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ORIGINAL ARTICLE

A large-scale clinicopathological and long-term follow-up study of solid papillary carcinoma of the breast

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Abstract

Solid papillary carcinoma of the breast (SPC) is a rare tumor of the breast with the unique histology and frequent neuroendocrine differentiation. However, a real nature and diagnostic importance of the neuroendocrine differentiation have not been properly handled. And relationship between SPC and the other types of invasive breast carcinoma, especially neuroendocrine tumor of the breast (NETb), has not been fully explained. We conducted a clinicopathological study of SPC to tackle these problems.

In the study, we included 127 cases of SPC with long-term follow-ups of up to 30 years. The incidence in the breast carcinoma was 2.0%. The patients with SPC had a significantly better prognosis and no patients died of the tumor. The 35 cases had only SPC in situ (SPC-IS), while the 92 cases had both SPC-IS and SPC with invasion (SPC-INV). Immunohistochemically, 123 of the 127 cases exhibited diffuse expression of one or more neuroendocrine markers. Fifty of the 92 cases had exclusively invasive SPC (iSPC) as the invasive component. Twenty-two cases of iSPC were combined with NETb and the 18 cases with MUC. Six of 8 cases with metastatic SPC-INV disclosed iSPC in the axillary lymph node.

This study suggests that SPC is immunohistochemically compatible with NET of the systemic organs (NETs). And the unique morphology of SPC may represent a traditional histology of NETs. The study also indicates that SPC has close relationship between NETb and type B MUC. And SPC and NETb may represent a spectrum of the same disease.

Keywords Breast cancer · Solid papillary carcinoma · Neuroendocrine tumor · Neuroendocrine carcinoma · Mucinous carcinoma

Introduction

Solid papillary carcinoma (SPC in situ and with invasion) of the breast is defined as a tumor characterized by a solid growth pattern with delicate fibrovascular cores and frequently showing neuroendocrine differentiation and indolent biological behavior. Diagnosis of SPC is usually made according to the characteristic morphology alone [1]. However, we occasionally encounter some benign intraductal lesions and malignant tumors

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of low nuclear grade that are histologically similar to SPC. Immunohistochemistry with neuroendocrine markers may help with differential diagnosis of SPC from these lesions [2–4]. Although frequent neuroendocrine differentiation is referred to the definition and criteria for SPC of the WHO classification, the real nature and diagnostic importance do not seem to be fully described. For the purpose of solving the issue, we conducted a semi-quantitative study of neuroendocrine differentiation of SPC with neuroendocrine makers such as synaptophysin (SYN), chromogranin A (CGA), and INSM1, a new neuroendocrine maker.

In the first report of SPC, the authors postulated SPC as a preinvasive counterpart of mucinous carcinoma with neuroendocrine differentiation due to frequent association of SPC with mucinous carcinoma [5]. On the other hand, they did not refer to invasive SPC (iSPC) as an invasive component of SPC. Several studies of the invasive component of SPC based on their own criteria demonstrated that it included iSPC, mucinous carcinoma (MUC), invasive breast carcinoma of no special type (IBC-NST), neuroendocrine carcinoma (NEC), carcinoma with neuroendocrine differentiation, and neuroendocrine-like carcinoma. But the proportion of the component greatly varied in their reports [6–9]. To clarify the relationship between SPC in situ (SPC-IS) and SPC with invasion (SPC-INV) including iSPC, MUC, neuroendocrine tumor of the breast (NETb), and IBC-NST, we examined the type and proportion of these invasive components in our 127 cases with SPC on the basis of WHO Classification of Tumors, Breast Tumors (2019) [1].

Although SPC could fulfill the criteria for designation as mammary neuroendocrine neoplasm, it is recommended that SPC should not be classified as NET or NEC because SPC is a "distinctive breast neoplasm" [1]. SPC was initially thought of as an intraductal carcinoma with neuroendocrine differentiation and the characteristic histology. On the other hand, NET of the systemic organs (NETs) and NETb have been traditionally recognized as an invasive tumor without any in situ lesions and/or multi-directional differentiation except mucinous differentiation. Several cases of intraductal NETs have been reported in various sites of our body [10–13]. A concept of mixed-neuroendocrine-non-neuroendocrine neoplasms has been recently proposed [14]. We believe that these emerging tumors and the concept challenge our traditional notion of NETs or NEC. According to the clinicopathological study of 127 cases with SPC, we will discuss the real neuroendocrine nature, diagnostic importance of the neuroendocrine differentiation, and relationship between SPC-IS and SPC-INV.

Materials and methods

Patients' data

In this study, we included 127 cases of 120 patients with SPC, who underwent a surgical operation at the Seirei Hamamatsu General Hospital (SHGH), Hamamatsu, Japan, or the Seirei Numazu General Hospital (SNGH), Numazu, Japan. All the cases were diagnosed at Department of Pathology, SHGH, from 1976 to 2021. During the period, a total of 6483 cases with primary breast cancer were registered at the department. They included 5088 cases of IBC-NST, 752 ductal carcinoma in situ, 218 invasive lobular carcinoma, 216 MUC, 127 SPC, and the others. The patient's clinical history, age at presentation, sex, laterality, surgical procedure, and presence or absence of distant metastasis and survival time were obtained from the database of SHGH and SNGH. During the research period, we had 92 cases of SPC-INV and 5088 cases of IBC-NST. We compared the clinical differences between them.

Histological materials and interpretation

Tissue samples were fixed in 10% buffered formalin and embedded in paraffin. Hematoxylin and eosin staining slides of all the SPC cases were reviewed by the authors. The primary tumor size, presence of stromal invasion, invasive size, type of invasive carcinoma, nuclear grade (N-grade), Nottingham histological grade (H-grade), and lymph node (LN) status were obtained from clinicopathological reports [1, 15].

We have selected all the cases at first based solely on the WHO morphological criteria (Fig. 1) [1]. We could make the definite diagnosis by the morphology alone with more than 80% of the cases. In the remaining cases that were difficult to make the diagnosis, we employed immunohistochemistry with SYN and CGA to differentiate SPC from the other benign and malignant mimicries. We thought that the cut-off value of IHC for the neuroendocrine markers at 1% or 5% was too low to make an immunohistochemical distinction between SPC and these mimicries. We provisionally set the positive cut-off value of the neuroendocrine differentiation at 10% or more. And we diagnosed the difficult case as SPC when 10% or more of the tumor cells were positive for SYN and/or CGA (Fig. 2). We excluded 7 cases from the study with this provisional algorithm.

For the immunohistochemical study, four micrometer-thick sections were cut from paraffin-embedded blocks, transferred on to silane-coated slides, dried at 60 degrees Celsius for 1 h in the oven, and immunostained using a Ventana BenchMark XT Autostainer (Roche Diagnostics; Indianapolis, IN). To retrieve the antigens, the slides were treated

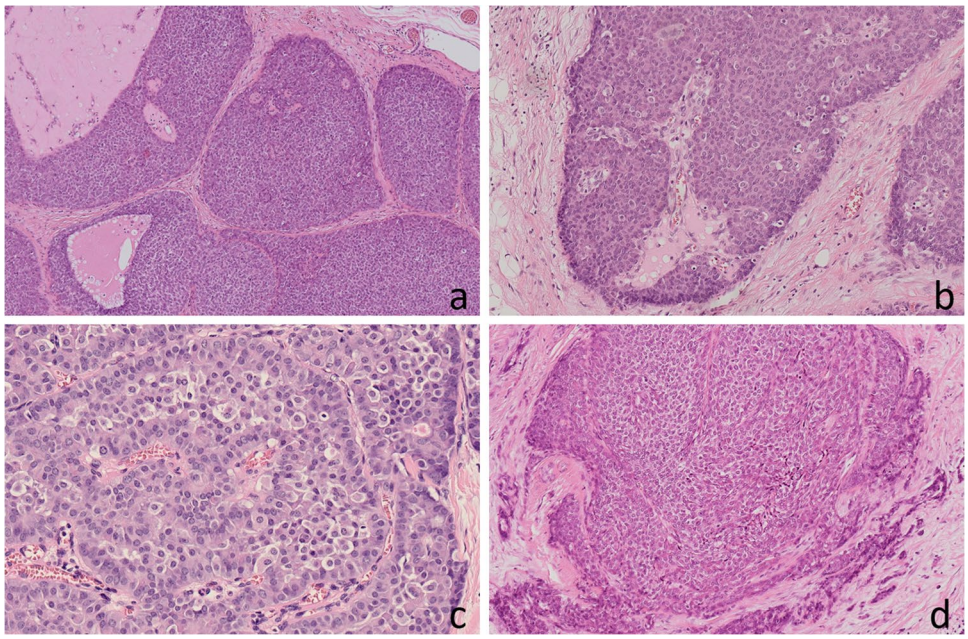

Fig. 1 Histological features of SPC (hematoxylin and eosin staining (H&E)). (**a**) SPC in situ shows expansive solid nests with delicate fibrous cores and smooth contours. (**b**) A fair amount of fibrovascular tissue is seen within the sloid nest but the overall contour is smooth, which means that the nest is noninvasive. (**c**) The tumor cells have ample, pale eosinophilic, granular cytoplasm, and small oval nuclei of mild atypia. Nuclear palisading around the fibrovascular cores is prominent. (**d**) Invasive SPC has ragged contours with a geographical jigsaw pattern and small irregular nests in the periphery

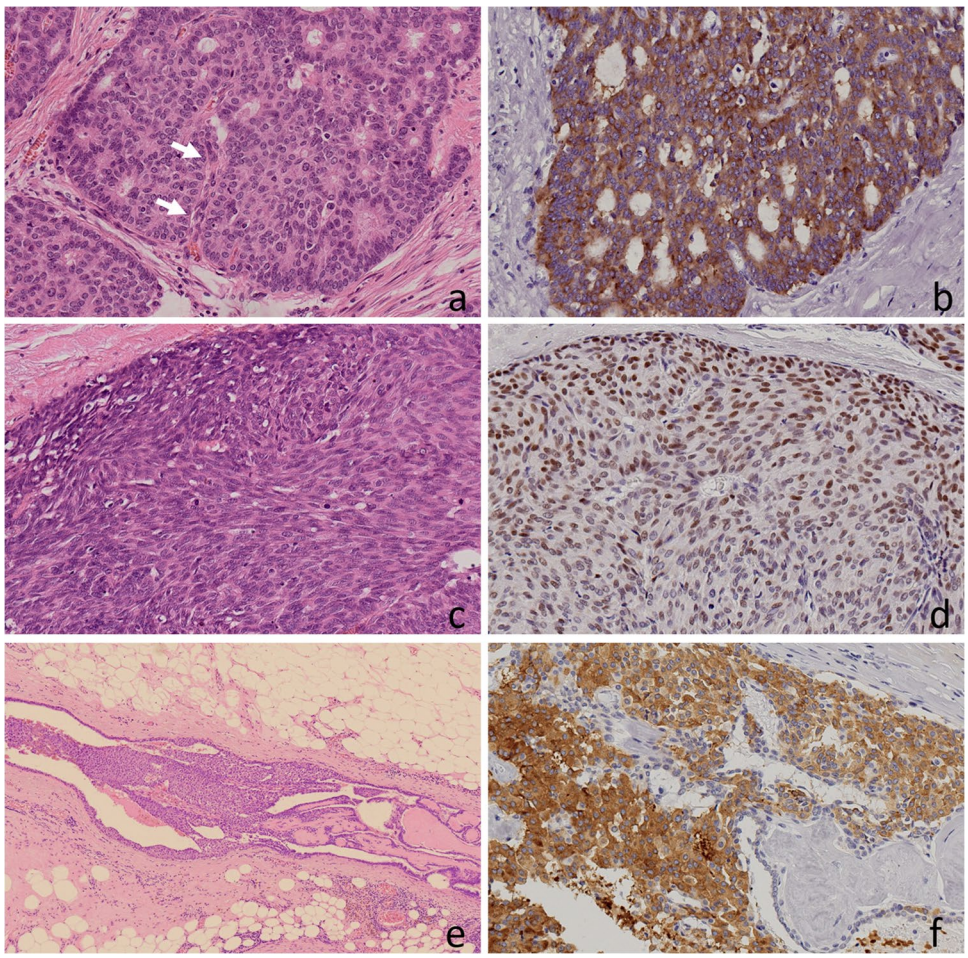

Fig. 2 Histological variations of SPC in situ that are required for the immunohistochemical test with neuroendocrine markers. (**a**, **b**) SPC with only few of the typical fibrovascular cores (arrow) is sometimes difficult to differentiate from intraductal carcinoma of low nuclear grade with cribriform pattern. Please look at Figs. 2.43., 2.45., and 2.64. in the WHO blue book 2019 to confirm the difference of various cribriform patterns ((**a**) H&E). The tumor cells of SPC showed diffuse positivity in the immunohistochemical specimen made from the same tumor tissue with (**a**) ((**b**). SYN). (**c**, **d**) SPC should be distinguished from florid intraductal hyperplasia with proliferating spindle cells ((**c**) H&E, (**d**) INSM1). (**e**, **f**) Intraductal papilloma-like growth is occasionally observed in some areas of SPC. The cells in this lesion are also diffusely positive for neuroendocrine marker ((**e**) H&E, (**f**) SYN)

with CC1. We employed the following antibodies in this study: Synaptophysin (27H12) and p53 (Do7) from Leica biosystems, Buffalo Grove, IL, Chromogranin A (LK2H10), Estrogen receptor (ER) (SP1), Progesterone receptor (PR) (IE2), and HER2 (4B5) from Roche Diagnostics, Indianapolis, IN, INSM1 (A-8) from Santa Cruz Biotechnology, Inc. Dallas, TX, and Ki67 (MIB1) from Agilent, Santa Clara, CA. All the antibodies were incubated at 42 degrees Celsius. An OptiView DAB IHC Detection kit (Roche Diagnostics; Indianapolis, IN) was used to detect the antigen–antibody complexes. After immunohistochemical staining, slides were processed by dehydration, cleared, and mounted in order. Positive and negative controls were included in each run. In the present study, we analyzed the neuroendocrine differentiation with three immunohistochemical neuroendocrine markers, i.e., SYN, CGA, and INSM1. And diffuse positivity was defined as positive staining with neuroendocrine marker of more than 50% of the tumor cells, whereas focal and weak or no positivity meant the positive staining of 10–50% and less than 10%, respectively. As for ER and PR, a positive result was defined as a positivity rate of 1% or higher of the tumor cells. High expression level of Ki67 was defined as a positivity rate of higher than 20% of the tumor cells. Low expression was 20% or lower of them. The cut-off value for Ki67 was decided following the suggestion by the 13th St. Gallen international breast cancer conference [16].

To conduct a histological study, the criteria for SPC-IS, SPC-INV, iSPC, MUC, IBC-NST, and the other types of breast carcinoma were based on the WHO classification 2019 [1]. We occasionally needed the immunohistochemical test with myoepithelial markers (p63 and SMA) when the histological distinction between SPC-IS and iSPC was difficult. We recognized an invasive breast tumor as NETb when it met the essential and desirable criteria of the WHO classification and had absence of delicate fibrovascular cores within the solid tumor nests (Fig. 3).

Statistical analysis methods

Statistical analysis was performed using the statistical software "EZR" (Easy R), which was based on R and R commander. EZR is freely available on a website (http://www.jichi.ac.jp/saitamasct/SaitamaHP.files/statmed.html) [17]. Chi-square/Fisher's test was used to compare the groups, and weighted kappa value and accuracy rate were calculated. Independent *t*-test and one-way analysis of variance (one-way ANOVA) were applied to compare the patient's age, tumor size, and positivity rate for immunohistochemistry. The overall survival curves and disease-free survival curves were constructed using the Kaplan–Meier method [18]. The differences among the groups were assessed with the log-rank test. When the survival curves and the risk of recurrence or death were analyzed, deaths from other diseases were excluded from the case series. For all the tests, *p* value of less than 0.05 was considered statistically significant.

Results

Clinicopathological findings of SPC-IS and SPC-INV

This series included 127 cases of SPC from 120 patients. The 35 cases had only SPC-IS while the 92 cases had both SPC-IS and SPC-INV. The incidence of SPC among all the

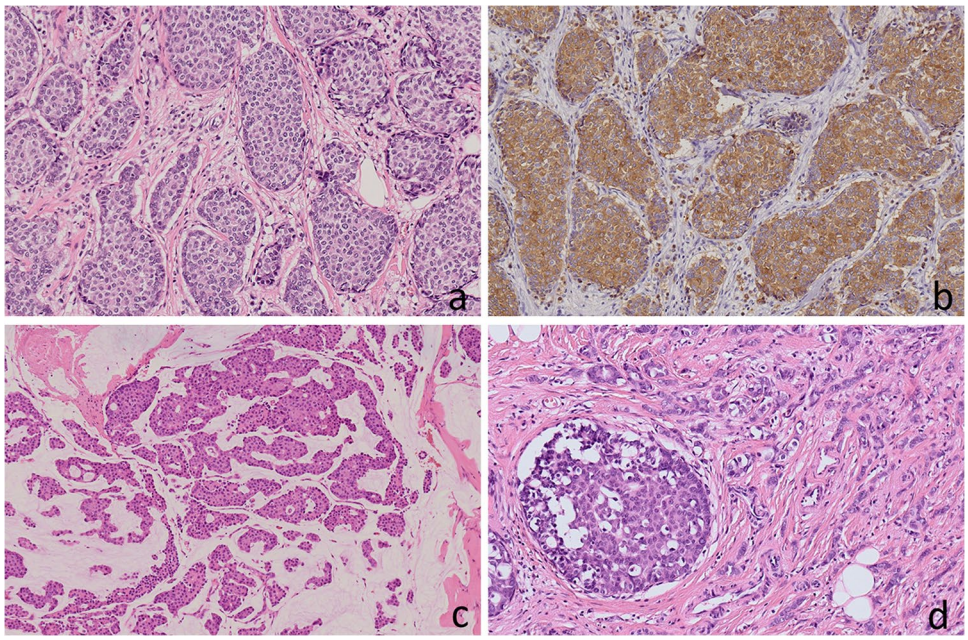

Fig. 3 In addition to invasive SPC, SPC with invasion is sometimes composed of 3 types of carcinoma, (**a**, **b**) NETb, (**c**) MUC, and (**d**) IBC-NST ((**a**, **c**, **d**) H&E, (**b**) SYN)

breast cancers (6483 cases) diagnosed at our department was 2.0%. The maximum follow-up period after mastectomy for SPC-INV and IBC-NST is 26 years and 44 years, respectively. And the mean follow-up period for SPC-INV and IBC-NST is 6.3 years and 10.6 years, respectively. The clinical features of SPC-INV and those of IBC-NST are summarized in Table 1. The case with SPC-INV has relatively older age and lower tumor stage than the case with IBC-NST. LN metastasis was found in 8.7% of SPC-INV and 36.8% of IBC-NST. Tumor recurrence occurred in 2 cases (2.2%) of SPC-INV and 15.9% of IBC-NST. The one case had sternal metastasis and multiple liver metastases of 7 cm in the maximum diameter and the other case revealed a, 6 mm sized, pulmonary metastasis. The former patient has been alive with the diseases for 6 y 7 m and the latter without the disease 3 y 8 m after resection of the lung tumor. No patient died of SPC-INV, whereas 12.3% of the patients with IBC-NST died of the disease. We found that SPC-INV had a significantly better prognosis than IBC-NST in OS ($p=0.008$) and DFS ($p=0.009$) (Supplementary Fig. 1).

Clinicopathological features of the case with SPC-IS and SPC-INV are shown in Table 2. The patients of SPC-IS were aged 44 to 82 years (mean: 66.6 years), and those of SPC-INV were aged 31 to 97 years (mean: 66.1 years). In SPC-IS cases, 16 cases were left-sided, and 19 cases were right-sided, while in SPC-INV cases, 40 cases were left-sided, and 52 cases were right-sided. The 108 patients had unilateral SPC. Seven patients (14 cases) had bilateral SPC with the 5 and 2 patients having the synchronous and metachronous tumors, respectively. And the 5 patients had SPC on one side of the breast, but conventional breast cancer on the opposite side. In the patients of SPC with bilateral breast cancer, the 2 patients were sisters but the other 5 patients did not have a familial history of breast cancer. The 63 and 64 cases with SPC underwent total and partial mastectomy, respectively. Axillary LN metastasis was found in 8 of the 92 cases of SPC-INV. The 5 cases revealed N-grade 1, one case N-grade 2, and two cases N-grade 3 with the mean Ki67 positivity rate of 6.3%. The size of metastatic lesion ranged from 0.3 mm to 16 mm, with an average of 4.99 mm. And the histology of the axillary LN metastasis displayed iSPC in the 6 cases, NETb in 1 case, and MUC in 1 case. One of the six cases with iSPC had metastases to the bone and liver. The one case with NETb demonstrated a metastasis to the lung. The case with MUC did not have any distant metastases. Both of the two cases with distant metastasis revealed N-grade 1 with the mean Ki67 positivity rate of 7.0%. Either ER or PR was positive in all cases of both SPC-IS and SPC-INV. All cases with SPC were negative for HER2 expression or amplification.

Histopathological findings of SPC-IS and SPC-INV

The pathological characteristics of the 35 cases with SPC-IS and 92 cases with SPC-INV are listed in Table 2. The maximum tumor size of SPC-IS and SPC-INV and maximum invasive size of SPC-INV is included in Table 2. Mitotic count of most of the case of SPC was 20 or lower than 20 per 2 square millimeters. As for N-grade, 97 cases of SPC showed N-grade 1, 20 cases N-grade 2, and 10 cases N-grade 3. Regarding H-grade, 53 cases of SPC-INV showed H-grade1, 39 case H-grade2, but no case H-grade3. The 120 cases of SPC demonstrated low expression of Ki67 whereas the other 7 cases had the high expression. In these high expression cases, the 3 cases showed N-grade 3, 2 cases N-grade 2, and 2 cases N-grade 1. The mean positive rate of p53 in all cases of SPC was 9.7%. 3 of the 35 cases with SPC-IS demonstrated focal mucin production without the tumor cells floating in the mucin. Eleven cases

Table 1 Comparison of SPC with invasion and conventional invasive ductal carcinoma about clinical features

	SPC with invasion	Invasive breast cancer of no special type	*P* value
No. of cases	92	5088	
Mean age (yr)	66.1 ± 14.6	56.3 ± 13.0	$P<0.05^*$
Mean invasive size (mm)	9.9 ± 9.1	19.5 ± 13.3	$P<0.05^*$
Sex			
Female	92	5073	$P=1.000$
Male	0	15	
Laterality			$P=0.248$
Left	40	1800	
Right	52	1828	
No. (%) of cases with positive LN	8/92 (8.7)	1395/3786 (36.8)	$P<0.05^*$
No. (%) of cases with recurrence	2/92 (2.2)	572/3599 (15.9)	$P<0.05^*$
No. (%) of cases with DOD	0/92 (0)	441/3599 (12.3)	$P<0.05^*$

*Statistically significant difference

Table 2 Summary of the clinicopathological features of SPC

	SPC	SPC in situ	SPC with invasion	*P* value
No. (%) of cases	127 (100)	35 (27.6)	92 (72.4)	
Mean age (yr)	66.2 ± 13.6	66.6 ± 10.8	66.1 ± 14.6	$P = 0.868$
Laterality				$P = 0.844$
Left	56	16	40	
Right	71	19	52	
Mastectomy				$P = 1.000$
Total	63	17	46	
Partial	64	18	46	
No. (%) of cases with positive LN	8 (6.3)	0 (0)	8 (8.7)	$P = 0.105$
No. (%) of cases with recurrence	2 (1.6)	0 (0)	2 (2.1)	$P = 1.000$
No. (%) of cases with DOD	0 (0)	0 (0)	0 (0)	-
ER				-
Positive	127	35	92	
Negative	0	0	0	
PR				$P = 0.561$
Positive	124	35	89	
Negative	3	0	3	
HER2				-
Negative	119	30	82	
Positive	0	0	0	
Mean total size (mm)	23.3 ± 18.2	21.7 ± 19.3	28.1 ± 17.5	$P = 0.079$
Mean invasive size (mm)			9.9 ± 9.1	
Nuclear grade				$P = 0.155$
1	97	30	67	
2	20	2	18	
3	10	3	7	
Mitotic count/2 mm^2				$P = 0.186$
< 2	48	17	31	
2 ~ 20	77	17	60	
> 20	2	1	1	
Immunohistochemistry				
Ki67				$P = 1.000$
High	7	2	5	
Low	120	33	87	
p53: positive rate (%)	9.7 ± 8.5	8.6 ± 7.6	10.1 ± 8.9	$P = 0.447$
Synaptophysin				$P = 0.234$
Diffuse	110	28	82	
Focal	5	2	3	
Weak or no positivity	11	5	6	
Chromogranin A				$P = 0.648$
Diffuse	51	14	37	
Focal	16	6	10	
Weak or no positivity	19	7	12	
INSM1				$P = 1.000$
Diffuse	101	27	74	
Focal	12	3	9	
Weak or no positivity	12	3	9	

with SPC showed small areas of the tumor with a cribriform and/or papillary pattern.

Concerning neuroendocrine features of SPC, diffuse expression with SYN, CGA, and INSM1 was seen in 110/126 cases (87.3%), 51/86 cases (59.3%), and 101/125 (80.8%) of SPC, respectively, as shown in the Table 2. There was statistical significance in the positive rate between SYN and CGA, and INSM1 and CGA by Chi-square test ($p<0.05$). The 38 cases revealed diffuse positivity (more than 50% of the tumor cells being positive) for all the markers. Diffuse positivity with the two markers was shown in the 10 cases for SYN and CGA, 50 cases for SYN and INSM1, and 3 cases for CGA and INSM1. Diffuse positivity with the only one marker was observed in the 12 cases for SYN, 10 cases for INSM1, and none for CGA. The 12 cases for SYN displayed focal positivity only for INSM1 and CGA in the 10 cases and in one case, respectively. Immunohistochemistry for INSM1 was performed in all the 12 cases while that for CGA was done in the 4 cases. The only one case showed weak or no positivity for CGA and INSM1. The 10 cases for INSM1 exhibited focal positivity only for SYN and CGA in the 3 cases and 6 cases, respectively. Immunohistochemistry for SYN was performed in all the 10 cases although that for CGA was done in the 7 cases. The only one case showed weak or no positivity for SYN and CGA. The 4 cases of SPC demonstrated no diffuse positivity for any of the three markers. All the 4 cases demonstrated weak or no positivity for two of the three markers. The two cases exhibited focal positivity for INSM1, the one for SYN, and the other for CGA.

We identified iSPC, NETb, MUC, and IBC-NST as the invasive component in the 92 cases with SPC-INV (Figs. 1d and 3). We did not find any of the other histological types of invasive breast cancer in the 92 cases. 50 of the 92 cases had iSPC as the sole invasive component. And NETb, MUC, and/or IBC-NST were confirmed as the invasive component combined with iSPC in the other 42 cases. Combination of iSPC + NETb was seen in the 21 cases, iSPC + MUC in 17 cases, iSPC + IBC-NST in 3 cases, and iSPC + NETb + MUC in one case. MUC was consisted of 2 cases of type A and 16 cases of type B. The three cases of IBC-NST disclosed no or weak positivity with the neuroendocrine markers. The one case of type A MUC indicated focal positivity with INSM1 and weak or no positivity with the other markers and the other case showed weak or no positivity with SYN and CGA. All the cases with NETb and type B MUC displayed diffuse positivity with one or more of the markers. Regarding the tumor diameter, tumor grade, recurrence rate, and LN metastasis rate, there was no statistically significant difference for all of the invasive combination.

Discussion

SPC is defined as a mammary tumor that frequently demonstrates neuroendocrine differentiation. Some degree of neuroendocrine differentiation occurs in 10–30% of IBC-NST [1]. Although criterion for neuroendocrine differentiation of NETb and neuroendocrine carcinoma is defined as diffuse and uniform immunoreactivity for neuroendocrine markers, the real nature of and criterion for neuroendocrine differentiation of SPC has not been clearly stated. To examine the neuroendocrine nature, we performed a semi-quantitative study of the neuroendocrine differentiation using neuroendocrine makers such as SYN, CGA, and INSM1, a new neuroendocrine maker.

According to the immunohistochemical results, the 38 cases revealed diffuse positivity (more than 50% of the tumor cells being positive) for all the markers. And the 63 cases disclosed diffuse positivity with two of the markers while the 22 cases exhibited diffuse positivity with one of the three markers. Accordingly, diffuse positivity with two or more and at least one of the three markers was observed in 101 (79.5%) and 123 (96.9%) of the 127 cases, respectively. The result indicates that SPC very frequently shows obvious neuroendocrine differentiation. We do not think that our diagnostic algorithm greatly affected the result that supported clear neuroendocrine differentiation of SPC because of our major criteria based on the morphology and the small number of the cases excluded from the study with this algorithm. It is, therefore, suggested that SPC commonly shares neuroendocrine nature with NETb and NETs on the immunohistochemistry [14].

The four cases, however, displayed no diffuse positivity with any of the three neuroendocrine markers. And all of them had weak or no positivity (less than 10% of the tumor cells being positive) with two of the three markers. Two of the 22 cases that showed diffuse positivity with only one of the three markers also indicated weak or no positivity with two of the three markers. These results suggest that the immunohistochemistry is not always helpful in the diagnosis with some of the cases with SPC. On the other hand, our preliminary study of neuroendocrine differentiation of cribriform carcinoma and papillary carcinoma in situ rarely shows weak or focal positivity of an ordinary neuroendocrine marker whereas no cases with these tumors exhibit the diffuse positivity (unpublished data). It would, therefore, be desirable to actively employ the immunohistochemistry to make the proper diagnosis with these difficult cases since the present study disclosed clear neuroendocrine differentiation of SPC. However, it remains unclear how to deal with the cases with ambiguous morphology and neuroendocrine differentiation.

The results of our study concerning the relationship between SPC-IC and SPC-INV revealed that the 50 cases (54.3%) had solely iSPC as the invasive component in the 92 cases with SPC-INV. Hence, it is suggested that SPC frequently exhibits unidirectional differentiation. The other type of the invasive component was found in 42 (45.7%) of the 92 cases: NETb in the 22 cases (23.9%), MUC in 18

cases (19.6%), and IBC-NST in 3 cases (3.3%). They were always accompanied by iSPC, which also suggests that SPC sometimes displays bidirectional differentiation and even tridirectional differentiation.

Interestingly, we observed that the 22 cases had both NETb and iSPC as the invasive component while the other reports did not describe coexistence of NETb and iSPC. Since it is sometimes difficult to distinguish histologically NETb from iSPC, we considered that the criteria to make a distinction between NETb and iSPC were required in the study as we mentioned above. Our results suggest that they are closely related tumors or may represent a spectrum of the same disease. And we also assume that SPC-IS would be a precursor of NETb since we had no cases of NETb in the absence of SPC-IS.

Combination of MUC with SPC has been well known since the first report of SPC [5]. In the present study, we reconfirmed that SPC-IS sometimes provide a precursor lesion for MUC as with the previous studies. It is of note that the number of type B MUC was much more than that of type A in the combined cases with MUC and iSPC. However, we believe that some cases with MUC develop through the other pathways since the cases of MUC without SPC-IS or iSPC (approximately 180 cases) are more predominant than the combined cases at our department. Compared with our result on IBC-NST in SPC, the previous studies reported much higher rates (60.5–14.5%) of the tumor [7–9].

The WHO classification suggests that SPC should not be classified as NET or NEC since it is a distinct breast neoplasm [1]. We believe that SPC is certainly the distinct neoplasm because it generally displays an intraductal growth and a precursor lesion for various types of the invasive breast carcinoma. And the intraductal growth and multi-directional differentiation are contrary to a general concept of NETs and NEC as they have been recognized as an invasive tumor without an in situ lesion and multi-directional differentiation [14]. This traditional notion, however, is challenged by the emerging intraductal NET, in situ neuroendocrine carcinoma, and mixed-neuroendocrine-non-neuroendocrine neoplasms [10–14]. We also acknowledge that SPC is the distinctive neoplasm because SPC had the specific morphology. Nonetheless, the endocrine mucin-producing sweat gland carcinoma usually displays almost the same morphology with SPC [19]. And, if these tumors disclosed diffuse positivity for neuroendocrine markers, it would be possible to suspect that the morphology is consistent with traditional histology of NETs which consists of trabecular, pseudoglandular, or solid nests separated by fibrovascular tissue. Hence, we think that the characteristic morphology of SPC may represent a typical histology of NETs.

In summary, we believe that the morphology, the neuroendocrine nature, and the clinical behavior of SPC are in agreement with NETs in the classification proposed by WHO expert consensus [20].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00428-023-03489-7.

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Author contribution Yoshiro Otsuki and Hiroshi Kobayashi designed and drafted the manuscript. Yoshiro Otsuki, Shunsuke Ohtsuka, Shinichi Shimizu, and Hiroshi Kobayashi made the histopathological diagnoses. Kaori Suwa, Natsuko Mori, Masayuki Yoshida, and Atsushi Serizawa collected the clinical data. All of the authors have read and approved the final manuscript.

Data Availability The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval This study has been approved by the institutional review board of Seirei Hamamatsu General Hospital.

Conflict of interest The authors declare no competing interests.

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