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Clinical and Radiographic Gastrointestinal Abnormalities in McCune-Albright Syndrome

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Abstract

Context

McCune-Albright syndrome (MAS) is a rare disorder characterized by fibrous dysplasia of bone, café-au-lait macules, and hyperfunctioning endocrinopathies. It arises from somatic gain-of-function mutations in *GNAS*, which encodes the cAMP-regulating protein Gα_s. Somatic *GNAS* mutations have been reported in intraductal papillary mucinous neoplasms (IPMNs) and various gastrointestinal (GI) tumors. The clinical spectrum and prevalence of MAS-associated GI disease is not well established.

Objective

Define the spectrum and prevalence of MAS-associated GI pathology in a large cohort of patients with MAS.

Design

Cross-sectional study.

Setting

National Institutes of Health Clinical Center and The Johns Hopkins Hospital.

Methods

Fifty-four consecutive subjects with MAS (28 males; age range, 7 to 67 years) were screened with magnetic resonance cholangiopancreatography (MRCP).

Results

Thirty of 54 subjects (56%) had radiographic GI abnormalities. Twenty-five (46%) of the screened subjects had IPMNs (mean age of 35.1 years). Fourteen of the 25 had IPMNs alone, and 11 had IPMNs and abnormal hepatobiliary imaging. The 30 patients with MAS-associated GI pathology had a higher prevalence of acute pancreatitis, diabetes mellitus, and skeletal disease burden of fibrous dysplasia than patients without GI disease.

Conclusions

A broad spectrum of GI pathology is associated with MAS. IPMNs are common and occur at a younger age than in the general population. Patients with MAS should be considered for screening with a focused GI history and baseline MRCP. Further determination of the natural history and malignant potential of IPMNs in MAS is needed.

McCune-Albright syndrome (MAS) is a rare disorder characterized by fibrous dysplasia of bone, hyperfunctioning endocrinopathies, and café-au-lait macules resulting from a somatic gain-of-function mutation in *GNAS*, which encodes the cAMP-regulating protein $G\alpha_s$. These mutations occur early in embryonic development, predominantly at codon R201, with arginine substituted by cysteine (R201C) or histidine (R201H), leading to ligand-independent constitutive activation of $G\alpha_s$ and dysregulated cAMP signaling (1). Gain-of-function *GNAS* mutations were previously described in pituitary, thyroid, appendiceal, and gonadal tumors and breast cancer (2–6). In recent years, the same activating mutations have been identified as somatic driver mutations in sporadic intraductal papillary mucinous neoplasms (IPMNs) and various gastrointestinal (GI) lesions, suggesting a potential role in pancreatic and GI tumorigenesis. Approximately 60% to 80% of sporadic IPMNs have activating *GNAS* mutations (7).

IPMNs are pancreatic mucin-producing cysts and are the most common type of neoplastic pancreatic cyst. There are three types of IPMNs: main-duct IPMN; branch-duct IPMN; and mixed-type IPMN, which involves both the main and branch ducts. IPMNs are incidentally noted in between 2% and 13% of MRI scans of the abdomen and are diagnosed with increasing frequency because of the widespread use of imaging modalities (8, 9). Gain-of-function mutations of *GNAS* have been detected in pancreatic cyst fluid samples, primary IPMN tissue, and duodenal collection of secretin-stimulated pancreatic juice (7, 10–17). IPMNs are a precursor lesion of invasive adenocarcinoma (18). In addition to their detection in IPMNs, the same *GNAS*-activating mutations have been increasingly reported in various other GI pathologies, including GI tumors, liver tumors, intraductal papillary neoplasms of the bile duct, and pyloric gland adenomas of the upper GI tract (19–24).

The precise timing of the development of *GNAS* mutations and the pathway(s) for IPMN development and tumorigenesis have not been established. In addition to *GNAS* mutations, activating *KRAS* and inactivating *RNF43*, *TP53*, *p16*/*CDKN2A*, and *SMAD4* gene mutations are frequently reported in IPMNs; however, the timing and order of these mutations have not been fully elucidated (17, 25–29).

GI abnormalities have been reported in MAS, including IPMNs, hepatic and biliary lesions, and gastric and duodenal polyps; however, the clinical spectrum and prevalence of MAS-associated GI disease are not well established (30, 31). This study investigated the spectrum of GI manifestations in the largest cohort of patients with MAS studied to date to define the prevalence of GI pathology in MAS and to outline optimal care for these patients.

Subjects and Methods

Study subjects

The discovery of *GNAS* mutations as driver mutations in IPMNs (7) led us to give more significance to previous reports of sporadic, idiopathic pancreatitis by three of our patients in the cohort. At that time, we began screening patients with a history of pancreatitis using magnetic resonance cholangiopancreatography (MRCP); having found major pancreatic pathology in these patients, we began performing screening MRCPs on enrolled patients in a long-standing MAS natural history study at the National Institutes of Health (NIH). Thus, 54 consecutive subjects (26 females; age range, 7 to 67 years) at the NIH were evaluated between 2013 and 2016. This study was approved by the National Institute of Dental and Craniofacial Research Institutional Review Board. Informed written consent and/or assent was obtained from all participants, including parents and children. Studies were conducted at the NIH Clinical Center in Bethesda, Maryland, and The Johns Hopkins Hospital in Baltimore, Maryland. In the majority of cases, the diagnosis of MAS was made on a clinical basis according to previously published guidelines, including the presence of fibrous dysplasia, café-au-lait macules, and/or hyperfunctioning endocrinopathies (32). In cases with an unclear clinical diagnosis (three of 54 subjects), genetic testing for *GNAS* mutation was performed on the affected tissue.

The remaining 136 subjects who were also enrolled in the long-standing MAS natural history study at the NIH and who did not undergo any clinical GI screening or baseline MRCP served as the unscreened control group. Clinical features of MAS have been well documented in these subjects.

Study design

Subjects underwent baseline screening at the NIH Clinical Center, which encompassed a history and physical examination, including a detailed GI history, and radiographic evaluation with contrast-enhanced abdominal MRI and MRCP. Pancreatitis was diagnosed per routine criteria (33). All MRI/MRCP images were reviewed by a single radiologist (A.Z.), and any radiographic abnormalities in the liver, pancreas, bile ducts, or gallbladder were documented. High-risk or worrisome features were documented on the basis of the 2012 International Consensus Criteria (34) (Table 1).

Thirty subjects in whom radiographic pancreatic abnormalities were identified were first categorized as having either high-risk or worrisome features (34). Ten subjects identified as having worrisome or high-risk features were then referred for further evaluation to the Pancreatic Cyst Clinic or Pancreatitis Clinic at The Johns Hopkins Hospital. Seven of these 10 subjects completed the testing. Patients with a history of acute pancreatitis or concerning features on MRI/MRCP underwent evaluation with endoscopic ultrasonography (EUS) and endoscopic retrograde cholangiopancreatography as indicated.

Statistical analysis

Statistical analyses were performed with GraphPad Prism 7 for Windows, version 7.01, using paired *t* tests, Mann-Whitney test, and Fisher exact test. Significance was established at $P < 0.05$. Data are presented as mean ± SD.

Results

Fifty-four consecutive subjects out of 190 total subjects in the cohort (28%) were screened with MRCP. There were no differences in age or sex between any of the groups (screened vs unscreened or within the screened cohort between those with and without GI pathology). Regarding features of MAS, the screened group had a higher prevalence of café-au-lait macules (88% vs 71%; $P = 0.01$) and GH excess (33% vs 19%; $P = 0.004$) than the unscreened group (Table 2). Within the screened group, those with GI pathology had more fibrous dysplasia than those without as assessed by the skeletal burden score, a validated measure of disease burden (35) (38.6% vs 23.0%; $P = 0.01$), but there were no differences in other features of MAS (Table 2).

Thirty of the 54 subjects screened (56%) had radiographic GI abnormalities on MRI of the abdomen (Fig. 1; Table 3). Twenty-five subjects (46%) had IPMNs, 14 of whom had IPMNs alone, whereas 11 had IPMNs and a range of hepatobiliary findings including hepatic adenomas (2), hemangiomas (2), hamartomas (2), focal nodular hyperplasia (1), biliary cysts (4), and fatty liver (2), all diagnosed radiographically on MRI. Five subjects (17%) had hepatobiliary abnormalities alone, consisting of hepatic adenomas (2), fatty liver (2), and biliary cysts (1). Three of the four subjects who had fatty liver had a

body mass index (BMI) in the obesity range (patients 7, 11, and 12 in Table 3), and patient 8 had a BMI in the overweight category. The mean age of the patients with an IPMN was 35.1 years (range, 18 to 67 years). In the screened cohort, a total of 10 subjects had either worrisome or high-risk features (Table 3; age and sex in boldface). Eight subjects had IPMNs with worrisome features. Seven had main-duct dilation between 5 and 9 mm, six had acute/acute recurrent pancreatitis, and two had pancreatic cysts >3 cm (Table 3). Two subjects (Table 3; subjects 23 and 30) had high-risk stigmata with main-duct dilation >10 mm. Subject 23 also had acute recurrent pancreatitis.

Sixteen subjects had branch-duct IPMNs, and nine had mixed-type IPMNs (Table 3). In subjects with a mixed-duct IPMN (defined as a main duct of 5 mm or larger), the main pancreatic duct diameter ranged from 5 to 13 mm (mean, 7.9 mm). Five subjects had segmental dilation of the main pancreatic duct, and four had diffuse involvement of the main pancreatic duct. Representative radiographic findings of GI pathology can be seen in Figs. 2 and 3, including IPMNs and biliary cysts (Fig. 2A) and hepatic lesions (Fig. 3). The screened cohort was more likely to have acute pancreatitis, gastroesophageal reflux disease, and diabetes mellitus than was the unscreened cohort ($P < 0.05$) (Table 2).

Seven subjects with identified radiographic pancreatic abnormalities (highlighted in Table 3) underwent additional GI testing. Descriptions of the gastric lesions and their histopathology have been reported in detail (36). All were found to have polyps of the upper GI tract on endoscopy; representative images are shown in Fig. 4. Surgery was indicated in two subjects. The first was a 27-year-old man (Table 3; patient 2) with idiopathic acute recurrent pancreatitis who had had five episodes of pancreatitis during the prior 8 years, for which he had no risk factors other than his IPMNs. On MRCP, he had a mixed-type IPMN, with the main pancreatic duct measuring 7 mm. Multiple pancreatic cysts were located in the head, body, and tail of the pancreas, with the largest cyst having a diameter of 34 mm. A pancreaticoduodenectomy was performed on the basis of his main pancreatic duct involvement and acute recurrent pancreatitis, which was thought to be secondary to his IPMNs. Surgical pathology confirmed a mixed-type IPMN with high-grade dysplasia. The second was a 55-year-old man (Table 3; patient 23) with a history of idiopathic acute recurrent pancreatitis. MRCP revealed a mixed-type IPMN with the main pancreatic duct measuring 13 mm and multiple pancreatic cysts, the largest of which measured 22 mm (Fig. 2A). In addition, a 5.5-cm polyp was identified at the gastroesophageal junction. Surgical pathology of the pancreas confirmed the presence of a mixed-type IPMN with low-grade dysplasia, whereas the gastric polyp was consistent with a gastric adenoma with high-grade dysplasia (36).

Discussion

In this cross-sectional study of the largest cohort of patients with MAS studied to date, we describe a spectrum of hepatobiliary and pancreatic pathology, including IPMNs, hepatic adenomas, and biliary cysts. In the general population, IPMNs typically occur at a mean age of 63 years (37, 38). IPMNs in MAS were found at an earlier age (mean age, 35.1 years). The finding of more fibrous dysplasia in the group with GI pathology has at least two possible explanations. The first is possibly the fact that the group with GI abnormalities was older, although the difference in ages was not statistically significant. We also hypothesize that GI involvement may be the reflection of the mutation arising earlier in development, suggesting that an earlier mutational event could result in more fibrous dysplasia and more tissues being involved, including the GI tract. The early presentation in MAS and the fact that the group with GI pathology was not older than the group without suggest that pancreatic disease may be present from a very early age in MAS. This is consistent with the hypothesis that in MAS the $G\alpha_s$ mutation arises early in development, before gastrulation. As such, MAS-associated pancreatic disease, especially IPMNs, represents an excellent model for studying the natural history and pathophysiology of $G\alpha_s$/IPMN-related GI disease.

The majority of the subjects in this screened cohort, who were found to have IPMNs, were asymptomatic. Those subjects with a history of acute or acute recurrent pancreatitis did not have any of the common risk factors associated with pancreatitis and had no history of alcohol excess, smoking, hypertriglyceridemia, or choledocholithiasis. Pancreatitis has not been reported as a common feature of MAS. In this large MAS cohort, a total of eight patients out of 190 had a clinical history of pancreatitis. Among these eight patients, six were screened with an MRCP, and all six had IPMNs. In three of the subjects (patients 2, 9, and 23 in Table 3), acute pancreatitis was thought to be due to their mixed-type IPMNs. A comprehensive

description of the histologic findings and tissue mutation testing results from seven subjects in the cohort with IPMNs who underwent EUS was previously reported (36). In these subjects, hotspot *GNAS* mutations (R201C or R201H) were detected in the upper GI polyps, in the IPMN tissue of the two patients who underwent pancreatic surgery, and in the adenomatous gastroesophageal junction polyp that was resected (36). In addition, hotspot mutations in *KRAS* (Q61H) and *PIK3CA* (Q546R) were detected in pancreatic cyst fluid of the 55-year-old patient (Table 3; patient 23), who underwent a distal pancreatectomy (36). A *GNAS* mutation (R201C) and an inactivating mutation in *CDKN2A* (V115fs) were detected in the cyst fluid of a 50-year-old patient with MAS (Table 3; patient 30) (36).

GI polyps were previously reported in patients who had MAS, and activating *GNAS* mutations were identified in these GI polyps (31, 36). Results of this study confirm these findings. The most important relationship between IPMNs and polyps of the upper GI tract is the detection of the same activating *GNAS* mutation in both. We hypothesize that these manifestations are direct effects of mosaic $G\alpha_s$ involvement in the upper GI and pancreatic tissues, respectively. We suspect that diffuse involvement of the GI tract, which includes both luminal and pancreatic involvement, reflects the possibility that the mutation arose in an early GI progenitor cell; this is similar to what is observed in the skeleton, wherein multiple skeletal compartments can be involved (craniofacial, axial, and appendicular).

The pathway of progression from an IPMN to invasive adenocarcinoma has not been defined yet. In a recent transgenic mouse model that mimicked human IPMNs, $GNAS^{R201H}$ and $Kras^{G12D}$ were shown to cooperatively promote murine pancreatic tumorigenesis (39). Identification of distinct genetic profiles of IPMNs can help to elucidate potential mechanisms of pancreatic tumorigenesis. *GNAS* is an early driver mutation in IPMN formation; however, its exact role in tumorigenesis remains unknown (7, 10, 15, 16). Additional genes potentially contribute to pancreatic disease progression, including mutations in *KRAS*, *TP53*, *p16*/*CDKN2A*, and *RNF43*; these genes are commonly associated with pancreatic neoplasia and were previously identified in sporadic IPMNs (10, 40). In addition to serving as diagnostic markers for IPMNs, *GNAS* and *KRAS* are postulated to have independent roles in tumorigenesis (10, 41). The timeline of mutation accrual and the potential role of additional mutations on pancreatic tumorigenesis remain unknown. MAS can be a potential model to study pancreatic tumorigenesis because the onset of the *GNAS* mutation *in utero* is precisely defined, which can provide a model to study the progression of IPMNs over time. Further studies on animal models and through screening and surveillance of patients with MAS can provide useful insights into potential pathways of progression from an IPMN to pancreatic cancer.

As described previously in the literature, the presence of hepatic lesions, including adenomas, was confirmed in this MAS cohort as well. It is important to note that hemangiomas, hepatic cysts, and focal nodular hyperplasia are commonly seen in normal individuals and may not be indicative of clinically significant, actual GI pathology in MAS (42). Activating mutations of $G\alpha_s$ have been reported in sporadic benign and malignant liver tumors, acting through cAMP and JAK/STAT pathways (16). Hepatocellular adenomas are rare benign tumors with hepatocellular differentiation, frequently associated with oral contraceptive use. They are linked to mutations in the *HNF1A* gene, *CTNNB1* gene, and several genes that promote the constitutive activation of the STAT3 pathway, including IL-6 signal transducer (*IL6ST*), Fyn-related kinase (*FRK*), *STAT3*, Janus kinase 1 (*JAK1*), and *GNAS* complex locus (43). Hepatic tumors with activating mutations in *GNAS* demonstrate an inflammatory type, as would be expected in STAT3 activation (16). Thus, the association of MAS and hepatocellular adenoma, both rare diseases, could potentially be explained by STAT3 activation induced by *GNAS* activation (16). It is possible that a similar cross-talk between *GNAS* activation and a distinct signaling pathway plays a role in IPMN development and pancreatic tumorigenesis.

An important goal in defining the spectrum of GI pathology in MAS is to define optimal screening and clinical management. IPMNs are one of three precursors to pancreatic adenocarcinoma, which has a very poor survival rate, with only 8% of patients alive at 5 years (18, 44). Despite the presence of a *GNAS* mutation since *in utero*, not all patients with MAS develop IPMNs. In this MAS cohort, 46% developed IPMNs, a much higher number than anticipated. Pancreatic adenocarcinoma is an extremely uncommon feature in MAS, with only one case reported to date (45). A retrospective review in a cohort of 272 patients who underwent surgery for IPMNs demonstrated that one patient (0.4%), a 62-year-old man who had been operated on for a large invasive colloid adenocarcinoma, had polyostotic fibrous dysplasia and café-au-lait macules, consistent with a clinical diagnosis of MAS (45). The low prevalence of pancreatic

adenocarcinoma in MAS is reassuring, yet makes it difficult to determine how best to follow up patients with MAS and whether the same criteria used in sporadic IPMNs to determine the need for surgical resection should be applied to MAS.

When this collaboration started, there were no reports of pancreatic adenocarcinoma in MAS. Ten of the 54 patients screened were found to have high-risk or worrisome features, and seven had completed a detailed GI evaluation. The options of surveillance vs surgical resection were discussed in detail with these seven patients. Two patients opted for surgical resection. The indication for surgical resection was the presence of acute recurrent pancreatitis in the 27-year-old male (Table 3; patient 23), who was found to have a mixed-type IPMN with high-grade dysplasia. The second patient was a 55-year-old male (Table 3; patient 30) with history of acute recurrent pancreatitis who had a mixed-type IPMN that was confirmed on surgical pathology as a mixed-type IPMN with low-grade dysplasia. The presence of high-grade dysplasia in the younger patient with MAS but not in the older patient with MAS highlights the difficulties in caring for these patients and the need for better markers to identify those at highest risk for progression to high-grade dysplasia or invasive adenocarcinoma. There does not appear to be a clear correlation between age and degree of dysplasia because we had only two subjects who underwent surgery with pathology results. However, the finding of high-grade dysplasia in the 27-year-old patient suggests that the prior hypothesis that MAS patients with IPMNs have minimal or no risk of progression may be incorrect.

In any screening program, the goal should be to minimize harm while maximizing benefit to the patient (46). Screening asymptomatic patients with MAS for GI lesions has potential benefits, such as early detection and removal of lesions with high-grade dysplasia in a young patient in his or her 20s, before development of an invasive adenocarcinoma. It also has potential risks, as we would discover findings that may not have clinical significance but could result in unnecessary surgery as well as costs associated with both screening and interventions. Given the prevalence of IPMNs in patients with MAS, though reflecting some degree of ascertainment bias in this cohort, evaluation with MRI/MRCP for patients with MAS and a history of acute pancreatitis may be considered. Those with evidence of IPMNs should undergo surveillance, with patients having symptoms and/or high-risk or worrisome features reviewed by a multidisciplinary pancreas group. Given the finding of a gastric adenoma with high-grade dysplasia, esophagogastroduodenoscopy should be considered in patients with MAS undergoing EUS. We propose that patients with MAS should be clinically evaluated, with careful attention to reports of GI symptoms that may prompt consideration of imaging and further detailed GI evaluation.

Diabetes mellitus is not an established feature of MAS and has been described in only two case reports (47, 48). In this screened MAS cohort who also had IPMNs, we identified seven patients with diabetes of unclear etiology, raising the possibility of a relationship between pancreatic cysts and diabetes in these patients. These seven patients did not have a family history of diabetes. Only one patient, a 29-year-old female, had a normal BMI. Other patients were in the overweight category, which is a risk factor for type 2 diabetes. The etiology and pathogenesis of MAS-associated diabetes warrant further investigation. A combination of insulin deficiency secondary to IPMNs and insulin resistance may contribute to the development of diabetes. Examples to support such a hypothesis are seen in various forms of pancreatogenic diabetes, which demonstrate differing mechanisms of hyperglycemia, but in which both inadequate pancreatic β-cell function and insulin resistance contribute differentially to hyperglycemia (49). In-depth study of patients with diabetes is needed to understand the pathophysiology of this intriguing finding in MAS. Further studies are required to better understand the natural history and spectrum of the GI phenotype in MAS and to determine the optimal treatment of these patients. Specifically, further studies are required to determine the true risk of progression to high-grade dysplasia or invasive adenocarcinoma in patients with MAS and IPMNs and the indications for surgical resection in this cohort.

In conclusion, we describe clinical and radiographic GI abnormalities in the largest MAS cohort screened to date. The results of this study indicate that GI manifestations in MAS are common and that patients with MAS may benefit from evaluation for GI pathology. The optimal care for GI findings in MAS remains to be defined; however, at a minimum, a thorough GI history at every visit and consideration of imaging with abdominal MRI/MRCP are warranted.

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Glossary

Abbreviations:

BMI	body mass index
EUS	endoscopic ultrasonography
IPMN	intraductal papillary mucinous neoplasm
GI	gastrointestinal
MAS	McCune-Albright syndrome
MRCP	magnetic resonance cholangiopancreatography
NIH	National Institutes of Health

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Figures and Tables

Table 1.

Criteria for Worrisome Features and High-Risk Stigmata of the IPMNs [34]

	Worrisome Features	High-Risk Stigmata
Clinical	Pancreatitis	Obstructive jaundice secondary to an IPMN
Imaging	Cyst ≥3 cm Thickened/enhancing cyst walls Main duct size 5–9 mm in diameter Nonenhancing mural nodule Abrupt change in caliber of pancreatic duct with pancreatic atrophy	Enhancing solid component within the cyst Main pancreatic duct ≥10 mm in diameter

Table 2.

Clinical Characteristics of Screened and Unscreened MAS Cohorts

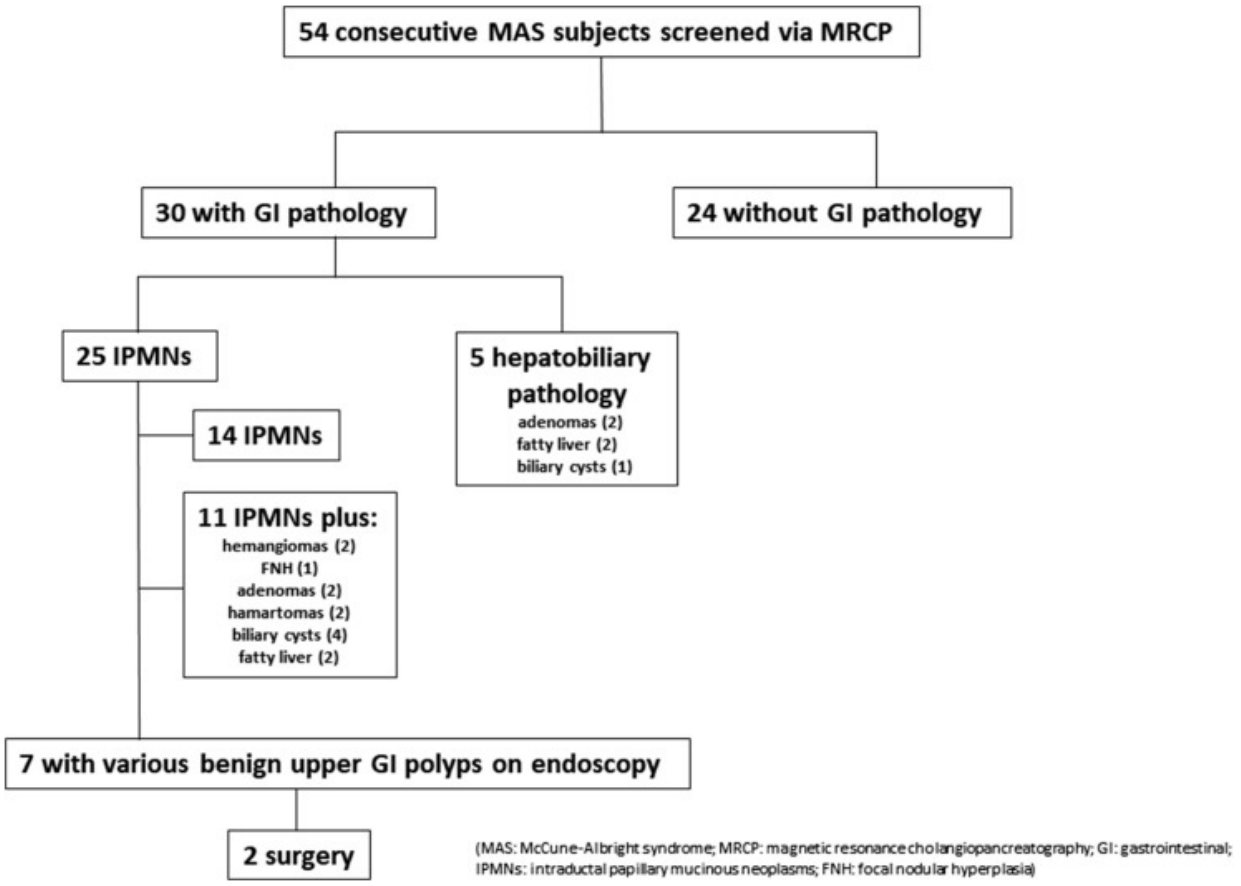
	Screened (n = 54)			Unscreened (n = 136)	
	GI Pathology (n = 30; 56%)	No GI Pathology (n = 24; 44%)	*P* [a]		*P* [b]
Female	17 (57%)	8 (33%)	NS	82 (60%)	NS
Age range, mean ± SD, y	13–67, 36.5 ± 16.2	7–31, 18.7 ± 5.8	NS	1–84, 25.1 ± 11.3	NS
Features of MAS					
FD	30 (100%)	24 (100%)	NS	132 (97%)	NS
Café-au-lait macules	27 (90%)	21 (88%)	NS	96 (71%)	0.01
Precocious puberty	18 (60%)	8 (33%)	NS	69 (51%)	NS
Hyperthyroidism	12 (40%)	4 (17%)	NS	38 (28%)	NS
GH excess	8 (27%)	10 (42%)	NS	19 (14%)	0.004
Hypophosphatemia	9 (30%)	3 (13%)	NS	32 (24%)	NS
Neonatal Cushing	2 (7%)	0	NS	8 (6%)	NS
Skeletal burden score, mean ± SD	38.56 ± 21.76	22.98 ± 18.7	0.01	26.12 ± 20.87	NS
History of pancreatitis	6 (20%)	0	0.02	2 (1%)	0.01
History of GERD/gastritis	6 (20%)	0	0.02	3 (2%)	0.02
History of diabetes mellitus	6 (20%)	0	0.02	3 (2%)	0.02

Data are presented as number of subjects (prevalence) unless otherwise indicated.

Abbreviations: FD, fibrous dysplasia; GERD, gastroesophageal reflux disease; NS, not significant; n, number of subjects; % refers to prevalence.

[a]Refers to differences between the screened group with and without GI pathology (Fisher exact test).
[b]Refers to differences between the screened group and unscreened group (Fisher exact test).

Figure 1.



Summary flow diagram describing the radiographic findings and clinical management of patients with MAS-associated pancreatic lesions. MRCP findings in 54 consecutively screened patients with MAS are shown. Thirty subjects were identified as having radiographic GI pathology. A total of 25 subjects had IPMNs; 14 had IPMNs only, and 11 had IPMNs and additional findings, most commonly benign liver lesions. Five of the 30 subjects had various GI abnormalities without IPMNs. Within the cohort who screened positive for GI pathology, seven subjects underwent detailed evaluation including esophagogastroduodenoscopy, EUS, and/or pancreatic cyst fluid analysis. All seven subjects were found to have benign upper GI polyps. Two subjects underwent pancreatic surgery.

Table 3.

Detailed Radiographic and Endoscopic Findings in the Screened MAS Cohort

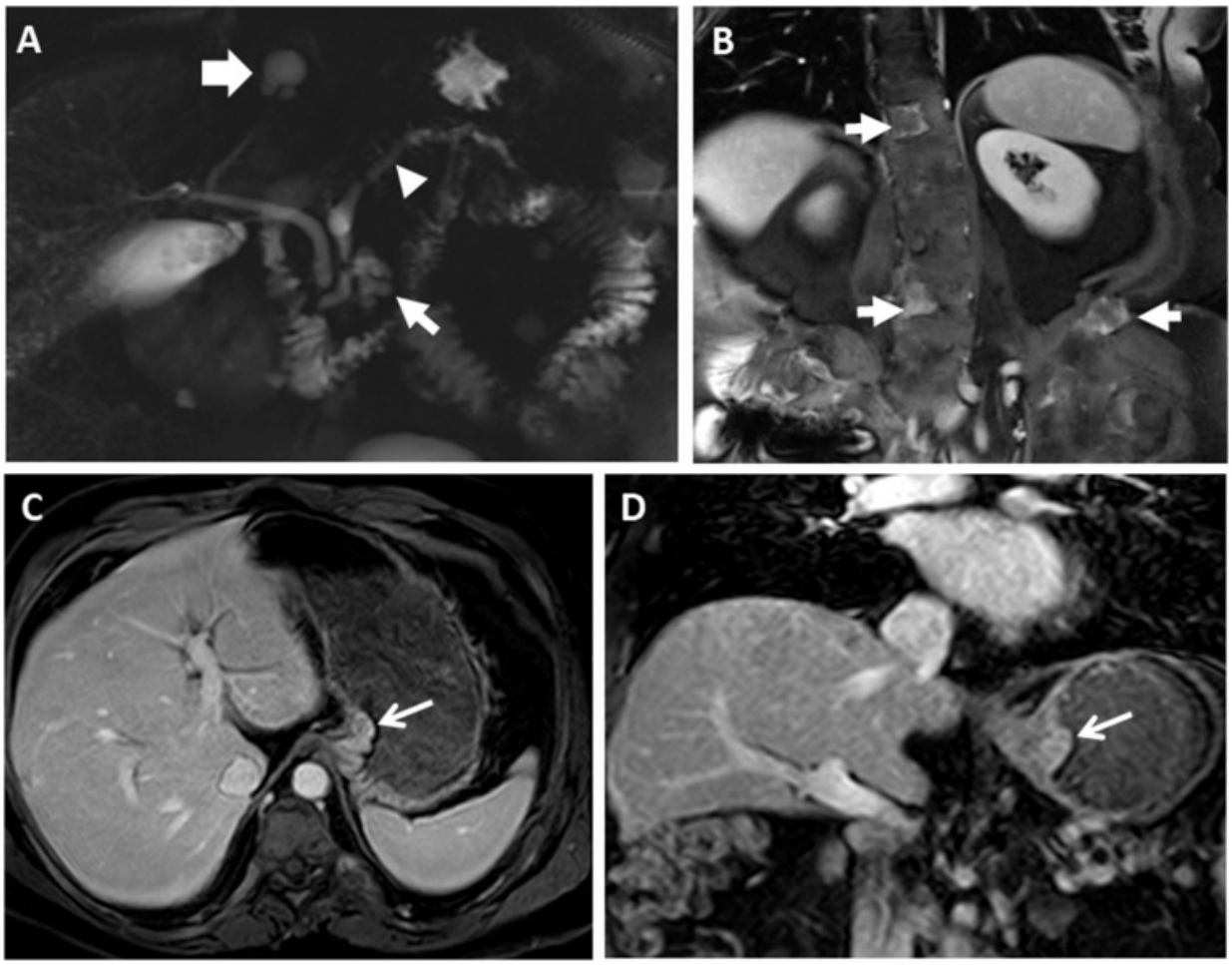
Patient	Age (y)	Sex	Type of IPMN	No. of Cysts	Location of Cysts	Largest Cyst Size (mm)	Main Duct Dilation (mm)	Liver Findings	GI Symptoms	GI Lesions: *GNAS* testi 35
1	**22**	**F**	Branch duct	>10	H,B,T	10		15.1- × 11.7-mm adenoma		Gastric hype polyps: Proximal stc Gastric heterotopia/r Duodenal bu (R201C) Du Ampulla
2	**27**	**M**	Mixed	>10	H,B,T	34	7 (S)		Acute recurrent pancreatitis	Gastric heterotopia/r Duodenum (
3	30	F	None					4.8-cm adenoma		
4	47	F	Branch duct	>10	H,B,T	5		Hamartomas		
5	15	M	None					5.2-cm adenoma		
6	53	F	Branch duct	5	H,B	3				
7	**59**	**M**	Mixed	>10	H,B,T	13	8 (D)	Fatty liver Hamartomas Small cysts	Acute pancreatitis	
8	16	M	Branch duct	3	H	12		Fatty liver		
9	**20**	**M**	Mixed	6	H,B	30	6.5 (S)		Acute recurrent pancreatitis	Fundic glanc Stomach boc Gastric heterotopia/r Proximal esc (R201C) Minor papill Hamartomat

Open in a separate window

Boldface indicates subjects with either worrisome or high-risk features on MRCP.

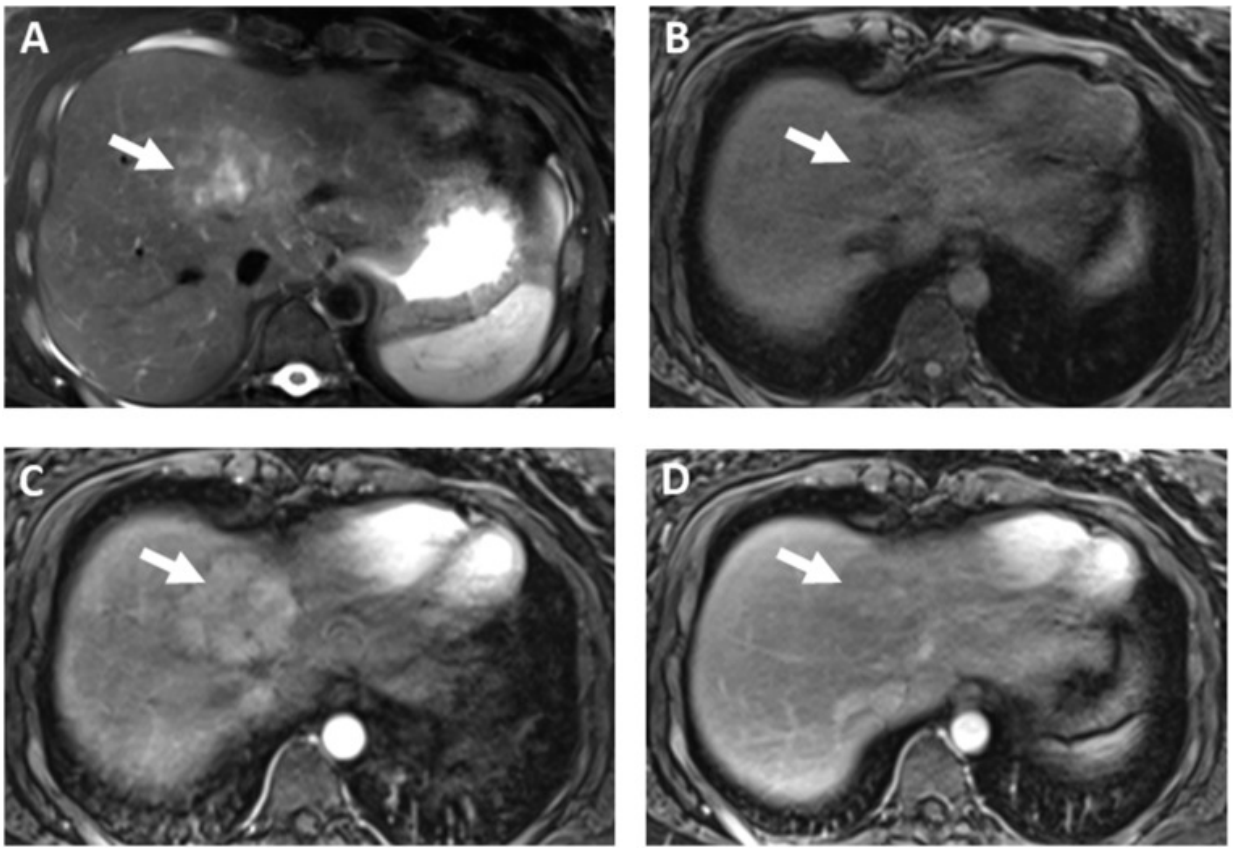
Abbreviations: B, body; D, diffuse, GE, gastroesophageal; H, head; S, segmental; T, tail.

Figure 2.



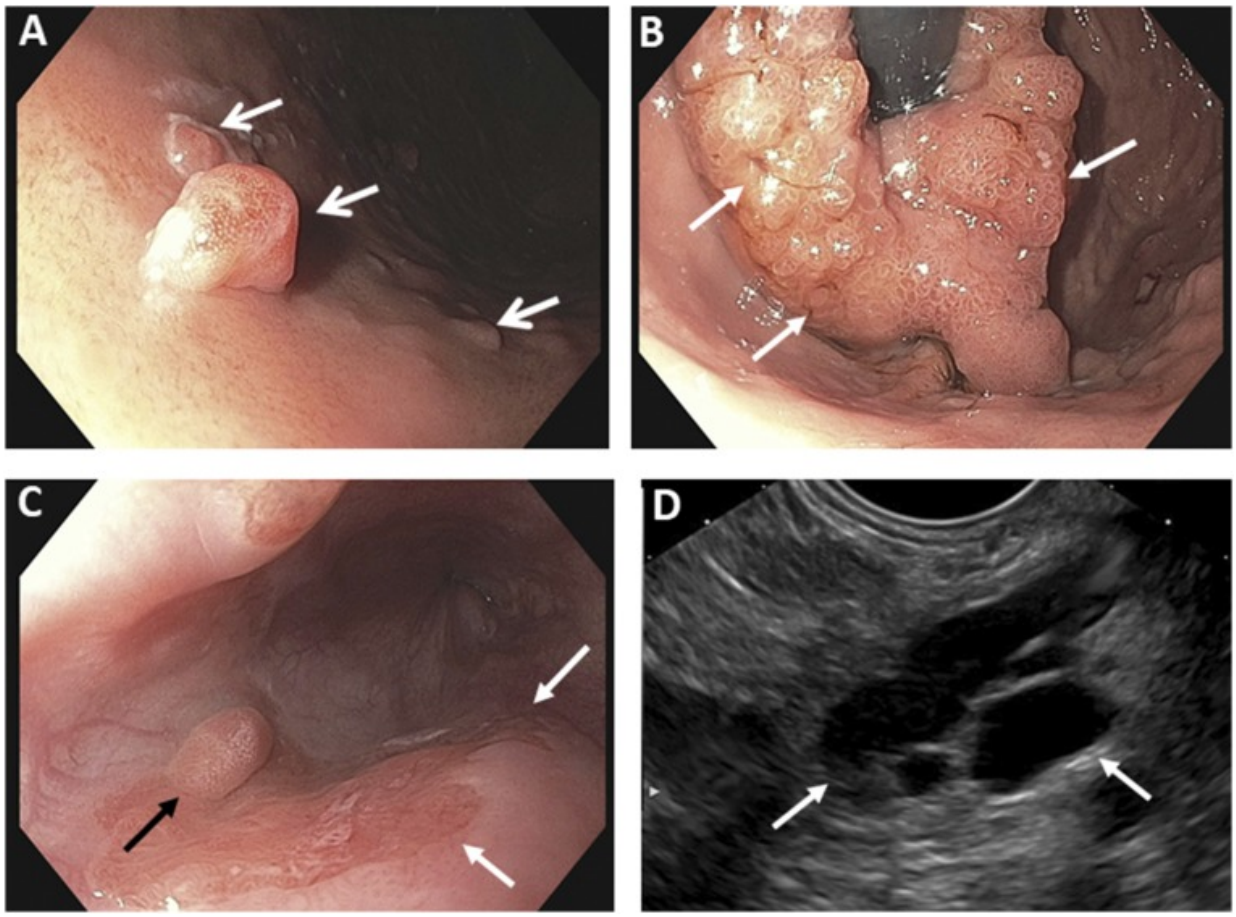
Representative radiographic GI findings in MAS. (A) MRCP imaging from a 55-year-old man shows diffuse dilation of the main pancreatic duct (arrowhead) along with a cystic lesion in the pancreatic head (thin arrow). A biliary cyst is also seen (thick white arrow). (B) Coronal postcontrast image demonstrates heterogeneously enhancing lesions in the spine and left iliac wing (arrows) in the same patient, consistent with fibrous dysplasia of the bone. (C and D) MRCP images in the same patient who underwent distal pancreatectomy and removal of a gastroesophageal junction polyp are shown. (C) Axial and (D) coronal postcontrast T1-weighted images show the gastroesophageal junction polyp (arrows).

Figure 3.



Representative hepatic lesions. (A–D) MRCP imaging from a 22-year-old woman with MAS shows (A) a heterogeneous hyperintense mass in the dome of the liver on axial T2-weighted image (arrow). (B) The mass is hypointense on T1-precontrast image (arrow), (C) shows arterial enhancement on the T1-postcontrast arterial phase image (arrow), and (D) washout on the venous phase postcontrast image (arrow). The signal and enhancement characteristics are suggestive of an adenoma.

Figure 4.



Representative endoscopic findings. (A) Several gastric polyps (arrows) are shown. (B) A retroflexed view shows the gastric cardia. The endoscope is seen as the black tube in the center of the image and is surrounded by a large mass (arrows), consistent with a gastric adenoma with high-grade dysplasia. (C) Endoscopic view of the distal esophagus shows a polypoid lesion (black arrow) and several flat lesions (white arrows). (D) Endoscopic ultrasonographic image of a large cyst (highlighted by arrows) is consistent with an IPMN in the pancreas.