

Specific new mucinous benign pancreatic cysts-a new pathological unit

Hilendarov A, Velkova K, Siracov N, Tchervenkov L, Georgiev AL

Department of Diagnostic Imaging, Medical University, Plovdiv, 4001, Bulgaria

SUMMARY Introduction: The cystic lesions of the pancreas consists of a range of pathologies which may be broadly divided into neoplastic, non- neoplastic cysts. Recently new non-neoplastic cystic lesion, called Mucinous Non-neoplastic Cyst (MNC), has been described.

Materials and Methods: Imaging (ultrasound and CT) methods, as well as invasive procedures for histological examination of the diagnosis, were used. Eleven cases of cystic lesions of the pancreas, accidentally detected by ultrasound and computed tomography, obtained for other reasons were presented.

Results and Discussion: The finding was a 26-33 mm cysts in the body of the pancreas, apparently communicating with the pancreatic duct. The Endoscopic Retrograde Cholangiopancreatography and laboratory tests of liver function, serum CEA and carbohydrate antigen C19-9 were within normal limits. After the distal pancreatectomy in six patients, the histological result showed a simple cyst, lined with mucinous epithelium. The other five cases are without any changes in size and structure under 2 years surveillance.

Conclusion: We recommend that patients diagnosed with 'benign' mucinous neoplasm should be closely monitored due to the inability to completely confirm the benign nature of the lesions. Moreover, the existence of the MNC, as a truly unique cystic lesion, remains controversial.

Key words: mucinous non-neoplastic cysts, US and CT examination, histological examination

Address for correspondence:

Atanas Hilendarov, Department of Diagnostic Imaging, Medical University, Faculty of Medicine, 66 Pestersko Shose str., Plovdiv, 4001, Bulgaria, email: dr_hill@abv.bg

Word count: 2467 **Tables:** 1 **Figures:** 05 **References:** 21

Received: - 29 August, 2019

Accepted: - 27 September, 2019

Published: - 03 October, 2019

INTRODUCTION

Pancreatic cystic lesions consist of a variety of pathological nodules and can generally be classified into neoplastic and non-neoplastic cysts [1]. The following types of cystic neoplasms are predominant: Mucinous Cystic Tumors (MCT), Intrauterine Papillary Mucinous Tumors (IPMTs) and Solid Pseudopapillary Neoplasms (SPPNs) that are both premalignant and malignant [2]. Serous cystic lesions from another large group of cystic neoplasms that are predominantly benign [3]. On the other hand, non-neoplastic cystic tumors consist of congenital cysts, lymphoepithelial cysts, retentive cysts and endometrial cysts [3]. Recently, a new group of non-neoplastic cystic lesions, called Mucinous Non-neoplastic Cysts (MNC), has been described. We present of pancreatic cystic tumors with signs witch increased possibility of this diagnosis [4, 5].

MATERIALS AND DESCRIPTION

Eleven patients aged from 49-73 years old (6 women and 5 men) were scanned by US, computer-tomographically (CT), ERCP and MRI. Cystic lesions of the pancreas ranged from 26 to 33 mm was detected. The major pancreatic canal is not dilated (Figure 1).

At a control US study 6 months later in five of the patients the finding was presented with an increase of the cystic lesion up to 38 mm (Figure 2).

An MRI study was conducted of the same patients to better characterize the cystic lesions. The finding is a 38 mm cyst in the pancreas, seemingly communicating with the pancreas canal (Figure 3).

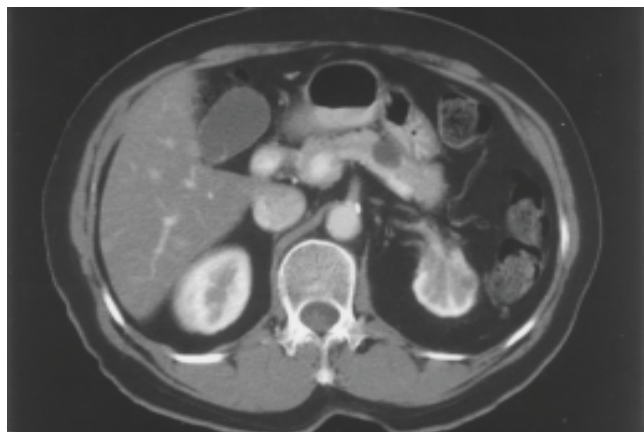


Fig. 1. CT image representing a cystic lesion in the pancreatic body (Non dilated pancreatic duct)

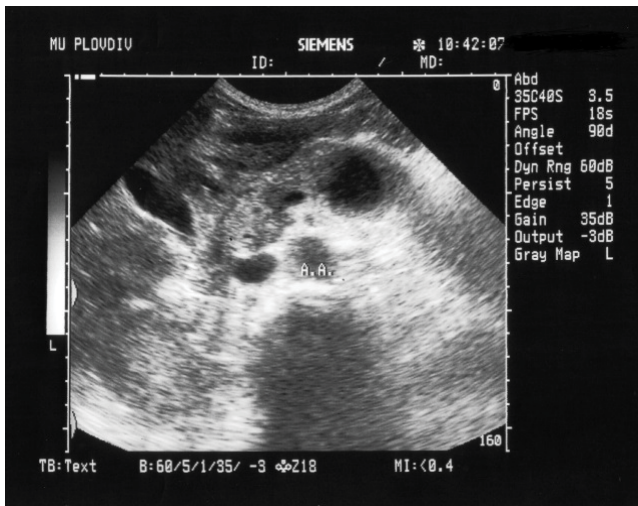


Fig. 2. Ultrasonic image of the cystic lesion at the pancreatic body with diameter of 38 mm

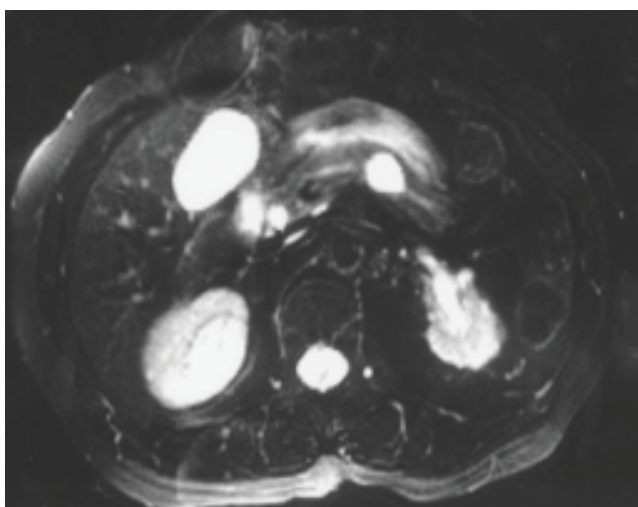


Fig. 3. MRI image of a cystic lesion of the pancreatic body that is suspected of communicating with the pancreas canal

The main pancreatic canal and its lateral branches are not dilated in all of our patients. Laboratory tests for liver function tests, serum carcinoembryonic antigen and carbohydrate antigen C 19-9 are within the normal range. Whipple's resection were performed in 6 patients. Due to an unspecified diagnosis of cystic neoplasm of the pancreas in three patients were performed distal pancreatectomy and in two cases central pancreatectomy. The histological preparation showed a simple cyst with a mucosal epithelium (Figure 4).

There is no abnormal presence of atypia and dysplasia of the epithelium as well as communication with the pancreatic duct. The pancreatic tissue was not histologically presented with significant changes. Within 2 year follow-up with US and CT investigation, no signs of tumor recurrence were found.

RESULT AND DISCUSSION

Kosmahl et al., describe a new cystic pancreatic change in five patients for whom the term Mucinous Non-neoplastic Cyst (MNC) is introduced [1]. The same group subsequently reported 4 cases (of 9 patients) presented this new group of cystic pancreatic changes in a retrospective review of 418 cases of cystic tumors [2].

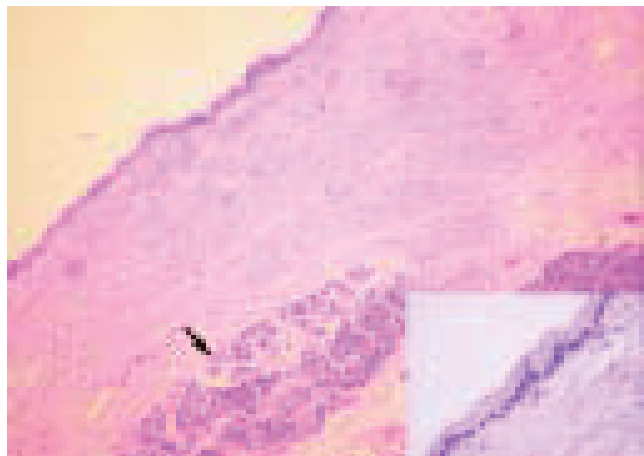


Fig. 4. Histological preparation stained with HE. A cystic wall with a cuboidal epithelium is seen, delimited by a fibro-collagen stroma without signs of atypia. Visible pancreatic acins

The pancreatic cysts of our study demonstrate histological features susceptible to MNCs, including single-cell cytoplasmic mucin cells, lack of cell proliferation or atypia without pathologically demonstrated communication with the pancreatic duct and fine sciatic support stroma. An argument against this diagnosis is the presence of communication with the major pancreatic duct presented on preoperative MRI, which makes retention cyst and IPMT difficult.

MNCs are characterized pathologically with mutant epithelial differentiation, lack of cellular atypia or increased proliferation, a fine layer of acellular stroma, and lack of communication with the pancreatic channel [1]. These cysts by definition do not exhibit any neoplastic features such as dysplasia, proliferative activity, signs of invasive growth or metastasis. The origin and development of this pathology is not known and can only be supposed [5, 6]. Clinical and pathological features are presented in Table 1.

Abnormal MNCs should be differentiated from other cystic neoplasms of the pancreas, which are covered with mucosal epithelium, such as Mucinous Cystic Tumours (MCTs), Intrauterine Papillary Mucinous Tumours (IPMTs) and retention cysts.

The images of MNCs upon MRI may be indistinguishable from that of MCNs, especially if the cysts are large and have thick walls. FNA cytology of the epithelium of MNCs shares that of retention cysts. Retention cysts can be excluded based on the absence of potential causes or evidence of ductal obstructions; however, this is not always possible. Nevertheless, although EUS-FNA could not distinguish MNCs from retention cysts, treatment and prognosis will not be affected owing to the benign nature of both diseases (Figure 5).

MCTs are large, well-differentiated cystic pancreatic tumours that are usually presented as single or multifocal pancreatic cysts in middle-aged women [7, 8-11]. These tumors, like MNCs, are covered with a mucosal epithelium, demonstrating a periodic positive acid-Schiff and Alcian blue reaction as well as positivity of cytokeratins 7, 8, 18, 19 and 20, 7, 8.

IPMT is a clearly defined clinicopathological unit described and demarcated by MCTs by the World Health Organization

in 1996 and by the Institute of Pathology of the Armed Forces in 1997 [12]. As well as retention cysts and MCTs, the walls of this tumor are covered with mucosal epithelium. This tumor is characterized by cystic dilation of the main pancreatic duct or its branches due to a large amount of produced and excreted mucin via a pathologically changed papillary aperture in elderly males [12]. IPMT is often associated with chronic pancreatitis, communication between cyst and pancreas and pancreas dilation [13]. These tumours have a high, colonic, mucin-containing epithelium, often with papillary proliferation and extensive involvement of the pancreatic duct [14]. IPMT epithelial cells, as well as MCT, are usually presented with varying degrees of atypia and dysplasia with high malignant potential.

Cytology and cyst fluid CEA analysis

Seven MNCs had an endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) prior to surgical resection. The FNA specimens were analyzed for: background (mucinous or necrotic), cellularity (hypercellular or scant cellular), architecture (honeycombed flat sheets or papillary clusters), nuclear features (membrane, chromatin, pleomorphism, nucleoli) and fibrotic

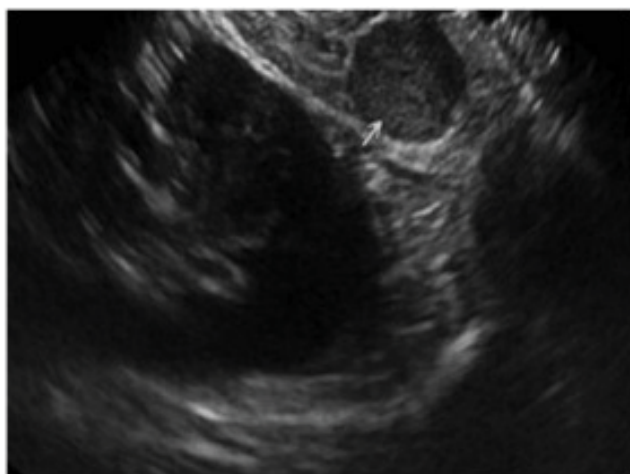


Fig. 5. EUS image showed a small homogeneous hypoechoic lesion in pancreas tail on endoscopic ultrasound

stroma. These features were reported as either present or absent (1 or 0). In addition, cyst fluid Carcinoembryonic Antigen (CEA) concentrations in 5 MNC were measured by a specific immunoassay.

Sometimes the ductal communication is not presented to the US, CT or ERCP, but can be seen on the MRI or pathological study and vice versa [15]. In the seven subjects presented, none of them were tested with MPTs and only one with ERCP, which does not prove communication with the duct [1]. The remaining four patients were studied with CT, which is not particularly reliable in portraying communication. The communications can be demonstrated in some of the patients if MRCP or ERCP is performed.

Multiple cystic fluid pathological parameters can be used to categorize the lesions, including fluid amylase, lipase, Carcinoembryonic Antigen (CEA), cancer antigen (CA)-125, mucin content, cytology, DNA content, and detection of genetic mutations. To date, CEA is the most reliable pathological marker in discriminating between mucinous and non-mucinous PCLs.

Brugge et al. reported that a CEA value ≥ 192 ng/mL indicates a mucinous lesion [16, 17]. CEA showed a sensitivity and specificity of 73% and 84%, respectively, in categorizing PCLs [17]. When combined with CEA, cystic fluid mucin (MUC) content analysis can add to the diagnostic accuracy [18]. Cysts with MUC5A, MUC2, and MUC1 overexpression have the highest risk of being premalignant or malignant [19]. Molecular analysis of the cystic fluid may provide a specific tool for detecting malignant cysts. Winner et al. documented that the presence of the K-ras mutation and >2 loss of heterozygosity was 96.2% specific for malignant cysts [20]. On the other hand, both of these parameters were less sensitive than CEA in discriminating between mucinous and non-mucinous cysts. A combination of these parameters with CEA is better at differentiation [20]. Micro RNA expression is a promising tool for categorization of different PCLs. Micro RNAs-noncoding RNA molecules that control mRNA processing-are expressed differently in various PCLs [21].

Tab. 1. Clinical and pathological features of 11 mucinous nonneoplastic cysts of the pancreas

Case#	Age/sex	Symptoms	Location	Cyst/fluid	Size	Cytology	Fluid CEA (ng/ml)	Surgical procedure
1	56F	abdominal pain	head	Unilocular/clear	13 mm	suspicious	N/A	Whipple's resection
2	60M	none	tail	Unilocular/mucoid	33 mm	N/A	N/A	Distal pancreatectomy
3	72M	none	head	Multilocular/mucoid	16 mm	suspicious	5488	Whipple's resection
4	56F	none	Body/tail	Unilocular/hemorrhagic	20 mm	suspicious	5975	Distal pancreatectomy
5	60F	none	head	Multilocular/clear	21 mm	N/A	4482	Whipple's resection
6	66F	none	head	Multilocular/clear	11 mm	negative	985	Whipple's resection
7	66F	loss of appetite	head	Unilocular/serous	31 mm	N/A	N/A	Whipple's resection
8	49M	none	neck	Unilocular/mucoid	19 mm	N/A	1581	Central pancreatectomy
9	73M	none	head	Multilocular/mucoid	19-38 mm	indeterminate	507	Central pancreatectomy
10	53F	abdominal pain	head	unilocular (2)/mucoid	24 and 26 mm	mucinous cystic neoplasm	3875	Whipple's resection
11	49M	abdominal pain	tail	multilocular/mucoid	28 mm	negative	2184	Distal pancreatectomy

CONCLUSION

Diagnosis of MNC can be significantly hampered by the overlapping of many clinical-pathological signs with retention cyst, MCTs and IPMTs.

We recommend that a patient with a diagnosis of “benign” MNC be closely monitored by US, CT or ERCP investigation, because of the inability to absolutely confirming the benign nature

of the lesion-well defined, without penetration in surrounding tissues and no metastasis. Moreover, the existence of the MNC, as a truly unique cystic lesion, remains controversial because the reported cases of this neuralgia may simply represent a variant of an existing pancreatic pathology that overlaps the underlying pathological features of pancreatic cystic tumours plagued with mucosal epithelium. All imaging diagnosticians, surgeons, and pathologists need to share their experience in order to increase diagnostic possibilities for this particular pathology.

REFERENCES

- Kosmahl M, Egawa N, Schroder S, Carneiro F, Luttges J, et al. Mucinous nonneoplastic cyst of the pancreas: a novel nonneoplastic cystic change? *Mod Pathol.* 2002;15:154-158.
- Kloppel G, Kosmahl M. Cystic lesions and neoplasms of the pancreas: the features are becoming clearer. *Pancreatol.* 2001;1:645-655.
- Kosmahl M, Pauser U, Peters K, Sipos B, Luttges J, et al. Cystic neoplasms of the pancreas and tumorlike lesions with cystic features: review of 418 cases and a classification proposal. *Virchows Arch.* 2004;445:168-178.
- Do Yang J, Soo Song J, Noh S, Moon WS. Mucinous Non-neoplastic Cyst of the Pancreas. *Korean J Pathol.* 2013;47:188-190.
- Kim YS, Cho JH. Rare nonneoplastic cysts of pancreas. *Clin Endosc.* 2015;48:31-38.
- Solcia E, Capella C, Kloppel G. Tumors of the pancreas. In: *AFIP atlas of tumor pathology, 3rd series, Fascicle 20.* Washington, DC: Armed Forces Institute of Pathology. 1997.
- Wilentz RE, Albores-Saavedra J, Hruban RH. Mucinous cystic neoplasms of the pancreas. *Semin Diagn Pathol.* 2000;17:31-42.
- Zamboni G, Scarpa A, Bogina G, Iacono C, Bassi C, et al. Mucinous cystic tumors of the pancreas. Clinicopathological features, prognosis and relationship to other mucinous cystic tumors. *Am J Surg Pathol.* 1999;23:410-422.
- Osborn M, van Essen G, Weber K, Kloppel G, Altmannsberger M. Differential diagnosis of gastrointestinal carcinomas by using monoclonal antibodies specific for individual keratin polypeptides. *Lab Invest.* 1986;55:497-504.
- Moll R, Lowe A, Laufer J, Franke WW. Cytokeratin 20 in human carcinomas. A new histodiagnostic marker detected by monoclonal antibodies. *Am J Pathol* 1992;140:427-447.
- Kloppel G, Solcia E, Longnecker DS, Capella C, Sobin LH. *Histological typing of tumours of the exocrine pancreas.* 2nd ed. WHO international histological classification of tumours. Berlin, Springer. 1996.
- Shyr YM, Su CH, Tsay SH, Lui WY. Mucin-producing neoplasms of the pancreas: intraductal papillary and mucinous cystic neoplasms. *Ann Surg.* 1996;223:141-146.
- Suzuki Y, Atomi Y, Sugiyama M, Isaji S, Inui K, et al. Cystic neoplasms of the pancreas. A Japanese multiinstitutional study of intraductal papillary mucinous tumor and mucinous cystic tumor. *Pancreas.* 2004;28:241-246.
- Sohn TA, Yeo CJ, Cameron JL, Iacobuzio-Donahue CA, Hruban RH, et al. Intraductal papillary mucinous neoplasms of the pancreas: an increasing recognized clinicopathologic entity. *Ann Surg.* 2001;234:313-322.
- Sugiyama M, Atomi Y. Recent topics in mucinous cystic tumor and intraductal papillary mucinous tumor of the pancreas. *J Hepatobiliary Pancreat Surg.* 2003;10:123-124.
- Brugge WR, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlo T, et al. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology.* 2004;126:1330-1336.
- Kauhanen S, Rinta-Kiikka I, Kempainen J, Grönroos J, Kajander S, et al. Ovaska J Accuracy of 18F-FDG PET/CT, Multidetector CT, and MR Imaging in the Diagnosis of Pancreatic Cysts: A Prospective Single-Center Study. *J Nucl Med.* 2015;56:1163-1168.
- Utomo WK, Braat H, Bruno MJ, van Eijck CH, Groot Koerkamp B, et al. Cytopathological analysis of cyst fluid enhances diagnostic accuracy of mucinous pancreatic cystic neoplasms. *Medicine (Baltimore).* 2015;94:e988.
- Jabbar KS, Verbeke C, Hyltander AG, Sjövall H, Hansson GC, et al. Proteomic mucin profiling for the identification of cystic precursors of pancreatic cancer. *J Natl Cancer Inst.* 2014;106:djt439.
- Winner M, Sethi A, Poneris JM, Stavropoulos SN, Francisco P, et al. The role of molecular analysis in the diagnosis and surveillance of pancreatic cystic neoplasms. *JOP.* 2015;16:143-149.
- Lee LS, Szafranska-Schwarzbach AE, Wylie D, Doyle LA, Bellizzi AM, et al. Investigating microRNA expression profiles in pancreatic cystic neoplasms. *Clin Transl Gastroenterol.* 2014;5:e47.