (3)	5 (2)	

*Values are presented as number and percentage of patients unless specified otherwise.

ADPKD indicates autosomal dominant polycystic kidney disease; CKD-EPI, chronic kidney disease–epidemiology collaboration; eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging; PCL, pancreatic cyst lesion.

TABLE 2.

Clinical and Radiologic Characteristics of PCLs According to *PKD* Gene Mutation

Characteristic	Total Group (n = 271)	Gene Mutation		P*
		PKD1 (n = 221)	*PKD2* (n = 50)	
PCL, n (%)	52 (19)	41 (19)	11 (22)	0.20
Age, mean (SD), y	43 (12)	41 (12)	49 (9)	0.05
Male sex with PCL, n (%)	22 (43)	18 (44)	3 (27)	0.20
No. PCL, mean (SD)	1.5 (1.2)	1.4 (1.00)	2.1 (1.59)	0.06
Size, mean (SD), mm	6.4 (4.1)	6.5 (4.8)	6.1 (2.6)	0.10
Multiple PCL, n (%)	10 (24)	7 (21)	3 (27)	0.20

*P values represent comparison between *PKD1* and *PKD2* tests (*t* test).

TABLE 3.

Characteristics of Pancreatic IPMN Cases

Case No.	Age at Diagnosis, y	Type of IPMN	Clinical Characteristics	Pancreatic Cyst			MPD Dilatation, mm	EUS/ERCP	CEA, ng/mL	Change in Cysts/ Progression	Current Status	Follow-up, mo	Image
				No.	Size, mm	Location							
1	69*	BD	Incidental finding, asymptomatic	7	30	Head	3	No	NA	NA	No follow-up since initial imaging	NA	Figure 3A
2	58†‡	BD	Incidental finding, asymptomatic Transplant	2	20	Head and tail	3	EUS—clear communication seen with MPD	NA	Increase	Alive—no complications	124	Figure 3B
3	72§	MD	Symptomatic, abdominal pain	NA	NA	NA	>10	ERCP—thick mucus from widely patent MPD	NA	Increase	Deceased—IPMN-related SBO	56	Figure 3C and 3D
4	60†‡	BD	Incidental finding during biliary sepsis, asymptomatic	8	5	Head, body, and tail	3	No	NA	No change	Alive—no complications	51	Supplemental Figure 2
5	72†	BD	Incidental finding, asymptomatic	2	11	Body and tail	3	No	NA	Minimal increase	Alive—no complications	27	Supplemental Figure 3
6	47†	BD	Incidental finding, asymptomatic	1	11	Head	2	No	NA	No change	Alive—no complications	12	Supplemental Figure 4
7	70§	BD	Incidental finding during biliary sepsis Transplant	3	14	Head and body	3	EUS—communi-cation with MPD	315	Decrease	Alive—no complications	33	Supplemental Figure 5
8	61*	BD	Incidental finding, asymptomatic Transplant	1	21	Head	2	EUS—irregular MPD with dilated branch ducts in tail	2,400	Increase	Deceased—unrelated to IPMN	88	Supplemental Figure 6
9	66*	MPD	Pancreatitis Transplant	No image available pre-subtotal pancreatectomy				ERCP—outside hospital	NA	Resected	NA—total pancreatectomy	NA	NA
10	75§	MPD	Incidental finding, asymptomatic	3	23	Head and tail	2	EUS—clear communication with MPD	NA	NA	Deceased—unrelated to IPMN	20	Supplemental Figure 7
11	60*	MT	Abnormal LFTs Transplant	1	40	Head	5	ERCP—dilated side branches with mucus extruding from major and minor papilla	1.9	No change	Deceased—unrelated to IPMN	112	Supplemental Figure 8
12	64*	MT	Transplant	Numerous	28	Head and body	8	EUS—upstream pancreatic duct dilation, smaller cysts in pancreas tail	40	Increase	Alive—proceeded to Whipple procedure at outside hospital; severe dysplasia on histologic evaluation	NA	Supplemental Figure 9

*Cysts and family history.

†*PKD1* mutation identified.

‡Patient in the ADPKD MRI cohort.

§Cysts only as per Pei criteria.

BD indicates branch duct; CEA, carcinoembryonic antigen; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; IPMN, intraductal papillary mucinous neoplasm; LFT, liver function test; MD, main duct; MT, mixed type; NA, not available; SBO, small-bowel obstruction.