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Serous oligocystic and ill-demarcated adenoma of the pancreas: a variant of serous cystic adenoma

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Abstract Serous cystic tumours of the pancreas are uncommon and are usually classified as microcystic adenomas (MCA). As new types of serous cystic tumours of this organ have been reported we reviewed a series of 14 lesions and from macroscopic findings two groups were distinguished: ten tumours revealed the features of MCA, while four were clearly distinct from MCA. Grossly, the latter tumours showed only few cysts which were irregularly assembled in fibrous stroma. On the cut surface, there was neither a central stellate scar nor a circumscribed tumour border, features characterizing MCA. Microscopically, the cysts were lined by cuboidal, non-mucin-producing cells. Immunocytochemical staining for cytokeratins 7, 8, 18 and 19 revealed a ductal phenotype. All non-MCA were found in the head of the pancreas and three of them occurred in men. There were no tumour recurrences or signs of malignant transformation after resection (mean follow-up, 2.9 years). These results suggest that there are serous cystic tumours distinct from MCA which may represent another variant of the category of serous cystic adenomas of the pancreas. We propose the term serous oligocystic and ill-demarcated adenoma (SOIA) for these tumours. It is possible that the recently described macrocystic sybtype of serous cystadenoma and SOIA are variants of the same tumour.

Key words Pancreas · Serous cystic tumours
Microcystic adenoma · Serous oligocystic
ill-demarcated adenoma

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Introduction

Serous cystadenoma of the pancreas has been considered to be a well-defined entity since it was separated from the mucinous cystic neoplasms by Compagno and Oertel and Hodgkinson et al. in 1978. Another term that is used synonymously with serous cystadenoma is microcystic adenoma (MCA; Compagno and Oertel 1978). Recently, however, serous cystic adenomas dissimilar to MCA (Lewandrowski et al.1992), as well as malignant counterparts (George et al. 1989; Kamei et al. 1991; Yoshimi et al. 1992), have been reported. This diversity within the group of serous cystic tumours of the pancreas indicates that the spectrum of these lesions may be broader than has previously been thought and prompted us to review our series collected during the last 20 years. Two groups could be distinguished: one that corresponded to the classical MCA and a second that was distinctly different in its gross features from MCA. This article compares the clinicopathological characteristics of the two groups and discusses their relationship to the other known variants.

Materials and methods

We investigated a series of 14 serous cystic tumours of the pancreas from hospitals in Europe ($n=13$) and Japan ($n=1$). The most important clinocopathological data are summarized in Table 1. In 12 patients the tumours were removed surgically. In two patients, the tumours were found at autopsy. All patients were adults (age range 56–91 years). The male to female ratio was 4:10.

The tissue was fixed in 10% formalaldehyde and processed for paraffin sections. The sections were stained with haematoxylin and eosin, periodic acid-Schiff (PAS) with and without diastase digestion, and alcian blue at pH 2.5. In addition, immunocytochemistry was performed using the avidin-biotin peroxidase complex technique and employing monoclonal (M) or polyclonal (P) antibodies against cytokeratins (CK) 7, 8, 18, 19 and 20 (CK 7, M, 1:1000, Biogenex, San Ramon, USA; CK 19, M, 1:20, gift of Dr. Raemaekers, Maastricht, The Netherlands; CK 20, 1:20, Dako, Copenhagen, Denmark; CK 8 and 18, CAM 5.2, M, 1:10, Becton Dickinson, Mountain View, Calif., USA), carcinoembryonic anti-

Table 1 Clinicopathological features of 14 serous cystic tumours of the pancreas (*LF* lost to follow-up; *AMI* died of acute myocardial infarction; *AW* alive and well; *F* female; *M* male)

Case	Age (years)	Sex	Symptoms	Location	Size (cm)	Follow-up (years)
Microcystic adenoma						
1	90	F	Incidental (at autopsy)	Tail	5×5×4.5	
2	91	F	Incidental (at autopsy)	Tail	6×5×5	
3	65	F	Abdominal mass	Tail	16×6×10	LF
4	75	F	Abdominal mass	Tail	8×7	LF
5	91	F	Abdominal mass	Tail	4×3	LF
6	77	F	Abdominal mass	Tail	2.5 maximum	LF
7	68	F	Abdominal mass	Head	7×6×4	LF
8	70	F	Abdominal mass	Tail	8.5×5	LF
9	56	F	Abdominal mass	Body and tail	6×5×5	15, AW
10	58	M	Abdominal mass	Head	6×4.5×4	1, AW
Serous oligocystic, ill-demarcated adenoma						
11	69	M	Incidental	Head	5×4.5	3.6, AMI
12	60	M	Obstructive jaundice steatorrhea	Head	7×4×4	4, AW
13	61	F	Obstructive jaundice	Head	4×3×2	3.3, AW
14	67	M	Oppressive sensations	Head	4 maximum	0.7, AW

gen (CEA 130b, M, 1:20, Behring, Marburg, Germany), carbohydrate antigen 19–9 (CA 19–9, M, 1:400, donated by Dr. Kalthoff, Kiel, Germany), B 72.3 (anti-TAG 72, M, 1:20, Sorin Biomedica, Brussels Bergium), mucin antigen M1 (M1, M, 1:8000, gift of Dr. Solcia, Pavia, Italy), trypsin (P, 1:1000, own source), synaptophysin (P, 1:100, donated by Dr. Jahn, New Haven, Conn., USA), and chromogranin A (M, diluted solution, Biogenex). Appropriate positive and negative controls were included.

Results

The 14 tumours conformed to two types, each of which had its characteristic gross features. Ten had the typical appearance of MCA, while four were clearly different from MCA and were here designated as serous oligocystic and ill-demarcated adenoma (SOIA).

In MCA the tumours showed a microcystic pattern. Their maximum diameter ranged from 2.5 to 16 cm (Table 1). They were well-circumscribed, slightly bosselated, round lesions. Their cut surface consisted of a honeycomb meshwork of numerous small cysts ranging from 0.1 to 1.0 cm in diameter filled with serous fluid (Fig. 1). The cysts were separated by thin septa and arranged around a more or less central stellate, dense fibrous core from which fibrous trabeculae radiated to the periphery. All but two tumours occurred in the tail of the pancreas.

In SOIA the tumours were characterized by an oligocystic pattern. The size ranged from 2.5 to 7 cm in diameter (Table 1). Their cut surface revealed few cysts filled with serous fluid (Fig. 2). These cysts, which ranged in diameter from 0.5 to 1.5 cm, were irregularly arranged within a fibrous framework that consisted of thin and broad septa and lacked a central stellate scar. The cysts and the supporting fibrous tissue extended into the adjoining pancreatic tissue so that the tumours appeared to be ill-demarcated. All SOIA were located in the head of the pancreas and two of them involved the preampullary portion of the common bile duct, causing a moderate stenosis.

On light microscopy of MCA the cysts were separated by thin fibrous septa and lined by a single layer of cuboidal or flattened epithelial cells (Fig. 3a). Their cytoplasm was pale or clear and contained a centrally located, regularly arranged, round to oval nucleus. Focal-

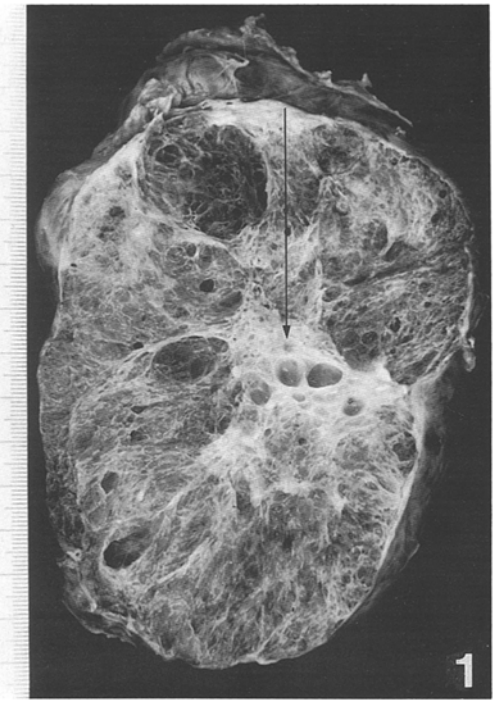

Fig. 1 Microcystic adenoma: resection specimen from the tail of the pancreas showing a well-demarcated tumour with numerous tiny cysts and a stellate scar (*arrow*)

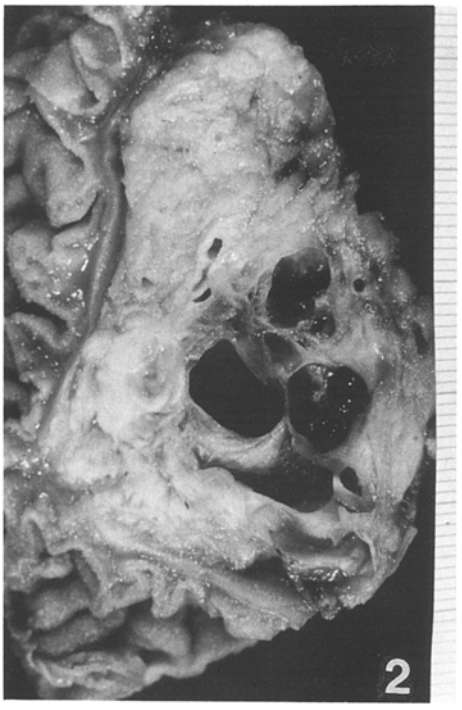

Fig. 2 Serous oligocystic and ill-demarcated adenoma: resection specimen from the head of the pancreas showing and ill-demarcated cystic lesion consiting of a few, relatively large cysts

ly microglandular and papillary structures were present. PAS staining without diastase digestion revealed intracytoplasmic glycogen and PAS staining with diastase digestion, as well as alcian blue staining, were negative. Mitoses were absent and there was no cytological atypia. The stroma supporting the cysts was thin and delicate, with only occasional areas where the stromal component was broader and hyalinized. Some fibrous septa contained single islets of Langerhans and small nerve trunks as well as lymphocytic aggregates. The cystic tissue was well demarcated and usually separated by a fibrous band from the adjoining pancreatic parenchyma (Fig. 3b), but complete fibrous encapsulation was not a consistent feature.

Basically, SOIA showed the same histological appearance as MCA. However, the lining epithelium was often more cuboidal, not flattened, and appeared even to be cylindrical in some areas (Fig. 4a). Also the nuclei were generally somewhat larger. The cytoplasm was either eosinophilic or had the same clear appearance due to the presence of glycogen as in MCA. Mitoses or cytological atypia could not be detected. The stromal framework was well developed and often hyalinized. Occasionally entrapped islets, single ducts, and nerves were found. The tumour border was not well defined because small cysts often extended into the adjoining pancreatic tissue (Fig. 4b).

Immunocytochemically, there were no differences between MCA and SOIA. Both tumour types expressed the cytokeratins CK7, CK8, CK18 and CK19 to a variable extent, the strongest reactivity being found with CK7 and CK19. CA19–9 was focally positive in four of the ten MCA and in three of the four SOIA, and B72.3 in only one MCA. Both MCA and SOIA were uniformly negative for M1, CEA, trypsin, chromogranin A and synaptophysin.

All but one patient in the MCA group were women, with an age range from 56 to 91 years (Table 1). Two

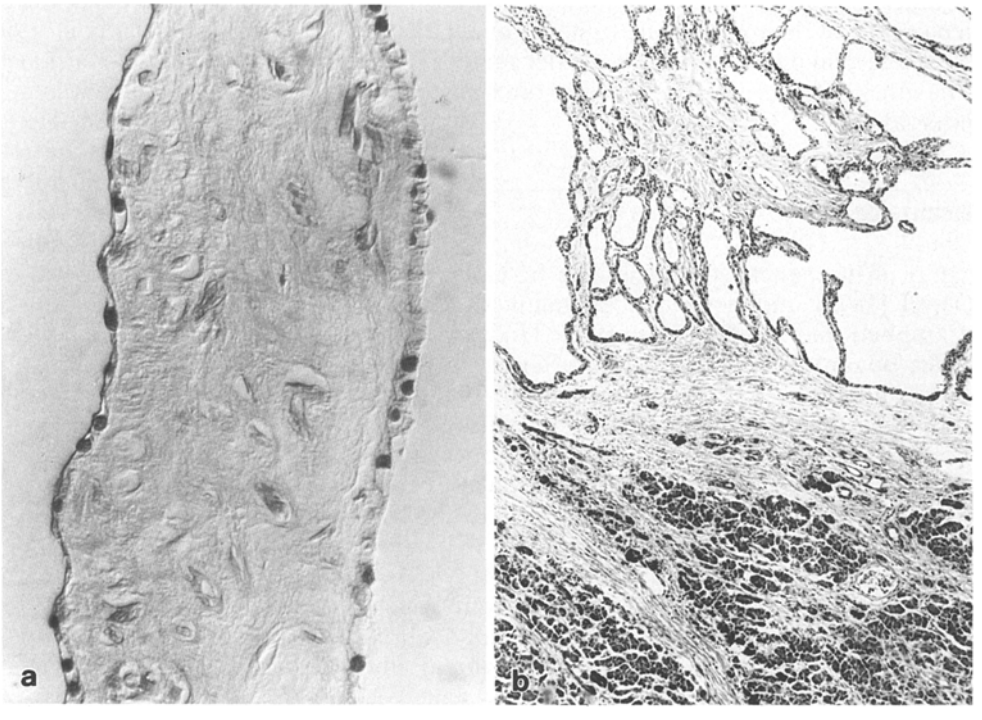

Fig. 3a, b Microcystic adenoma. **a** Cysts are lined by flattened epithelial cells with clear cytoplasm. H & E, ×240. **b** The cystic lesion is well demarcated from the adjoining pancreatic tissue. H & E, ×40

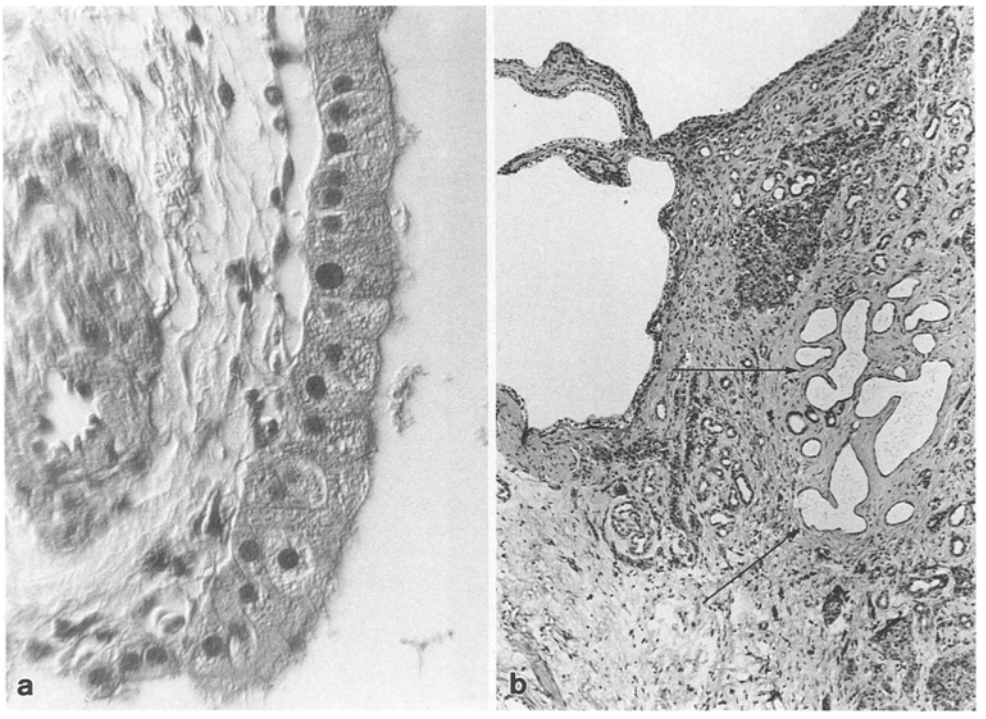

Fig. 4a, b Serous oligocystic and ill-demarcated adenoma. **a** An area of the cyst-lining epithelium showing cylindrical cells with granular (eosinophilic) cytoplasm. H & E, ×600. **b** Small cysts (*arrows*) at the margin of the lesion extending into the adjacent pancreatic tissue. H & E, ×40

MCA were detected incidentally at autopsy; the others presented either with a palpable mass or with epigastric discomfort and pain. The SOIA group included three men and one woman aged 60–69 years (Table 1). In the first patient, the tumour was discovered incidentally during an operation for a duodenal ulcer. In the fourth patient, oppressive sensations in the upper abdomen led to the discovery and removal of the tumour. Two other patients presented with jaundice; one of them also had steatorrhoea. None of these four patients developed a recurrence of their pancreatic tumour: one patient died of myocardial infarction 3.6 years after tumour removal. The other patients are alive and well after postoperative intervals of 0.7, 3.3 and 4 years.

Discussion

MCA of the pancreas, as classified by Compagno and Oertel (1978) and described by many other authors (Campbell and Cruickshank 1962; Hodgkinson et al. 1978; Bogomoletz et al. 1980; Shorten et al. 1986; Yamaguchi and Enjoji 1987; Alpert et al. 1988; Helpap and Vogel 1989; Pyke et al. 1992), presents as a well-circumscribed tumour with a sponge or honeycomb-like cystic cut surface that shows a central, stellate, occasionally calcified scar. This lesion is virtually always benign. In our series of 14 serous cystic tumours with a benign course, 10 had the typical gross features of MCA. Four differed in their macroscopic appearance in not being well demarcated, having fewer and usually somewhat larger cysts embedded in a relatively broad fibrous framework and lacking a central stellate scar. We believe that these tumours represent a variant of the pancreatic serous cystadenomas and have designated them SOIA of the pancreas.

Histologically, the SOIA were composed of the same type of epithelium as the MCA. The tumour cells thus disclosed a glycogen-rich cytoplasm that did not stain for mucins or mucin markers. They also showed a ductal phenotype since they expressed the four CKs (CK 7, CK 8, CK 18 and CK 19) which characterize pancreatic duct cells including the centroacinar cells (Osborn et al. 1986, Schüssler et al. 1992). Finally they were also positive for CA 19–9 and occasionally for B 72.3, but negative for CEA (Bätge et al. 1986; Shorten et al. 1986; Alpert et al. 1988; Helpap and Vogel 1989). These results suggest that the cells composing MCA and SOIA are of the same phenotype and are probably derivatives of the centroacinar cell (Lo et al. 1977; Bogomoletz et al. 1980; Alpert et al. 1988).

The morphological distinction of MCA from SOIA focusses on the finding that the SOIA lack the well-demarcated arrangement of cysts around a central stellate scar seen in MCA. Instead it exhibits irregularly assembled cysts which are embedded in a fibrous stroma and often extend deeply into the surrounding pancreatic parenchyma. Because of this (pseudo)infiltration of the surrounding pancreatic tissue the tumours have ill-defined margins and are not as clearly circumscribed as MCA.

Other differences found between MCA and SOIA include tumour localization and sex distribution. In ours and other series (Compagno and Oertel 1978; Bogomoletz et al. 1980; Helpap and Vogel 1989) MCA showed a predilection for the pancreatic body and tail. All four

SOIA, in contrast, occurred in the head. Moreover, the clear female preponderance of MCA was reversed in favour of men in SOIA. However, because of the small number of SOIA in this series these findings must be confirmed in a larger series.

Recently, some cases deviating from MCA in regard to size (Lewandrowski et al. 1992) and multiplicity of the cysts (Kim et al. 1990; Kamei et al. 1991) have been reported. When we compare the SOIA with those tumours we find similarities with the macrocystic variant of serous cystadenoma, but none with the multicentric variant. As judged from the illustrations the multicentric lesion is a typical MCA with the exception that it occurs multiply in the pancreas (Kim et al. 1990; Kamei et al. 1991). The macrocystic lesion, however, differs from MCA because of the presence of only one or a few large cysts and the absence of a central stellate scar. The fact that the SOIA also lacked a central stellate scar and contained only few cysts makes it similar to the macrocystic subtype of serous cystadenoma. Unlike the macrocystic subtype, however, the SOIA was ill-demarcated, had no unilocular cystic appearance and showed cysts which did not exceed 1.5 cm in diameter. Though these dissimilarities seem to favour the existence of two distinct lesions, further observations are needed to decide whether the SOIA and the macrocystic variant of serous cystadenoma are either different or closely related lesions which may represent a single entity.

Recently malignant serous cystic tumours called serous cystadenocarcinomas have been reported (George et al. 1989; Kamei et al. 1991; Yoshimi et al. 1992). The three cases which are on record were similar in gross appearance to MCA, but appear to be dissimilar to SOIA. Another malignant tumour, the non-mucinous glycogen-poor multilocular cystadenocarcinoma (Friedman et al. 1990), also differed from SOIA in gross morphology as well as histological structure. We therefore do not believe that SOIA has any relationship with the malignant counterparts of MCA. The poor demarcation of SOIA may also not be considered to be a sign of malignancy, as neither the cellular features nor the follow-up data available so far suggest any malignant potential.

Lewandrowski et al. (1992) proposed that the term serous cystadenoma be used for all benign serous cystic tumours of the pancreas. We agree with their suggestion because this name (or the synonym serous cystic adenoma) can be used as a term that covers the variants described to date: the serous microcystic adenoma, the serous macrocystic adenoma and the SOIA. Whether the macrocystic variant and the oligocystic, ill-demarcated variant are two different lesions or form one entity (which may be called serous non-microcystic adenoma) has to be clarified in future investigations.

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