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Intraductal Papillary Mucinous Tumors of the Pancreas: Incidence, Clinical Findings and Natural History

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Intraductal papillary-mucinous tumors of the pancreas are a category of recently described tumors of the exocrine pancreas. They were reported for the first time in 1982 [1] when Ohashi *et al*., based on the findings of four cases of mucous secreting pancreatic cancer, theorized that those cases belonged to a group of tumors with different features with respect to common pancreatic cancer. Some anecdotal reports of variably termed mucinous pancreatic tumors appeared in the subsequent ten years, but the absence of a uniform definition to identify these neoplasms hampered their characterization as a specific group. In 1994, Sessa *et al*. proposed calling the group of neoplasms characterized by intraductal papillary growth of mucin producing, hypersecreting, columnar cells "intraductal papillary-mucinous tumors (IPMTs)" [2]. Since that time, the number of citations of IPMT in the medical literature has constantly increased.

Definition

According to the WHO classification, IPMTs belong to the category of pancreatic cystic tumors. They are defined as intraductal papillary mucin-producing neoplasms, arising in the main pancreatic duct or its major branches. IPMTs are divided into benign, borderline, and malignant non-invasive or invasive lesions [3]. Despite the progress made regarding this type of tumor, the diagnostic pathologic criteria of IPMTs are not well established. The absence of immunohistochemical and molecular markers and the variability of the papillary component, degree of mucin secretion, cystic dilatation and invasiveness hamper its recognition among different exocrine neoplasms, such as pancreatic intraepithelial neoplasias (PanINs), mucinous cystic neoplasms and ductal adenocarcinoma. Recently, a consensus classification has been published to differentiate non-invasive IPMTs and PanINs [4], due to the considerable ambiguities between these two classes of precursors which existed in the previous classification.

Incidence

Data on the incidence can be influenced by the problematic identification of IPMTs; Sohn *et al*., reporting the experience at Johns Hopkins Hospital, described a small number of resected IPMTs per year until the late 1990s, when about a fivefold increase was observed [5]. Such an increase can not simply be ascribed to an increase in the total number of resections. A collective review of three tertiary referral institutions in the USA quoted an incidence of IPMTs between 17-25% of the resections for pancreatic neoplasm performed in the period 1998-2002 [6]. In our institution, the incidence of resected IPMTs has been much lower. Between 2001 and 2003, we performed 204 pancreatic resections; 20 of which were for cystic lesions (10%): 8 IPMTs, 7 mucinous cystic

neoplasms, 3 serous cystic neoplasms and 2 pseudocysts. Excluding non-neoplastic diseases and different periampullary cancers, IPMTs accounted for 5 % of 161 primary pancreatic tumors. The incidence variability probably reflects both the difficulties involved in the pathologic identification of IPMT and a different patient selection: IPMTs are frequently misdiagnosed as chronic pancreatitis and our Department is not a referral center for this disease.

Clinical Findings

There is a slight male predominance among the patients with IPMTs. The mean age is about 65 years; this is usually older than patients with serous and mucinous cystic neoplasms. In 20-30% of cases, IPMTs are an incidental finding, whereas most patients describe epigastric discomfort and more infrequently severe pain and backache. In one third of cases, the clinical presentation mimics a chronic pancreatitis, with pain, diabetes, weight loss and steatorrhea. Jaundice is present in about 20% of patients and its onset correlates with an invasive IPMT [5, 7].

Main Duct Type and Branch Duct Type

Recent series have classified IPMTs according to whether the neoplasm is located in the main pancreatic duct (main duct type) or in a secondary branch (branch duct type). Once more, the criteria to clearly differentiate between these two varieties are not established, and, based on pathologic findings, most cases involve either the main duct or the secondary branches. However, it is usually possible to distinguish the predominant component of the neoplasm, making its insertion into one of the two categories possible. Where this is not possible, the cases should be classified as "mixed" type. The importance of the recognition of the two types of IPMTs (main duct or branch duct type) depends on their different behavior. It has been shown that tumors confined to the secondary branches are less malignant than those involving the main duct. The frequency of malignancy in three series of more than 100 branch type IPMTs, has been about 30% [5, 8, 9], whereas malignancy in the main duct type varied from 63% to 70% in 5 recent series of about 300 cases involving this tumor [5, 7, 8, 9, 10]. Invasiveness in the branch duct type has been correlated to tumor size (greater than 3 cm), and to the presence of mural nodules [9, 10]. Based on these findings, some authors have suggested the possibility of careful observation in order to manage patients with small, branch type IPMTs [10, 11].

Natural History

IPMTs can express all degrees of differentiation ranging, from adenoma to invasive carcinoma. In many cases, the same lesion contains all three grades of dysplasia: adenoma, borderline and carcinoma in situ. IPMTs have a better prognosis than ductal carcinoma, because some of them are diagnosed and treated at a pre-malignant stage. The presence of invasive carcinoma is the main determinant for postoperative survival [5, 12], and the survival figure of IPMTs with nodal metastases resembles the one of ductal carcinoma [12] . The key question, unfortunately still unanswered, is if benign lesions will invariably evolve into an invasive form, or if they will remain benign over time. Increased knowledge of IPMTs and the improvement in preoperative diagnostic tools (EUS, MRCP), allow us to reliably identify pre-malignant IPMT (i.e. branch duct type, less than 3 cm, with no mural nodules). However, in absence of contraindications for resection, is it ethically acceptable to conservatively manage these patients? When considering groups of IPMTs with progressive degrees of dysplasia, it has been noted that the average age increased with the degree of dysplasia [5]. Similarly, a 6.4-year difference in age between patients with benign and those with malignant IPMTs was reported [7]. These observations support the hypothesis of oncogenic transformation from benign to invasive carcinoma. In high-volume pancreatic surgery centres, the mortality rate

after pancreaticoduodenectomy is lower than 5% and it is 0% after distal pancreatectomy [13, 14]. Five-year survival after resection of invasive IPMTs is less than 50%. Even if only 10-20% of pre-malignant IPMTs transformed to an invasive form during conservative management, this management would not be acceptable. Prospective studies are needed to compare surgery and conservative treatment in pre-malignant IPMTs. In the meantime, conservative management is strongly questionable.

Keywords Epidemiology; Incidence; Laboratory Techniques and Procedures; Natural History; Neoplasms, Cystic, Mucinous, and Serous /classification /surgery; Pancreatic Neoplasms

Abbreviations IPMT: intraductal papillary-mucinous tumor; PanINs: pancreatic intraepithelial neoplasias

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