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Pancreatic mucinous cystic neoplasms: a clinicopathological study of 11 cases and detailed review of literature

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Abstract

Background: Mucinous cystic neoplasms (MCNs) of pancreas are relatively rare, occur almost exclusively in middle-aged females, and are overwhelmingly located in the body and tail of the pancreas, histologically show an ovarian type stroma. MCNs are premalignant, low aggressive tumors. Here we describe the clinicopathologic and radiologic features and follow up of cases diagnosed in our practice. We also present a detailed review of recent literature.

Materials and methods: Based on strict criteria, 11 cases diagnosed between 2002 and 2016 were included in the study.

Results: All cases were reviewed histologically. Mean and median age was 46.7 and 46 years respectively. All patients were females and 9 out of 11 cases were located in the body and/or tail of the pancreas. Mean tumor size was 8 cm. Grossly, cysts were uni or multilocular and ranged from a few millimeters to several centimeters in diameter. Microscopically, all cases showed characteristic tall columnar, mucin producing epithelium and ovarian type stroma. Atypia was mild in 8 cases and severe in 3 cases. The latter 3 cases were classified as non-invasive MCNs with high grade dysplasia (2 cases) and MCN with an associated invasive carcinoma (1 case). On immunohistochemistry, all cases showed epithelial positivity for cytokeratin AE1/AE3 and stromal positivity for vimentin and smooth muscle actin. Follow up was available in 7 cases. All patients were alive and well with no recurrence.

Conclusions: Our cases show features similar to those described in other published studies although cases in our series tended to be larger in number. Since these tumors are relatively rare, premalignant and have strict diagnostic criteria, they must always be considered in the differential diagnosis of pancreatic mucinous cystic lesions. Larger studies incorporating greater number of patients and more detailed follow up will help in increasing our understanding of MCNs.

Keywords: Pancreas, Mucinous cystic neoplasm, Ovarian type stroma, Columnar mucin producing epithelium

Introduction

Mucinous cystic neoplasms (MCNs) of the pancreas are relatively rare neoplasms comprising about 8% of surgically resected cystic lesions of the pancreas. More than 95% occur in the body and tail of the pancreas and the vast majority, if not all, occur in females, with mean age between 40 and 50 years. These cystic neoplasms do not communicate with the pancreatic duct system and contain an ovarian type subepithelial stroma. These tumors are either premalignant (MCN with low or intermediate grade dysplasia) or malignant (MCN with high grade dysplasia or with an associated invasive carcinoma). Differential diagnosis mainly includes other mucinous cystic neoplasms of the pancreas such as intraductal papillary mucinous neoplasms (IPMNs), mucinous non-neoplastic pancreatic cysts and pancreatic pesudocysts. Surgical resection with negative margins is curative for almost all non-invasive MCNs while in cases with an invasive carcinoma, the prognosis depends on the depth of invasion, lymph node and distant metastases, and complete surgical

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resection. An associated invasive carcinoma is seen in up to one third of cases (Thompson et al. 1999; Zamboni et al. 1999; Kosmahl et al. 2004; Goh et al. 2006; Hruban et al. 2007; Crippa et al. 2008; Zamboni et al. 2010).

In older published series, MCNs were probably over represented due to poorly defined diagnostic criteria for these tumors in the past. Recently, however, a rise in the incidence of MCNs has been noticed probably owing to clearly defined diagnostic criteria and advances in imaging techniques (Zamboni et al. 2010). Herein we describe the clinicopathologic and radiologic features, follow up of 11 cases of pancreatic MCN, and present a detailed review of recent published literature.

Materials and methods

The surgical pathology files of the Section of Histopathology, Department of Pathology and Laboratory Medicine, Aga Khan University Hospital were searched for all cases of mucinous cysts, pseudocysts and mucinous cystic neoplasms of the pancreas reported over a 15-year period (2002 to 2016). Only those cases were included in which radiological films were available for correlation. All cases were correlated with radiological (imaging) studies including ultrasound (US), magnetic resonance imaging (MRI), computed tomography (CT) or endoscopic ultrasonography (EUS) and all those having communication with the pancreatic duct system were excluded. The remaining cases were reviewed histologically by the two principal authors (NU and ZA) and cases with cysts lined by columnar, mucin producing epithelium and subepithelial ovarian type stroma were included. All other mucinous cystic lesions (neoplastic or non-neoplastic as well as pseudocysts) which did not meet the above criteria were excluded. Based on the clearly defined criteria, 11 cases were identified and included in the study. Special stain for acid mucin was performed on all cases. Immunohistochemistry was performed on all 11 cases. Cytokeratin AE1/AE3 (mouse monoclonal antibody, DAKO North America, Carpinteria, California USA) was used for staining epithelial cells while vimentin (mouse monoclonal antibody, DAKO Denmark, Glostrip, Denmark) and anti-smooth muscle actin (ASMA, mouse monoclonal antibody, DAKO Denmark, Glostrip, Denmark) were used for staining the subepithelial ovarian type stroma. In selected cases, Calretinin (mouse monoclonal antibody, DAKO Denmark, Glostrip, Denmark) and Inhibin (mouse monoclonal antibody, DAKO North America, Carpenteria, California, USA) were also performed.

Results

Based on the strict inclusion and exclusion criteria, 11 cases were identified. The ages of patients ranged from 26 to 60 years (mean 46.7 years, median 46 years). All 11 patients were females. Out of 11 cases, 9 (81.8%) were located in the body and tail of the pancreas while 2 (16.7%) were located in the head. Tumor size, when available, ranged from 4 cm to 14 cm (mean 8 cm, median 9 cm). In all cases, CT and US revealed sharply demarcated, rounded, lobulated hypoechoic or low density masses mostly in the body and /or tail of the pancreas. These masses were cystic with one larger loculations. Some cases showed irregular hyperdense areas (Fig. 1a, b). The non-neoplastic pancreas demonstrated normal shape and enhancement. None of the cases showed any involvement of peripancreatic fat. On endoscopic retrograde cholangiography (ERCP), there was displacement of main pancreatic duct, and more importantly, absence of communication of main pancreatic duct with the cystic tumor locules was noted.

Gross examination typically revealed spherical masses with unilocular or multilocular cysts on cut surface with cysts ranging in size from few millimeters to several centimeters (Fig. 2). The cystic locules were filled with thick mucinous, gelatinous to yellowish material. Average thickness of cyst wall was 0.2 to 0.3 cm. Outer

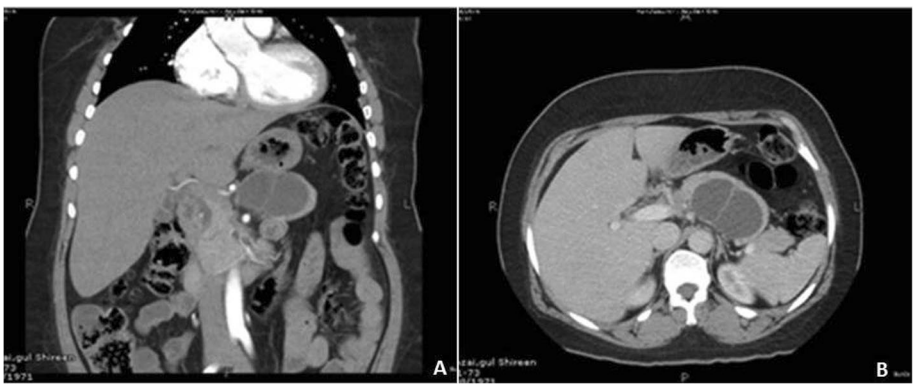

Fig. 1 a, **b**. CT scan, coronal and transverse planes shows a well-defined cystic lesion without solid component in the body of pancreas. No peripancreatic fat stranding seen

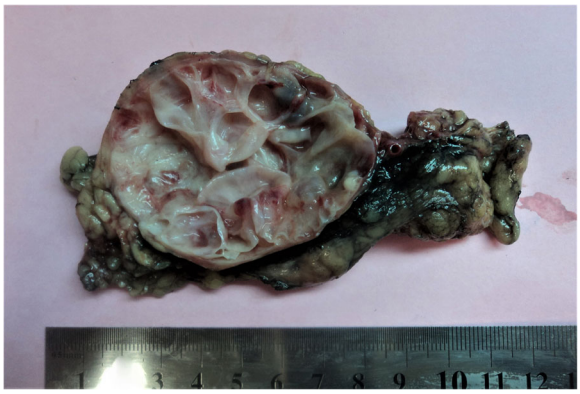

Fig. 2 Gross appearance of mucinous cystic neoplasm. A circumscribed tumor is seen in the tail of pancreas composed of variable sized cysts. The cysts are surrounded by thick fibrotic septae and contained mucoidy material

surfaces were mostly smooth. Histologically, all cases displayed characteristic tall, columnar, mucin producing cells which stained with diastase resistant periodic acid-schiff (PAS) and Alcian blue (AB). Atypia was uniform, benign appearing or mild (Fig. 3a, b) in 8 out of 11 cases and severe in 3 cases. Of these 3 cases, 2 cases were reclassified (on review), one as non-invasive MCN with high grade dysplasia (Fig. 4a, b) and the other as an invasive MCN with undifferentiated carcinoma (MCN with an associated invasive carcinoma). The third case was reported in 2015 as non-invasive MCN with high grade dysplasia. These three cases demonstrated nuclear stratification, loss of polarity, nuclear pleomorphism, prominent nucleoli and frequent mitoses (including atypical mitoses). All 11 cases showed characteristic subepithelial ovarian type stroma. In few cases, ovarian type stroma showed focal lutenization in form of clusters of epithelial cells. Epithelial denudation and/or atrophy was seen in 4 out of 11 cases (36.4%) (Fig. 5a). Acute and/or chronic inflammation was seen in 8 out of 11 cases (72.7%) (Fig. 5b). Epithelial lining was positive for mucin stain in all 11 cases. On immunohistochemistry, epithelial cells in all 11 cases demonstrated positivity for cytokeratin AE1/AE3, while stroma in all 11 cases demonstrated positivity for vimentin and ASMA. Inhibin and Calretinin were performed in only two cases and the result for both was negative. Follow up information was obtained from patients (or close relatives were contacted on phone by one of the authors (MZ) and follow up was available in 7 out of 11 cases. These included two cases with non-invasive MCN and high grade dysplasia. All 7 patients were alive and well with no history of recurrence or metastasis. None received any chemotherapy or radiation therapy following surgical resection (Table 1).

Discussion

All our patients were females and 9 out of 11 cases were located in the body and/or tail of the pancreas. Mean age at diagnosis was 46.7 years. Various published studies have shown that these tumors occur almost exclusively (over 95%) in middle aged, perimenopausal females and over 90% are located in the pancreatic body or tail. Studies have given median age over 45 years (47.5 years in our study). As diagnostic criteria for pancreatic MCNs were refined and standardized over the last several years, the diagnosis of MCN in males and head of pancreas considerably reduced in frequency and is seldom made now (Adsay 2008; Sakoratas et al. 2011; Schmid and Siveke 2014; Nilsson et al. 2016; Ethun et al. 2017; Griffin et al. 2017). All our patients presented with symptoms of abdominal pain and mass, mostly in the epigastric region. Palpable abdominal mass is the usual presenting symptom for larger tumors while tumors smaller than 3 cm are often found incidentally (Zamboni et al. 2010). Radiologically, all our cases presented as sharply demarcated lesions with one or more cystic locules on EUS, MRI or CT. The cystic locules of MCNs do not communicate with the main pancreatic duct

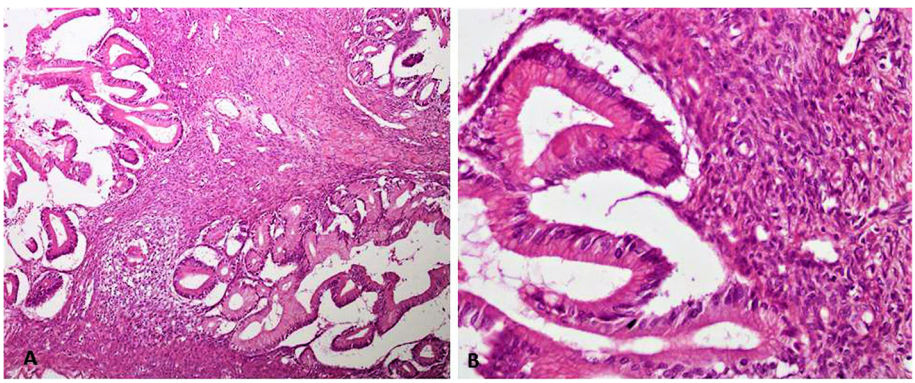

Fig. 3 a, **b** Histologically, mucinous cystic neoplasms are lined by tall columnar epithelium with basally placed mildly atypical nuclei and hypercellular subepithelial stroma

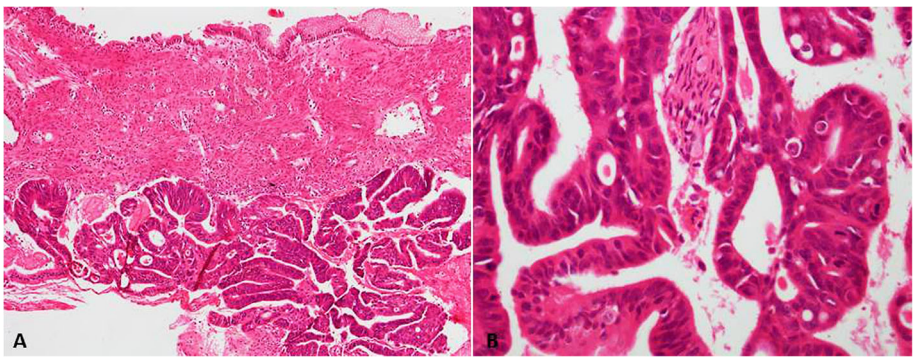

Fig. 4 **a**, **b** Mucinous cystic neoplasm with high grade dysplasia. The neoplasm shows both conventional tall columnar lining at top (**a**) and high grade dysplastic foci at bottom. There is nuclear pseudostratification, hyperchromasia and increased mitosis (**b**)

(Buetow et al. 1998; Oh et al. 2008). All 11 tumors in our study did not show any communication with the main pancreatic duct.

Mean and median tumor sizes in our cases were 8 and 9 cm respectively. Tumor size in our study was much larger than mean tumor size of 4.3 cm reported in a recent study (Griffin et al. 2017). According to the latest World Health Organization (WHO) Classification, mean size of MCNs is 6 to 10 cm while size ranges from 2 to 35 cm (Zamboni et al. 2010). Although premalignant, MCNs behave as low aggressive tumors and tumors less than 4 cm in size have exceptionally low rates of malignant transformation (Nilsson et al. 2016).

All 11 cases in our series showed cysts with smooth outer surfaces ranging in size from few millimeters to several centimeters on cut surface and filled with thick mucinous to gelatinous material. Cyst walls were 0.2 to 0.3 cm in thickness. These findings were similar to those usually found in MCNs (Zamboni et al. 2010). None of the cases in our series, not even the two non-invasive MCNs with high grade dysplasia or the single case with invasion and associated carcinoma showed any papillary projections or mural nodules on gross appearance which are seen in the cystic locules of MCNs with associated invasive carcinoma (Zamboni et al. 1999).

Histologically, all 11 of our cases demonstrated the columnar mucinous epithelium and subepithgelial ovarian type stroma characteristic of MCNs (Zamboni et al. 2010). Dysplasia was low grade in 8 cases while it was high grade in 3 cases. Ovarian type of stroma is now a requirement for diagnosis of these tumors (Tanaka et al. 2006; Adsay 2007). Dysplasia in MCNs can be low grade, intermediate grade or high grade (Hruban et al. 2007). One recent study showed that 71% MCNs have low grade dysplasia (Griffin et al. 2017). The percentage of invasive carcinoma in MCNs has ranged from as low as 6% to as high as 55% in various published studies (Griffin et al. 2017; Testini et al. 2010; Zamboni et al.

Table 1 Follow up information in our series ($n = 7$)

No.	Age (years)	Year of resection	Site in pancreas	Size (cm)	Original pathological diagnosis on resection specimen	Follow up (months)	Current status
1	≥ 50	2003	Head of pancreas	9x8x4	Benign mucinous cystadenoma	168	Alive and well. No recurrence. No chemo or radiation therapy given
2	≥ 50	2009	Tail of pancreas	Not known	Non-invasive Mucinous cystadenocarcinoma (reclassified as non-invasive MCN with high grade dysplasia)	94	Alive and well. No recurrence. No chemo or radiation therapy given
3	30–40	2010	Tail of pancreas	6.5x5x2.5	Benign mucinous cystadenoma	82	Alive and well. No recurrence. No chemo or radiation therapy given
4	40–50	2011	Tail of pancreas	13x9x4	Benign mucinous cystadenoma	70	Alive and well. No recurrence. No chemo or radiation therapy given
5	≥ 50	2011	Tail of pancreas	6.5x5x4.5	Benign mucinous cystadenoma	69	Alive and well. No recurrence. No chemo or radiation therapy given
6	40–50	2015	Tail of pancreas	7.5 × 5	Non-invasive MCN with high grade dysplasia	21	Alive and well. No recurrence. No chemo or radiation therapy given
7	40–50	2016	Tail of pancreas	6x5x4	Benign mucinous cystadenoma	11	Alive and well. No recurrence. No chemo or radiation therapy given

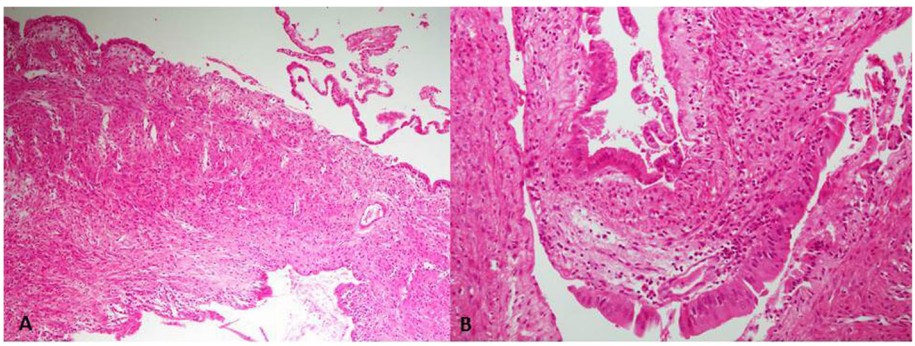

Fig. 5 **a**, **b** Lining epithelial denudation with focal inflammation (**a**), acute and chronic inflammation within cyst wall (**b**)

2010; Naveed et al. 2014). Since invasive component may be focal, careful and extensive sampling is required (Zamboni et al. 2010). All our cases were positive for immunohistochemical stains CKAE1/AE3 (epithelium) and vimentin plus anti-smooth muscle actin (stroma). In selected cases, inhibin and calretininn were performed which were positive in stroma. These findings were consistent with published studies (Thompson et al. 1999; Zamboni et al. 1999).

Both non-invasive and invasive MCNs of pancreas demonstrate activating point mutations in codon 12 of the KRAS gene. The prevalence of KRAS mutations increases with increase in the degree of dysplasia from low to high grade. KRAS driver mutations are now believed to be the major driver genetic alterations in these tumors and may be involved in disease progression occurring in low grade MCNs leading to tumor progression. Alterations in p53 tumor suppressor gene are seen more frequently in invasive MCNs. In MCNs, preoperative testing for KRAS mutations may be helpful in estimating the malignant potential (Jimenez et al. 1999; Kim et al. 2003; Conner et al. 2017; Fujikura et al. 2017). Thus, molecular biomarkers are now believed to be useful in improving the diagnostic workup and estimating the malignant potential of pancreatic cystic neoplasms (Plougmann et al. 2017).

A recent study comparing MRI and MR cholangiopancreatography with EUS in differentiating between benign and malignant mucinous neoplasms of the pancreas found that the diagnostic accuracy and specificity of MRI were higher than those of EUS (Hwang et al. 2018).

Follow up was available in only 7 out of 11 cases (Table 1). All these patients underwent surgical resection of their tumor and did not receive any chemo or radiation therapy. All patients were alive and well with no evidence of recurrence or metastasis at the time of follow up. These included a patient with non-invasive MCN with high grade dysplasia who underwent resection in 2009. She was fine at 94 months following resection. Follow up was also available for another patient with non-invasive MCN with high grade dysplasia who underwent resection in 2015. This patient was fine at the time of last follow up, but the follow up period was short (21 months).

Surgical resection is indicated and is curative for all non-invasive MCNs (Wilentz et al. 1999; Sarr et al. 2000; Crippa et al. 2008; Testini et al. 2010; Zamboni et al. 2010; Del Chiaro et al. 2013; Naveed et al. 2014). Since MCNs are premalignant, they provide a unique window of opportunity to clinicians for preventing the development of cancer (Dudeja and Allen 2015). Sendai (Tanaka et al. 2006) and Fukuoka (Tanaka et al. 2012) consensus guidelines were introduced in 2006 and 2012 respectively to determine the level of risk posed by suspected pancreatic MCNs. Recent studies have shown that both the Sendai and Fukuoka guidelines accurately determined the patients with MCNs who were likely to have advanced neoplasia. There was no statistically significant difference between the two guidelines in predicting which patients had advanced cancer. The updated Fukuoka guidelines were not found to be superior to the Sendai guidelines in identifying neoplasia (Kaimakliotis et al. 2015). In 2015, the American Gastroenterological Association (AGA) also published guidelines for the management of suspected pancreatic cystic neoplasms (Singhi et al. 2016). Recent studies compared the efficacy of the AGA guidelines with the Fukuoka consensus guidelines in predicting advanced neoplasia (AN) in these tumors and concluded that the AGA guidelines were not superior to the Fukuoka guidelines in identifying AN in pancreatic MCNs and both had more or less similar efficacy in this regard. These studies also concluded that the high risk features of both guidelines do not identify all MCN patients with advanced neoplasia accurately (Ma et al. 2016). A study published in 2017 however showed that the AGA and Fukuoka criteria were superior to the original Sendai guidelines for predicting diagnostic accuracy of advanced neoplasia in MCNs (Sighinolfi et al. 2017). Another recently published study demonstrated that MCNs could be readily distinguished from pancreatic Intraductal Papillary Mucinous Neoplasms (IPMNs) by their clinical and

demographic, radiologic and pathologic features. The study showed that most MCNs are slow growing and non-invasive, are cured by surgical resection and have an excellent prognosis (even in cases with invasive disease) with an 80% 10 year survival rate following resection (Griffin et al. 2017). There are recent studies which argue that since pancreatic MCNs are often asymptomatic and discovered incidentally, lack worrisome features on preoperative imaging studies and have exceptionally low rates of malignant transformation when less than 4 cm in size, and have not been found to recur following a resection, they do not need to be resected in the first place and if resected, do not require further follow up after resection. One study showed that 5-year survival after surgical resection of malignant MCNs was approximately 60% (Nilsson et al. 2016). However, it needs to be emphasized that the criteria for surgical resection in MCNs remain uncertain and differ between the various consensus European and American guidelines (Tanaka et al. 2006; Tanaka et al. 2012; Singhi et al. 2016).

Increasing numbers of cystic pancreatic neoplasms are now being diagnosed (as axial imaging becomes more widespread). MCNs are now being managed more optimally based on the consensus guidelines discussed above and ongoing current studies are attempting to identify tumors which may be treated non-surgically (Greer and Ferrone 2016). Since accurate diagnosis of MCNs and their differentiation from other pancreatic cystic neoplasms is crucial for accurate management of these tumors, and since this is often difficult using imaging studies only, novel biomarkers and molecular diagnostic tools which can differentiate between the cystic pancreatic lesions are coming up and may prove very useful in such differentiation and facilitate early and accurate diagnosis (Berger et al. 2017). Although so far, no definite molecular markers have been identified, search is actively underway. It is important to emphasize that the pathologist has a fundamental role in both the preoperative assessment of pancreatic cystic neoplasms as well as in the accurate postoperative diagnosis and thus in determining the prognosis, further treatment and follow up of pancreatic cystic neoplasms including MCNs (Esposito et al. 2015). A recent study by Xu et al. (Xu et al. 2017) concluded that all current guidelines including AGA, Fukuoka and American College of Radiology (ACR) have deficiencies and therefore it is important to determine the acceptable rate of false-positives in order to prevent a single true positive. A recent radiologic study found that new criteria developed using EUS findings and cyst fluid carcinoembryonic antigen (CEA) produce excellent results in accurately differentiating between pancreatic mucinous and serous neoplasms (Zhang et al. 2017).

Conclusion

Our cases show features similar to those described in other published studies although cases in our series tended to be larger in number. Since these tumors are relatively rare, premalignant and have strict diagnostic criteria, they must always be considered in the differential diagnosis of pancreatic mucinous cystic lesions. Larger studies incorporating greater number of patients and more detailed follow up will help in increasing our understanding of MCNs.

Abbreviations

AB: Alcian Blue; ACR: American College of Radiology; AGA: American Gastroenterological Association; AN: Advanced neoplasia; CEA: Carcinoembryonic antigen; CT: Computed tomography; ERCP: Endoscopic retrograde cholangiography; EUS: Endoscopic ultrasonography; IPMN: Intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasm; MRI: Magnetic resonance imaging; PAS: Periodic Acid Schiff; US: Ultrasound; WHO: World Health Organization

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Authors' contributions

NU and ZA performed the histological and immunohistochemical evaluation, literature review and drafted the manuscript; MZ helped to collect clinical and follow-up data of the cases; JA-G participated with the corresponding, reviewing, editing the drafted manuscript as per journal policy, and submission of the article. All authors participated in the design of the study. All authors read and approved the final manuscript.

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Availability of data and materials

Data and materials of this work are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Since this was a retrospective observational study and did not involve actual patients or patient's images, ethical approval was not sought for this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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