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Distinct patterns of peritumoral histological findings in subtypes of intraductal papillary mucinous neoplasms of the pancreas☆,☆☆

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ABSTRACT

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are primary pancreatic neoplasms that can act as precursors to invasive adenocarcinoma of the pancreas. The peritumoral stroma has been increasingly recognized to play an important role in many types of tumors. Therefore, to investigate the clinicopathological significance of the peritumoral stroma in IPMNs, we examined the histological features of the peritumoral stroma in each subtype and histological grade of IPMNs. Eighty-two patients with IPMN, who underwent surgical resection, were reviewed clinicopathologically. Intraductal papillary mucinous neoplasms (86 lesions in total) were histologically subclassified into gastric (n = 51), intestinal (n = 22), pancreatobiliary (n = 11), and oncocytic (n = 2) subtypes. Peritumoral histological features between the gastric and intestinal subtypes were evaluated by each histological grade. The results showed that subepithelial edema and inflammatory cell infiltration were more commonly observed in the gastric subtype (74% and 79%, respectively) than in the intestinal subtype (12% and 25%, respectively) of low-grade IPMNs. On the other hand, mucus lakes were more commonly observed in the intestinal subtype (100%) than in the gastric subtype (0%) of high-grade IPMNs. In addition, pancreatobiliary subtype IPMNs tended to exhibit acute inflammation such as neutrophil predominance. This study showed that peritumoral histological features differed among subtypes of IPMNs from low-grade tumors. These differences suggest the possibility that each subtype of IPMNs has a distinct mechanism from an early stage of tumor progression, which is reflected in the properties of the peritumoral stroma.

1. Introduction

An intraductal papillary mucinous neoplasm (IPMN) is now recognized as a precursor lesion in pancreatic cancer [1]. Intraductal papillary mucinous neoplasms show multistep progression that can be observed from the premalignant to invasive stages of cancer progression, and are classified into 4 subtypes: gastric, intestinal, pancreatobiliary (PB), and oncocytic [2]. To clarify the characteristic clinicopathological features according to these subtypes, several studies have reported that differences among IPMN subtypes reflect distinct mechanisms of tumor progression [3–6].

The peritumoral stroma has been increasingly recognized to play an important role in many types of tumors, including pancreatic cancer [7]. In addition, the possibility that the peritumoral stroma may affect drug and treatment efficacy has been suggested previously [8]. Although several studies have investigated the role of the peritumoral stroma in IPMN progression [5,9–13], the correlations between IPMN subtypes and the histological features of peritumoral stroma have not been elucidated in detail. Therefore, in this study, we assessed the histological characteristics of the peritumoral stroma according to each IPMN histological subtype and grade.

2. Materials and methods

2.1. Patients

Tissue samples were retrospectively evaluated from 82 patients (49 men and 33 women; mean age, 66.3 years; range, 32-82 years) who underwent surgical resection of IPMNs (86 lesions in total) at Jichi Medical University Hospital (Shimotsuke, Japan) from 2000 to 2013. The study protocol was approved by the Ethics Committee of Jichi Medical University.

2.2. Histological evaluation

Intraductal papillary mucinous neoplasms were classified into 3 histological grades based on the 2010 *WHO Classification of Tumours of the*

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Digestive System (4th Edition) [14]: low- or intermediate-grade dysplasia (IPMN-L), high-grade dysplasia (IPMN-H), and IPMN with associated invasive carcinoma (IPMN-IC). Furthermore, based on the immunological and histological profiles of proliferating epithelial cells, IPMNs were classified into 4 subtypes: gastric, intestinal, PB, and oncocytic. When 2 or more subtypes coexisted in the same lesion, the dominant subtype was used for analysis. With regard to the tumor size, we traced the outline of the IPMN and associated invasive carcinoma on each slide and put the tumor areas together on the gross photographs, then measured the largest dimension of the tumor. One case without a detailed report on the tumor volume was excluded from the analysis of tumor size. In terms of distribution predominance, we classified IPMNs into 2 groups according to the involvement of the main pancreatic duct or a branch of the pancreatic duct. In addition, we classified the histology of invasion as colloid carcinoma or tubular adenocarcinoma. When 2 different invasive features coexisted in the same lesion, the dominant component of invasive carcinoma was used for analysis.

The peritumoral histological features of IPMNs were evaluated and classified according to 6 criteria and then subclassified as "−" or "+" as follows: (1) subepithelial edema (none to <1/3 of the lesion vs >1/3 of the lesion; Fig. 1a and b); (2) subepithelial inflammatory cell infiltration; (3) congestion (none to sparsely vs moderately to diffusely; Fig. 1a, b, and f); (4) lymphoid follicles (0-2 vs ≥3; Fig. 1e); (5) parenchymal atrophy and fibrosis (none to focally vs multifocally to diffusely; Fig. 1c and d); (6) mucus lakes without floating tumor cells (presence vs absence; Fig. 1c and d). In IPMN-IC grade lesions, we evaluated stromal features surrounding the intraductal components, which are adjacent to the invasive carcinoma. Each section was reviewed by 2 authors (MS and NF), and a consensus was reached in all cases. In the analysis of peritumoral histological features, we excluded 6 lesions that had acute inflammation such as neutrophil predominance.

2.3. Immunohistochemistry

A representative section of each lesion was selected for analysis. Immunohistochemical analysis was performed on 4-μm sections of paraffin-embedded, formalin-fixed tissues. All procedures were performed using a BenchMark ULTRA fully automated staining instrument (Ventana Medical Systems Inc., Oro Valley, AZ, USA). Each section was deparaffinized and incubated in Cell Conditioning Solution 1 (pH 8.5; Ventana Medical Systems Inc.) for 64 minutes at 95°C for antigen retrieval. Then, the sections were incubated with primary antibodies

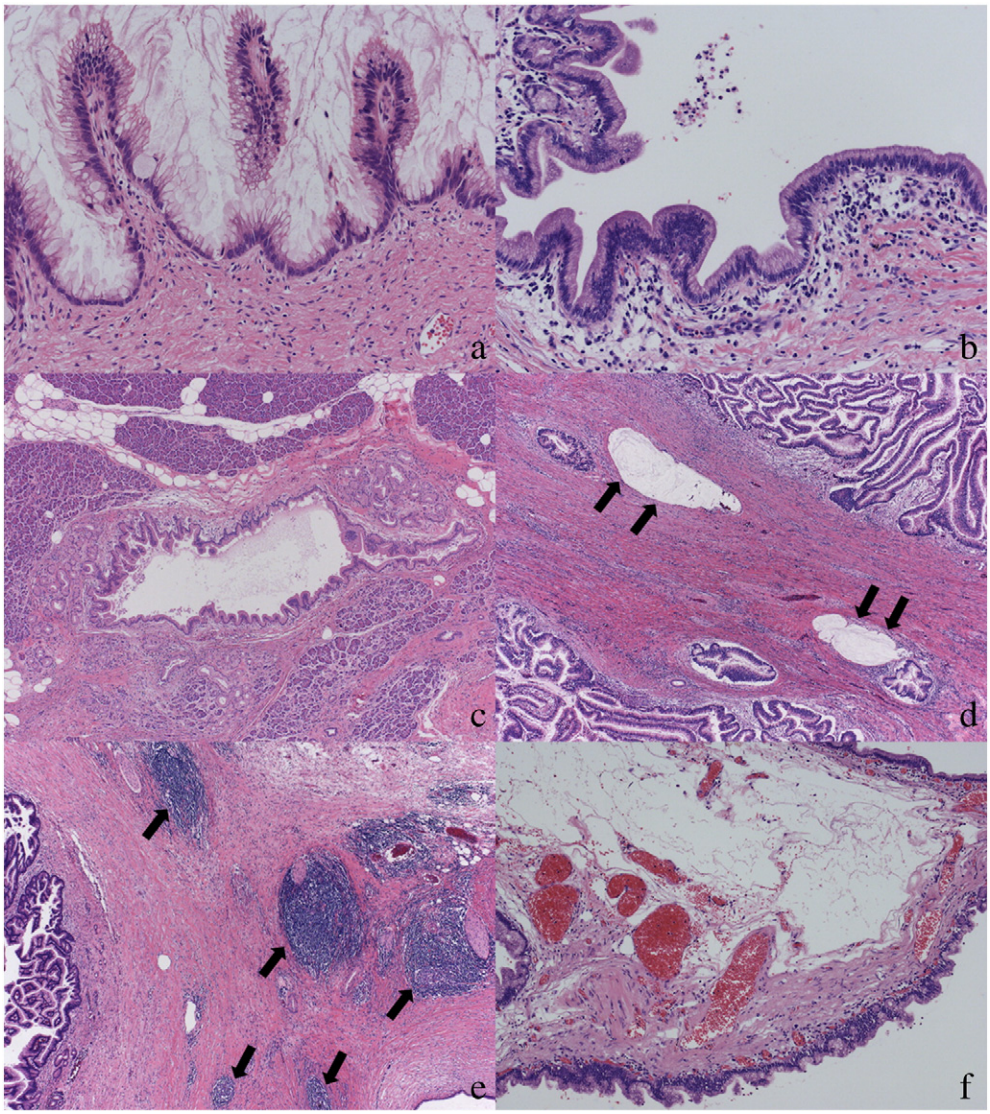

Fig. 1. Peritumoral histological features. (a) Intestinal subtype IPMN; subepithelial edema (−), inflammatory cell infiltration (−). (b) Gastric subtype IPMN; subepithelial edema (+), inflammatory cell infiltration (+). (c) Gastric subtype IPMN; atrophy and fibrosis (−), mucus lakes (−). (d) Intestinal subtype IPMN; parenchymal atrophy and fibrosis (+), mucus lakes (+, arrows). (e) Intestinal subtype IPMN; lymphoid follicles (+, arrows). (f) Gastric subtype IPMN; congestion (+).