

Solid Papillary Carcinoma of the Breast with Dual Neuroendocrine and Mucinous Differentiation: A Series of Seven Cases

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ABSTRACT

Solid Papillary Carcinoma (SPC) is a rare neoplasm of the breast. SPC was first reported by Maluf HM and Koerner FC in 1995. Other groups also described histological and cytological features of SPC. Recent World Health Organisation (WHO) classification (4th and 5th Editions) made definition of this disease. However, classification and definition of SPC has been still obscure, particularly on dealing with mucinous carcinoma. Present series prompted to create further properties of SPC using seven cases distinctly having both neuroendocrine and mucinous differentiation. Clinicopathological features of seven SPC cases of Japanese women diagnosed and underwent surgery in our hospital were examined. Clinical features were evaluated for age, site of tumours, initial symptoms, surgical treatment, lymph node metastasis and prognosis. Pathological features were evaluated for type of tumour, nuclear grade, Ki-67 index, loss of myoepithelial cell layer, type of mucin accumulation, Neuroendocrine Differentiation (NED) and hormone receptor status. Incidence of the SPC among all breast cancers (620 cases in last 11 years) was 1.13% and the mean patient age was 73.9±7.8 years. SPCs consisted of four cases (in situ) and three cases (invasive). All cases were characterised by nodules with a solid growth pattern with delicate fibrovascular cores. SPC in situ was diagnosed when the nodules had well-circumscribed contours and distribution pattern consistent with an in situ process. SPC invasive type was identified by the carcinoma with areas featuring strands or clusters of tumour cells. They had loss of myoepithelial cell layer at periphery of the tumour nodule confirmed by p63 staining. NED was confirmed by expression of synaptophysin and chromogranin A. The mucin accumulation was classified into three types (extracellular production, mucinous carcinoma and intracellular production). Intracellular mucin production was ascertained by Alcian blue mucin staining. Clinicopathological features of invasive SPC considerably resembled those of neuroendocrine carcinoma, mucinous carcinoma and Invasive Breast Carcinoma of No Special Type (IBC-NST). It is reasonable to regard SPC as a precursor lesion for neuroendocrine carcinoma, mucinous carcinoma and IBC-NST. No recurrence or distant metastasis was found in all cases suggesting a good prognosis of this disease.

Keywords: Clinicopathology, Mucinous carcinoma, Neuroendocrine differentiation, Solid papillary carcinoma

INTRODUCTION

The term “SPC” was first proposed by Maluf HM and Koerner FC to describe a distinctive breast lesion, occurring especially among the elderly females and microscopically characterised by solid cellular proliferation of neoplastic cells with fibrovascular cores and circumscribed nodules [1]. Other groups have also described the histological and cytological features of SPC [2-4]. SPC occurs primarily in postmenopausal woman, mainly during the seventh decades of life or later [5]. Occasionally, however, this tumour can affect patients younger than 50 years [6,7]. Furthermore, SPC can rarely occur in male patients [6]. It has an incidence of less 1%. SPC usually follows an indolent behaviour unless it is associated with invasion [5].

WHO classification (4th Edition, 2012) made a definition of SPC as that characterised by solid growth pattern with delicate fibrovascular cores. NED is frequent. Conventional invasive growth may be present, often having mucinous and/or neuroendocrine features [8]. WHO classification (5th Edition, 2019) of SPC (in situ and invasive) defined that the tumour cells frequently show NED and are biologically indolent [5]. Thus, definition of SPC is still obscure, particularly on dealing with mucinous carcinoma.

The SPC is diagnosed when the nodules with delicate fibrovascular core have rounded, well circumscribed contours and a distribution pattern consistent with an in situ process, regardless of whether a myoepithelial cell layer is present around the periphery of the nodules [9]. SPC with invasion is diagnosed when the nodules are lacking covering myoepithelial cell layers. SPC with invasion is associated with areas creating a geographical jigsaw pattern

within a desmoplastic stroma [5]. Usually, SPC with invasion often expresses extracellular mucin. Sometimes SPC with invasion has clusters of tumour cells within pools of extracellular mucin mucinous carcinoma type. Infrequently, mucin production is only recognised as an intracellular space. To prove such mucin production, mucin staining such as Alcian blue staining is recommended [10]. To identify expression of NED of the neoplasm, immunostaining of synaptophysin and chromogranin A is commonly used. Especially, NED frequently occurs when the tumour is associated with mucin production. Commonly, neoplastic cells of SPC are strongly and diffusely positive for the expression of Oestrogen Receptor (ER). However, that of Progesterone Receptor (PR) is rather variable. Usually, they do not show HER2 overexpression. The Ki-67 proliferation index is generally low or intermediate [6,11].

Up to date, several large-scale overview analyses of SPC have been done [6,7,11,12]. Nevertheless, such analyses are not always consistent with recent concept by WHO classification [5]. Thus, the concept of SPC is still a matter of controversy. Present authors report specific pathological features as well as clinical characteristics of seven cases having essentially both neuroendocrine and mucinous differentiation. All of these cases were diagnosed and underwent surgery in our hospital.

CASE SERIES

Clinicopathological features of SPC were examined with seven cases of women who were diagnosed and underwent surgery in Ogaki Tokushukai Hospital, Japan. The seven cases of SPC retrieved from the files of the Department of Diagnostic Pathology of 620 patients with all breast carcinomas (1.13%) underwent surgery

in last 11 years (from January 2015 to December 2025 years). All specimens were fixed in 10% formalin and embedded in paraffin. The tissues were then sectioned and stained with Haematoxylin and Eosin (H&E) for general examination. As special stain, Alcian blue staining to identify mucin was used. Immunostaining was performed using the labeled streptavidin-biotin system (VENTANA BenchMark ULTRA, Roche Diagnostics, Switzerland).

Classification of lesions: Presently, this study adopted WHO classification, 5th Edition [5] as the morphological and immunohistochemical criteria for the selection of SPC. The diagnostic criteria for the SPC were: (i) expansive nodules with a solid growth pattern and inconspicuous, delicate fibrovascular cores; ii) monotonous population of round to spindle-shaped epithelial cells with mild to moderate nuclear atypia and a variable mitotic count; iii) cells with eosinophilic granular cytoplasm; iv) nuclear palisading around the fibrovascular core; v) extracellular or intracellular mucin is present, but if the nodules are in association with large clusters with pools of extracellular mucin, SPC was regarded as mucinous carcinoma; vi) in cases of invasive SPC, the nodules devoid of a myoepithelial cell layer with ragged contours create a geographic jigsaw pattern with a desmoplastic stroma; vii) NED which is demonstrated by synaptophysin and/or chromogranin A expression, in particular when there is an associated mucinous component.

All the patients were Japanese women with the ages between 58 and 85 years (mean age 73.9±7.8 years). All cases were unilateral. Left upper inner quadrant lesion was common (3/7cases). One case had lesion in left central portion. All patients underwent surgical excision (6 cases received total mastectomy and one case was underwent to partial mastectomy). Size of the tumour measured by ultrasound findings ranged between 43×28×22 mm and 10×9×9 mm. The most frequent initial symptoms of the patients with the breast neoplasm was breast mass or pain. Nipple mass or bleeding from the nipple was recognised in three cases [Table/Fig-1].

Pathological features of these cases are summarised in [Table/Fig-2]. Ultrasound examination usually displayed the presence of frond like mass within a dilated duct in all cases [Table/Fig-3a]. Four cases were in situ type and other three cases were invasive type. Nuclear grade of five cases were low and remaining two cases were intermediate. All SPCs showed expansive nodules with a solid growth pattern and inconspicuous, delicate fibrovascular cores [Table/Fig-3b]. In cases of in situ type, nodules had rounded well-circumscribed contours and a distribution pattern consistent with an in situ process, regardless of whether a myoepithelial cell layer was present around the periphery of the nodules. The cells had eosinophilic granular cytoplasm. Nuclear palisading around the fibrovascular cores and streaming pattern consisting spindle cells were prominent. In the case of invasive SPC, nodules devoid of a myoepithelial cell layer with ragged contours created a geographic jigsaw pattern within a desmoplastic stroma [Table/Fig-3c]. Status of loss of myoepithelial cell layer at periphery of the nodule was

confirmed by p63 staining [Table/Fig-3d]. Fat infiltration by irregular solid papillary nests was also seen in the invasive cases. Four cases of in situ type indicated low labeling index of ki-67 (5-7%). Two cases of invasive type displayed moderate index (10 and 20%, [Table/Fig-2]), although one case exerted only 5%. In the present study, all of seven cases displayed mucinous carcinomas. Extracellular mucin production was frequent at the periphery of the nodules. Cases with pattern of tumour nodules within pools of extracellular mucin, were diagnosed SPC with mucinous carcinoma [Table/Fig-3e]. In one case, only small amount of intracellular mucin was present in the tumour cells. By Alcian blue staining, such intracellular mucin production was clearly identified [Table/Fig-3f]. NED of the neoplastic cells was confirmed by expression of synaptophysin and/chromogranin A [Table/Fig-3g,h]. Importantly, expression of synaptophysin was clear in all cases. However, that of chromogranin A was positive only in three cases. Neoplastic cells in all cases were strongly and diffusely positive for expression of ER. However, expression of PR was rather variable. All cases except two did not show overexpression of HER2 (HER2:0 and HER2:1+ were regarded as negative) [Table/Fig-2].

In the present study, recurrence and metastasis were not found in any patient [Table/Fig-1]. Distant metastasis was not recognised in all of seven cases, although two patients had developed metastatic lesions in the axillary lymph nodes at the surgery. Four patients are now receiving hormonal therapy (letrozole or anastrozole) [Table/Fig-1]. Unfortunately, remaining three patients refused additional drug therapy. All of the patients remained healthy with no symptoms or evidence of recurrence or metastases of the breast carcinoma.

DISCUSSION

The SPC is an uncommon malignancy of elderly females and is characterised by a solid growth pattern with delicate fibrovascular cores. SPCs frequently exert NED and are biologically indolent [2]. Up to date, several large-scale overview analyses for the clinicopathologic characteristics of SPCs have been done [6,7, 11,12]. Tan BY et al., examined a total of 250 cases of in situ and invasive carcinoma with immunohistochemistry and identified 108 (43.2%) cases of SPC (in situ and/or invasive) [12]. Nassar H et al., elucidated clinicopathologic characteristics of 58 SPCs together with long-term clinical outcome (mean follow-up, 9.4 years) [6]. Guo S et al., studied the clinicopathological features and outcomes of 11 cases of SPC [11]. They also performed a retrospective analysis of 253 cases of SPCs reported in the literature. In these studies, SPC cases were finely divided into multiple groups such as: 1) SPC alone; 2) SPC with extravasated mucin; and 3) SPC with invasive components consisting of neuroendocrine-like, colloid, ductal not otherwise specified, lobular, tubular or mixed [6]. Meanwhile, Otsuki Y et al., evaluated the clinicopathological and biological features of 20 cases of SPC [7]. In their study, invasive type of SPC was divided into two types of mucinous carcinoma and neuroendocrine carcinoma. All of these studies provide quite valuable information for

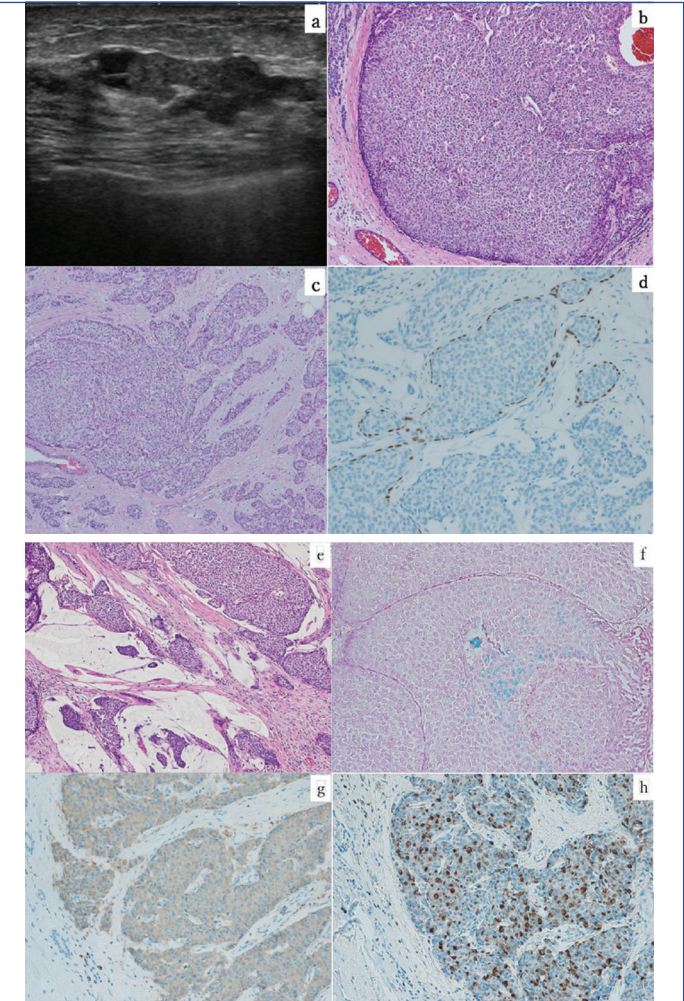
Patients	Age (years)	Site of tumour	Size of tumour (mm)	Initial symptoms	Treatment	Axillary lymph node metastasis (at the operation)	Time after the operation (years)	Prognosis
1	79	Right lower outer Q	30×28×11	Breast pain	Total mastectomy	–	7	Recurrence (–); Metastasis (–); On going of hormonal therapy (letrozole)
2	71	Left upper inner Q	10×9×9	Bleeding from the nipple	Total mastectomy	–	6	Recurrence (–); Metastasis (–)
3	73	Left central portion	43×28×22	Nipple mass	Total mastectomy	–	5	Recurrence (–); Metastasis (–); On going of hormonal therapy (letrozole)
4	58	Left upper inner Q	25×16×17	Breast pain	Total mastectomy	+	4	Recurrence (–); Distant metastasis (–)
5	85	Left upper inner Q	36×19×9	Breast mass	Partial mastectomy	–	2	Recurrence (–); Metastasis (–)

6	74	Left lower outer Q	19×14×6	Breast mass	Total mastectomy	–	2	Recurrence (–); Metastasis (–); On going of hormonal therapy (anastrozole)
7	77	Right lower inner Q	26×18×9	Nipple mass	Total mastectomy	+	1	Recurrence (–); Distant metastasis (–); On going of hormonal therapy (letrozole)

[Table/Fig-1]: Clinical features.
Q: Quadrant

Patients	Type of tumour	Nuclear grade	Ki-67 index (%)	Loss of myoepithelial cell layer at periphery of the nodule	Type of mucin accumulation	Neuroendocrine differentiation	Hormone receptor status
1	In situ	Low	5	–	Extracellular production	SYN+ CgA+	ER >90%, PR >90%, HER2: 0
2	In situ	Low	6	–	Extracellular production	SYN+ CgA–	ER >90%, PR >80%, HER2: 2+
3	Invasive	Intermediate	20	+	Mucinous carcinoma	SYN+ CgA+	ER >90%, PR >90%, HER2: 1+
4	Invasive	Intermediate	10	+	Mucinous carcinoma	SYN+ CgA–	ER >70%, PR 0%, HER2: 3+
5	In situ	Low	7	–	Extracellular production	SYN+ CgA–	ER >90%, PR 0%, HER2: 1+
6	Invasive	Low	5	+	Extracellular production	SYN+ CgA+	ER >90%, PR >90%, HER2: 0
7	In situ	Low	20	–	Intracellular production	SYN+ CgA–	ER >90%, PR >80%, HER2:1+

[Table/Fig-2]: Pathological features.
SYN: Synaptophysin; CgA: Chromogranin A; ER: Oestrogen; PR: Progesterone



[Table/Fig-3]: a) Ultrasonography shows a nodular lesion with horizontal extension within a dilated duct; b) Expansile nodule with a solid growth pattern has inconspicuous, delicate fibrovascular cores (H&E; 20x); c) Invasive SPC with a geographical jigsaw pattern within desmoplastic stroma (H&E; 20x); d) SPC with invasion. Some part is covered with a myoepithelial cell layer. Other parts are lacking the myoepithelial cell layer (p63 immunostaining; 40x); e) Rounded solid nodules in association with large clusters of tumour cells with pools of extracellular mucin (H&E; 20x); f) Intracellular mucin production recognised by Alcian blue staining; 40x; g) SPC with Neuroendocrine Differentiation (NED) (synaptophysin immunostaining; 40x); h) SPC with Neuroendocrine Differentiation (NED) (chromogranin A immunostaining; 40x).

understanding of SPC. However, the classification of SPCs in these studies is not always consistent with current WHO classification.

Present study used SPC cases which were considered positive for both neuroendocrine and mucinous differentiation since the dealing of mucinous differentiation in SPC has been obscure [5,8]. In this study, the mean age of the presentation was 74-year-old. This accords with the previous reports [5]. In this study, initial symptoms of two cases were nipple mass or bleeding from the nipple. Furthermore, five cases occurred in the central or inner quadrant. Such evidences are consistent with the reports that SPC arises commonly in the central area of the breast [1,13]. Invasive SPCs are often multinodular and have ragged contours creating the geographical jigsaw pattern within a desmoplastic stroma [5]. Loss of myoepithelial cell layer highlighted by the immunohistochemical loss of p63 is important to distinguish invasive SPC from in situ SPC. Nevertheless, it has been recommended by some authors that in cases with focal or complete absence of myoepithelial cells around the SPC, the tumour should be rendered as indeterminate for invasion [14].

The other helpful immunohistochemical feature for the definite diagnosis of SPC is the NED. In this study, four of seven cases displayed negative expression of chromogranin A in spite of that all cases exerted positive response of synaptophysin. Previous immunohistochemical analyses of SPC reported that synaptophysin was more expressed than chromogranin A [15]. Therefore, present evidence showed that synaptophysin is the best marker to prove NED in SPC. Even though NED in other types of breast carcinomas has been regarded as a poor prognostic marker, the same is not true for SPC. The NED demonstrable in SPC might therefore be considered more of diagnostic rather than prognostic marker [16]. Mucin production is one of representative features of SPC. With regard to types of mucin production, four cases showed extracellular production. Two cases displayed pattern of mucinous carcinoma with pools of extracellular mucin. Only one case exhibited type of intracellular production. For this case, recognition of intracellular mucin production was obvious under Alcian blue staining. Such staining will be useful for study of mucinous differentiation as well as detection of the tumour cells with mucin production in SPC.

Meanwhile, NED is recognised in some of IBC-NST and expression of NED is also present in hypercellular mucinous carcinoma which has similar gene expression of neuroendocrine carcinoma [17]. Furthermore, invasive component of SPC may also be of a more conventional type, such as IBC-NST [6]. These evidences suggest that SPC can be a precursor lesion of mucinous carcinoma, neuroendocrine carcinoma and IBC-NST. Recently, our group reported a unique case of hypercellular cystic mucinous carcinoma expressing NED of the breast with a growth pattern of encapsulated papillary carcinoma [10].

In this study, no case showed recurrence or metastasis. Patients of two cases who already had axillary lymph node metastasis did not develop distant metastasis. It is known that SPC has a good prognosis, particularly in case of non invasive type. In a recent review, spread to axillary lymph nodes was detected only in the cases with invasive SPC. Distant metastasis was observed also in the cases with invasive SPC [12]. Nonetheless, Maluf HM and Koerner FC reported a case of SPC in which lung metastasis occurred without axillary lymph node involvement [1]. However, in that case, an invasive mixed carcinoma was present. It has been described that invasive tumours associated with SPC are morphologically similar to the SPC. Thus, it is difficult to ascertain if the metastasis originated from the SPC or its invasive component [8,13]. Nassar H et al., described one SPC case in which distant metastasis developed 10 years after the diagnosis [6]. Such finding suggests that SPC has a metastatic potential, although this tumour type has certainly a favourable outcome.

Meanwhile, no clear data comparing the prognosis of SPC with other types of breast cancers have been achieved [7]. In this study, all of the present patients had >70% positive nuclei with expression of ER, and patients of five of seven cases showed >80% positive nuclei of PR. ER and PR status are well-known prognostic factors [18]. Accordingly, hormonal therapy with letrozole or anastrozole may improve prognosis, although the role of postoperative endocrine therapy in SPC (in situ and invasive) remains controversial [19]. To discuss precise prognosis of the patients with SPC, accumulation of further cases for long-term follow-up study is necessary.

CONCLUSION(S)

Clinicopathological features of seven cases of SPC (in situ and invasive) considerably resembled those of IBC-NST in addition to neuroendocrine carcinoma and mucinous carcinoma. It is reasonable to regard SPC as a precursor lesion or in situ lesion for IBC-NST, neuroendocrine carcinoma and mucinous carcinoma. No recurrence or distant metastasis was found; however, two

cases presented with axillary lymph node metastasis at the time of surgery.

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