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Serous Cystadenomas Follow a Benign and Asymptomatic Course and Do Not Present a Significant Size Change During Follow-Up

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ABSTRACT

Background: Serous cystadenoma is a benign pancreatic cystic neoplasm. Conservative management is favored. We studied the clinical characteristics and course of serous cystadenoma in patients undergoing surgery or conservative management only at an academic referral center. **Methods:** Patients presenting with serous cystadenoma in the years 2000-2013 were selected. Hospital records were evaluated for patient and serous cystadenoma characteristics. **Results:** A total of 22 patients with serous cystadenoma were identified. Mean age at diagnosis was 63 years and 82% were women. Diagnosis was incidental in 59%, and 18% presented with unspecific abdominal pain, 14% unexplained weight loss, 4.5% gastrointestinal obstructive symptoms, and 4.5% cholangitis. Location was pancreas body 36%, head 32%, tail 23%, and uncinate 9%. Mean serous cystadenoma diameter at diagnosis was 37 ± 23 mm. After diagnosis five patients underwent surgery. Initial size was similar between surgical and follow-up groups ($p = 0.9$). Four cases were lost to follow-up; 13 continued conservative management with a mean follow-up time of 54 ± 27 months. The initial and last serous cystadenoma size in the follow-up group remained similar ($p = 0.9$). Six cases presented significant tumor growth during follow-up ($p > 0.05$). All patients remained asymptomatic throughout follow-up. No malignancy or serous cystadenoma-related death occurred. **Conclusions:** Size change of serous cystadenoma was minimal and patients remained asymptomatic during follow-up. Surgery should be limited to symptomatic and selected cases. (REV INVES CLIN. 2015;67:344-9)

Key words: Serous cystadenoma. Pancreas cyst. Pancreas neoplasm. Cystic neoplasm. Pancreas surgery.

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INTRODUCTION

Serous cystadenoma (SCA) represents 1-2% of all pancreatic exocrine tumors, usually present in subjects over 60 years old and slightly more frequent in women. It is the third to fourth most common cystic pancreatic neoplasm[1,2]. It tends to follow a benign course, amenable to conservative treatment unless symptoms or rapid growth develop[3-5].

Serous cystadenomas are usually incidental findings; some patients present with unspecific abdominal pain, unexplained weight loss, or symptoms of compression to adjacent organs.

Some groups recommend an expectant management in all asymptomatic SCA, with the exception of those measuring ≥ 4 cm that bear an increased risk of rapid growth in which surgical treatment, even in asymptomatic patients, should be considered[6].

Although mortality from pancreatic resections has significantly decreased and outcomes are acceptable in high-volume centers[7-9], operating on SCA before they become large aims to avoid the increased technical difficulty and morbidity inherent in resection procedures for big masses[10,11]. Also, the type of resection carries different risks and morbidities and should be taken into consideration when management is decided.

An analysis of 219 SCA cases reported a steady and slow growth rate regardless of the initial size, suggesting that resection should be considered only when there are symptoms present or if the tumor size doubles in less than 12 years[12].

We aimed to analyze clinical characteristics and course of SCA at an academic referral center.

MATERIAL AND METHODS

We identified patients presenting with SCA between 2000 and 2013 by reviewing institutional charts as well as surgical and pathology logs. Using a questionnaire designed for a multinational study on SCA sponsored by the International Association of Pancreatology and the European Pancreatic Club (some cases presented in this manuscript were included in that study)[13], we retrospectively collected demographic (gender, age, diagnosis date, last follow-up date, fatalities), clinical (cyst-related symptoms, circumstances of discovery), imaging (computed tomography [CT], magnetic resonance imaging [MRI], endoscopic ultrasound [EUS]) findings, cyst characteristics (microcystic, macrocystic, mixed type, size, location in the pancreas, relationship with the pancreatic and bile ducts, contents, wall characteristics), fine needle aspiration and cyst fluid analysis at the moment of diagnosis and last follow-up as well as surgical (indications, findings, type of resection) and pathology data (gross and microscopic description).

Serous cystadenoma diagnosis was based on typical imaging characteristics (honeycomb pattern, multicystic lesion, central scar, no communication with main pancreatic duct) by either cross-sectional studies and/or EUS with or without cyst fluid analysis), and pathology reports in those resected specimens. Cyst fluid content typical of SCA included bland cytology, no or scant mucin on periodic acid-Schiff (PAS) staining, amylase < 200 mg/dl, carcinoembryonic antigen (CEA) < 5 mg/dl[12-14].

Serous cystadenoma size at diagnosis and during follow-up was calculated using the maximum tumor diameter from cross-sectional (CT, MRI) and/or EUS imaging.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) and qualitative variables as frequencies. Data comparisons were performed using X^2, Fisher exact test, Student's *t* test or Mann-Whitney test, accordingly. A p value < 0.05 was considered significant. All analyses were performed using SPSS V 22 (SPSS for Mac; IBM, Chicago, Illinois, USA).

RESULTS

We included 22 patients; mean age at diagnosis was 63 ± 14.5 SD years, and 18 (82%) were women. The SCA radiology appearance and pancreas location are shown in table 1.

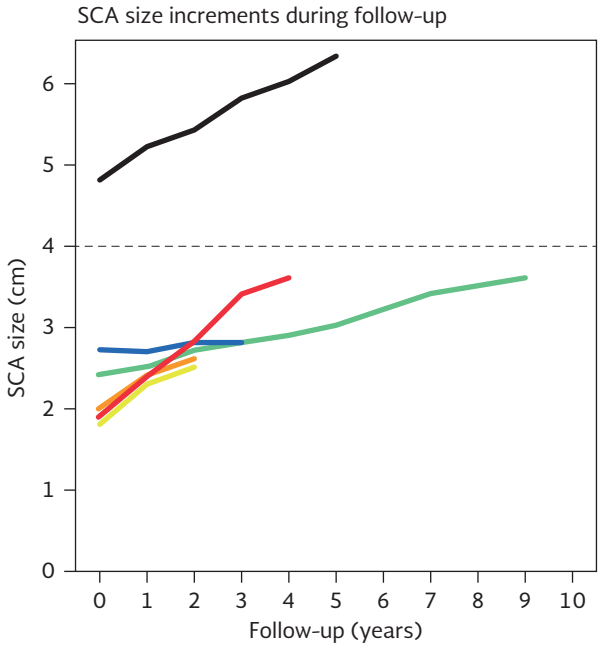
Serous cystadenoma was diagnosed during evaluation of unspecific abdominal pain (4, 18%), unexplained weight loss (3, 14%), gastrointestinal obstructive symptoms (1, 4.5%), cholangitis (1, 4.5%), and incidentally in 13 (59%) cases.

Table 1. Demographic, clinical and imaging characteristics

Variable	n (%)
Gender (male:female)	4 (18) : 18 (82)
Age at diagnosis (years)*	63.0 ± 14.5
SCA type	
– Microcystic	12 (55)
– Macrocystic	2 (9)
– Mixed	8 (36)
– Solid	0
Location	
– Uncinate	2 (9)
– Head	7 (32)
– Body	8 (36)
– Tail	5 (23)
Overall size at diagnosis*	37 ± 23 mm

*Mean (standard deviation).
SCA: serous cystadenoma.

Figure 1. Data from the 6 patients that presented serous cystadenoma during follow-up.



SCA: serous cystadenoma.

Serous cystadenoma mean size at diagnosis was 37 ± 23 mm. Five cases underwent surgical resection (distal pancreatectomy) at the time of presentation; indications for resection were: symptoms (pain, mass effect in 3, 14%), indeterminate diagnosis (1, 4.5%), and uncertainty of malignancy (1, 4.5%).

Initial tumor size was similar between surgical and non-surgical groups (39 ± 17 vs. 37 ± 27 mm, respectively; p = 0.9). Four cases were lost to follow-up and 13 continued conservative management; mean follow-up time was 54 ± 27 months. Overall, in the 13 non-surgical cases, initial SCA size remained similar when compared to the last follow-up size (29 ± 17 vs. 33 ± 18 mm SD; p = 0.9).

Only 6/13 (46%) cases presented significant growth during follow-up; the initial size was 25 ± 11 mm SD vs. final follow-up size 36 ± 14 mm SD (p < 0.05) (Fig. 1).

All patients remained asymptomatic at the last visit. Neither malignant transformation nor SCA-related deaths were registered.

DISCUSSION

Since first described in 1978[15], SCA has been considered a benign tumor. Most are incidentally found and remain asymptomatic during long periods of time regardless of their size. Conservative management has been widely advised, with surgery being considered only for symptomatic cases[6,16,17].

Differential diagnosis includes potentially malignant cystic lesions (e.g., mucinous cystadenoma, pancreatic intraductal papillary mucinous neoplasm, etc.). An accurate diagnosis is essential since management and prognosis differ according to the type of neoplasm[15,18-21].

Definitive diagnosis of SCA is achieved based on surgical pathology of resected specimens. However, presurgical diagnosis can be made when classic imaging features are present[22], except in those rare SCA variants[23-25]. In these cases, analysis of the cyst's contents can yield relevant diagnostic information.

Once a SCA is diagnosed, whether to follow-up or perform a surgical resection, especially in asymptomatic cases, remains under discussion. Two of the largest series reported similar results regarding the clinical presentation, but disagreed on when to consider surgery in asymptomatic cases[6,12]. One of them analyzed serial radiographic records in 24 patients. The overall median growth rate was 6 mm per year, but a significant difference in growth rate was noted in nine cases presenting with tumors ≥ 4 cm, having a growth rate

of nearly 20 mm per year and a doubling-size time of 0.64 years, compared with 2.84 years for SCA < 4 cm[6]. It is not clear whether SCA growth was associated with symptom onset; however, in this series, SCA ≥ 4 cm had a threefold risk of developing symptoms.

Another series[12] followed 194 SCA for a median time of 3.2 years; only five patients underwent resection during follow-up (median size: 3.5 cm; range: 2.6-18.7). Indications for surgery were symptoms development (n = 2), accelerated growth or mass effect (n = 2), or increased cyst fluid CEA in one case. It seems that with the exception of the last case, in the remaining four, symptoms and not tumor size were responsible for indicating surgery. The authors, instead of proposing a specific cut-off cyst size to consider surgery, advise to perform surgery if the size doubles in less than 12 years.

Our study replicates most clinical and imaging characteristics from prior SCA series, including the most frequent variant (microcystic); however, the second most common variant was the mixed one (36%) compared to other series in which the macrocystic subtype was the second most frequent[26-28]. It is uncertain if this could be related to ethnicity or other undetermined factors.

Three out of five of our surgical cases were symptomatic, and interestingly, in all of them the tumor measured < 4 cm.

Although our findings are limited by the small sample size, the follow-up time is slightly longer (five years) than previous reports and confirm that SCA has a minimal or non-significant size increment, with most patients remaining asymptomatic regardless of location and size (from 13 cases in follow-up, seven remained unchanged and six presented a mean 10 mm increment regardless of the initial size).

After serial CT imaging review of the six cases with increased size, four patients had four studies, one had three, and one had two. However, the small sample prevented us from performing a proper growth rate arithmetic calculation, limiting our analysis to report only changes in size during follow-up.

Considering a linear growth, the annual growth rate can be calculated by obtaining the cyst's difference in size by subtracting the initial size from the size on the last imaging, and then dividing it by the number of years of follow-up for each of the six cases in which the tumor grew and then obtaining the overall arithmetic mean value of growth from all of the six cases.

It is important to note that the mathematical model used and its validity will always limit growth rate assessments. Despite the limitations of our calculations that assume a linear rather than a curvilinear growth that could better resemble reality, this exercise (data not shown) yielded an overall growth rate of about 2 mm per year, with tumors < 4 cm growing slower (1.6 mm per year). These rates are similar to previous reports that estimated a 1.2 mm increase per year for small lesions[12,13].

Interestingly, one case with a tumor measuring 8 cm has remained stable, and another with a 4 cm lesion grew 24 mm in seven years, with both patients being asymptomatic. Thus, a cyst size of ≥ 4 cm did not represent a risk of increased growth or symptom development (observation from two cases with a short follow-up).

The lack of symptoms in patients even with big cysts could be the result of a slow tumor growth rate allowing the body to adapt. On the other hand, rapid growth rates could be responsible for a mass effect and secondary symptoms. It is unclear which factors other than size determine the growth rate as well as the presence of symptoms.

Serous cystadenoma shows a low rate (0.1-3.3%) of malignancy regardless of the presence of symptoms and size[3-5,13]. None of the patients in our series presented malignant transformation of the tumor.

Considering that a detailed imaging and evaluation of the cyst's content can lead to an accurate diagnosis of SCA[29], the low or null rate of malignancy, that not every cyst ≥ 4 cm shows a rapid growth rate, and that large cysts are not always symptomatic, it seems reasonable and safe that asymptomatic SCA be observed.

Periodical evaluation with serial CT imaging (every six months during the first two years and then annually as proposed by some groups)[6,28] appears to be sufficient and safe. The follow-up strategy remains under debate and amenable to consensus.

However, if we were to consider symptoms as the single factor to consider surgery, then serial imaging aiming to select potential surgical candidates (≥ 4 cm), and to assess stability or growth rate might be unnecessary, and control imaging should be considered only when patients become symptomatic. For such approach a 100% certainty in diagnosis is mandatory.

The study with the largest number of SCA with a follow-up of three years[13] found that relevant clinical symptoms occurred in a very small proportion of patients, with tumor size slowly increasing in less than half. They advocate an initial conservative management in the majority of patients, and surgery should be proposed only for uncertain diagnosis after a complete workup, with the presence of significant and cyst-related symptoms, or when malignancy is a concern.

A conservative and symptom-based strategy is supported by the fact that about 11% of cases become symptomatic during follow-up, regardless of cyst size[13]. However, significant difficulties in management could present in those initially asymptomatic cases with a large SCA that may be fit for surgery and years later become symptomatic, at an age in which surgery might not be feasible anymore.

Development in EUS therapeutics, such as EUS-guided ablation (using ethanol or other ablative agents), offers an alternative for cases with potentially malignant or malignant cysts not fit for surgery. This technique has proved to be safe, effective, and minimally invasive for the treatment of pancreatic cysts. Much of the information comes from clinical trials and case series that included mainly mucinous lesions, with information on SCA being extremely limited[30].

Serous cystadenoma may represent a challenge or limitation to this approach since the greatest chance of successful ablation is in unilocular or oligolocular cysts (fewer than 2 or 3 locules). The multiple, small locules that characterize SCA would represent a greater number of needle passes, increasing the procedure risks. Data on a large SCA sample is still needed, which leaves this approach in this subset of patients to be performed only as part of research clinical trials.

We consider that a precise SCA diagnosis is mandatory. Once diagnosis is certain, an initial conservative management is possible, and cyst-related symptoms could guide the treatment strategy. Surgery should be reserved for symptomatic cases and not recommended based on tumor size or doubling-size time. The surveillance strategy remains under debate and, along with surgical decisions, should be individualized.

In conclusion, change in SCA size was minimal and patients remained asymptomatic during follow-up. No malignant transformation or cyst-related fatalities were observed.

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