Clinical Features and Natural History of Serous Cystic Neoplasm of the Pancreas

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Key Words
Serous cystic neoplasm · Tumor classification · Tumor growth

Abstract
Aims: To clarify the clinical features and the natural history of serous cystic neoplasm (SCN) of the pancreas. Methods: We retrospectively analyzed data from 30 patients affected by SCN. SCNs were classified as (1) microcystic type, (2) micro- and macrocystic type, and (3) macrocystic type according to the modified WHO classification. Eighteen patients who underwent serial radiographic imaging were identified, and tumor growth rate in these patients was evaluated. Results: The median age was 62 years, and the female: male ratio was 2:1. Twenty-five patients (83%) were asymptomatic and 5 (17%) were symptomatic. The median tumor size was 2.6 cm. Fifteen cases (50%) had the microcystic type, 7 (23%) the micro- and macrocystic type, and 8 (27%) the macrocystic type. Age, gender, symptoms, location or tumor size did not differ significantly among the three subtypes. Eighteen patients were followed up for a median of 58 months. Morphological changes were observed in 3 patients (17%) and enlargement of tumor size in 9 patients (50%) during the follow-up. The growth rate was 0.29 cm per year and doubling time was 3.5 years; these rates did not differ among morphological subtypes or size of tumors. Conclusions: In asymptomatic patients with a clear imaging diagnosis of SCN, nonoperative management with a careful follow-up should be recommended. Surgery should be suggested in only symptomatic patients, those with giant tumors (>10 cm), rapid growing or when the presence of a potentially malignant tumor cannot be excluded.

Introduction
Serous cystic neoplasms (SCNs) of the pancreas are almost always benign, and are among the common primary pancreatic cystic neoplasms. SCNs constitute 10–15% of all cystic masses of the pancreas and 1–2% of all primary pancreatic neoplasms [1]. They are typically unicentric, well demarcated, often honeycombed cystic masses. The cysts are loculated, contain mucin-free serous fluid, and are lined by cuboidal or flattened epithelium [2]. The origin and etiology of serous cystadenomas are not completely known. Morphologic and immunohistochemical features favor the intralobular, centroacinar, and ductular cells of the pancreas. The World Health Organization (WHO) classifies them into serous microcystic adenomas and serous oligocystic adenomas [2]. Recently, there have been several case reports of a solid serous adenoma identified as a variant of a serous cystadenoma [3–5]. In addition, a handful of cases of serous cystadenocarcinoma have been reported [6–18]. Because
of the rarity and little understanding of the natural history of the SCN, there is still considerable controversy over the treatment of these tumors. Surgical resection is generally performed to relieve symptoms, if the SCN is large, or because of the inability to distinguish an SCN from a mucinous neoplasm, which has a greater malignant potential [19]. Resection of all cystic neoplasms of the pancreas has been recommended by some [20–22], whereas others have advocated more selective approaches based on individual cases [23, 24].

The aims of the present study were to identify the clinical features and evaluate methods of diagnosis of SCNs, to clarify their natural history by reviewing serial radiographs, and finally to propose guidelines for the accurate diagnosis and optimal management of patients with SCNs.

**Methods**

Enrolled in this retroactive study were 30 consecutive patients with the diagnosis of SCN at our institution, the Center for Gastroenterology, Teine-Keijinkai Hospital, Sapporo, between January 1998 and March 2009. Inpatient and outpatient medical records were reviewed in detail. Information regarding demographics, presentation, radiographic and endoscopic evaluation, follow-up after diagnosis, surgical treatment (if any) and pathology were obtained.

We have classified SCNs as (1) microcystic type, (2) micro- and macrocystic type, and (3) macrocystic type according to the modified WHO classification. SCNs were defined as microcystic when the cysts within the tumor were smaller than 1 cm; when the cysts were larger than or equal to 1 cm, they were classified as macrocystic. Microcystic SCNs were subdivided into honeycomb and solid types based on morphology. The SCNs with macrocysts were subdivided into micro- and macrocystic (macrocystic dominant) and macrocystic (macrocystic dominant) types. A unicellular type was not included because of the impossibility of a preoperative diagnosis (fig. 1).

Tumor size was calculated from radiographic images. Maximum diameter was used as the primary metric for tumor size. Tumor volume was determined using the formula \( \frac{4}{3} \pi \times \left( \frac{d_1 \times d_2 \times d_3}{6} \right) \) [25]. If fewer than three measurements of diameter were available, the formula was modified accordingly: \( \frac{4}{3} \pi \times \left( \frac{d_1^2 \times d_2}{6} \right) \) or \( \frac{4}{3} \pi \times (d^3) \).

All patients who were not treated by surgery agreed to follow-up through close observation. Imaging modalities with computed tomography (CT) and/or magnetic resonance cholangiopancreatography (MRCP) were performed once or twice a year. Serial changes in morphology and the maximum diameter of the tumor were monitored during the observation period. Tumors with an increase or decrease in the maximum diameter \( \geq 10 \) mm were defined as enlarged or reduced, respectively. To estimate tumor volume growth, doubling times (DTs) were calculated using the Schwartz equation: \( DT = \frac{[1 \times \text{Ln}(2) \times (t_2 - t_1)]/\text{Ln}(v_2/v_1)}{\text{v is volume [26, 27]}.} \)

**Results**

**Patient Characteristics**

The median age of the 30 patients was 62 years (range, 24–92), and the female:male ratio was 2:1. Overall, 25 (83%) patients were asymptomatic, with the tumor incidentally identified during a routine check-up or during an evaluation of another disease. Five patients (17%) were symptomatic: 2 had abdominal pain, 2 had nonspecific symptoms, and one patient presented with pancreatitis. Five patients (17%) presented in the context of other neo-
plasms, including one patient with hepatocellular carcinoma, one patient with breast cancer, one patient with colon cancer and 2 patients with von Hippel-Lindau disease. Twenty-nine cases (97%) were unifocal, and one case (3%) with von Hippel-Lindau disease had multifocal lesions. Of the 30 SCNs, 12 (40%) were localized in the head of the pancreas and 18 (60%) were in the pancreas body to tail. Median tumor diameter was 2.6 cm (range, 1.0–6.3 cm). Dilation of Wirsung duct was observed in 2 patients (7%) at diagnosis. These 2 patients (7%) underwent surgery and others were closely observed without surgical resection. When SCNs were classified by size and number of cysts, 15 patients (50%) had the microcystic type (all honeycomb type), 7 patients (23%) the micro- and macro-cystic type, and 8 patients (27%) had the macrocystic type. Comparisons of demographic findings among subjects with the three types of SCN are shown in table 1. Age, gender, symptoms, location or tumor size did not differ significantly between the three subtypes of SCN.

**Imaging Assessment**

Of the 30 patients with an SCN, 25 (83%) were studied with ultrasonography (US), 27 (90%) with CT, 21 (70%) with MRCP, and 28 (93%) with endoscopic US (EUS). Of the 25 tumors studied with US, 11 (44%) were demonstrated to have the typical characteristics (honeycomb pattern with central scar) that led to precise diagnosis of SCN, 8 (32%) were interpreted as intraductal papillary mucinous neoplasm (IPMN), 3 (12%) were a solid mass, and 3 (12%) were not detected. All 27 CT scans demonstrated a cystic mass, 18 (67%) of which were diagnosed as an SCN with the honeycomb pattern or central scar with calcifications, 8 (30%) were interpreted as IPMN,
and 1 (3%) was interpreted as a retention cyst. All 21 MRCP studies showed a high intensity mass on T₂-weighted images, 14 (67%) of which were diagnosed as an SCN with a honeycomb pattern and 7 (33%) were interpreted as an IPMN. All 28 patients who underwent EUS, including the 7 patients misdiagnosed by US, CT, or MRCP, were revealed by EUS to have closely aggregated microcysts in a portion of the cystic tumors (fig. 2).

**Operation**

Of the 30 patients with an SCN, 2 underwent surgery: one patient underwent pancreaticoduodenectomy due to pancreatitis and the other underwent distal pancreatectomy for resection of a large tumor in the pancreas tail. Figure 3 shows a serous cystadenoma involving the head of the pancreas in the patient who underwent the pancreaticoduodenectomy. There were no major perioperative complications.

**Tumor Growth**

Twenty-eight of the patients who were diagnosed with an SCN did not undergo surgery. All had results of imaging studies consistent with SCN. Of the 28 patients, 18 (64%) were followed by serial radiography. The interval between the first and last study ranged from 10 to 105 months, with a median of 58 months. Table 2 shows the clinical outcome of eighteen SCNs during long-term follow-up. During the follow-up period, morphologic changes were observed in three tumors (17%); microcystic SCN changed to macrocystic SCN with tumor enlargement in one patient, macrocystic SCN changed to micro- and macrocystic SCN with tumor enlargement in

![Fig. 3. A 24-year-old female with micro- and macrocystic SCN.](image)

<table>
<thead>
<tr>
<th>Table 2. Clinical outcome of SCN</th>
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<tr>
<td><strong>Clinical outcome</strong></td>
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<tr>
<td>Morphology</td>
</tr>
<tr>
<td>No change</td>
</tr>
<tr>
<td>Changed</td>
</tr>
<tr>
<td>Size of tumor</td>
</tr>
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</tr>
<tr>
<td>Reduced</td>
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<tr>
<td>Enlarged</td>
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1 Changes in size >10 mm were defined as enlarged or reduced.
Table 3. Data on 9 patients with enlarged SCN during follow-up

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<th>Location</th>
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<th>Initial size mm</th>
<th>Latest size mm</th>
<th>Change in size mm</th>
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<tr>
<td>47</td>
<td>M</td>
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<td>43</td>
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<td>62</td>
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<td>head</td>
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<td>47</td>
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<td>100</td>
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<td>F</td>
<td>tail</td>
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<td>15</td>
<td>31</td>
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<td>59</td>
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<tr>
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<td>M</td>
<td>body</td>
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<td>38</td>
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Table 4. Relationship between clinical characteristics and clinical outcome

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<th>Enlarged (n = 9)</th>
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<tr>
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<td>3/6</td>
<td>NS</td>
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<td>NS</td>
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<td>5/4</td>
<td>NS</td>
</tr>
<tr>
<td>Subtype, 1:2:3</td>
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<td>6:0:3</td>
<td>NS</td>
</tr>
<tr>
<td>Initial size, mm</td>
<td>31</td>
<td>26</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up, months</td>
<td>40</td>
<td>72</td>
<td>&lt;0.01</td>
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</table>

one patient, and in the third patient the macrocystic SCN changed to a microcystic SCN through tumor shrinkage from 30 to 25 mm. In 9 cases (50%), the tumor was enlarged, and in the remaining 9 cases (50%) there was no change in size during the follow-up period. The median growth rate in the maximum diameter was 0.29 cm per year; in those tumors showing growth, the median DT was 3.5 years. Dilation of the Wirsung duct with tumor growth was observed in one patient with VHL. This patient continued with follow-up because of multiple lesions in whole pancreas.

Data on patients with enlarged SCNs are shown in table 3. Of the 9 cases, there were 6 females and 3 males, with a median age of 62 years (range, 26–78 years) at the time of diagnosis. Five tumors were in the head, three in the body and one in the tail of the pancreas. The morphological subtype at the time of diagnosis was microcystic in 6 cases and macrocystic in 3 patients. Morphology of one microcystic SCN changed to the macrocystic type and that of one macrocystic SCN changed to the microcystic type with enlargement. All cases were asymptomatic and continued with regular follow-up.

Table 4 shows a comparison of various clinical factors between SCN patients whose tumor did not change and those whose tumor enlarged. There were no significant differences in age, gender, location, morphological subtype or initial size of the tumor between the two groups. The follow-up duration in SCN patients with an enlarged tumor was significantly longer than in those with no change.

Discussion

SCNs are being increasingly diagnosed with the more widespread use of imaging techniques and improvements in imaging technology [19, 27]. SCNs are subclassified as serous microcystic adenomas and serous oligocystic adenomas by WHO [2]. However, this WHO classification does not reflect the actual structures of SCNs. A systematic classification of SCNs based on radiological examination is needed. In this report, we present a modified morphological classification of SCNs according to radiological features and analyzed the clinical features of subtypes of the SCN. CT findings suggestive of SCN include a central scar with the ‘honeycomb’ appearance of microcysts, which is found in the more common microcystic type of SCN. However, the rare macrocystic type may be more difficult to differentiate from IPMN or MCN based on CT findings [23, 28]. Although other modalities such as MRI and MRCP may be more useful in differentiating IPMN or MCN from SCN, differentiating the macrocystic type of SCN from other cystic tumors is still difficult. EUS has been proposed as an ideal imaging technique for
pancreatic cystic lesions [29–31]. Ultrasound can readily characterize cysts, and high-resolution imaging of the pancreas can be achieved through endoscopic means. Accuracy of diagnosis can be improved when EUS is added to other imaging modalities, as it can detect small areas of closely aggregated microcysts. In this study, although 6 (75%) cases with the macrocystic type of SCN were misdiagnosed by US, CT and MRCP, EUS allowed the correct diagnosis in all cases. EUS-guided fine needle aspiration may provide a definitive diagnosis, but sensitivity of diagnosis is generally low due to the small amount of material obtained and may not contain diagnostic material [32–34]. Furthermore, in the case of a mucinous lesion, there remains the disturbing unresolved problem of potential spread of malignant cells [35]. Therefore, aspiration should be reserved only for selected cases [34].

Many SCNs are asymptomatic, and the overwhelming majority of these neoplasms are benign, with the exception of only a handful of case reports [6–18] of serous cystadenocarcinoma. However, the optimal treatment of these neoplasms remains controversial. This can be attributed to the limited understanding of their natural history. Bassi et al. [34] reported that among 100 consecutive cases of SCN, 34 cases were followed up, and 2 underwent surgical resection because of frank tumor growth (>2 cm/year), while the remaining 32 were conservatively followed up without any significant increase in the diameter of the lesion. Tseng et al. [23] reported that with a median follow-up of 2 years, the growth rate of SCNs was only 0.6 cm per year; however, the growth rate was significantly greater in tumors ≥4 cm in size (growth rate of 1.98 cm per year and DT of 0.64 years). These are the only studies investigating the natural growth of SCNs to our knowledge, and the natural history of SCNs over the long term remains unclear. In the present study, half of SCNs showed tumor growth, and the observation period was the only factor associated with the tumor growth. Though the growth rate was rather slow (0.29 cm per year and DT was 3.5 years) in our study, the result indicates that any SCNs have a possibility to grow with time irrespective of tumor subtype, size, or location, suggesting that all SCNs should be followed up regularly.

Since George et al. [6] first introduced a malignant variant known as serous cystadenocarcinoma, there have been several case reports [6–18] of SCNs with malignant behavior. Malignant SCN is defined by the presence of metastases to extrapancreatic organs or tissues. Vascular and perineural invasion and local invasion into the duodenum or stomach are not criteria for the diagnosis of a malignant variant [36]. According to the criteria, 9 cases of malignant SCN have been reported in the literature, with liver metastases in 6 patients and lymph node metastases in 3 patients. Eight of the 9 malignant SCNs (89%) were symptomatic and more than 10 cm in diameter. These findings suggest that SCNs acquire malignant potential according to the extent of growth and that symptomatic or giant (>10 cm) SCNs have a high risk of malignant potential. Since all patients were asymptomatic and all SCNs were less than 10 cm in size throughout the observation period in our study, the patients were all under conservative management with careful follow-up. In the past, most SCNs were resected because of the difficulty in distinguishing these tumors from other tumors with malignant potential. However, improvements in imaging technology and a better understanding of the pathological behavior of SCNs have resulted in a reduction in surgically managed cases. Based on data in the present study and in the literature, we propose the following guidelines for the management of SCNs. When the diagnosis of an SCN is confidently determined based on clinical and radiographic evidence, nonoperative management with a careful follow-up should be recommended. Based on the slow growth of these neoplasms observed in this study, we recommend serial imaging at 12-month intervals. Surgery should be suggested in only symptomatic patients, giant tumors (>10 cm), rapidly growing or, when the presence of a potentially malignant tumor cannot be excluded.

References

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