Published in final edited form as:

J Gastrointest Surg. 2012 April ; 16(4): 762–770. doi:10.1007/s11605-012-1823-8.

Intraductal Papillary Mucinous Neoplasm (IPMN) with Extra-Pancreatic Mucin: A Case Series and Review of the Literature

Laura H. Rosenberger,

Department of Surgery, University of Virginia Health System, Medical Research Building #4, Room 3116, P.O. Box 801359, Charlottesville, VA 22908, USA LHR2M@virginia.edu

Louis H. Stein,

Department of Surgery, Yale–New Haven Hospital, New Haven, CT, USA

Agnieszka K. Witkiewicz,

Department of Pathology, Thomas Jefferson University, Philadelphia, PA, USA

Eugene P. Kennedy, and

Department of Surgery, and the Jefferson Pancreas, Biliary and Related Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA

Charles J. Yeo

Department of Surgery, and the Jefferson Pancreas, Biliary and Related Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA

Abstract

Background—Intraductal papillary mucinous neoplasm (IPMN) is an increasingly recognized pancreatic neoplasm characterized by excessive mucin secretion by ductal epithelial cells resulting in a cystic dilation of the pancreatic duct.

Aim—The objective of this study was to review Thomas Jefferson University’s experience and the literature to determine the significance of extra-pancreatic mucin when associated with an IPMN.

Results—A retrospective analysis at our institution revealed only two cases of IPMN associated with extra-pancreatic mucin, which were classic IPMNs with rupture of the pancreatic duct and peritoneal mucin spillage. This specific finding is not previously described, although is assumed as five cases were reported in the literature with IPMN and mucin extension demonstrated by pseudomyxoma peritonei (PMP). We propose IPMN of the pancreas may be grossly compared to a mucocele of the appendix, as both are characterized by excessive secretion of mucin by ductal epithelial cells. A morbid complication of a mucocele is PMP. The presence of extra-pancreatic mucin with an IPMN could present a rare but important marker of the eventual seeding of tumor outside the primary IPMN. This has been documented with cases of iatrogenic spilling of pancreatic mucin, as well as multiple cases of IPMN associated with pseudomyxoma peritonei.

Conclusions—At this time, there is scant reporting and consensus for the treatment of IPMN with extra-pancreatic mucin.

Keywords

Intraductal papillary mucinous neoplasm (IPMN); Extra-pancreatic mucin; Pancreatic cancer; Pseudomyxoma peritonei

Introduction

Mucin-producing tumors of the pancreas represent a group of premalignant or malignant neoplasms forming multilocular cysts and lined by tall, columnar mucinous epithelium. These tumors are most broadly divided into mucinous cystic neoplasms (MCN) and intraductal papillary mucinous neoplasms (IPMN). IPMN is characterized by a cystic dilation of the main or branch pancreatic duct with excessive secretion of mucin by ductal epithelial cells. [1, 2] Its prevalence is now 5% to 7% of all pancreatic neoplasms [3, 4], and it represents the final pathology encountered in 17% to 25% of all pancreaticoduodenectomies in multiple contemporary large series. [2, 5, 6]

Two clinically distinct subtypes of IPMN have been reported: main pancreatic duct tumors and side branch duct tumors. Both groups have a slight male predominance, mean age of roughly 65 years old, and may present with symptoms of vague epigastric or back pain, and acute or chronic pancreatitis. [6] Patients with main duct IPMN are more likely to develop acute pancreatitis, steatorrhea, diabetes mellitus, weight loss, and have a longer duration of symptoms. [7] Despite these varying clinical presentations, two thirds of patients remain asymptomatic and their IPMN is discovered incidentally. [2]

The more common main duct IPMN is typically located in the head of the pancreas. It can produce enough mucin to enlarge the ampulla of Vater and reveal a wide-open orifice with mucin extrusion, a pathognomonic finding at endoscopy. [2, 7], [8-11] When the IPMN produces enough viscous mucin, then biliary obstruction, pancreatitis, and fibrosis may ensue. [2, 12] A retrospective analysis of 136 patients at the Johns Hopkins Hospital revealed 71% of patients had IPMN in the proximal pancreas (head, neck, or uncinate process). Only 10% of IPMN occurs in the tail of the pancreas with radiologic similarities to MCN. [13, 14] Although difficult to differentiate radiologically, IPMN typically exhibits multicentric occurrence along the main pancreatic duct with direct communication to the duct, while MCN is almost exclusively found in females, is a larger, well-circumscribed lesion with characteristic underlying ovarian stroma, is typically a pancreatic tail lesion, and is rarely contiguous with the main pancreatic duct. [7, 13, 14]

Few cases of IPMN are associated with extra-pancreatic mucin. The first case was described in 1998 with the development of pseudomyxoma peritonei as extension of mucin beyond the pancreatic duct after presumed mucin leakage from an IPMN. [15] Since then, four more cases of pseudomyxoma peritonei originating from IPMN of the pancreas have been reported. [11, 16-18] As so few cases have been described, further study is indicated to determine the significance of peritoneal or lesser sac infiltration of mucin. Herein, we present two cases at our institution of extra-pancreatic mucus from a primary IPMN of the pancreas.

Patients: Clinical History and Management

Our identification of these two cases of IPMN with extra-pancreatic mucin led us to examine our database in an effort to uncover previous but unrecognized cases. In an institutional review of operative and pathology reports from Thomas Jefferson University Hospital, we identified over 300 patients who underwent a pancreaticoduodenal resection for pancreatic or periampullary cancer over a 6-year period (2001–2007). IPMN was reported as the final surgical pathology for 21 and 15 of the pancreaticoduodenal resections and distal pancreatectomies, respectively. Of the 36 total patients with surgically treated IPMN, no additional cases reported a ruptured cystic lesion, a pancreatic duct rupture, or any extra-pancreatic spillage of mucin. In reviewing each operative report individually, there

was no evidence of any malignant ascites, carcinomatosis, or omental implants in the 34 patients without extra-pancreatic mucin.

Patient #1

A previously healthy 75-year-old man was noted to have a large cystic mass of the pancreas incidentally on computed tomography (CT). He was asymptomatic and had no history of obstructive jaundice, pancreatitis, or alcoholism. On physical examination, his abdomen was benign, with no hepatosplenomegally, masses, or lymph nodes.

Computed tomography (Fig. 1) and magnetic resonance imaging revealed a large 8 cm×10 cm×20 cm multiloculated and septated cystic mass arising from the tail of the pancreas, extending anteriorly and inferiorly along the transverse mesocolon. The pancreatic duct was dilated to 14.1 mm in the distal body and tail, and was continuous with the cystic component of the exophytic mass.

The patient underwent exploratory laparotomy that revealed a large multilobulated cystic lesion in the body and tail of the pancreas with what appeared to be extra-pancreatic mucin involving the lesser sac. Several focal deposits of a yellow-tan gelatinous material were encountered within the lesser sac, suggesting the neoplasm had ruptured, expelling extra-neoplastic mucin.

An open cholecystectomy, distal pancreatectomy, and en bloc splenectomy were performed. Final surgical pathology confirmed an IPMN of the pancreatic body and tail with focally moderate dysplasia (ductectatic mucin-hypersecretory type), no evidence of invasive cancer, and no regional lymph node metastases. Soft tissue samples from the lesser sac were reported as pauci cellular mucinous cyst, consistent with extension from a pancreatic IPMN. The patient recovered without incident and was alive and well at last follow-up, 48 months post-resection, with no evidence of recurrent disease.

Patient #2

A 75-year-old man had a cystic lesion in the neck of the pancreas found on computed tomography for workup of a cough. He was previously asymptomatic without evidence of abdominal pain, obstructive jaundice, or weight loss, and had no previous history of pancreatitis or neoplasia. On physical examination, he was a well-appearing, non-jaundiced male, with a benign abdomen and no evidence of hepatosplenomegally, lymphadenopathy, or masses.

The patient had liver function tests within normal limits and a CA 19-9 that was normal at 15 U/mL. His initial CT revealed a soft tissue abnormality within the anterior aspect of the head of the pancreas with an associated dilation of the main pancreatic duct (Fig. 2). The duct was dilated to 9.6 mm in the pancreatic body. A lymph node within the lesser sac, anterior to the pancreatic head, measuring 3.1 cm×1.7 cm was also reported. A helical CT was performed revealing a lobulated, low-density lesion measuring 3.5 cm×2.5 cm arising exophytically from the anterior aspect of the head of the pancreas with associated main pancreatic duct dilation. Endoscopic ultrasound and fine-needle aspiration were performed revealing the complex cystic neoplasm having multiple mural nodules and papillary projections. FNA cytopathology revealed mucinous material consistent with a mucinous neoplasm, and the patient was referred to surgery.

The patient underwent an exploratory laparotomy revealing a cystic lesion in the head and neck of the pancreas that appeared to have excavated out the anterior aspect of the gland. There was some evidence of extra-pancreatic mucin in the lesser sac and some mucin embedded within the lesser omentum.

An open cholecystectomy and extended pylorus-preserving pancreaticoduodenectomy were performed, and the frozen section pathology was initially reported as an IPMN with high-grade dysplasia and tumor-free margins. Excision of a portion of the lesser omentum and extra-pancreatic mucin was performed revealing an epithelial lined cyst with mucin extravasation. Final surgical pathology reported adenocarcinoma with abundant extracellular mucin of the lesser omentum and invasive adenocarcinoma (colloid type) associated with IPMN carcinoma in situ, without lymph node involvement. The patient had an uncomplicated recovery and received no chemoradiation therapy in the adjuvant setting. He subsequently was found to have an asymptomatic incisional hernia and a significant burden of intra-abdominal mucin on follow-up CT performed 21 months post-resection. He received palliative chemotherapy, declined surgical debulking, and succumbed to his disease 43 months post-resection.

Literature Review and Discussion

First formally described by Ohashi et al. in 1982, IPMNs are pancreatic neoplasms that accumulate mucin within dilated ducts, which he termed “mucus secreting pancreatic cancer.” [8] Throughout the early 1990s, this entity acquired many names including “mucinous ductal ectasia” [19-21], “mucin-hypersecreting tumor” [9, 22], “mucin-producing tumor” [23, 24], “intraductal mucin-hypersecreting neoplasm” [25], and “intraductal papillary-mucinous tumor”. [26, 27] In 1996, the World Health Organization officially classified these tumors as a distinct histological type of exocrine tumor of the pancreas and designated intraductal papillary mucinous neoplasm (IPMN) to replace the multitude of older terms. [28] IPMN have variable degrees of papillary epithelial dysplasia, mucin production, cystic dilation, and invasiveness. The WHO originally classified these tumors into four histopathologic stages, including benign adenomas, borderline lesions, malignant non-invasive (carcinoma in situ), or invasive carcinomas. [28] The newest nomenclature was published by the Armed Forces Institute of Pathology (AFIP), in 2007, in which they subclassified the non-invasive carcinomas into low-grade, moderate, and high-grade dysplasia. [29] IPMN can also be classified as either main duct or branch duct types with a differing incidence of benign and malignant lesions being associated with each type.

We conducted a literature review within Ovid MEDLINE searching the English language literature from 1948 to present. The search terms “IPMN” and “intraductal papillary mucinous neoplasm” were individually combined with each of the terms “extra pancreatic mucin”, “pancreatic duct rupture”, “malignant ascites”, “carcinomatosis”, “peritoneal implants”, and “pseudomyxoma peritonei”. In our review, five cases of IPMN were identified with associated extra-pancreatic mucin. Each case of IPMN was associated with pseudomyxoma peritonei, suggesting that the excessive mucin production of the IPMN ruptured the pancreatic duct, resulting in spillage of mucinous material into the peritoneal cavity. [11, 15-18] Characteristics of the five case reports from the literature and the two present cases are summarized in Table 1. All five previous patients were also male, with a mean age of 60.6 years, ranging from 49 to 82 years old. Three of the five previously reported patients presented with symptoms associated with a mass in the pancreas: abdominal fullness and loss of appetite. Two patients presented with IPMN of the tail of the pancreas, one with tumor of the body and tail, and one with diffuse tumor of the pancreas with secondary retroperitoneal involvement. Of the three previous cases with tumor size reported, the mean tumor size was 5.5 cm, ranging from 2 cm to 8.5 cm in diameter.

Both of the patients reported herein are male, keeping with the trend in the previously reported cases. In large studies of patients with IPMN, no significant gender prevalence is observed, although a slight male predominance is seen, nor is gender a predictor of malignancy. [13, 30] Both of our patients were 75 years old at presentation, slightly older

than the previously reported patients with extra-pancreatic mucin. Previous reports have demonstrated age correlates with the degree of dysplasia, with IPMN adenomas presenting approximately 5 years prior to those with invasive cancer. [13, 30, 31]

IPMN of the pancreas may be grossly compared to a mucocoele of the appendix, as both are characterized by excessive secretion of mucin by ductal epithelial cells. A simple mucocoele is typically a non-neoplastic lesion recognized by an epithelium that secretes mucin until a cystic, dilated appendix results. [32-34] The mucocoele cells continue mucin production, resulting in a dilated appendix with a distended lumen, much like an IPMN results in a dilated pancreatic duct. Occasionally, mucocoele can be caused by a neoplasm such as cystadenoma or cystadenocarcinoma of the appendix. In this neoplastic mucocoele, the epithelium is lined by columnar cells with papillary projections, precisely as the epithelium of an IPMN. Also consistent with IPMN, the cystadenocarcinoma within the mucocoele is typically non-invasive and does not commonly metastasize, although it can recur locally after surgical excision. Appendectomy is curative for benign lesions; however, a right hemicolectomy is recommended for all lesions invading beyond the mucosa. [32, 33]

A histologic comparison may be made between an IPMN of the pancreas and an appendiceal mucinous tumor. The histologic features of IPMN with extravasated mucin are shown in Fig. 3. In this figure, pseudomyxoma peritonei seen in association with IPMN is identical to pseudomyxoma peritonei arising in association with gastrointestinal malignancies, most commonly appendiceal mucinous tumors (Fig. 4).

A known and morbid complication of a mucocoele of the appendix is pseudomyxoma peritonei, of which the reported 5-year survival rates range from only 53% to 75%. [35] The risk of pseudomyxoma peritonei is so great that it has been suggested that a known mucinous tumor of the appendix should be surgically excised as an open procedure and not by laparoscopic technique. [34, 36, 37] A case of a mucinous adenocarcinoma of the appendix was laparoscopically resected without perforation or mucin spillage; however, diffuse mucinous peritoneal carcinomatosis subsequently developed. [36] Great care is taken to prevent manipulation or trauma to an appendix when a mucocoele is present, to prevent extravasation of mucin, mucinous tumor implants, or mucinous peritoneal carcinomatosis.

Pseudomyxoma Peritonei

The clinical entity of pseudomyxoma peritonei was first described in 1842 by Rokitsansky; however, it was Werth, in 1884, who coined the term pseudomyxoma peritonei (PMP) in regards to a case associated with an ovarian cystadenoma. [38, 39] In 1901, it again appeared in the literature, this time associated with a mucocoele of the appendix. [40] PMP is a rare form of intra-abdominal neoplasm characterized by large amounts of extracellular mucin collections with mucinous implants on peritoneal surfaces and the omentum. [35, 41] Often called “jelly belly”, PMP is characterized by this extensive gelatinous mucin and mucinous ascites. [41, 42] PMP is a neoplastic condition with the majority of cases found in association with a primary appendiceal or ovarian tumor. [43] A literature search from 1986 through 1997 revealed PMP associated with a range of primary lesions from a benign mucocoele with rupture to an advanced adenocarcinoma. [35] Non-appendiceal tumors have also been reported to result in PMP, such as ovarian carcinomas [38, 42], pancreatic carcinomas (including our case reports) [11, 15-18], carcinoma of the breast [44], and locally advanced colorectal tumors. [45, 46]

Much like the countless terms originally identifying IPMN, pseudomyxoma peritonei, and its primary mucin-producing tumor, have a multitude of names. Ronnett and colleagues classified PMP as either disseminated peritoneal adenomucinosis (DPAM) or peritoneal mucinous carcinomatosis (PMCA). [47] DPAM and PMCA were distinguished by the

abundance of mucinous epithelium in the peritoneal lesions, presence or absence of cytologic atypia, mitotic activity, and the structural characteristics of carcinoma. This differentiation subsequently revealed significant survival differences. [47]

We believe it is reasonable to compare IPMN of the pancreas with extra-pancreatic mucin to the other mucin-secreting tumors more commonly associated with PMP as described above. In addition to the previously described five cases of IPMN associated with extra-pancreatic mucin resulting in pseudomyxoma peritonei (PMP), and our two additional cases, two other cases have been reported of iatrogenic seeding of IPMN into the peritoneal cavity. One case describes an endosonography-guided fine-needle aspiration biopsy (EUS-FNAB), which leads to IPMN dissemination. [48] This case involved a 57-year-old man who had biopsy-proven IPMN of the pancreas diagnosed by EUS-FNAB. During operative management, prior to opening the omentum, peritoneal lavage cytology was performed revealing tumor cells. Initial cytology results staged the tumor as stage I (T1, N0, M0); however, positive tumor cells on peritoneal lavage cytology resulted in a stage IVB lesion (T1, N0, M1). Twenty months postoperatively, the patient developed carcinomatous peritonitis and died 5 months thereafter. [48] The authors concluded the EUS-FNAB led to seeding of the peritoneal cavity secondary to leakage of cancer cells by needle puncture through the IPMN in the pancreas. The second case reported mucin spillage from the main pancreatic duct into the operative field during a pancreatectomy leading to peritoneal seeding, tumor metastasis, and death 7 months postoperatively. [49] These two episodes illustrate the potentially grave result of mucus extravasation and spillage from the pancreatic duct.

Treatment of PMP

The clinical course of PMP is often an unrelenting sequence of recurrences with continued aggressive adjuvant treatments and ultimately an overall poor prognosis. Initial treatment for PMP was centered around radical, repetitive debulking operations and extensive cytoreductive surgery. [35, 43, 50] Radical surgical excision has included complete mucus removal, omentectomy, peritonectomy, as well as appendectomy, and bilateral oophorectomy. [41, 43, 51] An early nine-patient series reported numerous patients undergoing three laparotomies each, and a single patient enduring five. [50] With progressive operations comes significant morbidity, as seen by the numerous enterotomies, enterocutaneous fistulae, and subsequent operations required for repair of complications from this series.

Innumerable alternative treatments have been utilized including various mucolytic agents, phototherapy, adjuvant systemic chemotherapy, intraperitoneal radiotherapy (iodine I 131, gold Au 198, phosphate P 32), and intraperitoneal chemotherapy [5-fluorouracil (5-FU), cisplatin, mitomycin-C] with varying efficacies. [35, 41, 43, 51-54] In multiple large patient series, intraperitoneal chemotherapy and radiotherapy have provided an extended disease-free and overall survival benefit. [43, 51] Most commonly, intraperitoneal therapy is intended to eradicate residual tumor following initial operative debulking. This technique is called intraperitoneal hyperthermic perfusion (IPHP) in which a cisplatin and mitomycin-C infusate are infused into the peritoneal cavity under hyperthermic conditions at 42.5°C for 1 h. [51] Variations to this practice exist at different institutions. The Mayo Clinic reports its standard practice of administering intraperitoneal 5-FU and P 32 for three consecutive days following maximal surgical resection. [54] Overall, recommendations for treatment of PMP include aggressive operative resection, intraperitoneal therapies, with little support for serial debulking or initial systemic chemotherapy.

Treatment for IPMN

Broadly speaking, main duct IPMNs are thought to require surgical excision, as a histopathologic examination of the pancreatic tissue is required for accurate differentiation of benign from malignant IPMN, precluding an accurate pre-operative diagnosis. [6, 27, 31] IPMN has been compared to adenomatous polyps of the colon, as a precancerous lesion with an associated oncogenic transformation; however, we cannot 100% reliably predict non-invasive IPMN from invasive preoperatively. [27] The natural history of IPMN is also unclear in regards to whether the pathology is a localized process or a diffuse pancreatic disorder of the ducts, making the required extent of surgical resection difficult to determine.

It is well reported that IPMN has invasive malignancy encountered in 36% to 53% of resected IPMNs, with an average of approximately 40%. [1, 6, 13, 27, 30, 31] There is obvious bias toward the resection of larger, more suspicious main duct IPMNs and a tendency to observe smaller branch duct IPMNs. In a large patient series, the 5-year survival with invasive and non-invasive IPMNs are 43% to 60% and 77% to 100%, respectively. [13, 30] The recurrence rates for invasive and non-invasive IPMN have a wider range of 7% to 90% and 0 to 10%, respectively. [6, 30, 31] IPMNs, including low-grade, moderate, and high-grade dysplastic lesions, undoubtedly are capable of recurrence even after a “curative” resection, unlike mucinous cystic neoplasm in which absence of invasive carcinoma predicts cure.

In 2006, consensus guidelines for the treatment of IPMN were established in Sendai, Japan by the International Association of Pancreatology. [55] The current recommendations are to resect all main duct, mixed variant, and symptomatic branch duct IPMNs. Resection is based on the location and extent of the IPMN. In general, a pancreaticoduodenectomy is typically indicated for a main duct IPMN of the head, neck, or uncinate process. A distal pancreatectomy is indicated for IPMN of the body or tail, and a total pancreatectomy is indicated if the IPMN diffusely involves the gland, or a proximal IPMN extends through to the body and tail. [55] With each partial pancreatectomy, an assessment of the margin by frozen section is indicated to allow further resection for positive margins showing either high-grade dysplasia or invasive carcinoma. [55] Total pancreatectomy is not commonly recommended, as it results in obligate insulin-dependent diabetes, predictable malabsorption requiring pancreatic enzyme supplements, and other metabolic complications. Despite being a possible curative operation for extensive noninvasive IPMN, it does not universally prevent recurrence for invasive lesions. [6, 13, 27, 31] If partial pancreatectomy is performed, mandatory remnant surveillance is recommended with a regularly scheduled imaging assessment (typically annual or biannual MRI with MRCP).

No reported guidelines for treatment of IPMN address the presence of extra-pancreatic mucin. The clinical prognosis and treatment likely changes, however, if the mucin produced within the IPMN is ruptured into the retroperitoneum, lesser sac, or peritoneal cavity, as it does for ruptured mucocoeles of the appendix and PMP. If IPMN of the pancreas with extra-pancreatic mucin behaves much like mucocoele and has the potential for PMP, should we be following an equivalent adjuvant treatment schedule?

In the setting of this risk, the presence of extra-pancreatic mucin could present a rare but important marker of the eventual seeding of tumors outside of the IPMN. This has been documented with iatrogenic spilling of pancreatic mucin as well as cases of IPMN associated with PMP. At this time, there is scant reporting and very few numbers of such cases reported. Consensus for the treatment and follow-up of IPMN with extra-pancreatic mucin requires more research in the areas of staging, appropriate treatments, prognosis, and outcomes.

References

1. Serikawa M, Sasaki T, Fujimoto Y, Kuwahara K, Chayama K. Management of intraductal papillary-mucinous neoplasm of the pancreas: treatment strategy based on morphologic classification. *J Clin Gastroenterol*. 2006; 40:856–862. [PubMed: 17016145]
2. Tanaka M. Intraductal papillary mucinous neoplasm of the pancreas: diagnosis and treatment. *Pancreas*. 2004; 28:282–288. [PubMed: 15084972]
3. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. *Ann Surg*. 2006; 244:10–15. [PubMed: 16794383]
4. Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, Hodgins MB, Sauter PK, Hruban RH, Riall TS, Schulick RD, Choti MA, Lillemoe KD, Yeo CJ. 1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. *J Gastrointest Surg*. 2006; 10:1199–1210. [PubMed: 17114007]
5. Tollefson MK, Libsch KD, Sarr MG, Chari ST, DiMagno EP, Urrutia R, Smyrk TC. Intraductal papillary mucinous neoplasm: did it exist prior to 1980? *Pancreas*. 2003; 26:e55–58. [PubMed: 12657965]
6. Sarr MG, Murr M, Smyrk TC, Yeo CJ, Fernandez-del-Castillo C, Hawes RH, Freeny PC. Primary cystic neoplasms of the pancreas. Neoplastic disorders of emerging importance—current state-of-the-art and unanswered questions. *J Gastrointest Surg*. 2003; 7:417–428. [PubMed: 12654569]
7. Kobari M, Egawa S, Shibuya K, Shimamura H, Sunamura M, Takeda K, Matsuno S, Furukawa T. Intraductal papillary mucinous tumors of the pancreas comprise 2 clinical subtypes: differences in clinical characteristics and surgical management. *Arch Surg*. 1999; 134:1131–1136. [PubMed: 10522860]
8. Ohashi K, Murakami Y, Takeoshi T, Ohta H, Ohashi I. Four cases of mucin producing cancer of the pancreas on specific findings of the papilla of Vater (Japanese). *Prog Dig Endosc*. 1982; 20:348–351.
9. Yamaguchi K, Tanaka M. Mucin-hypersecreting tumor of the pancreas with mucin extrusion through enlarged papilla. *Am J Gastroenterol*. 1991; 86:835–839. [PubMed: 2058624]
10. Kim HJ, Kim MH, Lee SK, Yoo KS, Park ET, Lim BC, Park HJ, Myung SJ, Seo DW, Min YI. Mucin-hypersecreting bile duct tumor characterized by a striking homology with an intraductal papillary mucinous tumor (IPMT) of the pancreas. *Endoscopy*. 2000; 32:389–393. [PubMed: 10817178]
11. Imaoka H, Yamao K, Salem AA, Mizuno N, Takahashi K, Sawaki A, Isaka T, Okamoto Y, Yanagisawa A, Shimizu Y. Pseudomyxoma peritonei caused by acute pancreatitis in intraductal papillary mucinous carcinoma of the pancreas. *Pancreas*. 2006; 32:223–224. [PubMed: 16552347]
12. Trigg NA, El-Attar A, Berkelhammer C. Mucinous biliary obstruction in intraductal papillary mucinous neoplasm of the pancreas (IPMN): 615. *Am J Gastroenterol*. 2005; 100(Suppl 1):S233.
13. Sohn TA, Yeo CJ, Cameron JL, Hruban RH, Fukushima N, Campbell KA, Lillemoe KD. Intraductal mucinous neoplasms of the pancreas: an updated experience. *Ann Surg*. 2004; 239:788–797. [PubMed: 15166958]
14. Takahashi Y, Sakamoto Y, Shimada K, Sano T, Kosuge T, Onaya H, Mizuguchi Y, Hiraoka N. Imaging features of large intraductal papillary mucinous carcinoma of the pancreatic tail. *Pancreas*. 2006; 32:333–334.
15. Zanelli M, Casadei R, Santini D, Gallo C, Verdirame F, La Donna M, Marrano D. Pseudomyxoma peritonei associated with intraductal papillary-mucinous neoplasm of the pancreas. *Pancreas*. 1998; 17:100–102. [PubMed: 9667528]
16. Mizuta Y, Akazawa Y, Shiozawa K, Ohara H, Ohba K, Ohnita K, Isomoto H, Takeshima F, Omagari K, Tanaka K, Yasutake T, Nakagoe T, Shirono K, Kohno S. Pseudomyxoma peritonei accompanied by intraductal papillary mucinous neoplasm of the pancreas. *Pancreatol*. 2005; 5:470–474. [PubMed: 15983445]
17. Lee SE, Jang JY, Yang SH, Kim SW. Intraductal papillary mucinous carcinoma with atypical manifestations: report of two cases. *World J Gastroenterol*. 2007; 13:1622–1625. [PubMed: 17461460]

18. Nepka CH, Potamianos S, Karadana M, Barbanis S, Kapsoritakis A, Koukoulis G. Ascitic fluid cytology in a rare case of pseudomyxoma peritonei originating from intraductal papillary mucinous neoplasm of the pancreas. *Cytopathology*. 2009; 20:271–273. [PubMed: 19207311]
19. Bastid C, Bernard JP, Sarles H, Payan MJ, Sahel J. Mucinous ductal ectasia of the pancreas: a premalignant disease and a cause of obstructive pancreatitis. *Pancreas*. 1991; 6:15–22. [PubMed: 1994377]
20. Warshaw AL. Mucinous cystic tumors and mucinous ductal ectasia of the pancreas. *Gastrointest Endosc*. 1991; 37:199–201. [PubMed: 1851710]
21. Lew JI, Hart J, Michelassi F. Natural history of mucinous ductal ectasia of the pancreas: a case report and review of the literature. *Am J Gastroenterol*. 2002; 97:2127–2132. [PubMed: 12190189]
22. Yamaguchi K, Ogawa Y, Chijiwa K, Tanaka M. Mucin-hypersecreting tumors of the pancreas: assessing the grade of malignancy preoperatively. *Am J Surg*. 1996; 171:427–431. [PubMed: 8604836]
23. Yamada M, Kozuka S, Yamao K, Nakazawa S, Naitoh Y, Tsukamoto Y. Mucin-producing tumor of the pancreas. *Cancer*. 1991; 68:159–168. [PubMed: 2049738]
24. Obara T, Maguchi H, Saitoh Y, Itoh A, Arisato S, Ashida T, Nishino N, Ura H, Namiki M. Mucin-producing tumor of the pancreas: natural history and serial pancreatogram changes. *Am J Gastroenterol*. 1993; 88:564–569. [PubMed: 8385881]
25. Rickaert F, Cremer M, Deviere J, Tavares L, Lambilliotte JP, Schroder S, Wurbs D, Kloppel G. Intraductal mucin-hypersecreting neoplasms of the pancreas. A clinicopathologic study of eight patients. *Gastroenterology*. 1991; 101:512–519. [PubMed: 1648527]
26. Kloppel G. Clinicopathologic view of intraductal papillary-mucinous tumor of the pancreas. *Hepatogastroenterology*. 1998; 45:1981–1985. [PubMed: 9951851]
27. Loftus EV, Olivares-Pakzad BA, Batts KP, Adkins MC, Stephens DH, Sarr MG, Dimagno EP. Intraductal papillary-mucinous tumors of the pancreas: clinicopathologic features, outcome, and nomenclature. *Gastroenterology*. 1996; 110:1909–1918. [PubMed: 8964418]
28. Kloppel, G.; Solcia, E.; Longnecker, DS.; Capella, C.; Sobin, LH. *Histological Typing of Tumours of the Exocrine Pancreas*. 2. Berlin: Springer; 1996. World Health Organization International Histological Classification of Tumours; p. 1–61.
29. Hruban, RH.; Pitman, MB.; Klimstra, DS. *Armed Forces Institute of Pathology Atlas of Tumor Pathology: Tumors of the Pancreas*, Fascicle 6. Washington DC: American Registry of Pathology; 2007.
30. Salvia R, Fernandez-del Castillo C, Bassi C, Thayer SP, Falconi M, Mantovani W, Pederzoli P, Warshaw AL. Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. *Ann Surg*. 2004; 239:678–685. [PubMed: 15082972]
31. Chari ST, Yadav D, Smyrk TC, DiMagno EP, Miller LJ, Raimondo M, Clain JE, Norton IA, Pearson RK, Petersen BT, Wiersema MJ, Farnell MB, Sarr MG. Study of recurrence after surgical resection of intraductal papillary mucinous neoplasm of the pancreas. *Gastroenterology*. 2002; 123:1500–1507. [PubMed: 12404225]
32. Deans GT, Spence RA. Neoplastic lesions of the appendix. *Br J Surg*. 1995; 82:299–306. [PubMed: 7795991]
33. de Rezende Pereira JC, Trugilho JC, Sarmat AA. Mucocoele of the appendix. *Surgery*. 2004; 136:1096–1097. [PubMed: 15523409]
34. Ruiz-Tovar J, Teruel G, Castineiras M, Dehesa S, Quindos L, Molina M. Mucocoele of the appendix. *World J Surg*. 2007; 31:542–548. [PubMed: 17318706]
35. Hinson FL, Ambrose NS. Pseudomyxoma peritonei. *Br J Surg*. 1998; 85:1332–1339. [PubMed: 9782010]
36. Gonzalez Moreno S, Shmookler BM, Sugarbaker PH. Appendiceal mucocoele. Contraindication to laparoscopic appendectomy. *Surg Endosc*. 1998; 12:1177–1179. [PubMed: 9716778]
37. Dhage-Ivatury S, Sugarbaker PH. Update on the surgical approach to mucocoele of the appendix. *J Am Coll Surg*. 2006; 202:680–684. [PubMed: 16571440]

38. Weaver CH. Mucocele of appendix with pseudomucinous degeneration. *Am J Surg.* 1937; 36:523–526.
39. Werth R. Klinische und anatomische untersuchungen zur lehre von den bauchgeschwuelsten und der laparotomie. *Arch Gynecol Obstet.* 1884; 24:100–118.
40. Frankel E. Uber das sogenannte pseudomyxoma peritonei. *Muenchen Med Wochenschr.* 1901; 48:965–970.
41. Baradi H, Ponsky J. Pseudomyxoma peritonei. *Surgery.* 2002; 131:230–231. [PubMed: 11854707]
42. Fann JJ, Vierra M, Fisher D, Oberhelman HA Jr, Cobb L. Pseudomyxoma peritonei. *Surg Gynecol Obstet.* 1993; 177:441–447. [PubMed: 8211593]
43. Gough DB, Donohue JH, Schutt AJ, Gonchoroff N, Goellner JR, Wilson TO, Naessens JM, O'Brien PC, van Heerden JA. Pseudomyxoma peritonei: long-term patient survival with an aggressive regional approach. *Ann Surg.* 1994; 219:112–119. [PubMed: 8129481]
44. Hawes D, Robinson R, Wira R. Pseudomyxoma peritonei from metastatic colloid carcinoma of the breast. *Gastrointest Radiol.* 1991; 16:80–82. [PubMed: 1846836]
45. Sugarbaker PH, Kern K, Lack E. Malignant pseudomyxoma peritonei of colonic origin. Natural history and a presentation of a curative approach to treatment. *Dis Colon Rectum.* 1987; 30:772–779. [PubMed: 2820671]
46. Koyama S, Tomimatsu T, Sawada K, Kanagawa T, Tsutsui T, Kimura T. Pseudomyxoma peritonei originating from colorectal cancer during pregnancy. *J Obstet Gynaecol Res.* 2011; 37:254–258. [PubMed: 21114581]
47. Ronnett BM, Zahn CM, Kurman RJ, Kass ME, Sugarbaker PH, Shmookler BM. Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to “pseudomyxoma peritonei”. *Am J Surg Pathol.* 1995; 19:1390–1408. [PubMed: 7503361]
48. Hirooka Y, Goto H, Itoh A, Hashimoto S, Niwa K, Ishikawa H, Okada N, Itoh T, Kawashima H. Case of intraductal papillary mucinous tumor in which endosonography-guided fine-needle aspiration biopsy caused dissemination. *J Gastroenterol Hepatol.* 2003; 18:1323–1324. [PubMed: 14535994]
49. Yasuda H, Takada T, Amano H, Yoshida M. Surgery for mucin-producing pancreatic tumor. *Hepato-gastroenterology.* 1998; 45:2009–2015. [PubMed: 9951855]
50. Mann WJ, Wagner J, Chumas J, Chalas E. The management of pseudomyxoma peritonei. *Cancer.* 1990; 66:1636–1640. [PubMed: 2208015]
51. Deraco M, Baratti D, Inglese MG, Allaria B, Andreola S, Gavazzi C, Kusamura S. Peritonectomy and intraperitoneal hyperthermic perfusion (IPHP): a strategy that has confirmed its efficacy in patients with pseudomyxoma peritonei. *Ann Surg Oncol.* 2004; 11:393–398. [PubMed: 15070599]
52. Green N, Gancedo H, Smith R, Bernett G. Pseudomyxoma peritonei—nonoperative management and biochemical findings. A case report *Cancer.* 1975; 36:1834–1837.
53. Sindelar WF, DeLaney TF, Tochner Z, Thomas GF, Dachowski LJ, Smith PD, Friauf WS, Cole JW, Glatstein E. Technique of photodynamic therapy for disseminated intraperitoneal malignant neoplasms. Phase I study. *Arch Surg.* 1991; 126:318–324. [PubMed: 1998474]
54. Schomas DA, Miller RC, Donohue JH, Gill S, Thurmes PJ, Haddock MG, Quevedo JF, Gunderson LL. Intraperitoneal treatment for peritoneal mucinous carcinomatosis of appendiceal origin after operative management: long-term follow-up of the Mayo Clinic experience. *Ann Surg.* 2009; 249:588–595. [PubMed: 19300231]
55. Tanaka M, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, Shimizu M, Yamaguchi K, Yamao K, Matsuno S. International Association of Pancreatology. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatology.* 2006; 6:17–32. [PubMed: 16327281]

Fig. 1. Abdominal CT scan of patient 1. Large exophytic mass in communication with massively dilated distal main pancreatic duct. *M*=mass, *arrow*=communication to dilated main pancreatic duct

Fig. 2. Abdominal CT scan of patient 2. Exophytic mass from anterior aspect of pancreatic head associated with main pancreatic duct dilation. *M*=mass, *arrow*=dilated main pancreatic duct

Fig. 3.
IPMN with abdominal mucin. **a** IPMN in the pancreas with severe cytologic atypia (carcinoma in situ). **b** Colloid carcinoma present in same pancreas. **c** Omental lesion consisting of mucin with glandular epithelium. **d** Higher magnification of neoplastic glandular epithelium floating in pools of mucin. Image **a, b, c**: $\times 50$, image **d**: $\times 200$ magnification

Fig. 4. Appendiceal mucinous cystadenocarcinoma associated with pseudomyxoma peritonei. **a** Appendiceal tumor with complex papillary architecture and abundant mucin. **b** Pools of mucin in omentum. Images **a** and **b**: $\times 50$ magnification

Table 1

Case reports of IPMN with extra-pancreatic manifestations

References	Year	Age/sex	Site	Size (cm)	Duct dilation	Symptoms	Operation	Final path	Adjuvant Tx	Outcome	Survival (months)
Zanelli et al.	1998	49/M	1°—diffuse 2°—RP	1°—NS 2°—6 cm	NS	AP	PPPD, total	NS	SC	Recurrence	AWD, >17
Mizuta et al.	2005	53/M	Tail	2 cm	Mild	AF, LOA	Omental excision and IHCP	NS	IPC, SC	IPMN never resected	AWD, >24
Imaoka et al.	2006	64/M	Tail	NS	Severe	AP	DP	IV	None	NED	>6
Lee et al.	2007	55/M	Body/Tail	8.5 cm	NS	None	DP	IV	SC	NED	>3
Nepka et al.	2009	82/M	NS	NS	20 mm	Ascites	None	NS	None	IPMN never resected.	AWD, >12
Present Case 1	2007	75/M	Tail	20 cm	14.1 mm	None	DP	B	None	NED	>48
Present Case 2	2007	75/M	Head	3.5 cm	9.6 mm	None	PPPD	IV	SC, RAD	Recurrence	DWD, 43

RP retroperitoneal, *NS* not stated, *AP* abdominal pain, *AF* abdominal fullness, *LOA* loss of appetite, *PPPD* pylorus-preserving pancreaticoduodenectomy, *IHCP* intraperitoneal hyperthermic chemoperfusion, *DP* distal pancreatectomy, *B* borderline (moderate dysplasia), *IV* invasive carcinoma, *SC* systemic chemotherapy, *IPC* intraperitoneal chemotherapy, *RAD* radiation therapy, *NED* no evidence of disease, *AWD* alive with disease, *DWD* dead with disease