Original paper

Limited usefulness of histopathological features in identification of a clinically aggressive solid-pseudopapillary neoplasm of the pancreas

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Solid-pseudopapillary neoplasms (SPN) are rare tumours of the pancreas. Distant metastases and/or local recurrence following surgical resection occur in 10% to 15% of patients with SPN. In the present study, we aimed to systematically examine the usefulness of virtually all histopathological features of SPN which were previously considered potential risk factors of clinically aggressive behaviour of SPN following surgical resection. Seventeen SPN were included. None of the cases had an undifferentiated component. Follow-up data were available for 14 patients (median 52 months). One patient developed liver metastasis 17 months after resection of the primary tumour and fulfilled the criteria of a clinically aggressive disease. None of the histopathological features allowed identification of that case with an adequate diagnostic yield. At present, histopathological examination cannot identify patients who may develop tumour recurrence following resection of the primary lesion. A close follow-up should be offered to all patients treated for SPN.

Key words: solid pseudopapillary neoplasm, pancreatic neoplasms, pancreas.

Introduction

Solid-pseudopapillary neoplasms (SPN) are tumours of the pancreas of a peculiar histopathology and of a still uncovered cellular origin [1–4]. SPN constitute from less than 1% up to 6% of all pancreatic tumours [5-7], and from less than 5% up to 20% of cystic pancreatic tumours [6, 8]. The SPN occur usually but not exclusively in young females and only in a minor portion of cases behave in a clinically aggressive/malignant manner. Distant metastases and/or local recurrence following surgical resection occur in 10% to 15% of patients with SPN. Despite this, long-term survival can be achieved in many patients with metastatic and/or unresectable disease [9, 10]. CTNNB1 (β-catenin) mutation is a very typical feature of SPN at the genomic level [11] and the only repetitive mu-

tation in samples of SPN examined using whole-exome sequencing [12]. SPN was reported as a diagnostic entity in 1959 by Frantz [13], and Hamoudi et al. were the first who report ultrastructural features of SPN in 1970 [14]. The diagnostic category of solid-pseudopapillary carcinoma (SPC), defined based on presence of angioinvasion, perineural invasion, deep invasion into the surrounding tissues, and/or metastasis was included in the WHO reference book in 1996 [8] and in 2000 [15]. Despite significant efforts to find clinical, histopathological, or molecular features which would be useful as prognostic factors for patients with SPN, results of available reports are not fully satisfactory (as reviewed in [16-21]).

In the present study, we aimed to systematically examine the usefulness of virtually all histopathological features of SPN which were previously considered

potential risk factors of a clinically aggressive behavior of SPN following surgical resection.

Material and methods

Literature search

The PubMed database was searched (last search in March 2014) for studies on SPN describing clinical and histopathological features which may serve as prognostic factors for patients with SPN. Key words used were: "solid or pseudopapillary or solid-pseudopapillary or papillary-cystic or solid-cystic or papillary or cystic or Frantz or Frantz's or Hamoudi or Hamoudi's" and "pancreas or pancreatic". To identify studies on aggressive SPN, key words used were: "aggressive or aggressiveness or recurrent or recurrence or metastasis or metastases or metastatic or invasive or unresectable or non-resectable or death or died or mortality".

Study cases

SPN were identified in the institutional database of pancreatic specimens established in 1985. Cases between 2007 and 2013 were gathered prospectively, while cases prior to that period were found retrospectively based on re-evaluation of specimens irrespective of primary diagnoses. This allowed identification of SPN that could have been misdiagnosed as tumours of neuroendocrine differentiation in early years [22].

Aggressive behavior was defined as development of recurrence and/or metastasis during the follow-up period after surgical resection [5]. Follow-up data were gathered by telephone or personal interviews of the patients or their family members.

The diagnoses were established using reference sources [1, 2]. Hematoxylin-eosin slides were re-assessed for histopathological features potentially useful in predicting the aggressive behaviour of SPN, as detailed in the 'Results' section.

Tissue microarray

Tissue microarray (TMA) [23] was prepared using a manual instrument (MTA-1, Beecher Instruments, Sun Prairie, WI, USA). Four cores (diameter 1.5 mm) were taken from each case.

Immunohistochemical stains and their interpretation

Immunohistochemical (IHC) stains were performed using TMA slides, with the exception of a single recent case which was examined using conventional sections. IHC stains useful in diagnosis of SPN (β-catenin, CD10, CD56, progesterone receptor (PgR), synaptophysin, p53, Ki-67, claudin-5) were performed [22, 24-26]. Details on IHC protocols are described in Supplementary Table I. In brief, 4-mi-crometer thick sections were cut from TMA block and put onto Superfrost Plus slides (Menzel-Glaser, Braunschweig, Germany). Heat-induced antigen retrieval was performed using PT Link module (Dako, Glostrup, Denmark) or a water bath, and incubation in 3% H_2O_2 served as a peroxidase block. Diamino-benzidine and hematoxylin were used as a chromogen and a counterstain, respectively. For the negative control, primary antibodies were omitted. An automated IHC machine (Dako) was used for IHC assays.

The β-catenin stain was considered 'positive' if tumour cells showed nuclear and cytoplasmic staining, an indicator of activation of Wnt signalling pathway [27, 28]. The p53 stain was recognized as 'positive' if more than 30% of nuclei showed strong nuclear staining [29]. For CD10, CD56, synaptophysin and claudin-5 stains, stain intensity (0-none, 1+ weak, 2+ moderate, 3+ strong) and stain extent (as a percentage) was recorded. Histoscores were obtained by multiplying the particular values of intensity and values of stain extent and adding the products received for each stain score (histoscore range: 0-300) [30]. For PgR and Ki-67 stains, the stain extent was expressed as a in percentage but the stain intensity was not taken into account (histoscore range: 0-100).

Statistical analysis

Mann-Whitney U tests and Spearman's rank correlation coefficient were calculated using Statistica 10 software (StatSoft, Tulsa, USA). A heatmap was drawn with Gene-E software [31].

Ethics

The institutional Review Board allowed the study to be performed without a detailed protocol appropriate for interventional studies involving human subjects.

Results

Literature search

The literature search revealed that at least 10 clinical and at least 35 histopathological features were considered potential prognostic factors and/or risk factors of aggressive behavior of SPN. The clinical factors included: male gender [5, 18, 32], patient's age [5, 18, 32–34], body mass index [18], serum tumour markers [18, 33], presence of symptoms [18, 32], mean duration of symptoms [18, 32], non-resectability [35], extent of surgery [5, 36], familial occurrence of tumour [37], and multiple primary lesions in a single patient [38, 39]. Histopathological factors included: extrapancreatic localization of the main neoplastic mass [40, 41], localization of tumour within particular segment of the pancreas [5, 18, 32], tumour diameter [5, 32, 42], gross characteristics of

tumour (solid, cystic, or mixed) [18, 32, 43], tumour rupture [43-45], lack of a tumour capsule [46] and incomplete capsule [47], capsule invasion [17, 18, 33, 48], invasion into pancreatic parenchyma [17, 33, 49] or adjacent tissues or organs (invasion of duodenum, spleen, common bile duct, peripancreatic fat) [17, 18, 33, 44, 50], portal vein invasion with tumour thrombus [51], lymph node metastasis or distant metastasis at presentation and/or during resection of primary tumour [17, 33, 49, 50, 52-55], presence of tumour tissue at surgical margin [5, 46, 52, 54, 56], perineural invasion [5, 18], small vessels/lymphatic vessels invasion [5, 10, 52], muscular vessel invasion [5, 49, 57], diffuse growth pattern [33, 58, 59], calcifications, including "marginally calcified totally necrotic" tumour picture [18, 32, 43, 60], tumour necrosis, either infarct-type or geographical [18, 33, 49], necrobiotic nests [39, 49, 57, 61], nuclear features (e.g. size, chromatin pattern, nucleoli, atypia) [44, 49, 62, 63], with particular emphasis on nuclear pleomorphism [7, 10, 17, 18, 33, 46, 49, 52] and presence of multinucleated tumour giant cells [7, 25, 64], nuclear grade [49, 62], presence of features diagnostic of SPC, as defined using WHO 2000 criteria [18, 19, 32, 42, 43, 53, 60, 65-68], presence of undifferentiated component [33], mitotic count [33, 49, 52], tumour grade and stage according to the 2006 European Neuroendocrine Tumor Society (ENETS) classification for neuroendocrine neoplasms of the pancreas, and tumour stage according to the 2010 American Joint Committee on Cancer (AJCC) TNM7 classification [5]. Additionally, Nishihara *et al.* developed a histopathology-based scoring scheme potentially useful in differentiation of metastatic and non-metastatic SPN [49]. It included assessment of nuclear grade, mitotic rate, cellular pleomorphism, venous invasion, necrobiotic nests, and necrosis [49]. Some nuclear morphometric features may also be useful for prediction of clinical aggressiveness of SPN as well [69]. Some researchers tested IHC stains as potential predictors of aggressive behavior: CD10, CD56, PgR, synaptophysin, p53, Ki-67, α1-antitrypsin, α1-antichymotrypsin, neuron-specific enolase, galectin-3, vimentin, chromogranin, pan-cytokeratin, Cam5.2, and epithelial membrane antigen (EMA) [11, 24, 32, 33, 70, 71].

The number of patients included in many series did not allow formal documentation of statistical significance (p < 0.05) of particular features as predictors of aggressive behavior of SPN. This was possible only for male gender [72], tumour size [5, 35, 73], muscular vessel invasion [5], and ENETS primary tumour stage [5]. The association between male gender and clinical aggressiveness of SPN was seen in one [74], but not another [75] meta-synthetic study based on accumulative analysis of literature data.

Importantly, in patients with SPN, many potentially prognostic clinical and pathological features may be seen in patients with a clinically benign disease [5, 9, 32, 33, 46]. Moreover, clinically aggressive behavior may be observed in some patients without the clinico-pathological risk factors listed above [11, 33, 46].

Demographic data

Eighteen cases of SPN were identified. A single case of SPN in a child diagnosed in incisional biopsy was excluded. The study population included 17 cases diagnosed in adult patients in resection specimens.

TMA

Thirteen cases were included in TMA block. In a single case, core biopsy of tumour tissue was not successful and that case was excluded from IHC TMA evaluation. A single case was represented in TMA by separate core biopsies of primary tumour and liver metastasis, as described below.

Clinical features

Clinico-pathological data are presented in Table I and Supplementary Fig. 1 (a heatmap). In all cases, the tumour was considered potentially resectable. Seven patients were treated with pancreaticoduodenectomy, and in 6 cases distal pancreatectomy was performed. Four tumours were enucleated. All cases were solitary.

Macroscopic features

All cases of SPN originated in the pancreas. In one early case from outside surgical centre the exact localization of the tumour within the pancreas was not known. Diameter of tumours did not correlate with patients' age (Spearman's rank correlation coefficient, p=0.325). Three cystic lesions were consistent with "marginally calcified partially necrotic" SPN [60]. Tumour rupture was not documented in any case. Gross pictures of some SPN are presented in Supplementary Fig. 2.

Microscopic features

All the histopathological features (excluding morphometric measurements) previously recognized as potential indicators of clinically aggressive diseases and enumerated above in the 'Literature search' section were examined in the study cases. In particular: (a) tumour at surgical margin was documented in cases when neoplastic cells reached inked margin in perpendicular section or were seen in *en face* section; (b) muscular vessel invasion was recognized when neoplastic cells were found within vascular spaces with circumferential layer of smooth muscle cells [5]; (c) diffuse growth pattern was defined as solid growth pattern with little stroma [33]; (d) necrobiotic nests were defined as clusters of cells with eosinophilic cytoplasm and pyknotic nuclei [25, 49]; (e) nucle-

Table I. Clinico-pathological characteristics of the study cases[a]

Characteristics	Prevalence (n = 17)	Sensitivity[b]	Specificity[b]
Male gender	2/17 (11.8%)	0/1	14/16 (87.5%)
Age (years)	Median 36 (range: 22-69)	–	–
Age (years) – median or more	10/17 (58.8%)	1/1	7/16 (43.75%)
Enucleation *versus* partial pancreatectomy	4 : 13	0/1	12/16 (75%)
Tumour localization (head : body : tail : not known)[c]	8 : 1 : 7 : 1	0/1	7/15 (46.7%)
Tumour diameter (cm)	Median 7.8 cm (range: 1.4-16 cm)	–	–
Tumour diameter (cm) – median or more	8/15	1/1	7/14 (50%)
Tumour gross picture (solid : mixed : cystic : not known)[d]	4 : 9 : 3 : 1	1/1	3/15 (20%)
Lack of capsule	3/17 (17.6%)	0/1	13/16 (81.25%)
Incomplete capsule	11/13 (84.6%)	1/1	2/12 (16.7%)
Capsule invasion	13/14 (76.5%)	1/1	1/13 (7.7%)
Invasion of pancreatic parenchyma	11/15 (64.7%)	1/1	4/14 (28.6%)
Invasion of adipose tissue	5/14 (29.4%)	0/1	8/13 (61.5%)
Tumour at surgical margin	3/11 (17.6%)	0/1	7/10 (70%)
Perineural invasion	9/17 (52.9%)	0/1	7/16 (43.75%)
Small vessel invasion	4/17 (23.5%)	0/1	12/16 (75%)
Calcifications	5/17 (29.4%)	0/1	11/16 (68.75%)
Infarct necrosis	6/17 (35.3%)	0/1	10/16 (62.5%)
Geographical necrosis	1/17 (5.9%)	0/1	15/16 (93.75%)
Necrobiotic nests	4/17 (23.5%)	0/1	12/16 (75%)
Enlarged nuclei (more than 7.0 μm)[e]	12/17 (70.6%)	1/1	5/16 (31.25%)
Vesicular chromatin pattern (vs. fine chromatin)[e]	8/17 (47.1%)	1/1	9/16 (56.25%)
Enlarged nucleoli[e]	7/17 (41.2%)	1/1	10/16 (62.5%)
Nuclear atypia (moderate vs. minimal)[e]	7/17 (41.2%)	1/1	10/16 (62.5%)
Nuclear pleomorphism (minimal : moderate : marked)[f]	7 : 6 : 4	0/1	12/16 (75%)
Multinucleated giant tumour cells	7/17 (41.2%)	1/1	10/16 (62.5%)
Nuclear grade (1 : 2 : 3)[e]	6 : 5 : 6	1/1	11/16 (68.75%)
Solid-pseudopapillary carcinoma (WHO 2000 definition)	14/17 (82.4%)	1/1	3/16 (18.75%)
ENETS grade (1 : 2 : 3)[g]	16 : 1 : 0	0/1	15/16 (93.75%)
ENETS T stage (T1 : T2 : T3 : T4 : TX)[h]	1 : 4 : 10 : 0 : 2	1/1	5/14 (35.7%)
AJCC T stage (pT1 : pT2 : pT3 : pT4: pTx)[i]	0 : 9 : 5 : 0 : 3	0/1	8/13 (61.5%)
Lymph node metastasis (pN0 : pN1 : pNx)	10 : 0 : 7	–	–
Score according to the criteria of Nishihara *et al.* (1 : 2 : 3 : 4 : 5 : 6 : 7)	2 : 1: 2 : 5 : 1 : 3 : 3	–	–
Score according to the criteria of Nishihara *et al.* – 7 or more	3/17 (17.6%)	0/1	13/16 (81.25%)
Clear cells	16/17 (94.1%)	1/1	1/16 (6.25%)
Spindle cells	2/17 (11.8%)	0/1	14/16 (87.5%)
Oncocytic cells	4/17 (23.5%)	0/1	12/16 (75%)
Eosinophilic globules	13/17 (76.5%)	1/1	4/16 (25%)

Table I. Continue

Characteristics	Prevalence (n = 17)	Sensitivity[b]	Specificity[b]
Cholesterol clefts	12/17 (70.6%)	1/1	5/16 (31.25%)
Foamy cells	17/17 (100%)	1/1	0/16 (0%)
Microcystic growth pattern	14/17 (82.4%)	1/1	3/16 (18.75%)
Metachronous distant metastasis (pM1)	1/17 (5.9%)	–	–
Clinically aggressive disease	1/17 (5.9%)	–	–

[a] in some cases data were missing
[b] in identification of a clinically aggressive SPN
[c] localization of tumour in the pancreatic head was considered potential marker of an aggressive disease
[d] solid or mixed versus cystic architecture of the tumour was considered potential marker of an aggressive disease
[e] as proposed by Nishihara et al. {49}
[f] marked versus minimal to moderate nuclear polymorphism of the tumour was considered potential marker of an aggressive disease
[g] ENETS grade 2 versus grade 1 was considered potential marker of an aggressive disease
[h] ENETS stage T3 versus ENETS stage T1 and T2 was considered potential marker of an aggressive disease
[i] AJCC stage pT3 versus AJCC stage pT1 and pT2 was considered potential marker of an aggressive disease

ar features (size, chromatin pattern, nucleoli, atypia) and nuclear grade were described according to the definitions by Nishihara *et al.* [49]; (f) marked nuclear pleomorphism was recognized when variation of nuclear size was 4-fold or larger [7]; (g) ENETS tumour grade was assessed using criteria based on mitotic count and Ki-67 proliferative index [1, 76]; (h) SPC criteria were based on 2000 WHO publication [15]; (i) undifferentiated component was defined as area of diffuse growth pattern, tumour necrosis, nuclear atypia and 'unusually high' mitotic rate [33, 59]; (j) ENETS and AJCC tumour stage criteria were applied based on reference publications [76, 77]; and (k) histopathological score was documented as proposed by Nishihara *et al.* [49]. Additionally, cases were examined also for presence of clear cells (vacuolization change) [4, 25, 70, 78, 79], rhabdoid morphology [25], spindle cells [80, 81], oncocytic cells [14], eosinophilic (hyaline) globules [2], cholesterol clefts and foamy cells [2], as well as microcystic/pseudoglandular growth pattern [4, 13, 25, 82].

The number of histological slides containing neoplastic tissue among study cases ranged from 2 to 12 (median 5). In 2 cases cytological smears were available. Both cases showed cytological features of SPN [83]. Some microscopic features of SPN are shown in Figure 1. Invasion of peripancreatic fat tissue was relatively frequent (29.4%), but invasion of adjacent organs was not seen in any case. Lymph node metastases, invasion of muscular vessels, diffuse pattern of growth, rhabdoid cells and undifferentiated component were absent. The majority of cases showed features of SPC (82.4%). The mitotic index did not exceed 1 mitotic figure per 2 mm^2 in any of the cases. A single case showed a focal increase of Ki-67 proliferative index up to 7% (ENETS tumour grade 2, assessed using the ImmunoRatio programme [84], Supplementary Fig. 3C). In all other cases, Ki-67 index was below 1%. Clear cells were seen in all cases but one, but the proportion of that differentiation varied from case to

case. Multinucleated tumour giant cells [7, 64] were seen in 7 cases (41.2%). Tumours with multinucleated tumour cells were seen in significantly older patients than tumours with conventional cells only (median age 45 years and 34 years, respectively; Mann-Whitney U test, p = 0.028). Tumours with infarct-type necrosis were larger than those without such necrosis (median diameter 9 cm and 4 cm, respectively; Mann-Whitney U test, p=0.024).

Follow-up

Follow-up data were available for 14 patients and ranged from 7 to 246 months (median 52 months). A single patient developed liver metastasis (as described below). No case showed locoregional recurrence. All 14 patients were free of disease at the last follow-up.

Clinically aggressive solid-pseudopapillary neoplasm

A 45-year-old woman was treated with distal pancreatectomy due to a 7.8-cm partially encapsulated tumour of the pancreatic tail. Neoplastic cells invaded the pancreatic parenchyma, and for that reason the tumour was diagnosed as SPC. Perineural and vascular invasion, infarct-type necrosis, and necrobiotic nests were absent. Focally, tumour cells were moderately atypical; multinucleated neoplastic cells were also found. The ENETS tumour grade was G1. The Nishihara score was 5. ENETS and AJCC tumour stages were T3 and pT2, respectively. The distance between tumour tissue and the surgical margin was 1 mm. Following resection, the patient was treated with adjuvant chemotherapy but developed a solitary liver metastasis 17 months after pancreatic surgery. That 1.3 cm liver tumour was resected with a wide margin. Tumour cells in the metastatic lesion showed moderate cytological atypia. Multinucleated tumour cells and necrosis were absent. As in the primary tumour, hyaline globules were found. ENETS tumour grade was G1. At 29-months follow-up after resec-

tion of metastatic deposit the patient remained well without signs of locoregional or distal recurrence.

Immunohistochemical features

Some results of IHC analysis are shown in Supplementary Fig. 3. All examined tumours (13/13) showed diffuse nuclear and cytoplasmic β-catenin staining. CD10 expression was seen in 11/12 cases and it was usually strong and diffuse (median histoscore 270). CD56 expression was found in 12/12 cases (median histoscore 225). PgR expression was seen in 12/12 cases – median percentage of positive nuclei was 90%. Synaptophysin was expressed in 11/13 cases, but in many cases it was weak and focal (median histoscore 50). Two cases showed 'positive' p53 immunostain: a 1.4 cm-tumour in the pancreatic head of 42-year-old female (examined using conventional whole section) and a 10 cm tumour in pancreatic tail of 36-year-old female (examined using TMA). In the former case, strong p53 expression was seen in distinct portion of a tumour with many (degenerative) pleomorphic nuclei and multinucleated giant tumour cells, but it was not seen in other tumour areas. This was possibly caused by formation of subclone of tumoral cells with *TP53* mutation, as proposed by other investigators [7]. In the latter case, p53 expression was also seen in pleomorphic nuclei. As in the previous study [7], expression of other IHC markers was similar in p53-positive and p53-negative cells. Claudin-5 expression was found in 10/12 cases. However, in 4 out of 10 positive cases it was only focal and/or weak, and histoscore in these cases ranged from 10 to 80. The median histoscore among all evaluated cases was 100 (interquartile range 25-225). Results of IHC assays in a clinically aggressive tumour were very similar to benign SPN. The IHC profile of a liver metastasis in a single patient with clinically aggressive disease resembled the profile of the primary lesion.

Clinicopathological features as predictors of clinically aggressive disease

As presented in Table I, clinicopathological features did not show satisfactory diagnostic yield in identification of a clinically aggressive disease. In particular, many features previously recognized as useful for that purpose were seen in clinically benign cases.

Discussion

Solid-pseudopapillary neoplasm is a rare tumour. It develops almost exclusively in the pancreas, with the exception of extremely rare cases present in other areas/organs of the abdominal cavity [40, 41, 85, 86]. The origin of SPN is still unknown [4], but its relation to stem cells of the pancreas [87], centroacinar

cells [80, 88], genital ridge-related cells [78] or neural crest [89] was postulated. Recent gene expression studies provided new data on signalling pathways involved in SPN [89, 90]. An engineered mouse model of tumour compatible with SPN diagnosis is available [91].

Large series of patients with SPN treated in the USA, Europe and Asia are on record [5-7, 9, 10, 17-19, 32, 33, 35, 36, 38, 39, 42, 43, 46, 47, 51, 53–55, 59, 61, 64, 65-68, 71, 72-74, 75, 78, 92-102]. In contrast, single case reports or series up to 6 cases have been described in Polish literature [103-111], including at least 3 cases with aggressive behavior [105, 108, 109, 111]. Cumulative meta-synthetic reviews of clinicopathological features of SPN are also available [20, 56, 65, 74, 75, 87, 102, 112-115].

The clinicopathological profile of SPN reported in the present series was similar to previous studies [4-6, 9, 17-19, 32, 33, 35, 36, 38, 39, 42, 43, 46, 47, 49, 51, 53-55, 59, 61, 64, 65-68, 71-74, 75, 78, 92-98, 100-102, 113, 116]. Majority of patients were young females. Tumours were relatively large and occurred in all segments of the pancreas.

Surgery is the only curative option for patients with SPN [16, 20, 21, 56, 60]. Resection of locally invasive tumour and metastases should be attempted whenever possible as it may result in long-term survival [5, 10, 20, 32, 61, 97, 117]. The 10-year survival rate in SPN is 94-96% [5, 33]. It is not clear whether non-curative resection due to presence of neoplastic tissue at surgical margin is unfavourable prognostic factor in patients with SPN [9, 19, 35, 46, 53, 54, 60, 99], but a recent study based on cumulative data suggests so [56]. Long-term survivals in patients with non-curative resections were described [9, 35, 68]. Long-term survival can also be obtained following metastasectomy [9, 32]. Spontaneous regression of primary SPN and liver metastases is even possible [118]. The role of radiotherapy and chemotherapy in SPN treatment is not well defined [16, 108, 119].

Histopathological features of SPN are well described [1-4, 22, 25, 120]. Metastases of SPN usually resemble primary tumours morphologically [48, 57, 61, 117].

The immunohistochemical profile of SPN is relatively specific [24]. SPN usually express β-catenin (nuclear stain), CD10, CD56, and PgR [24]. Claudin-5 was identified as a new marker of SPN, particularly useful in differential diagnosis of SPN and other 'solid cellular' neoplasms of the pancreas [26]. Comper *et al.* observed claudin-5 immunoexpression in all 20 SPN tested using conventional tissue sections [26]. We largely confirmed those observations, but 2/12 of our cases were claudin-5 negative and another 4 showed focal and/or weak staining.
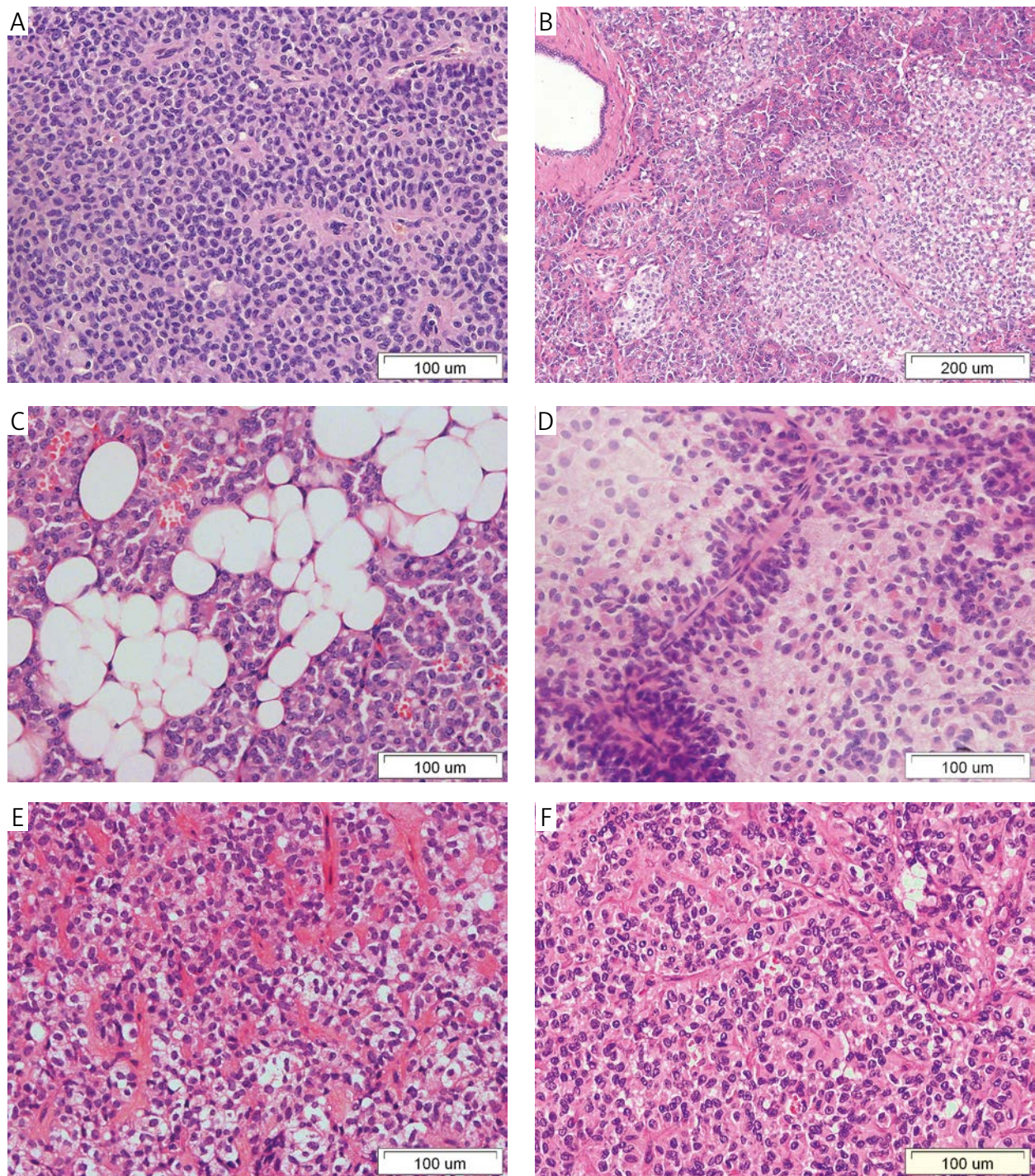
Fig. 1. Microscopical picture of SPN:
A) Solid growth pattern with delicate vessels; **B)** SPN and adjacent pancreatic parenchyma; **C)** Invasion of peripancreatic adipose tissue; **D)** Cytological picture of SPN; **E)** A clinically aggressive SPN – primary lesion; **F)** A clinically aggressive SPN – liver metastasis

This could be caused by differences in immunohistochemical protocols between studies, as well as usage of TMA in the present study. At present, lack of claudin-5 immunoexpression in a diagnostic sample does not exclude SPN diagnosis.

We noted a single clinically aggressive SPN in the present series (5.9%). The percentage of cases with malignant features varies between studies, from less than 4% to more than 20% [5, 19, 33, 35, 38, 49, 53, 85]. This may be related to differences in criteria of malignancy, follow-up protocols, adjuvant treatment, as well as patients' characteristics.

Despite systematic evaluation of large number of histopathological features, we were unable to identify

both sensitive and specific risk factors of aggressive behaviour of SPN. Similar observations have been made by other investigators [9, 16, 21, 33]. Importantly, aggressive behaviour may appear many years after potentially curative tumour resection [117]. At present, locoregional or distant recurrence of SPN after tumour resection is unpredictable [21].

According to other reports, SPC diagnosis is a sensitive but not specific risk factor for clinically aggressive disease [18, 19, 43, 66, 67]. The percentage of SPC in the present study was 82.4%, and it was high in comparison to previous reports. The percentage of SPC among SPN varied significantly between studies (from 8.2% up to 70%) [18, 19, 32, 42, 43, 53, 65, 66-68, 94, 97]. This may be related to differences between patient populations and possibly to somewhat imprecise criterion of SPC diagnosis [15]. "Deep invasion [of tumour] into the surrounding tissue" [15] may be interpreted as invasion of pancreatic parenchyma or invasion of peripancreatic adipose tissue, or invasion of adjacent organs. In the present series invasion of peritumoral pancreatic parenchyma was sufficient for the diagnosis of SPC. Restriction of that criterion to cases showing invasion of peripancreatic tissues resulted in lower percentage of SPC among SPN cases (64.7%).

p53 immunoexpression is rare but possible in SPN [11]. It may be associated with presence of pleomorphic nuclei and it usually correlates with TP53 mutation [7]. Pleomorphic nuclei and atypical multinucleated giant tumour cells possibly represent senescence-related tumour degeneration rather than true atypia [7, 64]. Pleomorphism is not associated with increased mitotic count, increased Ki-67 proliferative index, or importantly, with clinically aggressive behaviour [7, 64]. In the present series, 2 cases showed p53 immunoexpression in areas which were composed, but not exclusively, of cells with pleomorphic nuclei.

The Ki-67 proliferative index in conventional SPN ranges from 0 to 10% [57, 121-123]. Ki-67 expression may correlate to some extent with 'malignancy' or local invasion of SPN [20, 57, 71, 93, 116]. In some reports, Ki-67 expression was documented only in cases with invasion of pancreatic parenchyma [93, 116]. Ki-67 indices in SPN and SPC are similar [53, 123]. We observed a single SPN with a slightly increased Ki-67 index. During 90-month follow-up, that patient did not have a recurrence. Distant metastases of SPN usually retain low Ki-67 indices [45, 48]. We did not observe an increase of Ki-67 expression in liver metastasis in comparison to the primary tumour.

Some groups have suggested that there were some differences in IHC profile between clinically benign and malignant SPN. For example, the extent of CD56 stain may be slightly higher in SPN with synchronous liver metastases than in SPN without metastases during presentation [124]. In another study,

synaptophysin was seen in a single metastasizing tumor but not in 6 SPN without metastases [122]. We did not confirm these observations. Other investigators found differences in IHC pattern between primary and secondary deposits of SPN. Geers et al. observed weak/negative CD10, CD56, galectin-3 and PR staining in liver metastasis of SPN [70]. In other report, primary SPN and metachronous liver metastasis showed focally positive and negative CD10 staining, respectively [22]. Like another group [57], we did not find differences in results of IHC between pancreatic tumour and distant metastasis.

Results of molecular studies also did not allow identification of a highly specific genomic profile of aggressive SPN [125, 126]. Aneuploidy seems to be a feature of invasive and/or metastasizing SPN, and SPN in males [49, 62, 127], but these features may not be sensitive and specific enough [122].

In very rare cases, SPN may progress to an undifferentiated neoplasm of extreme clinical aggressiveness [33]. This may happen at the stage of primary tumour [33, 58, 59] or metastatic deposits [41, 82, 127]. Diffuse growth pattern, significant atypia, extensive necrosis, high mitotic index and high Ki-67 proliferative index are features of undifferentiated neoplasm derived from SPN [33, 41, 58, 59, 82, 127]. A high-grade tumour component may lose expression of some classical SPN markers (CD10, CD56) and gain expression of epithelial (EMA, Cam 5.2) or even melanocytic (HMB-45) markers [33, 58]. We did not observed undifferentiated SPN in the present series.

The limitation of our study is the relatively small number of examined cases, especially in comparison with recent large series from Asia [7, 19, 32, 38, 47].

Conclusions

In the present study we systematically evaluated a large number of histopathological features of SPN. At present, histopathological examination cannot identify patients who may develop locoregional or distant tumour recurrence following resection of a primary tumour. For that reason, a close follow-up should be offered to all patients treated for SPN.

Acknowledgements

Note

During the peer review of the manuscript we encountered another case of a clinically aggressive SPN.

Metastatic foci of SPN were found in several samples of peritoneal and peripancreatic tissues taken from a 38-year-old woman who underwent a distal pancreatectomy 20 years earlier at outside our institution. Secondary SPN deposits (slides of the primary lesion were not available for review) showed enlarged nuclei and nucleoli, moderate pleomorphism, scattered multinucleated giant cells and necrobiotic nests, and rare mitotic figures. Nuclear grade was 2, ENETS grade was 1, and Nishihara score was 7. The IHC profile was typical for SPN.

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