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Emerging role of tumor markers and biochemistry in the preoperative invasive assessment of intraductal papillary mucinous neoplasm of the pancreas

L. You [1], L. Ma [1], W.J. Zhao, Y.P. Zhao *, M.H. Dai *

Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences/Peking Union Medical College, Beijing, China

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ABSTRACT

Background: We explored the significance of laboratory examinations in predicting invasive carcinoma derived from intraductal papillary mucinous neoplasm (IPMN).
Methods: We retrospectively reviewed preoperative laboratory examination data and postoperative pathological data for 87 patients with IPMN who underwent surgical resection at Peking Union Medical College Hospital from February 2008 to March 2015.
Results: Histological review of 87 patients with surgical resection revealed 4 cases of mild-grade dysplasia (4.6%), 34 cases of intermediate dysplasia (39.1%), 16 cases of high-grade dysplasia (18.4%) and 33 cases of invasive carcinoma (37.9%). The first 3 grades were considered noninvasive. In univariate analyses, increased serum concentrations of CA19-9 ($p < 0.001$), CA24-2 ($p < 0.001$), CEA ($p < 0.001$) and hsCRP ($p = 0.027$) were significantly associated with invasive carcinoma. Multivariate analysis showed that increased serum concentrations of CA19-9 ($p = 0.009$) and CEA ($p = 0.042$) were significant independent predictors of invasiveness. The combination of CA19-9, CA 24-2 and CEA improved the accuracy of prediction, and the sensitivity and specificity were 71.0% and 87.7% respectively.
Conclusions: The development of diagnostic laboratory tests has important implications for pre-operative IPMN evaluation. Increased serum CA19-9 and CEA concentrations are independent predictors of invasive carcinoma derived from IPMN, and increased serum CA24-2 and hsCRP concentrations are significantly associated with the risk of invasiveness. Combined detection of CA19-9 + CA24-2 + CEA proved to be the most accurate in predicting the invasiveness of IPMN.

1. Introduction

Intraductal papillary mucinous neoplasms (IPMN) are epithelial tumors that arise from the main pancreatic duct or the branch ducts, causing ductal dilatation due to mucin production. IPMN of the pancreas was first reported in 1982 by Ohhashi as a category of pancreatic tumor distinct from known tumors of the exocrine pancreas. This type of tumor has a better prognosis than ordinary pancreatic ductal adenocarcinoma [1]. However, this tumor type was not precisely defined until 1996, when the name IPMN was first introduced into the classification of exocrine pancreatic tumors propagated by World Health Organization (WHO) and the fascicles of the Armed Forces Institute of Pathology [2]. A series of recent studies have shown that IPMN is the major premalignant cystic neoplasm of the pancreas along with mucinous cystic neoplasm [3,4]. With respect to dysplasia, IPMN encompasses a spectrum of precursor lesions within categories and within individual cases, ranging from innocuous lesions previously referred to as "hyperplasia" or adenoma (currently classified as "low-grade dysplasia") to invasive carcinoma [5,6]. However, the precise definition of "malignant" remains controversial. Most authors recommend defining the "malignant category" as invasive IPMN, excluding "carcinoma in situ". However, in some cases, high-grade dysplasia will also recur in the distant metastasis after resection [7,8]. IPMNs can be classified into three types: main duct IPMN (MD-IPMN), branch duct IPMN (BD-IPMN), and mixed type (in mixed-IPMN, there is dilation of both the main and branch ducts). These types are based on imaging studies and/or histology [9]. IPMN shows variable malignant potential, and MD-IPMN carries a significantly greater risk of malignancy with exclusively branch duct involvement, according to natural history studies and surgical series [10]. The differences in the proportions of each type and in the risks of malignancy can be established by a series of diagnostic examinations, as has been recommended for making the preoperative classification as accurate as possible. According to the characteristics identified by symptoms and imaging, "high-risk stigmata" and "worrisome features" have been used to stratify the risk of malignancy in IPMN, and resection is considered for an increased frequency of surveillance. However, a

* Corresponding authors.
E-mail address: zhao8028@263.net (Y.P. Zhao).
[1] These two authors contributed equally to this work.

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variety of non-invasive and invasive preoperative diagnostic tools do not take into account the results of laboratory testing.

2. Patients and methods

2.1. Patients and data collection

Using the Peking Union Medical College Hospital (PUMCH) patient information database, covering the period between February 2008 and March 2015, we identified 87 patients who underwent surgical resection and were pathologically diagnosed with IPMN at the PUMCH. Patients were excluded if they met the following criteria: (1) previously received any anticancer therapy; (2) a history of previous or synchronous malignant tumors and neuroendocrine tumors; (3) IPMN patients with autoimmune diseases or other inflammatory diseases. Data were recorded retrospectively and included patient age, sex, symptoms related to IPMN, and biochemical laboratory data (including liver and renal functions, blood glucose, blood lipids, and tumor markers).

2.2. Laboratory measurements

Fasting blood samples were collected via venipuncture from all study participants before treatment. Biochemical markers were measured using an AU5800 Clinical Chemistry System by Beckman Coulter. Tumor markers (CA 19-9, CA24-2 and CEA) were measured using the Modular E170 system by Roche.

2.3. Definition of analytical variables

Specimens were characterized using the World Health Organization IPMN grading system as mild-grade dysplasia, intermediate dysplasia, high-grade dysplasia and invasive carcinoma. According to this classification, only invasive carcinoma derived from IPMN is considered malignant. Based on the pathology results, patients were divided into noninvasive/invasive groups. Laboratory test cutoff values were within the reference range.

2.4. Statistics

The statistical correlation between the pathological nature and the lab examination results was analyzed using the χ^2 test and Fisher's exact test. Parameters identified by univariate analysis with p values <0.05 were further tested by multivariate logistic regression to identify independent predictive factors for invasiveness. Statistical significance was defined as $p < 0.05$. All analyses were carried out using SPSS ver 19.0.

3. Results

3.1. Patient clinicopathological characteristics

The mean patient age at the time of surgical management was 61.5 ± 9.2 y, and the gender ratio was 1.81:1 (56 males and 31 females). A total of 64 patients (73.6%) showed various symptoms before the operations. Of those, 60 (69.0%) had abdominal discomfort, 18 (20.7%) had jaundice, 39 (44.8%) had pancreatitis including acute pancreatitis, chronic pancreatitis or acute recurrent pancreatitis, and 23 (26.4%) had diabetes mellitus. The pathological characteristics, was classified by postoperative pathology, including 4 (4.6%) cases of mild-grade dysplasia, 34 (39.1%) cases of intermediate dysplasia, 16 (18.4%) cases of high-grade dysplasia and 33 (37.9%) cases of invasive carcinoma (Table 1).

Table 1
Clinical and pathological characteristics (n = 87).

	Value or n	Percentage
Demographic characteristics		
Age (mean ± SD)	61.5 ± 9.2	
Sex (M:F)	56:31 (1.81:1)	
Clinical characteristics		
Symptoms	64	73.6
Abdominal discomfort	60	69.0
Jaundice	18	20.7
Pancreatitis	39	44.8
Diabetes mellitus	23	26.4
Pathological characteristics		
Mild-grade dysplasia	4	4.6
Intermediate dysplasia	34	39.1
High-grade dysplasia	16	18.4
Invasive carcinoma	33	37.9

3.2. Laboratory examination

Laboratory examinations to detect tumor markers and biochemistry were performed for all patients. Of the 87 patients, the numbers of patients with increased serum CA19-9, CA24-2 and CEA concentrations were 30 (34.6%), 18 (20.7%), and 18 (20.7%), respectively. Biochemical examinations revealed increased concentrations of ALT, ALP, GLU, LDH, TC, TG and hsCRP in 9 (10.3%), 11 (12.6%), 23 (26.4%), 3 (3.4%), 4 (4.6%), 6 (6.9%) and 39 (44.8%) patients, respectively. Additionally, 4 (4.6%) patients showed subnormal TP concentrations, and 10 (11.5%) showed decreased CHE concentrations (Table 2).

3.3. Predictors of invasive IPMN by laboratory examination

In univariate analyses, increased serum concentrations of CA19-9, CA24-2, and CEA ($p < 0.001$), as well as heightened concentrations of hsCRP ($p = 0.027$), were significantly more associated with invasive carcinoma than non-invasive cases (Table 3).

Multivariate analysis revealed that tumor marker CA 19-9 was a statistically significant factor predicting of invasive IPMN ($p = 0.011$) independently. The tumor marker CEA was also an independent predictor of the invasiveness of IPMN ($p = 0.049$) (Table 4).

Moreover, the sensitivities of CA19-9, and CEA were 70.0% and 77.8% respectively, and the specificities were 78.9% and 72.4% respectively. We combine these indicators to predict the invasiveness of IPMN. As expected, combinations of these tumor markers CA19-9, CA24-2, CEA hsCRP improved their sensitivity and specificity to predict the invasiveness of IPMN. The combined detection of CA19-9 + CA24-2 + CEA is a comparatively accurate combination of markers with the highest Youden index (Table 5).

4. Discussion

According to the international consensus guidelines established in 2012, patients suspected of IPMN should be screened for whether they meet the 'high-risk stigmata' or the 'worrisome features' criteria. 'High-risk stigmata' are considered to be indicative of malignancy, whereas 'worrisome features' are possibly indicative of malignancy. Thus, cysts with obvious 'high-risk stigmata' on a computed tomography (CT) or magnetic resonance imaging (MRI) scan should undergo resection without further testing, and 'worrisome features' should be evaluated by endoscopic ultrasound (EUS). During these assessments, a series of imaging evaluations are completed, whereas no mention is made for laboratory examinations (with the exception of serum bilirubin).

The results of our retrospective analysis provide evidence that some tumor markers (CA19-9, CA24-2 and CEA), as well as several blood biochemical components (hsCRP), are associated with a risk of