Case Report

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Microcystic Serous Cystadenoma of the Pancreas: A Report of Two Cases with One of Diffuse Presentation

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Key Words
Microcystic adenoma · Serous cystadenoma of the pancreas · Multifocal/diffuse serous cystadenoma of the pancreas · Polycystic disease of the pancreas

Abstract
Microcystic adenoma or serous cystadenoma is an uncommon tumor and accounts for 1–2% of the exocrine neoplasms of the pancreas. Usually unifocal, they present as single, large, well-demarcated multiloculated cystic tumors, ranging in size from 1 to 25 cm. Multifocal variants or diffuse serous cystadenomas are extremely rare. We present 2 cases of which 1 is a diffuse variant affecting the body, tail and part of the neck of the pancreas. In both the patients the tumors were detected incidentally. We highlight on the diffuse variant in view of its rarity and present a review of literature. In this case the entire body and tail of the pancreas was spongy replaced by multicystic lobules and hyalinized fibrocollagenous stroma. The cysts were lined by low cuboidal glycogen containing bland cells. Such a unique presentation wherein the entire body and tail of the pancreas is replaced with multiple cysts is a diffuse presentation of microcystic adenoma and a search through literature revealed only 7 such cases among the 15 cases with multifocal presentation reported.

Introduction

Microcystic adenoma (MCA) or serous cystadenoma of the pancreas is an uncommon benign tumor accounting for 1–2% of neoplasms of the exocrine pancreas and 25% of cystic neoplasms [1]. These tumors are usually unifocal, mostly arising in the body and tail of the pancreas and are often incidentally detected. They present as single large, well-demarcated and multiloculated cystic tumors, and range in size from 1 to 25 cm. They are commonly seen in elderly women and are composed of cysts lined by epithelial cells that produce serous fluid and show ultrastructural evidence of centroacinar differentiation [2, 3]. Multifocal and diffuse presentations are rare. We describe 2 cases of MCA of which 1 had a diffuse presentation involving almost the entire pancreas. Such a diffuse presentation is not only rare but often as in this case shows different stages of disease evolution, which could help to understand the histogenesis of this disease.

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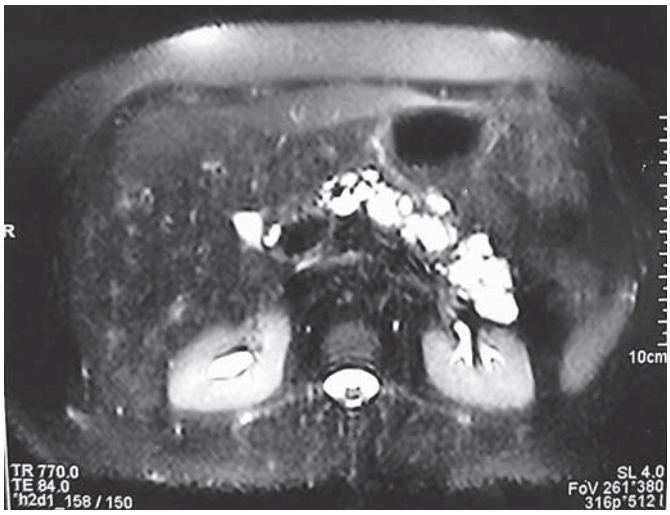

Fig. 1. MRI image showing multiple small cystic lesions in the body and tail of the pancreas.

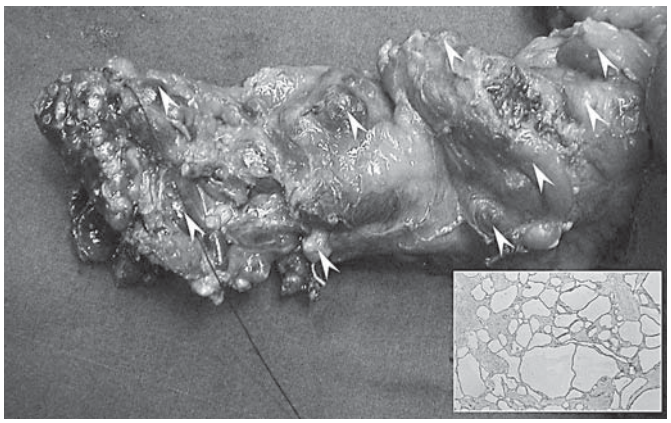

Fig. 2. Resected specimen of the pancreas showing multiple cysts in the region of the tail and body of the pancreas and extending up to the neck (*inset:* cystic spaces lined by cuboidal to flattened epithelium and separated by fibrous stroma. HE. ×100).

Case Report

We present 2 cases of MCA of the pancreas, of which 1 had a diffuse presentation.

Diffuse Microcystic Adenoma: Case 1

A 46-year-old female was incidentally detected to have a tumor in the pancreas on an abdominal sonographic evaluation performed for a urinary tract infection. A MR and MRCP revealed that multiple small cystic lesions, which were conglomerate forming larger masses, replaced the entire body and tail of the pancreas. Few discrete 5- to 15-mm sized lesions were also present in the head of the pancreas. The common bile duct and the main pancreatic duct at its termination in the head of the pancreas were normal. The pancreatic duct could not be visualized in the body and tail of the pancreas (fig. 1). At ERCP a normal cholangiogram was observed; the pancreatogram revealed a mildly irregular main pancreatic duct (3–4 mm) with a tight stricture in the mid-body of the pancreas beyond which a large cyst was seen. Endoscopic sonographic (EUS) evaluation confirmed the cystic nature of the lesion without vascular involvement. EUS-guided fine-needle aspiration cytology was not contributory. Her serum CA 19-9 levels were normal, i.e. 17.2 U/ml (normal range <37 U/ml). At exploratory laparotomy the body and tail up to the neck of the pancreas was replaced by multiple cystic masses without much distortion of the pancreatic dimensions. An intraoperative frozen section revealed a MCA. Normal pancreatic tissue was apparent only in a part of the head of the pancreas closest to the duodenum. A subtotal pancreatectomy with en masse splenectomy was performed.

Pathologic Features

The resected pancreas which included the body, tail and part of the head measured 12 cm in length and 3.5 cm in maximum diameter, and showed no significant alteration in dimensions. The surface was bosselated with several knobby fluid-filled protuberances (fig. 2). On the cut surface the entire length of the pancreas appeared spongy, the parenchyma being replaced by discrete and confluent varying sized cysts and cystic nodules, which exuded thin, clear fluid. The larger nodules showed firm central radiating scars, with focal calcification. The cysts and nodules varied in size from a few mm to 3.5 × 2.5 × 2.5 cm. Most of the nodules were confluent ill demarcated while some fibrosed-hyalinized areas demarcating the smaller nodules. At the surgical margin near the head of the pancreas, normal pancreatic lobules were seen with occasional 1- to 2-mm speck-like cysts.

Unifocal Presentation: Case 2

A 54-year-old male presented with left-sided abdominal pain of 15 days' duration. Abdominal ultrasound examination revealed a hypoechoic mass in the pancreas. A CT scan of the abdomen revealed a 3.3 × 2.6 cm sized irregularly marginated, hypodense mass in the body of the pancreas suggestive of MCA. An endoscopic ultrasound confirmed a lesion confined to the body of the pancreas with multiple cystic spaces and hypoechoic strands and without invasion of the surrounding vessels. The pancreatic duct in the tail of the pancreas was normal. No significant lymphadenopathy was present. Pancreatic serum enzyme studies and the serum CA 19-9 were normal. At exploratory laparotomy a 3 × 4 cm multiloculated cystic mass arising from the body of the pancreas was apparent. Intraoperative ultrasound excluded other foci in the remaining pancreas and the pancreatic duct. An intraoperative frozen section confirmed a MCA. The pancreatic duct ran in close proximity to the distal part of the mass. A spleen-preserving distal pancreatectomy was performed.

Pathologic Features

The resected body and the tail of the pancreas measured 11 × 3.5 × 2 cm. The cut surface showed a well-demarcated 2 × 2.7 × 2 cm mass with a central radiating scar, surrounded by multiple small cystic spaces giving a spongy appearance and exuding thin clear fluid. The cut margin of the pancreas was 1.5 cm from the mass and the rest of the body and tail of the pancreas was unremarkable with no further lesions.

On microscopic examination, in both cases, the lesions were identical and were made up of multicystic spaces of varying sizes lined by cuboidal to flattened epithelium with vacuolated cytoplasm and uniform centrally placed bland nuclei (fig. 2, inset). Special stains revealed abundant cytoplasmic glycogen. No mucin was present. Dense hyalinized scar-like fibrous septae were seen in some nodules with radiation towards the periphery and was also present between the cysts.

In the diffuse presentation the entire pancreatic parenchyma was replaced by cystic aggregates separated by hyalinized stroma. There was loss of acini but few surviving islets and ducts were seen entrapped within the stroma between the cysts (fig. 3). Near the head where pancreatic parenchyma was preserved, several small newly developing dilating cysts were seen within lobular units (fig. 4). Even the smallest developing lesions showed patches of hyalinized fibrous tissue between the tiny spaces beginning to show early cystic change.

In the first case (diffuse involvement) the peripancreatic fat showed foci of fat necrosis but no involvement by the tumor. However, there was no evidence of chronic pancreatitis in the residual pancreas near the head. The fat necrosis was probably a consequence of cyst rupture with release of its fluid into the peripancreatic fat. In the second (localized) case where the lesion was embedded deep within the pancreatic parenchyma, there was no evidence of peripancreatic fat necrosis. The peripancreatic lymph nodes and spleen were free from involvement.

Immunohistochemical studies were done in case 1 (diffuse presentation) and the lesional cells showed characteristic positivity for cytokeratins 7, 8 and 19. EMA showed apical staining characteristic for a cell type with polarity and secretory features. β-Catenin showed membranous staining as is mostly seen in cells not deviating much from normality. No neuroendocrine cells were visualized (negative results for chromogranin and synatophysin). No nuclei were reactive for p53 protein. A few nuclei labeled for Ki-67 (MiB1 antibody) but the overall proliferation fraction was lower than 1%.

Von Hippel-Lindau (VHL) syndrome was excluded in both cases by the CT scan of the abdomen which did not reveal cystic lesions outside the pancreas, a normal hematocrit and CT scan of the brain.

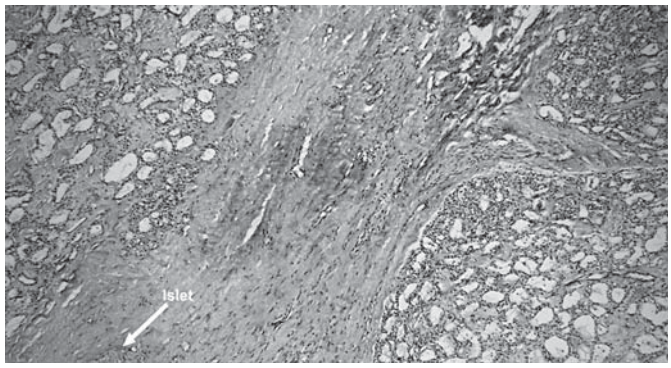

Fig. 3. Atrophic pancreatic parenchyma with residual islets between expanding cystic lesions. HE. ×40.

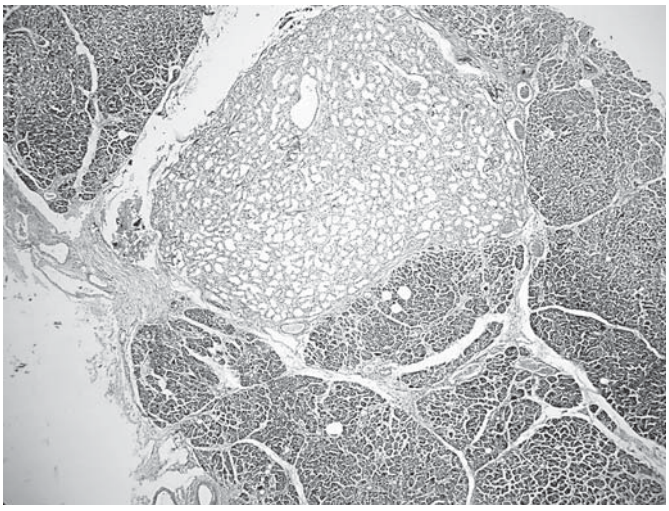

Fig. 4. Lesions resembling a lobule that has undergone cystic change. HE. ×40.

Discussion

MCAs were initially separated from the more common mucinous tumors of the pancreas due to their benign behavior and distinctive histological features [4]. MCA usually present as a large single asymptomatic mass, in elderly women and are often incidentally detected. Grossly they are large and multiloculated and range in size from 1 to 25 cm [1–3, 10]. MCAs most commonly arise in the body and tail of the pancreas and are well circumscribed with a bosselated appearance. Multifocal tumors have also been reported and they are especially interesting as they can help in understanding the evolution and histogenesis of these rare tumors [4–10, 21]. Ultrastructural and immunohistochemical studies suggest that the MCA originates from the centroacinar cells [2].

Several MCAs are associated with VHL syndrome, an autosomal dominant genetic disorder. A VHL tumor suppressor gene linked to chromosome 3p 2s has been identified. When both copies of this gene are inactivated, there is unchecked cell growth resulting in tumors and cysts in the pancreas, kidney and epididymis. Pancreatic manifestations of VHL are frequently symptomatically silent and consist of MCA or multiple serous cysts sometimes replacing the entire pancreas [11]. Reports of MCA without a family history of VHL have also been cited, in part probably due to sporadic inactivation of the gene. Our first case belongs to the category of muticentric serous tumors involving the entire body and tail of the pancreas with almost complete obliteration of pancreatic acini and

Table 1. Multifocal and diffuse presentation of MCA

No	Group (first author)	Age/sex	Site/number/size	Malignant manifestations	Associated tumors
1	Kim, 1990 [6]	63/M	MCA – multifocal Body (1) 4.3 × 3.8 cm 0.3 × 0.3 cm 0.2 × 0.1 cm Tail (1) 1.3 × 1.0 cm	No	No
2	Kim, 1990 [6]	32/F	MCA – diffuse Cysts throughout pancreas (diffuse variant) ranging in size from 0.2 × 0.3 to 4.5 × 4.0 cm	No	No
3	Kamei, 1991 [10]	72/F	MCA – multifocal Head (1) 10 × 10 × 8 cm Body (5) 0.5 cm each	Malignant	Islet cell tumor (1.5 cm) in tail
4	Tanno, 1998 [8]	48/F	MCA – multifocal Head (4 × 4 × 3.5 cm) Body 3.5 × 3.3 × 2 cm	No	No
5	Santos, 2002 [7] Oligocystic variant	53/F	MCA – multifocal Body 3 cm Minute satellite cysts	No	No
6	Compagno, 1976 [4]	–	MCA – multifocal and diffuse 4 multifocal and 3 which involved the entire pancreas (diffuse); no details available	No	No
7	Shorten, 1986 [5]	60/F	MCA – diffuse Lesion involved entire pancreas (diffuse variant); no details available	No	No
8	Kim, 1997 [21]	67/F	MCA – diffuse Lesion involved entire pancreas	No	Pancreatic endocrine tumor
9	Yasuhara, 2002 [9]	51/M	MCA – diffuse Lesion involved entire pancreas	No	No

ducts. The pancreatic tissue is replaced by varying sized nodular aggregates of cysts lined by characteristic clear glycogen-filled cells with bland nuclei. An extensive review of literature revealed only 7 such cases of diffuse presentation with involvement of the entire pancreas in the 15 cases reported with multifocal presentation [4–10, 21] (table 1). In our case, as in the few cases of diffuse MCA illustrated in literature, the pancreas is diffusely replaced by the cysts without much distortion of its shape.

On microscopy we observed submacroscopic cystic lesions in varying stages of dilatation and development ranging from the newly developing dilated structures (fig. 4) within lobular units, cystically dilated lobules to full-blown, well-demarcated, fluid-filled cysts surrounded by fibrosed parenchyma. Most of the reported cases of multicentric MCA also describe spatially distinct multicystic lesions of varying size and in different stages of dilatation and representing different growth centers. Some were submacroscopic, and some were detected only on giant gelatine slices of the entire pancreas. In the small lesions, the overall lobular architecture of the lesion is apparent as is seen in figure 4 and in the illustration of a submacroscopic lesion provided by Kim et al. [6]. Several authors have concluded that the larger lesions seem to be formed by coalescence or merging of smaller ones with obliteration of intervening parenchyma [6, 8]. A characteristic feature of most of these tumors is the presence of dense hyalinized centrifugal scars radiating as fibrous septae into the adjacent cystic lobules.

Very often, residual islet cells, ducts and thickened nerves are entrapped within the fibrous tissue indicating

that the mass is formed by confluence of separate cystic nodules and these are the remnants of normal pancreatic tissue compressed by the expanding cystic masses (fig. 3). This fibrous tissue is free from inflammatory cells and is probably formed due to the pressure effect of increasing individual cyst size.

Sclerosis, preservation of islet cells and thickened nerve fibers is a common theme running through most degenerative and chronic inflammatory pancreatic disease as is also acinar degeneration and ductal dilatation sometimes with ductular proliferation.

According to an interesting theory by Alpert et al. [2], this tumor could represent a peculiar form of atrophic change with loss of acinar and ductal elements and most of the islet cells, but with preservation of the resilient centroacinar cells, which collect initially as small residual ducts. This collection of ducts undergoes gradual dilatation to form cystic aggregates filled with fluid. It is observed that the areas with the smallest size cysts contain the most numerous cysts. As the number of centroacinar structures inherently remain the same the increase in volume would be due to the degree of dilatation, the fluid within the cysts and the increasing accumulation of the hyalinized intervening stroma and not due to a proliferation of lesional cells. This observation was faithfully reproduced in the various developing and dilating lesions in our case. It was also seen that the cysts were often larger peripherally than centrally, which indicates a passive dilatation due to fluid accumulation accounting for the increase in size.

The frequent presence of non-neoplastic residual islet cells, sometimes pancreatic acini and ducts incorporated within circumscribed lesions of MCA, also points away from a neoplastic nature. The frequent observation in multifocal tumors of small developing submacroscopic lesions with coalescence to form clinically evident masses is a form of expansion less common to neoplasm which are usually centrifugally expansile causing compression and rarely incorporation of surrounding structures.

In 1937, Nygaard et al. [12] reported a cystic lesion in the pancreas as 'polycystic' disease of the pancreas. This tumor was probably a MCA and they had associated it with VHL syndrome.

Polycystic diseases of both the liver and kidney have some similarities to MCA in that they are all formed of aggregates of non-communicating variably sized cysts lined by flattened epithelium with intervening atrophied non-neoplastic parenchyma, and form by passive dilatation of preexisting ductules and tubules. Is MCA also a polycystic disease as was suggested in the earliest published report and not a neoplastic disorder? Or whether, like cystic fibrosis does, MCA represents the end stage of a slowly evolving genetically programmed degeneration of the pancreas with selective preservation and dilatation of the centroacinar cell? The hypothesis of Alpert was the first indication that this may not be a neoplastic lesion. However, rather than a degenerate lesion, it is felt that the disease process is more akin to a polycystic disease, mostly focal, but sometimes diffusely involving the entire pancreas.

Mohr et al. [13] studied MCA and cysts of the pancreas occurring as part of the VHL syndrome in 9 patients. Both the simple serous cysts and the MCA showed a similar histological appearance with fibrous stroma and glycogen-rich epithelial cells. Molecular studies demonstrated loss of the VHL gene in all the lesions – whether simple serous cysts or MCA. The authors therefore concluded that the simple cysts and the MCA were a continuum of the same cystic disease process. However, from this we further conclude that MCA is a cystic disease, not necessarily neoplastic and is akin to the cysts that develop in polycystic renal disease or the epididymal cysts, etc., in the spectrum of cystic diseases of the VHL syndrome.

Occasionally some MCAs have been described as malignant on the basis of finding similar cytologically bland cysts in the liver, occasionally stomach or peripancreatic nodes [14, 15]. Compagno and Oertel [4] theorized that both liver and pancreas develop from adjacent portions of the foregut and therefore tumors could develop simultaneously with similar morphological features in both these organs and would explain the few 'metastatic, cytologically bland' lesions reported. Are these multiorgan cystic lesions developing as a function of the disease in the cyst-prone VHL patient?

Local invasion into the peripancreatic fat is reported – could this be cystic lesions in pancreatic parenchyma replaced by fat? A few have been called malignant on the basis of focal micropapillary structures and mild nuclear atypia; however, none of these cytologically atypical cysts showed local invasion or metastasis [16].

Kamei et al. [10] reported a case of a multifocal MCA with atypical cells and focal perineural invasion. They also demonstrated aneuploid nuclear DNA and a high proliferation index. This tumor had not metastasized or spread locally but was considered malignant. This patient also had a spatially distinct islet cell tumor.

It is noted that some of these unifocal and multifocal MCAs have been associated with neoplasms of other

types such as islet cell tumors and ductal adenocarcinomas [17–21]. This may be due to the frequent presence of residual islet cells and ducts in these lesions and merely a function of the elderly age group of these patients and not due to a biphasic differentiation of neoplastic cells.

It is agreed that a single case study is insufficient to draw conclusions – but the spectrum of developing lesions in this case and a review of literature revealing a similar phenomenon in many such reported multifocal cases by different authors – provokes an argument in favor of a polycystic disease process. These lesions require further study in the form of a wider molecular characterization and an analysis of clonality.

Conclusion

In the diffuse presentation of MCA, almost the entire pancreas shows a spectrum of dilating cysts in varying stages of dilatation and coalescence separated by compressed fibrous stroma containing residual islets and ducts. The presence of small dilating cysts within well-preserved lobules in the pancreatic head point to the multifocal evolution of this disease with gradual coalescence to form tumorous masses. The spectrum of disease evolution seems more akin to a polycystic disease than a neoplasm, loss of the VHL gene being associated equally with both cyst formation and neoplasm. However, a wider molecular characterization and analysis of clonality could clarify matters further.

It is noted that several of the multifocal lesions are submacroscopic and discovered only on subsequent gross or microscopic examination of tissue adjacent to clinically evident tumors, and often only after examination of giant gelatine slices of the adjacent pancreas. It is therefore possible that MCA of the multifocal type are more common than reported and much depends on the diligence with which the adjacent pancreatic tissue is examined.

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