Blood group type antigens in pancreatic intraductal papillary mucinous neoplasms

Adriana Handra-Luca

Bobigny, France and *Baltimore, USA*

BACKGROUND: **There are few data on blood group (BG) types and types of pancreatic cancers. The aims of this study were to study BG types and BG-antigens in pancreatic intraductal papillary mucinous neoplasms (IPMNs).**

METHODS: **BG type and tumor BG-antigen (glycoprotein) expression (studied by immunohistochemistry on tissue microarrays) were analyzed with regard to characteristics of 101 surgically resected pancreatic IPMNs.**

RESULTS: **Non-O BG type predicted invasive carcinoma independently from high serum CA19-9 and male gender. BG type A was observed more frequently in women than in men. Chronic pancreatitis was more frequently seen in patients with BG type B or AB. Aberrant tumor expression (with regard to BG type) of loss of A antigen expression type occurred in 15.0% of IPMNs and of loss of B antigen expression type in 62.5% of IPMNs. Intraneoplasm BG-antigen expression was not related to dysplasia grade or invasion.**

CONCLUSION: **The results of the study suggest that in pancreatic IPMN, non-O BG type predicted invasive carcinoma, whereas for intratumor BG-antigen expression no specific patterns were detected with regard to the progression of glandular epithelial dysplasia or invasion.**

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KEY WORDS: **blood group type;**
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Author Affiliations: Departments of Pathology, Sydney Kimmel Comprehensive Cancer Center, Johns Hopkins Medical Institutions, Baltimore, MD, USA; and APHP Universite Paris Nord Sorbonne Cite-Sce Anatomie Pathologique, GHU Avicenne, 125 rue Stalingrad, Bobigny 93000, France (Handra-Luca A)

Corresponding Author: Adriana Handra-Luca, MD, PhD, APHP Universite Paris Nord Sorbonne Cite-Sce Anatomie Pathologique, GHU Avicenne, 125 rue Stalingrad, Bobigny 93000, France (Tel: 0033-1-48955555ext2047; Fax: 0033-1-48955602; Email: adriana.handra-luca@avc.aphp.fr)

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Introduction

Blood group(BG) type is considered to be significantly associated with the risk of pancreatic cancer, particularly of pancreatic adenocarcinoma. Study participants with BG type O have a lower risk of pancreatic cancer than those with BG type A, AB or B.[1, 2] More recently, BG type A has been reported to be associated with pancreatic adenocarcinoma risk along with other patients' characteristics such as HBsAg-positive/anti-HBc-positive status, anti-HBs-positive/anti-HBc-positive status, diabetes mellitus, cigarette smoking, alcohol drinking, and a family history of other cancer.[3] Greer et al[4] reported a higher frequency of BG type A in pancreatic cancer patients compared to regional blood donors and, a lower frequency of BG type O relatively to blood donors, patients with pancreatic adenocarcinoma having less frequently BG type O as compared with those with other cancers.[5]

Intraductal papillary mucinous neoplasms (IPMNs) are part of the epithelial pancreatic tumor category, and are defined as macroscopically cystic or mass-forming epithelial neoplasms with ductal differentiation, derived primarily from the pancreatic duct system.[6] Risk factors for IPMNs overlap in part with those for pancreatic adenocarcinomas, a history of diabetes, especially with insulin use, chronic pancreatitis, and a family history of pancreatic ductal adenocarcinoma being relevant to the development of IPMNs.[7] These tumors are known to express several ductal cell keratins and glycoproteins such as CA19-9, CEA, TAG72 or mucin glycoproteins.[6] To our knowledge, glycoprotein expression of BG type A and B and BG type distribution in human IPMNs have not been reported since this tumor group, characterized by the entire spectrum of epithelial dysplasia and invasive carcinoma, has been identified and defined.[6]

The aims of this study were to determine the relationships between BG A and B antigens in IPMN patients, both when located on erythrocytes (defining the general background as BG type) and when located on epithelial cells, neoplastic or not (defining a local

pancreatic background) and clinicomorphological characteristics in pancreatic IPMNs.

Methods

Patients

Patients with pancreatic IPMN diagnosed between 1998 and 2006 at Johns Hopkins Medical Institutions who had been treated by surgical resection were analyzed in terms of clinical (gender, age, BG type, type and date of surgical resection, serum CA19-9 levels, date of death or of the last visit) and morphological data (tumor size, degree of dysplasia, lymph node metastases, vascular and perineural invasion, presence of mucinous morphology, presence of chronic pancreatitis or presence of pancreatic intraepithelial neoplasia-PanIN-lesions) available. An approval was obtained from the institutional review board. IPMNs were classified according to the WHO classification into invasive IPMNs and non-invasive IPMNs, the latter being further classified according to the highest degree of dysplasia present into low and/or intermediate grade and, into high grade IPMN.[6]

According to current guidelines, histological chronic pancreatitis was defined as pancreatic fibroinflammatory changes with unevenly distributed inter- and intralobular fibrosis (leaving the lobular pattern of the organ focally preserved) along with duct changes (obstruction, dilatation or distortion, lined by dystrophic, metaplastic or reactive epithelium) and with varied numbers of lymphocytes, plasma cells and macrophages (either in local accumulations or scattered diffusely throughout the fibrous tissue).[6, 8] Chronic pancreatitis lesions were assessed accordingly on the whole tissue section slides. Since there is no widely accepted standardized system of chronic pancreatitis classification and, that based on the degree and extent of lesions is considered not reproducible, the severity of chronic pancreatitis was not evaluated.[9] PanIN precursor pancreatic ductal lesions have been assessed according to current guidelines, being defined as papillary or flat epithelial ductal neoplasms (non-invasive, confined to the duct), less of 5 mm in size.[6] According to the degree of cytological and architectural atypical, 3 grades of PanIN have been assessed: PanIN1, PanIN2 and PanIN3. Only PanINs present on the tissue microarrays (TMA) slides tissue sections have been studied.

Immunohistochemistry

Immunohistochemistry was performed on slide sections obtained from TMA constructed as previously reported.[10-12] The BG A antigen/glycoprotein, monoclonal mouse (MA1-19693; dilution 1:200, Thermo Scientific, Pierce Protein Research, Rochford, IL, USA) and the BG B antigen/glycoprotein, monoclonal mouse (MA1-19691; dilution 1:100, Pierce Protein Research) have been used. The primary antibody was applied for 60 minutes, the secondary for 30 minutes (Dako EnVision+anti-mouse/HRP polymer, Carpinteria, CA, USA). The slides were treated for 3 minutes with DAB, 4 minutes in hematoxylin. Immunohistochemistry slides (Olympus BX51, 30× objective, Center Valley, PA, USA) were analyzed without knowledge of clinical or morphological data. Expression of A or B antigens was assessed in the non-invasive IPMN in the different dysplasia lesions (low or intermediate grade dysplasia and high grade dysplasia) and in invasive IPMNs (IPMN associated with adenocarcinoma). Cytoplasmic and/or membrane stainings in these lesions were evaluated as the percentage of stained cells with regard to the total number of neoplastic cells.[12] Membrane and/or cytoplasmic expression was also assessed in PanIN lesions available on the TMAs as well as in non-tumoral pancreatic acini and ducts, and the percentage of stained cells was noted. The highest percentage noted for each structure (acini, ducts) or lesion type (low or intermediate dysplasia, high grade dysplasia, adenocarcinoma, PanIN1, PanIN2, PanIN3) was retained. Subsequently, the expression pattern was classified as negative or positive (corresponding to the biological classification of expression patterns), and was used as such for the statistical analyses.

Statistical analysis

Patients' characteristics and tumor features including the immunohistochemical ones were compared by using Fisher's exact test or the Chi-square test. For all tests and models, the variables have been considered as binary. Multivariate logistic regression models have been constructed for predicting the presence of invasive adenocarcinoma in IPMN (invasive IPMN, IPMN associated with adenocarcinoma) and the presence of high grade dysplasia or invasive IPMN. The relationship to postsurgical survival was assessed by the Kaplan-Meier method and compared by the log-rank test. Variables associated with a statistical significance of $P<0.05$ on univariate survival analysis were studied in Cox multivariate survival models. All studied variables have been analyzed for redundancy before constructing the multivariable models. Statistical tests and graphics were performed with the Medcalc (v11.1.1, Belgium) software. A $P<0.05$ was considered statistically significant.[11, 13]