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Original contribution

Pleomorphic solid pseudopapillary neoplasm of the pancreas: degenerative change rather than high-grade malignant potential☆

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Summary Solid pseudopapillary neoplasms (SPNs) are rare tumors of the pancreas characterized by poorly cohesive uniform cells with solid and pseudopapillary growth patterns. Nuclear pleomorphism is not a well-recognized feature of SPNs and may complicate differentiation from other pancreatic neoplasms. We compared histologic, immunohistochemical, and clinical features of 18 pleomorphic SPNs with 121 conventional SPNs. The prevalence of pleomorphic SPN was 12.9% (18/139). Pleomorphic SPNs arose in older patients (median, 45 years versus 32 years; $P < .001$), but no differences were found in sex, tumor location, recurrence, and metastasis when compared with conventional SPNs. Except for pleomorphic nuclei, other cytologic and histologic features of pleomorphic SPNs, such as growth pattern, tumor size, infiltrative pattern, tumor extension, mitosis, and Ki-67 labeling index, were not different from those of conventional SPNs. Pleomorphic SPNs showed a significantly higher p53 protein expression (64.7% [11/17 cases]) than that of conventional SPNs (1.8% [2/112 cases], $P < .001$). However, immunoreactivity for β-catenin and E-cadherin was not different between pleomorphic and conventional SPNs. A *TP53* gene mutation was observed in 2 of 3 p53-immunoreactive pleomorphic SPNs. In summary, nuclear pleomorphism occurs in a subset of SPNs. They are more often p53 immunoreactive than SPNs without pleomorphism, and some harbor *TP53* gene mutations. However, pleomorphic SPNs do not appear to be more aggressive than conventional SPNs. Low mitotic rate and Ki-67 labeling index may suggest nuclear pleomorphisms as degenerative changes. Recognition of typical poorly cohesive tumor cells and immunohistochemical features could establish the correct diagnosis of SPNs.

1. Introduction

Solid pseudopapillary neoplasms (SPNs) are uncommon pancreatic neoplasms that account for approximately 1% to 6% of all exocrine pancreatic neoplasms [1,2]. Although most

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SPNs are cured by complete surgical resection alone, SPNs are considered as low-grade malignant neoplasms because 5% to 20% recur or metastasize to distant organs [2,3]. Long-term disease-free survival can be achieved in some patients with metastatic SPNs by resection of their metastases [1,3-6]. Differentiation of SPNs from other pancreatic neoplasms, such as pancreatic neuroendocrine tumors (PanNETs), acinar cell carcinomas, or ductal adenocarcinomas, is important because SPNs have much better prognosis compared with these other malignant pancreatic tumors.

Typical histologic and cytologic appearances of conventional SPNs are well described in the literature [1,7], helping differentiation between SPNs and other pancreatic neoplasms. SPNs have solid and pseudopapillary growth patterns variably mixed with microcysts. Severe degenerative changes with extensive necrosis, hemorrhage, and hyalinization are common histologic features. The neoplastic cells are uniform poorly cohesive polyhedral cells loosely arranged around delicate fibrovascular cores, which often are hyalinized. The neoplastic cells have indented or grooved nuclei and eosinophilic or clear foamy cytoplasm. Periodic acid-Schiff-positive and diastase-resistant hyaline globules are occasionally present inside or outside the neoplastic cells [8]. Foamy histiocytes and cholesterol clefts with foreign body–type giant cells are also characteristic features of the conventional SPNs. Although heterogeneous growth patterns with solid, pseudopapillary, or microcystic features are typical for SPNs, the cytologic uniform appearance is found, in general, throughout the tumors.

Nuclear pleomorphism with enlarged or atypical cells can rarely be seen in SPNs, obfuscating the diagnosis. This pleomorphism can be particularly problematic in the situations of needle-biopsied materials or endoscopic ultrasound (EUS)–guided cytology specimens and frozen examination. Despite the diagnostic and potential prognostic implications of pleomorphism in SPNs, this feature has not been well studied.

Almost all SPNs harbor mutations in the *CTNNB1* gene, which encodes for the β-catenin protein, but besides mutations in *CTNNB1*, SPNs have been shown to have remarkably few genetic alterations [5]. Alteration of p53 is found in many pancreatic tumors but has not frequently been investigated in SPNs.

Here, we describe SPNs with pleomorphic neoplastic cells and correlate this feature with histologic, immunohistochemical, cytologic features and clinical course, comparing them with conventional SPNs with monomorphic tumor cells.

2. Materials and methods

2.1. Case selection and classification of SPNs

After approval (2013-0618) from institutional review boards, a total of 170 pancreatectomy or excision cases of SPNs from October 2005 to March 2012 were retrieved from the pathology database of Asan Medical Center. Among them, 139 cases were available for slide review. We divided SPNs into 2 groups: conventional and pleomorphic SPNs. Pleomorphic SPNs were defined as SPNs in which more than 20% of the total tumor area had cells with significant nuclear pleomorphism. This cutoff was selected because it has been used to define pleomorphic neuroendocrine tumor [4]. Nuclear pleomorphism was defined as more than 4-fold nuclear size variation. SPNs consisting solely of monomorphic cells or having pleomorphic areas less than 20% of the total tumor area were considered conventional SPNs.

2.2. Histopathologic and cytologic evaluation

Representative sections were selected reviewing from 2 to 13 hematoxylin and eosin–stained slides from all cases. Preoperative cytology slides were available from 5 patients with SPN and nuclear pleomorphism. These were obtained by EUS-guided fine needle aspiration before their pancreatectomy. The aspirate of each case was smeared on 4 glass slides and immediately fixed in 100% alcohol and Papanicolaou solution.

2.3. Tissue microarray construction

To obtain uniform immunohistochemical labeling and limit intra-assay variation, tissue microarrays were constructed. Tissue microarrays were constructed from archived formalin-fixed, paraffin-embedded tissue blocks from 112 of 121 surgically resected conventional SPN cases that had available blocks using a manual tissue microarrayer (UniTMA Co Ltd, Seoul, Korea). Three cores (2-mm size) were punched from each conventional SPN and 1 core from matched nonneoplastic pancreatic tissue and placed into recipient blocks. Representative whole sectioned slides from pleomorphic SPNs were used for immunohistochemical labeling.

2.4. Immunohistochemistry

Immunohistochemical labeling was performed at the immunohistochemical laboratory of the Department of Pathology, Asan Medical Center. Tissue microarray sections from 112 conventional SPN cases and whole representative tissue sections from 17 of 18 pleomorphic SPNs with available paraffin blocks were labeled. In brief, 4-μm tissue sections were deparaffinized and hydrated in xylene and serially diluted alcohol solutions, respectively. Endogenous peroxidase was blocked by incubation in 3% H_2O_2 for 10 minutes, and then heat-induced antigen retrieval was performed. Primary antibodies with Benchmark autostainers (Ventana Medical Systems, Tucson, AZ) were used as per the manufacturer's protocol. Primary antibodies for β-catenin (1:2000, CAT-5H10; Zymed, San Francisco, CA), E-cadherin (1:400, 4A2C7; Zymed), synaptophysin (1:200; DiNona, Seoul, Korea), p53 (1:1500, DO-7; DAKO, Glostrup, Denmark),