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Intraductal papillary mucinous neoplasm of the pancreas. Personal series and synthetic review☆

Neoplasia mucinosa papillare intraduttale del pancreas. Casistica personale e revisione sintetica

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Summary Intraductal papillary mucinous neoplasms (IPMNs) are rare pancreatic tumors, accounting for less than 1-2% of all neoplasms of the pancreas. The main characteristic of IPMNs is their favorable prognosis, as these pre-malignant or malignant lesions are usually slow-growing tumors and radical surgery is frequently possible. According to the localization of the lesions, three different tumor types have been identified: the main-duct IPMN, the branch-duct IPMN and the mixed-type IPMN (involving both the main pancreatic duct and the side branches). IMPNs do not present pathognomonic signs or symptoms. The obstruction of the main pancreatic duct system may cause abdominal pain and acute pancreatitis (single or recurrent episodes). The tumor may be incidentally discovered in asymptomatic patients, particularly in those with branch-duct IPMNs. In clinical practice, any non-inflammatory cystic lesion of the pancreas should be considered as possible IPMN. Computed tomography, magnetic resonance imaging with cholangiopancreatography and endoscopic ultrasonography can localize an IPMN and assess its morphology and size. The choice between non-operative and surgical management depends on the risk of malignancy and on the definitive distinction between benign and malignant IPMNs. Main-duct IPMNs have a high risk of malignant degeneration, especially in older patients. The clinical and radiological features, as well as treatment and outcome, of eight patients with IPMN (five with main-duct, two with branch-duct and one with mixed-type) observed by the authors over the last ten years are presented.

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Introduction

Intraductal papillary mucinous neoplasms (IPMNs) are rare pancreatic tumors, accounting for less than 1-2% of all neoplasms of the pancreas [1,2]. Among the uncommon exocrine tumors of the pancreas, IPMNs have received increasing attention in recent years because of their favorable prognosis, obscure nature and their relationship with pancreatic adenocarcinoma. In addition, over the last ten years the number of diagnosed IPMNs has significantly increased and this tumor is more commonly recognized, even in asymptomatic patients, as an incidental finding. IMPNs now represent 10-30% of all resectable pancreatic tumors in high-volume referral surgical centers [3]. Physicians should become familiar with IPMNs, as it is possible that affected patients are admitted into internal medicine wards because of non-specific, general complaints or because of an incidentally discovered "cystic lesion" of the pancreas. This article presents an overview of the pathological/clinical features and diagnostic/therapeutic problems of IMPNs with a series of eight patients.

Pathology

IPMNs of the pancreas are characterized by the intraductal proliferation of neoplastic mucinous cells, which usually form papillae, and the cystic dilation of the pancreatic ducts, thus forming a clinically and macroscopically detectable mass [4]. IPMNs are grossly visible ($\geq$ 1 cm), mucin-producing neoplasms that arise in the main pancreatic duct and/or its branches. Two different tumor types were initially identified: the "main-duct" IPMN and the "branch-duct" IPMN [1,2]. Main-duct IPMNs may be associated with contemporary involvement of the side branches ducts; as a consequence, a third anatomo-clinical subtype of IMPN, termed "mixed" type, has been identified [5]. Macroscopically, the main-duct IPMN usually presents as a dilated, mucin-filled main pancreatic duct or as a cystic-like lesion along the main pancreatic duct [6]. The usual location is in the proximal portion of the pancreas, even if the tumor has spread to the entire main pancreatic duct. Sometimes the mucus may extrude through a bulging ampulla, and it is clearly identified at duodenoscopy (Fig. 1). The branch-duct IPMN frequently involves the side branches of the uncinate process, but it can also be observed in the remaining portions of the gland, with the possibility of the multifocal involvement of two or more distant side branches. Branch-duct IMPNs appear as cystic lesions communicating with a non-dilated main pancreatic duct.

According to the "*Morphology Code of the International Classification of Diseases for Oncology (ICD-O) and the Systematic Nomenclature of Medicine*" (http://snomed.org), there are different pathologic forms:

a) Intraductal papillary-mucinous adenoma (845/0)
b) Intraductal papillary-mucinous neoplasm with moderate dysplasia (845/1)
c) Intraductal papillary-mucinous carcinoma (845/3) with two subtypes: - non-invasive (845/2) and - invasive (845/3)

Tumor behavior is coded as follows: 0 for benign tumors; 1 for unspecified, borderline or uncertain behavior; 2 for in situ carcinoma; 3 for malignant tumors. To simplify, IPMNs may be divided into benign (adenoma and borderline) and malignant (in situ carcinoma and invasive carcinoma) [7,8]. The latter type (invasive carcinoma) accounts for more than 40% of the resected specimens at a rate of 43% for main-duct IPMN and 15% for branch-duct type [6]. Recently, the International Consensus Guidelines on IPMNs [5] stated that main-duct type and branch-duct type are associated with malignancy in 70% and 25% of the cases, respectively. Thus, side-branch IPMNs have a low risk for malignant transformation. Histologic sub-classification based upon the morphology of the proliferative nodules and papillae identifies five types of IPMNs: gastric foveolar type, intestinal type (Fig. 2), pancreatobiliary type, intraductal oncocytic papillary neoplasm, and intraductal tubulopapillary neoplasm [9,10]. It is not uncommon to discover multiple histologic types with multiple grades of dysplasia within the same surgical specimen [7].

Molecular Biology

Over the last ten years many studies have shown genetic alterations in ductal pancreatic adenocarcinoma [11]. Some of these alterations have also been described in IPMNs. The mutational activation of the K-ras oncogene was observed in 15 out of 23 (65%) resected IMPNs, while the loss of

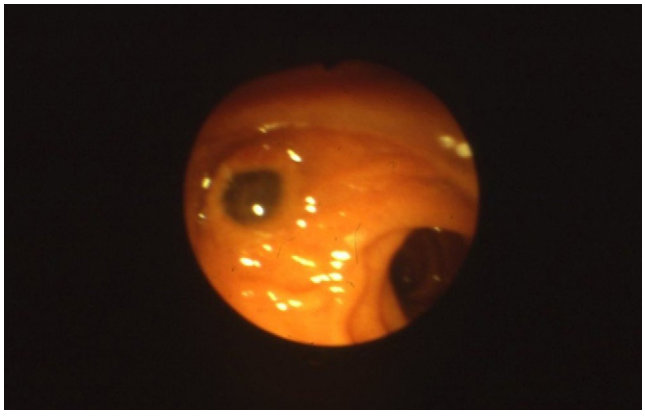

Figure 1 Duodenoscopy: characteristic mucin extrusion through the ampulla of Vater.

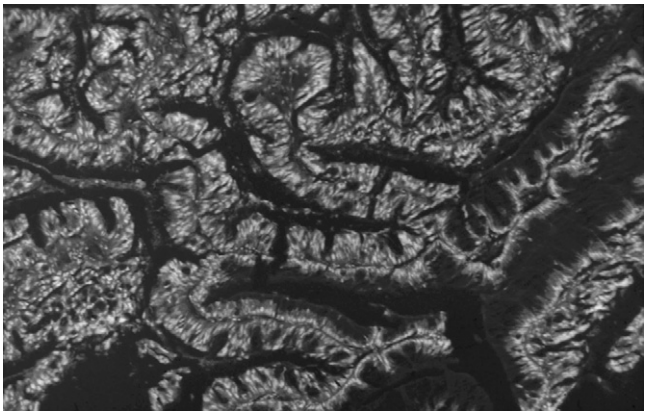

Figure 2 Intestinal-type IPMN resembling villous neoplasms showing columnar epithelial cells with severe epithelial dysplasia (H&E staining).

heterozygosity of the p16 oncosuppressor gene was found in 12.5% of adenoma and 75% of carcinoma IMPNs, respectively [12]. Similar results were observed by Yang and co-workers [13]: K-ras mutations were examined in 41 patients (resected specimens) and were detected in 20.8% of benign IPMNs and in 61.5% of malignant IPMNs. Another study [14] showed that K-ras and p53 mutations were present in 71% and 6% of 52 operated IPMNs, respectively. In vivo studies show slightly different results. Mizuno and co-workers [15] evaluated K-ras mutations in the pancreatic juice in a group of 53 IMPNs, and they observed mutations in 80% of the carcinoma group and 71% of the adenoma group. IPMN-cells secrete a thick mucin that causes dilatation of the pancreatic ducts. Recent studies identified different expression of various mucins in IPMNs with different degrees of malignancy. Mucin-1, mucin-4 and mucin-5AC were more frequently associated with invasive carcinoma, and mucin-2 was found only in the intestinal type and more frequently in adenomas or borderline IPMNs [13,16–18]. The composition of mucin products may be investigated in surgical specimens and in vivo by means of endoscopic ultrasound-guided fine-needle aspiration [19]. This is critically important as it is possible to identify a "molecular" prognosis to plan the timing and strategy of surgical treatment (limited pancreatectomy, extended resection, lymphoadenectomy).

Clinical features

IMPNs do not present pathognomonic signs or symptoms. The obstruction of the main pancreatic duct system may cause abdominal pain, pancreatitis, steathorrea, jaundice, diabetes and weight loss [2,3,5,7]. The last three symptoms have been described more frequently in patients with malignant IPMNs [3,20]. Asymptomatic patients account for 13.5% [21] of invasive main-duct IPMNs. Patients affected by branch-duct IPMN are often completely asymptomatic, and the lesion is incidentally discovered during ultrasound or during other radiologic examinations that are performed for various reasons [22,23]. A recent report on a large series of branch-duct IMPNs [23] showed that the neoplasm was incidentally discovered in 40% of the patients and that jaundice is more frequent in patients with invasive tumors (12.5% vs. 1.8% in benign lesions). Abdominal pain is predominant in patients with benign tumors (45% vs. 25% in malignancy). In clinical practice, it is not uncommon to observe patients with a "cystic lesion" of the pancreas with non-specific symptoms. First, it is necessary to exclude pseudocysts (lesions not presenting on the lining of the wall) such as those related with acute and chronic pancreatitis, paraduodenal wall cysts and infection-related pseudocysts. Then, the differential diagnosis of "true" cysts of the pancreas (lined by epithelium, acinar cells and other cells) includes several pathologic features (Table 1).

Table 1 Types of "true" (non-inflammatory) cystic lesions of the pancreas; these cysts may be lined by epithelium, acinar cells or other cells.

a) Cysts with mucinous epithelium
Intraductal papillary mucinous neoplasms with its variants
Mucinous cystic neoplasms
Mucinous non-neoplastic cysts (mucoceles and retention cysts)
Serous (clear-cell) cystic tumors
Serous cystadenoma and cystadenocarcinomas
Von Hippel Lindau-associated pancreatic cysts
Squamous-lined cysts
Lymphoepithelial cysts
Epidermoid and dermoid cysts
Squamoid cyst of pancreatic ducts
b) Cysts lined by acinar cells
Acinar cell cystadenoma and cystadenocarcinomas
Endothelial-lined cysts
Lymphangiomas
Degenerative or necrotic changes in solid tumors
Solid-pseudopapillary tumor
Cystic change in ordinary ductal adenocarcinoma
Cystic pancreatic endocrine neoplasia (islet cell tumors)
Cystic change in other invasive carcinomas and cystic mesenchymal tumors
c) Other rare cystic lesions
Cystic hamartomas
Enterogenous (congenital; duplication) cysts and duodenal diverticula
Endometriotic cyst
Secondary tumors
Congenital or developmental cysts
Unclassified cysts

Imaging

Diagnostic procedures for IPMN include endoscopic retrograde cholangiopancreatography (ERCP), computed tomography (CT), magnetic resonance imaging (MRI) with cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS). In the recent past, ERCP represented the gold standard, at least for the main-duct neoplasms. The detection of bulging ampulla of Vater, mucin secretion, and a dilated main pancreatic duct can lead physicians to a direct diagnosis. The relative invasiveness and poor visualization of the entire main pancreatic duct and side branches have relegated this procedure to an optional examination. Currently, the vast majority of IPMNs are characterized by means of cross-sectional imaging studies [9,22,24,25]. CT and MRI/MRCP can localize the tumor and assess its morphology and size. The characteristic feature of IPMNs is cystic dilation of the main pancreatic duct and/or of the side branch ducts (Figs. 3-5). Filling defects representing nodules and papillary projections may be found within the cystic lesions (Fig. 6). In addition, CT and MRI with contrast enhancement successfully assess the relationship of IPMN with local vessels and adjacent organs. MRCP is particularly useful in the characterization of single or multifocal branch-duct neoplasms. This procedure is able to examine the communication between the main pancreatic duct and the cystic lesions. The quality of the MRCP images is improved by the use of secretin stimulation. EUS may be very useful in patients who do not have a definite diagnosis after CT/MRCP. EUS can assess the main pancreatic duct and the presence of nodules and papillae in the main duct with limits only in patients with previous gastrointestinal surgery. In addition, EUS may be

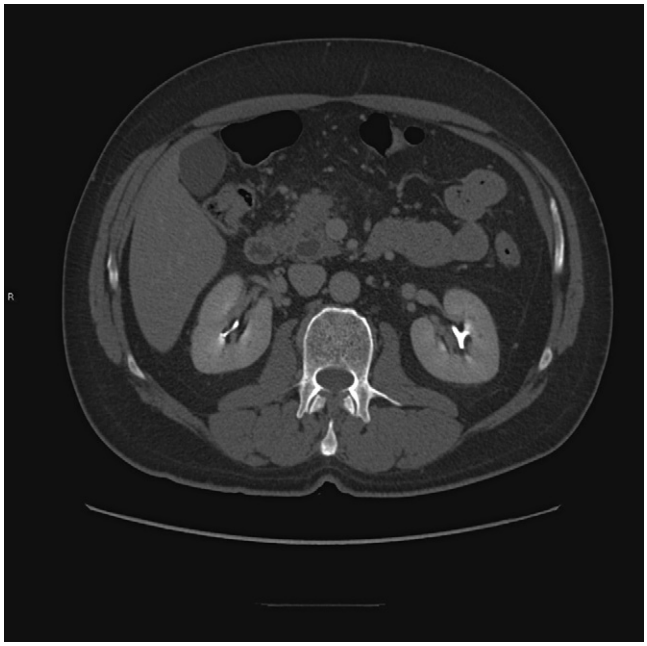

Figure 3 Contrast-enhanced CT scan; main-duct IPMN: the presence of multiple cystic lesions at the head of the pancreas.

completed with a fine-needle aspiration and cytologic and molecular/biochemical exams on the mucin/solid tissue samples [5,19]. International consensus guidelines [5] suggested that EUS should be considered as a second-level

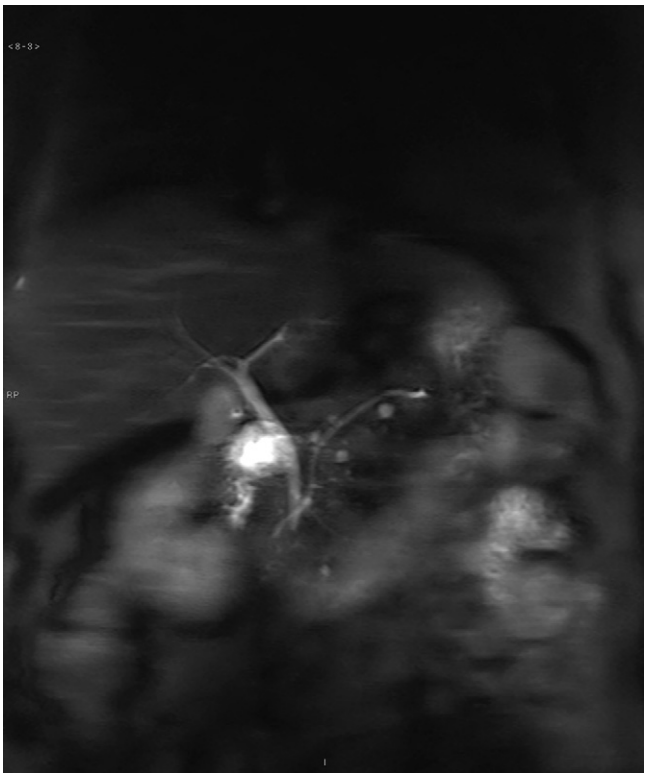

Figure 5 MRCP with secretin stimulation (1 IU/Kg/body weight); IPMN of the side branches (body-tail of the gland) in pancreas divisum.

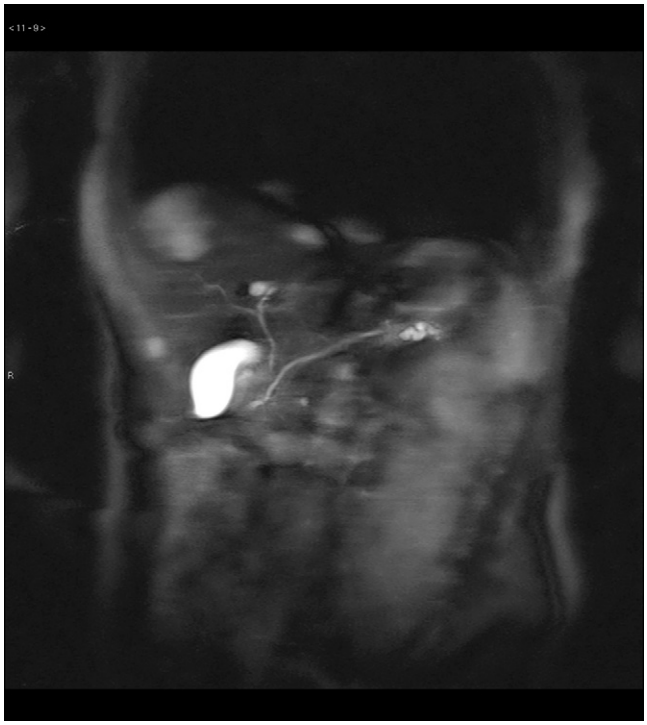

Figure 4 MRCP; IPMN of the distal main pancreatic duct (tail of the pancreas).

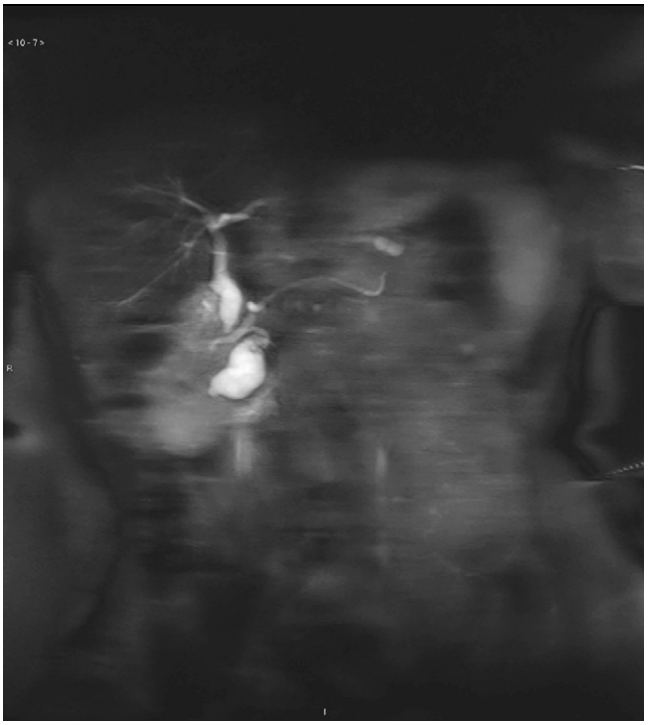

Figure 6 MRCP with secretin stimulation (1 IU/Kg/body weight); IPMN of the uncinate process: the presence of filling defects within the cystic lesion representing nodules and papillary projections.

procedure, which should be performed only in selected cases. Alternatively, over the last few years, EUS with fine-needle aspiration is more often utilized as valuable complementary pre-operative procedure in patients with an already established diagnosis. In recent years, contrast-enhanced abdominal ultrasound, intraductal pancreatic endoscopy and intraductal endosonography have been introduced for diagnostic purposes, but experience with these procedures is still limited and additional studies are needed [26].

Treatment

The choice between non-operative and surgical management strictly depends on the risk of malignancy and on the definitive distinction between benign and malignant IPMNs. Despite the fact that our understanding of the natural history of IPMNs is incomplete, recent data indicate that main-duct and branch-duct IPMNs show significant differences in terms of biological behavior, with main-duct IPMNs having a high risk of malignant degeneration. The frequency of malignancy (in situ and invasive) in main-duct IPMNs ranges between 60 and 92%, with a mean of 70%, and approximately two-thirds of these malignant neoplasms have been invasive [5]. Malignancy is more common in older patients, in symptomatic patients (mainly those presenting with jaundice and/or worsening of diabetes), in neoplasms with higher dilation of the main pancreatic duct, or with the presence of mural nodules and eggshell calcifications [7,18,20]. Evidence of 'clonal progression' in these neoplasms [12] and the age difference between patients with malignant and benign lesions [10] are indicative that most, if not all, benign main-duct IPMNs may progress into invasive cancer. Furthermore, the long-term follow-up of resected patients shows excellent survival for benign and non-invasive neoplasms and a 5-year survival between 36 and 60% for invasive carcinomas [7,27,28]. Based upon these considerations, there are no concerns about the management of main-duct neoplasms, while the management of branch-duct tumors is still uncertain. International guidelines stated that all suspected type-1 (main-duct) and type-3 (mixed-type) IPMNs should be resected, even in asymptomatic patients [5]. Various surgical procedures, such as pancreaticoduodenectomy, left pancreatectomy or total pancreatectomy (according to the site and extent of the neoplasm) with lymph node dissection, must be performed [3,6,7,21,29]. An intraoperative frozen section assessment of the pancreatic resection margin can guide the extent of the resection, keeping in mind that IPMNs are often multifocal. For these reasons, oncological radicality is of paramount importance and limited resections and/or laparoscopic approaches are occasionally indicated in this setting [21,28,29]. Branch-duct IPMNs have a less harmful biological behavior with the frequency of malignancy ranging from 6% to 46%, (mean 25%) and of invasive cancer from 0% to 31% (mean15%) [5,18]. This suggests a less aggressive surgical approach and the possibility of conservative management and careful follow-up [23]. Some malignancy-related parameters have been proposed: the presence of symptoms (in particular recent-onset or worsened diabetes), lesion lesion size $>$ 3.5 cm, the presence of nodules or thick walls, and a carbohydrate antigen 19.9 serum level $>$ 25 U/l. In a recent prospective study [30] in which these parameters were utilized, surgery was indicated in 18.3% of 109 patients with branch-duct IPMNs; in the remaining group (89 cases, 81.7%), only 5 patients (5.6%), after a mean follow up of 18.2 months, showed an increase in lesion size and underwent surgery. Similar results were observed in another recent study involving 194 patients from South Korea [31]: 34 patients (17.5%) were immediately operated on and 18 (11.8%) underwent surgical resection after a median follow up of 12.7 months. After surgery on non-invasive IPMNs (branch- and main-duct varieties), recurrence is rare ($<$ 6%), while recurrence occurs in 50-65% of patients resected for invasive IPMNs [20,22]. The *International Association of Pancreatology* guidelines [5] for the management of pancreatic IPMNs suggested a yearly follow-up for brunch-duct neoplasms if the lesion is $<$ 10 mm in size, a 6-12 monthly follow-up for lesions between 10 and 20 mm, and a 3-6 monthly follow-up for lesions $>$20 mm. The suggested diagnostic procedures for lesions up to 10 mm in size are CT/MRCP, while for lesions $>$ 10 mm, EUS with fine-needle aspiration cytology is added to the protocol. Additionally, branch-duct IPMNs are frequently multifocal, and as a consequence, when surgery is planned, total pancreatectomy or subtotal extensive pancreatectomy is required to perform radical surgery. Therefore, it remains questionable whether these high-risk surgical procedures, which are associated with secondary definite exocrine and endocrine insufficiency, are appropriate in elderly and asymptomatic patients suffering with pancreatic tumors with uncertain biological behavior [32].

Table 2 Main clinical characteristics of patients; AP: acute pancreatitis.

Patients	Age	Gender	IPMN type	Related symptoms	Comorbidity	Treatment	Follow-up
1	79	M	main-duct	AP (single episode)	pulmonary disease	conservative	died 6 yrs later
2	63	F	main-duct	AP (single episode)	diabetes	surgery	alive at 2,4 yrs
3	72	F	mixed	recurrent AP	coronary disease	surgery	alive at 3,1 yrs
4	59	F	main-duct	abdominal pain	diabetes	surgery	alive at 3,7 yrs
5	63	F	main-duct	recurrent AP	no	surgery	alive at 2,7 yrs
6	62	F	branch-duct	AP (single episode)	liver cirrhosis (transplanted)	conservative	died 2,6 yrs later
7	60	M	main-duct	no symptoms	peptic ulcer	surgery	alive at 3,5 yrs
8	54	M	branch-duct	no symptoms	no	conservative	alive at 2,4 yrs

Personal series

Our series included eight patients observed over the last ten years. The main clinical characteristics are shown in Table 2. The mean age was 64 years (range 54-79). The clinical presentation was related to acute pancreatitis in five patients: three with a single episode and two with recurrent attacks; one additional patient was observed because of non-specific dull abdominal pain. Only two patients (one with main-duct and one with branch-duct IPMN) were asymptomatic. A complete laboratory work-up, including serum tumor markers, was performed in all cases. The first two patients in this series underwent ERCP. All of the patients were examined by means of abdominal ultrasonography, contrast-enhanced CT scan and MRCP (five patients had secretin stimulation). Three patients were also examined with EUS and fine-needle aspiration. Five-year and global mortality are 12.5% and 25%, respectively. Both patients who died during the follow-up refused surgery. For an additional asymptomatic patient with an incidentally discovered branch-duct IPMN (2 cm at the tail of the gland) surgical resection was not indicated; the size of this lesion remained stable during the follow-up (last MRCP performed two years after the diagnosis). Thus, surgical resection was performed in 5 out of 8 patients (62.5%). The post-operative course was complicated by pleural effusion and pneumonitis in one patient, by pancreatic fistula in two patients (recovery in two and three months, respectively). No recurrence has been registered in the six patients remaining.

Conclusions

IPMN should be considered in any non-inflammatory cystic lesion of the pancreas and in patients suffering from a single episode or recurrent episodes of acute pancreatitis without a definite etiological factor. Physicians should become familiar with IPMNs, as these pre-malignant or malignant lesions are usually slow-growing tumors. As a consequence, curative resection is possible for the majority of cases, both for the more aggressive type (main-duct IPMN) and in the more favorable tumors (branch-duct type). Because malignancy is more common in older patients, the chances of complete resection often depend on comorbidity and on the anesthesiological class-risk more than local invasiveness.

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