Pathology - Research and Practice xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Indoleamine 2, 3-dioxygenase and B7-H1 expressions as prognostic and follow-up markers in human pancreatic carcinoma

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ARTICLE INFO

Keywords:
IDO
B7-H1
Pancreatic carcinoma
Prognosis
Human

ABSTRACT

This study was to test hypotheses that indoleamine 2, 3-dioxygenase and B7-H1 expressions can be used as prognostic markers in human pancreatic carcinoma (PC). Ninety-five patients were recruited who had undergone radical surgical resection for PC. IDO and B7-H1 expressions in PC tissue specimens were evaluated by immunohistochemistry (IHC) techniques. The clinical and pathological features of these specimens were analyzed.

IDO positive, B7-H1 positive, and combined IDO/B7-H1 positive tumors exhibited significant correlations with lymphocytic infiltration, perineural invasion, TNM status, and pathologic grade ($p < .05$), which tended to show strong correlations with malignant progression of PC. Also, IDO correlated with diabetes mellitus (DM) and HAD scale and B7-H1 correlated with smoke ($p < .05$). In addition, the correlation analysis indicated that IDO had a positive correlation with B7-H1 ($p < .05$). Moreover, the results showed that a combination of IDO and B7-H1 expressions could serve as independent prognostic marker after adjusting by Cox proportional hazards regression models ($p < .05$). IDO and B7-H1 expressions were observed in patient with PC tissues and are important markers for PC malignant progression. A combination of IDO and B7-H1 expression can be served as an independent prognostic marker for PC.

1. Introduction

Pancreatic carcinoma (PC) is a devastating and incurable disease with a median survival of 3–6 months and a 5-year survival rate of 1–4% [1]. Studied indicates that activation of the Indoleamine 2,3-dioxygenase (IDO) and B7-H1 pathway might act as a preferred nodal modifier pathway for immune escape and exhibit elevated expression of IDO and B7-H1 in PC tissues during cancer progression, which plays a role in tumor immunoediting by establishing peripheral tolerance to tumor antigens [2].

IDO is an immunoregulatory enzyme that is implicated in suppressing T-cell immunity in normal pancreatic tissue and PC tissue [3]. IDO is widely dysregulated in tumors and in tumor-draining lymph nodes [3]. Elevated IDO expression has been observed in various human PC [4,5]. Recent preclinical studies indicate that IDO inhibitors can suppress systemic tryptophan catabolism and growth of IDO-expressing tumors and enhance the efficacy of current chemotherapeutic agents [6,7].

B7-H1 is expressed on tumor infiltrating macrophages, dendritic cells, and in human cancers like PC. B7-H1 can contribute to immune evasion and facilitate tumor growth through the B7-H1/PD-1 pathway [8]. Blocking B7-H1 could enhance myeloid dendritic cell-mediated T-cell activation and reduce the growth of a transplanted human tumor in a mice model. The B7-H1positive tumor cell line can also introduce the apoptosis of immune effectors resulting in impairment of CTL lethal effects [9]. Blockade of B7-H1 and PD-1 could potentiate cancer therapeutic immunity [10]. Previous studies showed that IDO and B7-H1 was over-expressed in human PC tumor cells and correlated with TNM status and pathologic grade [11]. But like other prognostic scoring systems based on clinical and pathological features, B7-H1 alone was also less successful in predicting the prognosis of PC patients who had received radical pancreatoduodenectomy.

Therefore, we brought in IDO for this study as another promising immunosuppressive molecular to test its effects alone and combined with B7-H1 in order to investigate the clinical and prognostic significance for PC patients with radical pancreatoduodenectomy.

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https://doi.org/10.1016/j.prp.2018.02.016
Received 20 November 2017; Received in revised form 2 February 2018; Accepted 18 February 2018
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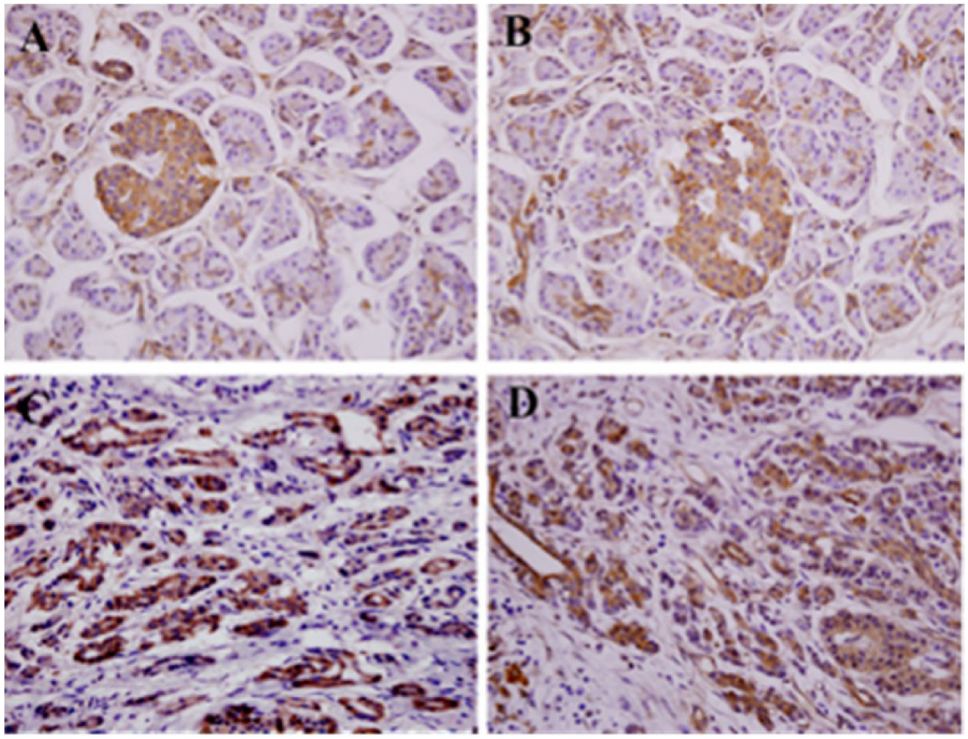

Fig. 1. IHC staining for the analysis of IDO and B7-H1 expressions in paraffin-embedded sections of normal pancreatic tissue and PC tissue. IDO and B7-H1 were positively expressed mainly in the islet cells of normal pancreatic tissues (A and B). IDO and B7-H1 were observed as highly expressed in pancreatic carcinoma tissues, which were located primarily in the cytoplasm and cytomembrane (C and D). Magnification of A–D × 400.

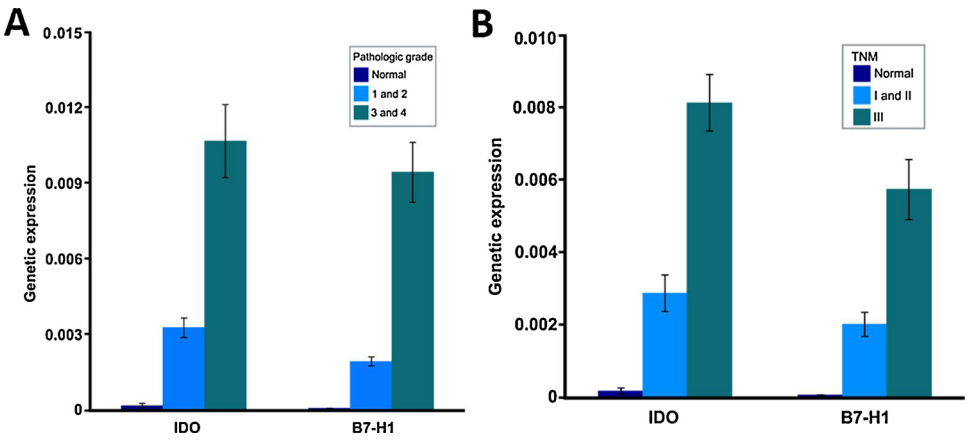

Fig. 2. The mean densities for IDO and B7-H1 expressions were correlated with pathologic grade (A) and TNM status (B). Both IDO and B7-H1 were highly expressed in poorly differentiated pancreatic carcinoma (pathologic grade 3 and 4 or TNM status III) when compared with well differentiated pancreatic carcinoma (pathological grade 1 and 2, or TNM I and II) and normal tissues ($p < .05$).

2. Patients and methods

2.1. Study population and eligibility

This was a retrospective study and was approved by our hospital institutional review board. The study was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent.

Patients with PC undergone radical pancreatoduodenectomy consecutively enrolled. Between January 2001–December 2010, 223 patients were reviewed. Ninety-five of them (58 males and 37 females, age 18–76 years with median age = 55 years) were recruited in this study. Inclusion criteria: patients with PC who undergone radical pancreatoduodenectomy, are identified with PC by postoperative final pathology diagnosis [12]. They received systematically integrated follow-up for these patient. The median follow-up period for all patients was 22 months with a range of 8–39 months. Overall cancer-specific survival time was calculated from the date of surgery to the date of death from PC. Exclusion criteria included the following: patients with any severe cardiopulmonary disease American Society of Anesthesiologists (ASA) classification or ejection fraction below 30% that might prolong the postoperative hospital stay, previous pancreatic operation, immunodeficiency such as that observed under HIV, emergency operation, and pregnancy [12,13].

2.2. Clinical and pathological features

The tumors were classified according to the World Health Organization (WHO) grading system based on WHO criteria and according to the tumor-node-metastasis (TNM) stage system of the International Union Against Cancer [12,13]. Clinical features included age, sex, abdominal or lumbodorsal pain, hypertension, diabetes mellitus, smoking, and local infections. Pathological features included tumor size, pathological grade, peripancreatic invasion, regional lymph node involvement, distant metastases, TNM status, and perineural invasion. Microscopic analysis results of all specimens were reviewed by a pathologist who did not have any prior knowledge of patient outcome or immunohistochemistry (IHC) results.