Serous neoplasms of the pancreas constitute a continuous spectrum of morphological patterns rather than distinct clinico-pathological variants. A study of 40 cases

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Serous neoplasms (SN) of the pancreas account for 1-2% of all pancreatic tumours. Six morphological variants of SN were previously recognized: serous microcystic (cyst)adenoma, serous macrocystic (cyst)adenoma, von Hippel-Lindau-associated serous cystic neoplasm, solid serous adenoma/neoplasm, mixed serous-neuroendocrine neoplasm and serous cystadenocarcinoma. It was recently postulated that SN shows a continuous spectrum of morphological patterns rather than distinct clinico-pathological subtypes. To address this issue, we performed a detailed review of 40 SN cases diagnosed at our institution between 1989 and 2011. We found 11 cases of serous microcystic (cyst)adenoma, 5 cases of serous macrocystic (cyst)adenoma, and a single case of von Hippel-Lindau-associated serous cystic neoplasm. Apart from that, we found 20 cases of SN which showed features of both microcystic and macrocystic (cyst)adenomas, 2 cases of small 'incipient' SN and a single case of a mixed microcystic and solid adenoma. In conclusion, we showed that 'borderline' lesions among SNs truly exist and are not rare. The reason for such a wide diversity of morphological patterns of SN remains unknown.

Key words: serous neoplasms of the pancreas, pancreatic neoplasms, pancreas.

Introduction

Serous neoplasms (SN) are uncommon lesions of the pancreas. They account for 1-2% of all pancreatic tumours and constitute up to one third of neoplastic cysts of that organ [1-3]. Compagno and Oertel in 1978 [4] distinguished SN from other cystic lesions of the pancreas.

The most frequent gross and microscopic picture of SN is compatible with the so-called microcystic SN [serous microcystic (cyst)adenoma, SMA]. Apart from this, 5 variants were distinguished: serous macrocystic (cyst)adenoma, von Hippel-Lindau-associated serous cystic neoplasm (VHL-SCN), solid serous adenoma/neoplasm (SSA) and mixed serous-neuroendocrine neoplasm (MSNN). A separate category is represented by the only malignant neoplasm among SNs, namely serous cystadenocarcinoma (SCAC).

Classic morphologic configurations of SMA and serous macrocystic (cyst)adenoma are well described [1-3]. Both types of tumours are composed of uniform, cuboidal, glycogen-rich epithelial cells.

Serous microcystic (cyst)adenoma form very numerous small cysts filled with watery fluid and usually have a central, stellate-like scar and incomplete fibrous pseudocapsule. Small papillary intraluminal projections into the cysts are common. Serous microcystic (cyst)adenoma measure up to 25 cm and may be

localized in any pancreatic segment. In almost all cases, communication between the cyst and pancreatic duct system is absent [1, 2, 5, 6], but rare examples of tumours with such a feature were observed [7, 8].

Serous macrocystic (cyst)adenomas are less common than SMAs and constitute less than 20% of SNs. They measure between 1 and 19 cm. Some researchers have stated that they occur usually in the pancreatic body or tail [9, 10]; others claim that they are more frequent in the pancreatic head [5, 6, 11-13]. Typically, they are composed of a few ('countable') relatively larger cysts (oligolocular lesions) lined by glycogen-rich epithelium. In some cases, macrocystic (cyst)adenomas are unilocular. They lack the central scar and are poorly demarcated from the adjacent pancreatic parenchyma [1, 2, 5, 6, 9]. For that reason, they were previously known as serous oligocystic and ill-demarcated adenomas (SOIA) [1, 2, 6, 12].

It is not clear whether clinical characteristics of SMA and SOIA are different enough to justify dichotomy of SNs between these variants [6, 9, 11]. Some investigators showed that SMA and SOIA differ in terms of mean patients' age, gender proportions and tumour localization [6, 13], but others did not confirm those observations [9, 10, 14].

Von Hippel-Lindau-associated serous cystic neoplasms are usually multifocal. They diffusely involve the pancreatic parenchyma. Microscopically, they are very similar to the other SNs [1-3, 5, 6, 15]. The diffuse or multifocal presentation of SNs outside the VHL disease is very rare but still possible [16].

Solid serous adenoma/neoplasm is a very rare solid variant of SN in which cysts are not grossly recognizable but may be seen microscopically. However, the majority of tumour volume is composed of acini or trabeculae without detectable cysts [1-3, 6, 17-19].

Additionally, SN may coincide with neuroendocrine neoplasm, forming a collision or a composite lesion (MSNN). Both components may also exist separately, but this does not allow the diagnosis of MNSS. This variant is highly suggestive but not diagnostic of a VHL disease [1, 2, 20, 21].

Serous cystadenocarcinomas are extremely rare and they may be safely diagnosed only when metastasized [1, 2, 5, 6, 22, 23].

Recently, several groups of researchers documented their experience in preoperative radiological assessment of SN using morphological categories which clearly did not parallel the gross pictures of variants of SN described above. This was based on the observation that these classic SN growth patterns are of limited usefulness in the context of differential diagnosis of SNs and other cystic lesions of the pancreas [14, 24-27].

Sun *et al.* in their recent study on computed tomography images suggested, that SN may show a continuous spectrum from purely solid lesions (SSA) to unilocular cysts (unilocular SOIA) [25].

In our practice we have also seen cases of SN which represented "borderline" lesions among established histopathological subtypes. To confirm pathologically results of Sun *et al.* in an independent collection of SNs we performed a histopathological review of 40 previously not described cases. This represented our institutional experience from 1989 up to 2011. To the best of our knowledge, this was the largest collection of SNs diagnosed in Poland.

Material and methods

Among 40 SN cases, 11 were diagnosed retrospectively. These cases were identified in a dedicated departmental database of pancreatic specimens established in 1985 which was fully re-examined between 2009 and 2010 irrespective of initial, signed-out diagnoses.

Additional 29 cases were gathered prospectively from 2007 to 2011. All these cases were examined grossly by one of us (LL) with emphasis on features which were previously shown to be important for distinguishing SN variants. In the majority of cases, the provisional diagnosis of SN was established during the gross examination. This precluded the use of a sampling technique which we developed for malignant pancreatic neoplasms [28] since it generates relatively high costs and is not necessary for benign lesions. Nevertheless, many blocks were prepared from the pancreatic specimens, including the central and peripheral portions of tumours. Smaller tumours (up to 3 cm) were sampled entirely. Extratumoral pancreatic parenchyma was also sampled entirely, but results of histopathological examinations of that tissue are to be published in a separate manuscript (in preparation).

All the specimens were fixed in 10% buffered formalin. Specimen processing and haematoxylin and eosin staining was performed in a standard manner. The histopathological diagnoses of SN were based on criteria provided by the reference sources [1, 2]. Several microcystic as well as macrocystic cases were submitted to immunohistochemical examination with carbonic anhydrase IX and GLUT1 antibodies, which are markers of *VHL* gene alterations as well as tumoral hypoxia, as described previously [29].

Results

Basic clinical and pathological data

The majority of 40 SN cases were diagnosed recently (2007 – 5, 2008 – 8, 2009 – 5, 2010 – 4, 2011 – 7 cases). This observation did not reflect an increase in SN incidence but it was rather related to the expertise of our centre in the treatment of pancreatic diseases.

The majority of SN cases (34 patients, 85%) were found in females. The patients' age ranged from 31 to

93 y (median 65.0 y, mean 63.2 y). The median age of females and males with SN did not differ (Mann-Whitney U-test, p = 0.493).

Two cases were diagnosed on autopsy. One of them was an incidental 4-cm neoplasm in the pancreatic tail of a 93-y male patient who died of unrelated reasons. Another case was multifocal SN which was found in a 32-y woman who died of cerebellar neoplasm. On post-mortem examination she was found to suffer from VHL disease (described later). All SNs except that case were solitary and sporadic.

Thirty-eight cases were found in surgical specimens. Seventeen cases involved the pancreatic head, 14 – pancreatic body, and 6 – tail. In one enucleated case tumour, localization was not known. Two cases were diagnosed in incision biopsy (one case in the pancreatic head and one case in the body), all other cases were resected.

Among 16 resected SNs in the pancreatic head, 13 were treated with pancreaticoduodenectomy, two with enucleation and a single case with Beger's duodenum-preserving resection of the pancreatic head. Among 13 resected SNs in the pancreatic body, 8 were treated with middle segment pancreatectomy, 4 with enucleation and a single case with distal pancreatectomy. All tumours in the pancreatic tail were found in distal pancreatectomy specimens. The distribution of SNs in the segments of the pancreas in males was similar to females (χ^2 test, p = 0.941). The median age of patients with SNs localized in different segments of the pancreas were also comparable (Kruskal-Wallis ANOVA, p = 0.146).

The tumour diameter ranged from 0.05 cm to 12 cm (median 3.5 cm, in 3 cases diameter was not known). The median tumour diameter did not differ in females and males (Mann-Whitney U test, p = 0.560). Larger tumours seemed to be more prevalent in the pancreatic head and tail comparing to the pancreatic body (median tumour diameters 4.0 cm, 4.0 cm and 2.25 cm, respectively); that difference was not far from statistical significance (Kruskal-Wallis ANOVA, p = 0.076). The tumour diameter did not correlate with patients' age (Spearman rank correlation coefficient, p = 0.345).

Gross picture (Fig. 1A-F)

All but four cases found prospectively showed the gross picture compatible with SN diagnosis (Fig. 1A).

Two cases in which gross diagnosis was uncertain were unilocular cysts (Fig. 1B). Another tumour was composed of two cysts. The gross differential diagnosis of these oligocystic tumours included SOIA, non-invasive intraductal pancreatic mucinous neoplasm of the branch duct type, non-invasive mucinous cystic neoplasm, cystic neuroendocrine neoplasm, acinar cystadenoma, lymphoepithelial cyst, mucinous nonneoplastic cyst, and pseudocyst, among others. The last case which was not diagnosed grossly was an incidental microscopic tumour of the maximum diameter of 0.05 cm.

The number of cysts in SN ranged from 1 to hundreds. As mentioned, two cases were unilocular, a single case was composed of two cysts. In four cases, the number of cysts ranged from 3 to 9 (including 0.05-cm tumour), in another two – from 10 to 99, in 28 cases the number of cysts exceeded 100 (Fig. 1A). In two cases diagnosed on incisional biopsy samples, the number of cysts within the entire tumour was not clearly known. Von Hippel-Lindau-associated serous cystic neoplasm case showed somewhat complicated gross picture (described later).

There was no association between the number of cysts (less than 100 vs. more than 100) and patients' age (Mann-Whitney U-test, p = 0.689), gender (χ^2 test, p = 0.574), and localization of the tumour (χ^2 test, p = 0.761). Tumours which contained more than 100 cysts were significantly larger than those with a smaller number of cysts (median diameter 4.0 cm vs. 2.2 cm, Mann-Whitney U-test, p = 0.028).

In a single case composed of more than 100 cysts, a significant (approximately 10% of tumour volume) solid component was found within a 5-cm tumour of the pancreatic body in a 65-y male treated with middle segment pancreatectomy (Fig. 1C). None of the cases showed purely solid growth, compatible with SSA diagnosis.

The central scar was found in 21 out of 37 cases (56.8%, VHL-SCN and cases diagnosed in biopsy were excluded). Presence of the scar was not associated with patients' gender (χ^2 test, p = 0.592), and tumour localization χ^2 test, p = 0.720). Patients with SN with a central scar were slightly older than those with tumour with no scar (median age 68.0 vs. 64.0), that difference was of not far from significance (Mann-Whitney U-test, p = 0.083). Tumours with a scar were larger than those without a scar (median diameter 5.0 cm vs. 2.5 cm, respectively, Mann-Whitney U-test, p = 0.005). Tumours composed of more than 100 cysts significantly more frequently contained a scar than tumours with less than 100 cysts (67.9% vs. 22.2%, χ^2 test, p = 0.016). Intratumoral calcifications were seen in 5 cases.

The macrocystic component (defined as a presence of at least a single cyst of 1 cm or more in diameter [26], Fig. 1D-E) was found in 18 out of 37 cases (48.6%, VHL-SCN and cases diagnosed in biopsy excluded). Cysts equal to 2 cm or larger were found in 6 out of 37 cases (16.2%). The macrocystic component was found with a similar frequency in males and in females (χ^2 test, p = 0.266), and its presence was not associated with tumour localization (χ^2 test, p = 0.391), the number of cysts (more than 100 vs. less than 100, χ^2 test, p = 0.506), presence of the scar (χ^2 test, p = 0.368), and patients' age (Mann-Whitney U-test, p = 0.141). Tumours with the macrocystic component were significantly larger than those without it (median diameter 4.0 cm vs. 2.5 cm, Mann-Whitney U-test, p = 0.032).

A single case (0.05 cm in diameter) was found in pancreaticoduodenectomy specimen of a 65-y female

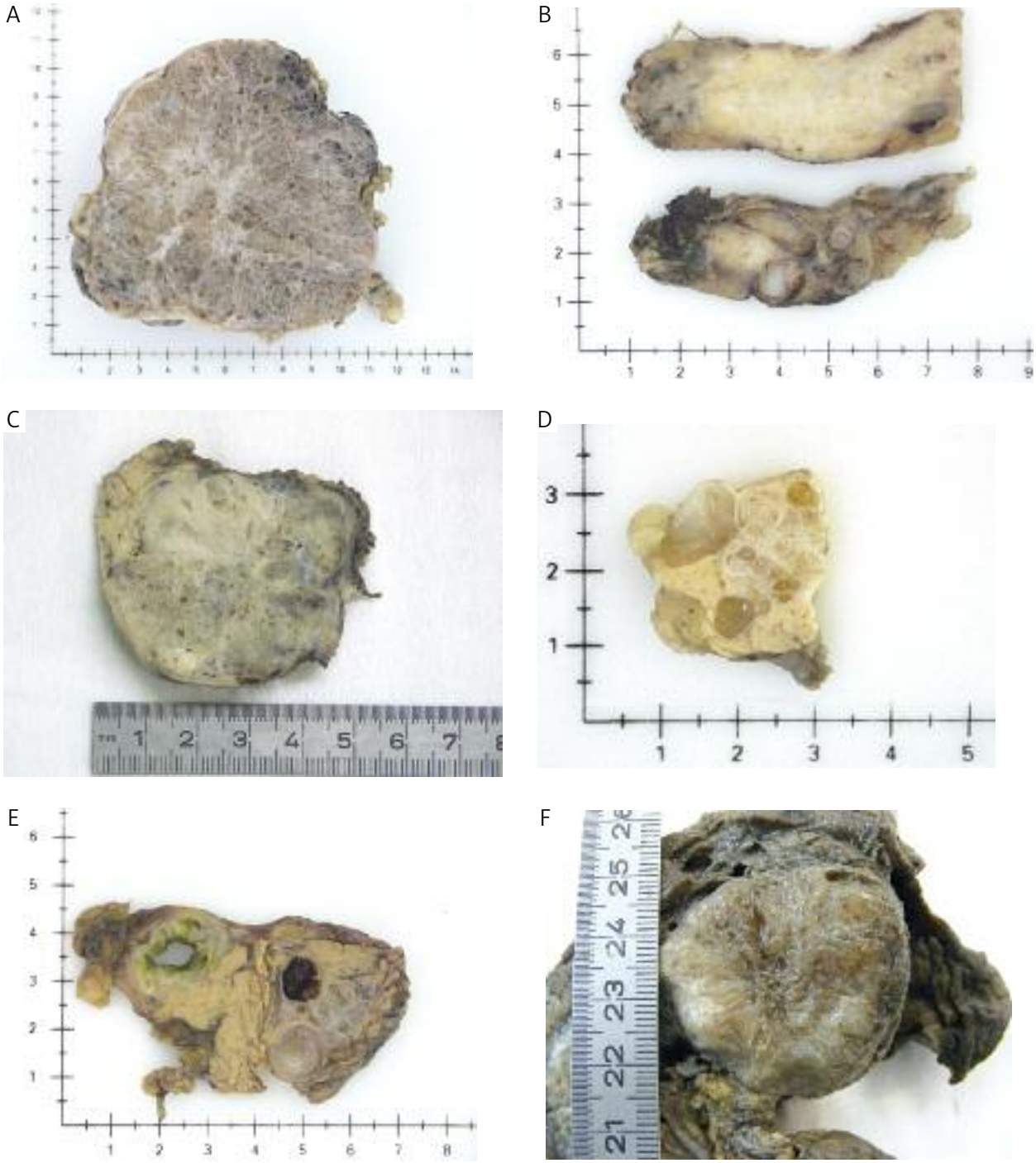

Fig. 1. Gross pictures of SN. A – 'classic' example of SMA. Multiple small cysts around central scar. Sharp tumour border. B – 1-cm unilocular SOIA (lower part of the picture) and adjacent conventional ductal adenocarcinoma of the pancreas. C – mixed SMA/SSA. Solid component in the upper portion of the tumour. D – mixed SMA/SOIA. Macrocystic component in the peripheral portion of the tumour. Additionally multiple small cysts around the central scar. Irregular tumour border. E – mixed SMA/SOIA. Macrocystic component in the peripheral portion of the tumour. Multiple small cysts around the central scar. F – SMA in a patient with VHL disease (SCN-VHL)

with well-differentiated neuroendocrine neoplasm. Both tumours were separated by uninvolved pancreatic parenchyma and therefore did not form MSNN.

Another single unilocular lesion coexisted with conventional ductal adenocarcinoma of the of pancreas in a 79-y female treated with distal pancreatectomy.

Microscopic picture (Fig. 2A-F and Fig. 3A, B)

Almost all tumours were composed of glycogen-rich cells with clear cytoplasm (Fig. 2A). A single case (tumour of unknown diameter in the pancreatic tail of a 65-y woman diagnosed in 1989) showed uniformly eosinophilic, oncocytic cytoplasm (Fig. 2B). This case

represented an exceedingly rare microscopic variant of SN [1, 30].

The diameter of cysts varied widely even within a single tumour. A single previously mentioned case showed a grossly solid component. On microscopy it was composed of small acini and nests virtually without lumina (Fig. 2C).

A single case showed a mild to moderate nuclear pleomorphism, a feature rarely seen in SN (Fig. 2D) [31]. Mitotic figures in that case and in other SNs were virtually absent.

Nontumoral elements (larger vessels, nerves, pancreatic acini, ducts, or islets) were frequently entrapped within SNs, particularly those composed of less than 100 cysts. Papillary structures (Fig. 2E) were seen in 14 (35%) cases. Rarely small intraepithelial lumina were seen.

Extrapancreatic extension of tumour into the peripancreatic adipose tissue was a relatively frequent find-

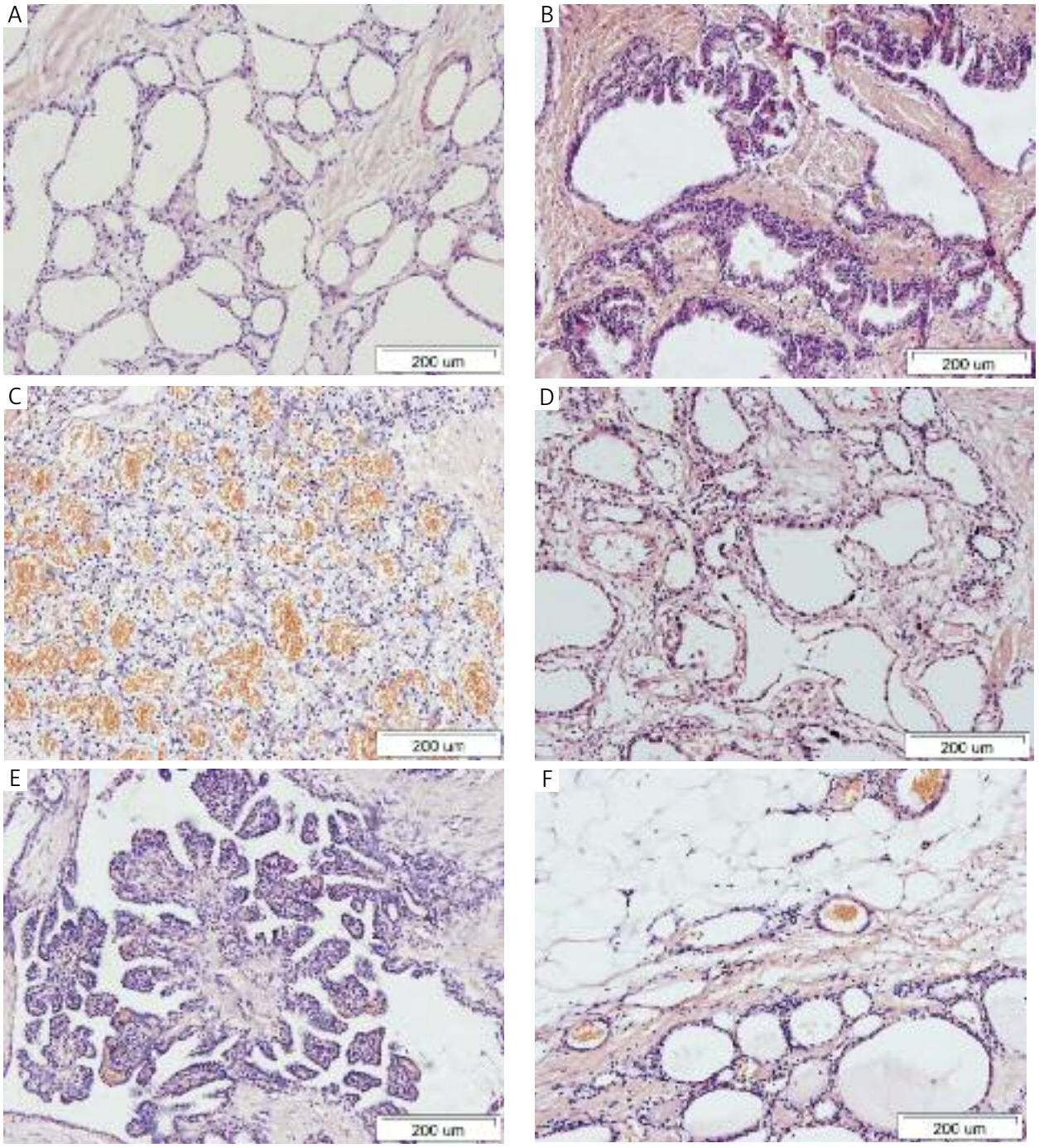

Fig. 2. Microscopic pictures of sporadic SN. A – multilocular structure of 'classic' SMA. Small cysts lined with glycogen-rich epithelial cells. B – SN with oncocytic features. C – mixed SMA/SSA. Solid component. D – SN with nuclear pleomorphism. E – SN with papillary formations. F – SN with microscopic extension into the peripancreatic adipose tissue

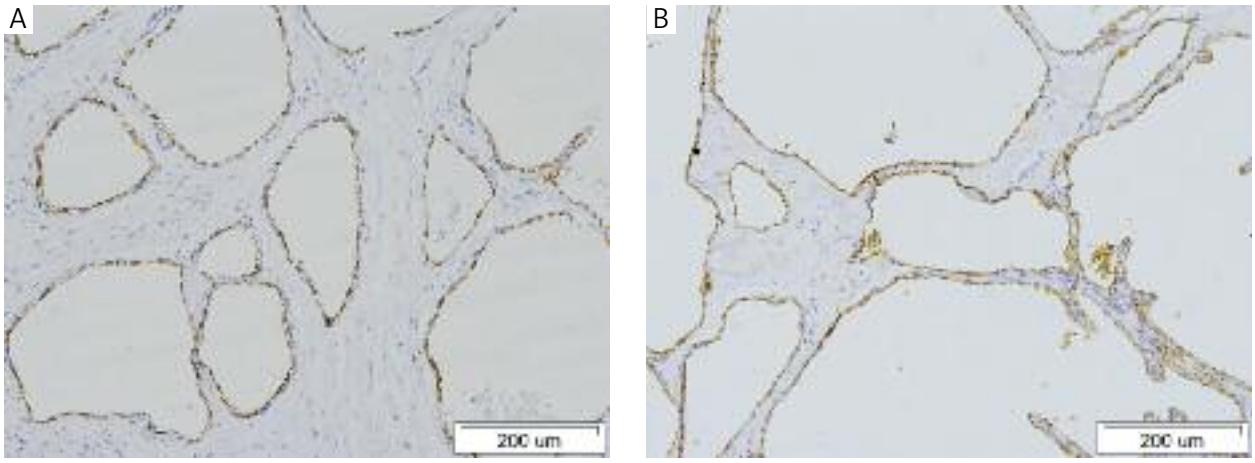

Fig. 3. Immunohistochemical characteristics of SN. A – carbonic anhydrase IX immunostaining. B – GLUT1 immunostaining

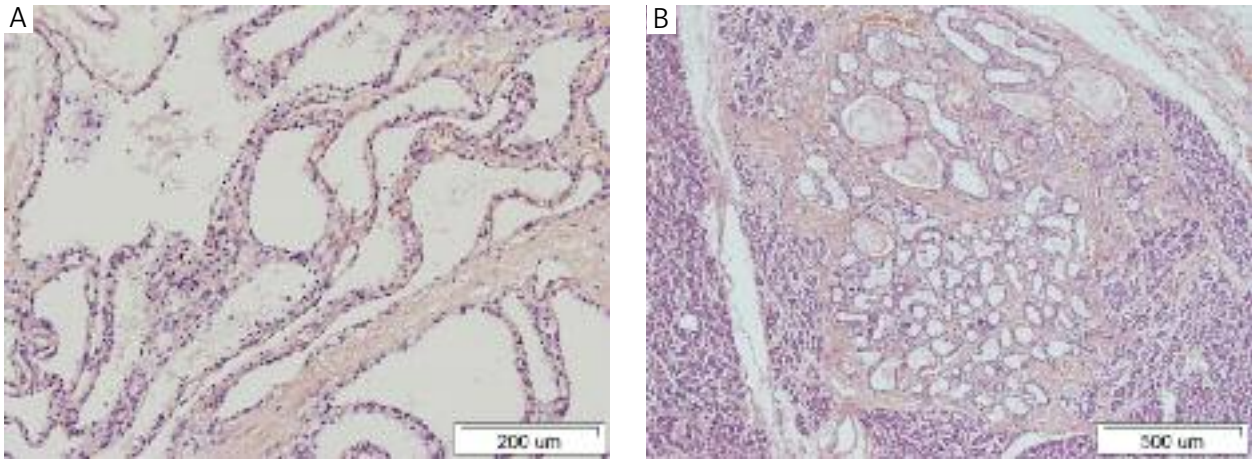

Fig. 4. Microscopic picture of VHL-SCN. A – multilocular tumour in the pancreatic head. B – small SN in the pancreatic body of a patient with VHL disease

ing (Fig. 2F, 7 cases), but it was always subtle, and unequivocal diagnosis of that feature was not established grossly in any case. No case of tumoral extension into the lymph node, duodenum, spleen, or large vessels [32] was found. No tumour showed perineural invasion or small vessels invasion.

In a single case, residual peritumoral pancreatic parenchyma showed extensive acinar-to-ductal metaplasia which could be potentially erroneously diagnosed as an invasive (adenocarcinomatous) growth. However, this was a small localized incidental lesion without a grossly visible solid component. Significant atypia and other features of invasive growth were lacking (not shown).

No tumour showed communication with pancreatic ductal system but 1 tumour localized in the pancreatic head showed compression of the intrapancreatic portion of common bile duct without its infiltration (not shown).

All tumours submitted to the immunohistochemical examinations showed diffuse staining with both carbonic anhydrase IX (Fig. 3A) and GLUT1 (Fig. 3B) antibodies.

VHL-SCN (Fig. 1F and Fig. 4A, B)

A single case of that SN variant was found on autopsy. A 32-y old woman with an insignificant familial history died of cerebellar tumour of uncertain histopathology which was not resected. During autopsy, SN of the pancreas was found. Considering the young age of the patient and a history of brain tumour, VHL disease was strongly suspected. This fact directed toward careful search for other VHL-related lesions. A single clear cell renal cell carcinoma of 0.1 cm in diameter was found. Cerebellar tumour on histopathologic examination was compatible with haemangioblastoma. No other VHL-related lesions were found, but the presence of 3 VHL-related lesions was diagnostic of VHL disease [33, 34]. That diagnosis had not been confirmed in any genetic test yet (in preparation).

The entire pancreas from that patient was taken for histopathology. Grossly, a 3.5-cm tumour composed of hundreds of cysts and containing the central scar was found in the pancreatic head (Fig. 1F). A 3-cm tumour composed of several large cysts without the scar was

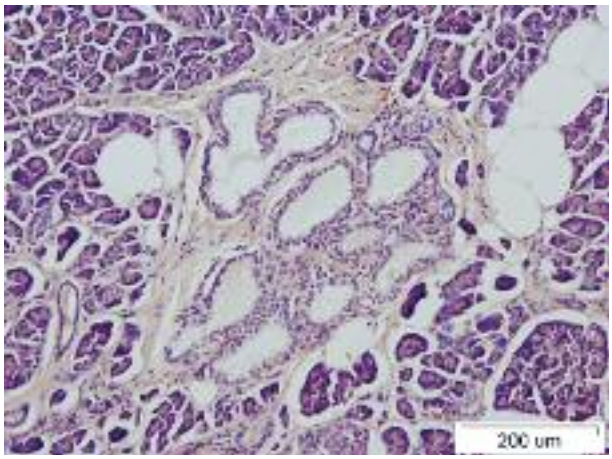

Fig. 5. "Incipient" SN in patients with neuroendocrine neoplasm

found in the pancreatic body. Additionally, several unilocular and oligolocular lesions up to 0.5 cm were randomly scattered in pancreatic parenchyma.

Microscopically, SNs in VHL patients were identical to the sporadic tumours (Fig. 4A). However, in pancreatic parenchyma multiple small SNs composed from 1 up to 100 cysts were found (Fig. 4B). Additionally, a pleomorphic neuroendocrine microadenoma of 0.15 cm in diameter was found (not shown). The histopathological picture of the pancreas was concordant with those reported previously in VHL patients [15].

Serous neoplasms variants – summary

Among 40 SN cases studied, 11 could be unequivocally diagnosed as typical examples of SMA (Fig. 1A). These tumours were composed of more than 10 cysts and contained a central scar but no macrocystic component. Another 5 cases showed features of typical SOIA – they contained less than 10 cysts, some of which were larger than 1 cm and lacked the central scar (Fig. 1B). A single case of VHL-SCN was found. No case of pure SSA, MSNN and SCAC was found.

Twenty-three cases were classified as "borderline" lesions, since they were not fully compatible with classic SMA, SOIA, and VHL-SCN patterns. They might be gathered in three separate groups of different morphology:

- Cases similar to SMA with some features of SOIA ('mixed SMA/SOIA', 20 cases, Fig. 1D, E)

Among them, 13 cases showed features resembling SMA but additionally showed a macrocystic component, usually in the form of one to several larger cysts in the peripheral portion of the tumour. This growth pattern was previously named as "mixed micro- and macrocystic" one [26]. Another 6 tumours were composed of more than 10 cysts without a macrocystic component but lacked a central scar. A single case was composed of more than 100 cysts and contained a macrocystic component but lacked a central scar.

- Small lesions showed features of both SMA and SOIA ('incipient SN', 2 cases, Fig. 5)

Two cases were composed of less than 10 cysts and lacked a central scar, and also lacked a macrocystic component. One of these was an incidental SN mentioned previously in a patient with neuroendocrine neoplasms, another one was a 1-cm SN composed of 2 cysts.

- Another tumour (1 case) showed a picture of SMA but also had a significant component of SSA ('mixed SMA/SSA', Fig. 1C)

Pathological features of 'classic' types of SN as well as 'borderline' lesions are summarized in Table I.

Discussion

Serous neoplasms are relatively rare neoplasms of the pancreas. Only scattered case reports or small series up to 5 patients with SMA but not other SN types are available in the Polish literature [35-40]. In contrast, several large series of SN in the world literature are on record [5, 6, 8, 13, 14, 32, 41-47]. To the best of our knowledge, a series of SN presented here is the *ex aequo* 10th largest one in the literature (details in Table II).

Table I. Basic clinico-pathological characteristics of the studied cases

DIAGNOSIS	SMA	SOIA	MIXED SMA/SOIA	'INCIPIENT' SN	MIXED SMA/SSA	VHL-SCN
No. of cases	11	5	20	2	1	1
Patients' gender (F : M)	10 : 1	3 : 2	18 : 2	2 : 0	0 : 1	1 : 0
Patients' age (median)	66.0 y	64.0 y	65.0 y	56.5 y	65.0 y	32.0 y
Tumour localization (head : body : tail : more than 1 segment)	3 : 4 : 3 (in a single case not known)	2 : 2 : 1	10 : 7 : 3 : 0	1 : 1 : 0 : 0	0 : 1 : 0 : 0	0 : 0 : 0 : 1
Tumour diameter (median, interquartile range)	2.5 (2.0-5.0) cm	2.5 (2.2-3.0) cm	4.5 (3.0-6.0) cm	0.5 cm	5.0 cm	multifocal disease

SMA – serous microcystic (cyst)adenoma, SOIA – serous oligocystic and ill-demarcated adenoma, SSA – solid serous adenoma/neoplasm, VHL-SCN – von Hippel-Lindau-associated serous cystic neoplasm

Table II. Series of patients with SN reported in the literature (only series which included at least 40 cases)

No.	First author and reference	Institution	Technique of acquisition of the cases	Time period	Number of cases	Patients' gender (F : M, %)	Patients' age	Tumor localization (head : body : tail : more than 1 segment, %)	Tumor diameter	SN types described in the text
1.	M.A. Khashab [32]*	Johns Hopkins Medical Institutions, Baltimore, USA	in-house	1988-2009	257 (257 resected)	69.6% : 30.4%	mean 61 y	39% : 21% : 31% : 9%	mean 4.9 cm	not described
2.	J. Le Borgne [8]	73 surgical units in France	in-house	1984-1996	170 (144 resected)	86% : 14%	mean 56.6 y	38% : 41% : 20% : 1%	mean 4.9 cm	VHL-SCN – 3 cases, MSNN – 2 cases, SMA and SOIA not ditinguished
3.	W.J. Yoon [45]	30 oncology units in Korea	in-house	1993-2005	162 (all cases pathologically confirmed, no. of resected cases not given)	68% : 32%	mean 52.6 y	43% : 27% : 22% : 8%	Not described	no case of SCAC, only benign lesions
4.	N.P. Valsangkar [6]**	Massachusetts General Hospital, Boston, USA	in-house	1990-2010	130 (130 resected)	66% : 34%	mean 63 y	Not described	mean 4.4 cm	not described (SOIA and MSNN men tioned in [42]
5.	C. Bassi [43]	University of Verona, Verona, Italy	in-house	1988-2000	100 (68 resected)	87% : 13%	mean 51.9 y (women), mean 53.8 y (men)	31% : 27% : 25% (isthmus 14%)	median 3.7 cm	SMA, SOIA
6.	P.J. Allen [47]	Memorial Sloan-Kettering Cancer Center, New York, USA	in-house	1995-2005	82 (76 resected)	Not described	Not described	Not described	mean 5.0 cm	no case of SCAC, only benign lesions
7.	S.E. Lee [14]***	Seoul National University College of Medicine, Seoul, Korea	in-house	1992-2006	52 (52 resected)	71% : 29%	mean 50 y	36% (head) : 64% (body and tail)	mean 4.18 cm	SMA, SOIA, SSA

Table II. continuous

No.	First author and reference	Institution	Technique of acquisition of the cases	Time period	Number of cases	Patients' gender (F : M, %)	Patients' age	Tumor localization (head : body : tail : more than 1 segment, %)	Tumor diameter	SN types described in the text
8.	M. Kosmahl [5]****	University of Kiel, Germany	in-house and consultation cases	1971-2003	46 No. of resected (cases not given)	SMA: 88% : 12% SOIA: 62% : 38%	SMA: mean 71y, SOIA: mean 63 y	SMA: 21% : 8% : 63% (not described: 8%) SOIA: 69% : 0% : 25% (not described: 6%)	SMA: mean 6.4 cm, SOIA: mean 7.2 cm	SMA, SOIA, VHL-SCN, SSA, SCAC
9.	J.S. Hung [44]	National Taiwan University Hospital, Taipei, Taiwan, Republic of China	in-house	1981-2006	44 (34 resected)	Not described	mean 58 y	not described	not described	not described
ex aequo 10.	C.M. Pyke [46]	Mayo Clinic, Rochester, USA	in-house	1936-1991	40 (40 resected)	65% : 35%	mean 62.7 y	42.5% (head): 12.5% (uncinate process) : 47.5% (neck and body) : 15% (tail) : 17.5% (multiple sites)	symptomatic: mean 7.5 cm, asymptomatic: mean 6.0 cm	not described
ex aequo 10.	present study		in-house	1989-2011	40 (36 resected)	85% : 15%	mean 63.2 y, median 65.0	40% : 37.5% : 17.5% : 2.5% (in another single case not known, 2.5%)	mean 4.1 cm, median 3.5 cm	SMA, SOIA, VHL-SCN, mixed SMA/SSA

SN – serous neoplasm, SMA – serous microcystic (cyst)adenoma, SOIA – serous oligocystic and ill-demarcated adenoma, SSA – solid serous adenoma/neoplasm, VHL-SCN – von Hippel-Lindau-associated serous cystic neoplasm, SCAC – serous cystadenocarcinoma
** partially described in {41}*
*** partially described in {42}*
**** majority of cases included in another series from this center, focused on preoperative imaging, which included 67 SN cases {25}*
***** partially described in {13}*

Although the clinical and histopathological pictures of SN are well known, many issues concerning these neoplasms are not fully understood.

It is not absolutely clear whether SNs are derived from centroacinar cells, as it was postulated. The alterations of the *VHL* gene were described in both hereditary and sporadic SN cases, but it is not clear why these alterations only rarely lead to the development of SN-related malignancy, in contrast to *VHL*-related tumours of the kidney. Moreover, it is not established which SNs may be safely managed conservatively and which ones should be resected because of the risk of aggressive behaviour when left without surgery. Additionally, less than half of SN cases are recognized as such on preoperative radiologic assessment. Up-to-date reviews on clinical characteristics of SN and optimal patient management in SN are available [48, 49].

When studying the histopathological literature on SN one may feel convinced that SN variants form easily distinguishable lesions without "borderline" cases. In the present study we showed that such "borderline" lesions do exist and form a heterogeneous group of tumours.

Similar observations but on radiological grounds have been made recently [25, 26]. Besides the study of Sun *et al.* [25] mentioned above, Fukasawa *et al.* described examples of SN which showed features of both SMA and SOIA [26]. They developed a classification of SN useful in differential diagnosis of SN and other cystic lesions of the pancreas [26]. Three categories (microcystic, macrocystic and mixed micro- and macrocystic) of SN were distinguished but patients with these 3 tumour types did not differ in the context of demographic data, presence of symptoms and localization and size of the neoplasm [26].

The basic clinico-pathological features of SN reported in the present series resembled those reported by others (Table II). According to previous reports, the majority of cases were seen in females [5, 6, 8, 14, 32, 43, 45, 46]. The mean patients' age was between 60 and 70 years, similarly to previous reports [6, 32], but some groups reported SNs in relatively younger [8, 14, 43-45] or older [5] patients. The young age of patients with VHL-SCN was also fully concordant with literature data [5, 13]. The number of patients with 'incipient' SN was too small for reliable clinico-pathological analysis.

We showed that SMA may be seen in any pancreatic segment but we did not show a predilection of SOIA to the pancreatic head, as postulated by others [5, 6, 11-13].

The median tumour diameter in the entire study group was similar [43] or lower [5, 6, 8, 32, 46] comparing to previously reported series.

We distinguished 3 tumour groups which did not parallel pure SN variants. The first and more prevalent one ('mixed SMA/SOIA') was composed of tumours which resembled SMA but showed one or two features not fully compatible with such a diagnosis, i.e. contained a macrocystic component, and/or lacked the central scar. These tumours were larger than 'classic' SOIA (Mann-Whitney U test, borderline significance of $p = 0.067$, Table I), but the difference between 'mixed SMA/SOIA' and 'classic' SMA was not significant (Mann-Whitney U test, $p = 0.226$). The localization of large cysts at the tumour periphery in the 'mixed SMA/SOIA' category might indicate that the presence of a macrocystic component was rather a biomechanical consequence of tumour expansion and did not represent an issue related specifically and directly to the tumour biology at the cellular level. Similarly, tumours which contained the central scar were larger than those without it (see Results). Since the central scar formation may serve as an indication of hypoxia in tumoral tissue, it became clear why small tumours rarely formed a scar.

Two "incipient SN" cases described here were small lesions composed of less than 10 cysts, one of these was found incidentally during the microscopic examination of the specimen with neuroendocrine neoplasm. These lesions were too small to form a central scar, multiple cysts or macrocystic component. They might constitute a form of "precursor lesion" of larger, more frequently symptomatic SN. However, the estimation of the prevalence of these small "precursor" SNs in the population was beyond the scope of the study.

Another "borderline" case was a tumour composed of SMA and SSA. This example was an indicator of related biology of both cystic and solid forms of SN. A mixed form of SMA and SSA with occasional necrotic foci was reported by Kosmahl *et al.* [13] and it showed synchronous lymph node metastases. This allowed for a diagnosis of SCAC [13]. A 'mixed SMA/SSA' case presented here did not contain necrotic foci.

We did not observe any cases of pure SSA, SCAC and MSNN. This was not surprising since they are also very rare. Less than 20 examples of each of these tumour types were reported [1-3, 5, 6, 17-22]. Moreover, a mixed neoplasm composed of both serous and mucinous component was reported [50]. A single report of macrocystic serous cystadenocarcinoma also exists [51].

As mentioned above, a single case of SN showed features of biliary obstruction, but none of these showed invasion or complete encasement of the bile duct. That was a 'classic' 6-cm SMA. Biliary obstruction by SN is a rare finding and it was reported previously [52].

A single case of SOIA with loss of hMLH1 protein in a patient with hereditary non-polyposis colorectal cancer was described [53]. We did not test our cases on microsatellite instability and we are not aware of synchronous or metachronous colorectal cancer in the described patients.

A single case coexisted with neuroendocrine neoplasm, but they did not form MSNN, in our opinion. Both components were not intermingled [1, 2, 20, 21], and a microscopic picture of extratumoral parenchy-

ma was not suggestive of VHL disease [15]. Another case coexisted with ductal adenocarcinoma. Such a coexistence was previously described in less than 10 cases [3, 54, 55].

There were also some controversies regarding the extrapancreatic extension of SN. We have seen cases which focally intermingled with peripancreatic adipose tissue but that finding was not diagnostic of SCAC. At present, only the presence of the metastatic deposits of SN outside the pancreas facilitates the diagnosis of SCAC [1, 2]. Previously reported examples of SN which extended to the organs adjacent to the pancreas [23, 35] do not fulfil the current SCAC diagnostic criteria since they showed tumoral extension rather than true invasion [42]. They may be classified as "aggressive" SNs, as it has been described very recently [32].

In the present study we described the largest collection of SNs diagnosed in Poland. We also showed that examples of SN that shared features of 'classic' clinicopathological variants of SN did exist and, surprisingly, they were not rare. Serous neoplasms truly showed a continuous spectrum of lesions [25]. Previous studies did not show any differences in ultrastructural, immunohistochemical, and genetic profile between different SN variants [12, 13]. Therefore, the reasons for such a morphologic diversity of SNs remained unknown and purely speculative.

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