Pathology – Research and Practice 213 (2017) 997–1001

Contents lists available at ScienceDirect

Pathology – Research and Practice

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

Original article

Post-obstructive cyst formation in pancreas and cystic acinar transformation: Are they same?

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ARTICLE INFO

Article history:
Received 29 January 2017
Accepted 28 March 2017

Keywords:
Pancreas
Acinar cell cystadenoma
Acinar cystic transformation
Cyst
Pancreatic neuroendocrine tumor

ABSTRACT

Pancreatic "acinar cell cystadenoma" (PACA) is a rare benign pancreatic cystic lesion showing acinar cell differentiation. The neoplastic nature of PACA has been questioned and its exact pathogenesis remains unclear. To investigate that acinar cell differentiation is a non-specific metaplastic phenomenon that can occur in pancreatic ductal system, especially when chronically inflamed and dilated, and doesn't necessarily imply an acinar cell neoplasm, we retrospectively analyzed cases diagnosed as PACA and cases with post-obstructive cystic dilatation of pancreatic ducts for acinar cell differentiation using immunohistochemistry for trypsin. The etiology of obstruction was microscopic periductal pancreatic neuroendocrine tumors (PanNET) and pancreatic ductal adenocarcinomas (PDAC). All cases of post-obstructive cystic dilatation showed multiple varying sized cysts distal to the obstruction with histologic findings virtually identical to PACAs. The cysts in both conditions were lined by a single layer of non-dysplastic flattened to columnar ductal-type epithelium with areas of acinar cell differentiation. Trypsin immunohistochemistry confirmed presence of acinar cell differentiation in all cases of post-obstructive cysts and PACAs. Our results suggest that acinar cell differentiation is common in post-obstructive cyst formation, and changes are identical to PACAs. These findings further support the notion that PACA is a benign non-neoplastic cystic lesion with acinar cell differentiation. The findings also suggest that in cases with histology resembling "PACA" or showing diffuse ductal cystic dilation, careful gross examination should be carried out for a proximal obstructive lesion, which can be subtle and easily be missed on initial examination.

1. Introduction

Increasing abdominal imaging in recent years has led to more frequent detection of pancreatic cystic lesions. Some of these cystic lesions are non-neoplastic and benign, while some are pre-neoplastic or neoplastic. Since distinction between benign and potentially malignant cystic lesions can be extremely difficult in some cases clinically, patients undergo pancreatic resection to exclude malignancy. This has led to the identification of a variety of cystic lesions in the pancreas, some of which are of obscure nature. One such lesion has been described as "pancreatic acinar cell cystadenoma" (PACA) [1,2]. This is a rare multicystic pancreatic lesion with acinar cell differentiation in the lining epithelium of the cysts, which was earlier described as cystic acinar transformation of the pancreas [3–5]. While initial reports suggested this to represent a unique type of acinar cell neoplasm, subsequent studies have questioned its neoplastic nature [6]. It is now largely believed that PACA may represent a non-neoplastic process, with acinar cell differentiation or metaplasia in the cystically dilated ducts [6]. The exact nature of this lesion currently remains unclear and the most recent World Health Organization (WHO) classification of pancreatic neoplasms lists PACA as a benign acinar neoplasm and the term continues to be used in practice [7].

We have previously reported extensive post-obstruction cystic dilatation of the pancreatic ductal system due to a small pancreatic neuroendocrine tumor (PanNET) that may mimic a benign intraductal papillary mucinous neoplasm [8]. The histology in such cases also reveals marked similarity of the cystic lesions to so-called PACA as well. We speculate that acinar cell differentiation is a non-specific metaplastic phenomenon that can occur in pancreatic ductal system, especially when chronically inflamed and dilated,

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http://dx.doi.org/10.1016/j.prp.2017.03.013
0344-0338/

and doesn't necessarily imply an acinar cell neoplasm. In order to investigate acinar cell differentiation in cystically dilated pancreatic ducts, we evaluated expression of trypsin in the cyst epithelial lining in cases of post-obstructive cystic dilation to confirm acinar differentiation. For comparison we also included cases diagnosed as PACA. The clinicopathologic features of these two groups were also compared.

2. Materials and methods

2.1. Case selection and clinical information

Nine cases of pancreatic resection specimens with post-obstructive pancreatic cystic lesions were included in the study (Table 1). The etiology of the obstruction was microscopic periductal PanNETs (n = 5) and pancreatic ductal adenocarcinomas (PDACs) (n = 4). Three of these patients with post-obstructive cystic dilation secondary to a PanNET have previously been reported by us [8]. We also included 6 cases diagnosed as PACA (Table 1) based on previously described histologic features: multilocular or unilocular cystic lesion with an epithelial lining containing acinar cells, the presence of eosinophilic periodic acid stain (PAS)-positive cytoplasmic granules, and immunohistochemical acinar markers (trypsin and/or chymotrypsin) without cellular atypia [3,4,9]. The hematoxylin & eosin (H&E) stained slides were reviewed in details in each case. Immunohistochemical staining using the avidin-biotin-peroxidase complex was performed on formalin fixed paraffin embedded 4-μm tissue sections with antibody against trypsin on a representative section in each case. Immunohistochemical staining was also performed for chromogranin A, synaptophysin and Ki-67 on a representative section in all 5 PanNET cases. Staining of the acinar cells of the background pancreatic parenchyma was used as the positive internal control, while lack of staining in the islets was used as negative internal control. Furthermore, a periodic acid stain (PAS) with diastase highlighting the acinar cells was also performed on a representative section in each case.

3. Results

3.1. Gross appearance

3.1.1. Post-obstructive cases

All the 5 cases of post-obstructive cystic dilatation caused by microscopic periductal PanNETs showed similar gross appearance with multilocular cysts (1.5–3.0 cm) (Fig. 1A). The tumor was not obvious at the initial examination in 2 of the cases; however, careful review of the gross and submission of additional sections established the correct diagnosis. All the 4 obstructive cystic lesions due to PDACs also showed multiple cystic lesions due to duct dilatation distal to the obstruction (Fig. 1B), however, the duct obstruction was often complete and the number of cysts was fewer. No excrescences or solid areas were identified within the cyst wall in any of the cases. Cyst fluid was serous in nature. White concretions were identified in 1 case with peri-ductal PanNET (Fig. 1A).

3.1.2. PACA

All the 6 PACA cases were also multilocular with 2 of them located in the head, 2 in the tail, 1 in the neck and 1 in the body and tail of pancreas. All the cystic lesions were ill defined and composed of numerous thin-walled cysts (0.5–4.6 cm). The uninvolved pancreas and the pancreatic parenchyma between the cysts were normal appearing. No excrescences or solid areas were identified in the cysts. Cyst fluid was serous in nature with white concretions in some cysts (Fig. 1C).

3.2. Microscopic findings

3.2.1. Post-obstructive cystic dilatation

All the 5 microscopic periductal PanNETs were small (5–11 mm, mean ± S.D. = 7.6 ± 0.28 mm) and were located at the junction of the dilated and normal part of the pancreatic duct. The duct in each case appeared compressed from the outside by the tumor along with its desmoplastic stroma; however, the lumen was found still to be patent. The pancreatic parenchyma and the duct proximal to the obstructive cystic lesions appeared histologically normal, while the lobules showed varying degrees of atrophy distal to the obstruction. All the 5 microscopic periductal PanNETs were histologically well differentiated and appeared unencapsulated with irregular/infiltrative borders with abundant stromal fibrosis (desmoplasia), and composed of small nests of cell showing mild to moderate nuclear pleomorphism. The tumor cells were positive for neuroendocrine markers (chromogranin A and synaptophysin) with low Ki-67 proliferation index (<2%). Notably, all the 5 cystic lesions caused by microscopic periductal PanNETs showed cysts with different sizes (Fig. 1D) and similar cystic epithelial lining as that of PDACs (Fig. 1E) and PACAs (Fig. 1F). Specifically, the small cysts were lined by single layer of cuboidal or columnar cells with focal intracellular mucin (mucinous metaplasia), and cells with features of acinar cells; the lining cells were often flattened to cuboidal (Fig. 1G) in the larger cysts. All the cysts showed scattered patchy areas of acinar cell differentiation (Fig. 1G–I). These acinar cells showed PAS positive and diastase-resistant fine granular cytoplasm. Similar to PACAs, some of the cysts contained eosinophilic inspissated enzymatic secretions, which were grossly also seen as white concretions (Fig. 1D). Squamous metaplasia was seen in cystic lining in one case (Fig. 2A). Distal to the obstruction there was often acinar atrophy of the pancreatic parenchyma, and variable amount of residual atrophic lobules and residual islets were noted interspersed between the cysts, being virtually nil in some cases.

The cystically dilated ducts (Fig. 1E) seen in PDACs were also similar to the cysts seen with the previous group, including squamous metaplasia in one case (Fig. 2B). The cysts were fewer in this group, the acinar atrophy distal to the obstruction was more severe and most of the cysts were of the larger type. The cysts also showed acinar cell differentiation that was PAS positive and diastase resistant.

3.2.2. PACA

Microscopically, regardless of whether the cysts in PACA were focal or diffuse distributed in the pancreas, the histological features were identical. One case showed squamous metaplasia (Fig. 2C) and one case showed osseous metaplasia in the cyst wall. Varying amount of lobules of pancreatic parenchyma with varying degrees of atrophy were intermingled with the cysts (Fig. 1F). The cysts were mainly lined by a single layer of cuboidal or columnar cells with granular cytoplasm suggestive of acinar differentiation (Fig. 1I). Similar to PanNETs (Fig. 2D) and PDACs (Fig. 2E), the granules were often in the apical cytoplasm and PAS positive granules that were diastase resistant (Fig. 2F). The nuclei were basally located, uniform, and normochromatic with small nucleoli; cellular atypia was absent. Mitoses were extremely rare or absent. Some of the pancreatic acini often appeared to be connected with the smaller cysts and seem to open into the cyst lumen. The larger cysts were lined by flattened cells resembling ductal epithelium admixed acinar cells. In all 6 cases, both the large and small cysts contained eosinophilic inspissated enzymatic secretions (Fig. 1F and I). None of these cystic lesions displayed an ovarian-like stroma or mucinous epithelium or tall papillary units like that seen in a mucinous cystic neoplasm or intraductal papillary mucinous neoplasm (IPMN).