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Original contribution

Carboxypeptidase A1 and regenerating islet-derived 1α as new markers for pancreatic acinar cell carcinoma☆,☆☆,☆☆☆

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Summary Acinar cell carcinoma (ACC) is a rare tumor that differentiates toward pancreatic acinar cells and shows evidence of pancreatic enzyme production. Mixed acinar-neuroendocrine carcinoma (MANC) is defined as having more than 30% of both acinar and neuroendocrine cell types as per immunohistochemistry analysis. Trypsin is currently the most commonly used stain for acinar differentiation. In this study, we investigate the utility of two novel markers, carboxypeptidase A1 (CPA1) and regenerating islet-derived 1α (REG1a), in diagnosing ACC/MANC. Immunohistochemical staining for CPA1 and REG1a was performed on 14 cases of ACC and 5 cases of MANC as well as on 80 other pancreatic tumors including 20 cases each of ductal adenocarcinoma, well-differentiated neuroendocrine tumor, mucinous cystic neoplasm, and solid pseudopapillary tumor. All ACCs and MANCs were positive for CPA1 (all diffuse) and REG1a (12 diffuse, 4 patchy, and 3 focal). A diffuse or patchy staining pattern was significantly more common in ACC/MANC cases (100% diffuse/patchy for CPA1 and 84% for REG1a) than in other pancreatic tumors (5% diffuse/patchy for CPA1 and 7.5% for REG1a), with a P-value of <0.0001 for both CPA1 and REG1a. The sensitivity and specificity of diffuse/patchy staining for CPA1 and REG1a in diagnosing pancreatic ACC/MANC were 100% and 95% for CPA1 and 84% and 93% for REG1a, respectively. In conclusion, CPA1 and REG1a are sensitive markers for ACC that can be used as additional acinar cell differentiation markers to help in the

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diagnosis of pancreatic ACC and MANC. A negative result for CPA1 virtually excludes ACC/MANC.

1. Introduction

Acinar cell carcinoma is a rare tumor that accounts for 1−2% of pancreatic neoplasms in adults [1−6]. It differentiates toward acinar cells and shows evidence of pancreatic exocrine enzyme production. Cases that also show expression of neuroendocrine markers in more than 30% of the tumor cells are classified as mixed acinar-neuroendocrine carcinoma [4,7−9]. The prognosis of acinar cell carcinoma is worse than that of pancreatic neuroendocrine tumor but better than that of pancreatic adenocarcinoma [1−5]. There are also some differences in the treatment [10], and therefore, a correct diagnosis is important. Although well-differentiated acinar cell carcinoma has substantial similarity to normal pancreatic acini, which might give a clue to the diagnosis, because of the rarity of this tumor and the morphologic overlap with other pancreatic tumors, immunohistochemical staining is often needed to confirm the diagnosis. Trypsin, chymotrypsin, lipase, carboxyl ester lipase, and amylase are markers that have been used to detect acinar differentiation. The sensitivity of trypsin is superior to the other markers, but in most studies, it is not 100% [4,11,12]. BCL10 is another marker that is commonly expressed in acinar cell carcinomas and in mixed acinar-neuroendocrine carcinomas, with performance characteristics close to those of trypsin [4,13].

We recently encountered an exceptional case of a patient with a very large abdominal mixed acinar-neuroendocrine carcinoma who developed acute kidney injury. Kidney biopsy exhibited myeloma-like cast nephropathy [14]. Analysis using laser microdissection−assisted liquid chromatography-tandem mass spectrometry and immunohistochemistry identified two acinar cell−specific proteins, regenerating islet-derived 1α (REG1a) and carboxypeptidase A1 (CPA1), in both renal tubular casts and tumor cells, suggesting that the acute kidney injury had resulted from distal tubular obstruction by REG1a and CPA1 secreted by tumor cells. Our experience with this case prompted us to conduct this study to determine whether immunohistochemical staining for these two pancreatic acinar cell−-specific proteins could serve as diagnostic markers for pancreatic acinar cell carcinoma.

2. Materials and methods

Institutional review board approval was obtained for this study. We searched the pathology records of patients from Mayo Clinic for diagnoses of acinar cell carcinoma and mixed acinar-neuroendocrine carcinoma from 1995 to 2018 and identified 18 cases (14 cases of acinar cell carcinoma and 4 cases of mixed acinar-neuroendocrine carcinoma). The index case (fine-needle aspiration with cell block of mixed acinar-neuroendocrine carcinoma), which was a referral case that was reported in the study by Nasr et al [14], was also included in the study. The acinar cell carcinoma cases included 7 resection specimens (some also had fine-needle aspiration with or without biopsies), 3 needle biopsies (and fine-needle aspiration), and 4 fine-needle aspiration with cell blocks. The mixed acinar-neuroendocrine carcinoma cases included 3 resection cases and 2 fine-needle aspiration cases with cell blocks. The control group was composed of 80 randomly selected cases of other pancreatic tumors (all resection specimens) including 20 cases of each of the following: ductal adenocarcinoma, well-differentiated neuroendocrine tumor, mucinous cystic neoplasm, and solid pseudopapillary tumor. Of the neuroendocrine tumors, 9 were of World Health Organization grade 1, 10 were of grade 2, and 1 was of grade 3. For the resected cases, a representative paraffin block was chosen. Immunostaining using trypsin and at least one neuroendocrine marker (synaptophysin with or without chromogranin) was performed on all 19 acinar cell carcinoma/mixed acinar-neuroendocrine carcinoma cases.

2.1. Immunohistochemical analysis

Four-micrometer-thick sections cut from the paraffin blocks with appropriate negative and positive controls were used for immunohistochemical staining. Trypsin, synaptophysin, and chromogranin immunostaining was performed on the Ventana BenchMark XT automated immunostainer (Ventana Medical System Inc.; Tucson, AZ). Antibody localization was visualized using diaminobenzidine (DAB), and the sections were counterstained with hematoxylin. CPA1 and REG1a immunostaining was performed using a Leica Bond RX stainer (Leica Biosystems; Buffalo Grove, IL).

In brief, formalin-fixed, paraffin-embedded tissue sections were retrieved for 20 min using Epitope Retrieval 1 (Citrate; Leica, Buffalo Grove, IL), incubated in Protein Block (Dako, Santa Clara, CA) for 5 min, and then incubated with CPA1 primary antibody (1:800, rabbit polyclonal; Sigma, St. Louis, MO) or REG1a primary antibody (1:200, rabbit polyclonal; Sigma, St. Louis, MO) for 15 min. The detection system used was the Polymer Refine Detection System (Leica, Buffalo grove, IL), which

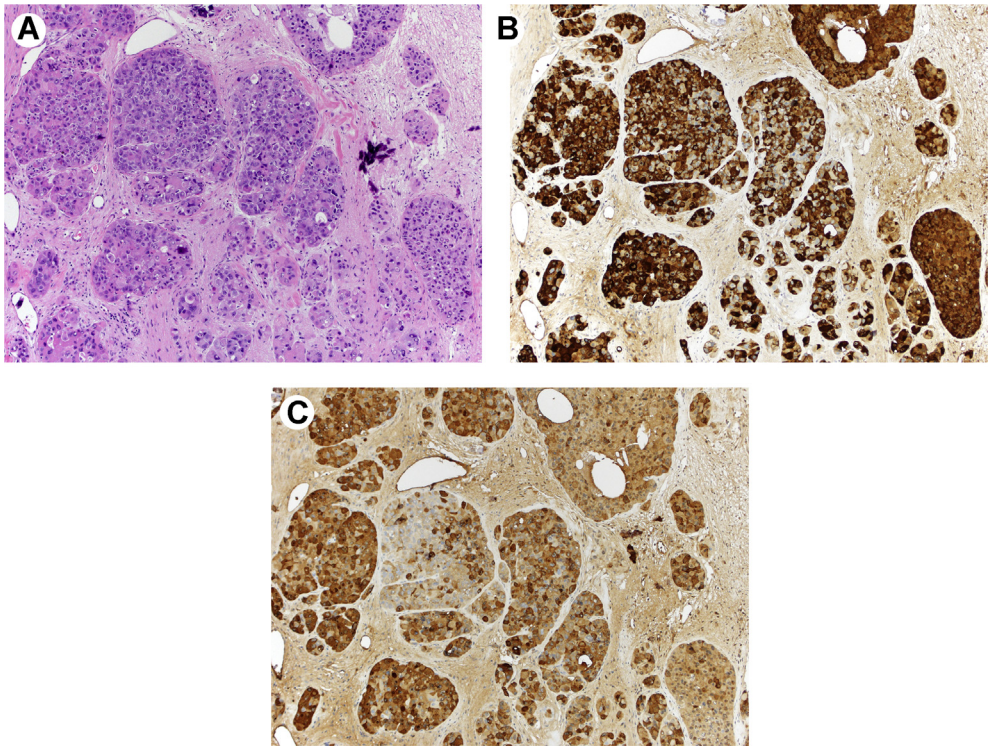

Fig. 1 Acinar cell carcinoma. The tumor has a nested pattern, and the cells show prominent nucleoli (A; hematoxylin and eosin, ×100). The neoplastic cells diffusely exhibit cytoplasmic staining for REG1a (B, ×100) and CPA1 (C, ×100). CPA1, carboxypeptidase A1; REG1a, regenerating islet-derived 1α.

included the hydrogen peroxidase block, post primary and polymer reagent, DAB, and hematoxylin.

CPA1 and REG1a staining was reported as negative (no cytoplasmic staining), focal (<25% of tumor cells with cytoplasmic positivity), patchy (25−50% of tumor cells with cytoplasmic positivity), or diffuse (>50% with cytoplasmic positivity).

Groups were compared, and the P-value was calculated using Fisher's exact test, wherein the expression of markers (CPA1 and REG1a) in acinar cell carcinoma and mixed acinar-neuroendocrine carcinoma was compared with their expression in other pancreatic tumors. P-value <0.05 was considered significant.

3. Results

When present in the section, normal pancreatic acinar cells in the background showed diffuse, strong cytoplasmic staining for CPA1 and REG1a. All 19 acinar cell carcinomas/mixed acinar-neuroendocrine carcinomas were positive for trypsin. In 5 cases, there was synaptophysin positivity in more than 30% of tumor cells; 4 of them were also positive for chromogranin. These cases were classified as mixed acinar-neuroendocrine carcinomas. Mixed acinar-neuroendocrine carcinoma cases showed uniform morphology throughout the tumor (ie, no discrete acinar and neuroendocrine components were appreciated on hematoxylin and eosin or immunohistochemical staining). All acinar cell carcinomas and mixed acinar-neuroendocrine carcinomas were positive for CPA1 (all diffuse) and REG1a (12 diffuse, 4 patchy, and 3 focal) (Figs. 1 and 2). Of the 5 mixed acinar-neuroendocrine carcinomas, 4 were diffusely positive for REG1a and 1 showed focal staining. CPA1 was also positive in 2 (10%) ductal adenocarcinomas (both focal), 10 (50%) well-differentiated neuroendocrine tumors (2 patchy and 8 focal), 2 (10%) mucinous cystic neoplasms (1 diffuse and 1 focal), and 1 (5%) solid pseudopapillary tumor (patchy) (Fig. 3). REG1a was positive in 13 (65%) ductal adenocarcinomas (1 patchy and 12 focal), 1 (5%) well-differentiated neuroendocrine tumor (focal), 9 (45%) mucinous cystic neoplasms (5 diffuse and 4 focal), and none of the solid pseudopapillary tumors (Table 1). Among the 5 mucinous cystic neoplasm cases with diffuse staining for REG1a, 2 had positive staining of both the epithelium and stroma (one of them was also diffusely positive for CPA1 in both epithelium and stroma), whereas in the remaining 3 cases, only the epithelium was positive. The 4 mucinous cystic neoplasm cases with focal staining for REG1a were only positive in the epithelium (one of them was also focally positive for CPA1 in the epithelium). The diffuse or patchy staining was significantly more common in acinar cell carcinoma/mixed acinar-neuroendocrine carcinoma (100% diffuse/patchy for CPA1 and 84% for REG1a) than

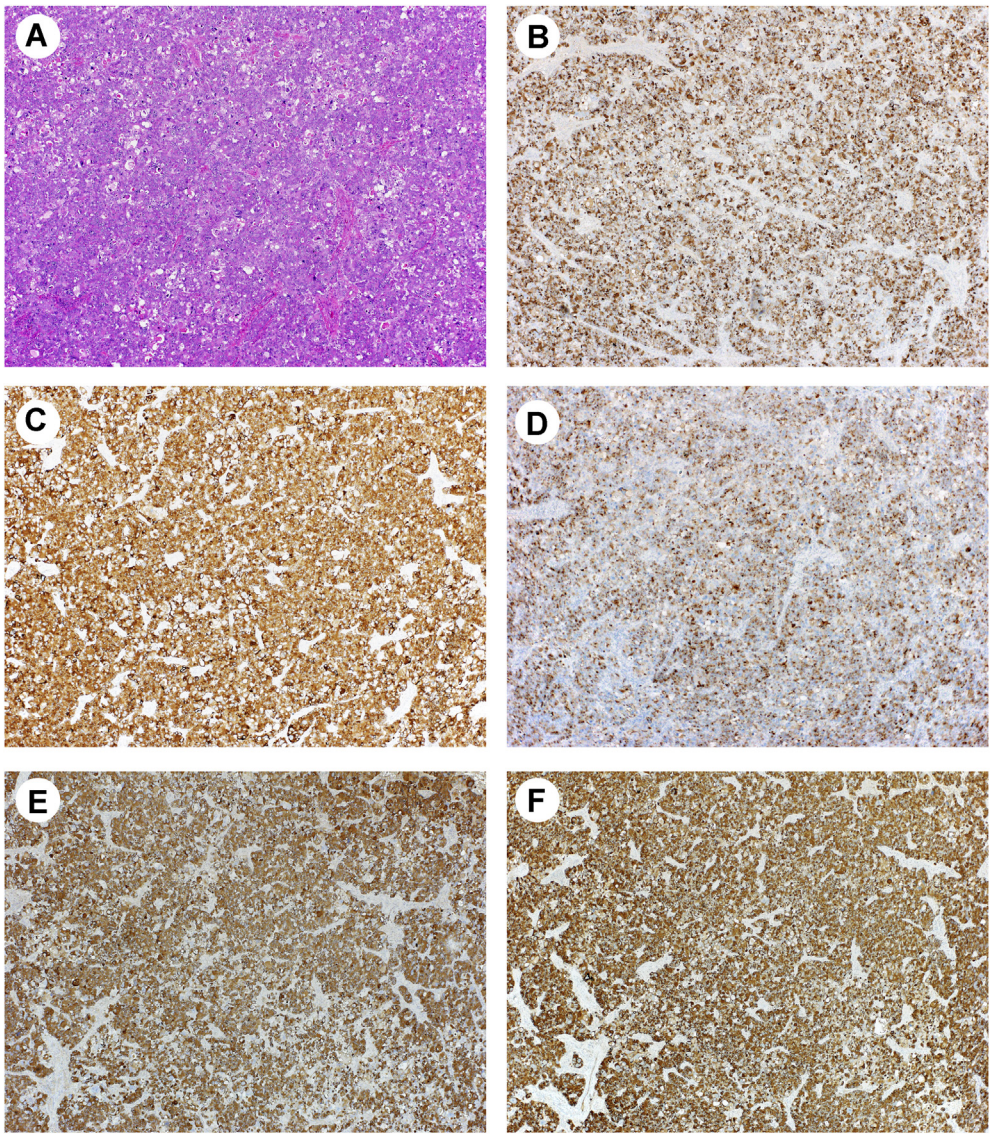

Fig. 2 Mixed acinar-neuroendocrine carcinoma. The tumor has a solid pattern (A; hematoxylin and eosin, ×40). The neoplastic cells are diffusely positive for trypsin (B, ×40), synaptophysin (C, ×40), chromogranin (D, ×40), CPA1 (E, ×40), and REG1a (F, ×40). CPA1, carboxypeptidase A1; REG1a, regenerating islet-derived 1α.

in other pancreatic tumors (5% diffuse/patchy for CPA1 and 7.5% for REG1a), with a p-value of <0.0001 for both CPA1 and REG1a. The sensitivity and specificity of diffuse/patchy staining for CPA1 and REG1a in diagnosing pancreatic acinar cell carcinoma were 100% and 95% for CPA1 and 84% and 93% for REG1a, respectively.

4. Discussion

Acinar cell carcinoma is a rare pancreatic tumor with multiple architectural patterns that can create diagnostic difficulty. Ultrastructurally, the tumor cells show abundant rough endoplasmic reticulum and mitochondria as well as electron-dense zymogen granules. It is an aggressive tumor; half of the patients have metastases at the time of the diagnosis, and another 23% develop metastases after resection of the primary tumor [12]. The overall survival, however, is better than that of pancreatic adenocarcinoma, with 5-year survival ranging between 36% and 72% depending on the stage at diagnosis, with surgical resection significantly improving survival [1–4]. Mixed acinar-neuroendocrine carcinoma has similar clinicopathologic features, cytogenetic backgrounds, and prognosis to acinar cell carcinoma and therefore is conventionally combined with acinar cell carcinoma [4,8,15]. The correct diagnosis of acinar cell carcinoma/mixed acinar-neuroendocrine carcinoma is important and usually requires immunohistochemistry to confirm the diagnosis and exclude its mimickers. Trypsin is the most sensitive marker for acinar differentiation, positive in 95–100% of acinar cell

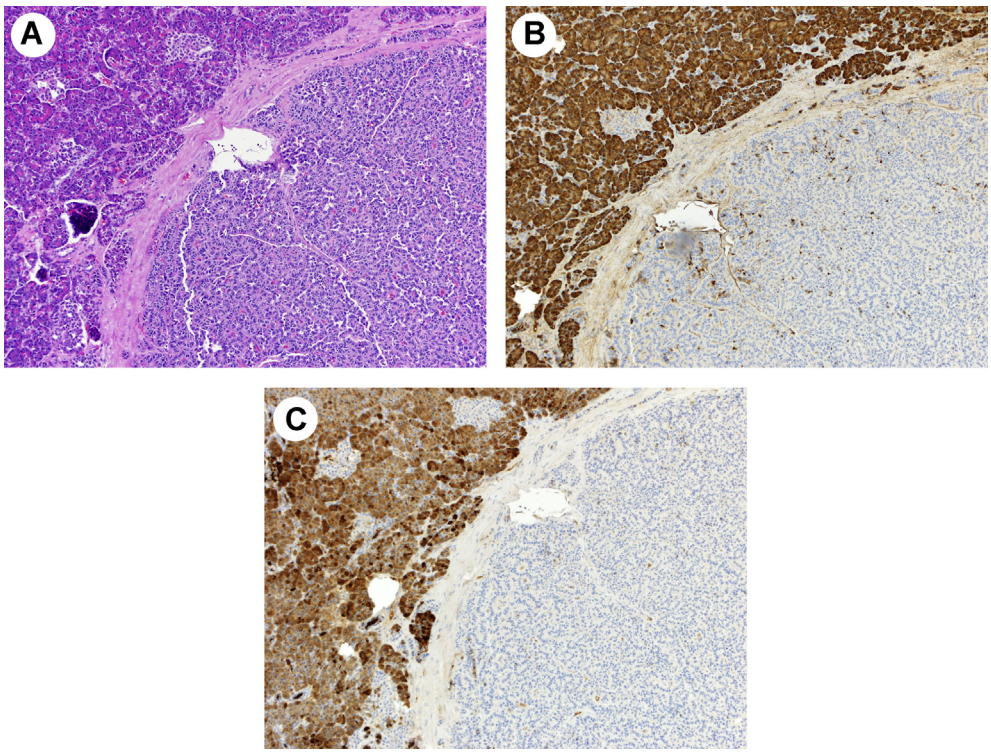

Fig. 3 Pancreatic well-differentiated neuroendocrine tumor. The image shows the tumor (right) with adjacent normal acinar cells (left) (A; hematoxylin and eosin, ×100). The tumor cells are negative for CPA1 (B, ×100) and REG1a (C, ×100). Note that the adjacent normal acinar cells are diffusely positive for both CPA1 and REG1a. CPA1, carboxypeptidase A1; REG1a, regenerating islet-derived 1α.

carcinoma/mixed acinar-neuroendocrine carcinoma cases [4,11−13,16]. Carboxyl ester lipase and a specific anti-BCL10 antibody (clone 331.1, which recognizes the COOH-terminal portion of pancreatic carboxyl ester lipase) also appear to be sensitive markers [4,13]. Amylase, chymotrypsin, and lipase, on the other hand, have low sensitivity [4,12,13]. Although trypsin alone can identify the majority of acinar cell carcinoma/mixed acinar-neuroendocrine carcinoma cases, the use of two markers is preferred and often necessary to confirm the diagnosis when the suspicion is high.

The regenerating (*REG*) gene was originally identified in pancreatic regenerating islets of rats [17]. Its human homolog encodes REG1α protein (lithostathine-1-alpha), which is predominantly expressed in normal pancreatic acinar cells. An immunocytochemical study using immunogold electron microscopy showed localization of REG1α to acinar cell zymogen granules, to condensing vacuoles, and to acinar and ductal lumen contents (supporting its acinar secretory origin). It has also been detected in secretory granules of Paneth cells, but is not present in hepatocytes, the gastric mucosa, or enterocytes [18]. REG1a is considered a useful marker for acinar cell differentiation, and it is positive in acinar cell carcinoma [19]. However, ectopic expression has been reported in a subset of nonacinar cell tumors including pancreatic ductal carcinoma [18,19], gastric carcinoma [20], intrahepatic cholangiocarcinoma and its precursors [21], and ulcerative colitis−associated colon cancer [22].

Procarboxypeptidase A1 (pro-CPA) is a zymogen originating exclusively in pancreatic acinar cells and is one of the most abundant proteins synthesized by the pancreas. It is activated by trypsin to form CPA1 in the intestinal lumen. Serum levels of pro-CPA and CPA are increased in patients with pancreatitis [23]. Furthermore, serum levels of pro-CPA are increased in early ductal pancreatic adenocarcinoma (thought to be due to damage to the upstream acinar cells, leading to a release of pro-CPA), and thus, serum levels of pro-CPA could serve as a serologic marker for early detection of this cancer [23,24]. However, the serum levels of pro-CPA and CPA have not been tested in patients with pancreatic acinar cell carcinoma. To the best of our knowledge, no prior studies have performed CPA1 immunohistochemistry on pancreatic tumors to determine whether this marker can serve as a tissue marker for acinar cell carcinoma of the pancreas.

Our data show that CPA1 and REG1a can be used as immunohistochemical markers for acinar cell differentiation. The normal pancreatic acinar cells show strong diffuse staining for both CPA1 and REG1a. All acinar cell carcinomas/mixed acinar-neuroendocrine carcinomas were positive for CPA1 and REG1a, although REG1a staining was focal in 3 cases. Both markers appear to be more sensitive than amylase, chymotrypsin, and lipase in detecting acinar cell differentiation, based on sensitivity

Table 1 Results of immunohistochemical staining for REG1a and CPA1 in acinar cell carcinoma/mixed acinar-neuroendocrine carcinoma and other pancreatic tumors.

Tumor type	No. of cases	Number of REG1a-positive cases (%) (diffuse, patchy, focal)	Number of CPA1-positive cases (%) (diffuse, patchy, focal)
Acinar cell carcinoma/mixed acinar-neuroendocrine carcinoma	19	19 (100%) (12, 4, 3)	19 (100%) (19, 0, 0)
Nonacinar cell carcinoma:	80	23 (29%) (5, 1, 17)	15 (19%) (1, 3, 11)
Ductal adenocarcinoma	20	13 (65%) (0, 1, 12)	2 (10%) (0, 0, 2)
Well-differentiated neuroendocrine tumor	20	1 (5%) (0, 0, 1)	10 (50%) (0, 2, 8)
Solid pseudopapillary tumor	20	0	1 (5%) (0, 1, 0)
Mucinous cystic neoplasm	20	9 (45%) (5, 0, 4)	2 (10%) (1, 0, 1)

Abbreviations: CPA1, carboxypeptidase A1; REG1a, regenerating islet-derived 1α.

data in previously published articles. CPA1, in particular, has an excellent sensitivity (100%) and a very good specificity (95%), and its performance seems to be close to that of trypsin. Thus, negative staining of tumor cells for CPA1 virtually excludes acinar cell/mixed acinar-neuroendocrine carcinoma. The majority of the positive REG1a (17 [74%]) and/or CPA1 (11 [73%]) nonacinar cell carcinoma cases showed only focal staining. In this group, 5 cases exhibited diffuse staining for REG1a; one of them was also diffusely positive for CPA1. However, all of these cases were mucinous cystic neoplasms, which usually have distinct morphologic appearance compared with acinar cell carcinoma. It is not clear why some mucinous cystic neoplasm cases show positivity for REG1a. This could represent ectopic expression as has been reported in pancreatic ductal carcinoma, intrahepatic cholangiocarcinoma, and gastric carcinoma [18–21]. Only 4 cases (5%) showed patchy REG1a or CPA1 staining (2 neuroendocrine tumors, 1 ductal adenocarcinoma, and 1 solid pseudopapillary tumor) (Table 1). When the cutoff for positive staining is set up at more than 25% of tumor cells with cytoplasmic staining (diffuse and patchy), the sensitivity and specificity of CPA1 and REG1a in diagnosing pancreatic acinar cell carcinomas/mixed acinar-neuroendocrine carcinomas were 100% and 95% for CPA1 and 84% and 93% for REG1a, respectively. Based on other studies and the results of our study, trypsin, BCL10, and CPA1 appear to be the most sensitive markers for acinar cell differentiation. Any of these markers can be used to evaluate for acinar cell differentiation, although the use of 2 markers is preferred as the sensitivity of both trypsin and BCL10 is less than 100% and while the sensitivity of CPA1 is 100% in our hands, this is based on a single study, and confirmatory studies from other centers are needed.

In conclusion, our results show that both CPA1 and REG1a can serve as additional markers for acinar cell differentiation for diagnosing acinar cell carcinoma and mixed acinar-neuroendocrine carcinoma. Sensitivity and specificity of CPA1 are superior to those of REG1a and appear to be comparable with those of trypsin. A negative result for CPA1 virtually excludes acinar cell carcinoma/mixed acinar-neuroendocrine carcinoma.

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