



# The Clinicopathologic Features of 22 Cases With Primary Invasive Papillary Carcinoma of the Breast Identified in 1153 Cases With Invasive Breast Carcinoma: Single-Center Experience

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## ABSTRACT

**Objective:** Invasive papillary carcinoma (IPC) of the breast is an uncommon histologic subtype with limited data in the literature. The aim of this study was to increase the evidence base by presenting clinicopathological findings of cases diagnosed as IPC.

**Materials and Methods:** Hematoxylin and eosin sections and immunostaining of surgical excision specimens diagnosed as invasive breast carcinoma were re-evaluated, retrospectively.

**Results:** IPC was detected in 22 cases (1.9%), of which 7 (0.6%) had pure and 15 (1.3%) had mixed morphology. Histologic types accompanying IPC were: Invasive ductal carcinoma (IDC) (15/15); invasive micropapillary carcinoma (3/15); and pleomorphic lobular carcinoma (1/15). Patient ages ranged between 36 and 89 (median 56.5) and the tumor size from 8 to 70 mm (median 19 mm). The histologic grade was 3 in five cases, 2 in 13, and 1 in four cases. The nuclear grade was 3 in 10 cases and 2 in 12. The values of positivity for estrogen receptor, progesterone receptor, human epidermal growth factor receptor-2, and Ki-67 index indicated Luminal B phenotype in 16 (72.7%), triple-negative in 5 (22.7%), and Luminal A in 1 case (4.6%). Ductal carcinoma *in situ* was noted in 19 cases (86.4%).

**Conclusion:** IPC was mostly detected as an accompanying carcinoma to IDC at postmenopausal ages and was mostly Luminal B phenotype with intermediate-to-high grade features.

**Keywords:** Invasive papillary carcinoma; breast; histopathological findings; clinical features

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## Key Points

- Invasive papillary carcinoma (IPC) of the breast is a rare type of tumor with usually Luminal B molecular phenotype.
- IPC is frequently detected as an accompanying carcinoma to invasive ductal carcinoma.
- Before diagnosing as IPC of the breast, metastases from other sites must be excluded.
- Encapsulated and/or Solid PC of the breast with invasive foci should not call as IPC.
- Most patients present in the early stages of breast cancer at postmenopausal age.

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## Introduction

Papillary neoplasms of the breast comprise a wide spectrum of lesions from benign intraductal papilloma to invasive papillary carcinoma (IPC). This group of lesions were described in the last two editions of World Health Organization guidelines as intraductal papilloma, papillary ductal carcinoma in situ (DCIS), encapsulated papillary carcinoma, solid papillary carcinoma and IPC (1-4). Intraductal papilloma defines a benign breast lesion arising within a duct either in a central (solitary) or peripheral (multiple) location. This lesion, generally composed of broad papillary projections with fibrovascular cores, is covered by epithelial and myoepithelial cell layers. Some of the intraductal papillary lesions may include a mixed type of epithelial cell proliferation composed of luminal epithelial, myoepithelial, and immature cells, histologically estrogen receptor + (ER+) and CK5/6+ complementary patchy staining, and so these lesions are described as “intraductal papilloma with usual hyperplasia” (3, 5). Beyond this, some intraductal papillary lesions may demonstrate monotonous epithelial cell proliferation (ER+, CK5/6-). When the extent of this epithelial proliferation is <3 mm, they are called intraductal papilloma with atypical ductal hyperplasia (5). When this extent is  $\geq 3$  mm, they are then called intraductal papilloma with DCIS (5). Papillary DCIS, another type of lesion, defines a morphological subtype of DCIS composed of delicate branching fibrovascular cores lined with neoplastic ductal epithelium without myoepithelial cells in papillae. Since these lesions are a subtype of DCIS, the myoepithelial cell layer is retained in the periphery of the lesion (4).

Encapsulated papillary carcinoma is a carcinoma present within a cystic space surrounded by a fibrous capsule. The lesion is composed of fine fibrovascular stalks covered by a neoplastic epithelium of low or intermediate nuclear grade. Myoepithelial cells are usually not found along the papillae or periphery of the lesion. Encapsulated papillary carcinoma with high-grade nuclear features, however, should be graded, staged, and managed as an invasive breast carcinoma (6). Solid papillary carcinoma is characterized by a solid growth pattern with inconspicuous delicate fibrovascular cores. This tumor may show neuroendocrine differentiation, as well as intracellular or extracellular mucin production. Myoepithelial cells may be present or absent within the solid papillary proliferation or on the periphery of the nodules. Both encapsulated papillary carcinoma and solid papillary carcinomas may display clearly invasive foci of breast carcinoma. In this situation, it is important not to label these foci as IPC. These invasive foci generally exhibit a non-papillary morphology (7). Since some papillary lesions have been misidentified in the past, resulting in conflicting data in the literature (8, 9).

IPC is an invasive carcinoma with fibrovascular cores covered by neoplastic epithelial cells. IPC of the breast is an extremely rare type of breast tumor. Therefore, there is limited knowledge of the histopathologic and clinical features of this tumor. Before diagnosing a tumor as IPC of the breast, metastasis from other sites to the breast must be excluded (3, 10). The previous history of the patient and radiologic findings provide information for accurate differential diagnosis. Additionally, the presence of a DCIS component, as well as positive immunostaining for ER, PR, and GATA-3, and negative immunostaining for PAX8, TTF-1, and thyroglobulin are useful tools for supporting a breast origin. In this study, we aimed to determine the incidence and clinicopathological features of primary IPC of the breast.

## Materials and Methods

### Data Collection

We retrospectively reviewed the slides of cases with primary invasive breast carcinoma to define the invasive papillary morphology within these tumors. For this purpose, we obtained hematoxylin and eosin (H&E) sections of surgical excision specimens of cases diagnosed between 2010 to 2018 and then re-evaluated them microscopically. Clinical features of the patients were obtained from patient files and clinicians.

We used the definition of “pure IPC” for invasive carcinoma that consists of papillary structures in  $\geq 90\%$  of the tumor (11).

### Exclusion-Inclusion Criterion

After re-examining the slides, 23 cases with invasive papillary morphology were identified, either as pure IPC or as IPC as a component within a mixed-type breast carcinoma. One of these cases was excluded due to retraction artefact around the groups of tumor cells that mimic papillary appearance.

One case had a history of neoadjuvant therapy. Secondary changes due to therapy were not prominent in this case. Following neoadjuvant chemotherapy, the nuclear grade of the tumor changed from 2 to 3 in the excision specimen (Case #20). The ER, progesterone receptor (PR), human epidermal growth factor 2 (HER2) and Ki-67 status of this tumor were similar to that of previous core needle biopsy and thus the molecular subtype stayed the same.

Two out of 22 cases with IPC showed no DCIS in the adjacent areas. Both cases showed pure-type IPC morphology (one was 100% of the tumor, the other 90%). The clinical history and radiographic findings of these cases were checked and then immunohistochemical staining was performed, including GATA3 (for breast origin), PAX8 (for Mullerian origin), TTF-1 (for lung origin), and Thyroglobulin (for thyroid origin) to exclude possible metastatic origin. Both cases showed positivity for GATA3 and were negative for PAX8, TTF-1, and Thyroglobulin; thus, several possible metastatic origins were excluded.

Eventually, a total of 22 cases, 1 of which had a history of neoadjuvant therapy, were included in the study. This project was approved by the Ethical Committee (protocol number: 1888-28/06/2019).

## Results

### Statistical and Clinical Characteristics

Review of 1153 invasive breast carcinomas, diagnosed in our clinic from 2010 to 2018, identified only 22 cases that showed an invasive component as found in a papillary form (22/1153; 1.9%). The invasive papillary morphology composed 10% of the tumors in two cases, 10-50% of the tumor in 11 cases, 50-90% of the tumor in a further two cases, and  $\geq 90\%$  of the tumor in seven cases. Therefore, pure-type IPC was found in 7 of 22 cases (7/1153; 0.6%) and identified as a component within mixed type carcinomas in 15 out of 22 cases (15/1153; 1.3%). The other invasive histologic types accompanying IPC were: IDC (15/15; 100%), micropapillary carcinoma (3/15; 20%), and pleomorphic-type lobular carcinoma (1/15; 6.7%). One case (Case #9) had two invasive foci, of which one was mixed-type histology (IPC + IDC + invasive micropapillary carcinoma) and the other was IPC only.

One of the 22 cases was male (4.5%). The ages of the patients with IPC ranged from 36 to 89 years (median 56.5), from 36 to 89 years for mixed-type IPC (median 52) and from 47 to 79 years for pure-type IPC alone (median 61). The tumor size was 8 to 70 mm (median 19 mm). The presenting features of the patients were palpable mass (15 cases), radiologic abnormality by mammographic screening and magnetic resonance imaging (5 cases), and bloody nipple discharge (2 cases; 1 accompanying to a palpable mass). Four of these cases also had a history of familial breast cancer.

The tumor was located in the left breast in 16 cases (72.7%) and the right breast in six (27.3%). Tumor locations were upper outer quadrant (n = 12), lower outer quadrant (n = 4), upper inner quadrant (n = 4), and the retroareolar region (n = 2). Five of these cases had multiple foci.

The previous diagnoses of the core needle biopsy specimens (CNBS) in these cases were invasive ductal carcinoma (IDC) (n = 9), invasive breast carcinoma (n = 5), mixed-type invasive ductal and IPC (n = 2), invasive breast carcinoma with focal micropapillary growth pattern (n = 2), invasive breast carcinoma with extensive papillary growth pattern (n = 1), invasive breast carcinoma with apocrine differentiation (n = 1), and invasive adenocarcinoma consistent with breast primary (n = 1). The latter case showed prominent desmoplastic stroma in between irregular-shaped glandular structures, reminiscent of Mullerian-type serous carcinoma. However, the neoplastic glandular epithelium was positive for GATA3 and negative for PAX8, TTF1, and Thyroglobulin.

None of the cases in this study showed positivity for PAX8, TTF1, and Thyroglobulin. However, all cases were positive for GATA3, which supported breast origin. The CNBS of one case was interpreted as “a lesion consistent with papillary neoplasia” and offered surgical excision with a clear margin. This biopsy was composed of a monotonous cell proliferation of low-grade nuclei in fibrovascular stalks; however, this neoplastic fragment was 1 mm in size. The second CNBS performed in this case revealed invasive breast carcinoma (Case #1). As a result, all cases but one demonstrated a clearly invasive morphology in the first CNBS, and IPC morphology was described in 3 of these 22 (13.6%) cases.

Breast conserving surgery was performed in 13 cases (with sentinel lymph node dissection in eight and axillary dissection in five cases); simple mastectomy in three cases (with sentinel lymph node dissection), and modified radical mastectomy in six cases. The follow-up time of the patients ranged between 7 to 108 months, with one patient dying 7 months after diagnosis. Follow-up time (months) and clinic status, as well as other clinicopathologic features of the patients are summarized in Table 1.

### Histopathologic Characteristics

The distribution of histologic grade was as follows: Grade 3 in five cases, grade 2 in 13 cases, and grade 1 in four cases. Nuclear grade was 3 in 10 cases and 2 in 12 cases. Lymphovascular invasion was noted in nine cases (9/22, 40.9%), perineural invasion in two (2/22, 9.1%), and DCIS in 19 (19/22, 86.4%). The DCIS patterns were noted in decreasing order as cribriform (12/19), micropapillary (10/19), solid (8/19), papillary (7/19), and flat type (3/19). Comedonecrosis was seen in 17 of 19 cases (89.5%). Tumor-associated microcalcification (for both invasive and *in situ* component) was seen in 10 of 22 cases. Different appearances of tumor in IPC are displayed through Figure 1a,b to Figure 5a,b.

The T-stages of the cases were as follows: pT1 n = 13, pT2 n = 8, pT3 n = 0, and pT4 n = 1. Axillary lymph node status was as follows: pNx n = 1, pN0 n = 10, pN1 n = 7, pN2 n = 2, and pN3 n = 2. Whereas lymph node metastasis was determined in 2 out of 7 pure-type IPC (28.6%), it was identified in 10 out of 15 mixed-type carcinomas (66.6%).

The histopathological findings determined within the surrounding breast parenchyma were as follows: ductal hyperplasia with atypia (n = 1), ductal hyperplasia without atypia (n = 3), columnar cell lesions with atypia/flat atypia (n = 6), columnar cell lesions without atypia (n = 9), complex sclerosing lesions (sclerosing adenosis, radial scar and/or papilloma, n = 3), papilloma only (n = 2), fibrocystic changes (n = 15), apocrine metaplasia (n = 10), ductal ectasia (n = 11), fibroadenoma or fibroadenomatoid nodules (n = 4), pseudoangiomatous stromal hyperplasia (PASH; n = 2), capillary hemangioma (n = 1), pseudolactational changes (n = 1), and fat necrosis (n = 1). There were no prominent changes in the non-tumoral breast tissue in seven cases.

### Immunohistochemical Findings

Seventeen cases showed positive immunostaining for ER and PR (Luminal phenotype; 17/22, 77.3%). The ER/PR/HER2/Ki-67 status for each case can be viewed in Table 2. The HER2 expression was found to be negative by immunohistochemistry in 19 cases (score 0 or 1) and positive by immunohistochemistry and/or the silver *in situ* hybridization (SISH) method in three cases (3/22; 13.6%). Among 22 cases, 20 showed a Ki-67 proliferation index  $\geq 20\%$  and the remaining two cases were  $< 20\%$ . According to the values of ER, PR, HER2, and Ki-67, the distribution of cases in the molecular subgroups were: 16 cases (72.7%) Luminal B (ER/PR/HER2 positive or ER/PR+, HER2- but Ki67  $\geq 20\%$ ), five cases (22.7%) triple negative (ER/PR/HER2 negative), and one case (4.6%) Luminal A (ER/PR+, HER2- and Ki67  $< 20\%$ ). There was no case in the HER2 subgroup (ER/PR- and HER2+). Pure-type IPC cases showed Luminal B phenotype in five cases and triple-negativity in two cases. Histopathologic and immunohistochemical findings are summarized in Table 2.

### Cases With Exceptional Findings

A prominent lymphocytic inflammatory cell infiltration was noted within the tumor in one of the cases (Case #8). This case showed mixed-type histology of IPC + IDC + invasive micropapillary carcinoma and high-grade nuclear and histologic features with triple negative phenotype. Axillary lymph node metastasis was found in seven out of 14 lymph nodes. The patient died 17 months after diagnosis.

An apocrine cytonuclear feature was described in one case (Case #3). This case showed mixed-type histology (IPC + IDC) in all invasive foci (four tumor foci) and Luminal A molecular phenotype as well as positive immunostaining for Androgen and GCDFP-15. Axillary lymph node metastasis was identified in one out of 18 lymph nodes.

A pagetoid involvement of large ducts and nipple dermis was identified in one case (Case #16). This case had two invasive tumor foci, one of which was located in the retroareolar region. The tumor (both foci) showed a mixed-type histology (IPC + IDC) and Luminal B molecular phenotype. Axillary lymph node metastasis was identified in 3/8 lymph nodes. The axillary metastases were of non-papillary IDC morphology.

Table 1. Clinical characteristics of the patients

Case	Sex	Age	Clinical history	Location	Tumor size (mm)	Histologic type	Mixed component	Follow-up time (months)	Survey (dead or alive)	Local recurrence (LR)/Metastasis (month)
Case 1	F	62	Palpable mass	R-UIQ	20	IPC	-	108	Alive	-
Case 2	F	52	Palpable mass	L-Retroareolar	18-15 (two foci)	Mixed carcinoma	30% IPC + 70% IDC	92	Alive	-
Case 3	F	45	Palpable mass	L-UOQ	16-12-11-3 (multiple foci)	Mixed carcinoma	50% IPC + 50% IDC	67	Alive	-
Case 4	F	47	Palpable mass	L-UOQ	21	IPC	-	74	Alive	Lung and bone met (53 m)
Case 5	F	61	Palpable mass (Family history+)	L-LOQ	20	IPC	-	32	Dead	Lung, bone and infra-supradiaphragmatic LN met (21 m)
Case 6	F	64	Palpable mass (Family history+)	R-UOQ	22	Mixed carcinoma	10% IPC + 90% IDC	72	Alive	-
Case 7	F	42	Palpable mass	R-UOQ	22	Mixed carcinoma	30% IPC + 70% IDC	55	Alive	-
Case 8	F	53	Palpable mass	L-UOQ	30	Mixed carcinoma	45% IPC + 45% IDC + 10% IMPC	17	Dead	LR (+)/multiple LN met (+malign pleural effusion) (17 m)
Case 9	F	55	Bloody nipple discharge + palpable mass	L-UOQ and UIQ	14-6.5	1. Mixed carcinoma 2. IPC	1. 45% IPC + 45% IDC + 10% IMPC 2. IPC	49	Dead	Brain, bone and infra-supradiaphragmatic LN met (46 m)
Case 10	F	58	Palpable mass	L-UOQ	16	Mixed carcinoma	35% IPC + 30% IDC + 35% IMPC	55	Alive	-
Case 11	F	70	Palpable mass	L-UOQ	8	Mixed carcinoma	30% IPC + 70% IDC	63	Alive	-
Case 12	M	70	Palpable mass	L-Retroareolar	15	IPC	-	58	Alive	-
Case 13	F	89	Palpable mass, prolabed to skin (Family history+)	L-UOQ	70	Mixed carcinoma	40% IPC + 50% IDC + 10% IMPC	12	Dead	Bone and supradiaphragmatic LN met (7 m)
Case 14	F	36	Mammographic screening	R-UOQ	26	Mixed carcinoma	30% IPC + 70% IDC	42	Alive	-
Case 15	F	61	Mammographic screening (Family history+)	L-UIQ	14	IPC	-	48	Alive	-
Case 16	F	63	Radiologic examination (MRI)	L-UOQ and retroareolar	15-10	Mixed carcinoma	50% IPC + 50% IDC	41	Alive	-

Table 1. Continued

	Sex	Age	Clinical history	Location	Tumor size (mm)	Histologic type	Mixed component	Follow-up time (months)	Survey (dead or alive)	Local recurrence (LR)/Metastasis (month)
<b>Case 17</b>	F	79	Bloody nipple discharge	R-LOQ	25	IPC	-	7	Dead- IDC in the left breast (31 m) *	-
<b>Case 18</b>	F	39	Palpable mass	L-UOQ	14-12	Mixed carcinoma	10% IPC + 80% IDC + 10% PLC	33	Alive	-
<b>Case 19</b>	F	41	Mammographic screening	L-UOQ	25	Mixed carcinoma	60% IPC + 40% IDC	31	Alive	-
<b>Case 20</b>	F	50	Mammographic screening	L-LOQ	17	Mixed carcinoma	40% IPC + 60% IDC	36	Alive	-
<b>Case 21</b>	F	64	Palpable mass	L-UIQ	16	Mixed carcinoma	20% IPC + 80% IDC	38	Alive	-
<b>Case 22</b>	F	40	Palpable mass	R-LOQ	26	Mixed carcinoma	70% IPC + 30% IDC	25	Alive	-

F: female; M: male; MRI: magnetic resonance imaging; R: right; L: left; UIQ: upper inner quadrant; UOQ: upper outer quadrant; LOQ: lower outer quadrant; IPC: invasive papillary carcinoma; IDC: invasive ductal carcinoma; IMPC: invasive micropapillary carcinoma; PLC: pleomorphic lobular carcinoma; m: month; LN: lymph node, \*metachronous tumors

## Discussion and Conclusion

### Differential Diagnoses and Controversies in the Literature

IPC of the breast was rare and poorly defined before 2003. Therefore, collecting reliable data for this tumor type is quite difficult. Before making a diagnosis of IPC, some important issues should be clarified. First, a possible metastasis to the breast must be excluded by clinical, radiological, and histopathological examination. Differential diagnosis comprises mostly gynecologic tractus, lung, and thyroid malignancies in women and prostate, lung, colon, and bladder carcinomas in men (1, 4, 12). Prostate-specific antigen has a limited value to differentiate between primary and metastatic carcinoma of the breast in men, since it may also show positive staining in breast carcinomas (1). The presence of a DCIS component, as well as positive staining for ER and/or PR receptors and GATA3 support breast origin. Second, if the tumor exhibits encapsulated papillary carcinoma or solid papillary carcinoma morphology associated with invasive breast carcinoma, these tumors should not be classified as IPC, but categorized according to the individual invasive component, which is generally non-papillary (6, 7, 9). The favorable prognosis for IPC reported in the literature mainly originates from cases of encapsulated papillary carcinoma and solid papillary carcinoma associated with invasion (9, 13). Moreover, IPC should be differentiated from invasive micropapillary carcinoma, which is a separate entity in terms of biological behavior and morphological appearance (3).

### Clinicopathologic Statistics

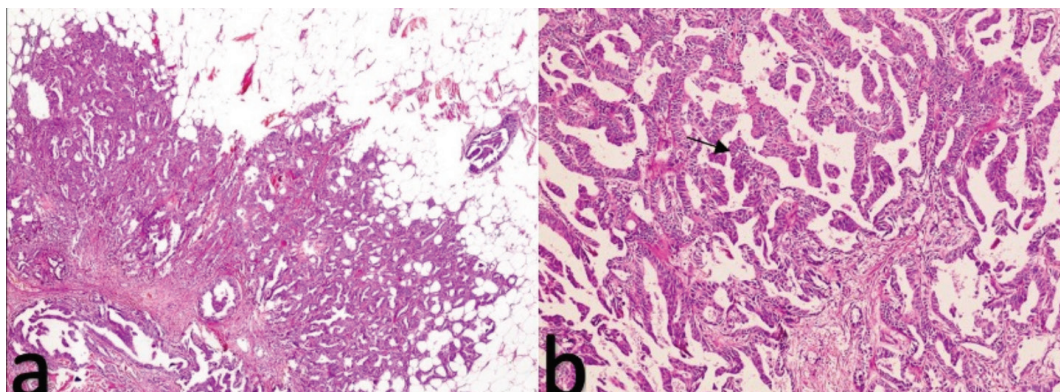
In the current study, whereas the median age of the patients with mixed-type IPC was 52, it was 61 for pure-type IPC. However, there was no significant difference in terms of patient age ( $p = 0.149$ ) between mixed or pure types of IPCs. Patient age at tumor diagnosis was reported as older in IPCs than in IDC in previous studies (14-16). The median size of tumor was 19 mm. IPC is more common in males than in females, accounting for approximately 2 to 4% of cases (11). One of the patients in our study was male. The presence of more papillary-type carcinoma in the male patient was explained by a less well-developed terminal duct lobular unit as well as the presence of more large ducts in the male breast (17, 18). Most of the cases in this study presented as a palpable breast mass and others were detected by routine clinic-radiologic examinations. Two cases had a history of bloody nipple discharge. Although the tumor was located mostly in outer quadrants, in almost one-third of the cases, it was located in the inner quadrant or retroareolar region. Multiple tumor foci were also identified in 23% of the cases. Similarly, in previous studies, the presentation of patients with IPC were reported as a palpable breast mass, nipple discharge, or radiographic abnormality (19). IPC may exhibit growth as a single nodule in the central portion of the breast or as multiple nodules that extend out from the retroareolar region to the periphery of the breast (20, 21). Therefore, tumor location in the central region (retroareolar/subareolar) or inner quadrants and the presence of multiple foci of tumor should indicate papillary neoplasms of the breast.

Invasive papillary morphology was determined in 1.9% of the cases diagnosed as primary invasive breast carcinoma in this study. Whereas invasive papillary morphology was identified in 10-90% of the tumor in 1.3% of the cases, pure-type IPC (in which the tumor showed invasive papillary morphology in  $\geq 90\%$

of the tumor) was found in 0.6% of the cases. The other histologic types accompanying IPC were IDC (15 cases), invasive micropapillary (3 cases), and pleomorphic lobular carcinoma (1 case). The overall incidence of IPC was reported as low, accounting for less than 1 to 2% of the cases with invasive breast carcinoma in the literature, as in this study (1, 22). IDC, invasive micropapillary carcinoma, and invasive lobular carcinoma have also been reported as other histologic types accompanying IPC (13). Lobular neoplasia was present in one case with mixed type breast carcinoma (IDC + pleomorphic type invasive

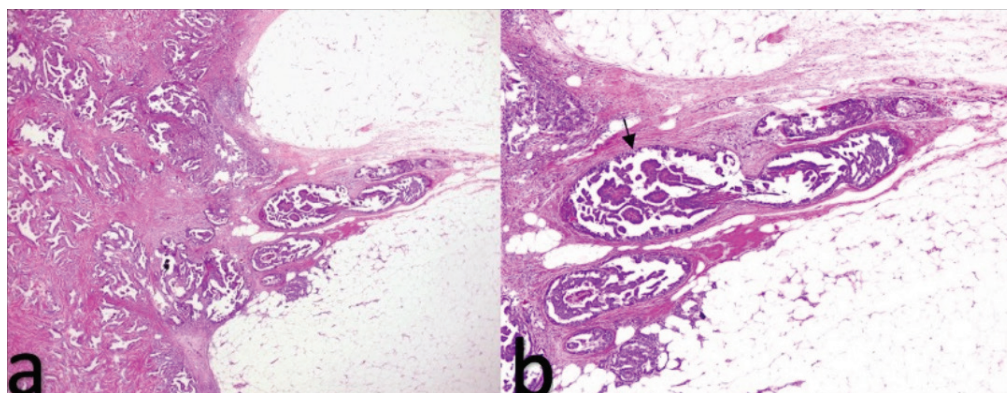
lobular carcinoma + IPC). DCIS was identified in most of the cases (86.4%) in this study and both the nuclear grade and the patterns of DCIS were consistent with primary invasive breast carcinoma. Tumor-associated microcalcification was found at a higher frequency (45.4%).

Contrary to other studies, in the present study most of the cases with IPC showed intermediate to high-grade nuclear and histological features (13, 19, 22). We partially explain this due to the high number of cases with mixed-type histology in which each component (IPC



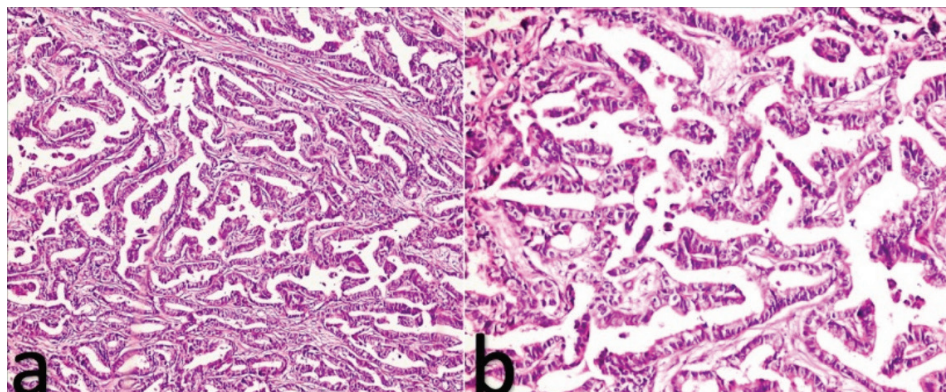
**Figure 1a.** Tumor shows infiltration within the adipose tissue (H&Ex100), **b.** Papillary structures lined by single or more layered cells with moderate nuclear atypia (H&Ex200)

H&E: hematoxylin and eosin



**Figure 2a.** Irregularly dilated invasive glands including papillary structures within their lumen are seen in the left part of the image (H&Ex40), **b.** Papillary type DCIS is seen (H&Ex100)

H&E: hematoxylin and eosin, DCIS: ductal carcinoma in situ



**Figure 3a, b.** Papillary structures within the irregularly dilated glands in a desmoplastic stroma (a: H&Ex200, b: H&Ex400)

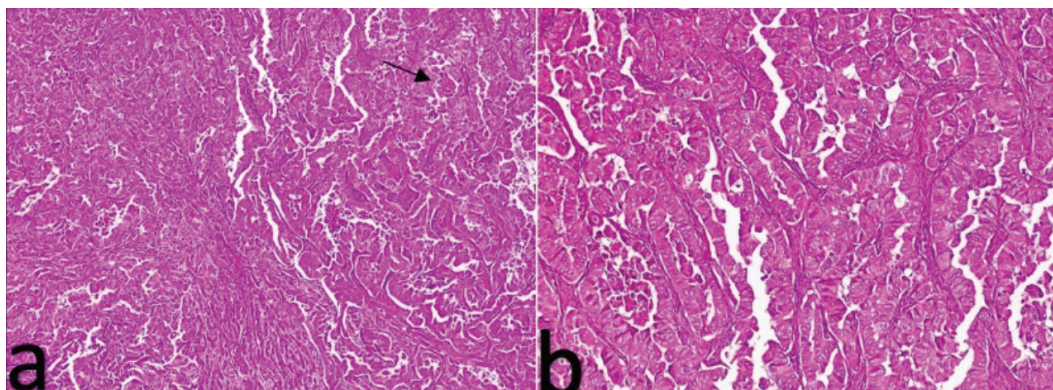
H&E: hematoxylin and eosin

with IDC and/or invasive micropapillary and/or pleomorphic lobular carcinoma) might have similar grade features. In pure-type IPC (n = 7), the high-grade nuclear feature was found in almost half of the cases (3 cases) and intermediate-grade histologic feature in four. Although IPC generally was reported as a lower-grade tumor, information for tumor grade was not available in a significant number of patients in some published studies. In one of the largest studies, based on Surveillance, Epidemiology and End Results population, the histologic grade of tumor was reported as 1 in 32.6% of the cases, 2 in 31.9% of the cases, 3 in 14.5% of the cases, and unknown in 21% of the cases (22).

Most of the cases presented in this study were in the early stages of breast cancer (pT1-2, N0-1) as in the other studies (13, 19). Previous studies reported characteristic clinical and pathologic features of IPC to be patients at older age presentation ( $\geq 50$ ), tumors presenting with smaller size, lower grades, reduced involvement of axillary lymph nodes, positive staining for hormone receptors (ER PR), and better survival rates (13, 14). In a study by Zheng et al. (22), the demographics and tumor characteristics of IPC (n = 524) were compared to those of IDC (n = 232,647). According to this study, patients with IPCs presented with smaller tumors (tumor size  $< 20$  mm, 67.4% versus 63.9%), more grade 1 disease (32.6% versus 18.6%), lower rate of LN involvement at diagnosis (11.6% versus 32.6%), more frequently presented with Stage I disease (61.5% versus 50.2%), a higher rate for ER positivity (87.2% versus 76.6%), a higher rate for PR positivity (80.7% versus 66.5%), a lower rate for HER amplification (2.1% versus 5.6%), higher rates for lumpectomy (68.7% versus 60.2%), and a lower rate for adjuvant radiotherapy (48.5% versus 56.6%) (22).

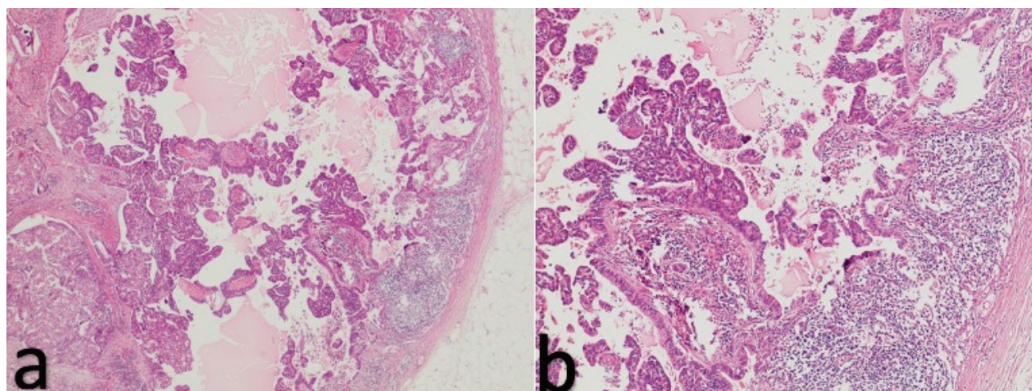
Comparison of survival rates between IPC and IDC demonstrated that disease-specific survival (DSS) was better in IPC patients than in the overall IDC population, with 5-year DSS rates in IPC and IDC 97.5% and 93%, respectively (22). Univariate analysis revealed that prognostic indicators included age, year of diagnosis, race, laterality, tumor grade, tumor size, LN status, and ER/PR/HER2 status (22). The type of treatment (radiation and surgery) was significantly associated with DSS so IPC histology was found to be a protective factor. Multivariate analysis also confirmed the prognostic factors identified in univariate analysis. However, histologic type was not found to be an independent prognostic factor after adjusting for other factors in multivariate analysis (22).

In the study by Liu et al. (13), the clinicopathological features and survival status of patients with IPC (n = 284) were compared to those with IDC (n = 300). The authors found that patients with IPC presented with an older age at diagnosis (postmenopausal), a low to intermediate grade of tumor, lower involvement of axillary lymph nodes, and a better 5-year overall survival (OS) and DSS than those of IDC. Additionally, tumors with Luminal A molecular phenotype showed a better 5-year OS and DSS than the other phenotypes. Therefore, the authors concluded that IPC was more favorable in terms of patient outcome than IDC. In addition, 11 out of 284 patients with IPCs were reported to have died from breast cancer. In these 11 patients, seven showed mixtures of other invasive histologic components such as IDC (n = 5), invasive micropapillary carcinoma (n = 1), and invasive lobular carcinoma (n = 1). Four of these 11 cases



**Figure 4a, b.** IPC with focal areas of comedonecrosis (H&Ex200), **b.** Tumor cells show high-grade cytonuclear features, such as pleomorphic vesicular nuclei with prominent nucleoli as well as ample eosinophilic cytoplasm (H&Ex400)

H&E: hematoxylin and eosin, IPC: invasive papillary carcinoma



**Figure 5a, b.** Although most of the axillary lymph node metastases were detected in IDC morphology, a few cases (as seen above) maintained their papillary appearance in lymph node metastasis (a: H&Ex40, b: H&Ex 100)

H&E: hematoxylin and eosin, IDC: invasive ductal carcinoma

Table 2. Histopathologic and immunohistochemical findings of the patients

Case	Surgical Procedure	Histologic Type	Focality	Mixed Component	NG	HG	LVI	PNI	Axillary LN	ER* %; intensity	PR* %; intensity	HER2	Ki-67 (%)	AR
Case 1	BCS+AD	IPC	U	-	2	2	-	-	0/20	90+++	10++	-	60	NA
Case 2	MRM	Mixed carcinoma	M	30% IPC + 70% IDC	3	2	-	-	+ 3 / 11	50++	20++	-	30	NA
Case 3	MRM	Mixed carcinoma	M	50% IPC + 50% IDC	3	2	+	-	+ 1 / 18	95+++	90++	-	10	+
Case 4	BCS+AD	IPC	U	-	3	2	+	-	+ 6 / 13	100+++	30++	+	17,5	NA
Case 5	BCS+SLN	IPC	U	-	3	2	+	+	0/2	-	-	-	90	NA
Case 6	BCS+AD	Mixed carcinoma	U	10% IPC + 90% IDC	2	1	-	-	+ 3 / 17	100+++	60++	-	22,5	NA
Case 7	BCS+SLN	Mixed carcinoma	U	30% IPC + 70% IDC	3	3	-	-	0/4	-	-	-	90	-
Case 8	BCS+AD	Mixed carcinoma	U	45% IPC + 45% IDC + 10% IMPC	3	3	+	-	+ 7 / 14	-	-	-	80	-
Case 9	SM+SLN+AD	1. Mixed carcinoma 2. IPC	M	1. 45% IPC + 45% IDC + 10% IMPC 2. IPC	3	3	+	-	+ 1 / 17	-	-	-	50	NA
Case 10	BCS+SLN	Mixed carcinoma	U	35% IPC + 30% IDC + 35% IMPC	2	2	-	-	+1 / 1 (<2 mm)	100+++	85+++	-	22	NA
Case 11	BCS+SLN	Mixed carcinoma	U	30% IPC + 70% IDC	2	2	-	-	0/1	-	< 5% +	-	80	-
Case 12	MRM	IPC	U	-	2	2	-	-	0/10	100+++	100+++	+	25	NA
Case 13	SM	Mixed carcinoma	U	40% IPC + 50% IDC + 10% IMPC	2	2	+	-	Malignantcytology	100+	-	-	27,5	NA
Case 14	BCS+AD	Mixed carcinoma	U	30% IPC + 70% IDC	3	3	+	-	+ 10 / 11	15+++	60+	-	40	NA
Case 15	BCS+SLN	IPC	U	-	2	2	-	-	0/1	100+++	95+++	-	35	NA
Case 16	MRM	Mixed carcinoma	M	50% IPC + 50% IDC	3	2	-	-	+ 3 / 8	100+++	80+++	-	24	NA
Case 17	SM+SLN	IPC	U	-	2	1	-	-	0/3	100+++	13++	-	37,5	NA
Case 18	BCS+SLN	Mixed carcinoma	M	10% IPC + 80% IDC + 10% PLC	2	2	-	-	0/3	95+++	85++	+	40	NA
Case 19	MRM	Mixed carcinoma	U	60% IPC + 40% IDC	2	2	+	-	+ 2 / 9	90++	90+++	-	30	NA



Table 2. Continued

Surgical Procedure	Histologic Type	Focality	Mixed Component	NG	HG	LVI	PNI	Axillary LN	ER* %; intensity	PR* %; intensity	HER2	Ki-67 (%)	AR
MRM (+Neoadjuvant therapy)	Mixed carcinoma	U	40% IPC + 60% IDC	3	3	+	-	+ 11 / 32	100 +++	90 +++	-	20	NA
BCS+SLN	Mixed carcinoma	U	20% IPC + 80% IDC	2	1	-	+	0 / 3	100 +++	100 +++	-	27,5	NA
BCS+SLN	Mixed carcinoma	U	70% IPC + 30% IDC	2	1	-	-	0 / 4	100 +++	95 +++	-	25	+

NG: nuclear grade; HG: histologic grade; LVI: lymphovascular invasion; PNI: perineural invasion; ER: estrogen; PR: progesterone; AR: androgen; BCS: breast-conserving surgery; AD: axillary dissection; MRM: modified radical mastectomy; SLN: sentinel lymph node dissection; SM: simple mastectomy; U: unifocal; M: multifocal; NA: not available; IPC: invasive papillary carcinoma; IDC: invasive ductal carcinoma; HER2: human epidermal growth factor 2. \*for ER and PR intensity: strong staining (+++); moderate staining (++) weak staining (+). HER2 (+): score 3 immunostaining or amplification detected by SISH

showed pure-type IPC. Liu et al. (13) found that patients with pure-type IPC had significantly more favorable prognoses than IDC. In other words, patients with mixed-type IPC appeared to have a poorer outcome.

In the current study, 5 out of the 22 patients died (Table 1). While 3/5 cases showed mixed-type histology (IPC+ IDC+ invasive micropapillary carcinoma) the remaining two showed pure-type IPC. However, one of these pure-type IPC cases (Case #17) had a history of IDC with Paget's disease in the other breast two years earlier (metachronous breast carcinoma). The previous breast carcinoma showed different tumor morphology and molecular subtype (ER-/PR-/HER2+) and there was no lymphovascular invasion or axillary nodal metastasis.

### Molecular Phenotypes

The distribution of cases by molecular phenotype in this study was Luminal B in 16 cases (72.7%), triple-negative in 5 cases (22.7%), and Luminal A in 1 case (4.6%). Although three cases showed HER2 positivity by immunohistochemistry and/or SISH methods, there was no case in the HER2 molecular subgroup. The Ki-67 proliferation index was ≥20% in most of the cases (90.9%). The pure IPC cases showed Luminal B phenotype in five and triple-negative in two cases. In recent studies, the majority of patients with IPC were found to be positive for ER and PR receptors and negative for HER2 (13). In terms of the four molecular subtypes, some studies reported Luminal A to be the most frequent subtype, in the current study and others Luminal B was found to be most common (13, 23). A considerable number of IPC cases showed triple negative phenotype in some other studies, as in this study (13).

Darvishian et al. (23) described a variant of papillary carcinoma called breast carcinoma with tubulopapillary features. This tumor exhibited a predominant (≥50%) tubulopapillary morphology characterized by infiltrating, gaping, and anastomosing tubules and small cysts in a retiform arrangement within a dense, abundant, sclerotic stroma. The tubules were lined with cuboidal to short columnar cells with moderate to high-grade nuclear atypia and occasional hobnail cells reminiscent of serous papillary carcinoma of Mullerian origin. They found that this type of IPC tends to have a significantly higher mitotic rate, higher Ki-67 proliferation index, nuclear grade 3 features, lymphovascular invasion, p53 overexpression, and axillary nodal involvement compared to the control group. Therefore, the authors concluded that invasive breast carcinoma with tubulopapillary features showed a significant correlation with adverse prognosis compared to ordinary papillary carcinomas. Their study group was composed of 12 cases, in which the molecular subtype was Luminal B in five, Luminal A in three, triple-negative in three, and HER2 in one case (23). One of our cases (Case #4) showed a morphology similar to this type of breast tumor, with tubulopapillary features. The CNBS of this case was described as "Invasive Adenocarcinoma" and after clinical-radiology evaluation and immunostaining results, it was reported as "tumoral proliferation compatible with breast primary." A similar morphology of tumor was also seen in the surgical excision material.

### Individual Cases

Individual cases in this study showed tumor with a prominent lymphocytic inflammatory cell infiltration or tumor with apocrine cytonuclear features, or tumor in association with pagetoid involvement of large ducts and nipple dermis. The coexistence of IPC and Paget's disease was reported in only one case in previous studies (24). The authors indicated unfavorable histological features for this case, contrary to IPC. Pagetoid involvement was identified in one of the cases in this study (Case #16). This case showed two invasive tumor foci and at the time of writing was alive and disease-free after 41 months of follow-up.

Lymphocyte-predominant breast cancer was defined by the presence of more than 50% of lymphocytes within the tumoral stroma (25). It has been recognized as an important prognostic and predictive factor, particularly for ER-negative carcinomas (25). One of the cases in this study (Case #8) showed mixed-type

histology and high-grade tumor features with triple-negative phenotype. However, after 17 months of follow-up, local recurrence, lymph node involvement and multiple visceral organ metastasis were detected and soon after, the patient died.

Apocrine differentiation in breast carcinoma was seen in IDC, tubular, lobular, micropapillary, and medullary carcinomas (1). These tumors may demonstrate solid-tubular or papillary growth patterns (1). However, an “apocrine molecular signature,” androgen receptor (AR) (+), GCDPF-15 (+), ER (-), PR (-), and HER2 (+), was described in almost half of the tumors that showed these morphologies (1, 26). One of our cases showed apocrine cytonuclear features and positivity for AR. However, the tumor showed Luminal A phenotype (ER+ PR+ HER2- and Ki-67 index 10%). The AR is a nuclear steroid hormone receptor and differentially expressed in breast cancer subgroups (27). Higher expression rates for AR were found in ER-positive breast carcinomas than for those of ER-negative tumors (27). AR expression was found in association with favorable clinicopathological features, such as lower grade, lower pT stage, and positivity for PR in ER-positive breast cancers (27).

#### **Histopathological Findings Within Non-Tumoral Breast Parenchyma**

We also described several findings within the non-tumoral breast parenchyma of patients with IPC. Columnar cell changes with or without atypia, apocrine metaplasia (mostly in the form of cystic papillary apocrine hyperplasia), fibrocystic changes, and ductal ectasia were the most frequent findings noted in surrounding breast parenchyma.

In conclusion, we retrospectively reviewed the H&E slides of cases diagnosed as invasive breast carcinoma between 2010 and 2018 and described the clinicopathological findings of the cases with pure and mixed-type IPC in our department. Consequently, IPC was detected in 1.9% of all the cases with invasive breast carcinoma, of which 0.6% was of the pure-type form and 1.3% exhibited a mixed-type histology. IPC was detected mostly as an accompanying carcinoma to IDC and showed Luminal B molecular phenotype with intermediate-to-high grade features. DCIS was usually coexistent with IPC. The patients mostly presented in the early stages of breast cancer with palpable breast mass and/or radiographic abnormality at postmenopausal age. Tumor location in the retroareolar region or inner quadrant and multiple tumors were detected at a higher frequency. Columnar cell changes, apocrine metaplasia, fibrocystic changes, and ductal ectasia were the most frequent findings within the non-tumoral breast parenchyma.

**Ethics Committee Approval:** Ethical approval for this study was obtained from the Ethics Committee of Istanbul Education and Research Hospital (protocol number: 1888, date: 28.06.2019).

**Informed Consent:** Informed consent information haven't been obtained since the methods currently used for diagnostic purposes were used in this study and no additional method without proven benefit was applied.

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#### **Authorship Contributions**

Surgical and Medical Practices: C.K.T., B.Y.E., E.A., M.A.N., Y.C., D.C.T.; Concept: C.K.T., B.Y.E., E.A., M.A.N., Y.C., D.C.T.; Design: C.K.T., B.Y.E., E.A., M.A.N., Y.C., D.C.T.; Data Collection and/or Processing: C.K.T., B.Y.E., E.A., M.A.N., Y.C., D.C.T.; Analysis and/ or Interpretation: C.K.T.,

B.Y.E., E.A., M.A.N., Y.C., D.C.T.; Literature Searching: C.K.T., B.Y.E., Y.C.; Writing: C.K.T., B.Y.E., Y.C.

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