Original Paper

Pathobiology

Pathobiology 2019;86:83–91
DOI: 10.1159/000490416

Received: April 9, 2018
Accepted after revision: May 28, 2018
Published online: October 11, 2018

Breast Tumours Resembling the Tall Cell Variant of Thyroid Papillary Carcinoma: Are They Part of the Papillary Carcinoma Spectrum or a Distinct Entity?

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Keywords
Papillary carcinoma · Tall cell variant · Breast · Mucinous carcinoma

Abstract
Background: Papillary tumours of the breast are diagnostically challenging lesions and represent a wide spectrum of diseases from papilloma to invasive papillary carcinoma. A rare subtype of breast papillary tumour resembling the tall cell variant of thyroid papillary carcinoma (BTRTPC) has been described. The nomenclature of this entity, its relationship to other papillary tumours, and its nature, whether in situ or invasive, remain unclear. ***Methods:*** Seventy-five papillary carcinomas (PCs) of the breast previously diagnosed in routine practice were reviewed and the presence of features ($n = 10$) characteristic of BTRTPC were assessed to determine whether BTRTPC comprises a distinct entity or is part of the spectrum of the previously defined PC variants. ***Results:*** Nuclear overlapping and eosinophilic granular cytoplasm were seen in 81 and 75% of the cases, whereas nuclear grooves, nuclear clearing, and tall cells were noticed in 51, 42, and 38% of the cases, respectively; 27% of the cases showed macro- and micro-follicular architecture filled with colloid-like material. Five cases (7%) lacked oestrogen receptor (ER) expression. Co-existing invasive carcinoma was seen in 25 cases (33%). Two cases displayed several features characteristic of BTRTPC, and both were ER-negative. ***Conclusion:*** Features characteristic of BTRTPC overlap with other PCs of the breast. Molecular and immunohistochemical biomarkers are needed to provide objective diagnostic criteria for the characterisation of such lesions in routine practice.

Introduction

Papillary lesions of the breast remain a challenging diagnostic entity and require a pragmatic approach for accurate diagnosis [1–6]. The spectrum of papillary lesions includes papilloma with or without atypia, intraductal papillary carcinoma (papillary DCIS), encapsulated (encysted/intracystic) papillary carcinoma (EPC), and solid papillary carcinoma (SPC). Also included within

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the papillary lesion spectrum are: (1) invasive SPC, defined as SPC but where the malignant cells are arranged in ill-defined solid nodules with a geographic jigsaw pattern, irregular outlines, and infiltrating the breast stroma [7], and (2) invasive papillary carcinoma (IPC), defined as mammary carcinoma in which tumour cells are arranged in papillary configuration with fibrovascular cores, an irregular outline, and lacking myoepithelial cells, with obvious infiltration into the surrounding breast stroma [2, 8, 9]. Although the diagnosis of papilloma and IPC is typically straightforward, the diagnosis and sub-classification of papillary DCIS, EPC, and SPC are often challenging. Morphological and immunophenotypic overlap exists between these entities. Papillary DCIS shows multiple variably dilated duct profiles, typically surrounded by a peripheral myoepithelial cell layer, and frequently associated with other histological subtypes of DCIS. EPC and SPC typically present as a solitary expansile mass, lacking myoepithelial cells in most cases. Although SPC is characterized by a solid growth pattern with frequent neuroendocrine and intracellular mucinous differentiation, nuclear palisading around the fibrovascular cores, and focal spindling of the cells, features that overlap with EPC exist. Challenges arise, not only in distinguishing between SPC and EPC but also between the in situ and invasive forms of EPC and SPC [7, 10]. Identification of the intracystic nature and presence of a peripheral fibrous capsule in EPC; and the solid growth pattern, intracellular mucinous differentiation, neuroendocrine differentiation, peripheral nuclear palisading, and spindling of cells in SPC may help to distinguish these 2 entities from one another [3]. Diagnostic challenges are further complicated by the fact that papillary breast lesions may show a wide range of metaplastic changes, and that other rare lesions in the breast may also show papillary architecture, including clear cell carcinoma [11], secretory carcinoma, and metastatic carcinomas with papillary architecture.

Rare variants of PC of the breast have been described in the literature, and the identification of these rare tumours as distinct entities is expected to make the diagnosis of PCs more challenging, as well as reduce their diagnostic concordance in routine practice [1]. There is a PC showing histologic features similar to those of the tall cell variant of thyroid PC, termed "breast papillary tumour resembling the tall cell variant of thyroid papillary carcinoma" (BTRTPC) [12, 13]. However, reflecting the uncertainty as to the nature and existence of this tumour as a distinct entity, several of its features are also seen in otherwise conventional PC variants [14], and variable terminology has been used to describe it [12–16]. Furthermore, despite being described as an oestrogen receptor (ER)-negative entity [16], a review of the literature reveals the existence of cases described as being ER-positive [13, 15, 17, 18]. Finally, specific mutations involving the *IDH2* gene have been reported in this entity [15, 19], although it is not clear whether this gene mutation is a prerequisite for its diagnosis and is restricted to BTRTPC. Foschini et al. [16] described these tumours as being invasive. EPC and SPC are currently managed as in situ diseases (TNM stage pTis) [7, 10]. Questions therefore arise: If BTRTPC is a distinct entity, should its management be similar to that of SPC and EPC (pTis), or is a different approach required? What criteria should be used for its diagnosis regarding the constellation of features and the cut-off values for each feature?

In this study, we examined 75 cases of PC of conventional variants previously diagnosed in routine practice to evaluate the presence of cytomorphological features resembling thyroid PC, alongside a critical review of the existing literature.

Methods

Seventy-five surgically excised PCs of the breast were identified from the National Health Service (NHS) database system at the Nottingham City Hospital. All available clinicopathological and immunohistochemical data was collected. The cohort included 49 cases (65%) of EPC, 16 (22%) of SPC, and 10 (13%) of papillary DCIS. The majority were of a low-to-intermediate nuclear grade (88%). An invasive carcinoma component was observed in 25 cases (33%): 15 invasive no-special-type (NST), 4 IPC, 4 diagnosed as invasive SPC, and the remaining 2 showed unusual features within both in situ and invasive components (described in detail below). The grade of invasive component was concordant with the adjacent PC (all were grade 1 and 2 tumours, except for two cases which were grade 3).

Diagnostic slides were retrieved and reviewed by 2 pathologists (M.S.T. and F.M.) for cytomorphological features resembling thyroid PC, including: (1) the presence of follicles filled with colloid-like material, (2) eosinophilic cytoplasm, (3) reversed cellular polarity (nuclei directed towards the luminal surface away from the basement membrane), (4) the presence of tall cells (i.e., cell height is at least 3 times cell width), (5) cellular stratification, (6) nuclear overlapping, (7) nuclear membrane grooves, (8) nuclear clearing, (9) nuclear pseudoinclusions, and (10) psammoma-like calcifications. The constellation of these features for each case was assessed and agreed on by both pathologists using the criteria previously described by Hameed et al. [14]: absent, present in <5% of examined high-power fields (HPF) of the lesion, present in 5–25% of examined HPF of the lesion, or present in >25% of examined HPF of the lesion. Discrepancies were resolved by agreement by the 2 pathologists using a double-headed microscope. Finally, the features were recorded, regardless of their extent. Data on ER status

was available for 64 cases (86%), 59 of which (79%) were ER-positive and 5 (7%) ER-negative. Follow-up data was available for 60 patients with a median follow-up period of 69 months (range 6–254 months). During this period, 6 patients developed local recurrence: 4 as invasive NST carcinoma and 2 as EPC.

Results

Seventy-five PCs were reviewed. Out of the features reminiscent of thyroid PC, nuclear overlapping and eosinophilic cytoplasm were the predominant cytomorphological features observed in 81 and 75% of cases, respectively. Nuclear stratification, reversed nuclear polarity, nuclear grooves, nuclear clearing, and tall cells were observed in 60, 59, 51, 42, and 38% of cases, respectively, and 27% of cases showed micro- or macro-follicles filled with eosinophilic colloid-like material. Calcification was observed in 18% of cases. Intra-nuclear pseudoinclusions were observed in only 1 case.

Sixteen cases (21%) showed 5 of the 10 assessed features whereas 6 and 3 features were observed in 15% of the cases each. Seven features were observed in 9% of cases, while 3 (4%) and 2 (3%) cases harbored 9 and 8 features, respectively. Only 2 cases did not show any feature described in BTRTPC. None of the reviewed cases showed a constellation of all 10 features. Table 1 summarizes the pathological features present in the reviewed cohort, as well as the percentage of cases displaying specific cytomorphological features. Figure 1 shows representative examples of the cytomorphologic features observed.

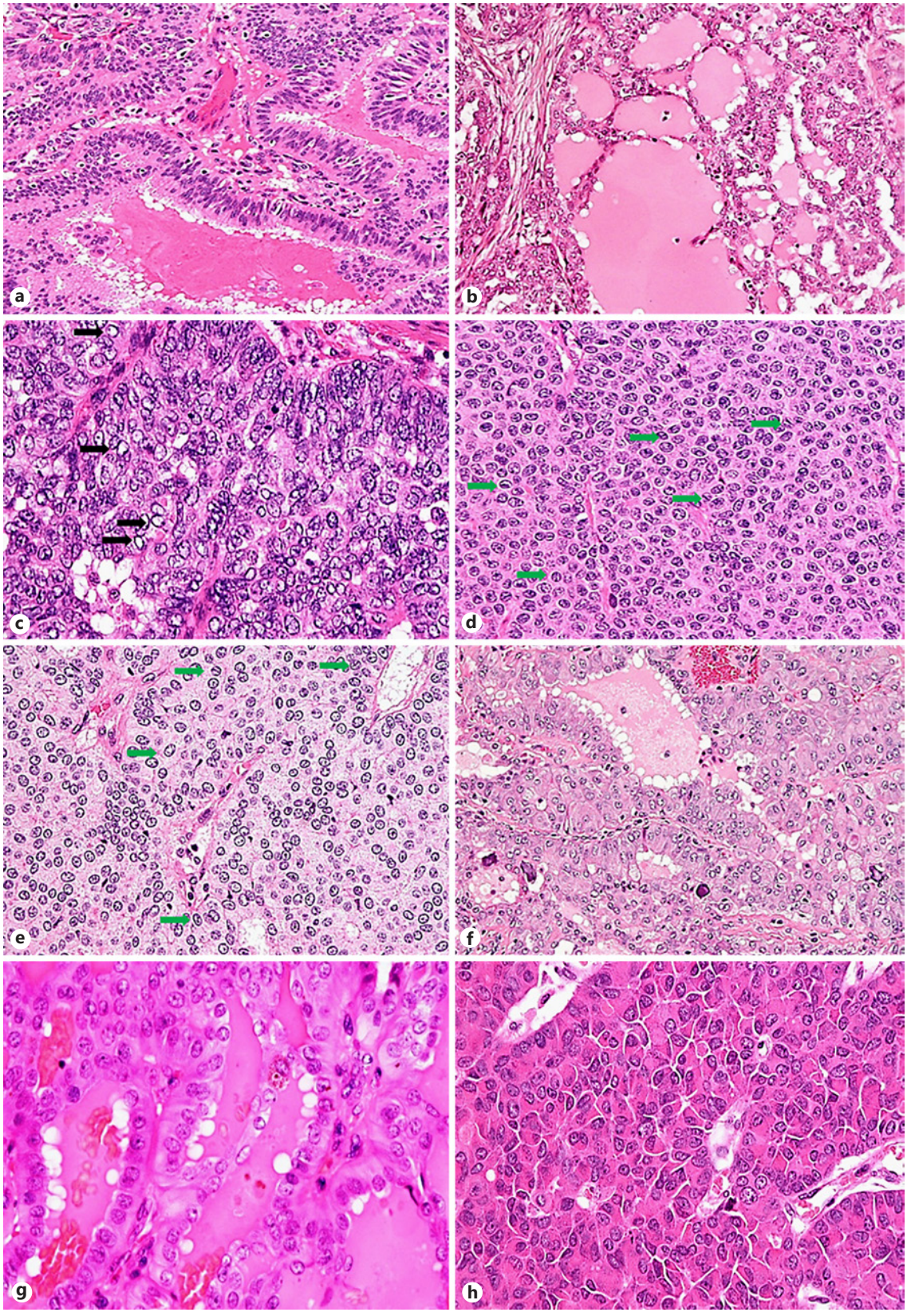
Two of the 5 ER-negative cases showed 9 features and the other 3 showed 5 features. None of the ER-negative cases showed a high nuclear grade. Seventeen ER-positive cases (29%) showed 6–9 BTRTPC features. Using the diagnostic criteria previously described for BTRTPC [12–17], the 2 ER-negative cases with 9 features, also showing infiltrative margins and a lack of peripheral myoepithelial cells, should be reclassified into BTRTPC instead of the original diagnosis of EPC. Two of the recurrent cases had 7 and 9 features, respectively, and the remaining 4 had ≤4 features.

Data on management was available for 53 cases. Nineteen were associated with invasive carcinoma NST, 12 of which were treated with breast-conserving surgery, and 2 of which had positive surgical margins and underwent complete mastectomy. Only 1 case showed metastasis in 2 ipsilateral axillary lymph nodes (LNs) and was treated with chemotherapy. Hormonal treatment was offered to 16 of these 19 patients and radiotherapy to 10 of them.

Table 1. Pathological features including the assessed cytomorphological features commonly seen in thyroid papillary carcinoma (PC) of the reviewed 75 cases

Features	Cases, *n* (%)
Type of tumour	
Encapsulated papillary carcinoma (EPC)	49 (65)
Solid papillary carcinoma (SPC)	14 (19)
Intraductal papillary carcinoma (papillary DCIS)	10 (13)
Invasive papillary carcinoma (IPC)	2 (3)
Type of co-existent invasive disease	
None	50 (67)
No otherwise-specified type (NST)	15 (20)
IPC	4 (5)
Invasive SPC	4 (5)
Invasive mucinous carcinoma	2 (3)
PC grade	
Low/intermediate	66 (88)
High	9 (12)
Oestrogen receptor (ER) status	
Positive	59 (79)
Negative	5 (6)
Unknown	11 (15)
Cytomorphological features of thyroid PC	
Follicles filled with colloid like materials	20 (27)
Nuclear overlapping	59 (81)
Nuclear stratifications	44 (60)
Nuclear grooves	37 (51)
Nuclear clearing	31 (42)
Nuclear pseudoinclusions	1 (1)
Eosinophilic granular cytoplasm	55 (75)
Reversed nuclear polarity	43 (59)
Tall cell morphology	28 (38)
Calcifications	13 (18)
Constellation of features	
None (0)	2 (3)
1	4 (5)
2	10 (13)
3	11 (15)
4	9 (12)
5	16 (21)
6	11 (15)
7	7 (9)
8	2 (3)
9	3 (4)
All (10)	0 (0)

Twenty-five of the remaining 34 cases (not associated with invasion) were treated with breast-conserving surgery; 4 had positive surgical margins and underwent re-excision. No LN metastasis was observed in this group. Post-operative radiotherapy was offered to 7 patients.



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Neither chemotherapy nor hormonal treatment was prescribed.

Interestingly, 2 cases were associated with invasive mucinous carcinoma, featuring a unique pattern of invasion with malignant papillary fronds floating in pools of mucin and sharing the same cytological features as the adjacent PC (Fig. 2, 3). These cases showed 6 features of BTRTPC, namely, tall columnar cells with eosinophilic granular cytoplasm, elongated nuclei with mild pleomorphism, occasional longitudinal grooves, and clearing. Areas of cellular stratification and reversed cellular polarity were also noticed. The conventional pattern of mucinous carcinoma, which usually shows solid, acinar, trabecular, cribriform or detached small clusters of SPC, or the "inside out" pattern of invasive micropapillary carcinoma within the mucinous material, was not observed. Using immunohistochemistry, tumour cells were positive for ER and cytokeratin 19. The neuroendocrine markers chromogranin A and synaptophysin were negative. TTF-1 staining was also negative which excluded the possibility of metastatic thyroid PC.

Discussion

PCs of the breast show a wide range of metaplastic changes, and the morphologic and immunohistochemical overlap between multiple variants of this entity makes their diagnosis and management a challenging task. A rare subtype of PC resembling the tall cell variant of thy-

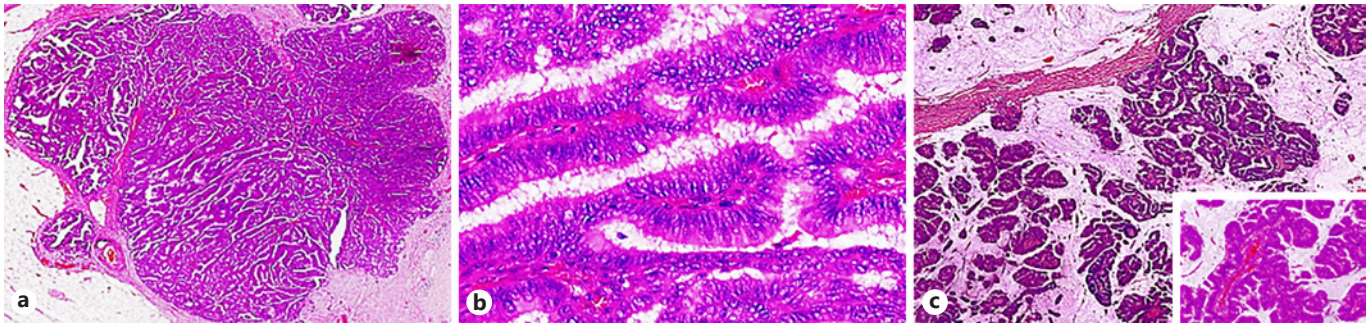

Fig. 2. Case 1. **a**, **b** Papillary carcinoma with tall cell features and nuclear overlapping, stratification, and occasional clearing. ×4; ×40. **c** Invasive mucinous carcinoma with papillary fronds floating on extracellular mucin and lined by tall eosinophilic columnar cells. ×10. **Inset** ×40.

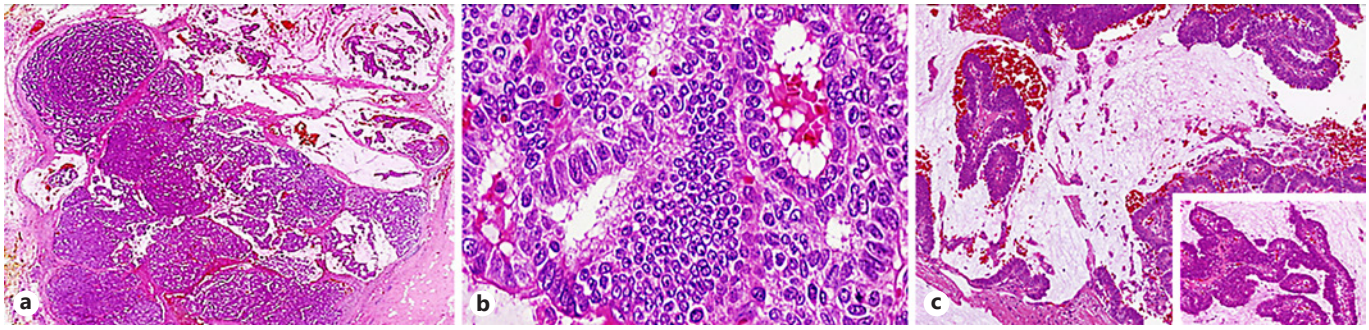

Fig. 3. Case 2. **a**, **b** Papillary carcinoma with occasional tall cells showing numerous nuclear grooves, nuclear overlapping, stratification, and occasional clearing. ×4; ×40. **c** Invasive mucinous carcinoma with papillary fronds floating on extracellular mucin and lined by tall eosinophilic columnar cells. ×10. **Inset** ×40.

Fig. 1. Papillary carcinoma (PC) of the breast with cytomorphological features resembling thyroid PC: follicles filled with colloid-like materials (**a**, **b**, **g**), nuclear stratification (**a**), nuclear overlapping (**a**, **c**–**f**), nuclear clearing (**c**, black arrows), nuclear grooves (**d**, **e**, green arrows), psammoma-like calcifications (**f**), reversed nuclear polarity (**g**), and cells with esinophilic granular (oncocytic) cytoplasm (**g**, **h**).

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Table 2. Description of previously reported cases of papillary breast tumour resembling the tall cell variant of thyroid carcinoma

First author [ref.]	Case No.	Age, years	Tumour size, mm	Morphology				Molecular subtype			Mitochondria	LN involvement or DM	Thyroid markers	*IDH2* mutation	Myoepithelial markers			Follow-up duration
				description	reversed polarity	calcification	pseudoinclusion	ER	PR	HER					p63	SMM	calponin	
Eusebi [12]	1	58	1.2	Papillae and follicles lined by columnar cells with eosinophilic cytoplasm, round clear nuclei and frequent nuclear grooves	NS	Yes	Yes	–ve	–ve	ND	+ve	NS	–ve	ND	ND	ND	ND	26 months CF
	2	70	1.3		NS	Yes	Yes	–ve	–ve	ND	+ve	NS	–ve	ND	ND	ND	ND	54 months CF
	3	57	1.6		NS	Yes	Yes	–ve	–ve	ND	+ve	NS	–ve	ND	ND	ND	ND	28 months CF
	4	74	2		NS	Yes	Yes	–ve	–ve	ND	+ve	NS	–ve	ND	ND	ND	ND	108 months CF
	5	56	0.8		NS	Yes	Yes	ND	ND	ND	NA	NS	ND	ND	ND	ND	ND	NS
Tosi [13]	1	80	2.5	Solid nests and cystic spaces associated with papillae and follicles filled with eosinophilic materials. Cells have nuclear grooves and clearing	NS	Yes	yes	–ve	–ve	ND	+ve	+ve 1 LN	–ve	ND	+ve	ND	ND	120 months CF
	2	45	6		NS	Yes	Yes	–ve	–ve	–ve	+ve	No	–ve	ND	–ve	ND	ND	5 months CF
	3	61	2		NS	Yes	Yes	+ve	+ve	ND	–ve	No	–ve	ND	ND	ND	ND	8 months CF
	4	47	2.3		NS	No	Yes	+ve	+ve	ND	+ve	No	–ve	ND	+ve	ND	ND	10 months CF
Cameselle-Teijeiro [17]	1	64	4.1	Solid, papillae, follicles and cribriform patterns lined with columnar-to-cuboidal cells with eosinophilic cytoplasm and nuclear grooves	NS	No	Yes	+ve	+ve	ND	+ve	LN and bone	–ve	ND	ND	ND	ND	32 months alive with bone metastasis
Chang [27]	1	66	1.1	Tightly packed papillae and follicles with eosinophilic materials lined by cuboidal-to-columnar cells with eosinophilic cytoplasm and nuclear clearing	Yes	No	Yes	+ve	–ve	–ve	ND	No	–ve	ND	–ve	ND	-ve	12 months CF
Masood [18]	1	57	3.7	Papillary lesion with follicles lined by cuboidal-to-columnar cells with eosinophilic cytoplasm and nuclear clearing	NS	NS	NS	+ve	+ve	ND	ND	No	–ve	ND	ND	ND	ND	NS
Colella [21]	1	79	3	Cystic spaces with eosinophil materials and some intra-cystic papillary proliferation. Cells are columnar with eosinophilic cytoplasm, nuclear clearing, and grooves	No	Yes	Yes	-ve	–ve	–ve	ND	No	–ve	ND	focal	ND	ND	18 months CF
Chiang [15]	1	68	0.9	Solid circumscribed nodules of columnar epithelial cells mimicking solid papillary architecture with eosinophilic cytoplasm. Nuclei are showing clearing and grooves	Yes	NS	NS	–ve	–ve	ND	ND	NS	–ve	No	–ve	–ve	-ve	NS
	2	62	0.8					–ve	–ve	–ve	ND	No	–ve	Yes	–ve	–ve	-ve	77 months CF
	3	63	1.2					+ve	+ve	–ND	ND	NS	ND	Yes	–ve	–ve	-ve	NS
	4	79	NS					–ve	–ve	–ND	ND	NS	–ve	Yes	–ve	–ve	-ve	NS
	5	64	1.8					–ve	–ve	–ve	ND	No	–ve	Yes	–ve	–ve	-ve	31 months CF
	6	51	0.8					+ve	+ve	–ve	ND	No	–ve	No	–ve	–ve	-ve	30 months CF
	7	64	1.4					+ve	–ve	–ve	ND	No	–ve	Yes	–ve	–ve	-ve	29 months CF
	8	58	0.6					–ve	–ve	–ve	ND	NS	–ve	Yes	–ve	–ve	-ve	NS
	9	66	0.9					–ve	–ve	–ve	ND	No	–ve	Yes	–ve	–ve	-ve	20 months CF
	10	65	1.5					+ve	–ve	–ve	ND	No	–ve	Yes	–ve	–ve	ND	37 months CF
	11	70	1.3					+ve	–ve	–ve	ND	No	–ve	No	–ve	–ve	-ve	12 months CF
	12	65	1.2					–ve	–ve	–ve	ND	No	–ve	Yes	–ve	ND	-ve	NS
	13	65	0.9					–ve	–ve	–ve	–ve	NS	–ve	Yes	–ve	–ve	ND	NS
Foschini [16]	1	58	1.2	Multinodular growth with pushing margins and focal infiltrative area. Papillae closely packed, giving solid pattern and follicles with eosinophilic materials and occasional cystic areas. Cells are columnar-to-cuboidal with eosinophilic cytoplasm and nuclear grooves and clearing	Most of the cases show these features			–ve	–ve	–ve	+ve	No	–ve	ND	–ve	–ve	ND	Recurrence after 60 months
	2	80	2.5					–ve	–ve	–ve	+ve	+ve 1 LN	–ve	ND	–ve	–ve	ND	120 months CF
	3	61	2					Few	–ve	–ve	–ve	No	–ve	ND	–ve	–ve	ND	132 months CF
	4	62	1					–ve	–ve	–ve	+ve	NS	–ve	ND	–ve	ND	ND	96 months CF
	5	51	2					–ve	–ve	–ve	+ve	NS	–ve	ND	–ve	ND	ND	NS
	6	58	0.8					Few	Few	–ve	+ve	No	–ve	ND	–ve	ND	ND	24 months CF
	7	61	0.6					–ve	–ve	–ve	+ve	NS	–ve	ND	ND	–ve	ND	84 months CF
	8	50	0.8					–ve	–ve	–ve	+ve	NS	–ve	ND	–ve	–ve	ND	76 months CF
	9	59	2.5					–ve	–ve	–ve	+ve	NS	–ve	ND	–ve	ND	ND	24 months CF
	10	48	2.2					–ve	–ve	–ve	ND	NS	–ve	ND	–ve	–ve	ND	NS
	11	85	1.5					–ve	–ve	–ve	+ve	NS	–ve	ND	–ve	ND	ND	36 months CF
	12	64	2					–ve	–ve	–ve	+ve	No	–ve	ND	–ve	–ve	ND	24 months CF
	13	77	1.2					Few	Few	–ve	–ve	NS	–ve	ND	–ve	–ve	ND	
Bhargava [20]	1	65	0.9	Papillae with bland-looking cells showing nuclear grooves.	Yes	NS	NS	–ve	–ve	ND	ND	No	ND	Yes	–ve	–ve	+ve	19 months CF
	2	77	1.7	Lobulated solid papillary pattern with crowded epithelial growth. Eosinophilic secretions seen. Bland cytology with grooves	Yes	NS	Yes	few	few	ND	ND	No	–ve	No	Focal	Focal	–ve	NS
	3	48	1.2	Solid papillary growth pattern with hyperplastic epithelium. Some glandular areas with eosinophilic secretions are seen. Nuclear grooves.	Yes	NS	NS	few	ND	ND	ND	NS	ND	Yes	–ve	–ve	ND	19 months CF

LN, lymph node; DM, distant metastases; ND, not done; NS, not stated; –ve, negative; +ve, positive; CF, clinically free.

roid PC has been reported in the literature [12, 13, 16–18, 20] (Table 2). These tumours are characterised by the presence of tall, columnar cells arranged in nests, papillae, and follicle-like structures, and are filled with eosinophilic colloid-like material. Nuclear grooves, nuclear overlap and stratification, nuclei with a ground-glass appearance, nuclear pseudoinclusions, and psammoma bodies are typically present, in addition to reverse polarity and a lack of hormone receptor expression [12, 13, 15–17].

The diagnosis of such tumours is based on a constellation of features. However, no definite guideline exists regarding the importance and contribution of specific features for making a final diagnosis or differentiating these lesions from other PCs. In addition, varying terminology is used to describe these tumours. They were originally designated "breast tumour resembling the tall cell variant of papillary thyroid carcinoma" [12, 13, 16, 17]. In a recent study of 13 cases, a different term was used "solid papillary breast carcinomas resembling the tall cell variant of papillary thyroid neoplasms" [16]; in line with Chiang et al. [15], the authors used the term "solid papillary carcinoma," which is a variant of papillary carcinoma with well-characterised histological features and is considered as in situ disease for management purposes [3].

To further highlight the lack of consensus on the terminology of this entity, a recent study used 2 terms: "solid papillary breast carcinomas resembling the tall cell variant of papillary thyroid neoplasms" and "solid papillary carcinomas with reverse polarity" [19]. Other authors [18] have proposed a new terminology "tall cell variant of papillary breast carcinoma," in an attempt to avoid confusion as well as unnecessary ancillary studies aimed at excluding the association of this entity with thyroid PC.

Hameed et al. [14] reported the cytoarchitectural features characteristic of this tumour in a proportion of papillary DCIS, EPC, and SPC cases. They reviewed 33 breast PCs and, similar to our findings, they reported nuclear overlapping in 73% of cases, nuclear grooves in 42%, nuclear stratification in 33%, nuclear clearing in 27%, and nuclear pseudoinclusions in 3%.

Although the cases of BTRTPC described in published series shared many morphological and immunohistochemical features, they were not identical. The reverse cellular polarity and psammoma body formation were not described in all cases. Some also appeared to be composed mainly of follicles rather than of papillae [21]. The majority had a triple-negative profile [15, 16]; some, however, were positive for ER. Of note, the only case previously described to have distant metastasis (to the bone) was positive for ER [17].

The variable terminology, overlapping histological features, and lack of consensus on the nature and management of these lesions complicate their histological diagnosis and further management in routine practice.

All previously described cases were distinct from thyroid PC, due to their negativity for thyroid markers or the absence of *RET/PTC* gene rearrangement. Generally, only a few breast tumours are known to show specific genetic alterations such as mucoepidermoid (*CRTC3-MAML2* fusion gene) [22], secretory (*ETV6-NTRK3* fusion gene) [23], adenoid cystic (*MYB-NFIB* fusion gene) [24], and lobular (*CDH1* gene mutation) carcinomas [25].

Recently, 3 studies [15, 19, 20] showed an association between BTRTPC and the isocitrate dehydrogenase 2 gene (*IDH2*) mutations. These mutation has been described in gliomas, acute myeloid leukemia, and cholangiocarcinoma [26], but their possible role in breast carcinogenesis has yet to be identified. In these 3 BTRTPC studies, 18 out of 22 cases showed mutations of *IDH2* (R172 hotspot somatic mutations), which appears promising in terms of providing diagnostic criteria for these tumours. In their recently published series, Foschini et al. [16] classified these lesions as BTRTPC, based entirely on their morphological features. Although this classification did not take the presence or absence of specific gene mutations into account, it would be interesting to speculate on the impact of *IDH2* mutations on the morphology and behaviour of these breast PCs, and whether these tumours can be further defined by the presence of specific gene mutations rather than the spectrum of morphological changes that they share with other PCs.

Although frank stromal invasion was identified in some of the reported cases, other cases showed a well-circumscribed growth pattern with preserved basal lamina around the papillae and follicles, and these were designated as invasive tumours based on the absence of surrounding myoepithelial cells [15, 16]. EPC and SPC typically lack the surrounding myoepithelial cells, and they have the ability to develop LN metastasis (despite this being a rare event [2]) and are currently managed as in situ disease [7, 10]. Reporting BTRTPC as IPC [15, 16, 18, 27] without sufficient evidence of metastatic behaviour can be confusing and may result in the overtreatment of these patients in routine practice.

The review of current cases highlights the fact that some characteristic features of thyroid PC can be seen in breast PCs which could otherwise be designated as EPC or SPC. This lends support to the argument that these cytoarchitectural changes can be identified in varying pro-

portions within a wide range of PCs, without amounting to any subtyping of these lesions. In addition, the unusual pattern of invasive mucinous carcinoma arising from the tumours described in detail, with retention of the well-developed papillary pattern, may reflect their unique behaviour. None of the previously described cases was reported to be associated with invasive "mucinous" carcinoma, which is frequently reported to arise on a background of SPC [28].

Although this study and a previous one [14], that both included 108 cases of PC, demonstrated a high degree of overlap in the cytomorphological features between BTRTPC and other established variants of breast PC, certain features appear to characterize this rare tumour and can be used in routine practice to reduce the subjectivity of its diagnosis. BTRTPCs that show an *IDH2* mutation [15, 19, 20] have very distinctive features that allow their identification in routine practice. They consist of solid, circumscribed, and/or infiltrative nodules of columnar epithelial cells, some exhibiting a geographic, jigsaw-like growth pattern. Fibrovascular cores are present, but myoepithelial cells are typically absent and lack the peripheral thick fibrotic capsule characteristic of EPC. Cytonuclear features characteristic of BTRTPC are typically diffuse but in other variants of PC they are mainly focal, as observed in this series. Neuroendocrine features and mucinous differentiation are not features of BTRTPC. Importantly, despite their ER negativity, these tumours appear bland-looking with histological grade 1 features, and typically express high-molecular-weight cytokeratin (CK5/6) in a diffuse pattern. Despite the high frequency of associated invasive disease, together with the ER negativity, the infiltrative growth pattern, and the lack of myoepithelial cells, which may support the designation of BTRTPCs as invasive tumours, further studies are warranted to provide sufficient evidence of the behaviour of these tumours so as to guide their management.

Conclusion

The morphological, immunohistochemical, and genetic profiles of BTRTPC are complex. More robust diagnostic criteria and investigations to determine whether this is a distinct morphological and clinical entity or just part of the spectrum of EPC and SPC with a prominence of specific features, whether it is driven by specific mutations of *IDH2*, and whether it should be managed as in situ or invasive disease are warranted. In view of the current difficulties in diagnosing, classifying, and managing PC of the breast, the introduction of new entities should be accompanied by sufficient evidence for their identification and classification in routine practice.

Disclosure Statement

There are no conflicts of interest.

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